Observation of Neighboring Group Participation in Organocatalytic Asymmetric Reactions: Scope and Synthetic Applications

A Thesis
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Doctor of Philosophy

By

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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 ***Dr. Dhevalapally B. Ramachary*** *and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on the findings of other investigators.*

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CERTIFICATE

*Certified that the work contained in the thesis entitled "**Observation of neighboring group participation in organocatalytic asymmetric reactions: scope and synthetic applications"** has been carried out by **Ms. R. Sakthidevi** under my supervision and the same has not been submitted elsewhere for a degree.*

Dr. Dhevalapally B. Ramachary

(***Thesis Supervisor***)

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PREFACE

Single amino acid-catalyzed asymmetric reaction found its discovery after many scientists scrutinized the importance of enamine and weak interactions involved in antibody catalyzed reactions. The first and foremost utilization and demonstration of the combination of covalent and non-covalent interactions of L-proline catalyst in the intermolecular aldol reactions began the revolution of amino acid catalysis. The development and growth of asymmetric amino acid-catalysis has become tremendous in the past decade due to the multi-tasking ability and multiple interactions of the catalyst in the transition state. Other asymmetric reactions include thiourea activated Michael reactions, amine activated Diels-Alder reactions through iminium or hydrogen bonding activation and imidazolinium salt catalyzed Michael reactions through π-π interactions and many more, discovered based on the construction of covalent and non-covalent interactions from catalysts. All these catalyses together shed light on the importance of weak interactions in the transition state for high selectivity in asymmetric reactions and it has been well explored in the past decade.

The new strategy where substrates with active neighboring group is used, gains the dual advantages of neighboring group participating in the transition state and also will be a part of subsequent cascade reactions leading to highly substituted polycyclic substances. This in turn, opens a way to understand and to explore the involvement of the functional group in the transition state, which in some instances opens a new paradigm of catalysis. This work is one-such result of studies towards understanding and observing the neighboring group participation in the organocatalytic asymmetric reactions.

*The present thesis entitled "**Observation of neighboring group participation in organocatalytic asymmetric reactions: scope and synthetic applications**" describes the asymmetric synthesis of highly functionalized chiral and drug-like molecules through neighboring ortho-hydroxyl group participation. 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 asymmetric synthesis of functionalized chiral benzopyrans via amino acid catalyzed Barbas-List aldol (BLA) reaction of ketones with 2-hydroxybenzaldehydes through neighboring ortho-hydroxyl group participation. The BLA reaction catalyzed by trans-4-OH-L-proline yielded aldol products with good yields and high selectivities. The existence of fast dynamic equilibrium between δ-hydroxyketone and lactol products was well studied and trapped to transform to functionalized chiral benzopyrans.

The second chapter describes an organocatalytic sequential Michael-acetalization (SMA) reaction for the asymmetric synthesis of functionalized 4-nitromethyl-chromans which are useful drug intermediates. The sequence of Michael reaction of 2-(2-nitrovinyl)phenols with acetone catalyzed by 9-amino-9-deoxyepiquinine/Ph_2CHCO_2H and acetalization reaction with alcohol catalyzed by p-TSA proceeded well to deliver the functionalized chromans through neighboring ortho-hydroxyl group participation with good yields and high selectivities. The dynamic equilibrium was observed between pseudo-diastereomeric hemiketals and δ-hydroxy ketone and has been successively utilized for the synthesis of various chroman and pyrrolidine molecules.

In continuation to study the involvement of ortho-hydroxy functionality in the transition state and in reaction strategy, 2-(2-nitrovinyl)phenols were reacted with cyclohexanone in the presence of D-proline and quinine-NH-thiourea catalytic mixture. These results are discussed in the third chapter. The sequential Michael/reductive etherification reactions yielded the chiral hexahydroxanthenes with high selectivities. The Michael reaction proceeded well, through a supramolecular 19-membered pre-transition state intermediate yielding Michael adducts with excellent yields, enantio- and diastereoselectivities. Furthermore, evidence for the asymmetric supramolecular catalysis has been given through ESI-HRMS technique.

The fourth chapter demonstrates an organocatalytic diastereoselective hydrogenation of bicyclic enones and Δ^4-3-ketosteroids catalyzed by amine/acid with Hantzsch esters. The catalyst (S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/D-CSA stereoselectively hydrogenated the cyclic enones to cis-A/B junction using organic hydrides, mimicking in-vivo 5β-reductase. The bio-mimetic hydrogenation through hydride delivery to the iminium salt formed between enone and amine/acid under refluxing conditions was confirmed through NMR and ESI-HRMS analyses. This strategy was successively utilized for the synthesis of various medicinally important 5β-3-ketosteroids. In addition, a formal total synthesis of sativene starting from hydrogenated diketones has been demonstrated.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
Ala	Alanine
Anal.	analysis
aq.	aqueous
Ar	aryl
BLA	Barbas-List aldol
[Bmim]BF_4	1-Butyl-3-methylimidazolium tetrafluoroborate
Bn	benzyl
Boc	butyloxy carbonyl
Bp	boiling point
br	broad
Bu	butyl
*t*Bu or ^{t}Bu	*tertiary*-butyl
n-BuLi	*n*-butyl lithium
calcd.	calculated
cat.	catalytic
cm	centimeter
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
DPP-OTMS	diphenyl prolinol silyl ether
dr	diastereomeric ratio
dt	doublet of triplet
ee	enantiomeric excess
eq.	equation
equiv	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
Fg	functional group
Fig.	figure
gm	gram (s)
h	hour (s)

Hz	hertz
Hex	hexyl
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
H-P ketone	Hajos-Parrish ketone
i-Pr	isopropyl
IR	infrared
lit.	literature
LUMO	lowest unoccupied molecular orbital
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
MVK	methyl vinyl ketone
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
PDC	pyridinium dichromate
PCC	pyridinium chlorochromate
Ph	phenyl
Pg	protecting group
ppm	parts per million
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
Trp	Tryptophan
TsCl	toluenesulphonyl chloride
Ts	Toluenesulphonyl
TS	Transition state
UV	ultraviolate
Val	Valine
W-M ketone	Wieland-Miescher ketone

ABOUT THE AUTHOR

The author, **Ms. R. Sakthidevi** was born on 6th February 1985 in Tiruchirapalli, Tamil Nadu. After her initial schooling in Tiruchirapalli, she obtained her B.Sc. degree in 2005 from Seethalakshmi Ramaswami College, affiliated to Bharathidasan University, Tiruchirapalli and she obtained her M.Sc. degree with organic chemistry specialization in 2007 from University of Madras, Chennai. She continued as a research scholar in the School of Chemistry, University of Hyderabad for the Ph. D. programme from July 2007 onwards.

LIST OF PUBLICATIONS

1. D. B. Ramachary and **R. Sakthidevi**, "Combining multi-catalysis and multi-component systems for the development of one-pot asymmetric reactions: stereoselective synthesis of highly functionalized bicyclo[4.4.0]decane-1,6-diones", ***Org. Biomol. Chem.*** **2008**, *6*, 2488-2492.

2. D. B. Ramachary and **R. Sakthidevi**, "Direct catalytic asymmetric synthesis of highly functionalized 2-methylchroman-2,4-diols via Barbas–List aldol reaction", ***Chem. Eur. J.*** **2009**, *15*, 4516-4522.

3. D. B. Ramachary and **R. Sakthidevi**, "Sequential combination of Michael and acetalization reactions: direct catalytic asymmetric synthesis of functionalized 4-nitromethyl-chromans as drug intermediates", ***Org. Biomol. Chem.*** **2010**, *8*, 4259-4265.

4. D. B. Ramachary, **R. Sakthidevi** and K. S. Shruthi, "Asymmetric Supramolecular catalysis: A bio-inspired tool for the high asymmetric induction in the enamine-based Michael reactions". ***Chem. Eur. J.*** **2012**, *18*, 8008-8012.

5. D. B. Ramachary, **R. Sakthidevi** and P. S. Reddy, "Mimicking human steroid 5β-reductase (AKR1D1) through organocatalysis: A facile route to stereoselective synthesis of chiral 5β-dihydrosteroids, 5β-dihydro-Wieland-Miescher ketones and 5β-dihydro-Hajos-Parrish ketones". (*Manuscript under preparation*).

Posters and Presentations

1. Given a flash oral presentation entitled "Sequential combination of aldol/Michael and acetalization reactions: direct catalytic asymmetric synthesis of functionalized chromans as drug intermediates" in 8th in-house symposium "***Chemfest-2011"*** held at University of Hyderabad, Hyderabad, India during February 25-26, 2011.

Observation of Neighboring Group Participation in Organocatalytic Asymmetric Reactions: Scope and Synthetic Applications

1. ABSTRACT

A practical and sustainable strategy has been described for the synthesis of highly substituted aldol↔lactol products through asymmetric Barbas-List aldol (BLA) reaction of 2-hydroxybenzaldehydes with acetone in the presence of the catalyst, *trans*-4-OH-L-proline at ambient temperature through neighboring *ortho*-hydroxyl group participation. The concept of aldol↔lactol dynamic equilibrium has been well-studied under different reaction conditions. The lactol products have been utilized for the synthesis of various functionalized chiral benzopyran molecules.

An asymmetric synthesis of 4-nitromethyl-chromans was achieved through sequential combination of Michael and acetalization reactions on 2-(2-nitrovinyl)phenols with acetone and alcohols in the presence of catalyst, 9-amino-9-deoxyepiquinine/Ph_2CHCO_2H followed by *p*-TSA through neighboring *ortho*-hydroxyl group participation. The dynamic equilibrium observed between pseudo-diastereomeric hemiketals and δ-hydroxy ketone has been successively utilized for the asymmetric synthesis of various chroman and pyrrolidine molecules.

Utilization of large-size supramolecular rings in the pre-transition state (pre-TS) of enamine-based Michael reactions for high asymmetric induction is described. Enantiomerically pure, drug-like hexahydroxanthenes with three contiguous stereocenters were synthesized through supramolecular catalysis by D-proline and quinine-N*H*-thiourea followed by reductive etherification from simple precursors under mild reaction conditions. Further experimental

evidence has been given for the existence of supramolecular assembly by trapping the pre-TS intermediate through ESI-HRMS analysis.

A direct and simple diastereoselective hydrogenation of variety of bicyclic enones and Δ^4-3-ketosteroids using Hantzsch ester as hydride source has been reported. The catalyst (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/D-CSA stereoselectively hydrogenated the cyclic enones to *cis*-A/B junction, mimicking *in-vivo* 5β-reductase. The bio-mimetic hydrogenation proceeded through hydride delivery to the iminium salt formed between enone and amine/acid under refluxing conditions which was confirmed through NMR and ESI-HRMS analyses. This strategy was successively utilized for the synthesis of various medicinally important 5β-dihydro-3-ketosteroids. In addition, a formal total synthesis of chiral sativene starting from hydrogenated diketones has been demonstrated.

2. INTRODUCTION

Direct organocatalytic sequential one-pot combination of multi-component and multi-catalysis cascade reactions make the organic synthesis easier by forming polycyclic molecules from simple starting materials with high yields and selectivities[1]. The enantiomeric induction in an organocatalytic asymmetric reaction is determined by its transition state where the reactants, catalysts and intermediates assemble in a favourable manner. Such a transition state is influenced by electronic and steric factors of the substrates, which may give beneficial or detrimental results. Any additional functionality in the neighboring position of substrates not only changes the transition state but also involves in the cascade reaction strategies to yield the highly functionalized molecules in one-pot.

As the research work described in this thesis deals with neighboring *ortho*-hydroxyl group participation in organocatalytic asymmetric cascade reactions[1], a brief account of sequential or cascade organocatalytic one-pot reactions through neighboring *ortho*-hydroxyl group participation is presented below.

Many fundamental concepts in organic chemistry have been developed by chemists and recognized by IUPAC, one of which is neighboring group participation (NGP).[2] It has been defined as the involvement of electrons (lone pair, π-bond or σ-bond electrons) with the reaction centre which would change the reactivity and in some instances, selectivity. The involvement of

any neighboring group to change the reactivity or the selectivity of the reaction from the classical view can be broadly classified into following three classes.

The first class of neighboring group participation concerns with the participation of lone pair of electrons to increase the reactivity. Sunko et al. in 1987, demonstrated that sulfur atom with lone pair of electrons increases the rate of S_N2 reaction by activating the electrophile intramolecularly. It has been well proven that the presence of sulfur tremendously increases the rate of the solvolysis reaction of **1** as shown in eq. 1.[3]

The second category of neighboring group participation would be concerned about the π-bond electrons involvement in the stabilization of *in situ* generated carbocations. The following example by Borčić et al. in 1979, clearly instructs that π-bond electrons induced positive charge is delocalized around the bonds making the carbocation intermediates **6**-**8** stable to undergo solvolysis reaction in ethanol as shown in eq. 2.[4]

Involvement of π-bond electrons of aromatic rings for the stabilization of *in situ* generated carbocation intermediates also falls under the second class of neighboring group participation, where the delocalization increases the stability, thus increases the solvolysis rate to 13-150 folds. Tanida et al. in 1985 demonstrated the participation of π-bond electrons of aromatic ring in the solvolysis of **9** as shown in eq. 3.[5]

The third category of NGP would be concerned about the σ-bond electrons involvement in the stabilization of carbocations. The participation of σ-bonds in the generation of non-classical carbocation for controlling the stability and the reactivity of the intermediate has been well understood in various solvolysis reactions. The fast solvolysis of **13** in AcOH was due to the non-classical carbocation, which was demonstrated by Roberts et al. in 1951 and this has been a synthetically useful strategy, an example of which has been shown in eq. 4.[6]

In an extension to the third category, cyclopropane ring also involves as σ-bond electrons for the rate enhancement. The remote cyclopropane ring makes the reaction faster through the involvement of σ-bond electrons. Sargent et al. in 1972 prove that the presence of cyclopropane ring in the γ-position increases the rate of saponification reaction of **19** by 600 times (eq. 5).[7]

The early observations on neighboring group participations in chemical reactions gave the inspiration to synthetic community to utilize the concept to increase the reactivity and the selectivity. Other than the electrons involvement (σ, π and lone pairs of electrons) as NGP for the rate enhancement of the reactions, hydrogen bonding activation also has been recognized as NGP to increase the rate of the well defined chemical and biochemical reactions. The well proven concept of this hydrogen bonding activation in biology has been well demonstrated in laboratory reactions also. This concept can be exemplified by the hydrolysis of mono ester phthalate **23** and *ortho*-carboxyl acetals **27** where *ortho*-carboxylic acid group facilitates rate enhancement of the reaction. The carboxylic group assisted hydrolysis through anhydride formations **26** or **30** has well been discussed and proven by Thanassi et al. in 1966 and Fife et al. in 1996 respectively. Their study suggested that the presence of carboxylic group increases the rate of the hydrolysis of **27** by 220 fold through anhydride formation as shown in the eq. 6.[8]

Thus, understanding and practice of electrons and hydrogen bonding activation as NGP gained much of attention during the development of new reactions in early 21st century, which then ended up with a new era, organocatalysis.

Organocatalysis found its rediscovery when scientists carefully examined the antibody catalyzed reactions. This led to the development of variety of organocatalysts, the privileged bio-inspired molecules. The development and growth of asymmetric organocatalysis has become tremendous in the past decade due to its multi-tasking ability and high enantiomeric induction during the course of the reactions. These small enzyme mimics have made the sequential reactions possible in one-pot to yield highly functionalized chiral molecules with high selectivity by virtue of their multi-activation mode.

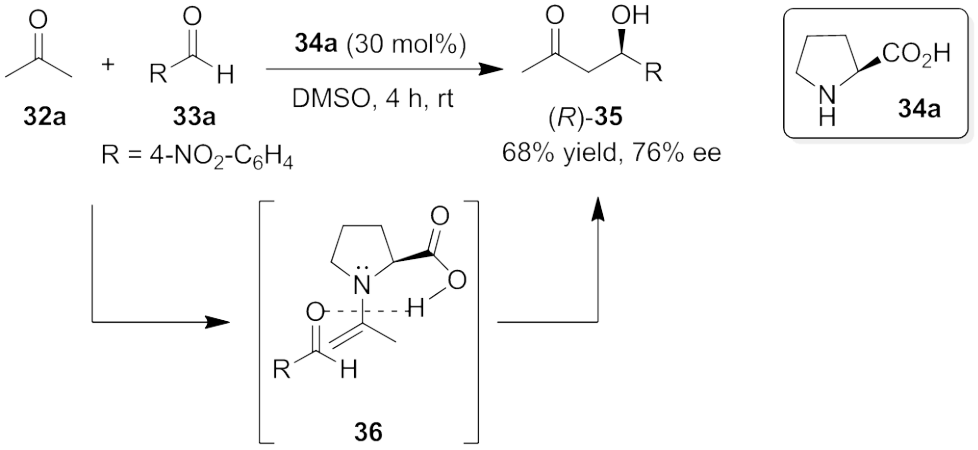
Active neighboring group present in proximity allows a way to cascade reactions leading to highly substituted polycyclic substances. Achieving high enantioselectivity in the renowned reactions with substrates having active functional groups in neighboring position requires a complete optimization procedure. This optimization strategy involves understanding the various interactions including covalent (iminium and enamine formations) and weak interactions (hydrogen bonding, π-stacking interactions and dipole-dipole interactions) among catalyst and substrates. Well designed collection and combination of these interactions in the transition state would lead to high enantiomeric induction in an asymmetric reactions.

Utilization of collection of interactions in a favored manner makes any asymmetric design fruitful for the synthesis of functionalized chiral molecules. When the combination of interactions makes a way for enantio induction, combination of catalyses also holds hands in making the syntheses efficient. Same catalyst acts in different activation modes during the catalyses. While on the other hand, the combination of metalcatalysis with organocatalysis opened another era for activating different functional groups in the starting material.[9] All these combinations together require a clear understanding to explore the involvement of the functional groups in the transition state and in the subsequent reaction strategy.

In recent years, our research group has been actively involved in engineering novel organocatalytic cascade reactions for the synthesis of highly functionalized chiral molecules with high selectivity.[10] The strategy utilized for the asymmetric induction includes the utilization of various covalent and non-covalent interactions among the substrates and catalysts in the

transition state to render high asymmetric environment. The active functionalities present in the substrate would not only involve in the transition state but also be a part of reactive sites during the subsequent cascade processes. The selection and position of active moiety has been designed in such a way that the transition state can be bent to attain the desired selectivity. For the past few years in our laboratory, the neighboring group participation in transition state and followed by cascade process has been the topic of investigation for the synthesis of chiral natural products and drug-like molecules.[1,10q,10r]

The early example of asymmetric organocatalysis was reported by Barbas and List in 2000 as shown in eq. 7.[11] The aldol reaction of 4-nitrobenzaldehyde **33a** and acetone **32a** in the presence of L-proline **34a** catalyst in DMSO solvent resulted the aldol product **35** in good yield and ee. The L-proline termed as the simplest enzyme,[12] catalyzes the reaction by activating the nucleophile through enamine formation and electrophile through the directed hydrogen bonding. Thus the activation of the substrates by the neighboring groups in catalyst initiated the bio-mimetic cellular type reactions (eq. 7). There are many ways and terminologies to define the activity of catalysts. Classicaly, neighboring group participation can be defined as the involvement of many functional groups from catalysts in the transition state.



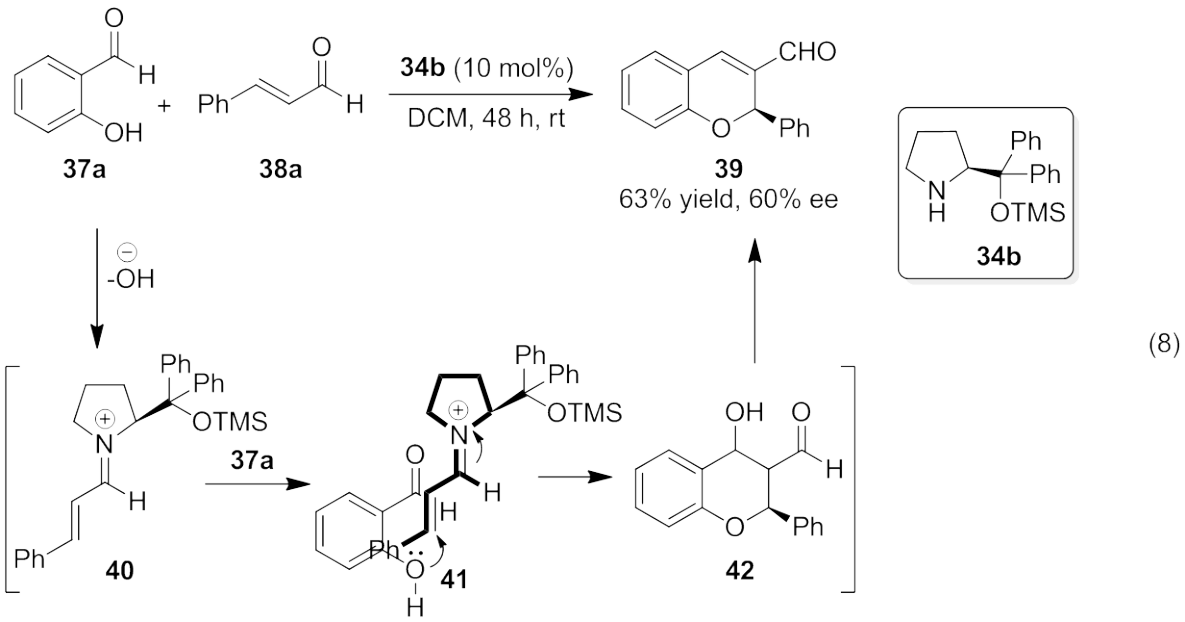
(7)

After understanding the neighboring group participation or synergistic activation from L-proline catalysis to render high enantiomeric induction in BLA reaction, a variety of catalysts was developed in order to increase the number of neighboring sites to anchor or to activate the substrates in various reactions. And quite a considerable number of reviews also have come up for defining the catalysts effect and thier activation modes in a variety of reactions.[13] Thus far,

the groups to participate in the transition state are from catalysts. On the other way round, the active functional groups which participate in the transition state can be from the substrates, which have dual advantages like transition state involvement and also can be the active site for the subsequent cascade processes.

A careful study of the literature revealed that the synthetic utility of neighboring group participation from the substrates in the transition state and subsequent cascade reactions seems to be an efficient strategy in synthetic organic chemistry. As such the neighboring group participation of active funcitontional groups in organocatalysis was not realized, even though the concept was utilized for the organocatalytic syntheses of many heterocycles unknowingly. A breif overview of the literature reports on neighboring group participation has been described as follows.

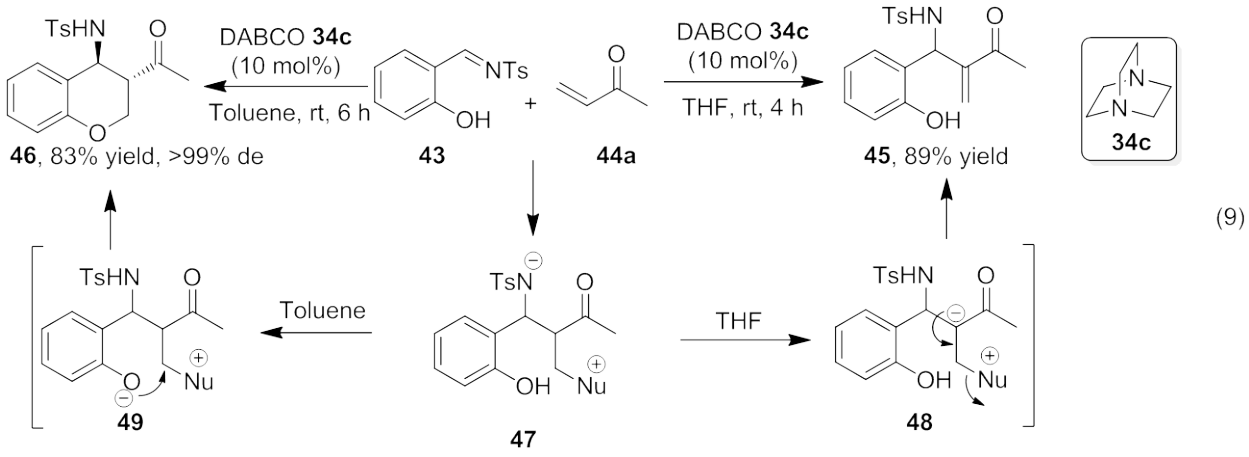
The asymmetric version of neighboring group participation was unknown till late 2006. In the year of 2006, Arvidsson et al. came up with first asymmetric oxa-Michael/intramolecular aldol reaction of 2-hydroxybenzaldehydes **37a** with α,β-unsaturated aldehyde **38a** in the presence of diphenylprolinol silyl ether **34b** to result the chiral chromene **39** as shown in eq. 8. Even though, moderate yields and selectivities were obtained in these reactions, this approach gains the credit of first asymmetric organocatalytic approach utilizing the neighboring *ortho*-hydroxyl group for the cascade reactions.[14] The presence of both electrophilic and nucleophilic centres in a



(8)

single substrate makes it an efficient cascade reaction, where the neighboring phenolic O*H* group initiates the sequence through oxa-Michael reaction followed by intramolecular aldol condensation to result chromene **39**.

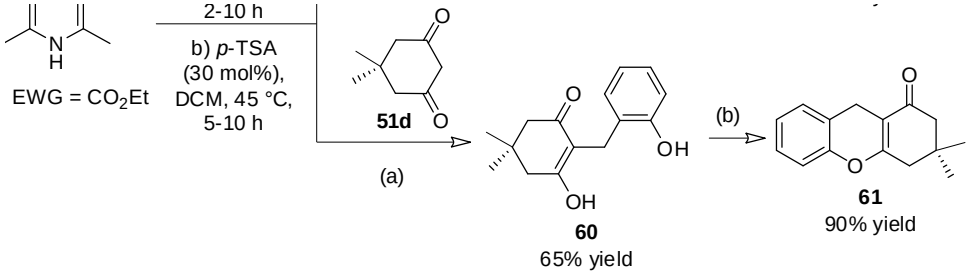
The synthesis of racemic chromans utilizing neighboring group participation was reported by the group of Shi in 2007, through the reaction between salicyl *N*-tosylimine **43** and methyl vinyl ketone **44a** as shown in eq. 9. Interestingly, DABCO **34c** catalyzed reaction of **43** with **44a** in toluene solvent to furnish the cyclized product **46** in 83% yield and >99% de, while the same reaction in THF solvent provided the aza-Baylis-Hillman type product **45** in 89% yield. As such, the reaction was found to go through the aza-Baylis-Hillman type intermediate **47** rather than simple oxa-Michael reaction which was confirmed through the controlled experiments. The controlled experiments, where 4-hydroxy-*N*-tosylamine was reacted with methyl vinyl ketone **44a** under similar reaction conditions, gave aza-Baylis-Hillman type product rather than simple oxa-Michael product taking 8 days reaction time to furnish 33% yield. This result confirms the enhancement in reactivity by neighboring group participation and also the reaction pathway. The mechanism is such that the common intermediate **47** gave chroman **46** through cyclization of intermediate **49** in toluene solvent. Whereas in THF, the intermediate **47** undergoes simple proton transfer due to hydrogen bonding of OH with THF molecules resulting aza-Baylis-Hillman type product **45** through intermediate **48** as shown in eq. 9.[15]



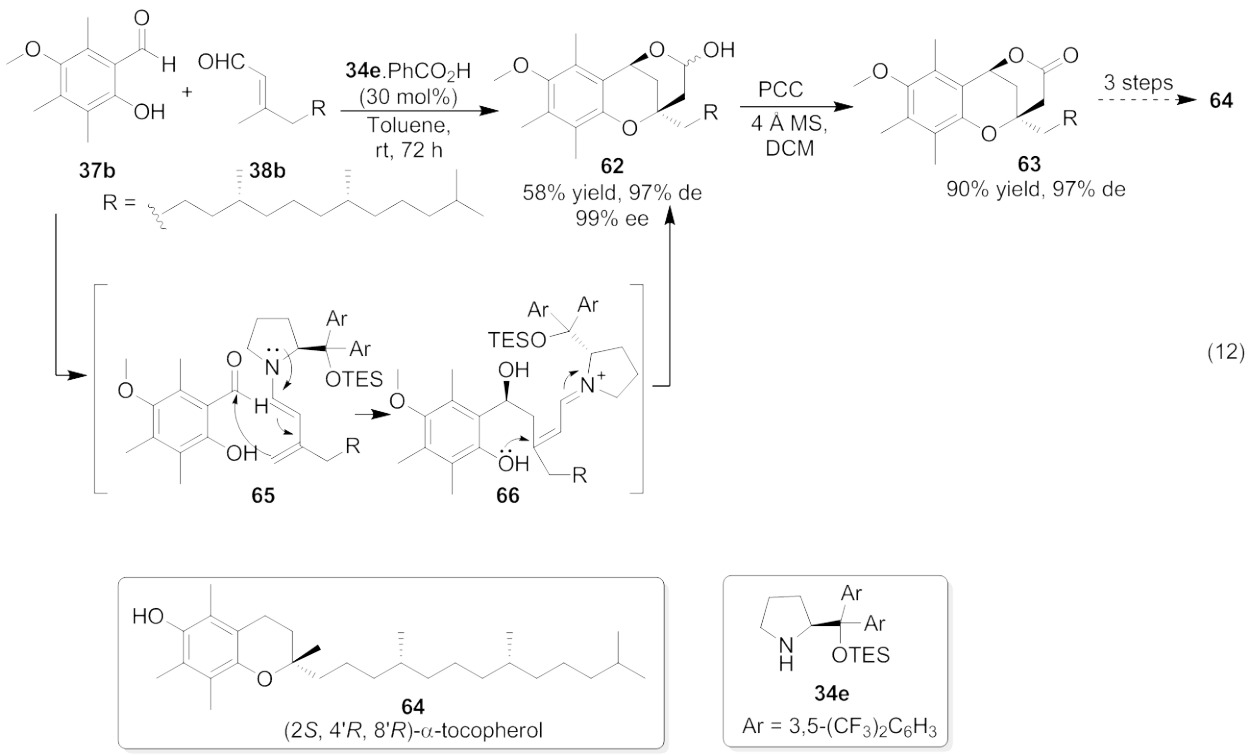
The first observation of neighboring group participation by phenolic O*H* in intramolecular hydrolysis was reported by our group in 2008. The water promoted cascade olefination/hydrogenation/hydrolysis (O/H/H) reaction of Meldrum's acid **51a** or malononitrile

51b with 2-hydroxybenzaldehyde **37a** and Hantzsch ester **50a** yielded the products **53** or **56** in excellent yields through NGP. The involvement of phenolic hydroxyl neighboring group in the lactonization was successfully demonstrated as shown in eq. 10. The water promoted cascade olefination/hydrogenation product **52** of Meldrum's acid **51a** with 2-hydroxybenzaldehyde **37a** and Hantzsch ester **50a** formed *in situ*, undergoes intramolecular hydrolysis to furnish the cyclized product **53** in 75% yield. In a similar manner, O/H intermediate **55** of malononitrile **51b** with 2-hydroxybenzaldehyde **37a** and Hantzsch ester **50a** at 70 °C furnished the chromene **57** in 90% yield as shown in eq. 10.[10g]

In 2008, our group reported a multi-component organocatalytic sequential one-pot olefination/hydrogenation/oxa-Michael/dehydration methodology for the synthesis of 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-one **59** and 3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one **61** from commercially available 2-hydroxybenzaldehydes **37a**, cyclopentane-1,3-dione **51c** or dimedone **51d** and Hantzsch ester **50a** utilizing NGP. Aniline **34d** catalyzed olefination/hydrogenation followed by *p*-TSA catalyzed oxa-Michael/dehydration reactions resulted the product chromenes **59** or **61** with upto 90% yield as shown in eq. 11.[10j]

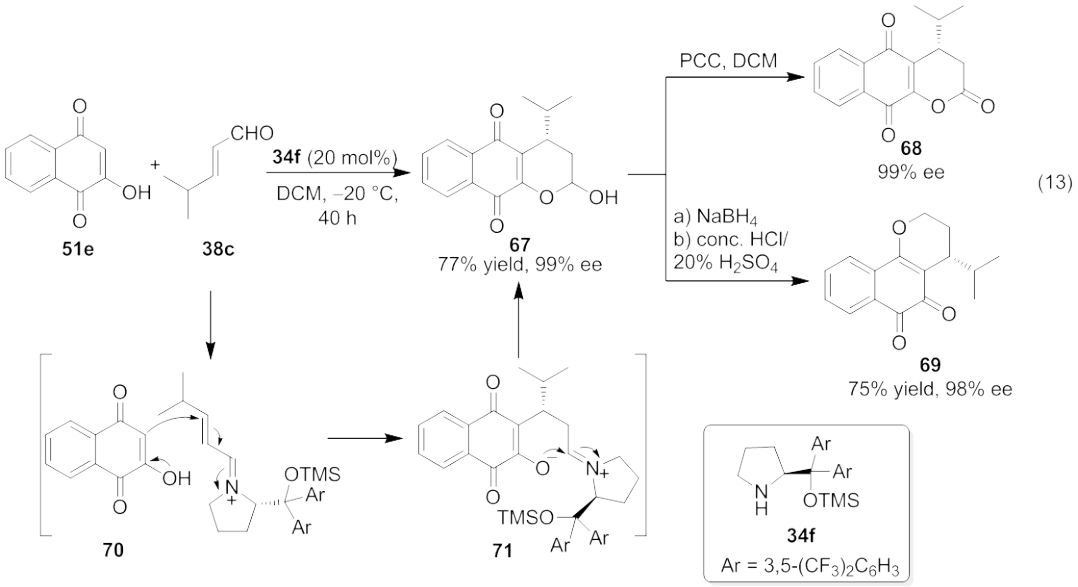


A landmark of asymmetric organocatalytic cascade reaction using neighboring group participation by phenolic O*H* group as the shortest route for the synthesis of α-tocopherol **64** was reported by Woggon et al. in the year of 2008 utilizing NGP. The domino aldol/oxa-Michael reaction between functionalized 2-hydroxybenzaldehyde **37b** and phytenal **38b** in the presence of diarylprolinol silyl ether **34e** in toluene resulted the hemiacetal **62** with 58% yield and 97% de, which on *in situ* PCC oxidation gave lactone **63** with 90% yield and 97% de as shown in eq. 12. The *in situ* formed dienamine **65** of amine **34e** with phytenal **38b** reacts with functionalized 2-hydroxybenzaldehyde **37b** in an aldol fashion to yield the intermediate **66** which on further oxa-Michael reaction with *ortho* OH group results the hemiacetal **62** (eq. 12).[16] This strategy eventhough has the drawbacks of reaction times and yield, this became the first report on organocatalytic quaternary chiral centre formation through phenolic O*H* neighboring group participation, which was directly applied to the total synthesis of (2*S*, 4'*R*, 8'*R*)-α-tocopherol **64** through three chemical transformations.



(12)

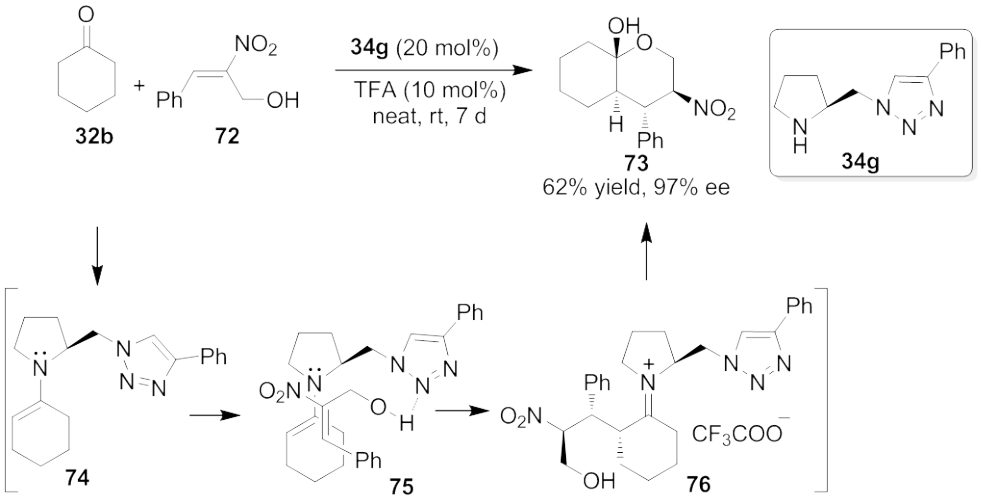
In 2008, Rueping and co-workers reported the enol hydroxyl neighboring group involvement in cascade reactions for the asymmetric synthesis of lactones **68** and pyranonaphthoquinones **69** as shown in eq. 13. Their approach involved cascade conjugate addition/hemiacetalization of α,β-unsaturated aldehyde **38c** with 2-hydroxy-1,4-naphthaquinone **51e** in the presence of diarylprolinol silyl ether **34f** at -20 °C for 40 h to result the hemiacetal **67**



(13)

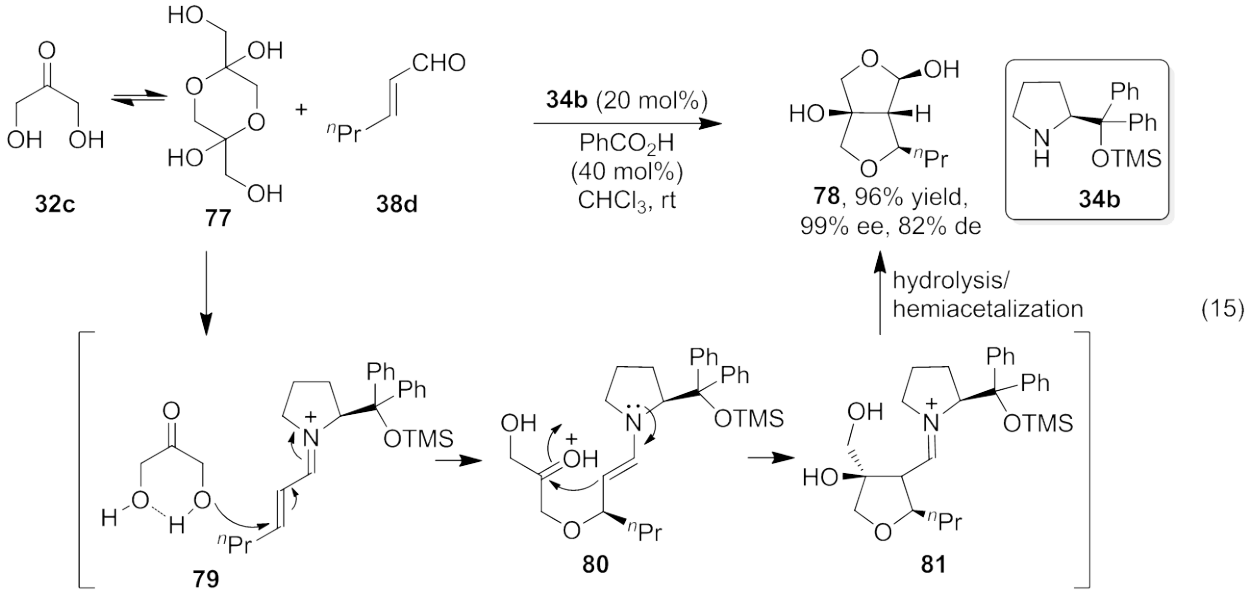
with 77% yield and 99% ee. Further synthetic transformations were shown on this hemiacetal through either oxidation with PCC or reduction followed by cyclization with $NaBH_4$/acid as shown in eq. 13.[17] The neighboring group participation by hydroxyl group in enol form of active methylene compound for the cascade hemiacetalization thus has created another efficient synthetic strategy towards heterocyclizations.

In 2009, Chandrasekhar et al. reported an interesting domino Michael/ketalization for the asymmetric synthesis of tetrahydropyrans **73**. Their methodology was based on the neighboring group participation by allyl alcohol in the cascade reactions. It involved the Michael addition of cyclohexanone **32b** to 2,3-disubsituted nitroolefins **72** catalyzed by pyrrolidine-triazole catalyst **34g** followed by intramolecular ketalization to result the tetrahydropyran **73** with 62% yield and 97% ee as shown in eq. 14.[18] The excellent asymmetric induction and selectivity has been attributed to the hydrogen bonding between the catalyst and the allyl alcohol of the substrate as shown in intermediate **75**. Thus the neighboring participation of allyl alcohol was utilized in the transition state to control the selectivity and also in the subsequent cascade processes as shown in eq. 14.



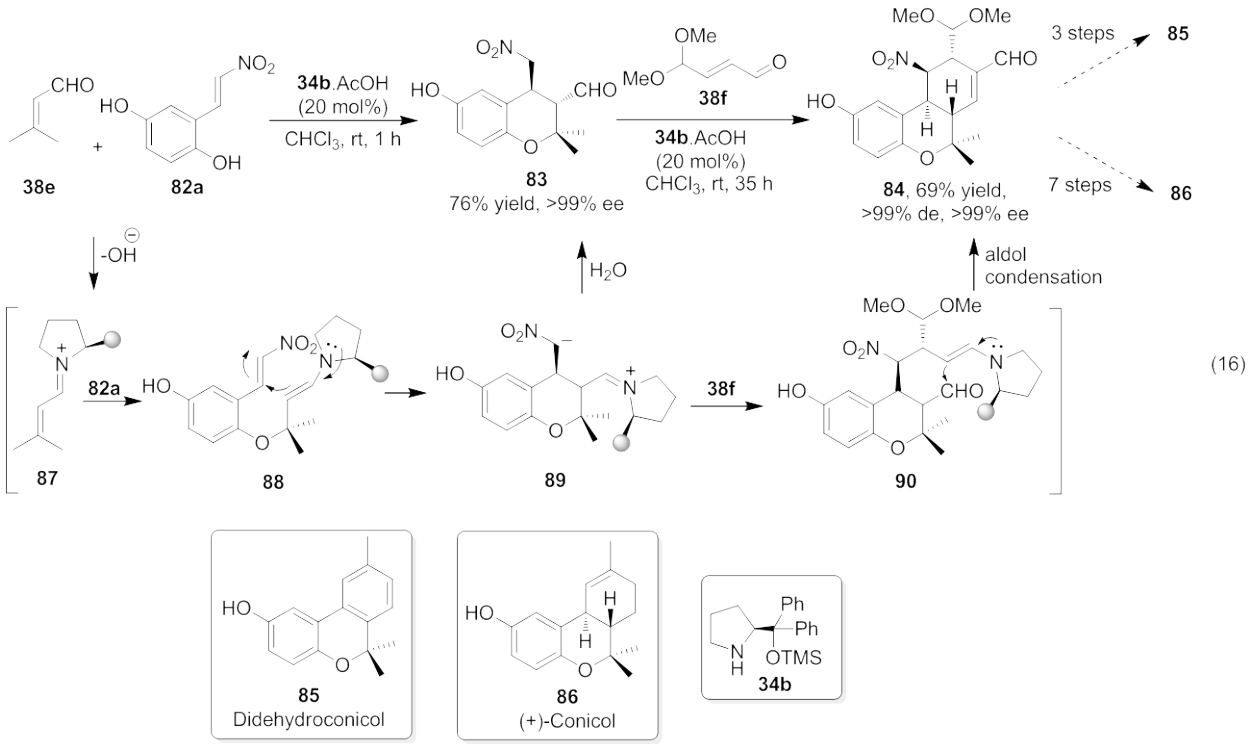
The potent reactivity of organocatalysts was well demonstrated by Vicario et al. in 2009 during the one-pot synthesis of hexahydrofuro[3,4,*c*]furanes **78**. In their communication, they have demonstrated the one-step synthesis of compound **78** via domino oxa-Michael/aldol/hemiacetalization sequence by utilizing the concept of NGP. The oxa-Michael reaction of dihydroxyacetone dimer **77** to α,β-unsaturated aldehyde **38d** in the presence of diphenylprolinol silyl ether **34b** catalyst resulted the intermediate **80**. This intermediate then

undergoes intramolecular aldol reaction with keto group activated by the $PhCO_2H$ co-catalyst to result **81**, which on hydrolysis/hemiacetalizaion gives the final product **78** with 96% yield, 82% de and 99% ee as shown in eq. 15. Eventhough, studies are further required to understand the mechanism unambiguously, a preliminary understanding explains that the initial asymmetric oxa-Michael reaction is made irreversible by follow-up aldol reaction and also the hemiacetalization gains importance as it forms the most stable diastereomer at the anomeric carbon. This communication takes the credit of employing oxygen nucleophile in NGP with high pk_a value in the neighboring group participation.[19]



(15)

The first organocatalytic Michael addition with 2-(2-nitrovinyl)phenols **82a** was reported by Hong et al. in 2009 for the quadruple cascade reaction with α,β-unsaturated aldehydes **38e** and **38f**. The sequence of oxa-Michael/Michael/Michael/aldol condensation strategy resulted the tetrahydro-6*H*-benzo[*c*]chromene **84** with excellent yield and enantiomeric excess as a single diastereomer as shown in eq. 16. In the presence of catalyst diphenylprolinol silyl ether **34b** and acetic acid as co-catalyst, the reaction of substituted 2-(2-nitrovinyl)phenol **82a** with dissimilar α,β-unsaturated aldehydes **38e** and **38f** proceeded through sequence of tandem processes effectively initiated by oxa-Michael reaction by neighboring phenolic O*H* to result the product **84** with great selectivity. The quadruple cascade product **84** was utilized for the total syntheses of didehydroconicol **85** and marine meroterpene (+)-conicol **86** through a few chemical transformations (eq. 16).[20]



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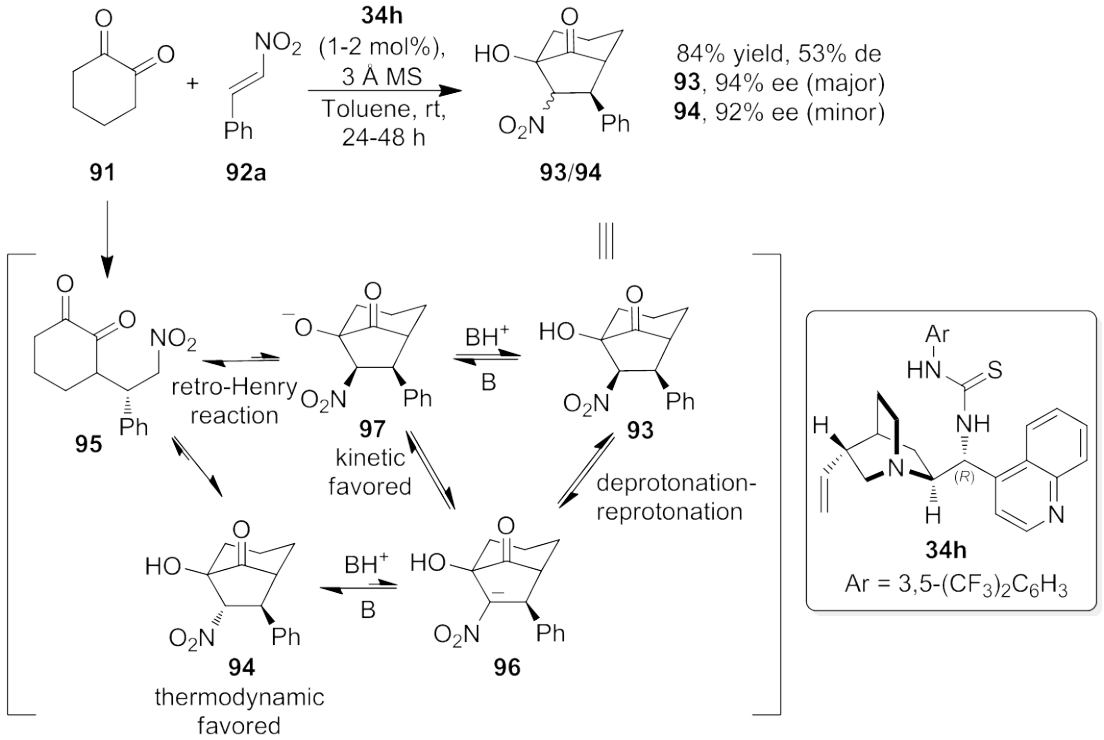
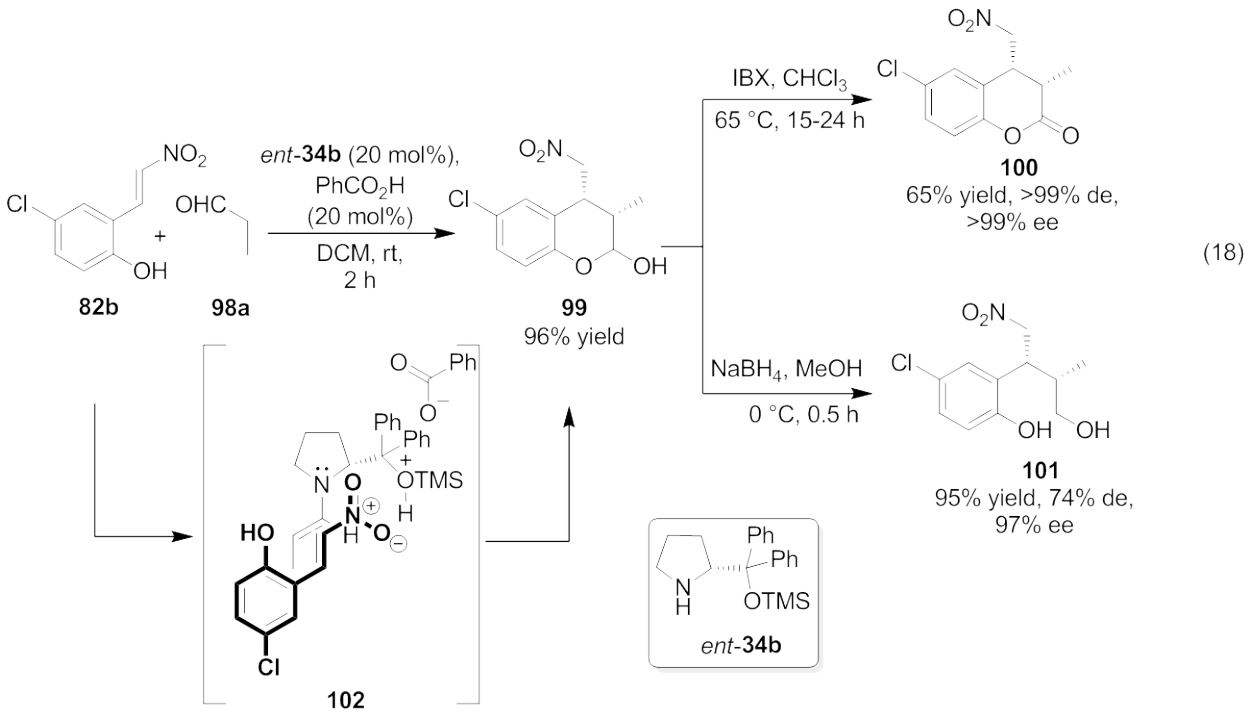
The potent reactivity of 1,2-diketones **91** in asymmetric domino reactions was explored by Rueping et al. in 2010 for the synthesis of polyfunctionalized bicyclic compound **93**/**94**. The



(17)

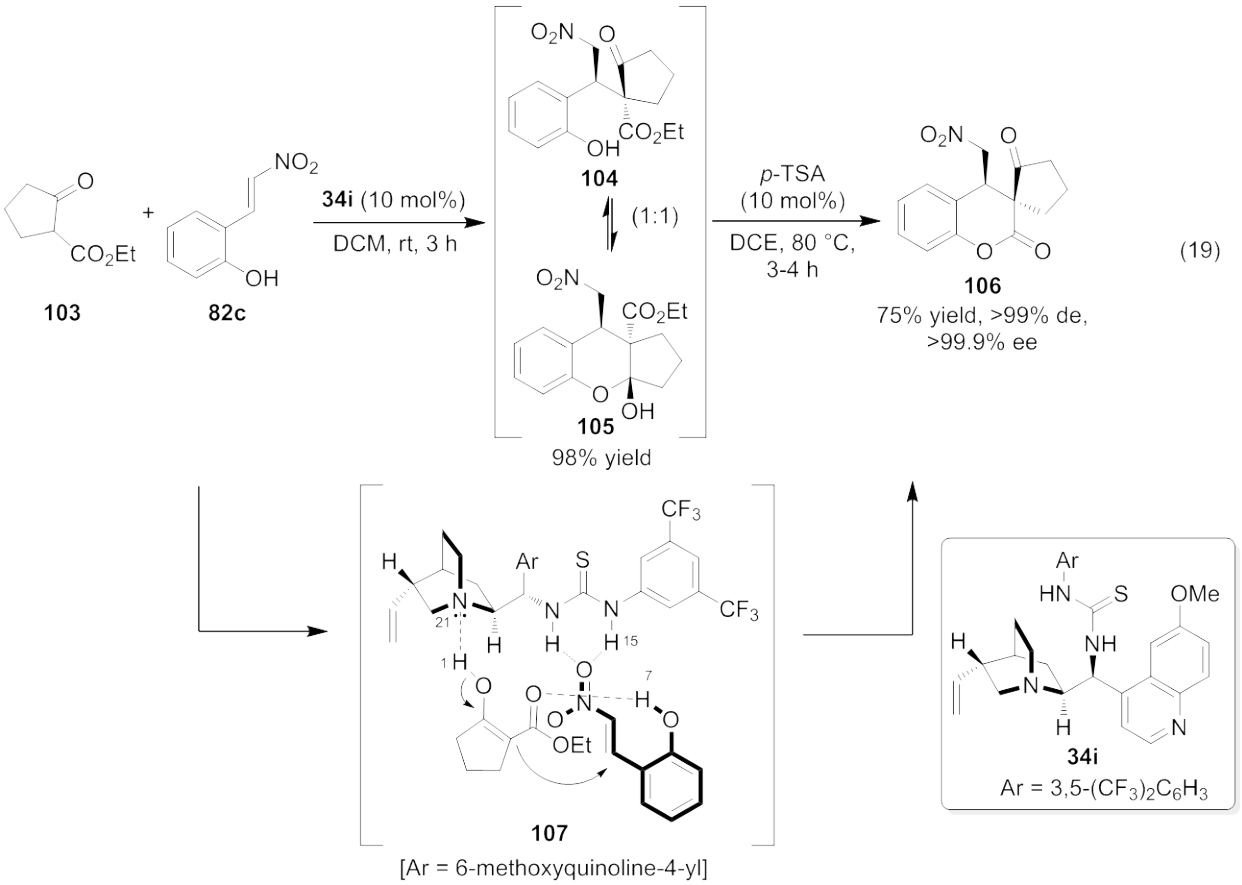
cascade Michael/Henry reaction of diketone **91** with nitrostyrene **92a** catalyzed by cinchonidine derived thiourea catalyst **34h** results the bicyclic compound **93**/**94** with four stereocentres in excellent yield and selectivities as shown in eq. 17. The base induced epimerization ends up with both kinetic and thermodynamic controlled products reducing the diastereomeric excesses. Fast deprotonation-reprotonation at α–nitrocarbon atom or the slow retro-Henry reaction of the deprotonated hydroxyl group gives a way for the equilibrium between kinetic controlled product **93** and thermodynamic controlled product **94** as shown in eq. 17.[21]

In 2011, our group reported the Barbas-Michael reaction of aldehyde **98a** with 2-(2-nitrovinyl)phenol **82b** for the best utilization of the neighboring group in the cascade processes. The Michael reaction of aldehyde **98a** with substituted 2-(2-nitrovinyl)phenol **82b** followed by the hemiacetalization reaction resulted the chromanol **99** with high yield and selectivity. The synthetic utility of chromanol was established by subjecting to oxidation with IBX to result the chromanone **100** or reduction with $NaBH_4$ to result diol **101** without any compromise in the enantiopurity as shown in eq. 18. The catalyst diphenyl prolinol silyl ether *ent*-**34b** catalyzed Michael/hemiacetalization strategy proves the potent activity of phenolic O*H* towards the cascade hemiacetalization processes.[10q]



(18)

Very recently, our group reported the neighboring group participation by O*H* group in supramolecular catalysis for the synthesis of spirodihydrocoumarins **106**. Quinine derived thiourea catalyst **34i** catalyzed Michael reaction followed by intramolecular lactonization reaction catalyzed by *p*-TSA between 2-(2-nitrovinyl)phenol **82c** and ethyl cyclopentanone-2-carboxylate **103** resulted the spirodihydrocoumarins **106** with high yield and selectivity. An attractive aspect of this strategy lies in the transition state **107**, where multiple hydrogen bonding interactions operate among catalyst and substrates to form a 21-membered supramolecular catalytic assembly as shown in eq. 19. This supramolecular organocatalysis is novel for high asymmetric induction, which became possible through the involvement of O*H* in hydrogen bonding with catalyst and substrates in the transition state. Thus this has turned out to be the best example of showing the neighboring group participation in the transition state and subsequent cascade processes.[10r]



As a part of our on-going research for the development of sequential or cascade reactions for the synthesis of chiral functionalized molecules, research work was carried out to utilize organocatalytic strategies involving neighboring group participation for the synthesis of chiral drug intermediates and biologically active compounds and the results are presented in this thesis.

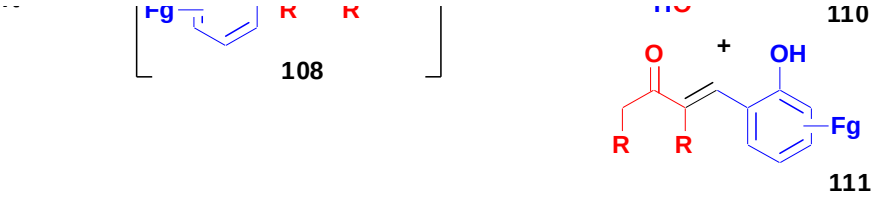
3. Direct Catalytic Asymmetric Synthesis of Highly Functionalized 2-Methylchroman-2,4-Diols via Barbas–List Aldol Reaction

3.1 Introduction

Chromans and chromenes form an important class of heterocycles, which display a range of biological activities and are quite commonly used as drug intermediates and ingredients in pharmaceuticals (Chart 1).[22] Since their applications are enormous in many fields, their catalytic asymmetric synthesis has ever been a fascinating era.[23] 2-Methylchroman-2,4-diols fall in one-such category, which would serve as intermediates for many functionalized bio-active chromans and benzopyrans. Direct asymmetric catalytic strategy for their synthesis has been unexplored thus far. Hence, a novel, organocatalytic, metal-free approach has been developed for the asymmetric synthesis of functionalized 2-methylchroman-2,4-diol products via "Barbas–List aldol reactions" [24] and the results on these findings are disclosed in the present chapter.

Chart 1: Some Biologically Active Chromans.

Recently, Barbas and co-workers discovered a mild, novel and efficient method for aldol reactions through organocatalysis. Their novel strategy involves amine/amino acid catalyzed intermolecular aldol reactions of ketones/aldehydes with a variety of carbonyls to deliver chiral aldol products in good yields with high enantioselectivity defined as the Barbas–List aldol (BLA) reaction.[24] This revolutionary methodology encouraged the synthetic community to synthesize enantiomerically pure aldol products through bio-mimetic enamine catalysis, thus providing an urge for the development of cellular type cascade reactions.[13]



The amino acid catalyzed aldol reaction of ketones/aldehydes **32** with functionalized 2-hydroxybenzaldehydes **37** has not been described thus far, although the resulting aldol products **109** and **110** have a wide range of potential applications in pharmaceutical chemistry (Chart 1 and eq. 20); also, there is no direct methodology available to date to prepare these compounds by classical reaction strategies. Hence, a metal-free, novel methodology for the synthesis of highly substituted 2-methylchroman-2,4-diols **109/110** using organocatalytic BLA reactions from commercially available 2-hydroxybenzaldehydes **37**, ketones **32** and amines/amino acid **34** has been achieved (eq. 20). In addition, the existence of fast dynamic equilibrium between 2-methylchroman-2,4-diols (lactol) **110** and 4-hydroxy-4-(2-hydroxyphenyl)-butan-2-one (δ-hydroxyketone) **109** under the normal reaction conditions has been described.[25]

Over past few years, our laboratory has been actively involved in amine/amino acid mediated multicatalysis reactions from multiple components for the generation of highly functionalized molecules via C-C, C-H, C-O and C-N bonds formation in one-pot.[10] During the course of the investigation of new reactive species for such multicatalytic processes, the potential ability of 2-hydroxybenzaldehydes **37** was tested to participate in an amine/amino acid catalyzed BLA reaction with acetone **32a**. It was envisaged that the reaction of 2-hydroxybenzaldehyde **37a** with *in situ* generated enamine from acetone **32a** would lead to 4-hydroxy-4-(2-hydroxyphenyl)butan-2-one (**109aa**). However, aldol product **109aa** was not only detected; but also product **109aa*** was found to exist in a fast dynamic equilibrium with 2-methylchroman-2,4-diol **110aa*** under standard reaction conditions. This observation lead to a novel strategy for

the preparation of 2-methylchroman-2,4-diols and also a new advent for the reactivity for amino acid catalysts. The results of these new BLA reactions are as follows.

3.2 Results and Discussions

3.2.1 Reaction optimization for asymmetric BLA reaction:

Studies were initiated on the BLA reactions by screening a number of known and novel organocatalysts for the aldolization of 2-hydroxybenzaldehyde **37a** by 14 to 28 equivalents of acetone **32a**. A few representative results are shown in Table 1. Interestingly, reaction of **37a** with 28 equiv of acetone **32a** in DMF under 20 mol% of L-proline (**34a**) catalysis furnished a 1:1 ratio of the aldol↔lactol product **109aa/110aa** in 50% yield with only 17% ee. The aldol product was accompanied with byproduct enone **111aa*** in 20% yield (Table 1, entry 1). The aldol reaction of **37a** with 28 equiv of acetone **32a** in the presence of 20 mol% of **34a** in DMSO solvent produced the aldol↔lactol product **109aa/110aa** in 50% yield and 19% ee (Table 1, entry 2). Reaction of **37a** with 28 equiv of **32a** in *N*-methylpyrrolidone (NMP) with 20 mol% of **34a** furnished a 1:1 ratio of **109aa/110aa** in 50% yield with increased (36%) ee value and enone **111aa** in 20% yield (Table 1, entry 3). Reaction of **37a** with 14 equiv of **32a** with 20 mol% *ent*-**34a** (D-proline) in NMP for 38 h furnished the 1:1 ratio of **109aa/110aa** in 60% yield with decreased (11%) ee and byproduct **111aa** in 20% yield (Table 1, entry 4). Interestingly, L-proline-catalyzed BLA reaction of **32a** with **37a** in H_2O furnished the expected aldol↔lactol product **109aa/110aa** in 50% yield and 0% ee (Table 1, entry 5).

Proline-catalyzed BLA reaction of **32a** with **37a** is a solvent dependent reaction, which performs well in aprotic and protic polar solvents such as DMSO, DMF, NMP, and H_2O; however, only <5% conversion was observed in other solvents such as CH_3CN, CH_2Cl_2, $CH_3C_6H_5$, and [bmim]BF_4 (results not shown). Bifunctional catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **34j**/TFA and L-thiaproline (**34k**) also catalyzed the BLA reaction of **32a** with **37a** in NMP at –10 or 25 °C to furnish **109aa/110aa*** in moderate yields and increased ee values compared to **34a** as shown in Table 1, entries 6–7. When 20 mol% of *trans*-

*In the compound representation **109xy, 110xy** and **111xy**, **x** denotes ketone component **32** and **y** denotes 2-hydroxybenzaldehyde component **37**.

4-OH-L-proline (**34l**) was tested as catalyst for the reaction of **37a** with 14 equiv of **32a** in NMP for 24 h, a 1:1 ratio of (+)-**109aa/110aa** was resulted in 70% yield with 77% ee; however, the same reaction under *trans*-4-OTBS-L-proline (**34m**) catalysis was found to be inferior in terms of ee (33%) and the side product formation (40%, Table 1, entries 8–11). The dynamic equilibrium between **109aa** and **110aa** was confirmed by NMR and HPLC analyses (Figures-1 to 2).

Table 1: Reaction Optimization for the BLA Reaction of **32a**, **37a** and **34**.

*In the compound representation **109xy, 110xy** and **111xy**, **x** denotes ketone component **32** and **y** denotes 2-hydroxybenzaldehyde component **37**.

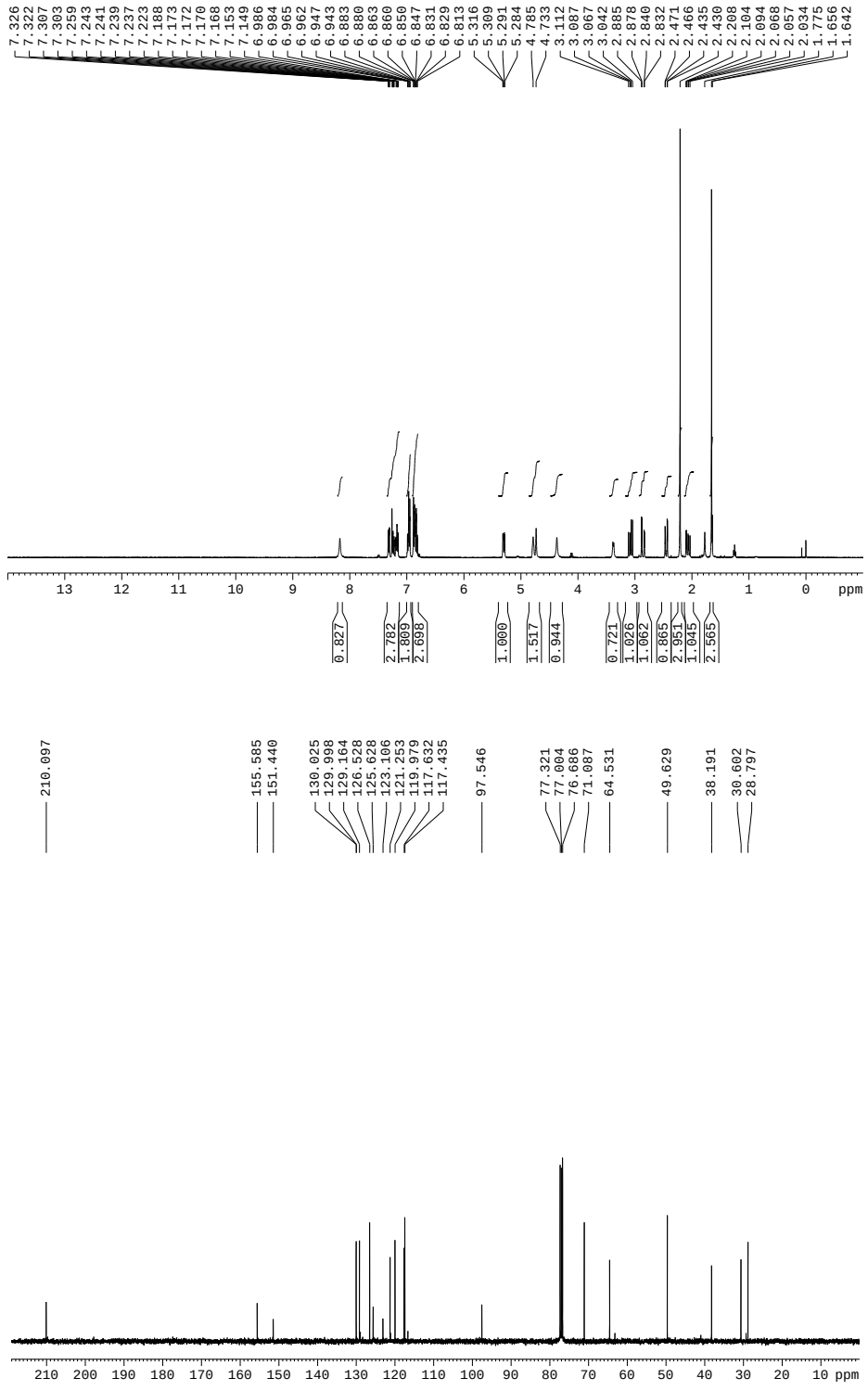
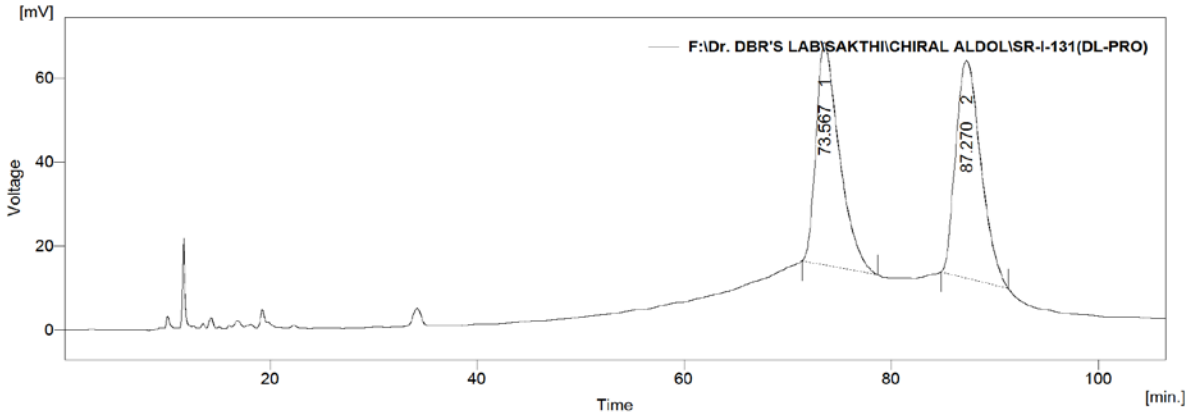


Figure-1: ^{1}H and ^{13}C NMR spectra of the product **109aa↔110aa**.

Racemic **109aa↔110aa**:

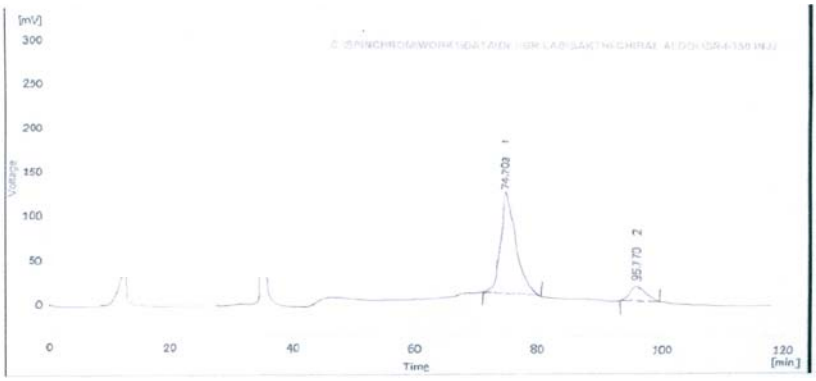


Daicel Chiralcel OD-H Column, Hexane/i-PrOH = 96:4, Flow Rate 0.3 mL/min, λ = 254 nm.

Result Table (Uncal - F:\Dr. DBR'S LAB\SAKTHI\CHIRAL ALDOL\SR-I-131(DL-PRO))

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	73.567	8315.591	53.057	48.7	50.6	2.34
2	87.270	8750.853	51.877	51.3	49.4	2.64
	Total	17066.444	104.934	100.0	100.0	

Chiral **109aa↔110aa** (77% ee):



Daicel Chiralcel OD-H Column, Hexane/i-PrOH = 96:4, Flow Rate 0.3 mL/min, λ = 254 nm.

Result Table (Uncal - F:\Dr. DBR'S LAB\SAKTHI\CHIRAL ALDOL\SR-I-150 INJ2)

	Area [mV.s]	Area [%]	Height [%]	W05 [min]
1	7671.825	88.7	78.5	2.29
2	976.485	11.3	21.5	1.21
	8648.310	100.0	100.0	

Figure-2: HPLC of the product **109aa↔110aa**.

***Table 2*:** Synthesis of Racemic aldol↔lactol Products **109/110**.[a]

Products **109/110**	Ratio[b] (**109/110**)	Products yield (%)[c] **109/110**	**111**
.09aa/110aa	1:1	50	5
.09ac/110ac	1:1	56	4
09ad/110ad	1:99	50	5
.09ae/110ae	1:1	65	–
l09af/110af	1:1	85	–
09ag/110ag	1:1	65	3
09ah/110ah	1:1	70	2
l09ai/110ai	1:1	70	2
l09aj/110aj	99:1	85	–
.09ak/110ak	3:1	90	–
l09al/110al	5:1	40	–

:h 14 equiv of **32a** relative to the **37a-l** (0.5 mmol) in
tio is based on NMR analysis. [c] Yield refers to the

A number of primary and secondary amines such as L-Trp-OH (**34n**), L-Ala-OH (**34o**), L-Val-OH (**34p**), L-aminophenylacetic acid (**34q**), L-Thr(O*t*Bu)-OH (**34r**), 4-benzyl-1-methylimidazolidine-2-carboxylic acid (**34s**), L-DPP (**34t**) and L-DPPOTMS (**34b**) were also tested as catalysts for the BLA reaction of **32a** with **37a** in NMP or H_2O where the conversion was very poor (results not shown in Table 1). After the thorough investigation of a number of catalysts and conditions, the optimization condition is stated to be, 20 mol% catalyst **34l** in NMP solvent at rt for the aldol reaction of **32a** with **37a** where 1:1 ratio of (+)-**109aa/110aa*** was resulted in 70% yield and 77% ee (Table 1, entry 8).

3.2.2 Synthesis of Racemic BLA products:

To generalize the concept of fast dynamic equilibrium, **32a** was reacted with other functionalized 2-hydroxybenzaldehydes **37a–l** in H_2O in the presence of 20 mol% of **34a** at rt. This in turn, generated a library of racemic **109/110** in excellent yields. The results are presented in Table 2. Rapid equilibrium between aldol **109** and lactol **110** products in solution was confirmed by NMR analyses and also finally confirmed by X-ray structure analysis (Figures-1 to 4). ^{1}H NMR analysis on **109ae/110ae** in $CDCl_3$ at different temperatures (50, 25, 0, -15, -30 and -45 °C) and also in $CDCl_3$+D_2O at 25 °C indicated that the compound is bearing four OH groups, that is, two secondary, one tertiary and one phenolic OH. It was found that the equilibrium between aldol **109** and lactol **110** products is greatly influenced by electronic factors as shown in Table 2 (entries 3 and 9). Reaction of 2-hydroxynaphthalene-1-carbaldehyde (**37d**) with acetone **32a** under proline catalysis furnished lactol **110ad** as the major product and 2-hydroxy-5-nitrobenzaldehyde (**37j**) with acetone **32a** under L-proline catalysis produced δ-hydroxy ketone **109aj** as the major product (Table 2, entries 3 and 9).

3.2.3 Synthesis of Chiral BLA products:

With the optimized reaction conditions in hand, the scope and generalization of the amino acid catalyzed asymmetric BLA reactions was investigated. A series of substituted 2-hydroxybenzaldehydes **37a-l** was reacted with 14 equiv of **32a** in the presence of 20 mol% **34l** at 25 °C in NMP (Table 3). Starting materials bearing neutral, electron withdrawing and electron-

*In the compound representation **109xy, 110xy** and **111xy**, **x** denotes ketone component **32** and **y** denotes 2-hydroxybenzaldehyde component **37**.

donating substituents generated the expected BLA products **109/110** with excellent yields and ee values (Table 3). The enone byproducts **111aa–ae** were obtained in very poor yields and **111af–al** were not observed at all. Fascinatingly, reaction of 2-hydroxynaphthalene-1-carbaldehyde (**37d**) with acetone **32a** and **34l** furnished lactol (-)-**110ad*** as the major product with only 26% ee (Table 3, entry 3). In contrast, BLA reaction of 2-hydroxy-5-nitrobenzaldehyde (**37j**) with **32a** in the presence of catalyst **34l** furnished aldol (+)-**109aj** as major product with 85% yield and 52% ee (Table 3, entry 9). A deuterated 1:1 ratio of chiral (+)-**109dh/110dh*** was furnished in 50% yield with 86% ee, when **32d** was used (Table 3, entry 12). Equilibrium between aldol **109** and lactol **110** of BLA products **109aa–al/110aa–al** was confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (+)-**110ah** and (+)-**109aj** as shown in Figures-3[26] and 4.[27]

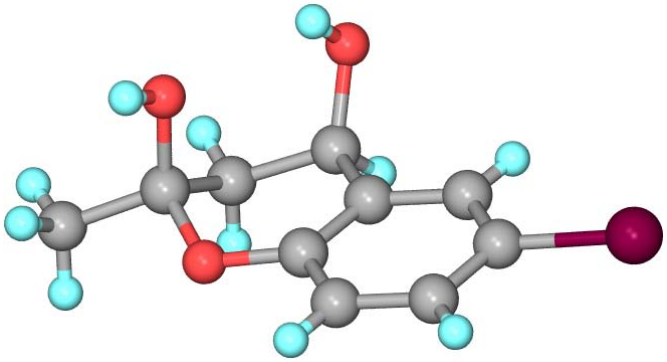


Figure-3: X-ray crystal structure of chiral (+)-6-bromo-2-methyl-chroman-2,4-diol (**110ah**).

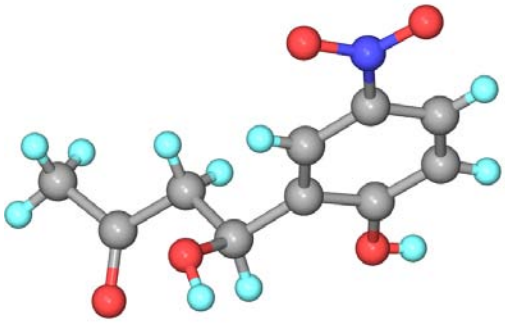
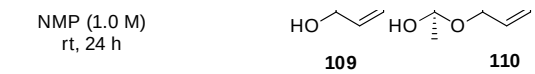


Figure-4: X-ray crystal structure of chiral (+)-4-hydroxy-4-(2-hydroxy-5-nitro-phenyl)-butan-2-one (**109aj**).

* In the compound representation **109xy, 110xy** and **111xy**, **x** denotes ketone component **32** and **y** denotes 2-hydroxybenzaldehyde component **37**.

Table 3: Synthesis of Chiral aldol↔lactol Products **109/110**.[a]



37	Products 109/110	Ratio[b] (109/110)	Yield (%)[c] 109/110	ee of 109/110[d]
37a	**109aa/110aa**	1:1	70	77
37c	**109ac/110ac**	1:1	65	90
37d	**109ad/110ad**	1:99	50	26
e **37e**	**109ae/110ae**	1:1	65	89
37f	**109af/110af**	1:1	65	87
l **37g**	**109ag/110ag**	1:1	65	88
r **37h**	**109ah/110ah**	1:1	70	86
Me **37i**	**109ai/110ai**	1:1	70	87
O_2 **37j**	**109aj/110aj**	99:1	85	52
l **37k**	**109ak/110ak**	3:1	90	86
37l	**109al/110al**	5:1	40	75
r **37h**	**109dh/110dh**	1:1	50	86

MP (1.0 M) with 14 equiv of **32a** relative to the **37a-l** (0.5 mmol) in alyst **34l**. [b] Ratio is based on NMR analysis. [c] Yield refers to the etermined by CSP HPLC analysis. [e] Byproducts **111aa-ae** were OCD_3 **32d** (14 equiv) was used and reaction time is 48 h.

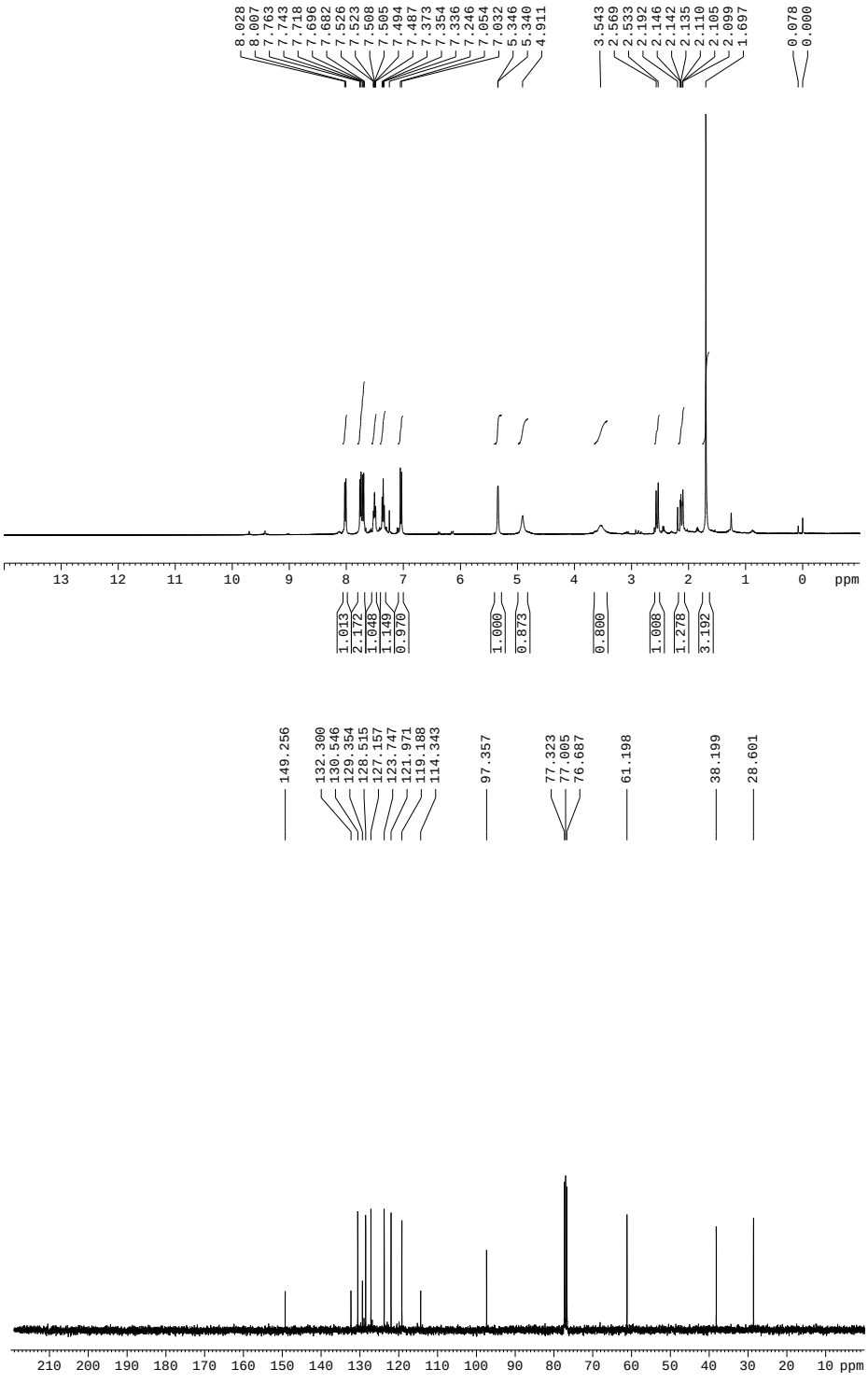


Figure-5: ^{1}H and ^{13}C NMR spectra of the product **110ad**.

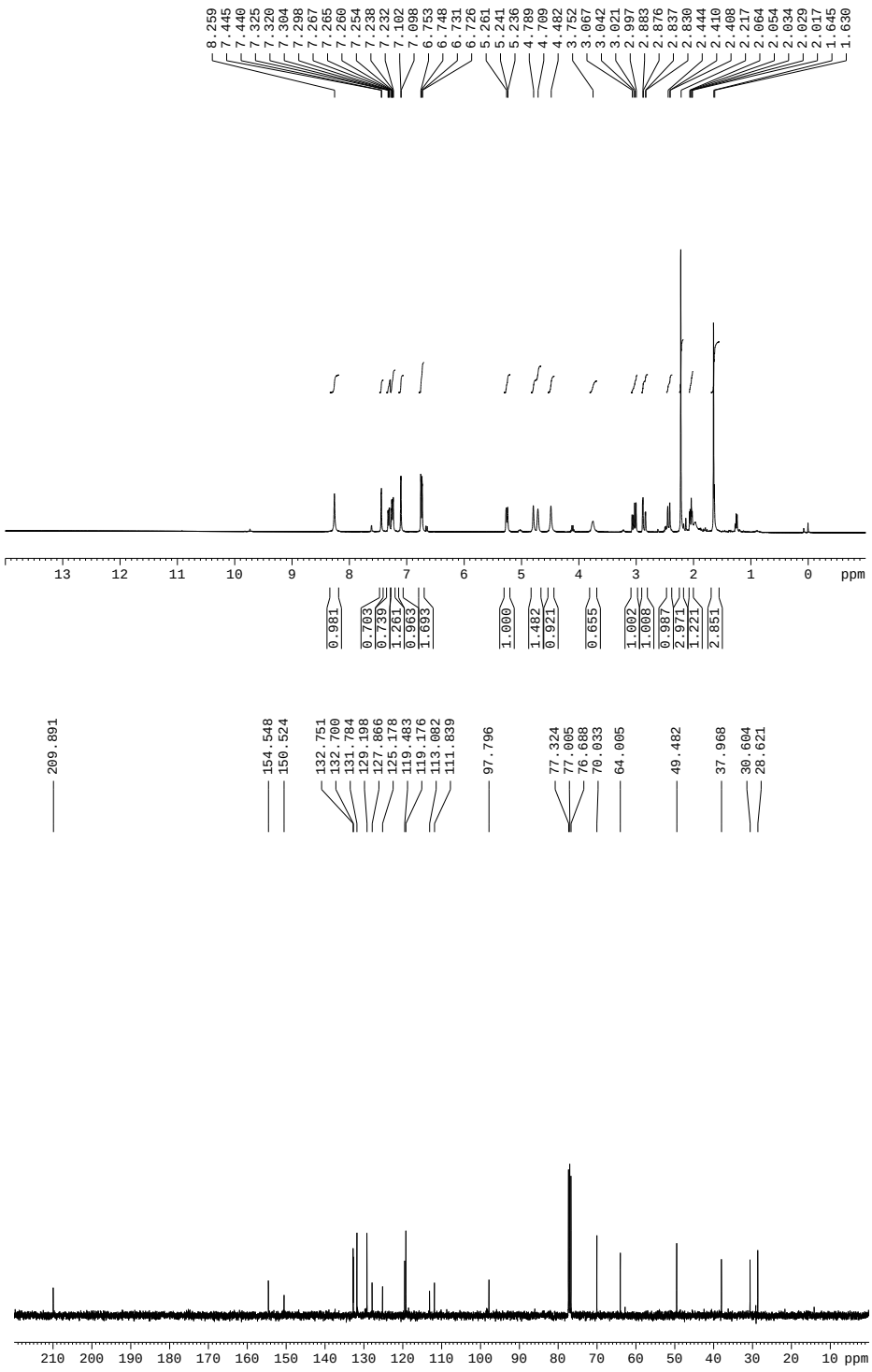


Figure-6: ^{1}H and ^{13}C NMR spectra of the product **109ah↔110ah**.

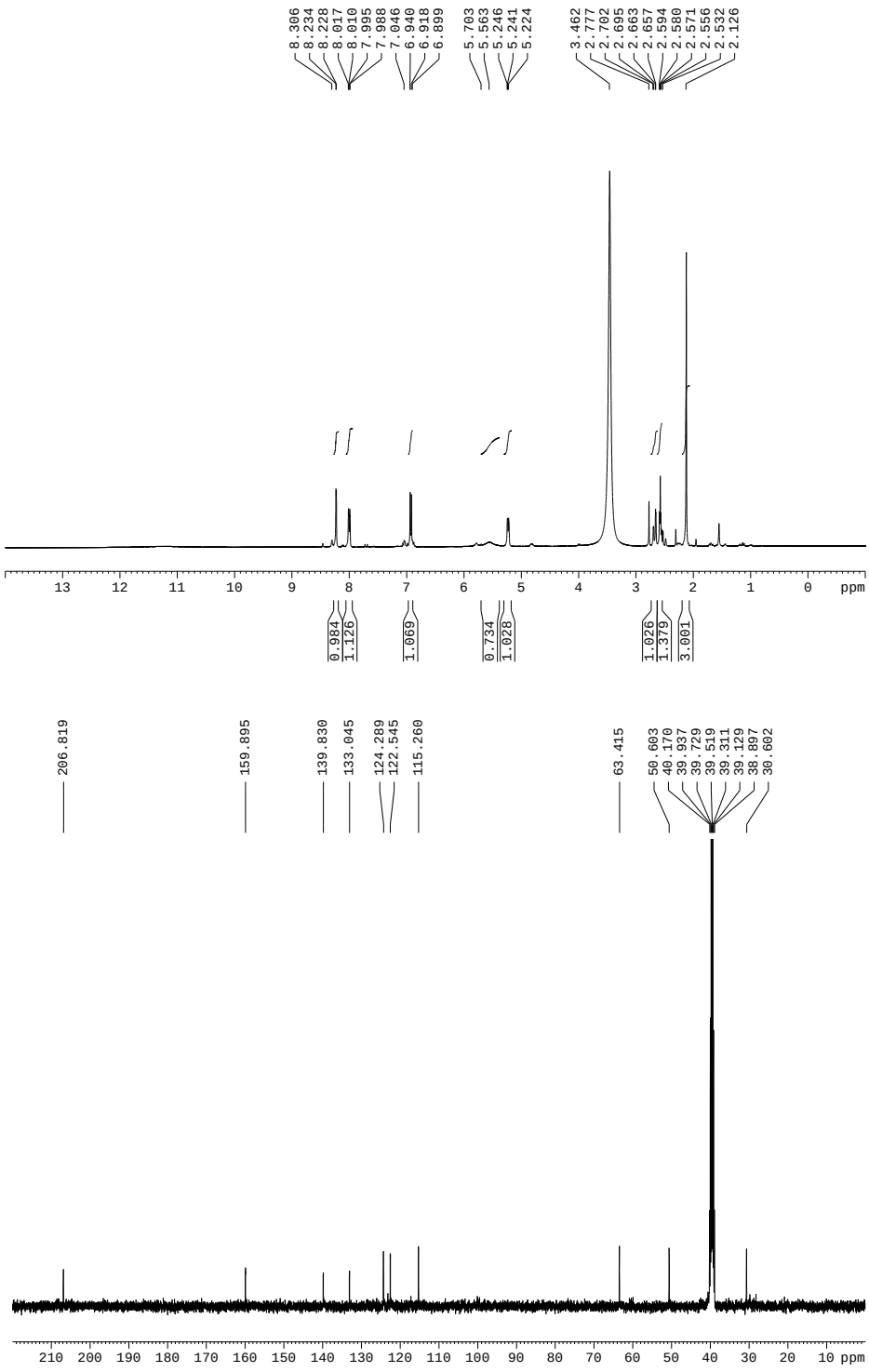


Figure-7: ^{1}H and ^{13}C NMR spectra of the product **109aj**.

3.2.4 Controlled experiments to understand the neighboring ortho-hydroxyl group participation in BLA reactions:

To understand and prove the neighboring group participation by *ortho*-OH group in the transition state of the aldol reaction as depicted in TS (**108**) of eq. 20, various experiments were carried out as shown in Scheme 1. Substituting or displacing *ortho*-OH in the aldol reaction, in other way disturbing the hydrogen bonding showed tremendous change in reactivity. 2-methoxybenzaldehyde **33b** with 14 equiv of acetone **32a** in the presence of *trans*-4-OH-L-proline **34l** in NMP for 72 h resulted the aldol product **112ab*** with 22% yield and 73% ee, thus with diminished reactivity yet maintaining selectivity. Similar experiments with 3-hydroxybenzaldehyde **33c** and 4-hydroxybenzaldehyde **33d** did not produce any product even after 72 h of reaction time (Scheme 1). This experimental evidence proves that neighboring group participation through hydrogen bonding activation among OH group of 2-hydroxybenzaldehyde **37a**, ketone **32** and the catalyst **34l** as shown in **108** of eq. 20 is crucial in determining the rate of the reactions.

Scheme 1: Controlled Experiments to Understand the Neighboring Group Participation by *ortho*-OH Group.

3.2.5 Applications of chiral BLA products:

After successful demonstration of the *trans*-4-OH-L-proline-**34l** catalyzed asymmetric BLA reactions of **32a** with **37**, the utility of the aldol↔ lactol equilibrium was explored in the synthesis of functionalized molecules via acid/base catalysis under one-pot conditions as shown in eq. 21 and 22. BLA reaction of **32a** with **37a** under **34l** catalysis at 25 °C in NMP furnished

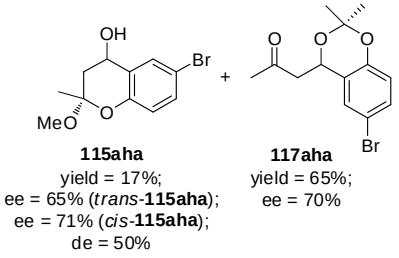
* In the compound representation **112xy**, **x** denotes ketone component **32** and **y** denotes functionalized benzaldehyde component **33**.

(+)-**109aa/110aa** in 70% yield with 77% ee, which on subsequent treatment with *p*-TsCl and Et_3N in one-pot reaction furnished selectively the tosylated product (+)-**114aa** in 50% yield with 77% ee as shown in eq. 21. In a similar manner, treatment of reaction intermediate (+)-**109aa/110aa** with *p*-TSA in MeOH (**113a**) at 25 °C in one-pot furnished selectively *trans*-2-methoxy-2-methylchroman-4-ol ((+)-**115aaa***) in 55% yield with 77% ee and >95% de as shown in eq. 21. This equation clearly shows the conditions under which the equilibrium can be shifted to lactol form or aldol form to react.

The application of acid-catalyzed lactonization methodology was further extended with reaction of pure isolated (+)-**109ah/110ah*** with various alcohols **113a**–**c**, CH acids **51** and 2,2-dimethoxypropane as shown in eq. 22. All expected 2-alkoxy-2-methylchroman-4-ols (+)-**115aha–(+)–ahc*** were furnished in very good yields with good de values from the reaction of (+)-**109ah/110ah** with methanol **113a**, ethanol **113b** and allyl alcohol **113c** under acid catalysis (eq. 22). Acid catalyzed lactonization of aldol-lactol product (+) -**109ah/110ah** was further applied to CH acids like dimedone **51d** and cyclohexane-1,3-dione **51f**. Interestingly, reaction of (+)-**109ah/110ah** with 2 equiv of dimedone **51d** under *p*-TSA catalysis in toluene at 120 °C for 4–6 h furnished a tetracyclic product **116ahd** in 90% yield with <5% ee and >99% de. No simple chiral addition product was observed and there is no reaction observed at rt also. Generation of unexpected tetracyclic product from acid catalysis on (+)-**109ah/110ah** with CH acid was confirmed with cyclohexane-1,3-dione **51f** also as shown in eq. 22, which furnished **116ahf** in

* In the compound representation **109xy** and **110xy**, **115xyz** and **116xyz**, **x** denotes ketone component **32** and **y** denotes 2-hydroxybenzaldehyde component **37** and z denotes alcohol component **113** or CH-acid component **51**.

85% yield with <5% ee and >99% de. The structure and regiochemistry of cascade products **116** were confirmed by X-ray structure analysis on **116ahd** as shown in Figure-8.[28]



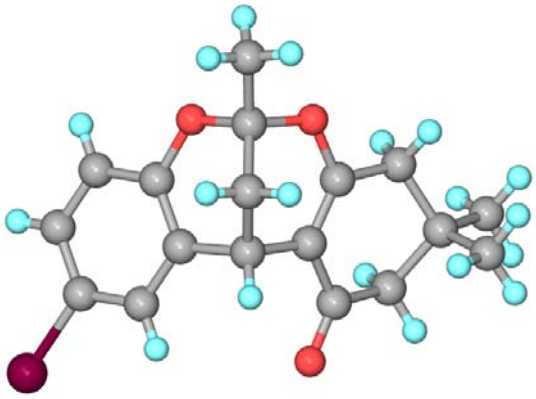


Figure-8: X-ray crystal structure of chiral (–)-2,3,4,12-tetrahydro-10-bromo-3,3,6-trimethyl-6,12-methano-1*H*-dibenzo[*d*,*g*][1,3]dioxocin-1-one (**116ahd**).

2,2-Dimethoxypropane is known to serve as a source of methyl esterification, methylation, acetonation of acids and alcohols, respectively,[29] and herein this reagent has been utilized for the acetonation of BLA product (+)-**109ah/110ah***. Interestingly, reaction of (+)-**109ah/110ah** with 5 equiv of 2,2-dimethoxypropane and 1.2 equiv of NMP as co-solvent under *p*-TSA catalysis in acetone (0.5 M) at 25 °C for 4 h furnished two products namely, i) acetonation product (+)-**117aha** in 65% yield, ii) *trans*-2-methoxy-2-methylchroman-4-ol ((+)-**115aha**) with 17% yield and 50% de (eq. 22). The same reaction without NMP as co-solvent furnished three products namely, i) *trans*-6-bromo-2,4-dimethoxy- 2-methylchroman ((+)-**118aha**) in 50% yield with >99% de, ii) *trans*-2-methoxy-2-methylchroman-4-ol ((+)-**115aha**) in 25% yield with 80% de, iii) acetonation product (+)-**117aha** in 6% yield as shown in eq. 22. The 2,2-disubstituted 2*H*-1-benzopyran structural unit (compounds **115** and **118**) is found in many natural products and designed products which exhibit a wide range of biological activities.[22p] This reaction is an ideal example for the trapping of both forms of aldol **109** and lactol **110** from fast dynamic equilibrium. Utilization of 1.2 equiv of NMP as co-solvent is crucial for the selectivity and generation of acyclic product (+)-**117aha** in good yield as shown in eq. 22 and Scheme 2. Unfortunately, 86% optical purity of the product (+)-**109ah/110ah** was decreased by 10-20% in products **115**, **117** and **118** and 80% in product **116** under acid catalysis as shown in eq. 22.

* In the compound representation **109xy** and **110xy**, **115xyz** and **116xyz**, **x** denotes ketone component **32** and **y** denotes 2-hydroxybenzaldehyde component **37** and z denotes alcohol component **113**.

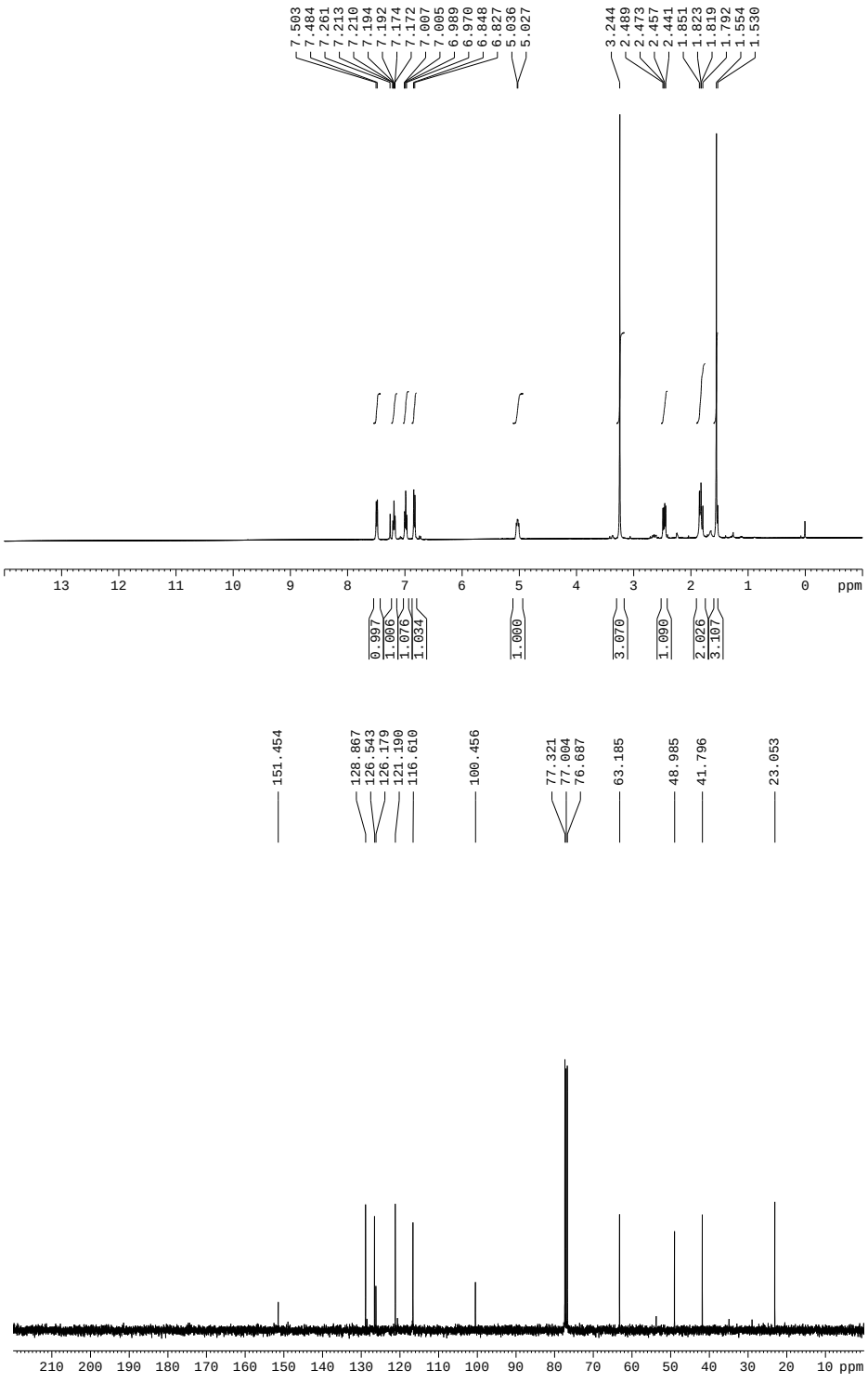


Figure-9: ^{1}H and ^{13}C NMR spectra of the product **115aaa**.

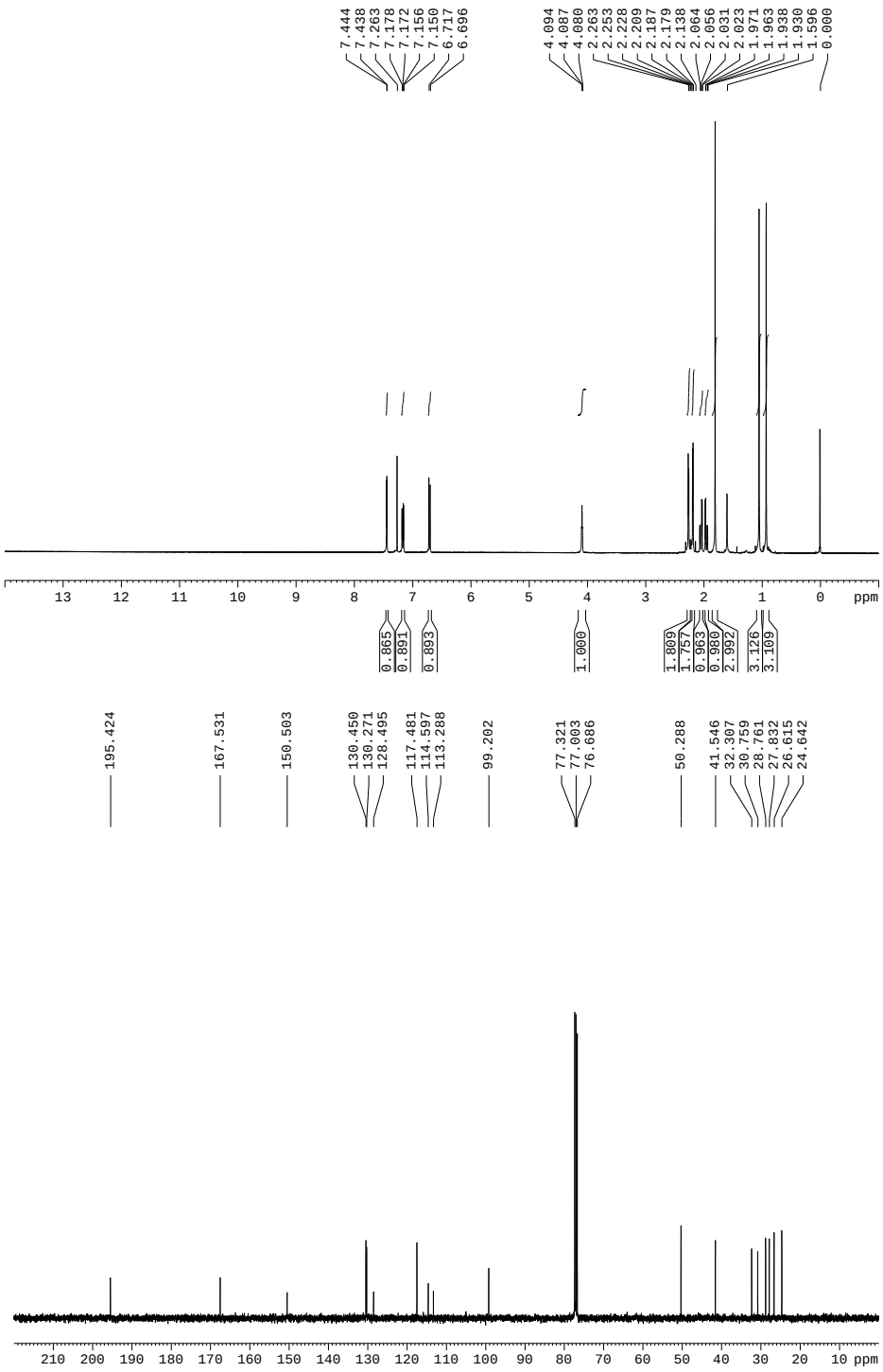


Figure-10: ^{1}H and ^{13}C NMR spectra of the product **116ahd**.

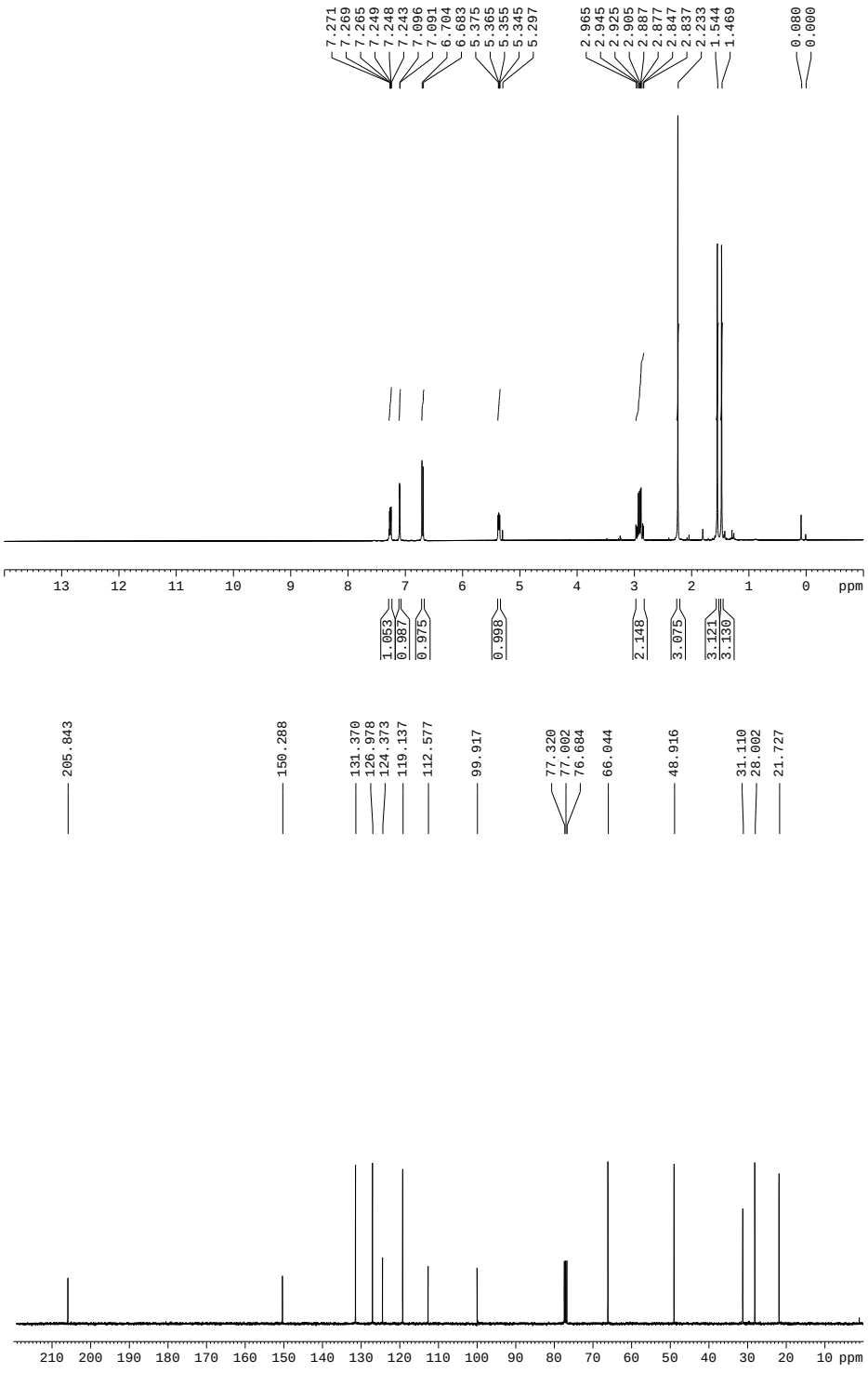


Figure-11: ^{1}H and ^{13}C NMR spectra of the product **117aha**.

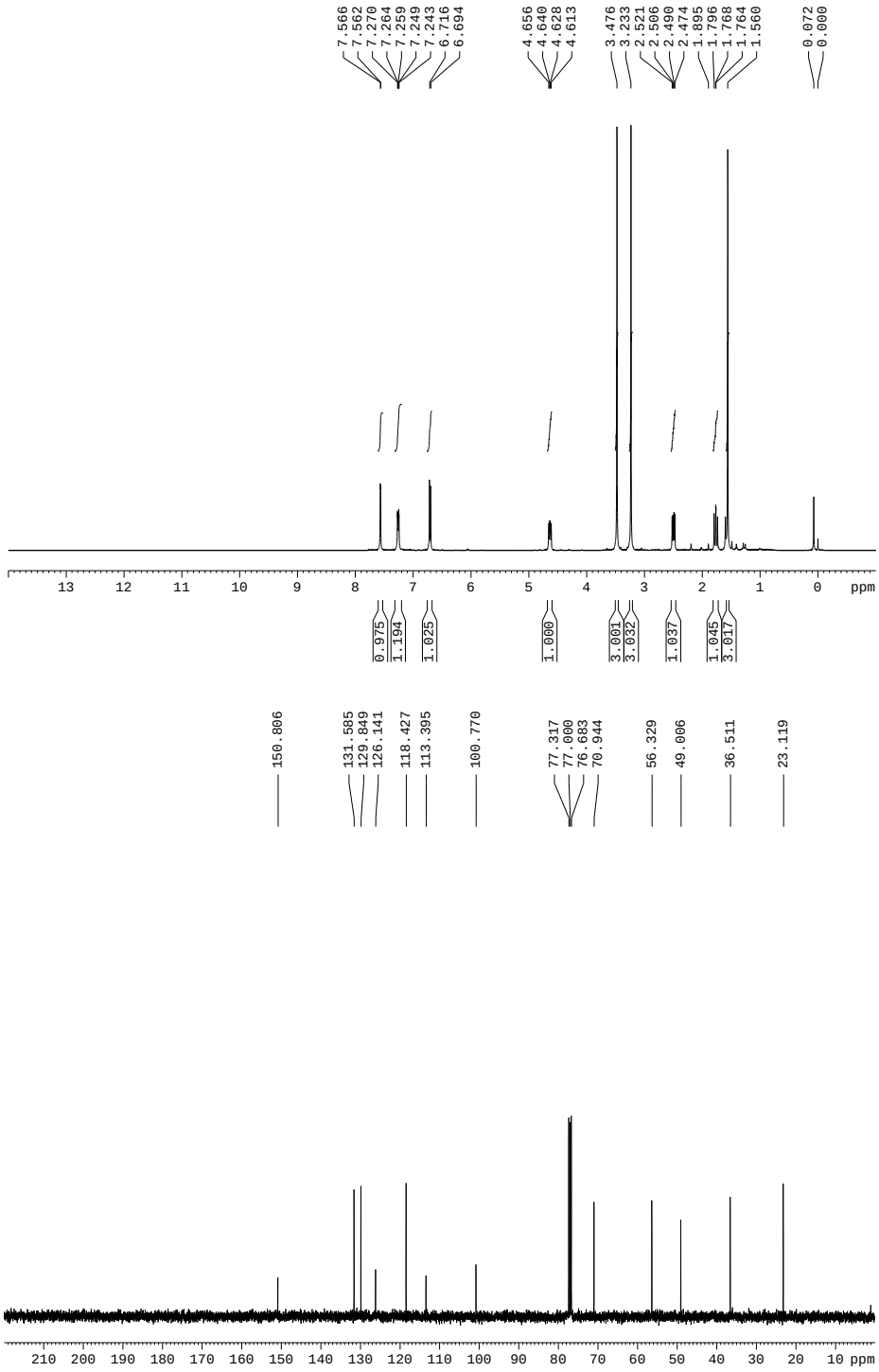
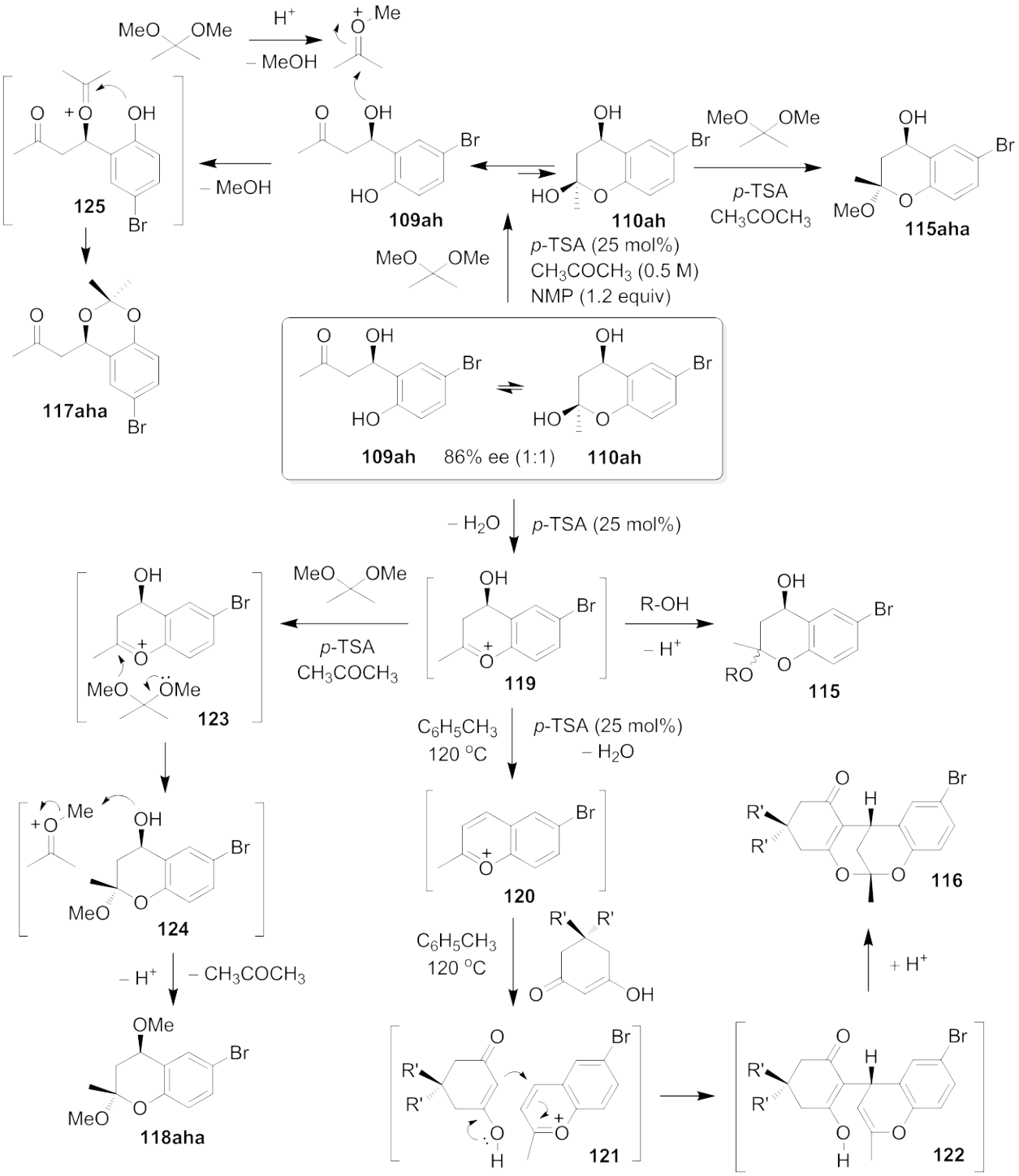


Figure-12: ^{1}H and ^{13}C NMR spectra of the product **118aha**.

3.3 Mechanistic Insights

The possible reaction mechanism for the synthesis of functionalized compounds **115**–**118** for the reaction of BLA product (+)-**109ah/110ah** with alcohols, CH acids, and 2,2-dimethoxypropane under *p*-TSA catalysis is illustrated in Scheme 2. In the first step, catalyst *p*-TSA selectively reacts with (+)-**109ah/110ah** to generate substituted chroman oxonium ion **119** via a dehydration reaction in the solvents such as alcohols, toluene and acetone (**109/110→119**). In the following second step, *in situ* generated chroman ion **119** selectively reacts with different nucleophiles as shown in Scheme 2. Direct selective addition of variety of alcohols to chroman ion **119** leads to the formation of compounds **115**. *In situ* reaction of **119** with *p*-TSA at 120 °C in toluene generates racemic 6-bromo-2-methylbenzopyrylium tosylate (**120**), which upon treatment with 1,3-diones at 120 °C in toluene generates the cyclic intermediates **122** via transition state **121**, which upon further treatment with *p*-TSA furnishes the observed products **116**. Reaction of *in situ* generated **119** with 2,2-dimethoxypropane generates compounds **115** and in addition, methyloxonium ion via methoxy-transfer reaction (see **123**), which on further intermolecular methyltransfer reaction through **124** generates **118aha** with high selectivity. Interestingly, the reaction of (+)-**109ah/110ah** with *p*-TSA in 2,2-dimethoxypropane and NMP as the co-solvent gave different results to without NMP, it is assumed that the 1:1 equilibrium of **109ah↔110ah** is shifted towards aldol compound **109ah** due to the basic nature of NMP and major isomer δ-hydroxyl ketone **109ah** is transformed to acetonation product **117aha** via **125** as shown in Scheme 2. Minor isomer lactol **110ah** is also transformed into compounds **115aha** via **119→123→115aha** sequence as shown in Scheme 2.

Scheme 2: Proposed Reaction Mechanism for Acid-Catalyzed Reactions on aldol↔lactol Product **109ah/110ah**.



3.4 Conclusions

In summary of this chapter, a metal-free approach for the synthesis of chiral functionalized 2-methylchroman-2,4-diols has been described through **34l**-catalysis via Barbas-List aldol reaction from 2-hydroxybenzaldehydes and acetone. The BLA reaction proceeds in good yields with high selectivity using *trans*-4-OH-L-proline as the catalyst. Furthermore, the application of chiral aldol↔lactol products **109/110** in the synthesis of highly functionalized molecules was demonstrated. This, in turn explains the potential ability and participation of neighboring OH group in the cascade reaction and also in the transition state and proves that proper design and synthetic plan using neighboring group participation would make the asymmetric heterocycle synthesis, a much more efficient.

ANNEXURE-I: Tosylation of BLA products 109↔110.

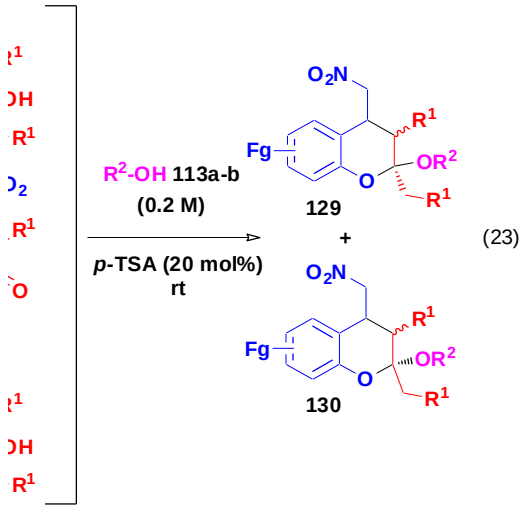
4. Sequential Combination of Michael and Acetalization Reactions: Direct Catalytic Asymmetric Synthesis of Functionalized 4-Nitromethyl-chromans as Drug Intermediates

4.1 Introduction

Functionalized chromans display a broad range of biological activities and are widely used as drug intermediates and ingredients in pharmaceuticals (Chart 2).[30,22c] Due to their varied applications in the field of biology, direct catalytic asymmetric method for their synthesis has always been an ever-green task.[31,22p,23f,23o] 2-hydroxy-2-methyl-4-nitromethyl-chromans are attractive intermediates to form functionalized chromans and benzopyrans. Asymmetric synthesis of such an important key intermediate has not been known through organocatalytic strategy. This necessitates a way to develop a novel metal-free approach to the asymmetric synthesis of functionalized 2-hydroxy-2-methyl-4-nitromethyl-chromans via "sequential Michael and acetalization (SMA) reactions"[32] results of which are disclosed in the following section.

Chart 2: Various Biologically Active Chromans.

Recently, Barbas and co-workers discovered a mild and efficient method for Michael reactions through organocatalysis. Their novel strategy involves amine or amino acid-catalyzed intermolecular Michael reactions of ketones/aldehydes with various activated olefins to deliver Michael adducts in good yields with high enantioselectivity. This revolutionary methodology encouraged the synthetic community to synthesize enantiomerically pure Michael adducts through bio-mimetic enamine catalysis.[33,24e]



Organocatalyzed Michael reaction of ketone **32** with 2-(2-nitrovinyl)phenols **82** would be of great synthetic utility as the resulting products **126–128** have a wide range of applications in the field of pharmaceutical chemistry (Chart 2 and eq. 23). Here, the asymmetric synthesis of functionalized 2-hydroxy-2-methyl-4-nitromethyl-chromans **127**/**128** and 2-alkoxy-2-methyl-4-nitromethyl-chromans **129**/**130** is reported using organocatalytic SMA reactions from readily available 2-(2-nitrovinyl)phenols **82**, ketones **32**, amine/amino acid **34** and/or alcohols **113** (eq. 23). Furthermore, the existence of a fast dynamic equilibrium between the pair of pseudo-diastereomeric hemiketals of 2-hydroxy-2-methyl-4-nitromethyl-chromans **127**/**128** and 4-(2-hydroxy-phenyl)-5-nitro-pentan-2-one **126** under normal reaction conditions is described.[25,1c]

While exploring new reactive species for the development of MCC reactions,[10] the potential ability of the 2-(2-nitrovinyl)phenols **82** was tested to participate in an amine-catalyzed SMA reaction with acetone **32a**. It was envisioned that the reaction of 2-(2-nitrovinyl)phenol **82c** with *in situ* generated enamine from acetone **32a** would lead to 4-(2-hydroxy-phenyl)-5-nitro-

pentan-2-one **126c**. However, the isolated Michael adduct **126c**, was found to exist in dynamic equilibrium with both *cis*-2-hydroxy-2-methyl-4-nitromethyl-chroman **127c** and *trans*-2-hydroxy-2-methyl-4-nitromethyl-chroman **128c** under the standard reaction conditions. This observation led to a novel methodology for the preparation of 2-hydroxy-2-methyl-4-nitromethyl-chromans **127**/**128** through amine or amino acid catalysis.

4.2 Results and Discussions

4.2.1 Reaction optimization of SMA reactions:

The studies were initiated towards chiral SMA reactions by screening a number of organocatalysts for the Michael reaction of 2-(2-nitrovinyl)phenol **82c** with 14 equiv of acetone **32a** and some primary results are shown in Table 4. The reaction of **82c** with 14 equiv of acetone **32a** in DMSO under 20 mol% of L-proline **34a-**catalysis furnished a 1:1:1 ratio of Michael↔*cis*-lactol↔*trans*-lactol products **126c**/**127c**/**128c** in 92% yield with only ≤7% ee (eq. 23 and Table 4, entry 1). Rapid equilibrium between Michael adduct **126c** and lactols **127c**/**128c** in solution was confirmed by NMR and HPLC analyses and also by acetalization with methanol (see Figures-13 to 14). For the clear understanding of the dynamic equilibrium between **126c** and **127c**/**128c**, and also for clear HPLC separation, the crude product **126c**/**127c**/**128c** was transformed into two easily separable SMA products, *cis*-**129ca*** and *trans*-**130ca*** in 1:1 ratio with 92% yield via *p*-TSA-catalyzed acetalization reaction in MeOH **113a** at 25 °C in 2 h (Table 4).

Taking this as SMA strategy, further optimization was carried out with **32a** and **82c** in DMSO in presence of 20 mol% of L-Thr(O*t*Bu)–OH **34r**. Michael reaction followed by acetalization furnished 1:1 ratio of **129ca** and **130ca** in <30% yield (Table 4, entry 2). Reaction of **32a** with **82c** in DMSO in the presence of 20 mol% of L-2-methoxymethyl-pyrrolidine **34u**/$PhCO_2H$ followed by acetalization furnished **129ca/130ca** in 94% yield with increased (18%/16%) ee (Table 4, entry 3).

*In the compound representation **129xy** and **130xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes alcohol component **113**.

The same reaction with 20 mol% of L-diamine **34j**/Ph_2CHCO_2H catalyst in DCM for 24 h followed by acetalization in MeOH furnished **129ca/130ca*** in 95% yield with an increased (25%/21%) ee (Table 4, entry 5). No product formation was observed with (*S*)-α,α-diphenylprolinol trimethylsilyl ether (L-DPPOTMS) **34b**/D-CSA in DMSO. Results were not superior even with bifunctional catalyst (*R*,*R*)-1,2-diphenylethane-1,2-diamine **34w**/AcOH and L-(3,5-bis-trifluoromethylphenyl)-3-pyrrolidin-2-ylmethyl-thiourea **34v** (Table 4, entries 7-8).

Table 4: Reaction Optimization for the SMA Reaction of **32a**, **82c** and **113a**.

rea **34v**	DMSO	24	<15	<15	–30	–30
	DMSO	24	40	40	<5	<5
	$C_6H_5CH_3$	24	35	35	18	18
	$C_6H_5CH_3$	24	42	43	60	58
	DCM	**72**	**47**	**42**	**84**	**82**
	DCM	**72**	**40**	**42**	**82**	**82**

d product. [b] Ee determined by CSP HPLC analysis. [c] Similar results
S)-1-(3,5-Bis-trifluoromethyl-phenyl)-3-pyrrolidin-2-ylmethyl-thiourea
with each 10 mol% of **34x** and Ph_2CHCO_2H

*In the compound representation **129xy** and **130xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes alcohol component **113**.

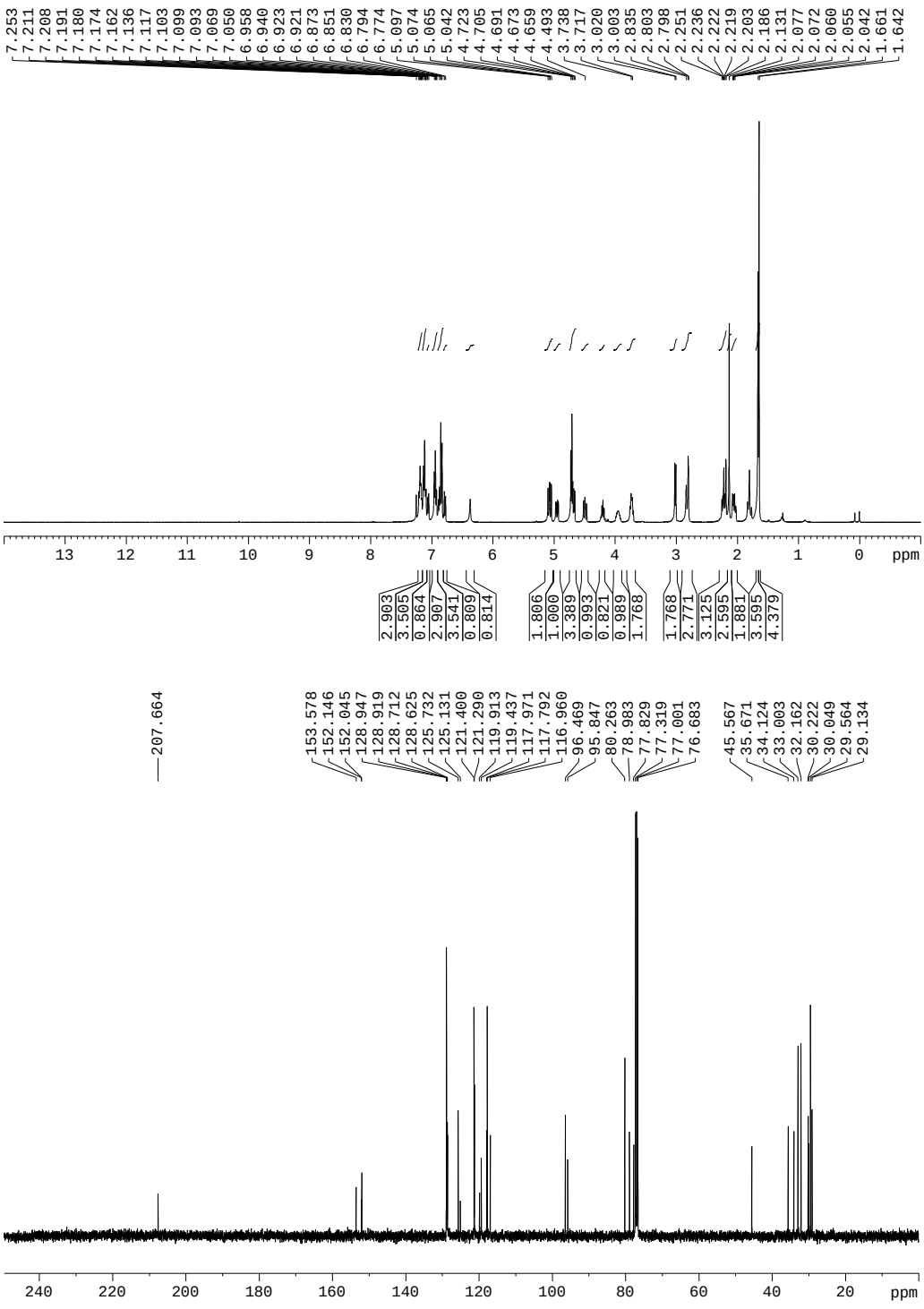
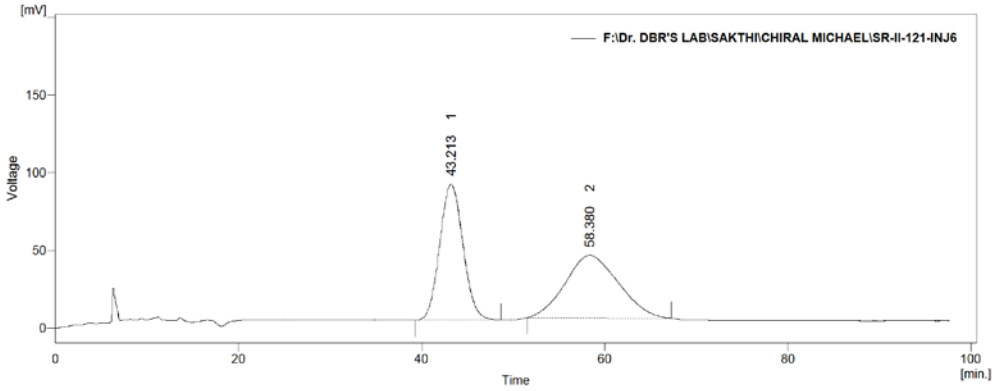


Figure-13: ^{1}H and ^{13}C NMR spectra of the product **127c↔126c↔128c**.

Racemic **127c↔126c↔128c**:

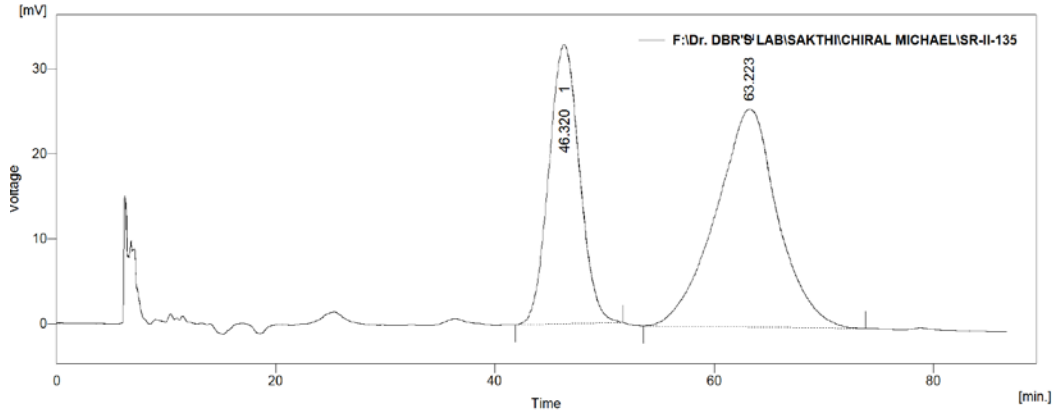


Daicel chiralpak AD-H, Hexane/i-PrOH = 95:5, Flow Rate 0.5 mL/min, 254 nm.

Result Table (Uncal - F:\Dr. DBR'S LAB\SAKTHI\CHIRAL MICHAEL\SR-II-121-INJ6)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	43.213	10318.546	58.262	48.7	68.4	2.77
2	58.380	10879.922	26.908	51.3	31.6	6.38
	Total	21198.468	85.170	100.0	100.0	

Chiral **127c↔126c↔128c** (22% ee):



Daicel chiralpak AD-H, Hexane/i-PrOH = 95:5, Flow Rate 0.5 mL/min, 254 nm.

Result Table (Uncal - F:\Dr. DBR'S LAB\SAKTHI\CHIRAL MICHAEL\SR-II-135)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	46.320	4268.462	21.914	38.8	56.2	3.04
2	63.223	6740.005	17.083	61.2	43.8	5.83
	Total	11008.467	38.997	100.0	100.0	

Figure-14: HPLC of the product **127c↔126c↔128c**.

As the SMA reaction of **32a**, **82c** and **113a** with pyrrolidine based catalysts was not superior in terms of ee, the catalytic ability of alkaloid based primary amines was tested. When 20 mol% of 9-amino-9-deoxyepiquinine **34x** was employed as catalyst for the SMA reaction (see Table 4)[34] of **82c** with 14 equiv of **32a** in toluene for 24 h at rt followed by acetalization under *p*-TSA-catalysis in methanol, **129ca/130ca*** were resulted with 70% overall yield, each with 18% ee; While employing the co-catalyst $PhCO_2H$ with 9-amino-9-deoxyepiquinine **34x** in toluene solvent, the reaction yielded the SMA products (+)-**129ca** in 42% yield with 60% ee and (-)-**130ca** in 43% yield with 58% ee as shown in Table 4, entries 9–10. After getting profound increase in ee with addition of co-catalyst, a number of acids as co-catalysts was tested with **34x** for the high asymmetric induction in SMA reaction of **32a**, **82c** and **113a** in different solvents at 25 °C for 72 h (Table A1, See Annexure-II).

It was pleasing to find that when Ph_2CHCO_2H was used as co-catalyst with **34x** in the Michael reaction followed by acetalization the SMA products; (+)-**129ca** was isolated in 40% yield, 82% ee and (-)-**130ca** in 42% yield, 82% ee (Table 4, entry 12). Other alkaloid based primary amines like 9-amino-9-deoxyepicinchonidine **34y**, 9-amino-9-deoxyepiquinidine **34z**, 9-amino-9-deoxyepihydroquinine **34aa** and 9-amino-9-deoxyepihydroquinidine **34ab** as catalysts for the SMA reaction of **32a** with **82c** in DCM solvent didn't provide any superior results. (Table A1, Annexure-II).

*In the compound representation **129xy** and **130xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes alcohol component **113**.

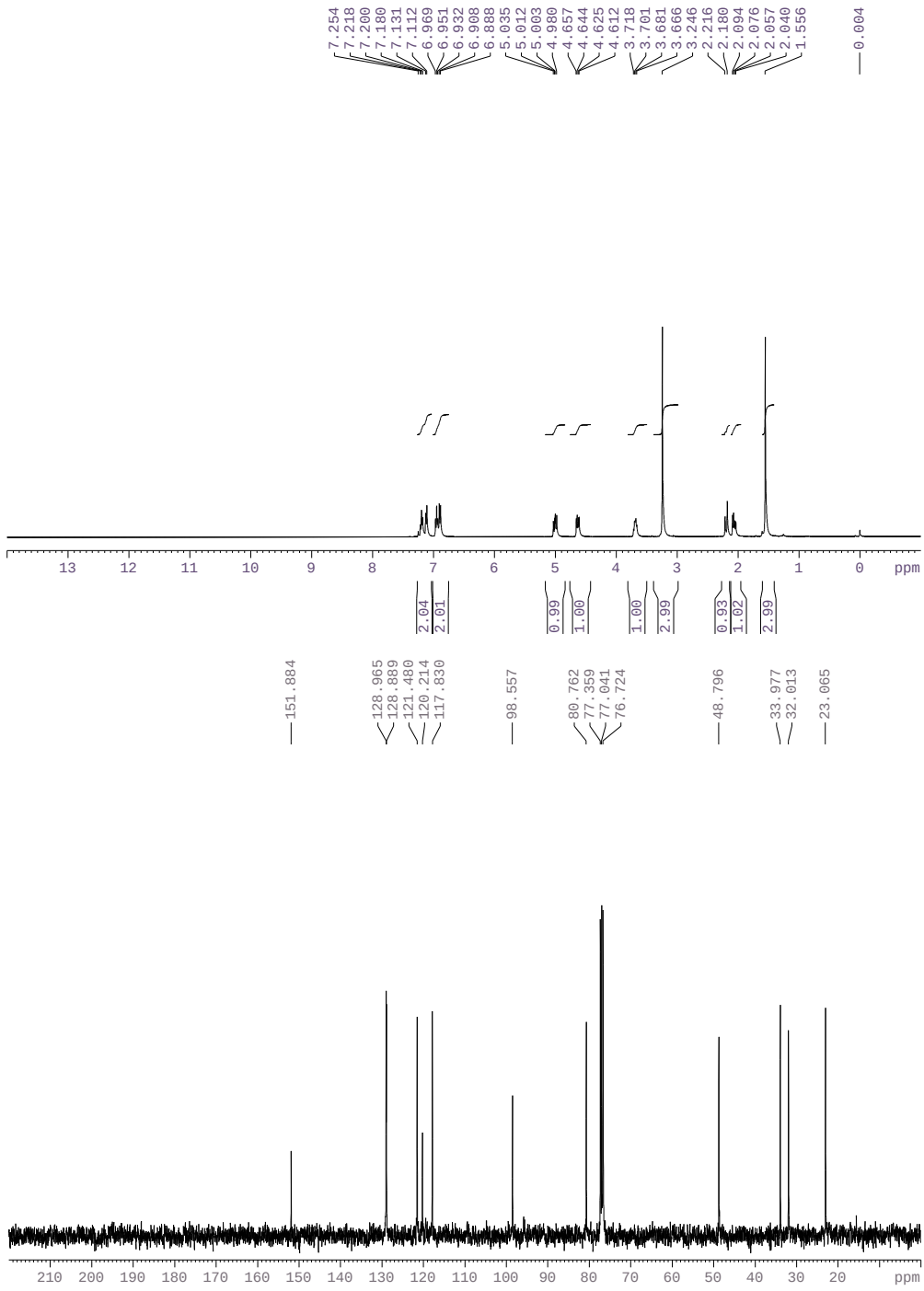


Figure-15: ^{1}H and ^{13}C NMR spectra of the product **129ca**.

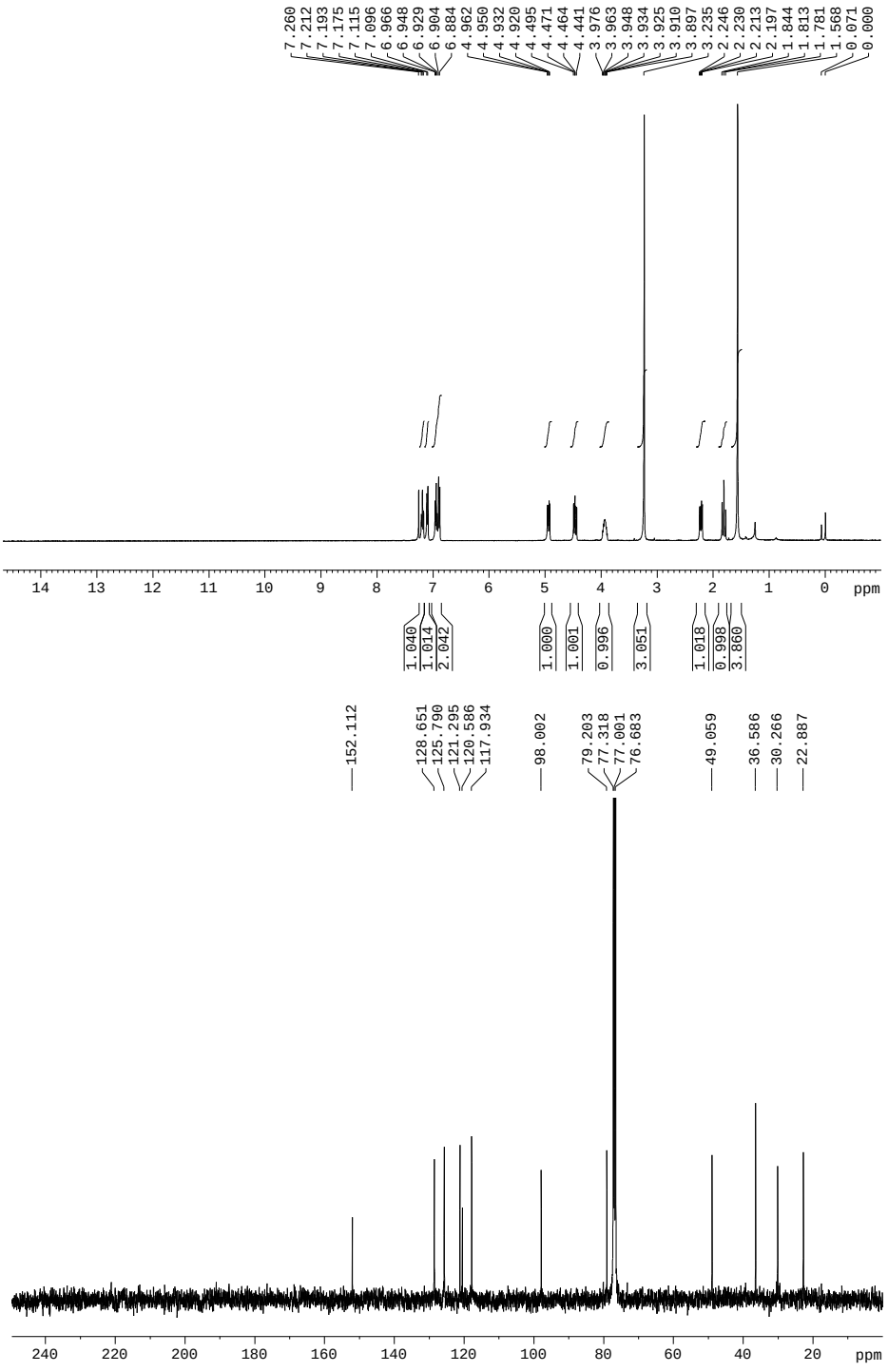


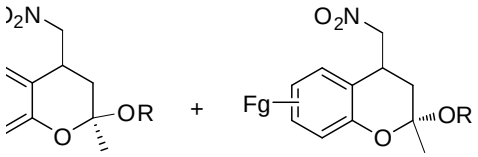
Figure-16: ^{1}H and ^{13}C NMR spectra of the product **130ca**.

4.2.2 Library generation of chiral SMA products:

With the optimized reaction conditions in hand, the scope of the amine/acid-catalyzed asymmetric SMA reactions was investigated. The organocatalytic synthesis of substituted 2-(2-nitrovinyl)phenols **82b-l** and racemic products **129ba-fb** and **130ba-fb** in good yields has been shown in Tables A2 and A3 in Annexure-II. A series of substituted 2-(2-nitrovinyl)phenols **82b-l** was synthesized following method **A** or method **B** (Table A2, Annexure-II). The racemic products were synthesized through L-proline catalysis in DMSO solvent, which was tested to result 0% ee, followed by acetalization of crude product in MeOH in the presence of *p*-TSA (Table A3, Annexure-II). The generation of chiral products were initiated by reacting a series of 2-(2-nitrovinyl)phenols **82b-l** with 14 equiv of acetone **32a** in the presence of 10 mol% of **34x**/Ph_2CHCO_2H at 25 °C in DCM for 72 h followed by acetalization on crude products **126**/**127**/**128** with alcohols **113a–b** under *p*-TSA catalysis at 25 °C for 2 h (Table 5). The chiral products **129ba**–**fb** and **130ba**–**fb** were obtained in 1:1 ratio with excellent yields and enantiomeric excesses. Electronic factors and steric factors had little or no influence towards yield and enantiomeric excess of the reaction except in the reaction of **82d** (see Table 5).

Fascinatingly, reaction of 1-(2-nitrovinyl)naphthalen-2-ol **82d** with acetone **32a** in the presence of **34x**/Ph_2CHCO_2H furnished the *cis*-chroman (+)-**127d** as the single product in 80% yield with 98% ee, which on further acetalization with methanol also furnished the *cis*-chroman (+)-**129da** as the single product with 98% ee (Table 5, entry 2). The high stereoselectivity in the synthesis of *cis*-chromans (+)-**127d**/(+)-**129da** can be explained using $A^{(1,3)}$-strain as discussed by Johnson and Hoffman in their reviews.[35] The selectivity may be due to $A^{(1,3)}$-strain, the relatively larger nitromethyl group in **127d**/**129da** existing in the axial position in the cyclohexane conformation, preventing another large group from approaching on the same side thus minimizing 1,3-*syn*-diaxial repulsions. Without showing much kinetic influence, deuterated products (+)-**129la–d**$_5$ and (-)-**130la–d**$_5$ were furnished in 37% yield with 89% ee (Table 5, entry 12). The structure and stereochemistry of SMA products **129ba**–**fb**/**130ba**–**fb** were confirmed by NMR analyses and also finally confirmed by X-ray structure analyses of (+)-**129da**, (-)-**129ha** and (-)-**130ia** as shown in Figures-17 to 19. [36-38]

Table 5: Synthesis of Chiral SMA Products **129** and **130**.[a]



ba-la: R = Me **113a:** MeOH **130ba-la:** R = Me
cb/fb: R = Et **113b:** EtOH **130cb/fb:** R = Et

Ratio[b]	Products yield (%)[c]		*ee* (%)[d]	
129/130)	**129**	**130**	**129**	**130**
1:1	42	42	82	82
99:1	72	<1	98	–
1:1	43	43	82	76
1:1	40	40	69	70
1:1	41	41	87	86
1:1	41	41	88	91
1:1	38	38	79	79
1:1	33	38	79	79
1:1	37	37	80	80

Table 5: Synthesis of Chiral SMA Products **129** and **130**.[a] (*Contd*..)

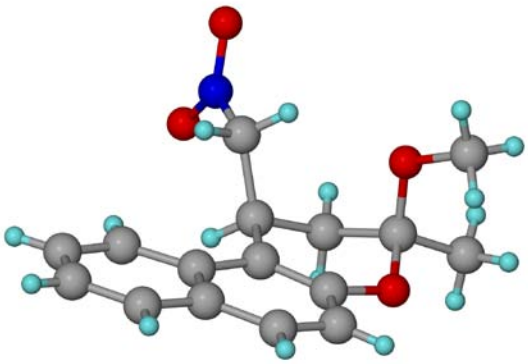


Figure-17: X-Ray crystal structure of chiral (+)-3-methoxy-3-methyl-1-(nitromethyl)-2,3-dihydro-1*H*-benzo[*f*]chromene (**129da**).

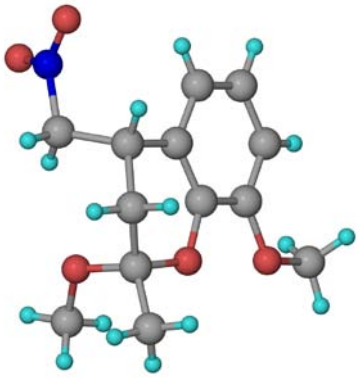


Figure-18: X-Ray crystal structure of chiral (–)-2,8-dimethoxy-2-methyl-4-nitromethyl-chroman (**129ha**).

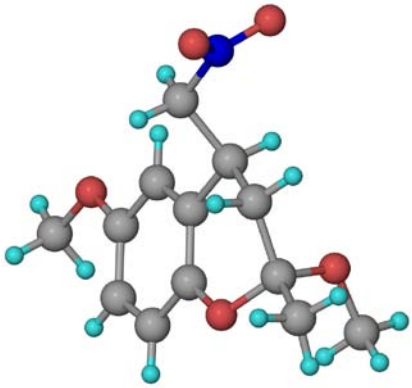


Figure-19: X-Ray crystal structure of chiral (–)-2,6-dimethoxy-2-methyl-4-nitromethyl-chroman (**130ia**).

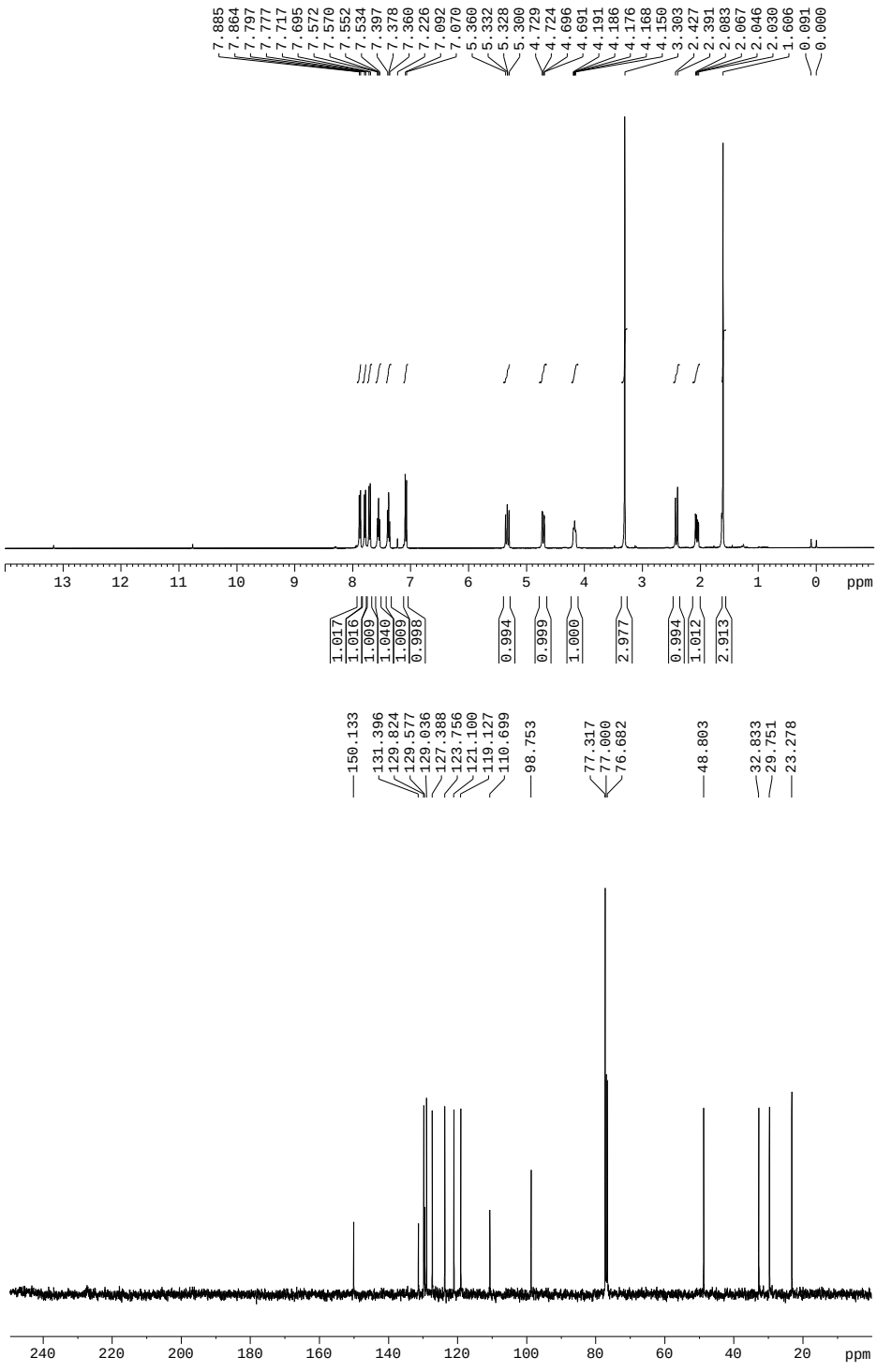


Figure-20: ^{1}H and ^{13}C NMR spectra of the product **129da**.

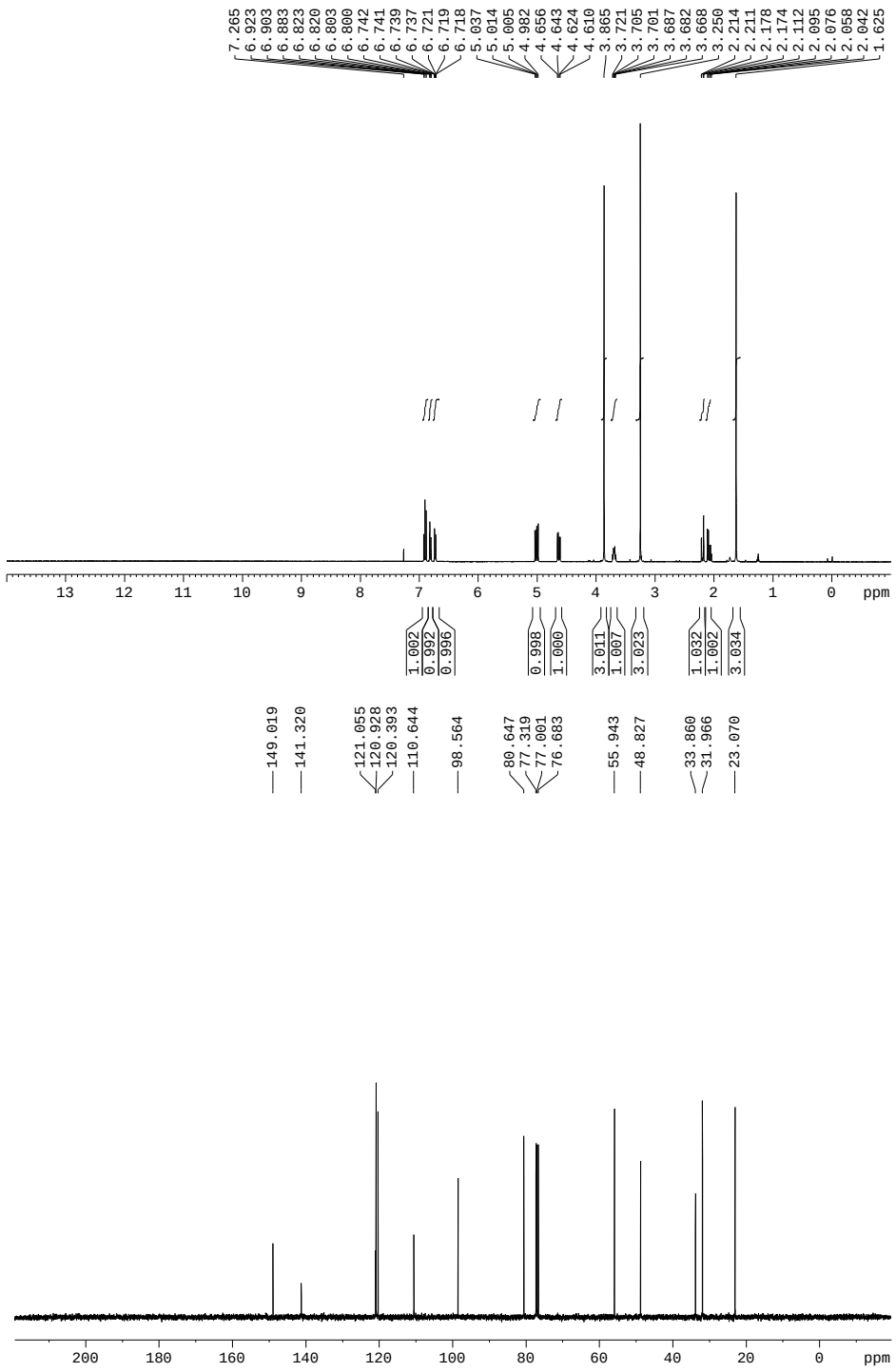


Figure-21: ^{1}H and ^{13}C NMR spectra of the product **129ha**.

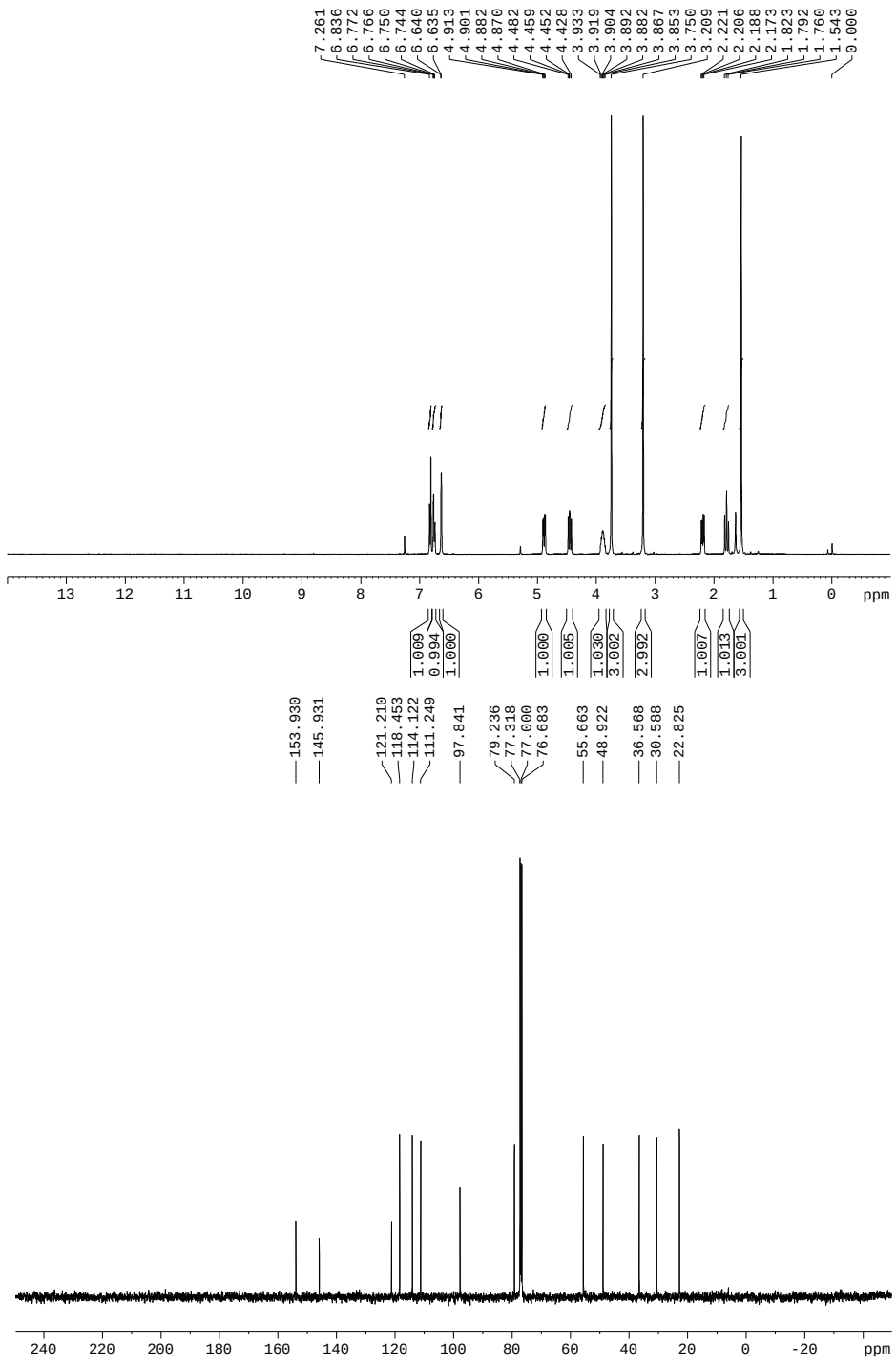


Figure-22: ^{1}H and ^{13}C NMR spectra of the product **130ia**.

4.2.3 Controlled experiments to understand the neighboring ortho-hydroxyl group participation in SMA reactions:

It was strongly believed that the *ortho*-OH group not only involves in the cyclization, but also in the transition state of the Michael reaction through neighboring group participation. To provide experimental proof for the neighboring group participation by *ortho*-OH in the Q-NH_2 **34x** /Ph_2CHCO_2H catalyzed reactions between **32a** and **82** in DCM, various experiments were carried out as shown in Scheme 3. The reaction of 2-methoxynitrostyrene **92b** with acetone **32a** in the presence of **34x**/Ph_2CHCO_2H in DCM at rt for 96 h resulted the product (+)-**131ba** in 48% yield and 66% ee. Thus replacing OH by OMe in the *ortho* position of nitrostyrene affects reactivity and enantioselectivity.

Changing the position of OH group to *meta* or *para* positions also showed similar trend of changes in reactivity and selectivity. The reaction of 3-hydroxynitrostyrene **92c** with acetone **32a** in the presence of **34x**/Ph_2CHCO_2H in DCM at rt for 120 h resulted the product (-)-**131ca** in 32% yield and 67% ee. The same reaction with 4-hydroxynitrostyrene **92d** under the same conditions for 120 h resulted the product (-)-**131da** in only 16% yield with 67% ee (Scheme 3). These set of experiments clearly make it evident that *ortho*-OH group enhances the reactivity and selectivity through neighboring group participation and disturbing OH position changes the selectivity and reactivity of SMA reaction drastically (Scheme 3).

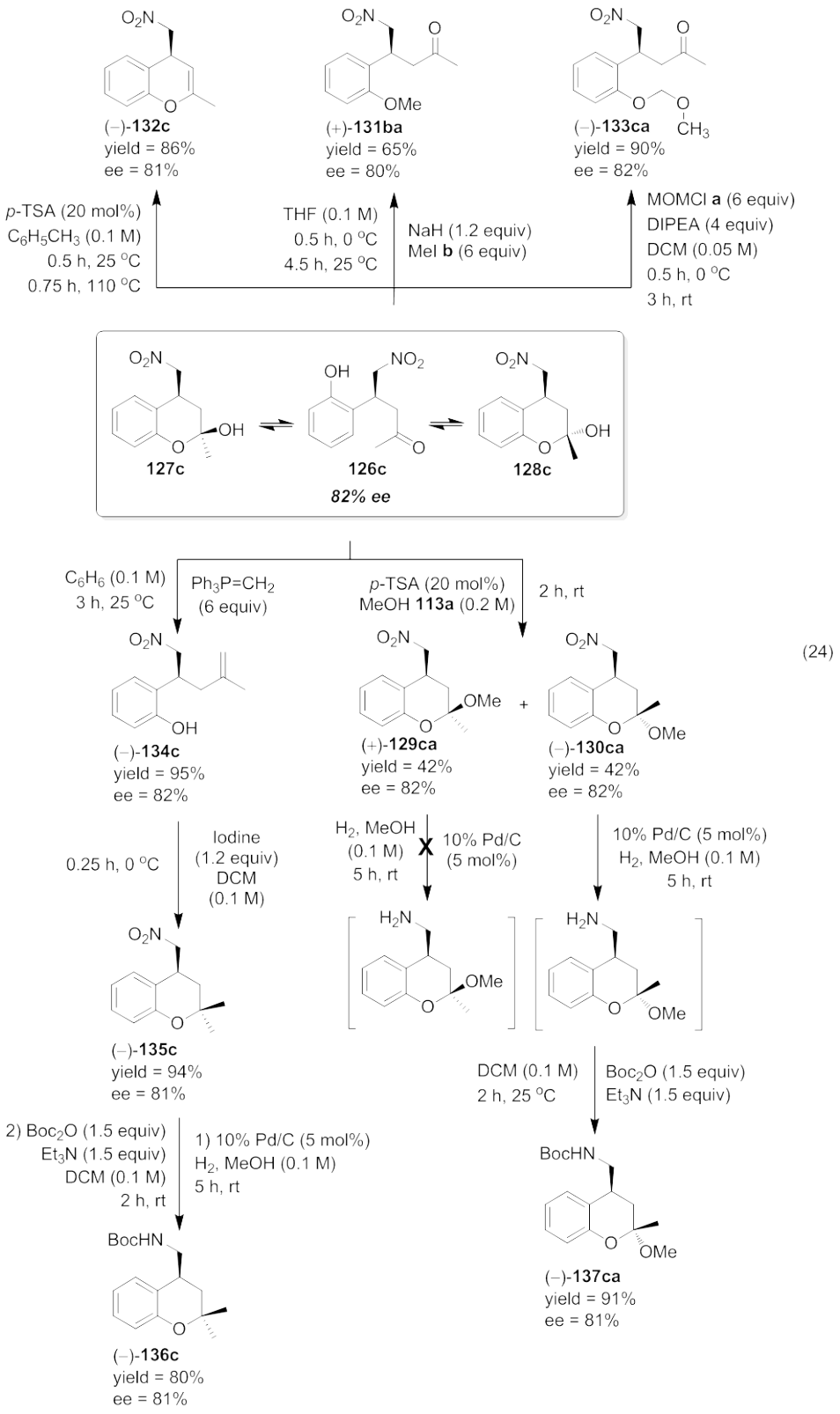
Scheme 3: Controlled Experiments to Understand the Neighboring Group Participation by *ortho*-OH Group.

4.2.4 Applications of chiral SMA products for the synthesis of various benzopyrans:

After successful demonstration of the **34x**/Ph_2CHCO_2H catalyzed asymmetric SMA reactions of **32a** with **82**, the synthetic utility of δ-hydroxyketone↔lactol isomerization was explored in the synthesis of functionalized chiral molecules through acid/base catalysis in a sequential manner as depicted in eq. 24. Refluxing δ-hydroxyketone↔lactol products (+)-**126c**/**127c**/**128c** in toluene with catalytic amount of *p*-TSA for 0.75 h furnished the selectively cyclized 2-methyl-4-nitromethyl-4*H*-chromene product (-)-**132c** in 86% yield with 81% ee (eq. 24). When attempts were made to protect the hydroxyl group and treated (+)-**126c**/**127c**/**128c** with methoxy methyl chloride (**a**), the reaction yielded the selectively protected product 4-(2-methoxymethoxy-phenyl)-5-nitropentan-2-one (-)-**133ca*** in 90% yield and 82% ee and the corresponding protection with methyl iodide (**b**) resulted 4-(2-methoxy-phenyl)-5-nitro-pentan-2-one (+)-**131ba*** in 65% yield, 80% ee (eq. 24).

To further explore the reactivity of (+)-**126c**/**127c**/**128c**, it was treated with methylenetriphenylphosphorane in benzene at 25 °C for 3 h, which resulted the olefin phenol (-)-**134c** in 95% yield with 82% ee. Treatment of (-)-**134c** with 1.2 equiv of iodine in DCM at 0 °C for 0.25 h furnished the selectively cyclized 2,2-dimethyl-4-nitromethyl-chroman product (-)-**135c** in 94% yield with 81% ee. Hydrogenation of (-)-**135c** with 10% Pd/C in methanol at 25 °C for 5 h, followed by the protection of resulting primary amine with Boc_2O in DCM at 25 °C for 2 h furnished protected amine (-)-**136c** in 80% yield with 81% ee. A similar hydrogenation followed by protection strategy was applied to molecule (-)-**130ca** under similar conditions as before, furnishing the protected amine (-)-**137ca** in 91% yield with 81% ee. Surprisingly, the corresponding *cis*-isomer (+)-**129ca** didn't undergo hydrogenation under similar reaction conditions, perhaps due to steric hindrance (eq. 24).

*In the compound representation **129xy, 130xy** and **137xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes alcohol component **113**, while in **133xy**, **x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes protection component.


(−)-132c
yield = 86%
ee = 81%
(+)-131ba
yield = 65%
ee = 80%
(−)-133ca
yield = 90%
ee = 82%
p-TSA (20 mol%)
C6H5CH3 (0.1 M)
0.5 h, 25 °C
0.75 h, 110 °C
THF (0.1 M)
0.5 h, 0 °C
4.5 h, 25 °C
NaH (1.2 equiv)
MeI b (6 equiv)
MOMCl a (6 equiv)
DIPEA (4 equiv)
DCM (0.05 M)
0.5 h, 0 °C
3 h, rt
127c
126c
82% ee
128c
C6H6 (0.1 M)
3 h, 25 °C
Ph3P=CH2
(6 equiv)
p-TSA (20 mol%)
MeOH 113a (0.2 M)
2 h, rt
(−)-134c
yield = 95%
ee = 82%
(+)-129ca
yield = 42%
ee = 82%
(−)-130ca
yield = 42%
ee = 82%
0.25 h, 0 °C
Iodine
(1.2 equiv)
DCM
(0.1 M)
H2, MeOH
(0.1 M)
5 h, rt
10% Pd/C
(5 mol%)
10% Pd/C (5 mol%)
H2, MeOH (0.1 M)
5 h, rt
(−)-135c
yield = 94%
ee = 81%
DCM (0.1 M)
2 h, 25 °C
Boc2O (1.5 equiv)
Et3N (1.5 equiv)
2) Boc2O (1.5 equiv)
Et3N (1.5 equiv)
DCM (0.1 M)
2 h, rt
1) 10% Pd/C (5 mol%)
H2, MeOH (0.1 M)
5 h, rt
(−)-136c
yield = 80%
ee = 81%
(−)-137ca
yield = 91%
ee = 81%

(24)

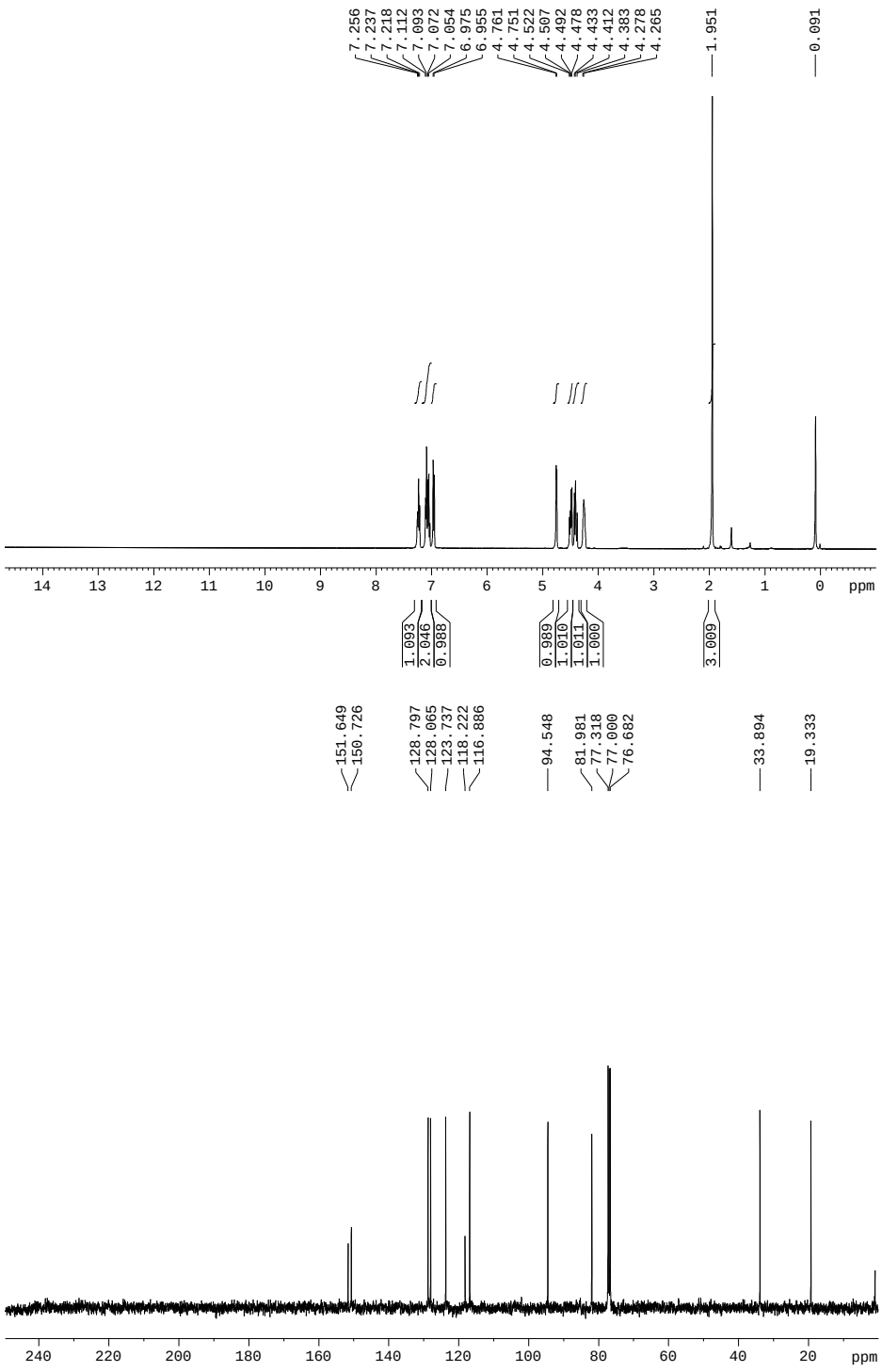


Figure-23: ^{1}H and ^{13}C NMR spectra of the product **132c**.

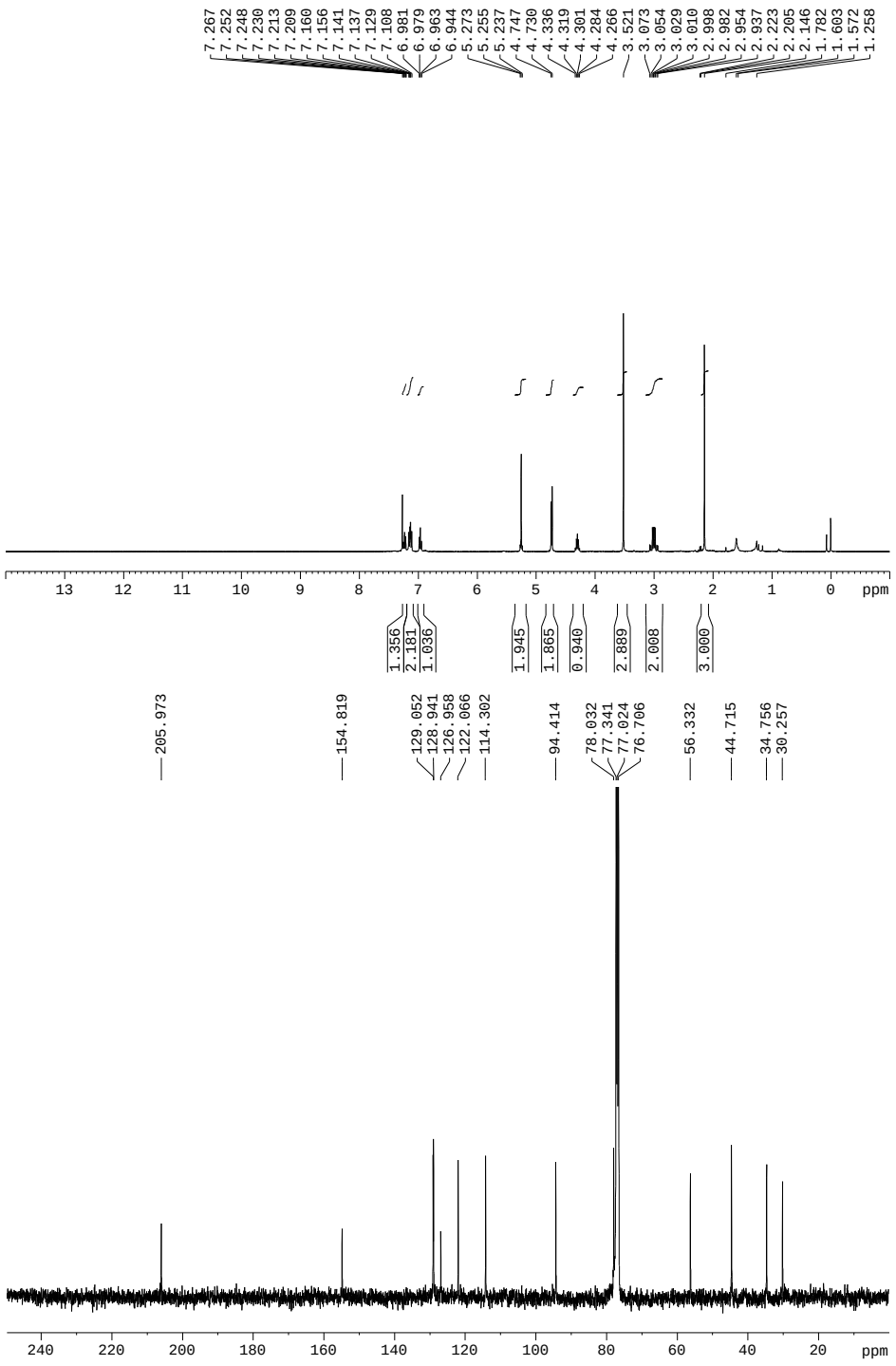


Figure-24: ^{1}H and ^{13}C NMR spectra of the product **133ca**.

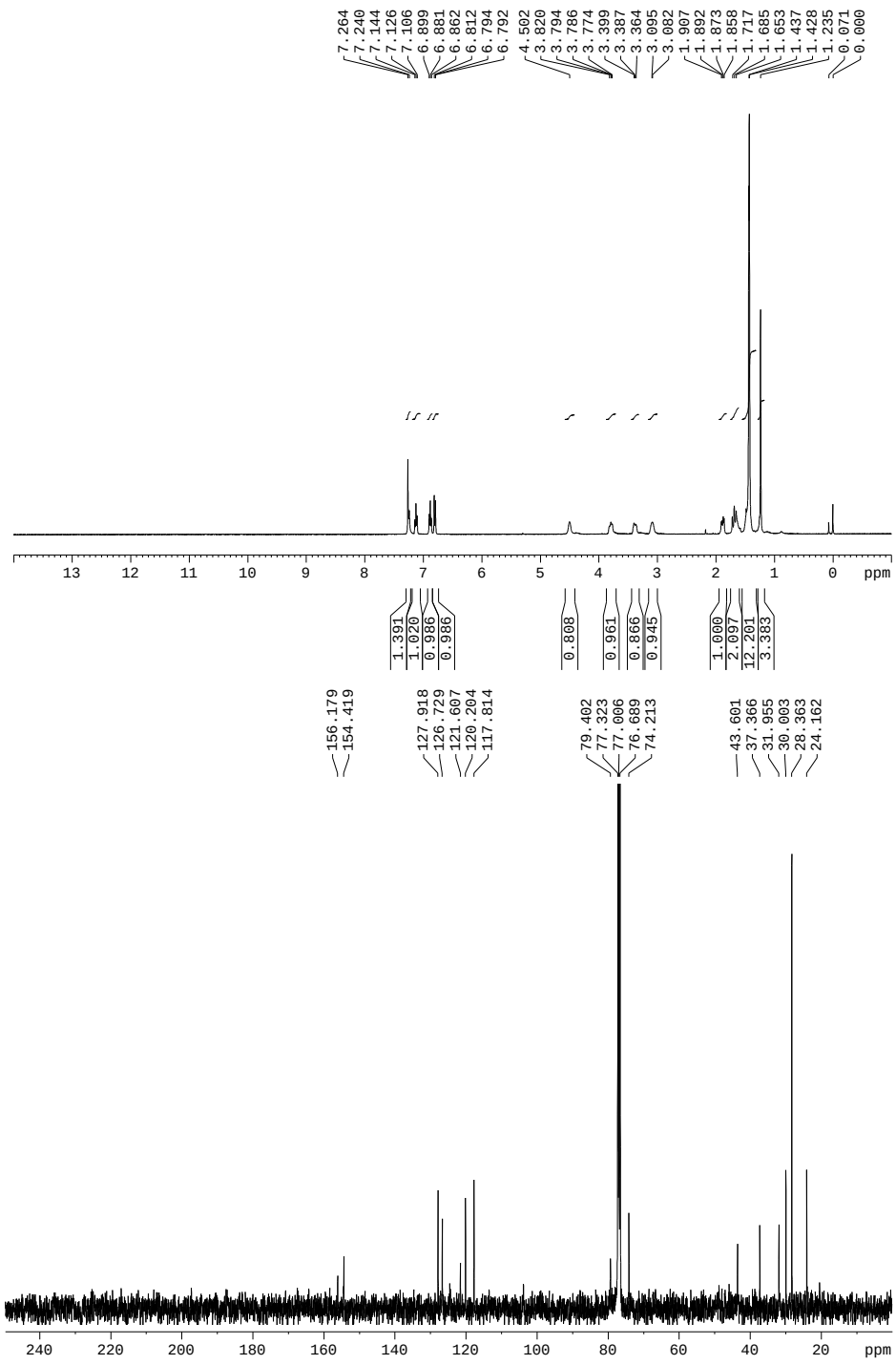


Figure-25: ^{1}H and ^{13}C NMR spectra of the product **136c**.

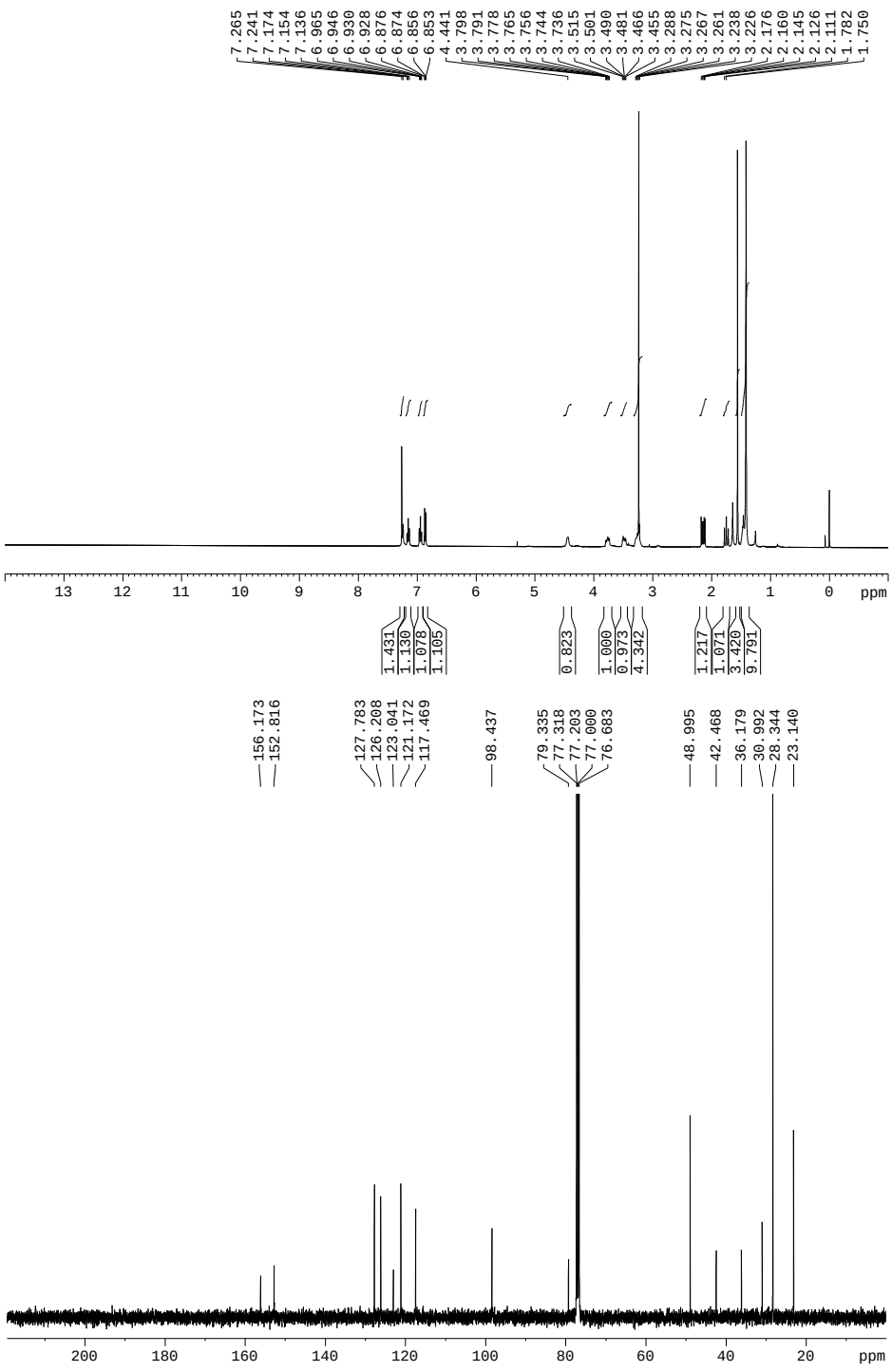


Figure-26: ^{1}H and ^{13}C NMR spectra of the product **137ca**.

4.2.5 Applications of chiral SMA products for the synthesis of chiral pyrrolidines:

Cascade hydrogenation–reductive amination of (+)-**131ba** under H_2 atmosphere over Pd/C followed by protection with *p*-TsCl, provided the stereoselectively substituted pyrrolidine-sulfonamide (+)-**139cb** in 64% overall yield with 80% ee and 70% de as shown in eq. 25.

Thus these experiments show the ways of trapping both the modules of SMA products **126**/**127**/**128** from fast dynamic equilibrium. Compound (-)-**136c** and analogue (-)-**137ca** are important compounds as they possess potent anti-ischemic properties, and useful as anti-hypertensives, spasmolytics for blood vessels and potassium channel blockers (**D–G**, see chart 2), which emphasizes the value of this SMA approach to the pharmaceuticals.[30] Also functionalized pyrrolidine-sulfonamide (+)-**139cb** and their analogues are useful in the form of drugs for modulators of serotonin 5HT6 receptors and dopamine D3 receptors for the treatment of CNS disorders.[30f] Moreover, the disubstituted-2*H*-1-benzopyran structural unit (**136** and **137**) is found in many natural products and designed products which exhibit a range of biological activities.[22p]

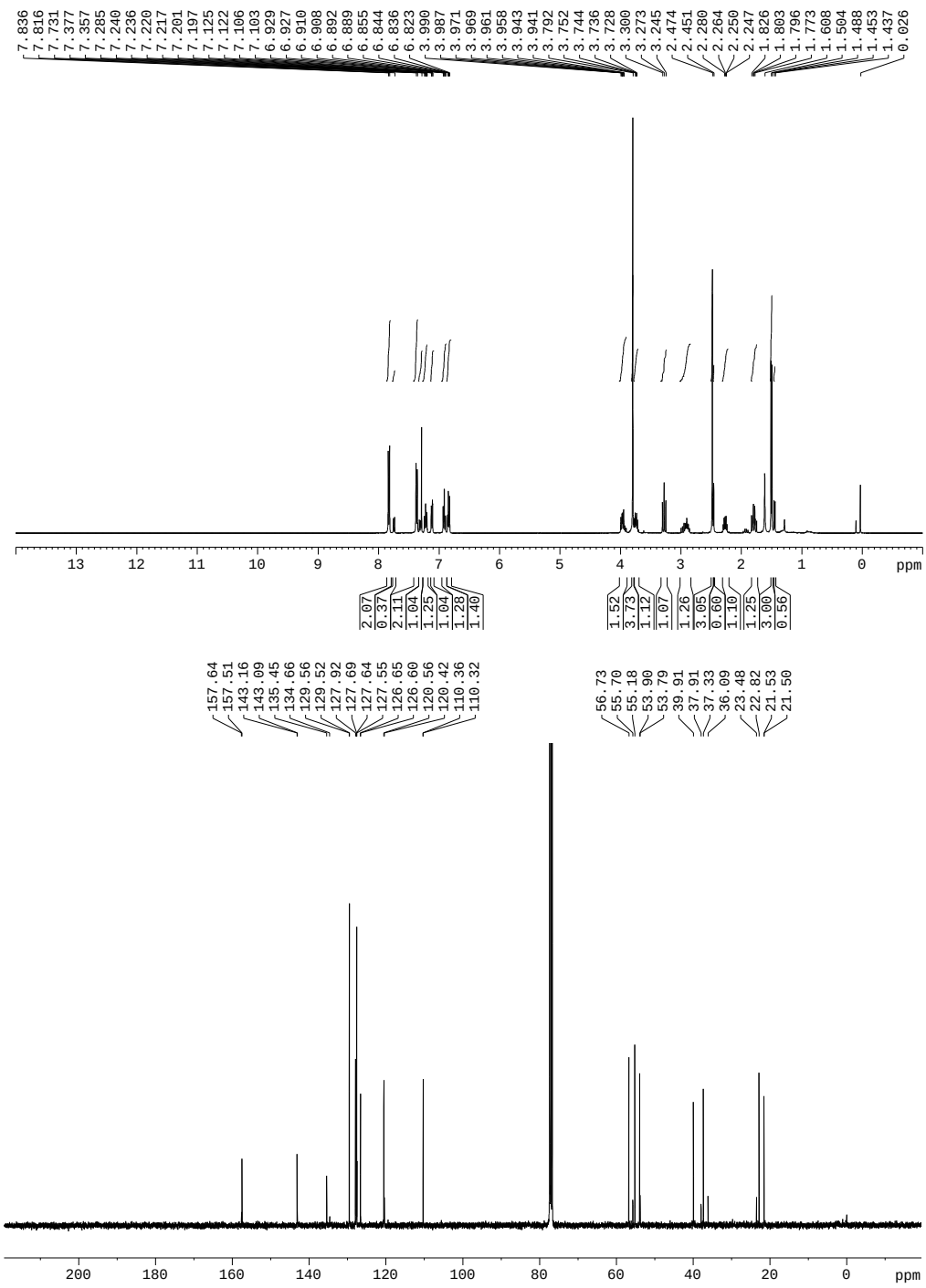


Figure-27: ^{1}H and ^{13}C NMR spectra of the product **139cb**.

4.3 Mechanistic Insights

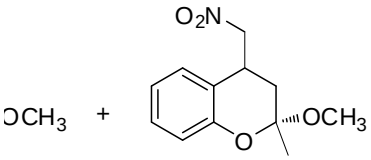
The reaction catalyzed by **34x**/Ph_2CHCO_2H proceeds via an enamine mechanism (see eq. 26). While considering the favorable transition state for diamine **34j** catalyzed reaction (Table 4, entries 4 and 5), the observed stereochemistry of the product states that the enamine approaches 2-(2-nitrovinyl)phenol **82** through the less hindered *Re* face as shown in **TS-1**. In the case of **34x**/Ph_2CHCO_2H-catalysis, the observed opposite selectivity may be explained by model **TS-2**. In **TS-2**, there are favorable electrostatic interactions, (i) between the partially positive nitrogen of quinine and the partially negative nitro group, (ii) between the partially positive phenolic OH and the partially negative quinine OMe (eq. 26). The observed stereochemistries of the products **126** could be explained by the enamine approach to 2-(2-nitrovinyl)phenol **82** through less hindered *Si* face (**TS-2**, eq. 26).

4.4 Conclusions

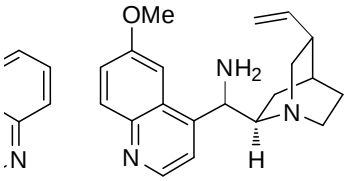
In summary, first time 9-amino-9-deoxyepiquinine **34x**/Ph_2CHCO_2H-catalyzed asymmetric SMA reaction of acetone with 2-(2-nitrovinyl)phenols was developed under ambient conditions. The sequential asymmetric reaction proceeds in good yields with high selectivity using **34x**/Ph_2CHCO_2H as the catalyst. The advantage of neighboring group participation by phenolic OH was shown to increase the reactivity and also participate in further cascade processes. Furthermore, the application of chiral δ-hydroxyketone↔lactol products **126**/**127**/**128** in the synthesis of highly functionalized chroman and pyrrolidine molecules has been demonstrated.

ANNEXURE-II: Further Optimization of SMA Reaction, Organocatalytic Synthesis of Substituted 2-(2-nitrovinyl)phenols 82 and Synthesis of Racemic SMA Products 129ba-fb and 130ba-fb.

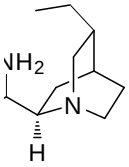
Table A1: Further Optimization of SMA Reaction of **32a**, **82c** and **113a**.



130ca



34z



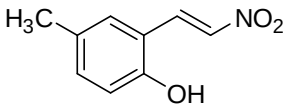
ab

e	Products yield (%)[a]		ee (%)[b]	
	129ca	**130ca**	**129ca**	**130ca**
	42	43	60	58
	44	46	49	52
	47	42	64	64
	19	11	64	64
	49	42	39	38
	47	36	75	72
	–			–
	32	25	70	76

(*Contd.*).

Table A1: Further Optimization of SMA Reaction of **32a**, **82c** and **113a**. (*Contd.*).

Table A2: Synthesis of Substituted 2-(2-nitrovinyl)phenols **82**.[a]

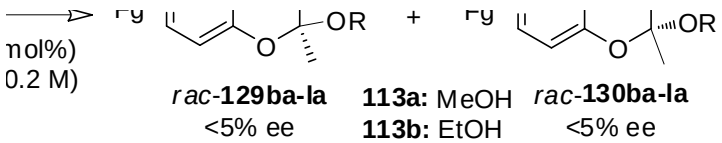


61% (82l)[b]

---

s and conditions for **Method-A:** To a mixture of 2-
e (15 mmol) in dry DCM (20 mL), added activated
mol%) and stirred at rt overnight. [c] Reagents and
enzaldehydes **37** (3 mmol) and nitromethane (15
nd refluxed for 45 min.

Table A3: Synthesis of Racemic SMA Products **129** and **130**.[a]



Products **129/130**	Ratio[b] (**129/130**)	Products yield (%)[c] **129**	**130**
129ca/130ca	1:1	46	46
129da/130da	99:1	82	<1
129ea/130ea	1:1	44	44
129ba/130ba	1:1	44	44
129fa/130fa	1:1	46	46
129ga/130ga	1:1	40	40
129ha/130ha	1:1	42	42
129ia/130ia	1:1	45	45

Table A3: Synthesis of Racemic SMA Products **129** and **130**.[a] (*Contd.*)

5. Asymmetric Supramolecular Catalysis: A Bio-Inspired Tool for the High Asymmetric Induction in the Enamine-Based Michael Reactions

5.1 Introduction

The early discovery of L-proline as a small asymmetric catalyst initiated a new era in asymmetric synthesis.[12] There are a considerable range of asymmetric reactions, effectively catalyzed by L-proline reported in last decade, however, it has some limitations. Although the design and synthesis of proline like molecules has emerged as alternate route to achieve high enantioselectivity, these catalysts also have some limitations. Because when the well-defined catalytic conditions are applied to substrates with additional functionality in known reactions, they fail to give the product with desired selectivity.[1c]

Recently, the Barbas and other research groups developed the amine-catalyzed asymmetric Michael reaction of ketone/aldehyde with simple nitrostyrene to give the Michael adducts with high enantioselectivities through enamine activation.[39,13,33] As a part of our research for the synthesis of the highly functionalized chiral Michael adducts for synthetic applications, when the enamine-based Michael reaction of functionalized 2-(2-nitrovinyl)phenols with cyclohexanone was performed under known conditions, low yields were obtained.

As a continuation of Michael addition of acetone to 2-(2-nitrovinyl)phenols[1b], when the reaction was tested with cyclohexanone **32b** as the donor under the optimized conditions established in the previous chapter, the results were not much impressive (Table 6). When 20 mol% of 9-amino-9-deoxyepiquinine **34x** with co-catalyst $PhCO_2H$ was used for the reaction of **82c** with 5 equiv of **32b** under neat conditions in 72 h, it resulted the Michael adduct **140cb** (Table 6, entry 1). For the clear understanding of selectivity, the crude **140cb** was either subjected to reductive etherification conditions with triethylsilane and $BF_3{\cdot}OEt_2$ at -10 °C to 25 °C for 2 h (**Method-A**)[40] or dehydration conditions with $BF_3{\cdot}OEt_2$ at 0 °C to 25 °C for 0.5 h (**Method-B**). When the Michael adduct in entry 1 was subjected to **Method-A**, it resulted **141cb** with 90% yield, 85% de and 94% ee (Table 6, entry 1). The higher catalyst loading and longer

reaction times of this condition required further optimization. No improvement in ee and de was obtained even after screening a number of co-catalysts under neat conditions (Table 6, entries 3-5). Use of solvents like DCM also was not found to increase the selectivity, yet decreased the reactivity drastically (Table 6, entry 6).

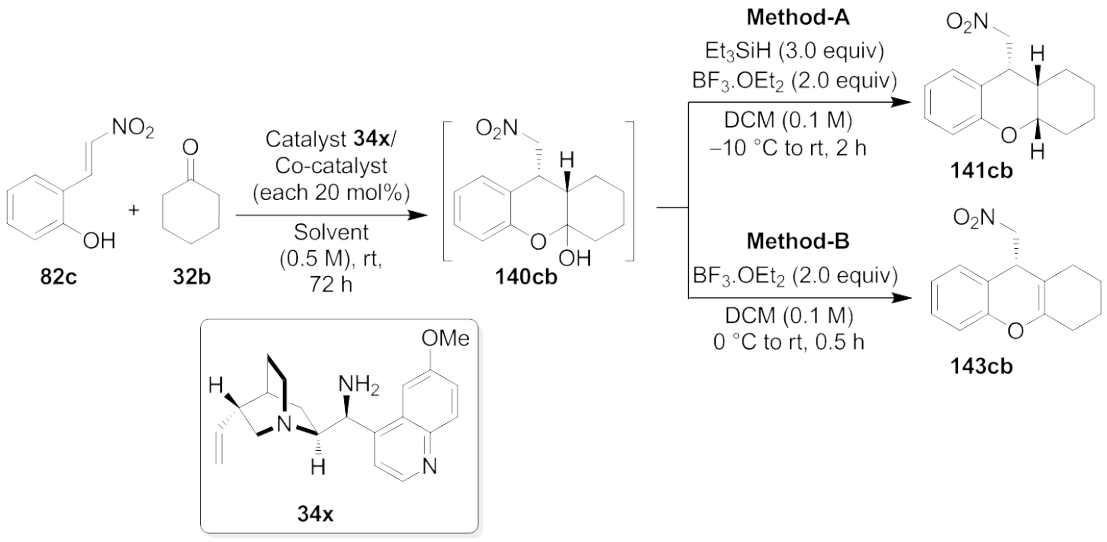


Table 6: Preliminary Optimization of Michael Reaction of **82c** with **32b**.[a]

Entry	Co-catalyst	Solvent	Method	Product yield (%)[b] **141cb** or **143cb**	de (%)[c]	ee (%)[d]
1[e]	$PhCO_2H$	Neat	A	90	85	–94
2[f]	$PhCO_2H$	Neat	B	86	–	–86
3	$2\text{-}FC_6H_4CO_2H$	Neat	B	92	–	–84
4	Naphthoic acid	Neat	B	82	–	–87
5	Ph_2CHCO_2H	Neat	B	90	–	–70
6[g]	$PhCO_2H$	DCM	B	–	–	–

[a] Unless otherwise stated, all reactions were carried out with 2-(2-nitrovinyl)phenol **82c** (0.5 mmol), cyclohexanone **32b** (2.5 mmol, 5.0 equiv), catalyst **34x** with co-catalyst (20 mol% each) in solvent mentioned at rt. [b] Yield refers to the column-purified product after 2 steps. [c] de was determined based on ^1H NMR or HPLC analysis. [d] ee was determined by CSP HPLC analysis. [e] Minor diastereomer was obtained in 51% ee. [f] 10.0 equiv of cyclohexanone **32b** was used. [g] Conversion was less than 10% through TLC.

To overcome this problem, it was envisioned that the reaction has to go through a rigid pre-transition state (pre-TS) assembly, in which all the active functional groups of substrates and catalysts should get involved. Thus, by assembling the suitable chiral catalysts with substrates through combination of covalent and weak interactions, one can possibly build up asymmetric supramolecular environment for high asymmetric induction through the stable pre-TS assembly (Figure-28). This new paradigm of catalysis seems to be beyond organocatalysis, predicted to be a bio-mimetic supramolecular catalysis.[41]

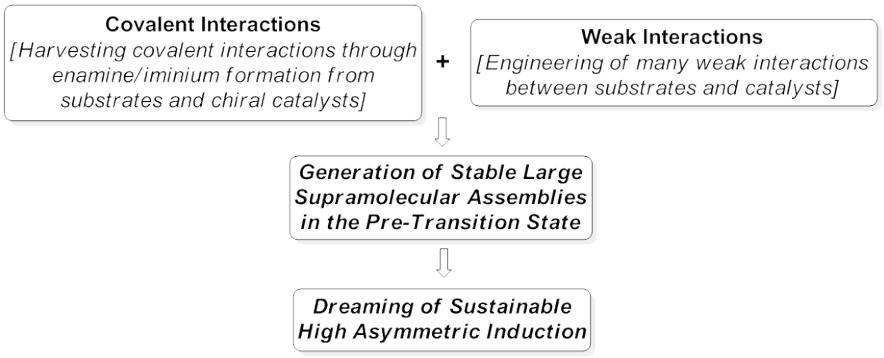


Figure-28: Proposal for asymmetric supramolecular catalysis.

5.2 Results and Discussions

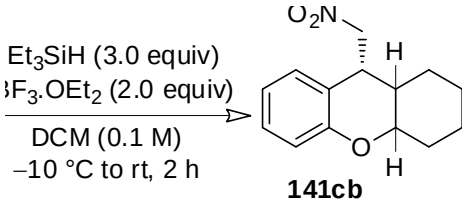
5.2.1 Reaction optimization to study the supramolecular catalysis:

To verify this hypothesis of pre-TS supramolecular assembly, based on our previous experience,[41a] the Michael reaction of 2-(2-nitrovinyl)phenol **82c** with 7 equiv of cyclohexanone **32b** was carried out in the presence of each 5 mol% of D-proline *ent*-**34a** and quinine-*N*H-thiourea **34i** in dichloromethane (DCM) at 25°C. Surprisingly, within 5 h, the reaction yielded 1:1 ratio of lactol products (+)-**140cb*** in quantitative yield with 97% enantiomeric excess (ee) and 92–95% diastereomeric excess (de) at the Michael reaction stage as shown in Figures-29 to 30 (Table 7, entry 1). For the clear understanding of selectivity, the crude **140cb** was then subjected to reductive etherification conditions with triethylsilane and $BF_3 \cdot OEt_2$ at -10 °C to 25 °C for 2 h.[40] To our delight, the reductive etherification product (-)-**141cb*** was isolated in 90% yield with 94% de and >99% ee (Table 7, entry 1). This result gave inspiration to start believing that there is a highly organized supramolecular assembly in the Michael reaction pre-TS, which is responsible for the highest enantioselectivity. Interestingly, the lactols **140cb** were isolated in 92–95% de at the Michael reaction stage, but were found to get enriched to >99% de after the reductive etherification reaction may be due to the decomposition or hydrolysis of minor isomer of lactols **140cb**.

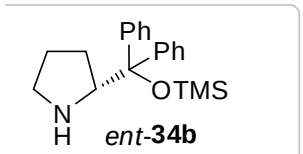
---

*In the compound representation **140xy** and **141xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes ketone component **32**.

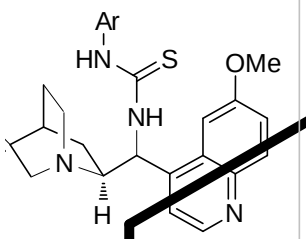
Table 7: Reaction Optimization to Study the Asymmetric Supramolecular Catalysis.[a]



141cb



ent-**34b**



34a–e

	(%)[b]	de (%)[c]	ee (%)[d,e]
		94	>99
		98	–96
		88	80
		93	97
		94	**>99**
		–	–
		–	–
		–	–
		–	–

with 2-(2-nitrovinyl)phenol **82c** (0.5 nd **34** (5 mol% each) in DCM at rt. [b] as determined based on ^{1}H NMR or In all entries except entry 3, minor ier in entry 3 is 57%. [f] 7.0 equiv of ated brine solution. [h] 20 mol% of *ent*-

To further understand the direction of hypothetical pre-TS supramolecular assembly, the Michael reaction was performed with opposite catalysts combination of L-proline **34a** and

quinidine-*N*H-thiourea **34ad**. The reaction yielded the anticipated opposite enantiomer of (+)-**141cb*** in 86% yield after two steps with a little compromise in enantioselectivity of 96% ee and 98% de (Table 7, entry 2). When the catalyst combination is shuffled to be L-proline **34a** and quinine-*N*H-thiourea **34i**, there was a strong mismatching of catalysts observed to deliver the product **141cb** in moderate ee (80%) and de (88%) taking a longer reaction time (Table 7, entry 3). Replacing the quinine-*N*H-thiourea **34i** with hydroquinine-*N*H-thiourea **34ae** in catalyst combination of *ent*-**34a**/**34i** for sequential Michael reaction/reductive etherification reaction was not found to give superior results (Table 7, entry 4).

Employing five equiv of cyclohexanone **32b** under *ent*-**34a**/**34i** catalysis followed by reductive etherification gave the product (-)-**141cb** in 90% yield with 94% de and >99% ee, same as entry 1, in which seven equiv of cyclohexanone **32b** was used (Table 7, entry 5). The use of 1.5 equiv of cyclohexanone **32b** took longer reaction time (72 h), resulted **141cb** with reduced yield (26%), yet maintained the de (98%) and ee (>99.9%) (result not shown in Table 7). Interestingly, the precatalyst assembly components *ent*-**34a** or **34i** were not effective in promoting the Michael reaction separately (Table 7, entries 6 and 7). Instead of D-proline *ent*-**34a**, when acyclic amino acid (D-phenylglycine) was used, the reaction was found to be not proceeding at all (result not shown in Table 7). As a further support to the hypothetical pre-TS supramolecular assembly, when the same Michael reaction was carried out under known Michael reaction conditions, no product formation was observed even after 72 h (Table 7, entries 8 and 9).

*In the compound representation **141xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes ketone component **32**.

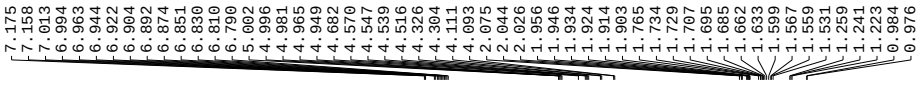
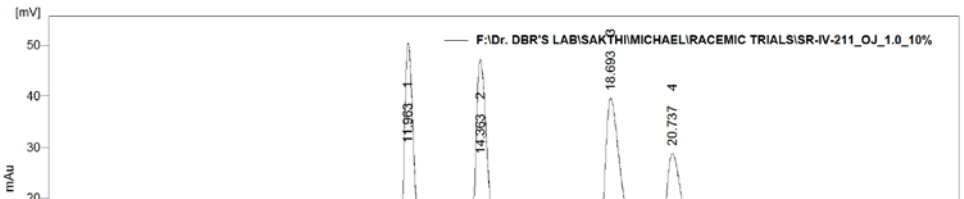


Figure-29: ^{1}H and ^{13}C NMR spectra of the product **140cb**.

Racemic **140cb**:



Chiral **140cb** (97% ee):

Figure-30: HPLC of the product **140cb**.

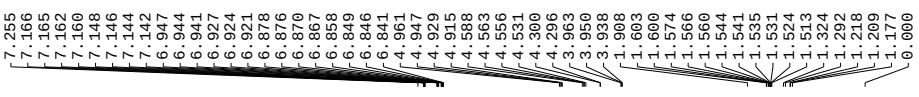


Figure-31: ^{1}H and ^{13}C NMR spectra of the product **141cb**.

5.2.2 Controlled experiments to test the neighboring ortho-hydroxyl group participation and supramolecular catalysis:

The possible pre-TS supramolecular assembly (generated by multiple interactions) described here stands different from the dual or cooperative activation[42] and is cross examined by the controlled experiments as shown in Scheme 4. It is proven from the fact that a modification in the pre-TS assembly by decreasing possible hydrogen bonding interactions between carbonyl group of D-proline *ent*-**34a** and *ortho*-phenolic OH group disturbs the hypothetical cyclic supramolecular assembly and diminishes ee of the reactions (Scheme 4). Obtaining very poor ee values of Michael reaction products **142bb-db** from the reaction of **92b–d** with **32b** under the *ent*-**34a**/**34i** catalysis proves that hydrogen bonding activation between *ortho*-phenolic OH group of 2-(2-nitrovinyl)phenol (**82**) and carbonyl group of D-proline (*ent*-**34a**) is crucial in determining the ee of the Michael reaction.

Scheme 4: Controlled Experiments to Prove the Involvement of Supramolecular Assembly for High Asymmetric Induction.

5.2.3 Experimental evidence for supramolecular catalysis through ESI-HRMS:

An evidence for the existence of stable pre-TS supramolecular assembly has been given through careful investigation of the Michael reaction of **82c** and **32b** under the *ent*-**34a**/**34i** catalysis by using electrospray ionization with high-resolution mass spectrometry (ESI-HRMS) technique, which made possible to identify all critical proposed catalytic intermediates (Figure-32). The ESI-HRMS spectrum of an on-going reaction of **82c** and **32b** (5 equiv) in the presence of *ent*-**34a**/**34i** (each 10 mol%) in DCM at 25 °C showed the presence of [**140cb**·Na^+] (m/z 286.1043) and [**143cb**·H^+] (m/z 246.1135), and the formation of the key catalytic intermediates [**A**·H^+] (m/z 361.1777) and [**B**·H^+] (m/z 955.3651). Interestingly, catalytic pre-TS assembly ions [**A**·H^+] and [**B**·H^+] were observed from the first moments of reaction (see Scheme A1, Annexure-III for HRMS experiment details).[43]

Figure-32: The ESI-HRMS (positive mode) spectrum of the reaction of **82c** and **32b** catalyzed by *ent*-**34a**/**34i** in DCM at rt after 120 min.

Figure-33: a) The observed ESI-HRMS isotopic pattern of pre-TS intermediate [**B**+H]$^+$. b) The simulated ESI-HRMS isotopic pattern of pre-TS intermediate [**B**+H]$^+$.

5.2.4 Mechanistic Insights:

With controlled experimental results in hand, the mechanism of asymmetric Michael reaction through cyclic 19-membered pre-TS assembly by *ent*-**34a**/**34i** catalysis has been proposed as follows. The reaction most likely proceeds through the mechanism, where TS-3 is involved (Figure-34). Herein, four important interactions are observed among the substrates and the catalysts to favor a cyclic 19-membered pre-TS assembly (TS-3) to give the highly enantioselective Michael reaction product over the simple acyclic pre-TS (TS-4). According to our observations, 1) carboxylic group of D-proline undergoes proton exchange with quinoline moiety of quinine-*N*H-thiourea, thus bringing the electronic and steric environment closer to the reaction center; 2) two *N*H groups of quinine-*N*H-thiourea engage themselves in hydrogen bonding with NO_2 group of 2-(2-nitrovinyl)phenol to activate the electrophilic nature; 3) secondary amine group of D-proline forms *syn*-enamine[44,33e,33d] with cyclohexanone to activate the nucleophilic nature; 4) phenolic OH group of 2-(2-nitrovinyl)phenol protonates carbonyl group of D-proline, thus closing the rigid 19-membered supramolecular cyclic pre-TS to control the facial selectivity (see Figure-34).

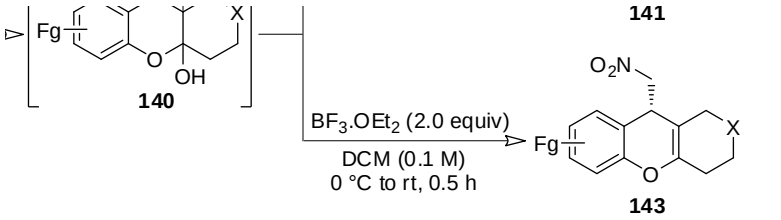
Figure-34: Proposed reaction mechanism through pre-TS supramolecular assembly.

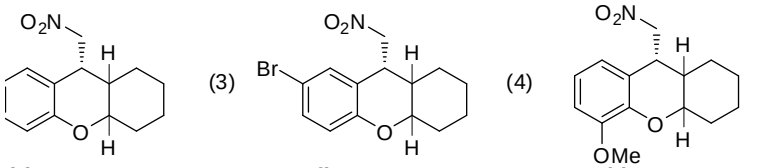
5.2.5 Scope of asymmetric supramolecular catalysis:

The generality of the asymmetric supramolecular catalysis was further supported by reacting a series of substituted 2-(2-nitrovinyl)phenols **82b-l** with five equiv of functionalized cyclohexanones **32b,e-g** and acetone **32a** catalyzed by 5 mol% of *ent*-**34a**/**34i** at 25 °C in DCM for 5 h followed by reductive etherification on crude products **140** with triethylsilane and $BF_3 \cdot OEt_2$ at -10 °C to 25 °C for 2 h (Table 8). The chiral products **141bb–cf*** were isolated in excellent yields, de and ee values, tolerating the electronic and steric influence of the substrates. Interestingly, treatment of 2-(2-nitrovinyl)phenol **82c** with simple acetone **32a** also gave the expected chiral product **141ca** in 93% yield with >99% de and 94% ee after two sequential reactions as shown in Table 8, entry 10. Due to the structural importance of chromene moiety in medicinal chemistry, the crude products **140** were treated only with $BF_3 \cdot OEt_2$ to influence the dehydration reaction and a series of chromenes **143cb–cg*** were isolated in excellent yields and ee values. When tetrahydro-4*H*-pyran-4-one (**32f**) was used in the sequential Michael reaction and reductive etherification reaction, the dehydration reaction of **140cf** was found to influence over the reductive etherification reaction (Table 8, entry 11). The structure and absolute stereochemistry of the Michael products **140**, reductive etherification products **141**, and chromenes **143** were confirmed by NMR spectroscopy analysis and also finally confirmed by correlation of specific rotation reported[45,44c] with Michael reaction derived product (-)-**142bb** and X-ray diffraction structural analysis on (-)-**141fb** as shown in Scheme 5 and Figure-35.[46]

*In the compound representation **141xy-143xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes ketone component **32**.

Table 8: Scope of Asymmetric Supramolecular Catalysis.[a-d]





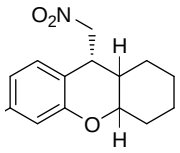
1bb: 75% yield
87%; ee 98%

(3)

141fb: 78% yield
de 94%; ee 99%

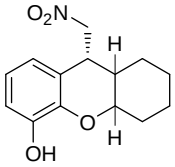
(4)

141hb: 74% yield
de 95%; ee 90%



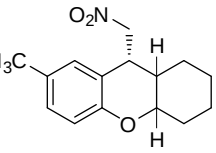
1jb: 69% yield
91%; ee 99%

(7)

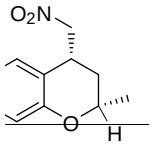


141kb: 74% yield
de >99%; ee 97%

(8)

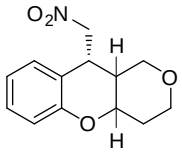


141lb: 94% yield
de 90%; ee 97%



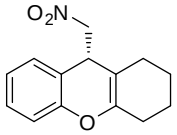
1ca: 93% yield
>99%; ee 94%

(11)[f]

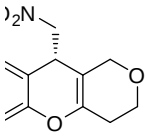


141cf: 68% yield
de >99%; ee >99%

(12)

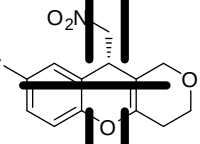


143cb: 87% yield
ee 98%



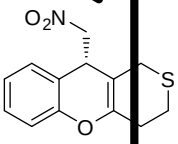
3cf: 82% yield
ee 98%

(15)



143ff: 8[illegible]% yield
ee 96%

(16)[e]



143cq: 72% yield
ee 99%

were carried out with 2-(2-nitrovinyl)phenol **82** (0.5 mmol), cyclohexanone **32** a and **34i** (5 mol% each) in DCM at rt for 5 h. [b] Yield refers to the column- determined by ^{1}H NMR or HPLC analysis. [d] ee was determined by CSP HPLC on was 24 h. [f] Compound **141cf** was accompanied with **143cf** in 1:1 ratio.

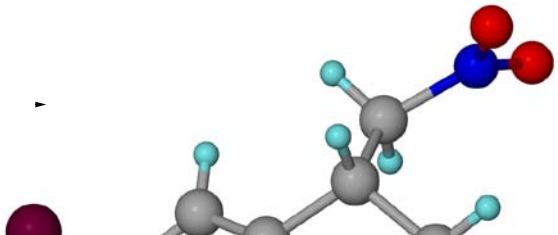


Figure-35: X-ray crystal structure of chiral (–)-7-bromo-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (**141fb**).

Scheme 5: Determination of absolute configuration by comparing with literature.

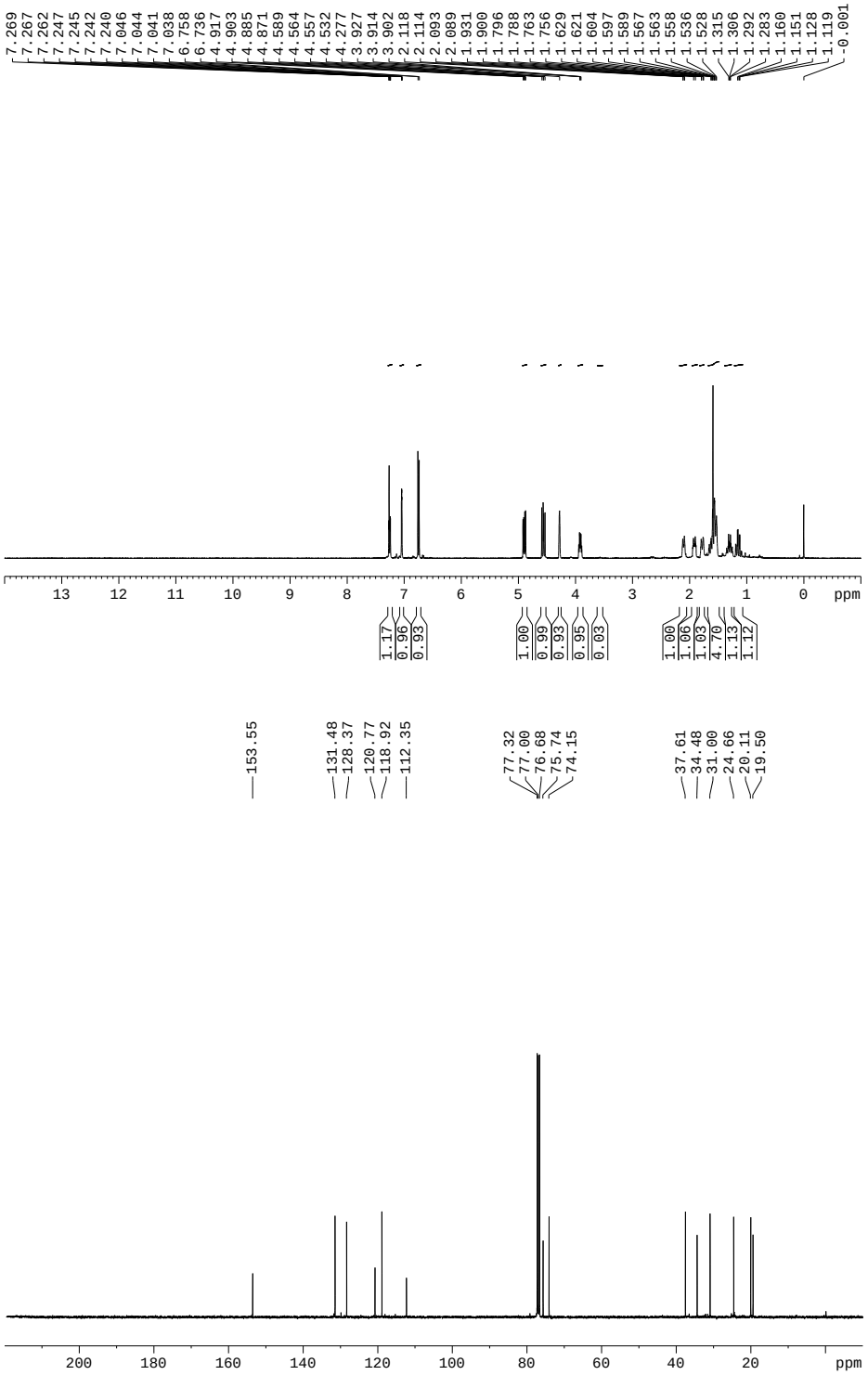


Figure-36: ^{1}H and ^{13}C NMR spectra of the product **141fb**.

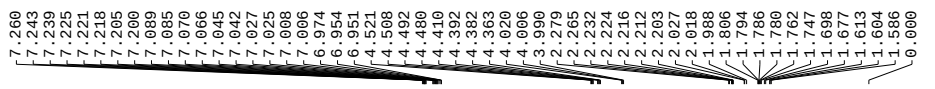


Figure-37: ^{1}H and ^{13}C NMR spectra of the product **143cb**.

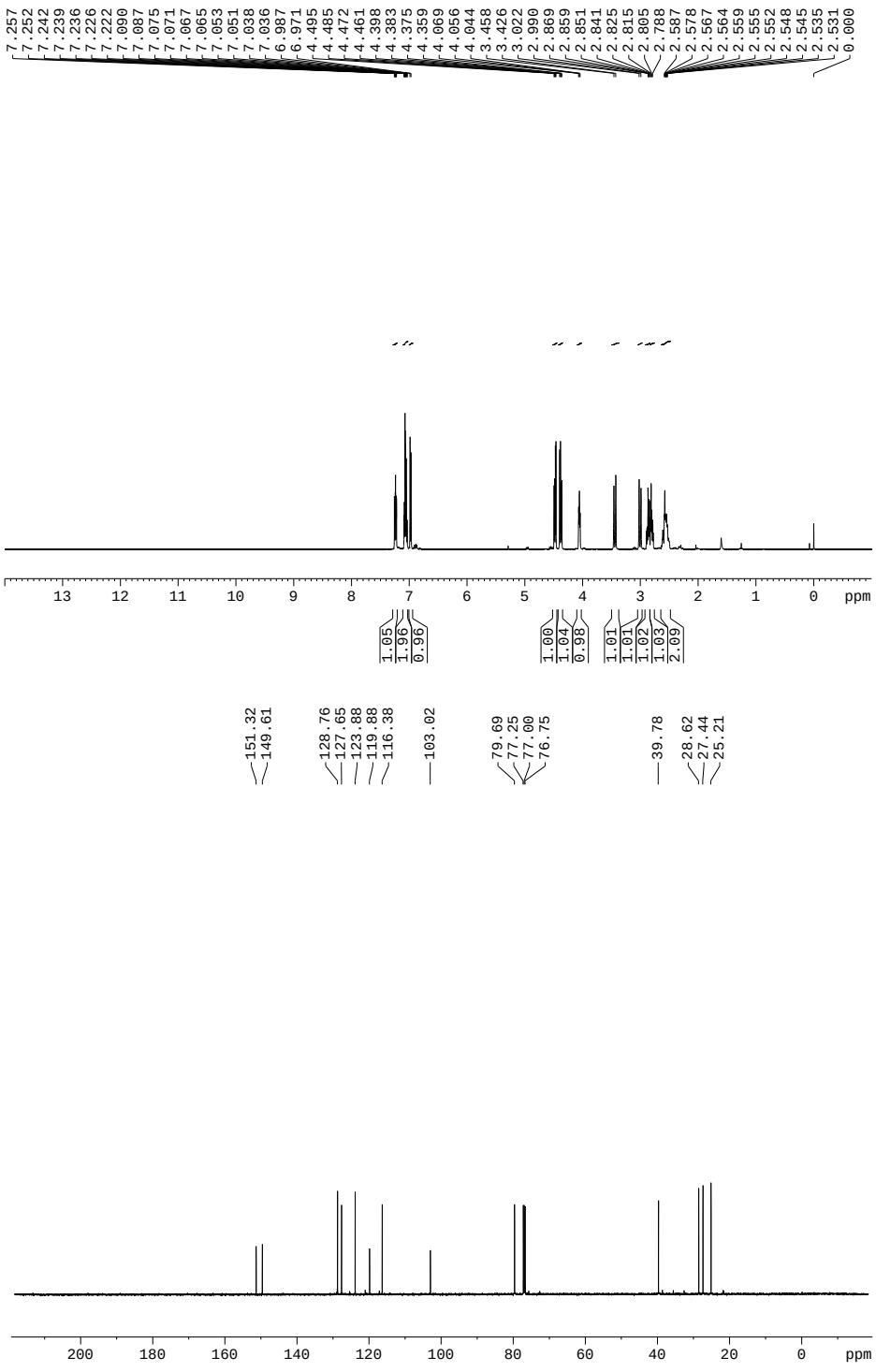


Figure-38: ^{1}H and ^{13}C NMR spectra of the product **143cg**.

5.2.6 Synthetic applications of chiral Michael adducts:

To explore the utility of the chiral lactols **140**, lactols were subjected to simple reduction followed by spiro etherification protocol to give the analogues of antifungal drug griseofulvin (eq. 27).[47] Fascinatingly, Lewis-acid induced dehydration on chiral diol (+)-**144cb*** (75% de and 99% ee) obtained from (+)-**140cb** resulted in spiroetherification of major (*R*,*S*,*S*)-diol to spiro compound (+)-**145cb** in 73% yield with 98% ee. Perhaps, this selective spiroetherification of (*R*,*S*,*S*)-diol **144cb** may be due to the antiperiplanar orientation of hydrogen (hydride) α to the leaving secondary OH group during water elimination, leading to the formation of the spiro compound **145cb** in 73% yield without racemization. The selective reduction/spiroetherification strategy was demonstrated with one more substrate, **140fb** to (+)-**145fb** in 65% yield with 97% ee (eq. 27). Interestingly, Brønsted acid *para*-toluenesulfonic acid (*p*-TSA)-catalyzed dehydration reaction of (+)-**144cb** at reflux in benzene for 48 h gave the inseparable mixture of **145cb** and **141cb** in the ratio of 5:1 with an overall yield of 64% without racemization (Scheme 6). The spiro compounds **145** are structural analogues of orally used antifungal drug griseofulvin,[47] which highlights the importance of sequential reduction/spiroetherification approach to synthesize these medicinally important analogues compounds.

*In the compound representation **140xy**, **144xy** and **145xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes ketone component **32**.

Scheme 6: Cyclization of Diol **144cb** under *p*-TSA Conditions (isolated as inseparable mixture).

To further demonstrate the synthetic application of the chiral hexahydroxanthenes **141** in the heterocyclic compounds synthesis, (-)-**141cb** was successfully transformed into the azide (-)-**146cb** through the intermediacy of amine and finally to the triazole (-)-**147cb** under the click-reaction conditions without loss of selectivity (eq. 28).

*In the compound representation **141xy-147xy, x** denotes 2-(2-nitrovinyl)phenol component **82** and **y** denotes ketone component **32**.

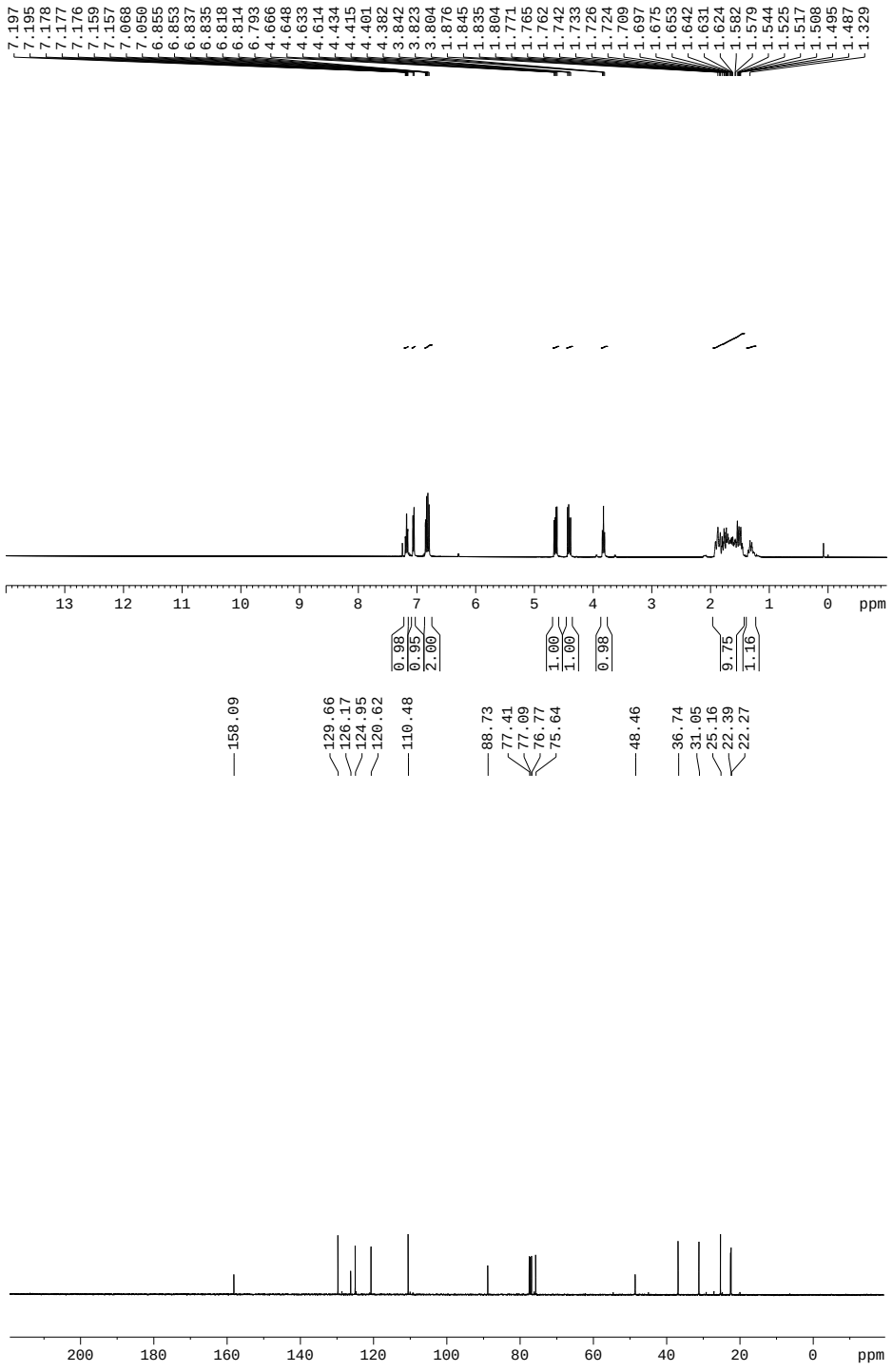


Figure-39: ^{1}H and ^{13}C NMR spectra of the product **145cb**.

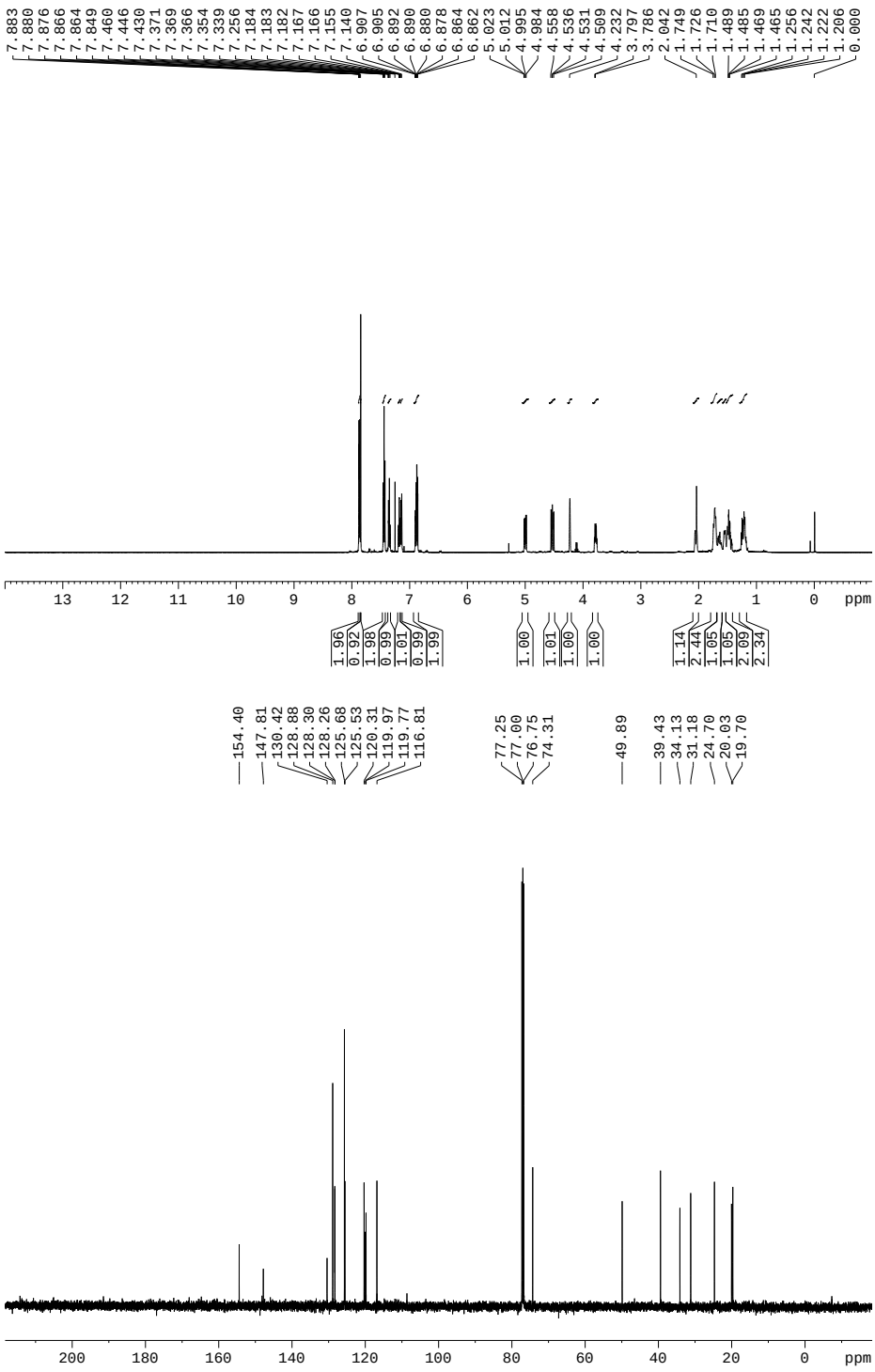


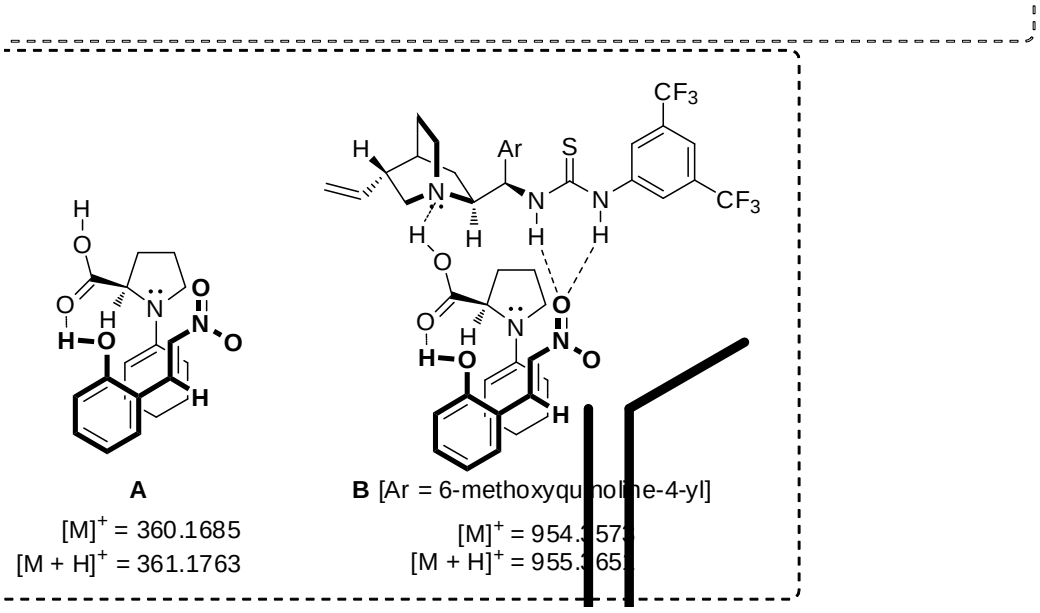
Figure-40: ^{1}H and ^{13}C NMR spectra of the product **147cb**.

5.3 Conclusions

In conclusion, a new and efficient supramolecular catalysis for the asymmetric Michael reaction of cyclohexanone with 2-(2-nitrovinyl)phenols to give the desired hexahydroxanthenols **140** with high yield, ee and de values has been reported, which were further applied in the chiral synthesis of medicinally important compounds. With ESI-HRMS technique, strong evidence to the existence of proposed 19-membered cyclic pre-TS supramolecular assembly has been given. Asymmetric supramolecular catalysis would become a promising future catalytic system for the functionalized substrates, as the examination of the potential ability of these catalysts would also reveal certain mechanistic insights into enzyme-catalyzed reactions.

ANNEXURE-III: Experimental details for the on-line monitoring of supramolecular-catalysis through ESI-HRMS; High-yielding synthesis of racemic products 140-147 and the optimization of dehydration reaction of 140cb.

Scheme A1: Experimental Details of the HRMS Experiment: Reaction of **82c** and **32b** in the Presence of *ent*-**34a**/**34i**.



For the detection of key intermediate species in ESI-HRMS spectra see Figures-A1 to A3.

Analysis Info

Analysis Name	D:\Data\2012\Dr.D.B.Ramachary 30min d	Acquisition Date	1/21/2012 9:39:49 AM
Method	tune_low_Pos.m	Operator	UOH
Sample Name		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	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

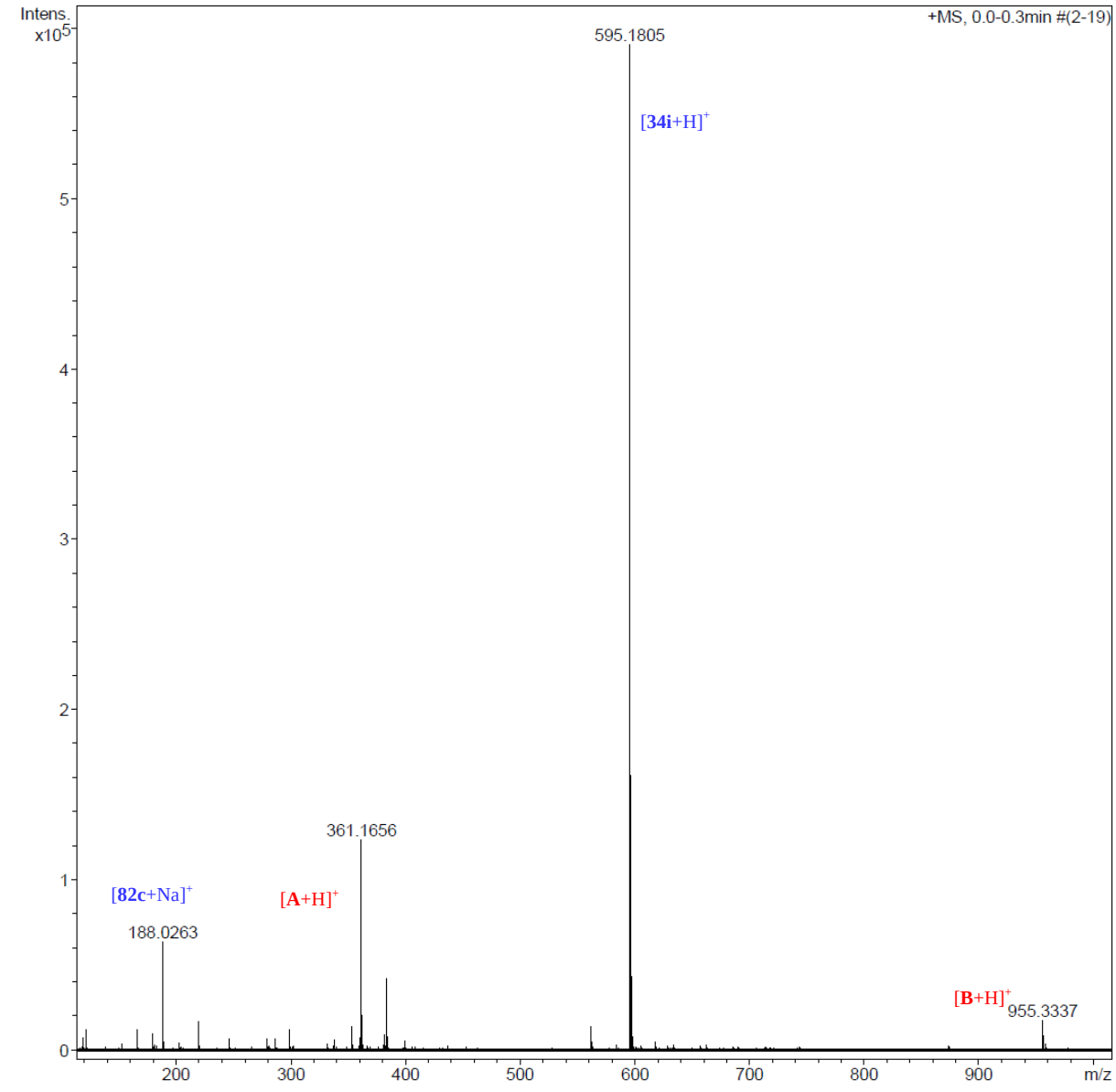


Figure-A1: The ESI-HRMS (positive mode) spectrum of the reaction of **82c** and **32b** catalyzed by *ent*-**34a**/**34i** in DCM at rt after 30 min.

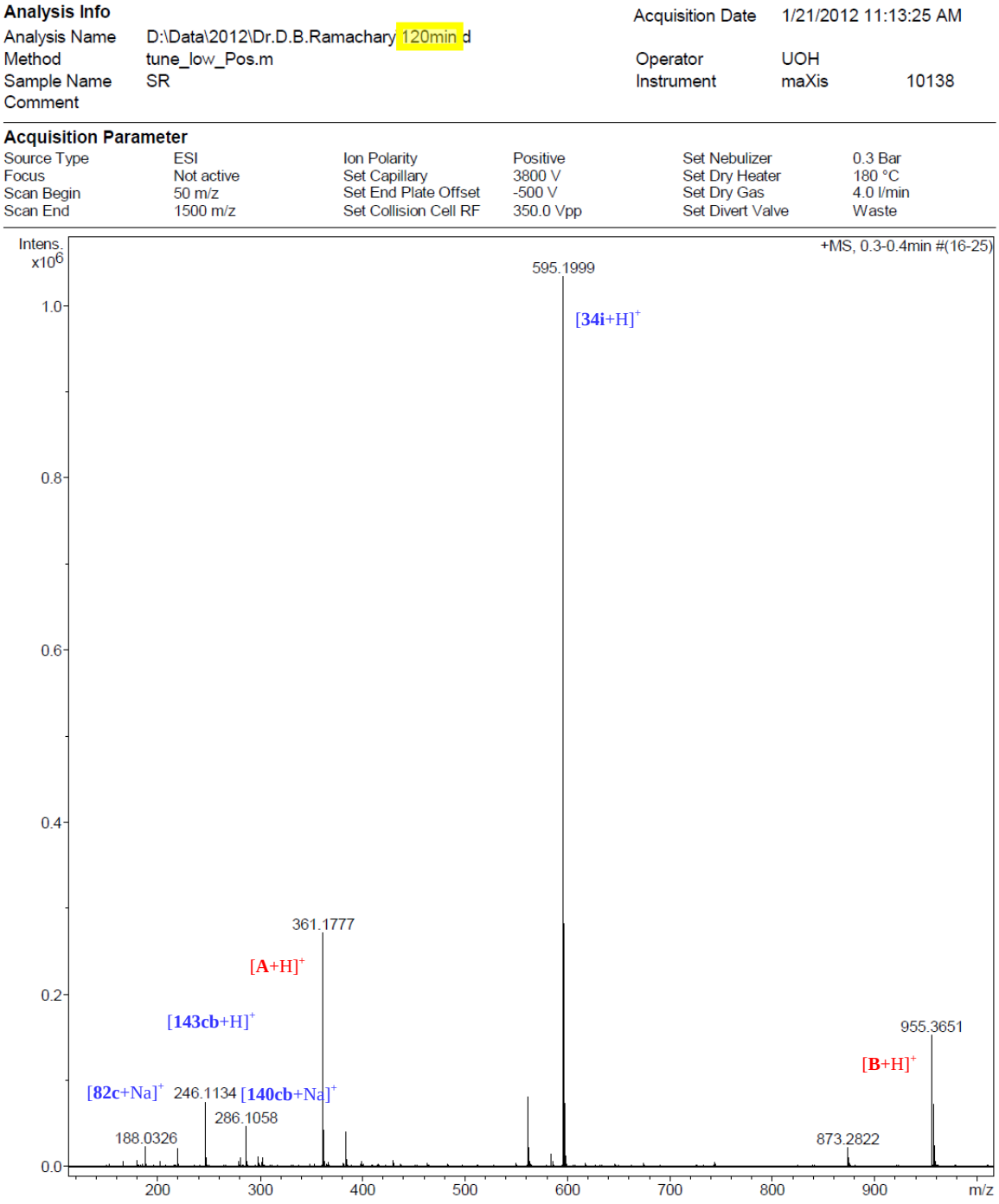


Figure-A2: The ESI-HRMS (positive mode) spectrum of the reaction of **82c** and **32b** catalyzed by *ent*-**34a**/**34i** in DCM at rt after 120 min.

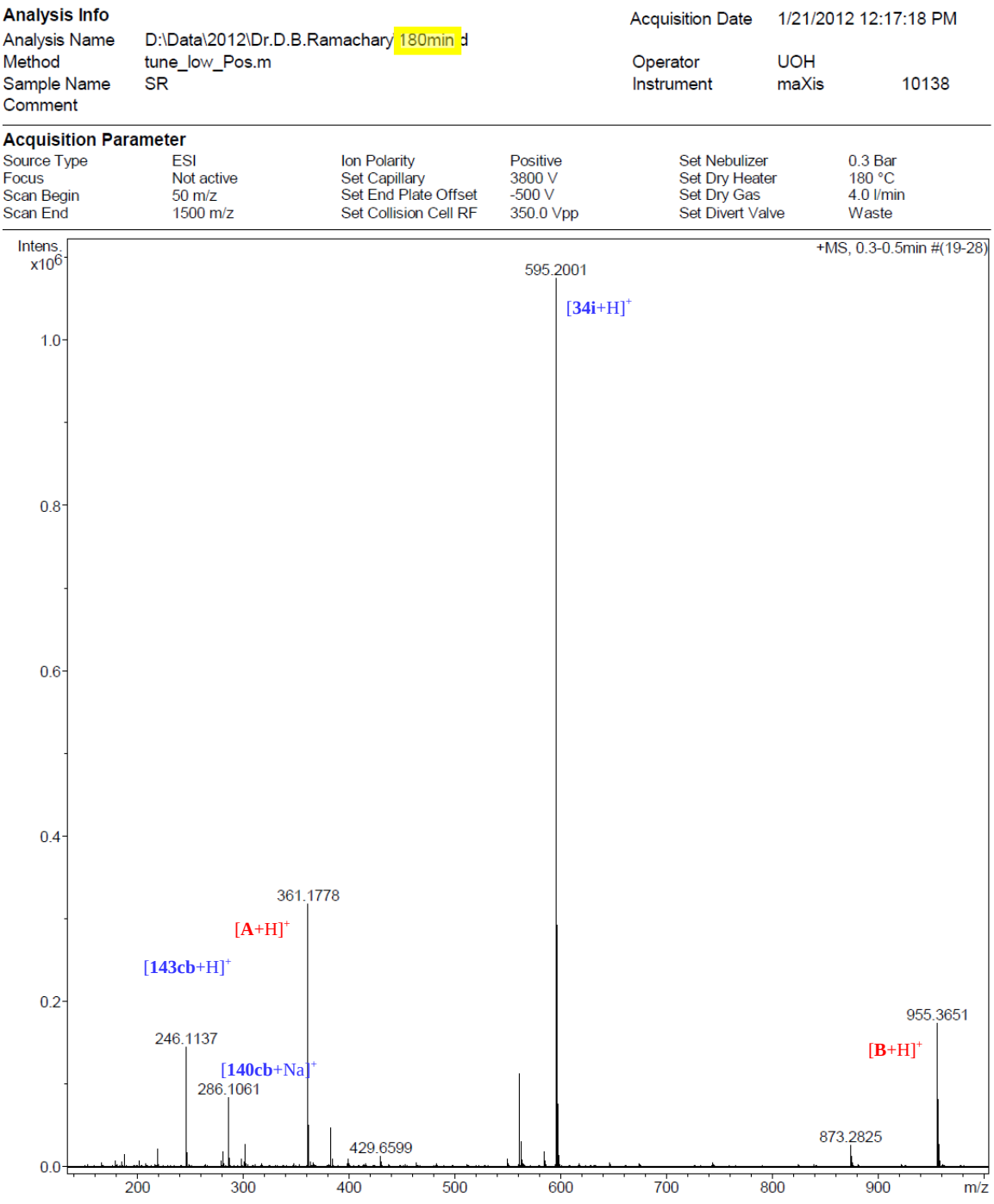
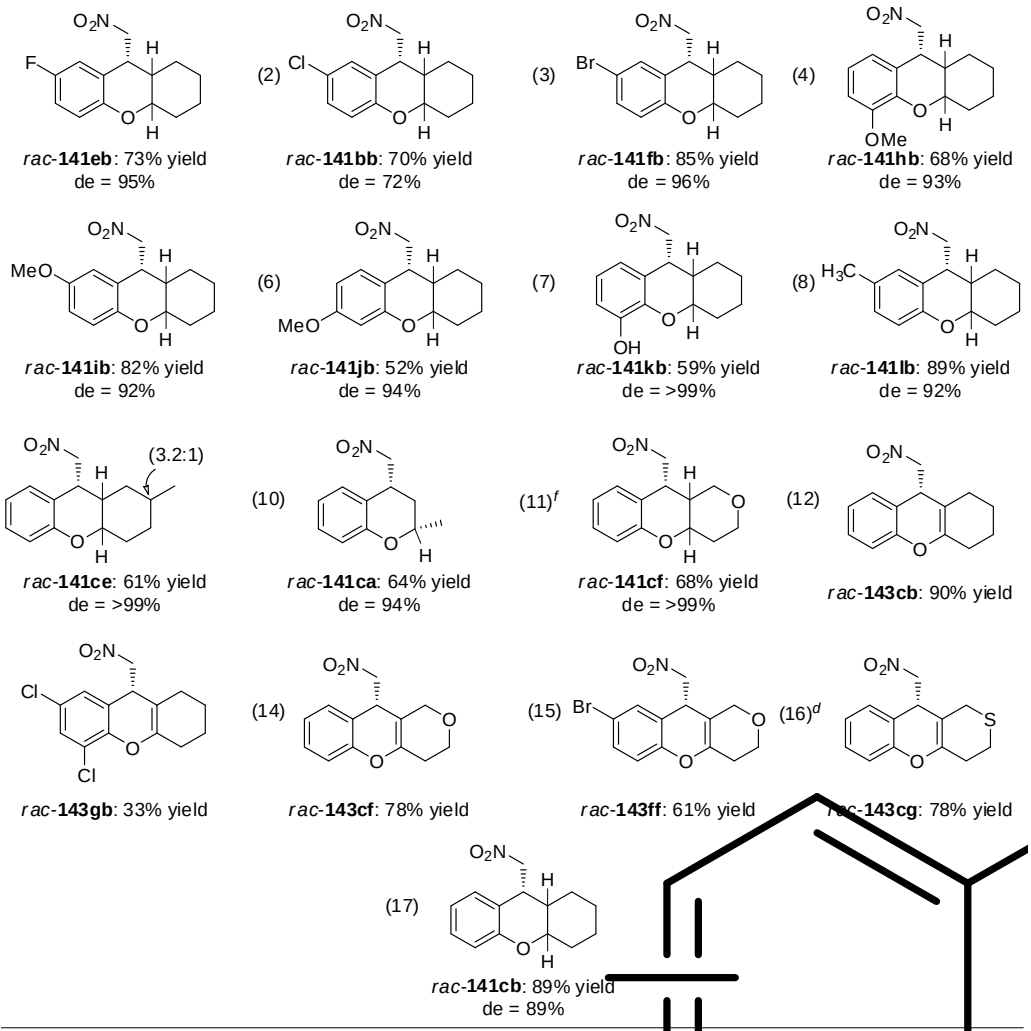


Figure-A3: The ESI-HRMS (positive mode) spectrum of the reaction of **82c** and **32b** catalyzed by *ent*-**34a**/**34i** in DCM at rt after 180 min.

Table A4: Optimization for Dehydration Reaction of **140cb**.

Scheme A2: Synthesis of Racemic Products **142**.

Table A5: Synthesis of Racemic Products **141** and **143**.[a-c]



[a] Unless otherwise mentioned, all reactions were carried out with 2-(2-nitrovinyl)phenol **82** (0.5 mmol), cyclohexanone **32** (2.5 mmol, 5.0 equiv), DL-proline (20 mol%) in DMSO at rt for 5 h. [b] Yield refers to the column purified product after 2 steps. [c] de was determined based on ^{1}H NMR or HPLC analysis. [d] Time taken for Michael reaction was 24 h. [e] unidentified minor diastereomer was also isolated in 9%. [f] *rac*-**141cf** was accompanied with *rac*-**143cf** in 1:1 ratio.

Scheme A3: Synthesis of Racemic Products **145**.

Scheme A4: Synthesis of Racemic Products **146** and **147**.

6. Mimicking Human Steroid 5β-Reductase (AKR1D1) through Organocatalysis: A Facile Route to Stereoselective Synthesis of Chiral 5β-Dihydrosteroids, 5β-Dihydro-Wieland-Miescher Ketones and 5β-Dihydro-Hajos-Parrish Ketones

6.1 Introduction

The enzyme 5β-reductase catalyzes the reduction of Δ^4-double bond of cholesterol and many steroid hormones bearing Δ^4-3-one moiety to 5β-dihydro-3-ones and thus plays a major role in the biosynthesis of bile acids and metabolism of many steroid hormones.[48] In contrast, the enzyme 5α-reductase influences the biology and physiology of mammalian species by catalyzing the reduction of testosterone to 5α-dihydrotestosterone.[48] Thus the difference between these two enzymes lies in the selective reduction of Δ^4-double bond leading to two distinct metabolisms.

In particular, 5β-reductase (Figure-41) has been the topic of research since many decades, as it plays a vital role in the bile acid homeostasis and its deficiency causes fatal effects like accumulation of bile acid intermediates in blood and urine.[49] In addition, it involves in the androgen, steroid hormone metabolic and cholesterol catabolic processes.[50] Chart 3 shows some important bile acids and steroid hormones which are synthesized *in vivo* through 5β-reductase catalysis.[51]

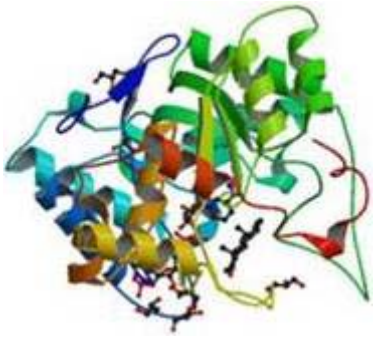
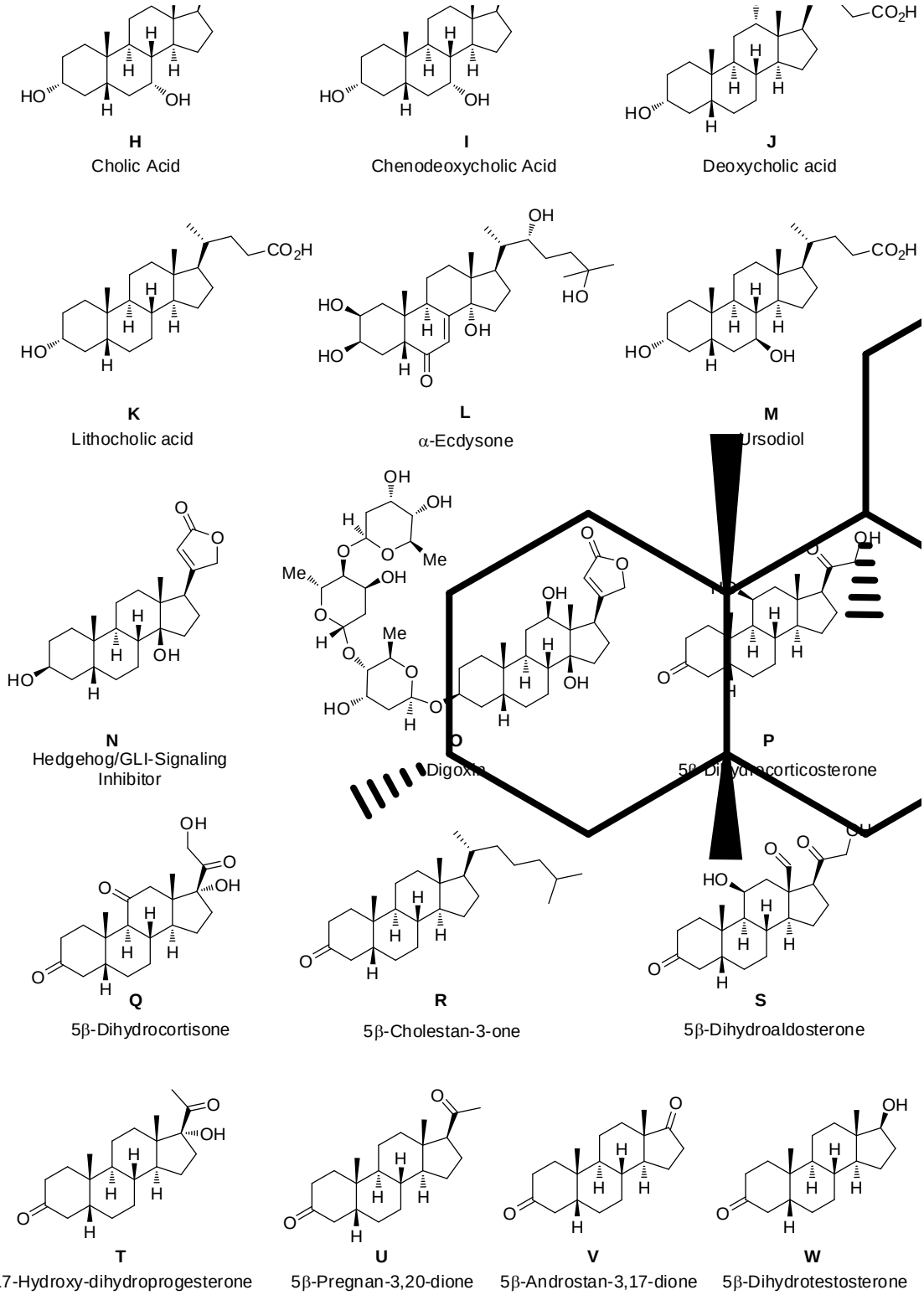


Figure-41: Human steroid 5β-reductase (AKR1D1) enzyme.

Chart 3: Biologically Active 5β-Dihydrosteroids Synthesized through Human Steroid 5β-Reductase Catalysis.



The mechanism proposed for *in vivo* 5β-reductase catalysis by Penning et al. explains the activation of C-3 carbonyl of Δ^4-3-ones by Tyr-58 residue, which has the ability to act as acid. This facilitates the hydride transfer from NADPH to C-5 through β face, which determines the construction of *cis*-A/B ring junction, and this is considered to be the rate determining step. Subsequent enzyme or solvent bound protonation of C-4 yields the reduced *syn*-product (Figure-42).[52]

Figure-42: Active site and reaction mechanism of human steroid 5β-reductase catalysis.

In the bile acid family, deoxycholic acid (DCA) plays a prime role in the absorption of fats in intestine and it has been used as drug in a range of medicines.[53] Interestingly, DCA is an attractive component not only in medicinal chemistry, but also in nanotechnology and microlithography fields.[54] The *in vitro* synthesis of DCA involves a decisive step of fixing the A-B ring junction to *cis* which is thermodynamically less stable.

Commercially available hydrocortisone or adrenosterone are the two important precursors to commence with the synthesis of DCA as shown in Scheme 7. The primary step in the synthetic strategy of DCA involves the stereoselective reduction of hydrocortisone or

adrenosterone to thermodynamically less stable *cis*-A/B configuration. Surprisingly, only quite a few number of patents or papers are available for the selective reduction, using drastic conditions resulting moderate selectivity.[55] To achieve a fruitful synthesis of DCA, the Δ^4-double bond has to be reduced stereoselectively under mild reaction conditions for which a retro-synthetic approach has been proposed as shown in Scheme 7. Revising the synthetic strategy is quite possible by changing the sequence of oxidation and organocatalytic hydrogenation reactions to obtain 5β-dihydroadrenosterone from which DCA can be synthesized through a few chemical transformations, starting from hydrocortisone (Scheme 7).

Scheme 7: Retro Synthetic Approach to Deoxycholic acid by Mimicking the 5β-Reductase through Organocatalysis.

On the way to explore MCC reactions[10] based on the bio-mimetic reductions using the organic hydrides,[56,13u] It was envisaged that adrenosterone could be reduced to dihydroadrenosterone under mild reaction conditions. With the evolution of organocatalysis as better bio-mimetic catalysis, it was envisioned that it would be feasible to activate the carbonyl through iminium formation and to deliver the hydride to C-5 carbon stereoselectively, similar to the 5β-reductase-catalysis.

For the demonstration of mimicking 5β-reductase with small molecular systems, various reaction Conditions (1-16) have been designed with combination of catalyst amine, co-catalyst acid and hydrogen source as shown in Figure-43. Interestingly, Pd/C was also used as a catalyst in combination with organic hydrides as hydrogen source as shown in Figure-43.[57,58,10n,10c]

Figure-43: Various hydrogenation conditions to mimic the 5β-reductase.

6.2 Results and Discussions

6.2.1 Bio-mimetic Hydrogenation of Adrenosterone and Hydrocortisone-Reaction Optimization:

Studies towards organocatalytic hydrogenations to mimic 5β-reductase were initiated with hydrogenation of adrenosterone **148a** and hydrocortisone **148b** to generate 5β-dihydroadrenosterone *cis*-**149a** and 5β-dihydrohydrocortisone *cis*-**149b** respectively, by applying various reaction conditions shown in Figure-43 (Table 9). The combination of secondary amine (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **34j** and co-catalyst D-CSA with Hantzsch ester **50a** as hydrogen source (Condition-1) in CH_3CN was found to be inefficient to carry out the

expected hydrogenation reaction (Table 9, entry 1). When (*S*)-*tert*-butyl-2-amino-3-phenylpropanoate **34af** with co-catalyst TFA was employed with 2 equiv of Hantzsch ester **50a** (Condition-10) in CH_3CN solvent under refluxing for 30 h, the reaction yielded the anticipated *cis*-**149a** with 80% yield and 58% de (Table 9, entry 2). After understanding the ability of catalyst **34af** in the hydrogenation of **148a**, various solvents and conditions were investigated with the scope of increasing the diastereoselectivity of the reaction.

Table 9: Reaction Optimization for Hydrogenation of Adrenosterone **148a**.[a]

Catalyst **34af**.TFA with **50a** hydrogen source (Condition-10) in 1,4-dioxane under sealed tube conditions at 60 °C, yielded **149a** in 76% yield with 70% de (Table 9, entry 3). Although selectivity of the reaction is good, the longer reaction time (72 h) and some unidentified impurities associated with the product made the solvent inferior. Changing the solvent to THF

and $CHCl_3$ under Condition-10 did not help improving the diastereoselectivity (Table 9, entries 4 and 5). Using bulkier hydrogen source **50b** (Condition-11) rather decreased the yield to 77% and de to 48% taking prolonged reaction times 78 h (Table 9, entry 6). (*S*)-methyl-2-amino-3-phenylpropanoate **34ag**.TFA (Condition-12) was not better than (*S*)-*tert*-butyl-2-amino-3-phenylpropanoate **34af**.TFA (Condition-10) in terms of de and reaction times. Under Condition-12, the product *cis*-**149a** was obtained in 68% yield and 50% de in 72 h (Table 9, entry 7). The reaction did not take place, when catalyst **34ag**.D-CSA (Condition-13) was employed with **50a** in CH_3CN (Table 9, entry 8). The reaction Condition-13 explains the importance of co-catalysts also along with amine catalyst in the bio-mimetic hydrogenation of **148a** as shown in Table 9.

As the selectivities were moderate with organocatalysts, the potential ability of Pd/C as catalyst for the hydrogenation reactions was tested to result the product **149a** with good selectivity. Interestingly, Hantzsch ester **50a** as hydrogen source over 5 mol% of 5% Pd/C (Condition-14) in EtOH solvent under refluxing for 18 h, resulted the product *trans*-**149a** in 82% yield with 19% de (Table 9, entry 9). To obtain the anticipated selectivity, other solvents like 3-picoline were tested. However solvent 3-picoline at rt under Condition-14 did not yield the product **149a** and starting material was recovered (Table 9, entry 10). Switching over to different hydrogen source like ammonium formate **50f** as hydrogen source over Pd/C in MeOH solvent at refluxing temperature (Condition-15) did not serve the purpose and only starting material was recovered (Table 9, entry 11). The similar trend of opposite selectivity was observed when neat hydrogen gas over Pd/C (Condition-16) was used in 3-picoline solvent at rt, resulting the *trans*-**149a** in 71% yield and 32% de (Table 9, entry 12). The structure and stereochemistry of the product *cis*-**149a** was confirmed by NMR.

It was obvious through the optimization results that organocatalyst is superior to metal catalysts to yield the anticipated *cis*-**149a**, mimicking 5β-reductase. Still further improvement was required in terms of de, as only moderate de was obtained thus far. Hence, the reaction strategy was revised as shown in Scheme 7. It was envisaged that hydrocortisone **148b** from which adrenosterone **148a** was prepared would result better de in hydrogenation reactions due to the presence of polar functional groups.

The optimization for reduction of **148b** was initiated with employing various conditions shown in Figure-43 (Table 10). Catalyst **34j**.D-CSA (Condition-1) and **34af**.TFA (Condition-10)

with Hantzsch ester **50a** as hydrogen source in CH_3CN solvent under refluxing for 48-72 h did not furnish **149b** rather starting material was recovered (Table 10, entries 1 and 2).

Table 10: Reaction Optimization for Hydrogenation of Hydrocortisone **148b**.[a]

To our delight, Pd/C mediated hydrogenation with 3 equiv of Hantzsch ester **50a** (Condition-14) in EtOH under refluxing conditions resulted the anticipated *cis*-**149b** with 86% yield and 72% de in 8 h (Table 10, entry 3). Surprisingly, the same reaction did not take place in 3-picoline solvent under Condition-14 at 80 °C and the starting material was recovered (Table 10, entry 4). However, the utilization of hydrogen gas over Pd/C (Condition-16) in 3-picoline at rt for 24 h yielded the *cis*-**149b** in 97% yield with improved (89%) de (Table 10, entry 5). After careful examination of the efficiency of various conditions, the optimization condition is stated to be Pd/C with 3 equiv of Hantzsch ester **50a** (Condition-14) in EtOH solvent at refluxing temperature. This condition was found to be superior over Pd/C with hydrogen gas (Condition-16), due to the *in situ* generation of controlled number of active hydrogen molecules.

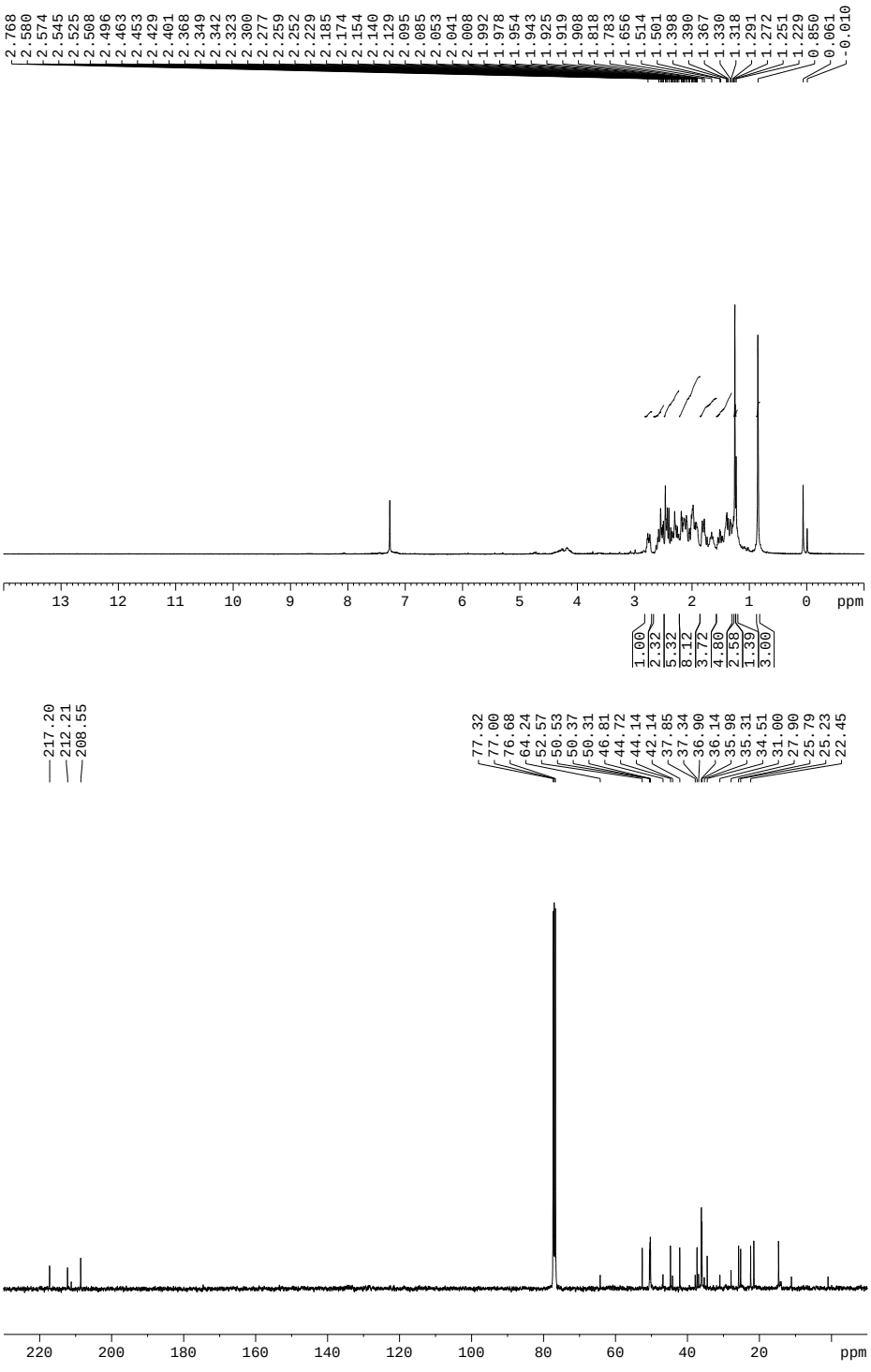


Figure-44: ^{1}H and ^{13}C NMR spectra of the product **149a**.

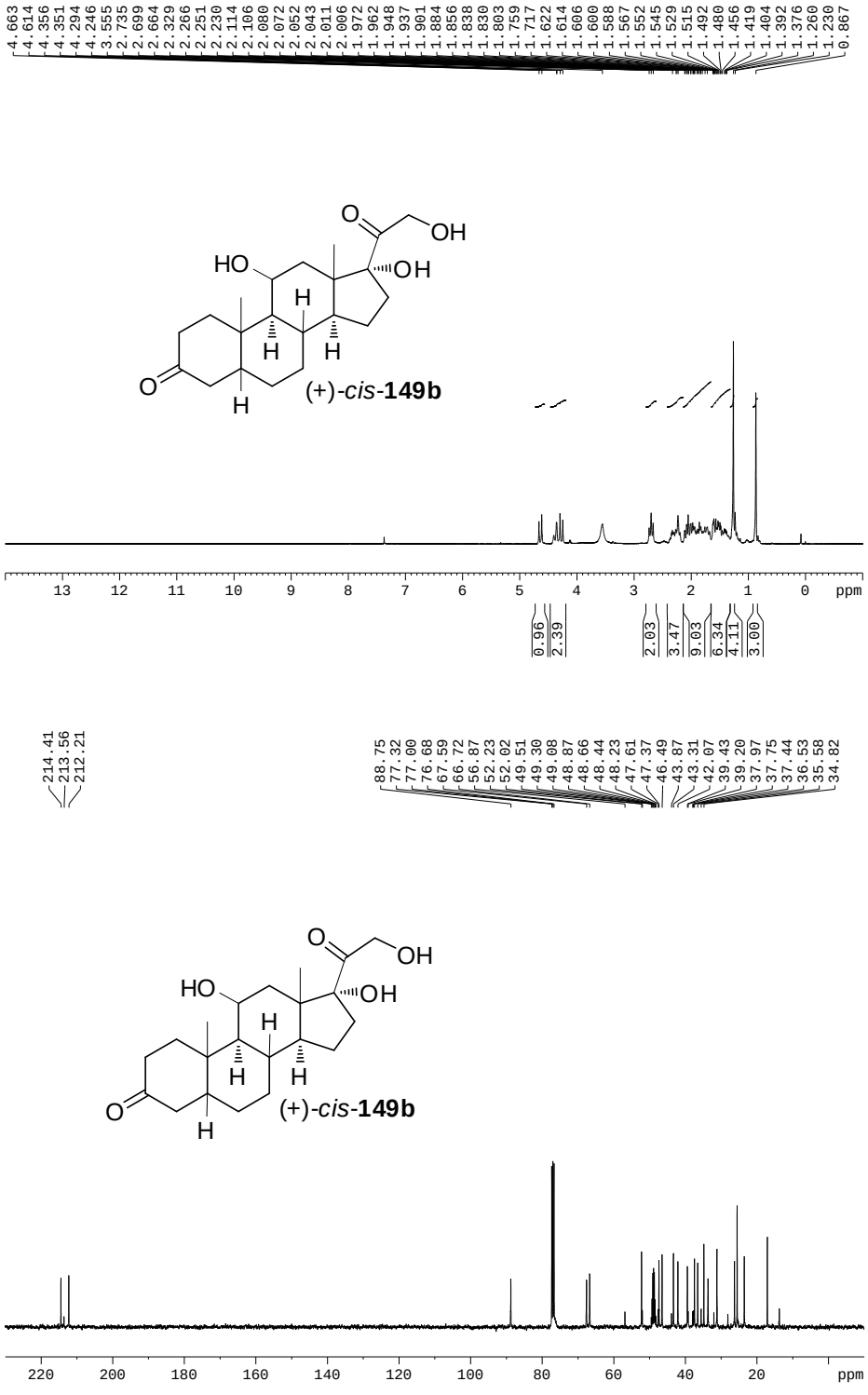


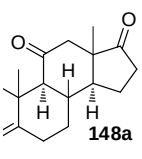
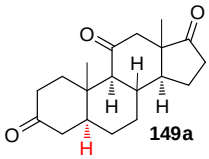
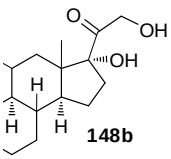
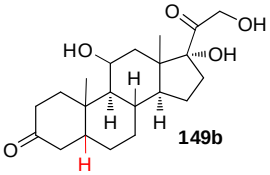
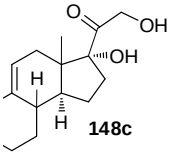
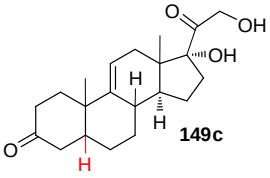
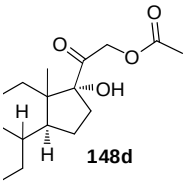
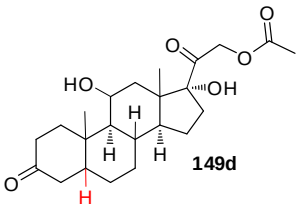
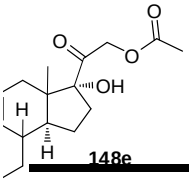
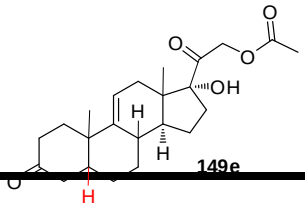
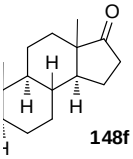
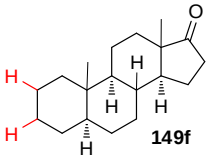
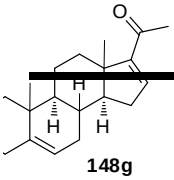
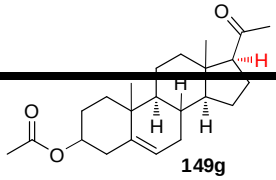
Figure-45: ^{1}H and ^{13}C NMR spectra of the product **149b**.

6.2.2 Diversity Oriented Synthesis of Chiral 5β-dihydrosteroids:

With optimized conditions in hand, the generality of the novel Condition-14 was tested with chemo- and stereoselective hydrogenation of various functionalized 4-ene-ketosteroids. The presence of polar groups was found to increase the selectivity of the reaction a little, with no compromise in the yield of the reaction. The products **149a-l** were obtained in excellent yields and moderate selectivities (Table 11). The selectivity in the Pd/C mediated reactions was good to provide the anticipated *cis*-5β-dihydro-3-ketosteroids as the major products in all cases except in the case of **149a** where *trans*-**149a** was obtained as the major product (Table 11, entry 1). Interestingly, reaction of non-activated double bond containing steroid **148f** with Hantzsch ester under Pd/C-catalysis furnished the hydrogenated steroid **149f** in good yield (Table 11, entry 6). This example is suitable to explain the mechanism of hydrogenation under the Condition-14.

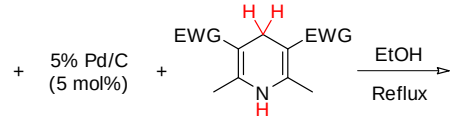
The enone **148g** under Pd/C-catalyzed hydrogenation with **50a** (Condition-14) yielded the product **149g** with >99% de as an inseparable mixture with pyridine byproduct (Table 11, entry 7). Later the mixture was deacetylated and determined the de of **149g** unambiguously. Interestingly, hydrogenation of dienones **148h**, **148j** and trienone **148l** resulted a mixture of totally hydrogenated products **149h**, **149j**, **149l** as major products and also partially hydrogenated enones **148i** and **148k** as minor products. The use of lesser equiv of Hantzsch ester also could not help the regioselective product generation (Table 11, entries 8-10). 5β-3-Ketosteroids are synthetically useful precursors, especially the product **149g** has been used as an important precursor in the synthesis of vitamin D_3, inhibitors of ecdysone and potent anti-tumour reagents.[59]

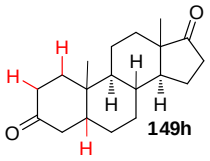
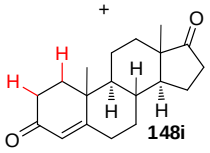
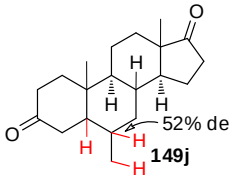
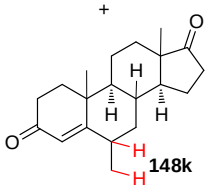
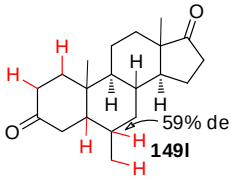
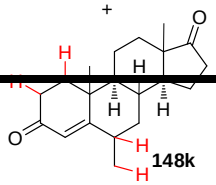
Table 11: Diversity Oriented Synthesis of Chiral 5β-Dihydrosteroids **149a-l**.[a]

 **148a**	 **149a**	21	82	19
 **148b**	 **149b**	6	86	72
 **148c**	 **149c**	6	73	87
 **148d**	 **149d**	5	80	51
 **148e**	 **149e**	16	79	65
 **148f**	 **149f**	6	87	–
 **148g**	 **149g**	6	64	>99

(*Contd..*)

Table 11: Diversity Oriented Synthesis of Chiral 5β-Dihydrosteroids **149a-l**.[a](*Contd*..)



	product(s)	time (h)	yield (%)[b]	de (%)[c,d]
	 **149h**	22	58	78
18h	 **148i**		27	–
	 52% de **149j**	18	56	52
18j	 **148k**		14	23
	 59% de **149l**	18	62	59
18l	 **148k**		19	18

, all reactions were carried out in 0.2 mmol of enone **148a-l** applying modified f Hantzsch ester **50a** in EtOH under refluxing. [b] Yield refers to the column-rmined based on NMR analysis. [d] Unless otherwise mentioned, *cis*-**149a-l** were eomers. [e] *trans*-**149a** was the major diastereomer. [f] **149g** was isolated as an line, de was determined after deacetylation of resulting mixture. [g] **148k** was regioisomers.

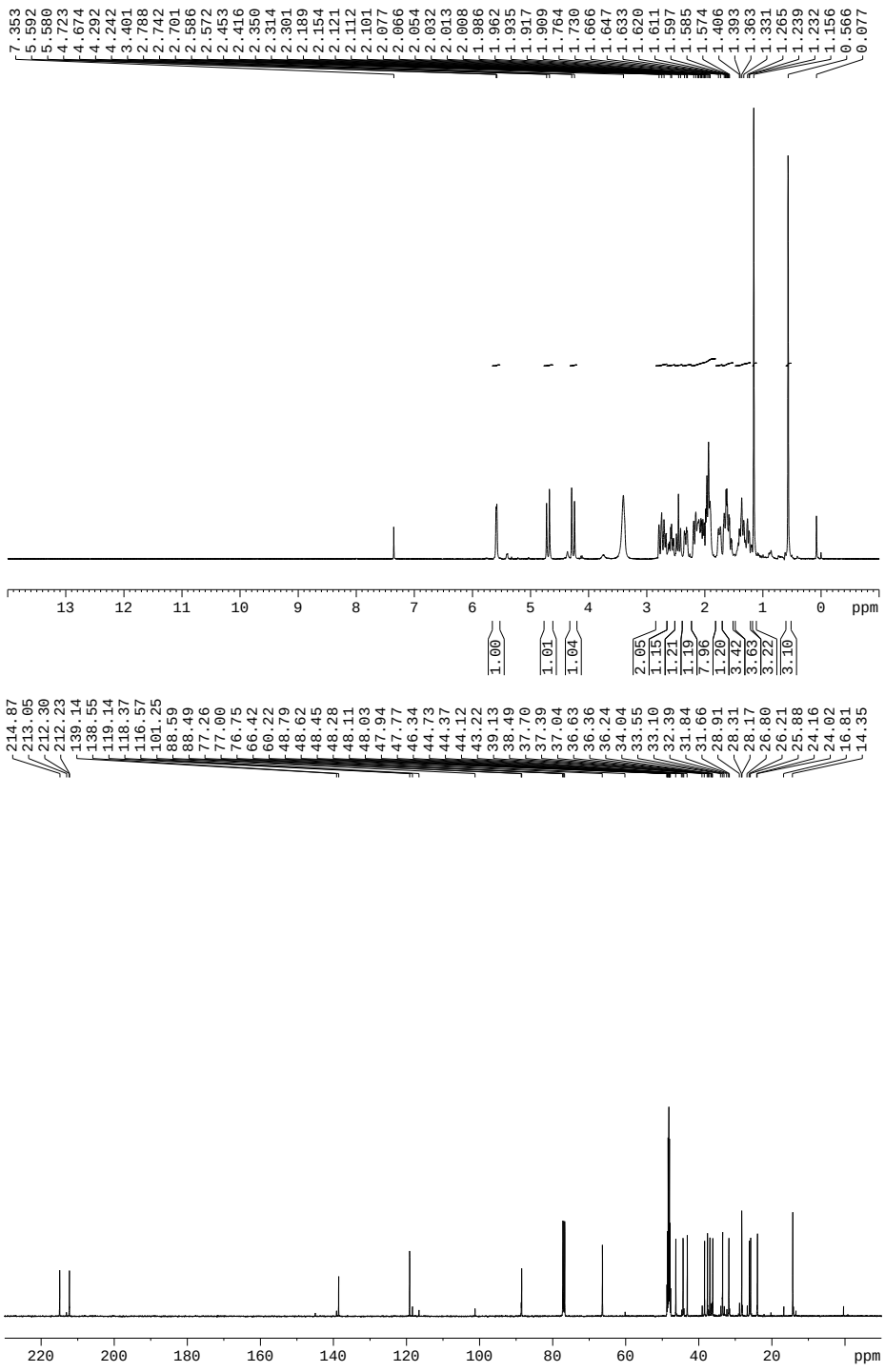


Figure-46: ^{1}H and ^{13}C NMR spectra of the product **149c**.

6.2.3 Bio-mimetic Hydrogenation of Wieland-Miescher, Hajos-Parrish Ketones and their Analogues-Reaction Optimization:

After demonstrating the bio-mimetic hydrogenation by using Hantzsch ester **50a** as hydrogen source over Pd/C catalyst, the focus was turned towards simple bicyclic enones like W-M ketones and H-P ketones **150**, which are excellent starting materials for the synthesis of many steroids, terpenes and other useful natural products.[60] The optimization for the hydrogenation of W-M ketone **150a** was initiated with testing various conditions shown in Figure-43 (Table 12). Interestingly, the treatment of W-M ketone **150a** with 2 equiv of Hantzsch ester **50a** in the presence of 25 mol% of catalyst **34j**.D-CSA (Condition-1) in CH_3CN solvent under refluxing condition resulted the product *cis*-**151a** in 80% yield and >99% de in 24 h (Table 12, entry 1). Almost similar results were obtained when $HClO_4$ was used in the place of D-CSA (Condition-2) resulting *cis*-**151a** in 75% yield and >99% de in 6 h (Table 12, entry 2).

Table 12: Reaction Optimization for Hydrogenation of W-M Ketone **150a**.[a]

Conditions 3-5, where the co-catalysts like *p*-TSA, $PhCO_2H$ and $4\text{-}NO_2C_6H_4CO_2H$ are used with catalyst **34j** and **50a** as hydrogen source in CH_3CN did not give better results compared to Condition-1 and 2 in terms of yields and reaction times (Table 12, entries 3-5). Surprisingly, the reaction did not take place when TFA was used as co-catalyst under the same reaction conditions and the starting material was recovered (Table 12, entry 6). Similarly, in the place of hydrogen source **50a**, when **50c**, **50d** or **50e** was used (Conditions 7-9), no reaction was observed and simply the starting material was recovered (Table 12, entries 7-9).

The primary amine organocatalysts (*S*)-*tert*-butyl-2-amino-3-phenylpropanoate **34af** and (*S*)-methyl-2-amino-3-phenylpropanoate **34ag** were less efficient than **34j** in carrying out the selective hydrogenation of **150a** under the similar reaction conditions (Table 12, entries 10 and 11). After the recent exploration into the crystal structure of 5β-reductase, it became obvious that the amino acids tyrosine and glutamic acid involve in the active site of the enzyme catalysis.[52] Hence, to understand the efficiency of amino acids in hydrogenation reactions, the reaction of W-M ketone **150a** with the hydrogen source **50a** was performed under the catalysis of the amino acids tyrosine, glutamic acid and mixture of both. Disappointingly, no product formation was observed in the reaction and the starting material was recovered (results not shown in the Table). To further understand the bio-mimetic reaction, various other solvents like EtOH, $CHCl_3$, DMSO and DMF were also used for the organocatalytic hydrogenation of **150a** under Condition-1, but the results were not superior to CH_3CN (results not shown in the Table).

To our delight, almost under all organocatalytic hydrogenation conditions the product **151a** was obtained in >99% de with *cis*-configuration. The yield and reaction time were totally influenced by the co-catalyst and solvent used in the reaction. The previously explored Pd/C/ Hantzsch ester **50a** conditions were also tested for the hydrogenation of W-M ketone **150a**. Interestingly, **50a** as the hydrogen source over 5% Pd/C (Condition-14) in EtOH solvent at refluxing temperature for 5 h resulted *cis*-**151a** in 82% yield with 90% de (Table 12, entry 12). Similarly, when ammonium formate **50f** was used as the hydrogen source over Pd/C (Condition-15), *cis*-**151a** was obtained in 85% yield with 90% de (Table 12, entry 13). Both the reactions resulted in the formation of minor diastereomer up to 10% yield.

During the process of understanding the hydrogenation of W-M ketones, hydrogen gas was envisaged as hydrogen source over Pd/C (Condition-16). But the literature reports by Karimi

and others revealed that the hydrogenation of *racemic*-**150a** over Pd/C using hydrogen gas resulted in *cis*-**151a** as a single diastereomer, [58j-o] and so the reaction was not performed. Although the method seems simpler, even minor modifications in the solvent or in the base affected the diastereoselectivity resulting in the formation of *trans*-**151a** as the minor product. This ultimately implied that this condition is not universal to attain the *cis*-diastereoselectivity and it has some limitations, which led us to proceed with organocatalytic conditions.

Hence, the optimization condition was stated to be **34j**.D-CSA (25 mol% each) with 2 equiv of **50a** (Condition-1) in CH_3CN at refluxing temperature, which is the organocatalytic condition mimicking the human steroid 5β-reductase.

It was quite interesting to study the efficiency of Condition-1 during the hydrogenation of other functionalized bicyclic ketones **150** as the optimization substrate **150a** was very flexible resulting >99% de under all catalytic conditions (Table 12).

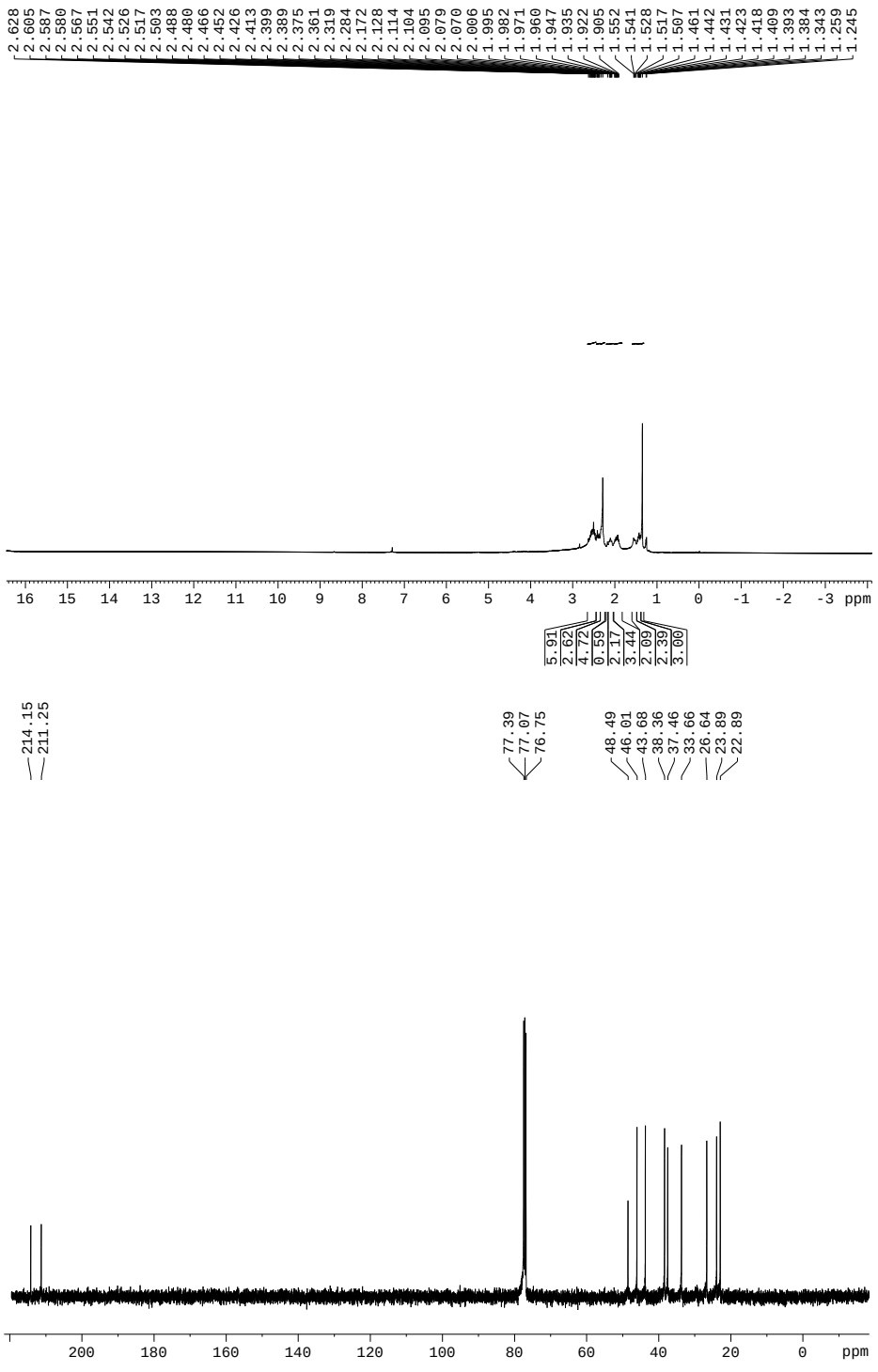


Figure-47: ^{1}H and ^{13}C NMR spectra of the product **151a**.

6.2.4 Diversity Oriented Synthesis of Chiral 5β-Dihydro Wieland-Miescher, Hajos-Parrish Ketones and their Analogues:

The optimized conditions were tested on a variety of bicyclic enones **150a-l**[61] (See Annexure-IV for the starting material synthesis) to yield stereoselectively the *cis*-fused bicyclic ketones **151a-l**. As the *cis* fused bicyclic enones are useful synthetic precursors in medicinal chemistry, their diastereoselective synthesis gains much importance.[62] The organocatalytic diastereoselective hydrogenation reaction with **50a** was found to be substrate and steric controlled reaction. The selectivities and reactivities were anchored by the angular alkyl group and the group present α to angular substitution. With the increase in the bulkiness of angular alkyl group and/or the group present α to angular substitution, the selectivity goes on decreasing (Table 13).

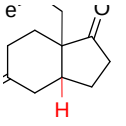
The W-M ketone **150a** and its enantiomer *ent*-**150a** were stereoselectively reduced to *cis*-**151a** and *cis*-*ent*-**151a** respectively with good yield and >99% de (Table 13, entries 1 and 2). The angular allyl substituted bicyclic enone **150b** and benzyl substituted bicyclic enone **150c** were hydrogenated to yield **151b** and **151c** respectively in good to excellent selectivities, yet taking longer reaction times due to the bulkiness of the substitution (Table 13, entries 3 and 4). Angular acetylenic enone **150d** under **34j**.D-CSA catalysis with **50a** as the hydrogen source in CH_3CN solvent at refluxing temperature for 48 h resulted *cis*-**151d** with 74% yield and >99% de (Table 13, entry 5).

The larger angular steric crowding of the phenyl group in enone **150e** seems to prevent the reaction to undergo through organocatalytic hydrogenation conditions. The reaction was then performed with Pd/C and Hantzsch ester **50a** (Condition-14) in EtOH under refluxing for 6 h to furnish *cis*-**151e** in 71% yield with >99% de (Table 13, entry 6). After understanding the effects of angular substitution on the selectivity of the hydrogenation reaction, further experiments were carried out on keto reduced enones **150**, in order to understand the real mechanistic insights of the effect of keto group present α to angular substitution in B-ring.

The carbonyl reduced W-M keto alcohol **150f** under Condition-1 in CH_3CN solvent for 48 h resulted the product **151f** in 78% yield with reduced diastereoselectivity (83% de) (Table 13, entry 7). The reduced de the product **151f** compared to **151a** may be due to the presence of

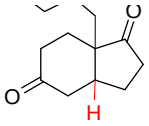
sp^3 carbon imposing much steric crowding to the incoming hydride source. This steric crowding influence on the selectivity was further confirmed by the reaction of **150g** to provide *cis*-**151g** in 79% yield and only 53% de (Table 13, entry 8). Thus it is obvious that the increase in bulkiness of the group α to the angular substitution decreases the selectivity drastically due to the steric repulsion between the incoming hydride and the bulkier β-face groups.

Table 13: Diversity Oriented Organocatalytic Hydrogenation of Chiral W-M and H-P Ketones **150a-l**.[a]



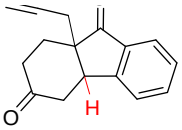
2 h, 50% yield;
ee; 59% de

(11)[f]



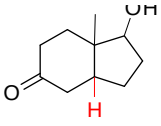
151j: 72 h, 35% yield;
89% ee; 24% de

(12)[h]



151k: 72 h, 27% yield;
69% ee; >99% de

(13)



151l: 33 h, 62% yield;
99% ee; 82% de

:rwise mentioned, all reactions were carried out applying Condition **1** in CH_3CN (0.1 M) at refluxing
) Yield refers to the column-purified product. [c] ee corresponds to the ee of starting enone determined
stationary phase HPLC. [d] de was determined based on NMR analysis. [e] Unless otherwise mentioned, *cis*-
otained as major diastereomers. [f] Condition **2** was applied in CH_3CN solvent under refluxing. [g] Condition **14**
EtOH solvent under refluxing. [h] Condition **10** was applied in CH_3CN solvent under refluxing.

Library of H-P ketones was also reacted under Condition-1 with **50a** in CH_3CN solvent under refluxing condition. H-P ketones took much longer reaction times than W-M ketones and gave reasonably moderate yields. H-P ketone **150h** under the hydrogenation Condition-2 resulted **151h** with 70% yield and >99% de (Table 13, entry 9). When angular position was further

substituted with higher alkyl groups, the reactivity and selectivity were drastically decreased, taking prolonged reaction times and resulting relatively lesser yields and diastereoselectivities (Table 13).

The propyl and butyl substituted H-P ketones **150i** and **150j** under Condition-2 in CH_3CN solvent at refluxing temperature yielded the bicyclic diones *cis*-**151i** and *cis*-**151j** in 50% yield, 59% de and 35% yield, 24% de respectively taking 72 h reaction times (Table 13, entries 10 and 11). The chiral enone **150k** derived from indane dione was found to be less reactive towards hydrogenation under **34j**-catalysis and reacted under Condition-10 (catalyst **34af**.TFA) to yield product *cis*-**151k** in 27% yield and >99% de (Table 13, entry 12). The synthetic importance of this methodology was well proven through the synthesis of **151k** as it is a useful synthetic precursor for the synthesis of Gibbane framework.[62] The trend of selectivity observed in W-M ketone was followed by H-P ketone, while the carbonyl was reduced to O*H*. The treatment of H-P keto alcohol **150l** under Condition-1 in CH_3CN for 33 h at refluxing temperature resulted **151l** in 62% yield with 82% de (Table 13, entry 13). The structure and relative stereochemistry of the hydrogenated products **151** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis of (+)-**151a** as shown in Figure-48.[63]

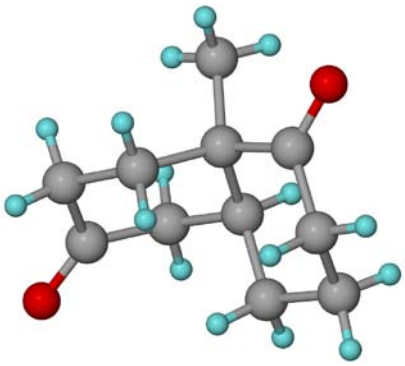


Figure-48: X-ray crystal structure of (+)-(4a*R*,8a*S*)-8a-methylhexahydronaphthalene-1,6(2*H*,7*H*)-dione (**151a**).

After successful demonstration of bio-mimetic hydrogenation of W-M, H-P ketones and their analogs **150**, *the one-pot asymmetric synthesis has been demonstrated for the synthesis of hydrogenated W-M and H-P ketones cis-**151a** and cis-**151h** via sequential combination of multi-catalysis and multi-component in a single flask as analogy to cellular reactions* (for the full details, see Scheme A5, Annexure-IV).

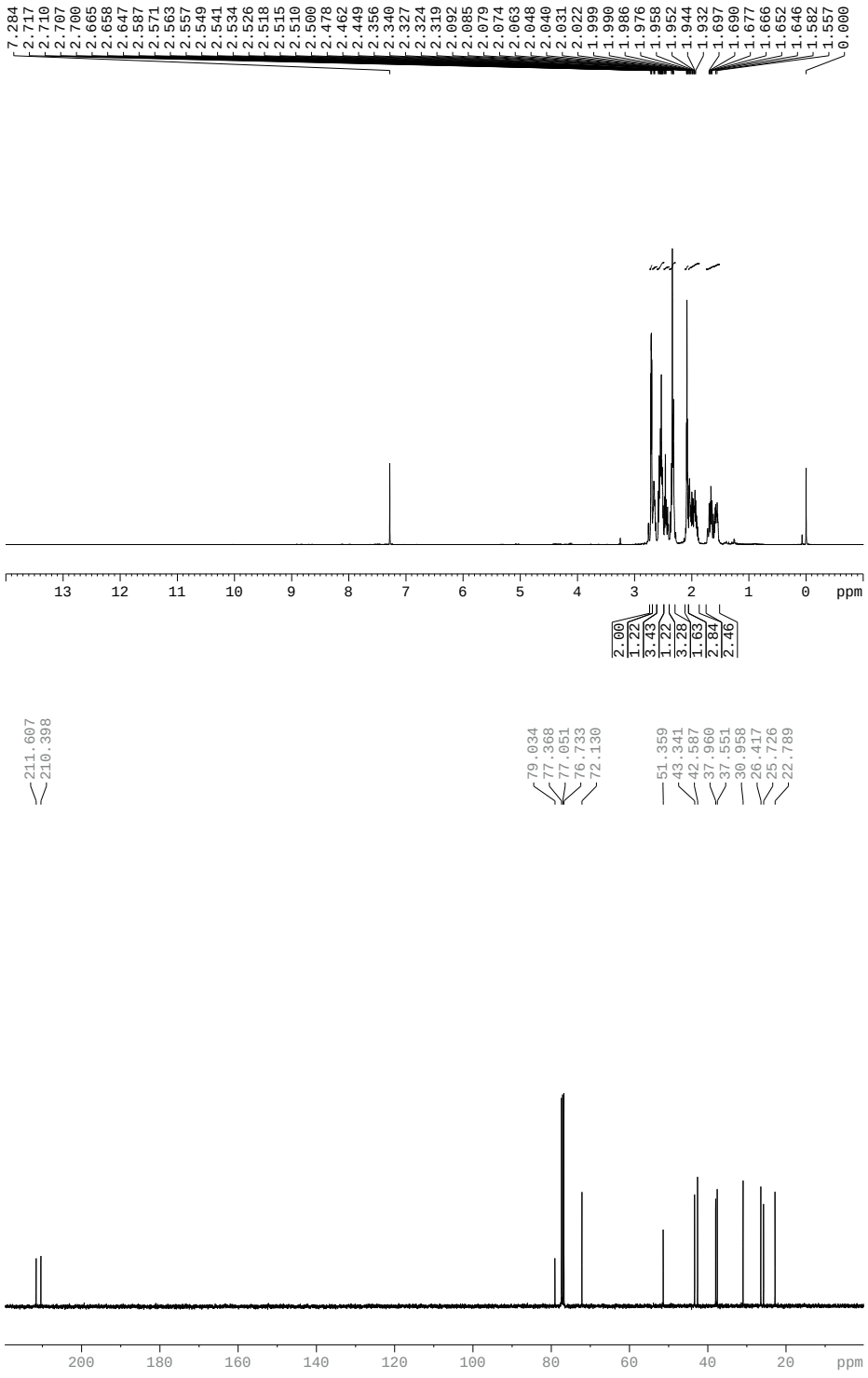


Figure-49: ^{1}H and ^{13}C NMR spectra of the product **151d**.

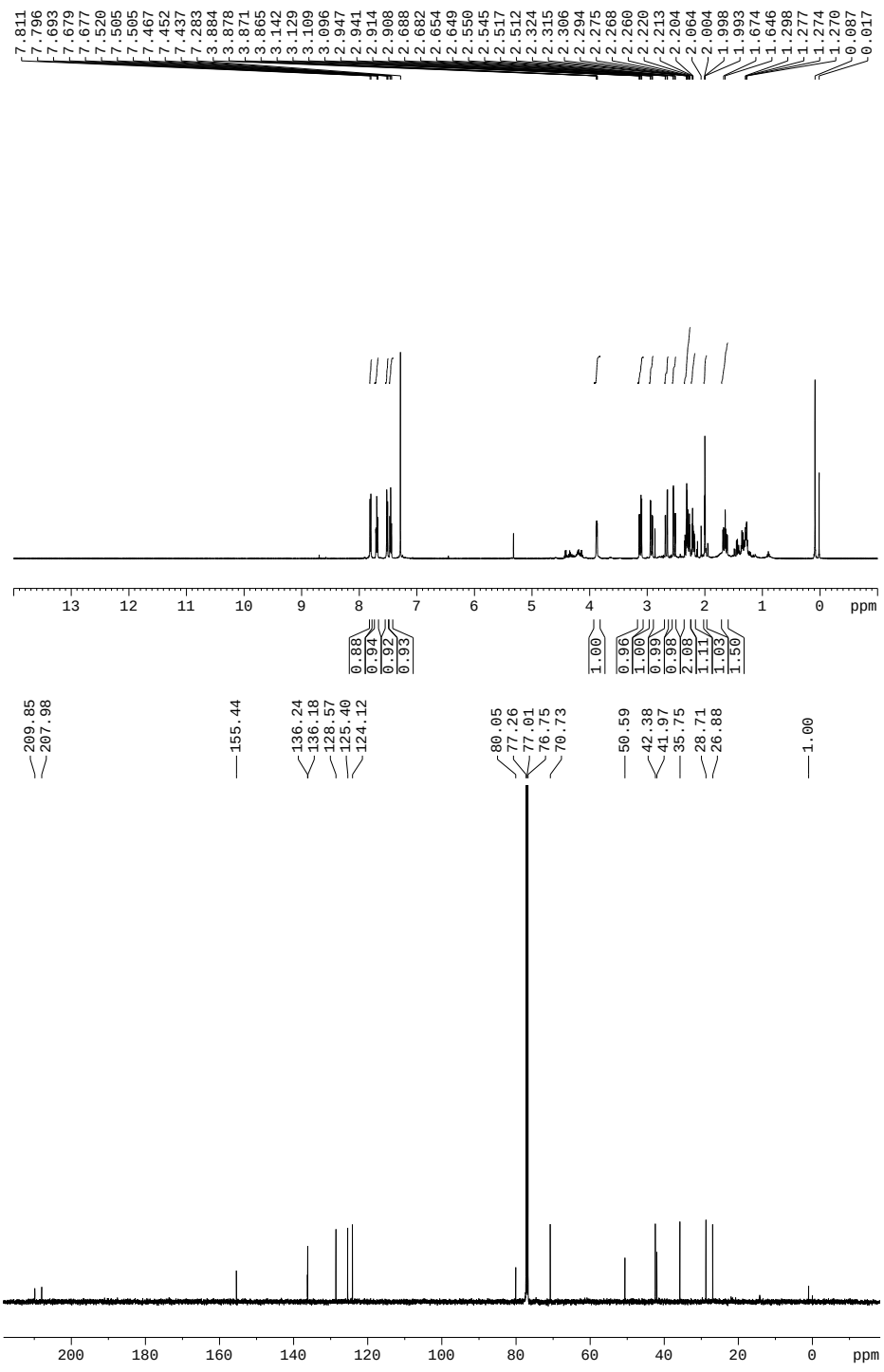


Figure-50: ^{1}H and ^{13}C NMR spectra of the product **151k**.

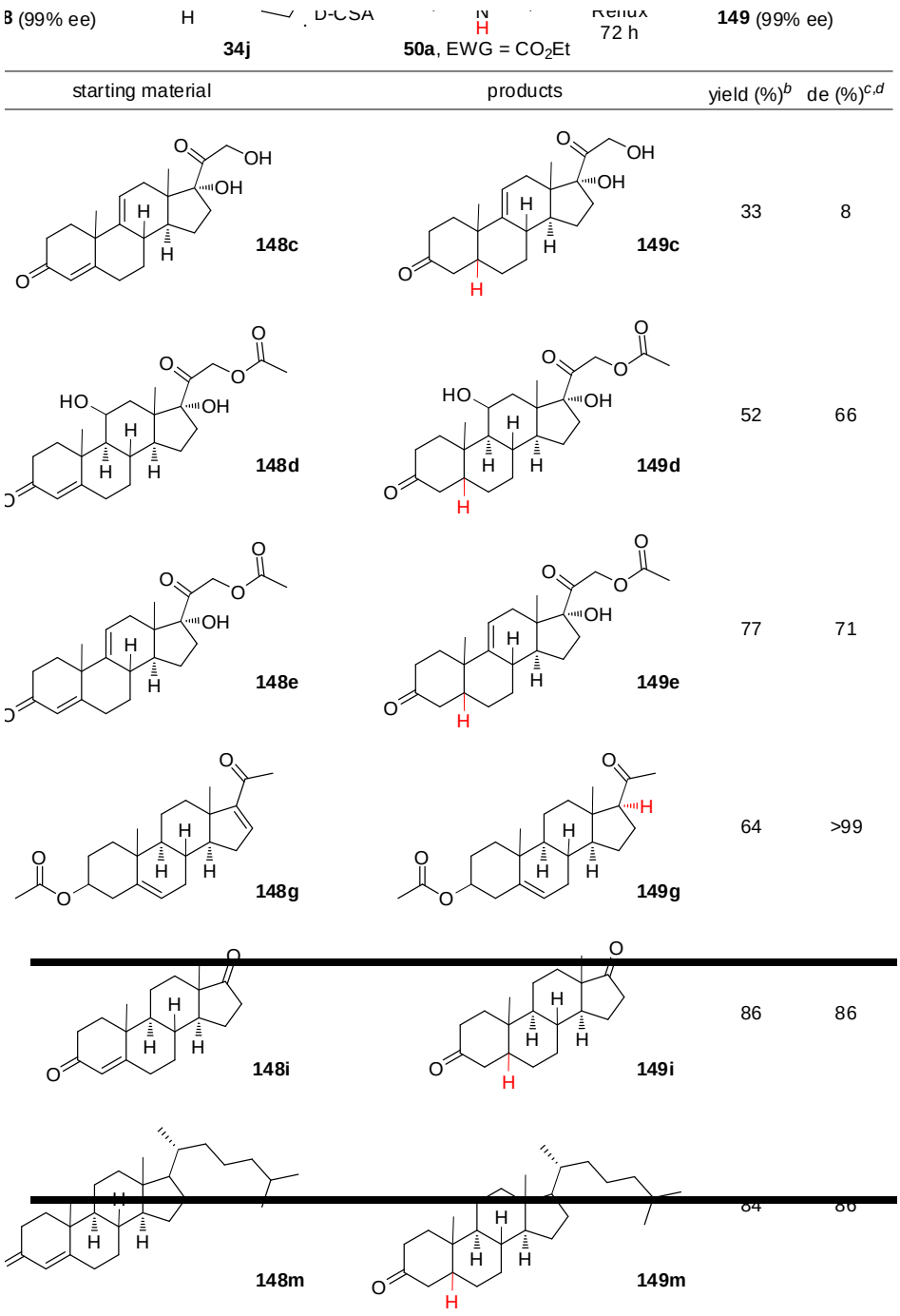
6.2.5 Diversity Oriented Synthesis of Chiral 5β-Dihydrosteroids Applying Organocatalytic Conditions:

After understanding the potential ability of organocatalysts in the reduction of various functionalized bicyclic enones, similar strategy was applied to a number of functionalized 4-ene-3-ketosteroids (Table 14). The synthetic and biological importance of compounds **149** necessitated a way to develop a diastereoselective synthesis.[64] Functionalized steroidal enones **148** were reacted with bio-mimetic catalyst **34j**.D-CSA and hydrogen source **50a** (Condition-1) in CH_3CN solvent at refluxing temperature for 72 h. As expected, 5β-dihydo-3-ketosteroids were obtained as major isomers mimicking the *in vivo* 5β-reductase (Table 14).

The organocatalytic hydrogenation was found to be slower with the steroids **148c** and **148d** resulting only moderate yields and diastereoselectivities. The hydrogenated product **149c** was obtained with 33% yield and 8% de and **149d** with 52% yield and 66% de after 72 h (Table 14, entries 1 and 2). Although **148b** and **148c** were poor and non-reactive substrates under Condition-1, their corresponding acetates were found to be much more reactive. E.g. **148e**, the acetylated steroid of **148c**, resulted the product **149e** with 77% yield and 71% de (Table 14, entry 3). This observation clearly explains that the reactivity and selectivity is also dependent on the solubility of the substrate, which is controlled by the functional groups. Steroid **148g** was regioselectively reduced only in D-ring during the hydrogenation reaction and furnished **149g** with 64% yield and >99% de (Table 14, entry 4). Compound **149g** was isolated with pyridine byproduct and the mixture was subjected to deacetylation conditions to isolate the pure product **152g** and to determine the de of the product **149g** unambiguously.

Bio-mimetic hydrogenation of 4-androsten-3-one **148i**, 4-cholesten-3-one **148m**, testosterone **148n** and dehydroprogesterone **148o** resulted the corresponding 5β-dihydro-3-ketosteroids **149** in excellent yields and diastereoselectivities (Table 14, entries 5-8). Without much of steric influence, angular hydroxymethyl substituted 4-androsten-3-one **148p** provided the product **149p** in 72% yield and 79% de (Table 14, entry 9). 10-Nor-testosterone **148q** was less selective providing **149q** in 82% yield and 82% de (Table 14, entry 10), compared to its acetate **148r** which resulted **149r** in 90% yield and 96% de (Table 14, entry 11), perhaps due to solubility causes. The dienone **148s** resulted the total hydrogenated product **149s** with 64% yield

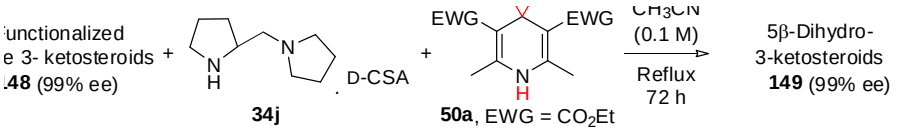
Table 14: Diversity Oriented Diastereoselective Synthesis of Chiral 5β-Dihydrosteroids **149** through Organocatalysis.[a]

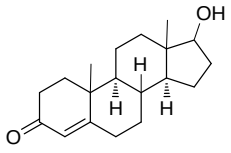
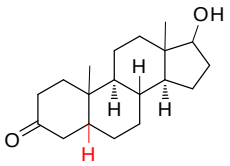
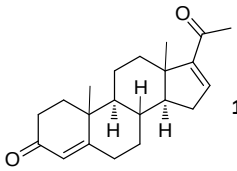
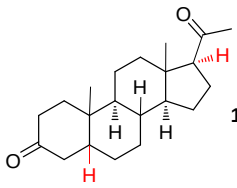
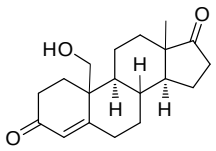
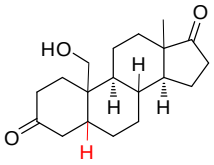
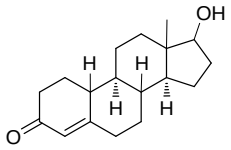
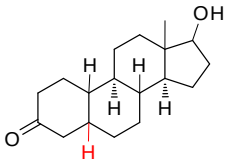
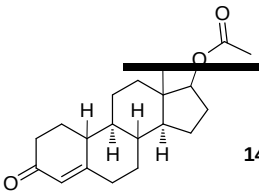
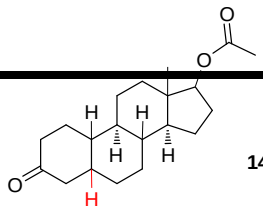
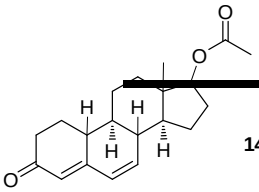
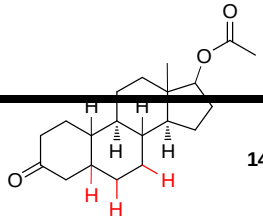


starting material	products	yield (%)[b]	de (%)[c,d]
148c	**149c**	33	8
148d	**149d**	52	66
148e	**149e**	77	71
148g	**149g**	64	>99
148i	**149i**	86	86
148m	**149m**	84	86

(Contd..)

Table 14: Diversity Oriented Diastereoselective Synthesis of Chiral 5β-Dihydrosteroids **149** through Organocatalysis.[a](*Contd..*)



starting material	products	yield (%)[b]	de (%)[c,d]
 **148n**	 **149n**	82	94
 **148o**	 **149o**	78	86
 **148p**	 **149p**	72	79
 **148q**	 **149q**	82	82
 **148r**	 **149r**	90	96
 **148s**	 **149s**	64	92

otherwise mentioned, all reactions were carried out in 0.2 mmol of functionalized 4-ene-3-ketosteroids ing Condition **1** in CH_3CN (0.1 M) under refluxing temperature for 48-72 h. [b] Yield refers to the column- oduct. [c] de was determined based on NMR analysis. [d] Unless otherwise mentioned *cis*-**149** were as major diastereomers. [e] **149g** was isolated as an inseperable mixture with pyridine, de was d after deacetylation of resulting mixture and the reaction time was 48 h. [f] 4 equiv of Hantzsch ester sed.

and 92% de (Table 14, entry 12). The use of lesser equiv of **50a** did not improve the regioselectivity of the reaction. The structure and relative stereochemistry of the hydrogenated products **149** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis of (+)-**149i** and (+)-**149r** as shown in Figure-51 and Figure-52 respectively.[65]

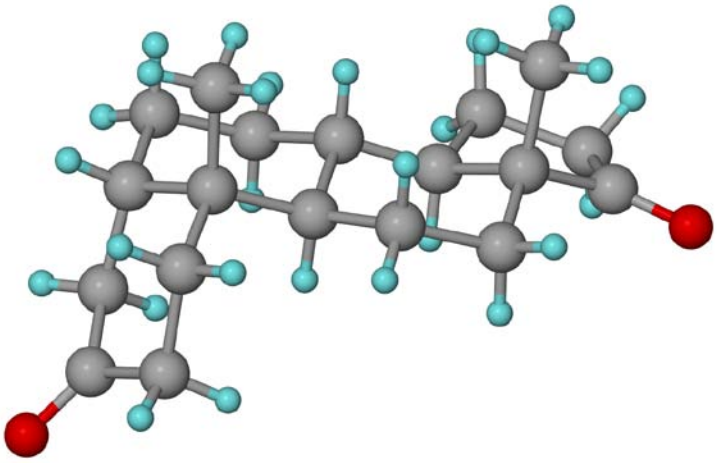


Figure-51: X-ray crystal structure of (+)-(5*R*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyldodecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17(2*H*,4*H*)-dione (**149i**).

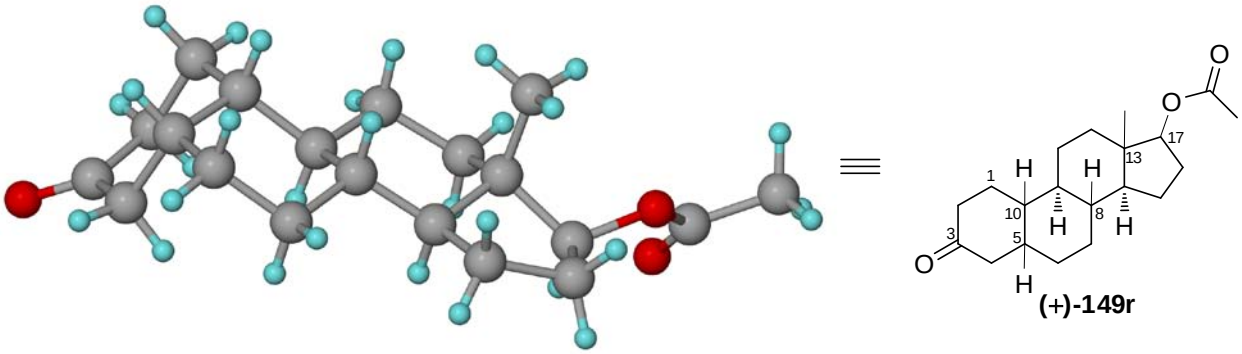


Figure-52: X-ray crystal structure of (+)-(5*R*,8*R*,9*R*,10*S*,13*S*,14*S*,17*S*)-13-methyl-3-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl acetate (**149r**).

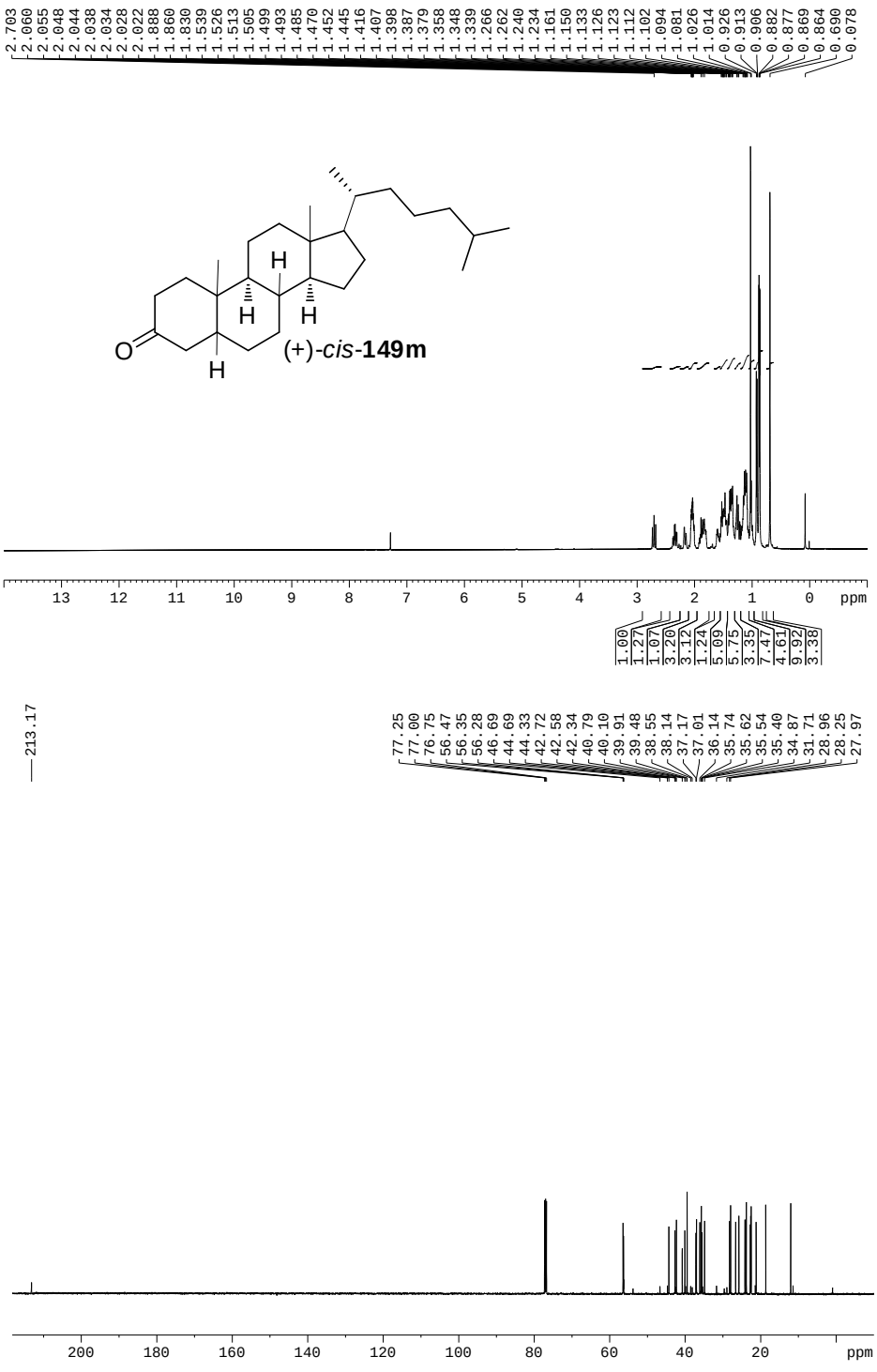


Figure-53: ^{1}H and ^{13}C NMR spectra of the product **149m**.

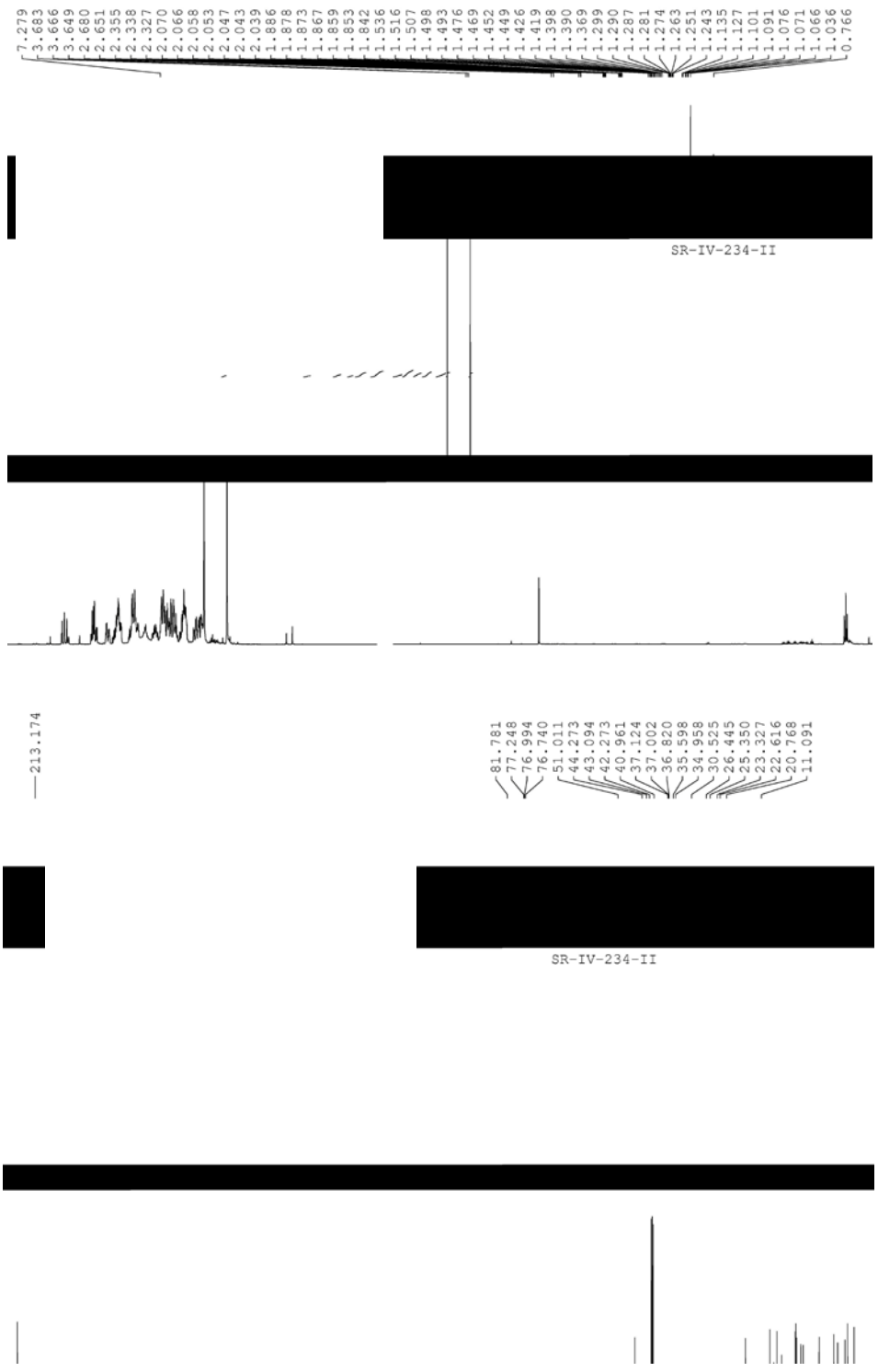


Figure-54: ^{1}H and ^{13}C NMR spectra of the product **149n**.

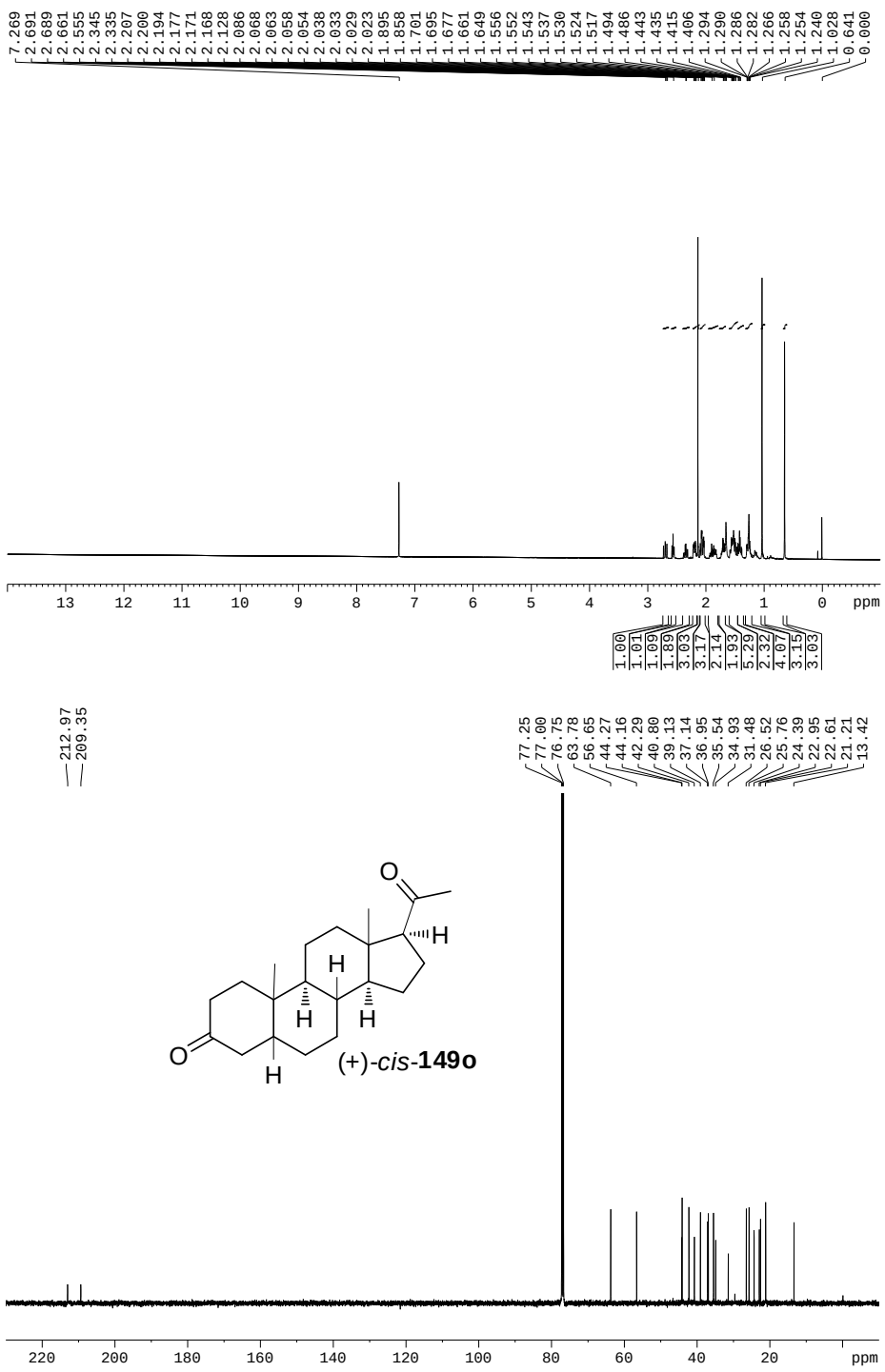


Figure-55: ^{1}H and ^{13}C NMR spectra of the product **149o**.

6.3 Mechanistic Insights

6.3.1 Controlled Experiments to Study Mechanistic Insights:

The organocatalytic (**34j**.D-CSA catalyzed) hydrogenation reaction was found to be substrate and catalyst controlled. To further understand the mechanism unambiguously, the enone **150d** was subjected to hydrogenation reaction with *ent*-**34j**.D-CSA and 2 equiv of **50a** in CH_3CN solvent at refluxing temperature for 48 h. The reaction gave the product *cis*-**151d** in 69% yield and >99% de (eq. 29). The selectivity is similar to the reaction where **34j** was used as the catalyst under the same conditions (Table 13, entry 5). The formation of *cis*-isomer even after changing the catalyst configuration may be due to the strong steric repulsion between incoming Hantzsch ester **50a** and α-face of the pre-transition state intermediate iminium ion generated from amine and enone.

To further confirm the effect of the carbonyl group present in α-position to angular substitution in inducing conformational strain in α-face of the B-ring, controlled reactions were carried out as shown in eq. 30. Surprisingly, hydrogenation of (*R*)-**150m** with **50a** under (*S*)-**34j**.D-CSA-catalysis furnished the product (-)-**151m** in 86% yield with only 15% de. However, the same reaction under (*R*)-**34j**.D-CSA-catalysis furnished the expected product (-)-*cis*-**151m** in

82% yield with 70% de. In a similar manner, treatment of *rac*-**150m** with **50a** under (*S*)-**34j**.D-CSA-catalysis furnished the product *rac*-**151m** in 86% yield with 43% de as shown in eq. 30.

These results clearly indicate that the carbonyl group in B-ring of the W-M and H-P ketones **150** induces the conformational strain at the α-face of the B-ring, that creates much amount of repulsion with incoming organic hydride **50a** at the α-face.[66] That would be possibly the reason that the major products were *cis*-isomers in Tables 12 and 13.

6.3.2 Proposed mechanism and experimental evidence through NMR spectroscopy and ESI-HRMS analysis:

With the results of controlled experiments, mechanism for the organocatalytic hydrogenation of bicyclic enones **150** has been proposed as shown in Scheme 8. The approach of the organic hydride source (Hantzsch ester **50a**) to iminium ion (**I**) generated *in situ* is the main controlling factor apart from the thermodynamic stability of the resulting hydrogenated products *cis*-**151a–l**/*trans*-**151a–l**. Approach of the Hantzsch ester **50a** through the *exo*-face of the iminium ion (**I**) (the same side as the alkyl group), **TS-7** is more favourable than through the *endo*-face (opposite to the alkyl group), **TS-8**. This may be due to the existence of more steric hindrance in an *endo* approach and also based on the formation of *Z*-iminium ion. As shown in Scheme 8, steric strain control is the main controlling factor, not product stability control, because the thermodynamically stable isomers *trans*-**151a-l** are formed as *minor* products. This is in agreement with results in Table 13, where the bulkiness of the alkyl group decreases the amount of *cis*-attack and increases the *trans*-attack of hydride source to the *in situ* generated imines.[67]

The selective formation of proposed active iminium species between **150a** and **34j** was confirmed by carrying out the NMR experiment as shown in Scheme 8. Surprisingly, the iminium ion (**I**) was obtained in >99% stereoselectivity within 5 min. The observation of two non-equivalent *N*-CH_2 carbons of pyrrolidine ring (C9 and C12) in the *in situ* formed iminium ion (**I**) strongly supports the *Z*-imine formation. Further, the formation of iminium ion (**I**) was confirmed by ESI-HRMS analysis as shown in Figure-56. The ESI-HRMS spectrum of an on-going reaction of **150a** and **34j** in CD_3CN at rt revealed the presence of $[\mathbf{I}]^+$ (m/z 315.2436) as shown in Figure-56.

Scheme 8: (a) Proposed Mechanism for the Diamine **34j**-Catalyzed *syn*-Selective Hydrogenation Reactions of **150**.; (b) NMR Experiment to Detect the Pre-transition State Intermediate (**I**).

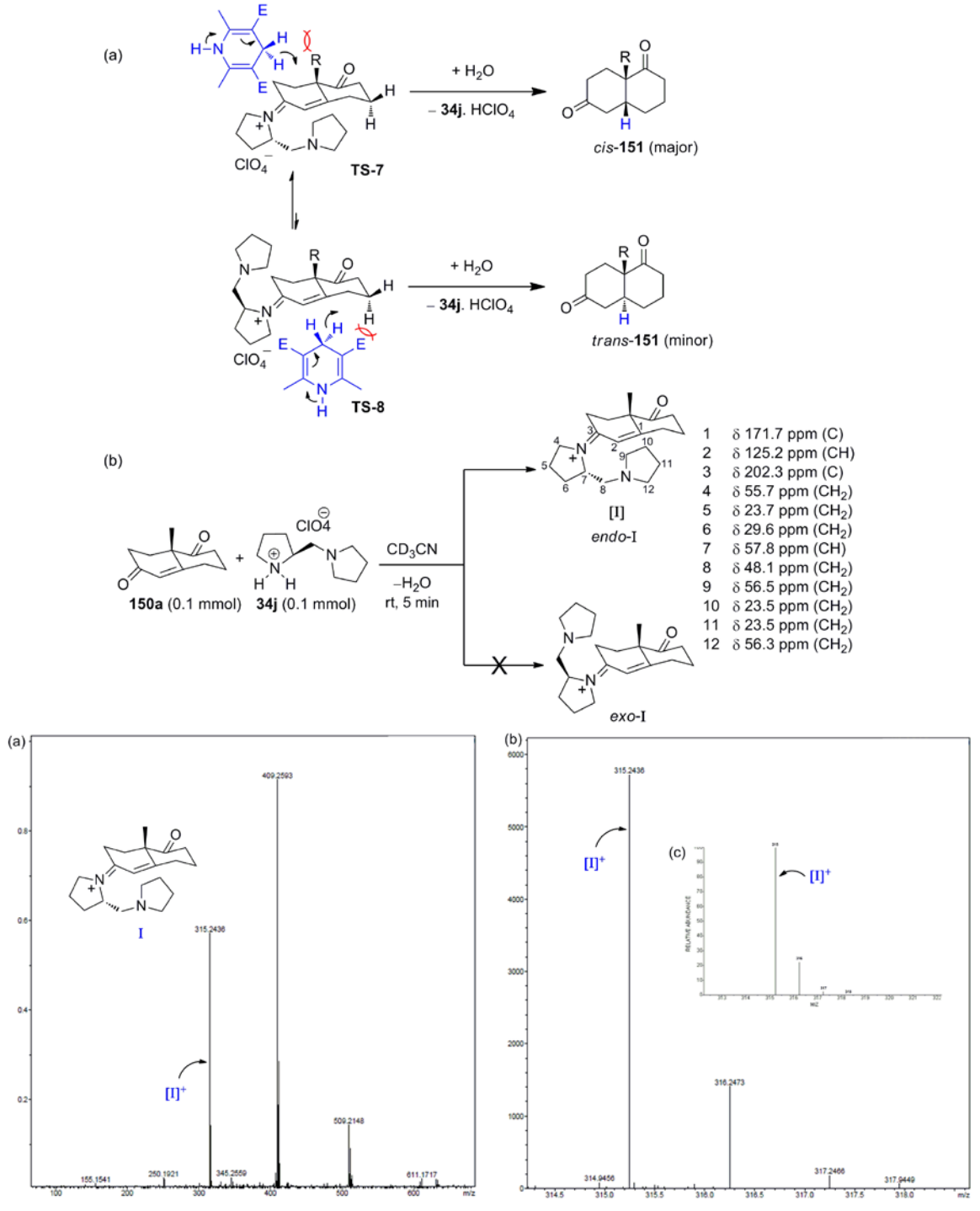


Figure-56: (a) ESI-HRMS (positive mode) spectrum of the reaction of **150a** and **34j** in CD_3CN after 5 min at rt. (b) The observed ESI-HRMS isotopic pattern of pre-transition state intermediate $[\mathbf{I}]^+$. (c) The simulated ESI-HRMS isotopic pattern of pre-transition state intermediate $[\mathbf{I}]^+$.

After explaining the reaction mechanism of chiral bicyclic enone reduction through bio-mimetic diamine-catalysis, attention was turned to explain the organocatalytic stereoselective hydrogenation of steroids in a similar manner (Scheme 9). In diamine-catalyzed hydrogenation of steroids **148** with **50a**, **TS-9** was the feasible transition state due to the lesser steric crowding experienced during hydride delivery to *Z*-iminium ion (**II**) compared to **TS-10**. As an additional support to our hypothesis, NMR experiment was also carried out between **148i** and **34j** in CD_3CN at rt. In the present case also, the *in situ* generated iminium ion (**II**) was obtained in >99% stereoselectivity within 5 min, which is possibly *Z* selective. The similar trend of observing two non-equivalent *N*-CH_2 carbons of pyrrolidine ring (C9 and C12) imparts evidence to *Z* selectivity. Further, the *in situ* formed iminium ion (**II**) has also been confirmed with ESI-HRMS analysis of an on-going reaction of **148i** and **34j** as shown in Figure-57.

The stereoselective synthesis of *cis*-isomers as the major product during hydrogenation reactions makes it possible to compare the reaction transition state **TS-9** in Scheme 9 with *in vivo* transition state **TS-5** in Figure-42. In both the transition states *endo*-face has been selectively shielded by the chiral components which are present to activate the carbonyl towards conjugate reduction. This in turn, allows the hydride delivery only through *exo*-face resulting stereoselective *cis*-isomer formation. Comparison of the transition states undoubtedly states that **34j**.D-CSA catalysis is nothing but the enzyme mimic of 5β-reductase.

***Scheme 9*:** (a) Proposed Mechanism for the Diamine **34j**-Catalyzed *syn*-Selective Hydrogenation Reactions of **148**.; (b) NMR Experiment to Detect the Pre-transition State Intermediate (**II**).

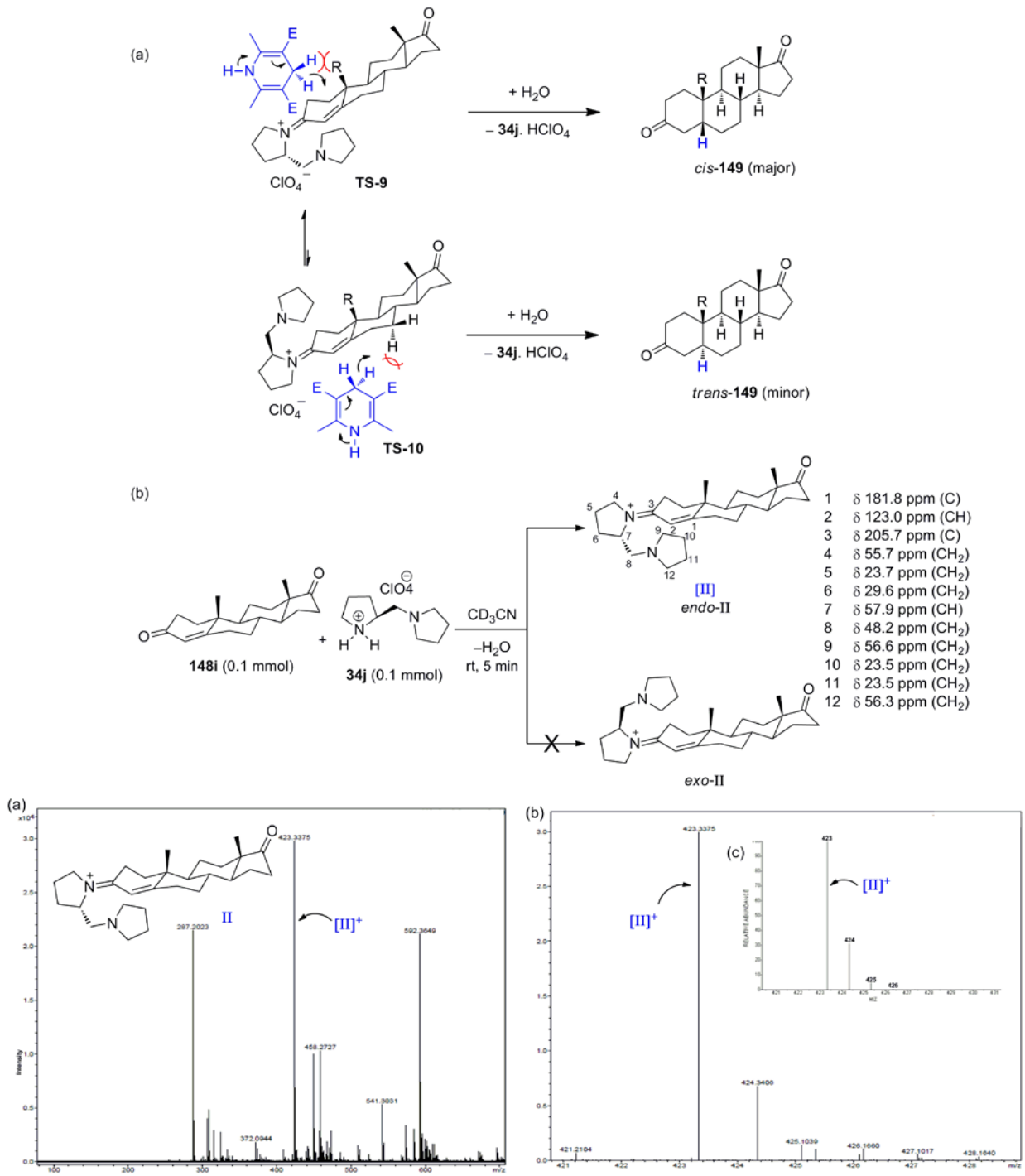
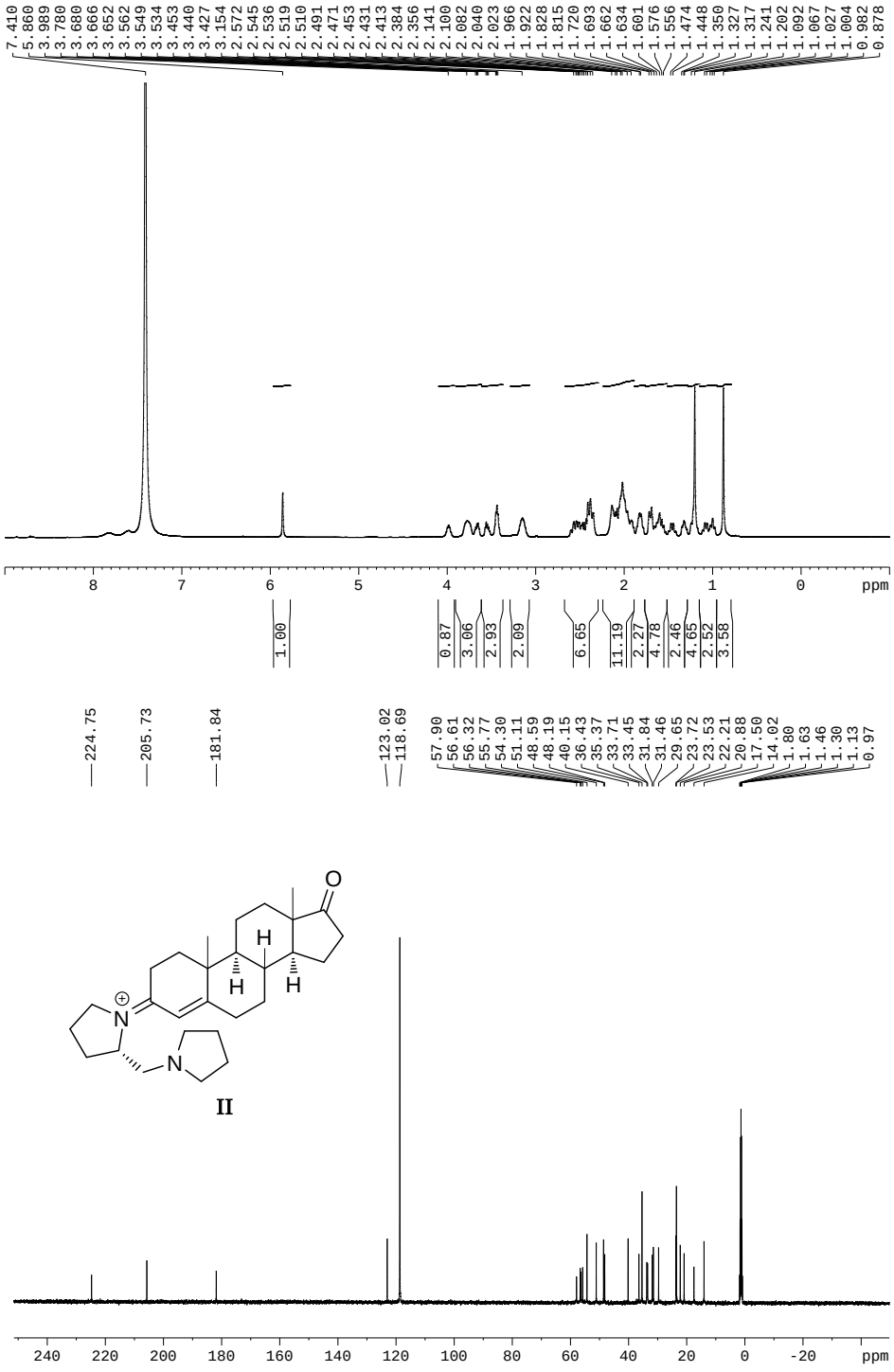


Figure-57: (a) ESI-HRMS (positive mode) spectrum of the reaction of **148i** and **34j** in CD_3CN after 5 min at rt. (b) The observed ESI-HRMS isotopic pattern of pre-transition state intermediate $[\mathbf{II}]^+$. (c) The simulated ESI-HRMS isotopic pattern of pre-transition state intermediate $[\mathbf{II}]^+$.



II

Figure-58: ^{1}H and ^{13}C NMR spectra of the pre-transition intermediate (**II**).

Finally, a comparative study was carried out to understand the selectivity and reactivity of various catalyses in the reduction of steroid **148e** (eq. 31). The hydrogenation of **148e** catalyzed by **34j**.D-CSA with Hantzsch ester **50a** as hydrogen source (Condition-1) in CH_3CN under refluxing for 72 h yielded *cis*-(+)-**149e** in 77% yield with 71% de. The same steroid **148e** under Pd/C catalysis with **50a** (Condition-14) in EtOH under refluxing for 16 h resulted *cis*-(+)-**149e** in 79% yield with reduced 65% de. When hydrogen gas was used as the source with Pd/C (Condition-16) for the hydrogenation of **148e**, opposite isomer *trans*-(+)-**149e** was obtained as the major product with 37% yield and only 41% de. Thus organocatalytic hydrogenation (Condition-1) and Pd mediated hydrogenation (Condition-14) with Hantzsch ester **50a** as hydrogen source are better conditions compared to hydrogen gas over Pd/C condition, which highlights the importance of NADPH-mimicking organic hydrides in hydrogenations.

In a similar manner, the mechanism for Pd-catalyzed Hantzsch ester **50a** mediated hydrogenations can be proposed based on the controlled experiments and also recent Pd-mediated hydrogenations reported by Liu et al.[57a] The observation of generation of hydrogen gas from Hantzsch ester **50a** over Pd surface under refluxing condition and hydrogenation of non-activated double bond in steroid **148f** (see Table 11, entry 6) reveal that the reaction goes through hydrogen addition rather than hydride addition. Although, *in situ* generated hydrogen molecules participate in the hydrogenation reactions, it is found to be more selective than the

hydrogenation, where neat hydrogen gas is used (eq. 31). The reason may be due to the fact that the Hantzsch ester releases a controlled number of active H_2 molecules to the reaction mixture which are readily consumed during hydrogenation. The availability of sufficient number of hydrogen molecules makes the reaction more selective compared to the condition where the atmosphere is totally filled up with hydrogen gas.

6.3.3 Synthetic applications:

Due to the wide pharmaceutical applications of the 5β-dihydro-3-ketosteroids, various synthetic transformations were carried out on the products **149** to provide many important key intermediates of natural and designed products. As a part of synthetic utility, 5β-cholestan-3-one **149m** was successfully transformed to *epi*-coprostanol[64] (+)-**152m** with 1.5 equiv of $NaBH_4$ in EtOH at 0 °C for 5 min. The product (+)-**152m** was obtained in 95% yield with 78% de (eq. 32). With the scope of getting synthetically useful precursor (+)-**152g**[59], the hydrogenated product **149g** was deacetylated using 20% methanolic KOH at rt for 2 h to yield (+)-**152g** in 92% yield and >99% de (eq. 33).

For the demonstration of better synthetic strategies for the preparation of key intermediate *cis*-**149a**, hydrogenated product *cis*-**149b** was oxidized using 14 equiv of PDC in DCM for 48 h at rt. The product *cis*-**149a** was isolated in 85% yield with 74% de (eq. 34). Same oxidation methodology was applied for the synthesis of (+)-**149t** from **149c**, where **149t** was isolated in 80% yield with >99% de (eq. 34). The product **149t** is the key intermediate in the total synthesis of deoxycholic acid (DCA) and thus emphasizes the synthetic importance of the organocatalytic hydrogenations.[55]

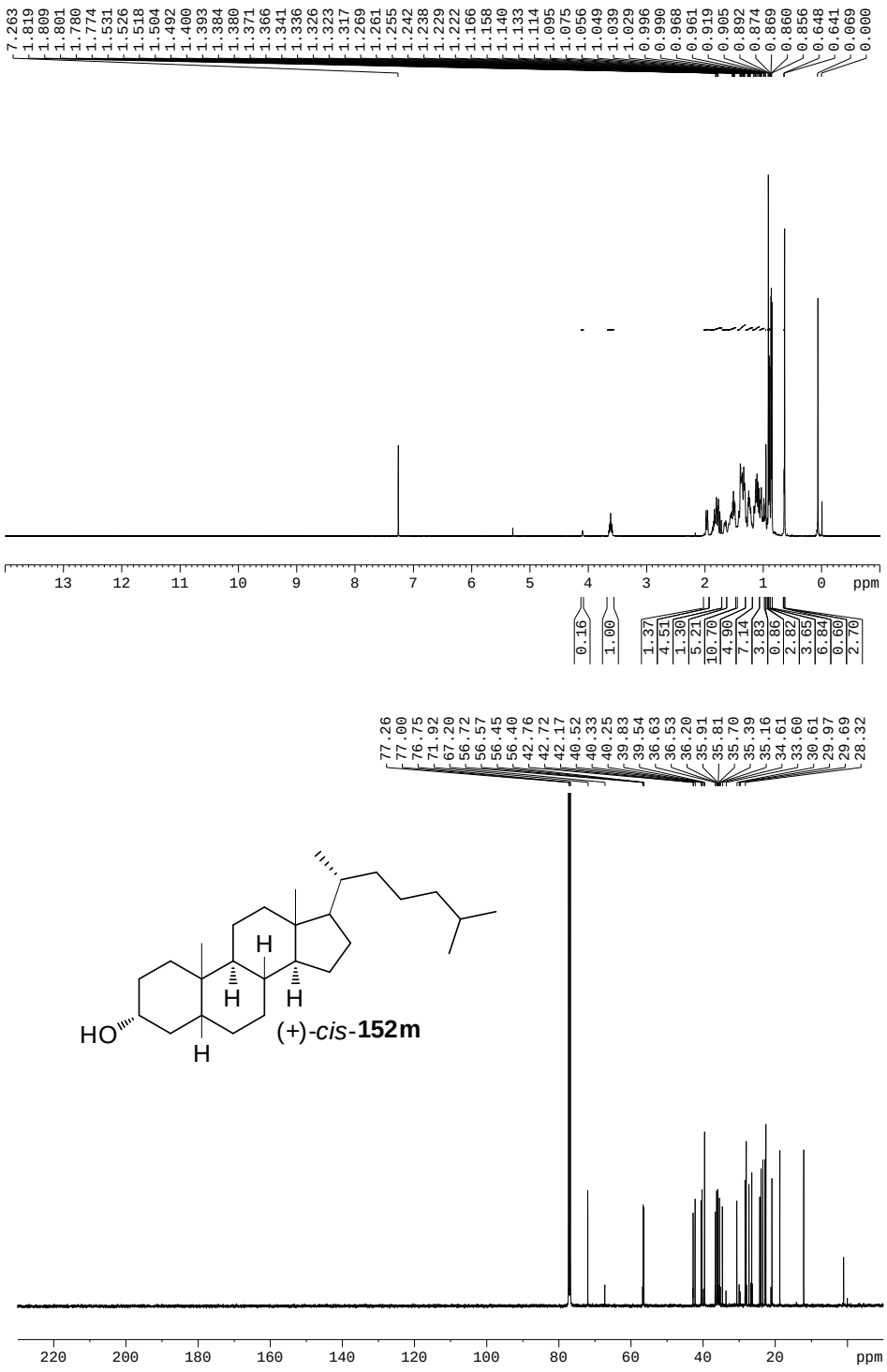


Figure-59: ^{1}H and ^{13}C NMR spectra of the product **152m**.

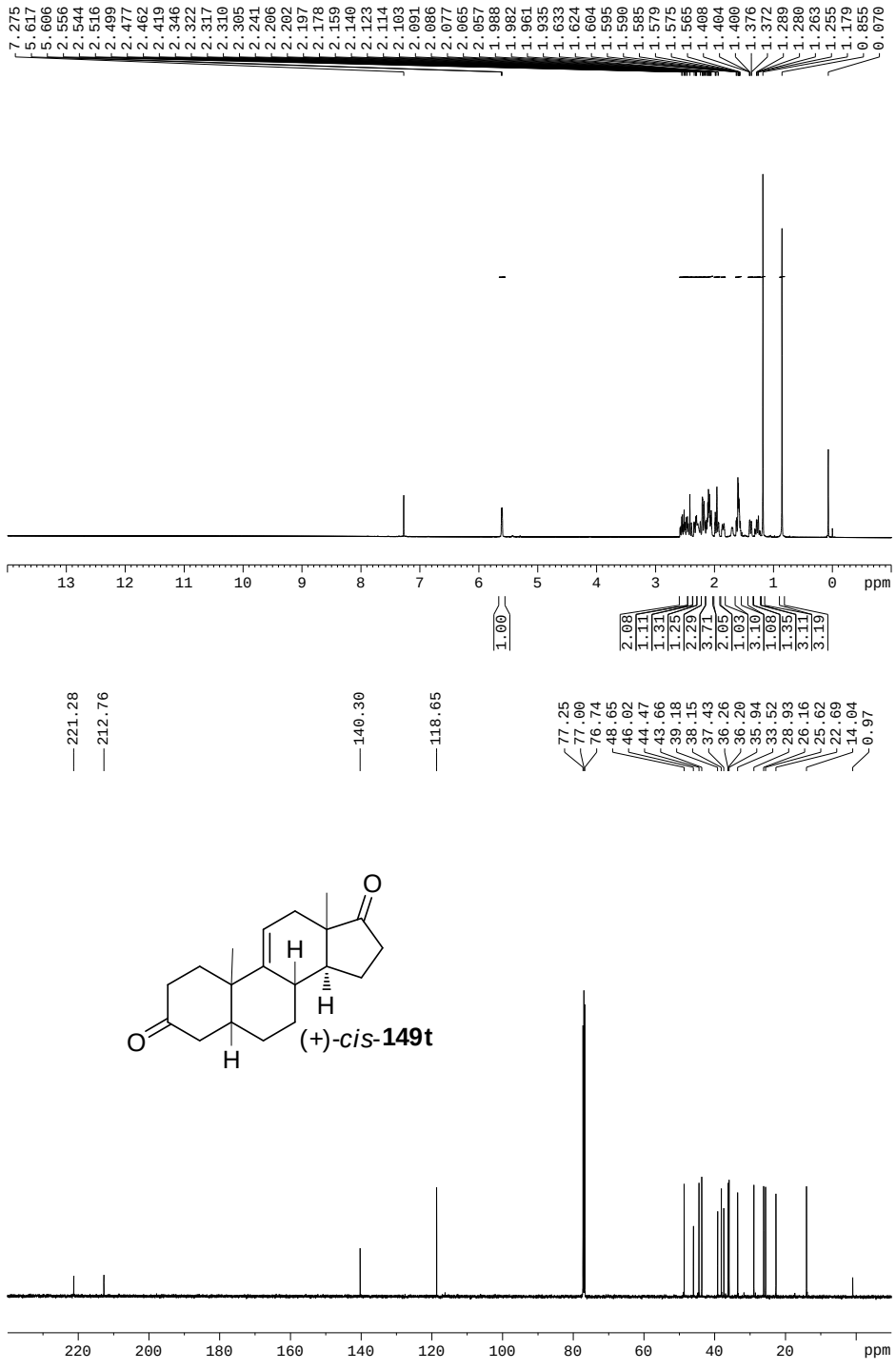
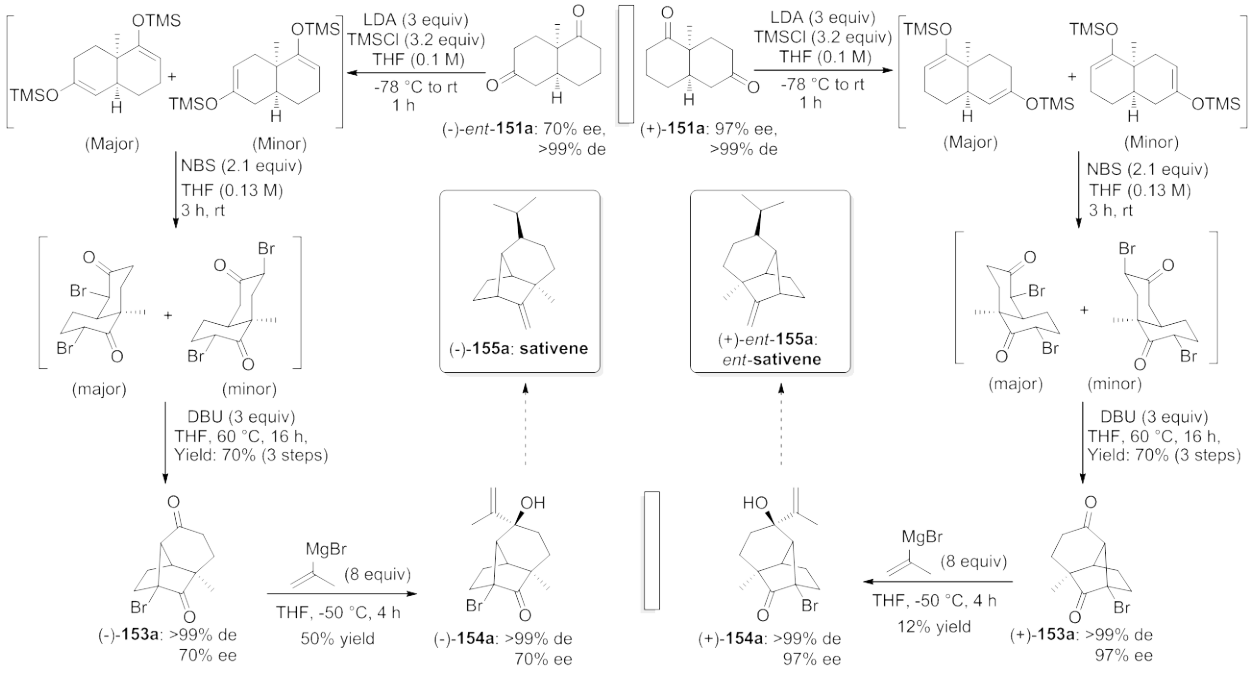


Figure-60: ^{1}H and ^{13}C NMR spectra of the product **149t**.

6.3.4 Formal total synthesis of sativene 155:

The direct synthetic application of *cis*-bicyclo diketone has been exemplified through a formal total synthesis of terpene sativene **155a** and its enantiomer *ent*-**155a** (Scheme 10).[68,58j] In the initial step, the diastereomerically pure hydrogenated product (-)-**151a** with 70% ee was transformed to silyl enol ether by reacting with LDA (3 equiv) and TMSCl (3.2 equiv) in THF at -78 °C to rt for 1 h. The crude mixture containing regio-isomeric silyl enol ethers was treated with NBS in THF at rt for 3 h, which yielded a mixture of dibromides. The crude dibromide after aqueous work-up was subjected to dehydrohalogenation condition by heating with DBU in THF at 60 °C for 16 h. The tricyclic ketone (-)-**153a** was obtained as a single diastereomer with an overall yield of 70% after 3 consecutive steps without any intermediate purification (Scheme 10).

Scheme 10: Formal Total Synthesis of Sativene **155a** and *ent*-Sativene *ent*-**155a**.



The subsequent Grignard reaction of (-)-**153a** with isopropenyl magnesium bromide (8 equiv) in THF at -50 °C for 4 h resulted the tricyclic alcohol (-)-**154a** in 50% yield, >99% de and 70% ee. The product **154a** is the key core structure, from which (-)-sativene **155a** can be synthesized through few synthetic transformations as demonstrated by Karimi in his total synthesis (Scheme 10).[58j] The enantiomer of tricyclic alcohol **154a** was also synthesized by following a similar sequence from (+)-**151a** with 97% ee and the product (+)-**154a** was isolated

in 12% yield, >99% de and 97% ee, which could be driven to the total synthesis of *ent*-sativene (+)-**155a** (Scheme 10). Thus, high-yielding chiral formal total synthesis of sativene (-)-**155a** and its enantiomer (+)-**155a** was demonstrated starting from the hydrogenated bicyclic ketones (-)-*ent*-**151a** and (+)-**151a** respectively.

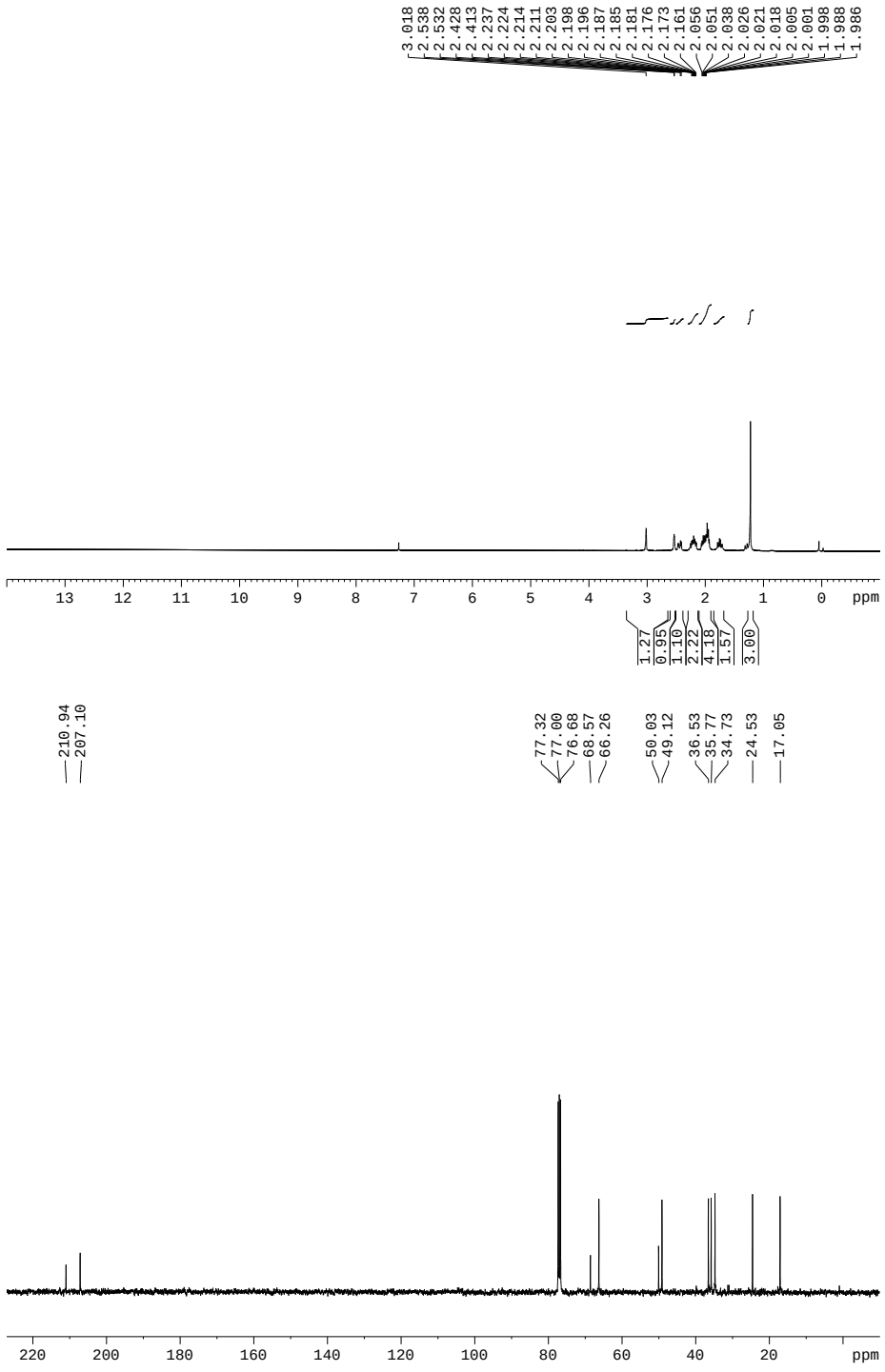


Figure-61: ^{1}H and ^{13}C NMR spectra of the product **153a**.

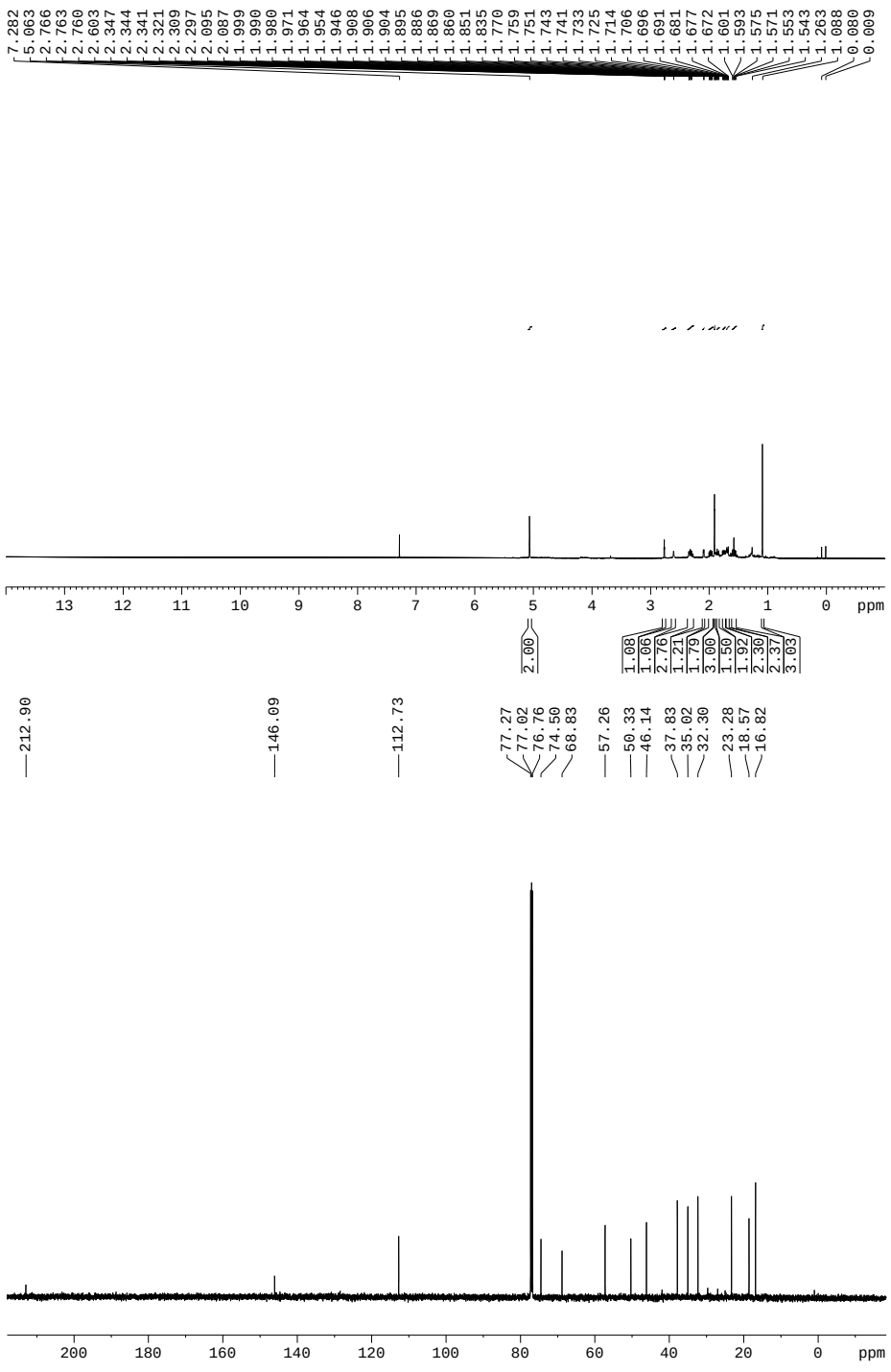


Figure-62: ^{1}H and ^{13}C NMR spectra of the product **154a**.

6.4 Conclusions

In conclusion, an organocatalytic hydrogenation methodology has been successfully demonstrated to mimic the 5β-reductase for the hydrogenation of various chiral cyclic enones. Diversity oriented diastereoselective synthesis of many 5β-dihydro-3-keto steroids is reported, which have broad medicinal and pharmaceutical applications. The mechanistic studies and the selectivity of the products clearly indicate that the catalyst **34j**.D-CSA acts as an enzyme mimic of 5β-reductase during organocatalytic hydrogenations with Hantzsch ester **50a** (a NADPH analogue) as hydrogen source. Further evidence for the selective formation of intermediate iminium species $[\mathbf{I}]^+$ and $[\mathbf{II}]^+$ has been given through NMR and ESI-HRMS analyses. A clear understanding of reactivity and selectivity of amine **34j**-catalysis would definitely shed light on the puzzle in the substrate/product selectivity of *in vivo* 5β-reductase catalysis.

ANNEXURE-IV: Synthesis of Functionalized 4-Ene-3-ketosteroids 148 and Enones 150.

All steroid starting materials were used as received generous gift from Dr. C. S. Venkatesan, Gland Pharma Limited, Hyderabad, India. Starting materials **148a**,[61e] **148n** (Procedure **4k**, see Experimental Section), **148o** (Procedure **4l**, see Experimental Section), **150a-j**,[61a,61d] **150e** (Procedure **4j**, see Experimental Section), **150f** and **152l**,[61b] **150g**,[61f] **150k**,[61c] **150m**[61g] were prepared following the literature or modified procedures (eq. A-5 to A-12).

Relative and absolute stereochemistry of the product (+)-**151f** was established through oxidation and X-ray crystallography on the resulting product (+)-**151a** as shown in eq. A-13.

Demonstration of Sequential One-pot Combination of Multi-catalysis Cascade and Multi-component Reactions:

The synthetic importance of one-pot asymmetric strategy has been demonstrated by the synthesis of hydrogenated W-M and H-P ketones *cis*-**151a** and *cis*-**151h** via combination of multi-catalysis and multi-component in a single flask as shown in Scheme A5.[69] Reaction of three equiv of methyl vinyl ketone with 2-methyl-cyclohexane-1,3-dione under Et_3N-catalysis in CH_3CN at 25 °C for 24 h furnished the expected Michael adduct, 2-methyl-2-(3-oxo-butyl)-cyclohexane-1,3-dione in good yield. Catalysts 50 mol% of L-proline **34a** and 25 mol% of $HClO_4$ were added to the crude reaction mixture and stirring continued at 85 °C for 24 h to furnish the expected W-M ketone **151a** in good yield with 75% ee, which on treatment with two equiv of Hantzsch ester **50a** and 25 mol% of (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **34j** and stirring continued at 85 °C for 24 h to furnish the expected hydrogenated W-M ketone *cis*-**151a** in 45% yield with >99% de as shown in Scheme A5. Successful combination of multi-catalysis and multi-component reactions under amine-, amino acid-, acid- and amine/acid-catalysis was demonstrated by one more example as shown in Scheme A5 and this one-pot synthetic strategy will show much impact on asymmetric synthesis of functionalized small molecules.

Scheme A5: Combining multi-catalysis and multi-component systems for the one-pot asymmetric bio-mimetic reactions.

Interestingly, multi-catalysis and multi-component strategy did not show much difference in terms of enantioselectivity compared to two-component reaction under amino acid-catalysis for hydrogenated W-M ketone *cis*-**151a** synthesis; but difference is shown in one-pot synthesis of hydrogenated H-P ketone *cis*-**151h**. In one-pot, multi-catalysis and multi-component synthesis of hydrogenated H-P ketone *cis*-**151h**, ee of the *cis*-**151h** is drastically decreased from 86% to 20% as shown in Scheme A5 may be due to the involvement of Et_3N in the transition state of proline-mediated asymmetric intramolecular aldol reaction.

Thus the new concept of combination of multi-catalysis and multi-component in one-pot has been developed to deliver the highly functionalized molecules. This combination resulted due to the inspiration from cellular reactions, compliments conventional organic synthesis.

7. Experimental Section

1. General experimental procedures for the asymmetric BLA reactions

1a. ***General procedure for amino acid-catalyzed BLA reaction of acetone 32a with 2-hydroxybenzaldehydes 37:*** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of 2-hydroxybenzaldehydes **37**, 20 mol% of amino acid **34**, added 0.5 mL of solvent followed by 7.0 mmol of acetone **32a/d** and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1, 2 and 3. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure BLA products **109/110** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1b. ***Amino acid/amine-catalyzed one-pot BLA/tosylation reactions:*** In an ordinary glass vial equipped with a magnetic stirring bar, to 2-hydroxybenzaldehydes **37** (0.5 mmol), *trans*-4-OH-L-proline **34l** (13 mg, 20 mol%), added 0.5 mL of NMP followed by acetone **32a** (0.5 mL, 7 mmol) and the reaction mixture was stirred at 25 °C for 24 h. Then the reaction mixture was cooled to 0 °C, and added *p*-TsCl (669 mg, 3.5 mmol), dry Et_3N (0.42 mL, 3 mmol) and 2 mL of dry dichloromethane under N_2 atmosphere, stirred at same temperature for 1 h and slowly brought to 25 °C. After 1 h stirring at 25 °C, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **114** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1c. ***Tosylation reaction of BLA products:*** In an ordinary glass vial equipped with a magnetic stirring bar, to BLA product **109ah/110ah** or **109ak/110ak** (0.1 mmol) in 1 mL dry DCM under N_2 atmosphere, cooled to 0 °C were added *p*-TsCl (133 mg, 0.7 mmol), dry Et_3N (83 mL, 0.6 mmol). The reaction mixture was stirred at same temperature for 1 h and slowly brought to 25 °C. After 1 h stirring at 25 °C, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure tosylated products **114ah** or **114ak** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*R*)-4-Hydroxy-4-(2-hydroxy-phenyl)-butan-2-one (109aa) and (2*R*, 4*R*)-2-Methyl-chroman-2,4-diol (110aa): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The BLA product **109aa/110aa** was found to exist in rapid equilibrium with 1:1 ratio of aldol↔lactol products in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 96:4, flow rate 0.3 mL/min, λ = 254 nm), t_R = 73.57 min (major), t_R = 87.27 min (minor). **$[\alpha]_D^{25}$ = +9.7°** (*c* = 1.0 g/100 mL, CH_3OH, **77% *ee***); IR (Neat): ν_{max} 3412 (O-H), 1699 (*C*=O), 1606 (C=C), 1489, 1458, 1248, 1111 and 885 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of δ-hydroxy ketone **109aa** and lactol **110aa**) δ 8.17 (1H, br s, Ar-O*H*), 7.33-7.13 (3H, m), 6.99-6.94 (2H, m), 6.88-6.80 (3H, m), 5.30 (1H, dd, *J* = 10.0, 2.8 Hz), 4.78 (1H, br s, OH), 4.73 (1H, s), 4.37 (1H, br s, OH), 3.38 (1H, br d, *J* = 8.0 Hz, OH), 3.08 (1H, dd, *J* = 18.0, 10.0 Hz), 2.86 (1H, dd, *J* = 18.0, 2.8 Hz), 2.45 (1H, dd, *J* = 14.4, 2.0 Hz), 2.21 (3H, s, C*H*$_3$), 2.08 (1H, dd. *J* = 14.6, 4.0 Hz), 1.66 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of δ-hydroxy ketone **109aa** and lactol **110aa**) δ 210.1 (C, *C*=O), 155.6 (C), 151.4 (C), 130.02 (CH), 130.00 (CH), 129.2 (CH), 126.5 (CH), 125.6 (C), 123.1 (C), 121.3 (CH), 120.0 (CH), 117.6 (CH), 117.4 (CH), 97.5 (C), 71.1 (CH), 64.5 (CH), 49.6 (CH_2), 38.2 (CH_2), 30.6 (CH_3), 28.8 (CH_3); HRMS m/z 203.0684 (M + Na), calcd for $C_{10}H_{12}O_3Na$ 203.0684.

(4*R*)-4-(2,3-Dihydroxy-phenyl)-4-hydroxy-butan-2-one (109ac) and (2*R*, 4*R*)-2-Methyl-chroman-2,4,8-triol (110ac): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The BLA product **109ac/110ac** was found to exist in rapid equilibrium with 1:1 ratio of aldol↔lactol products in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 95:5, flow rate 0.3 mL/min, λ = 254 nm), t_R = 226.57 min (major), t_R = 281.41 min (minor). **$[\alpha]_D^{25}$ = +3.3°** (*c* = 1.5 g/100 mL, CH_3OH, **90% *ee***); IR

(Neat): ν_{max} 3384 (OH), 1708 (*C*=O), 1479 (C=C), 1373, 1253, 1205, 1105, 1050, 737 and 648 cm^{-1}; ^1H NMR ($CDCl_3$ + 4 drops MeOH-d_4, 1:1 mixture of δ-hydroxy ketone **109ac** and lactol **110ac**) δ 6.90-6.80 (3H, m), 6.80-6.75 (1H, m), 6.72 (1H, t, *J* = 7.6 Hz), 6.66 (1H, dd, *J* = 7.6, 1.2 Hz), 5.33 (1H, dd, *J* = 9.2, 3.6 Hz), 4.75 (1H, br s), 3.03 (1H, dd. *J* = 16.8, 9.2 Hz), 2.86 (1H, dd, *J* = 17.2, 3.6 Hz), 2.41 (1H, dd, *J* = 14.6, 2.4 Hz), 2.20 (3H, s, C*H*$_3$), 2.08 (1H, dd, *J* = 14.4, 4.0 Hz), 1.66 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$ + 4 drops of MeOH-d_4, DEPT-135, 1:1 mixture of δ-hydroxy ketone **109ac** and lactol **110ac**) δ 209.7 (C, *C*=O), 144.8 (2 x C), 142.2 (C), 139.2 (C), 127.8 (C), 123.6 (C), 120.9 (CH), 120.7 (CH), 120.0 (CH), 117.4 (CH), 115.0 (CH), 114.3 (CH), 97.9 (C), 68.4 (CH), 64.0 (CH), 50.3 (CH_2), 38.4 (CH_2), 30.5 (CH_3), 27.9 (CH_3); LRMS m/z 195.00 (M - H^+), calcd for $C_{10}H_{12}O_4$ 196.0736; HRMS m/z 219.0620 (M + Na), calcd for $C_{10}H_{12}O_4Na$ 219.0633.

(1*R*, 3*R*)-3-Methyl-2,3-dihydro-1H-benzo[*f*]chromene-1,3-diol (110ad): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as solid. The BLA product **109ad/110ad** was found to exist only in lactol form **110ad** in solution. The enantiomeric excess (ee) of **110ad** was determined via tosylated product **114ad** by chiral stationary phase HPLC analysis as shown below (see A-1, Annexure-I). Mp 104 °C. **$[\alpha]_D^{25}$ = –7.0°** (*c* = 0.4 g/100 mL, CH_3OH, **26% *ee***); IR (Neat): ν_{max} 3326 (O*H*), 2928, 2855, 1712, 1403, 1265, 1223, 1168, 1097, 1075, 1034, 879, 820 and 652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (1H, d, *J* = 8.4 Hz), 7.75 (1H, br d, *J* = 8.0 Hz), 7.70 (1H, br d, *J* = 8.0 Hz), 7.50 (1H, br t, *J* = 7.2 Hz), 7.35 (1H, t, *J* = 7.6 Hz), 7.04 (1H, d. *J* = 8.8 Hz), 5.34 (1H, d, *J* = 2.4 Hz), 4.91 (1H, br s, OH), 3.54 (1H, br s, OH), 2.55 (1H, br d, *J* = 14.4 Hz), 2.12 (1H, br dd, *J* = 14.4, 4.4 Hz), 1.70 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.3 (C), 132.3 (C), 130.6 (CH), 129.3 (C), 128.5 (CH), 127.2 (CH), 123.8 (CH), 122.0 (CH), 119.2 (CH), 114.3 (C), 97.4 (C), 61.2 (CH), 38.2 (CH_2), 28.6 (CH_3); LRMS m/z 229.00 (M - H^+), calcd for $C_{14}H_{14}O_3$ 230.0943; HRMS m/z 253.0852 (M + Na), calcd for $C_{14}H_{14}O_3Na$ 253.0841.

(1*R*)-Toluene-4-sulfonicacid-2-(1-hydroxy-3-oxo-butyl)-naphthalen-1-yl ester (114ad): Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as solid (see A-1,

Annexure-I). The ee was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/i-PrOH = 80:20, flow rate 0.8 mL/min, λ = 254 nm), t_R = 17.54 min (major), t_R = 20.33 min (minor). Mp 80 °C; **$[\alpha]_D^{25}$ = –1.4°** (*c* = 1.425 g/100 mL, $CHCl_3$, **26% *ee***); IR (Neat): ν_{max} 3408 (OH), 1706 (*C*=O), 1364, 1171, 1090, 949, 820, 714 and 677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.67 (1H, d, *J* = 8.4 Hz), 7.82 (3H, d, *J* = 8.4 Hz), 7.71 (1H, d, *J* = 9.2 Hz), 7.54-7.47 (2H, m), 7.37 (2H, d, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 8.8 Hz), 6.00 (1H, dd, *J* = 10.4, 4.0 Hz), 3.47 (1H, dd, *J* = 17.8, 10.0 Hz), 3.09 (1H, br s, OH), 2.77 (1H, dd, *J* = 17.8, 2.4 Hz), 2.46 (3H, s, C*H*$_3$), 2.20 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (C, *C*=O), 145.7 (C), 143.8 (C), 133.0 (C), 132.7 (C), 132.0 (C), 130.0 (3 x CH), 129.9 (C), 128.7 (CH), 128.5 (2 x CH), 126.6 (CH), 126.5 (CH), 126.1 (CH), 120.9 (CH), 64.5 (CH), 49.5 (CH_2), 30.3 (CH_3), 21.7 (CH_3); LRMS m/z 384.85 ($M + H^+$), calcd for $C_{21}H_{20}O_5SH$ 384.1031; Anal. calcd for $C_{21}H_{20}O_5S$ (384.1031); C, 65.61; H, 5.24. Found: C, 65.648; H, 5.199%.

(4*R*)-4-Hydroxy-4-(2-hydroxy-5-methyl-phenyl)-butan-2-one (109ae) and (2*R*, 4*R*)-2,6-Dimethyl-chroman-2,4-diol (110ae): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as solid. The BLA product **109ae/110ae** was found to exist in rapid equilibrium with 1:1 ratio of aldol↔lactol products in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 95:5, flow rate 0.3 mL/min, λ = 254 nm), t_R = 76.78 min (major), t_R = 87.53 min (minor); Mp 84 °C; **$[\alpha]_D^{25}$ = +1.7°** (*c* = 0.575 g/100 mL, CH_3OH, **89% *ee***); IR (Neat): ν_{max} 3381 (O*H*), 1695 (*C*=O), 1661, 1477, 1416 and 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of δ-hydroxy ketone **109ae** and lactol **110ae**) δ 7.99 (1H, br s, Ar-OH), 7.12 (1H, br s), 7.03 (1H, br d, *J* = 8.0 Hz), 6.95 (1H, br d, *J* = 8.0 Hz), 6.77-6.75 (3H, m), 5.24 (1H, br dd, *J* = 8.6, 2.0 Hz), 4.86 (1H, s), 4.72 (1H, br s, OH), 4.37 (1H, br s, OH), 3.60 (1H, br s, OH), 3.05 (1H, dd, *J* = 18.0, 9.6 Hz), 2.83 (1H, dd, *J* = 17.8, 2.8 Hz), 2.41 (1H, dd, *J* = 14.6, 0.8 Hz), 2.27 (3H, s, C*H*$_3$), 2.23 (3H, s, C*H*$_3$), 2.19 (3H, s, C*H*$_3$), 2.05 (1H, dd. *J* = 14.6, 4.0 Hz), 1.63 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of

δ-hydroxy ketone **109ae** and lactol **110ae**) δ 210.1 (C, *C*=O), 153.0 (C), 149.1 (C), 130.7 (CH), 130.5 (C), 130.2 (CH), 129.5 (CH), 129.1 (C), 127.0 (CH), 125.6 (C), 122.7 (C), 117.3 (CH), 117.1 (CH), 97.4 (C), 70.8 (CH), 64.5 (CH), 49.8 (CH_2), 38.3 (CH_2), 30.6 (CH_3), 28.7 (CH_3), 20.4 (2 x CH_3); LRMS m/z 192.55 (M - H^+), calcd for $C_{11}H_{14}O_3$ 194.0943; HRMS m/z 217.0841 (M + Na), calcd for $C_{11}H_{14}O_3Na$ 217.0841.

(4*R*)-4-(5-Fluoro-2-hydroxy-phenyl)-4-hydroxy-butan-2-one (109af) and (2*R*, 4*R*)-6-Fluoro-2-methylchroman-2,4-diol (110af): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The BLA product **109af/110af** was found to exist in rapid equilibrium with 1:1 ratio of aldol↔lactol products in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 96:4, flow rate 0.3 mL/min, λ = 254 nm), t_R = 71.98 min (major), t_R = 102.04 min (minor); **$[\alpha]_D^{25}$ = +15.6°** (*c* = 0.925 g/100 mL, CH_3OH, **87% *ee***); IR (Neat): ν_{max} 3356 (OH), 1707 (*C*=O), 1492 (C=C), 1441, 1379, 1245, 1196, 1142, 1087, 875 and 818 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of δ-hydroxy ketone **109af** and lactol **110af**) δ 7.99 (1H, br s, Ar-OH), 7.02 (1H, dd, *J* = 8.4, 3.2 Hz), 6.93 (1H, td, *J* = 8.6, 3.2 Hz), 6.87-6.73 (3H, m), 6.72 (1H, dd, *J* = 8.8, 2.8 Hz), 5.25 (1H, br d, *J* = 8.8 Hz), 4.74 (1H, s), 4.69 (1H, br s, OH), 4.44 (1H, br s, OH), 3.88 (1H, br d, *J* = 6.8 Hz, OH), 3.04 (1H, dd, *J* = 18.0, 9.6 Hz), 2.86 (1H, dd, *J* = 18.0, 3.2 Hz), 2.41 (1H, dd, *J* = 7.6, 1.6 Hz), 2.21 (3H, s, C*H*$_3$), 2.04 (1H, dd, *J* = 14.4, 1.4 Hz), 1.64 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of δ-hydroxy ketone **109af** and lactol **110af**) δ 210.0 (C, *C*=O), 157.1 (C, d, *J* = 238.3 Hz), 156.5 (C, d, *J* = 236.6 Hz), 151.1 (C, d, *J* = 3.5 Hz), 147.3 (C, d, *J* = 3.5 Hz), 127.2 (C, d, *J* = 6.5 Hz), 124.2 (C, d, *J* = 6.6 Hz), 118.6 (CH, d, *J* = 7.7 Hz), 118.1 (CH, d, *J* = 7.7 Hz), 116.8 (CH, d, *J* = 23.0 Hz), 115.8 (CH, d, *J* = 22.2 Hz), 115.3 (CH, d, *J* = 22.5 Hz), 113.0 (CH, d, *J* = 23.8 Hz), 97.7 (C), 69.8 (CH), 64.2 (CH), 49.5 (CH_2), 38.1 (CH_2), 30.2 (CH_3), 28.7 (CH_3); LRMS m/z 197.00 (M - H^+), calcd for $C_{10}H_{11}FO_3$ 198.0692; HRMS m/z 221.0579 (M + Na), calcd for $C_{10}H_{11}FO_3Na$ 221.0590.

(4*R*)-4-(5-Chloro-2-hydroxy-phenyl)-4-hydroxy-butan-2-one (109ag) and (2*R*, 4*R*)-6-Chloro-2-methyl-chroman-2,4-diol (110ag): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as solid. The BLA product **109ag/110ag** was found to exist in rapid equilibrium with 1:1 ratio of aldol↔lactol products in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis. The enantiomeric excess (ee) was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 95:5, flow rate 0.3 mL/min, λ = 254 nm), t_R = 79.97 min (major), t_R = 96.67 min (minor); Mp 70 °C; **$[\alpha]_D^{25}$ = +10.7°** (*c* = 0.9 g/100 mL, CH_3OH, **88% *ee***); IR (Neat): ν_{max} 3384 (O*H*), 1692 (*C*=O), 1479, 1423, 1256 and 1118 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of δ-hydroxy ketone **109ag** and lactol **110ag**) δ 8.23 (1H, br s, Ar-OH), 7.31 (1H, d, *J* = 2.4 Hz), 7.18 (1H, dd, *J* = 8.6, 2.8 Hz), 7.11 (1H, dd, *J* = 8.8, 2.4 Hz), 6.96 (1H, d, *J* = 2.4 Hz), 6.80 (2H, d, *J* = 8.8 Hz), 5.26 (1H, br d, *J* = 9.6 Hz), 4.72 (1H, br s, OH), 4.68 (1H, s), 4.47 (1H, br s, OH), 3.67 (1H, br d, *J* = 7.2 Hz, OH), 3.04 (1H, dd, *J* = 18.4, 10.0 Hz), 2.87 (1H, dd, *J* = 18.2, 3.2 Hz), 2.44 (1H, dd, *J* = 14.6, 2.0 Hz), 2.23 (3H, s, C*H*$_3$), 2.05 (1H, dd, *J* = 14.6, 4.4 Hz), 1.65 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of δ-hydroxy ketone **109ag** and lactol **110ag**) δ 209.9 (C, *C*=O), 154.1 (C), 150.0 (C), 129.9 (CH), 129.7 (CH), 128.9 (CH), 127.2 (C), 126.3 (CH), 125.9 (C), 124.6 (2 x C), 119.0 (CH), 118.7 (CH), 97.8 (C), 70.2 (CH), 64.1 (CH), 49.4 (CH_2), 38.0 (CH_2), 30.6 (CH_3), 28.7 (CH_3); LRMS m/z 212.55 (M - H^+), calcd for $C_{10}H_{11}ClO_3$ 214.0397; HRMS m/z 237.0295 (M + Na), calcd for $C_{10}H_{11}ClO_3Na$ 237.0294.

(4*R*)-4-(5-Bromo-2-hydroxy-phenyl)-4-hydroxy-butan-2-one (109ah) and (2*R*, 4*R*)-6-Bromo-2-methyl-chroman-2,4-diol (110ah): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as solid. The BLA product **109ah/110ah** was found to exist in rapid equilibrium with 1:1 ratio of aldol↔lactol products in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis. The enantiomeric excess (ee) was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 96:4, flow rate

0.3 mL/min, λ = 254 nm), t_R = 118.86 min (major), t_R = 136.90 min (minor); Mp 62 °C; **$[\alpha]_D^{25}$ = +5.9°** (*c* = 1.1 g/100 mL, CH_3OH, **86% *ee***); The enantiomeric excess (ee) of **109ah/110ah** was also confirmed via tosylated product **114ah** by chiral stationary phase HPLC analysis as shown below (see A-2, Annexure-I). IR (Neat): ν_{max} 3433 (OH), 1659 (*C*=O), 1650, 1409, 1304, 660 and 620 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of δ-hydroxy ketone **109ah** and lactol **110ah**) δ 8.26 (1H, br s, Ar-OH), 7.44 (1H, d, *J* = 2.0 Hz), 7.31 (1H, dd, *J* = 8.6, 2.0 Hz), 7.25 (1H, dd, *J* = 8.8, 2.4 Hz), 7.10 (1H, d, *J* = 1.6 Hz), 6.75-6.73 (2H, m), 5.25 (1H, br dd, *J* = 10.0, 2.0 Hz), 4.79 (1H, s), 4.71 (1H, br s, OH), 4.48 (1H, br s, OH), 3.75 (1H, br s, OH), 3.03 (1H, dd, *J* = 18.2, 10.0 Hz), 2.86 (1H, dd, *J* = 18.2, 2.8 Hz), 2.43 (1H, d, *J* = 14.0 Hz), 2.22 (3H, s, C*H*$_3$), 2.04 (1H, dd, *J* = 14.4, 4.0 Hz), 1.65 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of δ-hydroxy ketone **109ah** and lactol **110ah**) δ 210.2 (C, *C*=O), 154.4 (C), 150.8 (C), 132.80 (CH), 132.78 (CH), 131.8 (CH), 129.3 (CH), 128.0 (C), 125.2 (C), 119.6 (CH), 119.2 (CH), 113.1 (C), 111.9 (C), 97.8 (C), 70.1 (CH), 60.0 (CH), 49.4 (CH_2), 37.9 (CH_2), 30.7 (CH_3), 28.6 (CH_3); LRMS m/z 256.50 (M - H^+), calcd for $C_{10}H_{11}BrO_3$ 257.9892; HRMS m/z 280.9788 (M + Na), calcd for $C_{10}H_{11}BrO_3Na$ 280.9789.

(1*R*)-Toluene-4-sulfonic acid 4-bromo-2-(1-hydroxy-3-oxo-butyl)-phenyl ester (114ah): Prepared following the procedure **1c** and purified by column chromatography using EtOAc/hexane and isolated as liquid (see A-2, Annexure-I). The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 92:8, flow rate 0.8 mL/min, λ = 254 nm), t_R = 10.93 min (minor), t_R = 14.18 min (major). **$[\alpha]_D^{25}$ = +9.5°** (*c* = 0.5 g/100 mL, $CHCl_3$, **85% *ee***); IR (Neat): ν_{max} 3470 (O*H*), 1712, 1596, 1472, 1374, 1178, 1807, 858, 821, 747 and 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (2H, d, *J* = 8.4 Hz), 7.70 (1H, d, *J* = 2.4 Hz), 7.36 (2H, d, *J* = 8.4 Hz), 7.33 (1H, dd, *J* = 8.8, 2.8 Hz), 6.91 (1H, d, *J* = 8.0 Hz), 5.20 (1H, dd, *J* = 8.2, 2.0 Hz), 3.38 (1H, br s, O*H*), 2.78 (1H, dd, *J* = 17.6, 2.8 Hz), 2.67 (1H, dd, *J* = 17.6, 9.6 Hz), 2.47 (3H, s), 2.17 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (C, *C*=O), 146.0 (C), 144.7 (C), 138.2 (C), 132.2 (C), 131.5 (CH), 130.8 (CH), 130.0 (2 x CH), 128.3 (2 x CH), 123.7 (CH), 121.0 (C), 63.6 (CH), 50.1 (CH_2), 30.4 (CH_3), 21.7 (CH_3); LRMS m/z 412.10 (M^+), calcd for

$C_{17}H_{17}O_5BrS$ 411.9980; Anal. calcd for $C_{17}H_{17}O_5BrS$ (411.9980): C, 49.40; H, 4.15. Found: C, 49.35; H, 4.215%.

(4*R*)-4-Hydroxy-4-(2-hydroxy-5-methoxy-phenyl)-butan-2-one (109ai) and (2*R*, 4*R*)-6-Methoxy-2-methyl-chroman-2,4-diol (110ai): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The BLA product **109ai/110ai** was found to exist in rapid equilibrium with 1:1 ratio of aldol↔lactol products in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis. The enantiomeric excess (ee) was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 96:4, flow rate 0.3 mL/min, λ = 254 nm), t_R = 143.68 min (major), t_R = 197.17 min (minor); **$[\alpha]_D^{25}$ = +2.7°** (*c* = 0.375 g/100 mL, CH_3OH, **87% *ee***); IR (Neat): ν_{max} 3363 (O*H*), 1708 (*C*=O), 1495, 1432, 1378, 1266, 1241, 1204, 1153, 1091, 1036 and 815 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of δ-hydroxy ketone **109ai** and lactol **110ai**) δ 7.78 (1H, br s, Ar-OH), 6.84 (1H, d, *J* = 2.4 Hz), 6.80-6.76 (3H, m), 6.72-6.69 (1H, m), 6.56 (1H, d, *J* = 2.8 Hz), 5.23 (1H, d, *J* = 8.8 Hz), 4.93 (1H, s), 4.69 (1H, br s, OH), 4.40 (1H, br s, OH), 3.92 (1H, br d, *J* = 5.6 Hz), 3.74 (3H, d, *J* = 0.8 Hz, OCH_3), 3.72 (3H, d, *J* = 1.2 Hz, OCH_3), 3.05 (1H, dd, *J* = 18.0, 9.6 Hz), 2.83 (1H, dd, *J* = 18.0, 2.8 Hz), 2.40 (1H, md, *J* = 14.8 Hz), 2.19 (3H, s, CH_3), 2.03 (1H, dd, *J* = 14.4, 4.4 Hz), 1.62 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of δ-hydroxy ketone **109ai** and lactol **110ai**) δ 209.9 (C, *C*=O), 153.7 (C), 153.0 (C), 148.9 (C), 145.2 (C), 127.0 (C), 123.5 (C), 118.3 (CH), 117.8 (CH), 116.6 (CH), 114.0 (CH), 113.9 (CH), 112.1 (CH), 97.4 (C), 70.2 (CH), 64.6 (CH), 55.70 (CH_3, O*C*H_3), 55.67 (CH_3, O*C*H_3), 49.7 (CH_2), 38.2 (CH_2), 30.6 (CH_3), 28.7 (CH_3); LRMS m/z 209.10 (M - H^+), calcd for $C_{11}H_{14}O_4$ 210.0892; HRMS m/z 233.0788 (M + Na), calcd for $C_{11}H_{14}O_4Na$ 233.0790.

(4*R*)-4-Hydroxy-4-(2-hydroxy-5-nitro-phenyl)-butan-2-one (109aj): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as solid. The BLA product **109aj/110aj** was found to exist only in δ-hydroxy ketone **109aj**

form in solution. The enantiomeric excess (ee) was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/i-PrOH = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 18.43 min (minor), t_R = 23.09 min (major); Mp 134 °C; **$[\alpha]_D^{25}$ = +19.8°** (*c* = 1.0 g/100 mL, CH_3OH, **52% *ee***); IR (Neat): ν_{max} 3361 (OH), 3186, 1713 (*C*=O), 1593, 1521, 1494, 1435, 1372, 1341, 1279, 1167, 1086, 1046 and 812 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.23 (1H, d, *J* = 2.4 Hz), 8.00 (1H, dd, *J* = 8.8, 2.8 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 5.23 (1H, br dd, *J* = 7.8, 2.0 Hz), 2.68 (1H, dd, *J* = 15.4, 2.8 Hz), 2.59-2.56 (1H, m), 2.13 (3H, s, C*H*$_3$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 207.2 (C, *C*=O), 160.3 (C), 140.2 (C), 133.4 (C), 124.7 (CH), 122.9 (CH), 115.6 (CH), 63.8 (CH), 50.9 (CH_2), 31.0 (CH_3); LRMS m/z 223.50 (M - H^+), calcd for $C_{10}H_{11}NO_5$ 225.0637; HRMS m/z 248.0525 (M + Na), calcd for $C_{10}H_{11}NO_5Na$ 248.0535.

(4*R*)-4-(3,5-Dichloro-2-hydroxy-phenyl)-4-hydroxy-butan-2-one (109ak) and (2*R*, 4*R*)-6,8-Dichloro-2-methyl-chroman-2,4-diol (110ak): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The BLA product **109ak/110ak** was found to exist in rapid equilibrium with 3:1 ratio of aldol↔lactol products in solution. The enantiomeric excess (ee) of **109ak/110ak** was determined via tosylated product **114ak** by chiral stationary phase HPLC analysis as shown below (see A-3, Annexure-I). **$[\alpha]_D^{25}$ = +7.9°** (*c* = 0.825 g/100 mL, CH_3OH, **86% *ee***); IR (Neat): ν_{max} 3340 (OH), 1709 (*C*=O), 1458, 1316, 1262, 1226, 1164 and 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 3:1 mixture of δ-hydroxy ketone **109ak** and lactol **110ak**, major isomer **109ak**) δ 7.64 (1H, br s, Ar-OH), 7.25 (1H, d, *J* = 2.0 Hz), 7.08 (1H, d, *J* = 2.4 Hz), 5.32 (1H, t, *J* = 6.0 Hz), 4.30 (1H, br s, OH), 2.91 (2H, d, *J* = 7.2 Hz), 2.20 (3H, s, C*H*$_3$); ^1H NMR ($CDCl_3$, 3:1 mixture of δ-hydroxy ketone **109ak** and lactol **110ak**, minor isomer **110ak**) δ 7.30 (1H, d, *J* = 2.4 Hz), 7.27 (1H, d, *J* = 2.4 Hz), 4.70 (1H, m), 4.63 (1H, s), 3.85 (1H, m), 2.47 (1H, br d, *J* = 14.8 Hz), 2.09-2.04 (1H, m), 1.73 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 3:1 mixture of δ-hydroxy ketone **109ak** and lactol **110ak**, major isomer **109ak**) δ 209.6 (C, *C*=O), 148.6 (C), 129.5 (C), 128.3 (CH), 125.3 (CH), 125.1 (C), 121.8 (C), 68.2 (CH), 49.3(CH_2), 30.6 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 3:1 mixture of δ-hydroxy ketone **109ak** and lactol **110ak**, minor

isomer **110ak**) δ 146.2 (C), 129.9 (CH), 128.5 (CH), 126.2 (C), 125.6 (C), 125.7 (C), 98.7 (C), 64.0 (CH), 38.1 (CH_2), 28.6 (CH_3); LRMS m/z 248.90 (M + H^+), calcd for $C_{10}H_{10}Cl_2O_3H$ 249.0007; HRMS m/z 270.9901 (M + Na), calcd for $C_{10}H_{10}Cl_2O_3Na$ 270.9905.

(1*R*)-Toluene-4-sulfonic acid-2,4-dichloro-6-(1-hydroxy-3-oxo-butyl)-phenyl ester (114ak): Prepared following the procedure **1c** and purified by column chromatography using EtOAc/hexane and isolated as liquid (see A-3, Annexure-I). The enantiomeric excess (ee) was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/i-PrOH = 80:20, flow rate 0.8 mL/min, λ = 254 nm), t_R = 8.80 min (major), t_R = 10.48 min (minor). **$[\alpha]_D^{25}$ = +4.4°** (*c* = 1.0 g/100 mL, $CHCl_3$, **86% *ee***); IR (Neat): ν_{max} 3437 (OH), 1713 (*C*=O), 1440, 1372, 1181, 1151, 1093, 866, 789, 736, 688 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) 7.89 (2H, d, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 2.0 Hz), 7.38 (2H, d, *J* = 8.0 Hz), 7.32 (1H, d, *J* = 2.4 Hz), 5.48 (1H, d, *J* = 8.4 Hz), 3.67 (1H, br s, OH), 2.97 (1H, dd, *J* = 18.4, 2.0 Hz), 2.70 (1H, dd, *J* = 17.6, 9.6 Hz), 2.48 (3H, s, C*H*$_3$), 2.19 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) 208.1 (C, *C*=O), 146.1 (C), 140.9 (C), 140.8 (C), 133.3 (C), 132.9 (C), 129.9 (2 x CH), 129.5 (CH), 129.1 (C), 128.4 (2 x CH), 126.6 (CH), 64.3 (CH), 50.2 (CH_2), 30.3 (CH_3), 21.7 (CH_3); LRMS m/z 402.10 (M^+), calcd for $C_{17}H_{16}Cl_2O_5S$ 402.0095; Anal. calcd for $C_{17}H_{16}Cl_2O_5S$ (402.0095); C, 50.63; H, 4.00. Found: C, 50.646; H, 3.955%.

(4*R*)-4-Hydroxy-4-(2-hydroxy-3-methoxy-phenyl)-butan-2-one (109al) and (2*R*, 4*R*)-8-Methoxy-2-methylchroman-2,4-diol (110al): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The BLA product **109al/110al** was found to exist in rapid equilibrium with 5:1 ratio of aldol↔lactol products in solution. The enantiomeric excess (ee) of **109al/110al** was determined via tosylated product **114al** by chiral stationary phase HPLC analysis as shown below (see A-4, Annexure-I). **$[\alpha]_D^{25}$ = +1.9°** (*c* = 0.125 g/100 mL, CH_3OH, **75% *ee***); IR (Neat): ν_{max} 3464 (O*H*), 2928, 1696 (*C*=O), 1483, 1360, 1272, 1226 and 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 5:1 mixture of δ-hydroxy ketone **109al** and lactol **110al**, major isomer **109al**) δ 6.92-6.89 (3H, m), 6.60 (1H,

br s, Ar-OH), 5.38 (1H, t, *J* = 6.0 Hz), 3.86 (3H, s, OC*H*$_3$), 2.92 (2H, d, *J* = 6.4 Hz), 2.18 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 5:1 mixture of δ-hydroxy ketone **109al** and lactol **110al**, major isomer **109al**) δ 209.5 (C, *C*=O), 146.7 (C), 142.6 (C), 127.9 (C), 119.7 (CH), 118.5 (CH), 110.0 (CH), 66.9 (CH), 55.9 (CH_3, OCH_3), 49.9 (CH_2), 30.5 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 5:1 mixture of δ-hydroxy ketone **109al** and lactol **110al**, minor isomer **110al**) δ 148.4 (C), 140.9 (C), 124.1 (C), 121.8 (CH), 120.7 (CH), 111.4 (CH), 97.6 (C), 64.2 (CH), 55.8 (CH_3, OCH_3), 38.2 (CH_2), 28.6 (CH_3); HRMS m/z 233.0788 (M + Na), calcd for $C_{11}H_{14}O_4Na$ 233.0790.

(1*R*)-Toluene-4-sulfonic acid 2-(1-hydroxy-3-oxobutyl)-6-methoxyphenyl ester (114al): Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as liquid (see A-4, Annexure-I). The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/i-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.43 min (minor), t_R = 13.02 min (major). **$[\alpha]_D^{25}$ = +10.9°** (*c* = 1.0 g/100 mL, $CHCl_3$, **75% *ee***); IR (Neat): ν_{max} 3457 (O*H*), 2926, 1711 (*C*=O), 1588, 1478, 1364, 1282, 1177, 1149, 1083, 1051, 862, 815, 757, 715 and 662 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.84 (2H, d, *J* = 8.0 Hz), 7.34 (2H, d, *J* = 8.0 Hz), 7.23 (1H, t, *J* = 7.6 Hz), 7.17 (1H, d, *J* = 7.6 Hz), 6.78 (1H, br d, *J* = 7.6 Hz), 5.51 (1H, dd, *J* = 9.3, 2.4 Hz), 3.50 (3H, s, OC*H*$_3$), 3.46 (1H, br s, OH), 2.95 (1H, dd, *J* = 17.2, 2.4 Hz), 2.76 (1H, dd, *J* = 17.2, 9.6 Hz), 2.46 (3H, s, C*H*$_3$), 2.18 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) 208.7 (C, *C*=O), 151.8 (C), 145.1 (C), 138.3 (C), 135.4 (C), 134.1 (C), 129.4 (2 x CH), 128.3 (2 x CH), 128.0 (CH), 118.8 (CH), 111.6 (CH), 64.3 (CH), 55.5 (CH_3, OCH_3), 50.5 (CH_2), 30.4 (CH_3), 21.7 (CH_3); LRMS m/z 363.00 (M - H$^+$), calcd for $C_{18}H_{20}O_6S$ 364.0981; Anal. calcd for $C_{18}H_{20}O_6S$ (364.0981); C, 59.33; H, 5.53. Found: C, 59.200; H, 5.567%.

(4*R*)-4-(5-Bromo-2-hydroxy-phenyl)-4-hydroxy-butan-2-one-1,1,1,3,3-D5 (109dh) and (2*R*, 4*R*)-6-Bromo-2-methyl-chroman-2,4-diol-1,1,1,3,3-D5 (110dh): Prepared following the procedure **1a** and purified by

column chromatography using EtOAc/hexane and isolated as liquid. The BLA product **109dh/110dh** was found to exist in rapid equilibrium with 1:1 ratio of aldol↔lactol products in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis. The enantiomeric excess (ee) was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 96:4, flow rate 0.3 mL/min, λ = 254 nm), t_R = 113.78 min (major), t_R = 131.37 min (minor). **$[\alpha]_D^{25}$ = +6.5°** (*c* = 0.325 g/100 mL, CH_3OH, **86% *ee***); IR (Neat): ν_{max} 3376 (O*H*), 1697 (*C*=O), 1478, 1418, 1242, 1178, 1031 and 816 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of δ-hydroxy ketone **109dh** and lactol **110dh**) δ 8.24 (1H, br s, Ar-OH), 7.44 (1H, d, *J* = 2.0 Hz), 7.31 (1H, dd, *J* = 8.6, 2.0 Hz), 7.25 (1H, dd, *J* = 8.0, 2.4 Hz), 7.09 (1H, d, *J* = 2.0 Hz), 6.74 (2H, dd, *J* = 8.6, 2.0 Hz), 5.24 (1H, s), 4.69 (2H, br s), 4.44 (1H, br s, OH), 3.66 (1H, br s, OH); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of δ-hydroxy ketone **109dh** and lactol **110dh**) δ 210.1 (C, *C*=O), 154.6 (C), 150.5 (C), 132.8 (CH), 132.7 (CH), 131.8 (CH), 129.2 (CH), 127.8 (C), 125.2 (C), 119.5 (CH), 119.2 (CH), 113.1 (C), 111.8 (C), 97.7 (C), 70.0 (CH), 63.9 (CH); LRMS m/z 260.00 (M - $2H^+$), calcd for $C_{10}H_6D_5BrO_3$ 263.0200; HRMS m/z 286 (M + Na), calcd for $C_{10}H_6D_5BrO_3Na$ 286.0098.

4-(2-Hydroxy-phenyl)-but-3-en-2-one (111aa): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as solid. IR (Neat): ν_{max} 3349 (O*H*), 3273, 1697 (*C*=O), 1639, 1612, 1486, 1458, 1304, 1356, 1248, 1228, 1194, 1158, 1111 and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.89 (1H, d, *J* = 16.0 Hz), 7.83 (1H, br s, Ar-OH), 7.47 (1H, dd, *J* = 8.0, 1.6 Hz), 7.26 (1H, dt, *J* = 8.0, 4.0 Hz), 7.03 (1H, d, *J* = 16.0 Hz), 6.93 (2H, m), 2.43 (3H, s, C*H*$_3$); ^{13}C NMR (CDCl3, DEPT-135) δ 201.4 (C, *C*=O), 156.2 (C), 141.0 (CH), 132.0 (CH), 129.6 (CH), 127.6 (CH), 121.5 (C), 120.6 (CH), 116.6 (CH), 26.8 (CH_3).

(*R*)-4-hydroxy-4-(2-methoxyphenyl)butan-2-one (112ab): Prepared following the procedure **1a** 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 1.0 mL/min, λ = 254 nm), t_R = 10.24 min (major), t_R = 11.65 min (minor). **$[\alpha]_D^{25}$ = +33.4°** (*c* = 0.33 g/100 mL, $CHCl_3$, **73% *ee***); IR (KBr): ν_{max} 3426 (O*H*),

2938, 2839, 1705 (*C*=O), 1601, 1490, 1461, 1438, 1359, 1286, 1237, 1162, 1050, 1024, 943, 810 and 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.43 (1H, dd, *J* = 7.6, 1.6 Hz), 7.26-7.21 (1H, m), 6.96 (1H, dt, *J* = 7.6, 0.4 Hz), 6.85 (1H, d, *J* = 8.0 Hz), 5.39 (1H, dd, *J* = 9.2, 3.2 Hz), 3.81 (3H, s, OC*H*$_3$), 3.54 (1H, br s, O*H*), 2.90 (1H, dd, *J* = 17.0, 3.2 Hz), 2.77 (1H, dd, *J* = 17.0, 9.2 Hz), 2.17 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.3 (C, *C*=O), 155.6 (C), 130.8 (C), 128.2 (CH), 126.2 (CH), 120.6 (CH), 110.1 (CH), 65.4 (CH), 55.1 (CH_3, O*C*H_3), 50.3 (CH_2), 30.4 (CH_3); HRMS m/z 217.0841 (M + Na), calcd for $C_{11}H_{14}NO_3Na$ 217.0841.

(1*R*)-Toluene-4-sulfonic acid-2-(1-hydroxy-3-oxo-butyl)-phenyl ester (114aa): Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/i-PrOH = 80:20, flow rate 0.8 mL/min, λ = 254 nm), t_R = 10.54 min (major), t_R = 13.06 min (minor). **$[\alpha]_D^{25}$ = +4.4°** (*c* = 1.0 g/100 mL, CH_3OH, **77% *ee***); IR (Neat): ν_{max} 3437 (O*H*), 3372, 1696 (*C*=O), 1674, 1604, 1482, 1451, 1376, 1294, 1255, 1193, 1190, 1180, 1173, 1086, 876, 813, 774, 718 and 663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77 (2H, d, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 7.2 Hz), 7.35 (2H, d, *J* = 8.0 Hz), 7.29 (1H, br t, *J* = 7.2 Hz), 7.21 (1H, br t, *J* = 7.2 Hz), 7.02 (1H, d, *J* = 8.4 Hz), 5.29 (1H, dd, *J* = 8.8, 2.4 Hz), 3.27 (1H, br s, OH), 2.82-2.70 (2H, m), 2.46 (3H, s, Ar-C*H*$_3$), 2.16 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.7 (C, *C*=O), 145.9 (C), 145.8 (C), 136.0 (C), 132.7 (C), 130.0 (2 x CH), 128.7 (CH), 128.4 (2 x CH), 127.65 (CH), 127.58 (CH), 122.1 (CH), 63.9 (CH), 50.4 (CH_2), 30.5 (CH_3), 21.7 (CH_3); HRMS m/z 357.0760 (M + Na), calcd for $C_{17}H_{18}O_5SNa$ 357.0773.

1d. ***Amino acid/Brønsted acid-catalyzed one-pot BLA/lactonization reactions:*** In an ordinary glass vial equipped with a magnetic stirring bar, to 2-hydroxybenzaldehydes **37** (0.5 mmol), *trans*-4-OH-L-proline **34l** (13 mg, 20 mol%), added 0.5 mL of NMP followed by acetone **32a** (0.5 mL, 7 mmol) and the reaction mixture was stirred at 25 °C for 24 h. Then it was cooled to 0 °C, added *p*-TSA.H_2O (19 mg, 20 mol%), 1.0 mL methanol, stirred at same temperature for 30 min, then slowly brought to 25 °C and stirred for 36 h. The crude reaction mixture was worked up with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and

concentrated. Pure one-pot products **115** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1e. ***Brønsted acid-catalyzed Lactonization reaction***: In an ordinary glass vial, to the BLA product **109ah/110ah** (129 mg, 0.5 mmol), added alcohol **113a-c** (1 mL), then cooled to 0 °C, and added *p*-TSA.H_2O (19 mg, 20 mol%). The reaction mixture was stirred at same temperature for 30 min and slowly brought to 25 °C and stirred till the completion of the reaction followed by TLC. The crude reaction mixture was loaded on the silica column with or without aqueous work up. Pure products **115aha-115ahc** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(2*S*, 4*R*)-2-Methoxy-2-methyl-chroman-4-ol (*trans*-115aaa): Prepared following the procedure **1d** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +25.6°** (*c* = 0.25 g/100 mL, CH_3OH, **77% *ee***); IR (Neat): ν_{max} 3367 (O*H*), 2991, 2942, 2834, 1613, 1585, 1484, 1456, 1382, 1356, 1298, 1273, 1197, 1069, 1036, 1004, 944, 882, 830, 757 and 607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (1H, d, *J* = 7.6 Hz), 7.19 (1H, dt, *J* = 8.8, 1.2 Hz), 6.99 (1H, dt, *J* = 8.8, 1.2 Hz), 6.84 (1H, d, *J* = 8.4 Hz), 5.03 (1H, dd, *J* = 8.0, 3.6 Hz), 3.24 (3H, s, OC*H*$_3$), 2.47 (1H, dd, *J* = 12.8, 6.4 Hz), 1.82 (1H, dd, *J* = 12.4, 11.6 Hz), 1.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.5 (C), 128.9 (CH), 126.5 (CH), 126.2 (C), 121.2 (CH), 116.6 (CH), 100.5 (C), 63.2 (CH), 49.0 (CH_3, OCH_3), 41.8 (CH_2), 23.1 (CH_3); LRMS m/z 194.70 ($M + H^+$), calcd for $C_{11}H_{14}O_3H$ 195.0943; Anal. calcd for $C_{11}H_{14}O_3$ (194.0943); C, 68.02; H, 7.27. Found: C, 68.053; H, 7.291%.

(2*S*, 4*R*)-6-Bromo-2-methoxy-2-methyl-chroman-4-ol (*trans*-115aha): Prepared following the procedure **1e** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 72 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/i-PrOH = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 6.66 min (minor), t_R = 8.48 min (major). **$[\alpha]_D^{25}$ = +23.5°** (*c* = 0.375 g/100 mL, CH_3OH, **65% *ee***); IR (Neat): ν_{max} 3274 (O*H*), 1476, 1262, 1193, 1068, 1006, 840 and 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (1H, d, *J* = 1.2 Hz), 7.26 (1H, dd, *J* = 8.6, 2.0 Hz), 6.70 (1H, d, *J* = 8.8 Hz), 4.97 (1H, dd, *J* = 10.8, 6.4 Hz), 3.21 (3H,

s, OC*H*$_3$), 2.41 (1H, dd, *J* = 12.8, 6.4 Hz), 2.23 (1H, br s, OH), 1.76 (1H, dd, *J* = 12.4, 11.2 Hz), 1.53 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.6 (C), 131.7 (CH), 129.5 (CH), 128.2 (C), 118.7 (CH), 113.4 (C), 100.7 (C), 62.8 (CH), 49.0 (CH_3, OCH_3), 41.3 (CH_2), 22.9 (CH_3); LRMS m/z 272.30 (M^+), calcd for $C_{11}H_{13}O_3Br$ 272.0048; Anal. calcd for $C_{11}H_{13}O_3Br$ (272.0048): C, 48.37; H, 4.80. Found: C, 48.395; H, 4.890%.

(2*R*, 4*R*)-6-Bromo-2-methoxy-2-methyl-chroman-4-ol (*cis*-115aha): Prepared following the procedure **1e** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 62 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/i-PrOH = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 5.86 min (minor), t_R = 8.95 min (major). **$[\alpha]_D^{25}$ = –38.1°** (*c* = 0.2 g/100 mL, CH_3OH, **71% *ee***); IR (Neat): ν_{max} 3257 (OH), 1476, 1386, 1261, 1193, 1068, 1006, 883, 839 and 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (1H, d, *J* = 2.0 Hz), 7.32 (1H, dd, *J* = 8.6, 2.0 Hz), 6.78 (1H, d, *J* = 8.8 Hz), 4.52 (1H, dd, *J* = 11.2, 4.8 Hz), 3.86 (1H, d, *J* = 11.6 Hz), 3.25 (3H, s, OC*H*$_3$), 2.49 (1H, d, *J* = 14.8 Hz), 2.08 (1H, dd, *J* = 14.6, 5.2 Hz), 1.59 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.7 (C), 133.3 (CH), 132.3 (CH), 127.2 (C), 119.0 (CH), 113.7 (C), 100.3 (C), 63.3 (CH), 49.1 (CH_3, O*C*H_3), 39.6 (CH_2), 22.8 (CH_3).

(2*S*, 4*R*)-6-Bromo-2-ethoxy-2-methyl-chroman-4-ol (*trans*-115ahb): Prepared following the procedure **1e** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 82 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/i-PrOH = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 5.98 min (minor), t_R = 7.01 min (major). **$[\alpha]_D^{25}$ = +11.3°** (*c* = 0.9 g/100 mL, CH_3OH, **76% *ee***); IR (Neat): ν_{max} 3290 (O*H*), 1477, 1396, 1261, 1197, 1157, 1068, 1011 and 819 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.61 (1H, d, *J* = 1.2 Hz), 7.21 (1H, dd, *J* = 8.8, 0.4 Hz), 6.67 (1H, d, *J* = 8.4 Hz), 5.03 (1H, dd, *J* = 10.8, 6.4 Hz), 3.60-3.49 (2H, m, OC*H*$_2$CH$_3$), 2.43 (1H, dd, *J* = 12.8, 6.4 Hz), 2.12 (1H, br s, OH), 1.75 (1H, t, *J* = 11.6 Hz), 1.55 (3H, s, C*H*$_3$), 1.00 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.7 (C), 131.6 (CH), 129.4 (CH), 128.2 (C), 118.4 (CH), 113.2 (C), 100.7 (C), 62.9 (CH), 56.9 (CH_2, O*C*H_2CH_3), 41.5 (CH_2), 23.7 (CH_3), 15.3 (CH_3, OCH_2CH_3);

LRMS m/z 284.00 (M^+), calcd for $C_{12}H_{15}O_3Br$ 286.0205; Anal. calcd for $C_{12}H_{15}O_3Br$ (286.0205): C, 50.19; H, 5.27. Found: C, 50.085; H, 5.329%.

(2*R*, 4*R*)-6-Bromo-2-ethoxy-2-methyl-chroman-4-ol (*cis*-115ahb): Prepared following the procedure **1e** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/i-PrOH = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 5.48 min (minor), t_R = 7.13 min (major). **$[\alpha]_D^{25}$ = –60.9°** (*c* = 0.375 g/100 mL, CH_3OH, **64% *ee***); IR (Neat): ν_{max} 3528 (O*H*), 2978, 1476, 1412, 1385, 1254, 1232, 1176, 1152, 1124, 1096, 1052, 934 and 872 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (1H, d, *J* = 2.0 Hz), 7.30 (1H, dd, *J* = 8.8, 2.4 Hz), 6.74 (1H, d, *J* = 8.8 Hz), 4.51 (1H, dd, *J* = 11.4, 4.4 Hz), 4.00 (1H, d, *J* = 11.2 Hz, O*H*), 3.64-3.51 (2H, m, O*C*H_2CH_3), 2.44 (1H, d, *J* = 14.4 Hz), 2.04 (1H, dd, *J* = 14.8, 5.2 Hz), 1.60 (3H, s, C*H*$_3$), 1.02 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.8 (C), 133.3 (CH), 132.2 (CH), 127.3 (C), 119.0 (CH), 113.6 (C), 100.2 (C), 63.4 (CH), 57.2 (CH_2, O*C*H_2CH_3), 39.8 (CH_2), 23.5 (CH_3), 15.4 (CH_3, OCH_2CH_3).

(2*S*, 4*R*)-2-Allyloxy-6-bromo-2-methyl-chroman-4-ol (*trans*-115ahc): Prepared following the procedure **1e** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/i-PrOH = 96:4, flow rate 0.8 mL/min, λ = 254 nm), t_R = 13.30 min (minor), t_R = 14.96 min (major). **$[\alpha]_D^{25}$ = +8.8°** (*c* = 0.125 g/100 mL, CH_3OH, **75% *ee***); IR (Neat): ν_{max} 3264 (OH), 1476, 1410, 1384, 1256, 1194, 1154, 1114, 1070, 1000, 887 and 819 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (1H, br s), 7.28 (1H, dd, *J* = 8.8, 2.4 Hz), 6.69 (1H, d, *J* = 8.8 Hz), 5.75-5.68 (1H, m, OCH_2CH=CH_2), 5.15-5.01 (3H, m, OCH_2CH=CH_2), 4.10-4.03 (2H, m, O*C*H_2CH=CH_2), 2.51 (1H, dd, *J* = 12.8, 6.4 Hz), 1.81 (1H, t, *J* = 11.2 Hz), 1.58 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.6 (C), 134.6 (CH), 131.7 (CH), 129.5 (CH), 128.2 (C), 118.4 (CH), 116.1 (CH_2, OCH_2CH=*C*H_2), 113.5 (C), 100.8 (C), 62.9 (CH), 62.6 (CH_2, O*C*H_2CH=CH_2), 41.6 (CH_2), 23.8 (CH_3); LRMS m/z 299.00 (M^+), calcd for $C_{12}H_{15}O_3Br$

298.0205; Anal. calcd for $C_{13}H_{15}O_3Br$ (298.0205): C, 52.19; H, 5.05. Found: C, 52.283; H, 5.050%.

(2*R*, 4*R*)-2-Allyloxy-6-bromo-2-methyl-chroman-4-ol (*cis*-115ahc): Prepared following the procedure **1e** and purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (Neat): ν_{max} 3434 (O*H*), 1482, 1413, 1338, 1293, 1234, 1175, 1103, 882, 813, 732, 652, 626 and 604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (1H, d, *J* = 2.4 Hz), 7.31 (1H, dd, *J* = 8.6, 2.0 Hz), 6.74 (1H, d, *J* = 8.8 Hz), 5.75-5.68 (1H, m, OCH_2CH=CH_2), 5.15-5.04 (2H, m, OCH_2CH=CH_2), 4.60-4.50 (1H, m), 4.08 (2H, OCH_2CH=CH_2), 3.89 (1H, d, *J* = 11.6 Hz, OH), 2.50 (1H, dd, *J* = 14.8, 1.2 Hz), 2.07 (1H, dd, *J* = 14.8, 4.8 Hz), 1.64 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.6 (C), 133.9 (CH), 133.4 (CH), 131.7 (CH), 127.2 (C), 119.1 (CH), 117.3 (CH_2, OCH_2CH=CH_2), 113.7 (C), 100.3 (C), 63.3 (CH), 62.9 (CH_2, OCH_2CH=CH_2), 39.7 (CH_2), 23.7 (CH_3).

1f. ***New cyclization reaction*:** In an oven dried round bottom flask, to the BLA product **109ah/110ah** (26 mg, 0.1 mmol), added CH-acid (0.2 mmol) and 1 mL toluene, then cooled to 0 °C, and added *p*-TSA.H_2O (4 mg, 20 mol%). The reaction mixture was stirred at same temperature for 30 min and slowly brought to 25 °C then refluxed for 4-6 h. The crude reaction mixture was loaded on the silica column with or without aqueous work up. Pure bicyclic products **116ahd/116ahf** was obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

(6*S*,12*S*)-10-bromo-3,3,6-trimethyl-2,3,4,12-tetrahydro-1*H*-6,12-methanodibenzo[*d*,*g*][1,3]dioxocin-1-one (116ahd): Prepared following the procedure **1f** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 150 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH= 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 5.61 min (minor), t_R = 6.74 min (major). **$[\alpha]_D^{25}$ = –2.8°** (*c* = 0.25 g/100 mL, $CHCl_3$, **<5% *ee***); IR (Neat): ν_{max} 2952, 1621 (*C*=O), 1472, 1382, 1254, 1162, 1136, 1064, 814 and 635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (1H, d, *J* = 2.4 Hz), 7.16 (1H, dd, *J* = 8.8, 2.4 Hz), 6.71 (1H, d, *J* = 8.4

Hz), 4.09 (1H, t, *J* = 2.8 Hz), 2.30-2.10 (4H, m), 2.04 (1H, dd, *J* = 13.2, 3.2 Hz), 1.95 (1H, dd, *J* = 13.2, 3.2 Hz), 1.80 (3H, s, C*H*$_3$), 1.05 (3H, s, C*H*$_3$), 0.92 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.4 (C, C=O), 167.5 (C), 150.5 (C), 130.5 (CH), 130.3 (CH), 128.5 (C), 117.5 (CH), 114.6 (C), 113.3 (C), 99.2 (C), 50.3 (CH_2), 41.5 (CH_2), 32.3 (C), 30.8 (CH_2), 28.8 (CH), 27.8 (CH_3), 26.6 (CH_3), 24.6 (CH_3); LRMS m/z 361.05 (M – H^+), calcd for $C_{18}H_{19}O_3Br$ 362.0518; Anal. calcd for $C_{18}H_{19}O_3Br$ (362.0518): C, 59.52; H, 5.27. Found: C, 59.465; H, 5.258%.

(6*S*,12*S*)-10-bromo-6-methyl-2,3,4,12-tetrahydro-1*H*-6,12-methanodibenzo[*d*,*g*][1,3]dioxocin-1-one (116ahf): Prepared following the procedure **1f** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 138 °C; **$[\alpha]_D^{25}$ = –2.0 °** (*c* = 0.25 g/100 mL, $CHCl_3$, **<5% *ee***); IR (Neat): ν_{max} 2926, 1625 (*C*=O), 1375, 1259, 1138, 858, 820, 758 and 634 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46 (1H, d, *J* = 2.4 Hz), 7.17 (1H, dd, *J* = 8.6, 2.4 Hz), 6.71 (1H, d, *J* = 8.4 Hz), 4.09 (1H, t, *J* = 2.8 Hz), 2.39 (2H, t, *J* = 6.4 Hz), 2.35-2.29 (2H, m), 2.03 (1H, dd, *J* = 13.2, 2.8 Hz), 1.95 (1H, dd, *J* = 13.2, 2.8 Hz), 1.97-1.90 (2H, m), 1.80 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.7 (C, *C*=O), 169.2 (C), 150.5 (C), 130.6 (CH), 130.3 (CH), 128.5 (C), 117.5 (CH), 115.8 (C), 113.3 (C), 99.1 (C), 36.3 (CH_2), 30.7 (CH_2), 27.8 (CH_2), 26.6 (CH), 24.6 (CH_3), 20.7 (CH_2); LRMS m/z 334.05 (M^+), calcd for $C_{16}H_{15}O_3Br$ 334.0205; Anal. calcd for $C_{16}H_{15}O_3Br$ (334.0205): C, 57.33; H, 4.51. Found: C, 57.171; H, 4.514%.

1g. ***Dimethoxy lactol formation*:** In an ordinary glass vial, to the BLA product **109ah/110ah** (129 mg, 0.5 mmol), added 1 mL acetone then cooled to 0 °C and added 2,2-dimethoxypropane (0.3 mL, 2.5 mmol), *p*-TSA.H_2O (24 mg, 25 mol%). The reaction mixture was stirred at same temperature for 30 min and slowly brought to 25 °C, stirred for 5 h. The crude reaction mixture was worked up with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **118aha,** *trans*-**115aha**, *cis*-**115aha** and **117aha** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1h. ***Protection of BLA product*****:** In an ordinary glass vial, to the BLA product **109ah/110ah** (129 mg, 0.5 mmol), added 1 mL acetone and NMP (55 mL, 0.6 mmol) then cooled to 0 °C and added 2,2-dimethoxypropane (0.3 mL, 2.5 mmol), *p*-TSA.H_2O (24 mg, 25 mol%). The reaction mixture was stirred at same temperature for 30 min and slowly brought to 25 °C, stirred for 4 h. The crude reaction mixture was worked up with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **117aha** and *cis*-**115aha** and *trans*-**115aha** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*R*)-1-(6-Bromo-2,2-dimethyl-4*H*-benzo[1,3]dioxin-4-yl)-propan-2-one (117aha): Prepared following the procedure **1h** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 4.66 min (major), t_R = 5.36 min (minor). **$[\alpha]_D^{25}$ = +82.5°** (*c* = 1.575 g/100 mL, $CHCl_3$, **70% *ee***); IR (Neat): ν_{max} 1659 (*C*=O), 1503, 1409, 1303, 1264, 1174, 1118, 662 and 635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (1H, dd, *J* = 8.4, 1.6 Hz), 7.09 (1H, d, *J* = 2.0 Hz), 6.69 (1H, d, *J* = 8.4 Hz), 5.36 (1H, dd, *J* = 8.0, 4.0 Hz), 2.90 (2H, dABq, *J* = 16.0, 8.0 Hz), 2.23 (3H, s, C*H*$_3$), 1.54 (3H, s, C*H*$_3$), 1.47 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 205.8 (C, *C*=O), 150.3 (C), 131.4 (CH), 127.0 (CH), 124.4 (C), 119.1 (CH), 112.6 (C), 99.9 (C), 66.0 (CH), 48.9 (CH_2), 31.1 (CH_3), 28.0 (CH_3), 21.7 (CH_3); LRMS m/z 299.00 (M^+), calcd for $C_{13}H_{15}O_3Br$ 298.0205. Anal. calcd for $C_{13}H_{15}O_3Br$ (298.0205): C, 52.19; H, 5.05. Found: C, 52.241; H, 5.017%.

(2*S*, 4*R*)-6-Bromo-2,4-dimethoxy-2-methyl-chroman (118aha): Prepared following the procedure **1g** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/i-PrOH = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 10.61 min (major), t_R = 12.07 min (minor). **$[\alpha]_D^{25}$ = +35.5°** (*c* = 0.625 g/100 mL, $CHCl_3$, **67% *ee***); IR (Neat): ν_{max} 2989, 2827, 1475, 1411, 1379, 1319, 1258, 1197, 1149, 1101, 1068, 1036, 946, 885, 843 and 817 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, d, *J* = 1.6 Hz), 7.26 (2H, dd, *J* = 8.4, 2.4 Hz), 6.70 (1H, d, *J*

= 8.8 Hz), 4.63 (1H, d, *J* = 11.2, 6.4 Hz), 3.47 (3H, s), 3.23 (3H, s), 2.49 (1H, dd, *J* = 12.6, 6.0 Hz), 1.76 (1H, dd, *J* = 12.6, 11.2 Hz), 1.56 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.8 (C), 131.6 (CH), 129.8 (CH), 126.1 (C), 118.4 (CH), 113.4 (C), 100.8 (C), 70.9 (CH), 56.3 (CH_3), 49.0 (CH_3), 36.5 (CH_2), 23.1 (CH_3); LRMS m/z 286.30 (M^+), calcd for $C_{12}H_{15}O_3Br$ 286.0205; Anal. calcd for $C_{12}H_{15}O_3Br$ (286.0205): C, 50.19; H, 5.27. Found: C, 50.177; H, 5.235%.

2. General experimental procedures for the asymmetric SMA reactions

2a. ***General procedure for amine-catalyzed asymmetric Michael reaction of acetone 32a with 2-(2-nitrovinyl)phenols 82:*** In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of 9-amino-9-deoxyepiquinine **34x** (16 mg, 0.05 mmol) and diphenylacetic acid (11 mg, 0.05 mmol) in DCM (2.0 mL), was added acetone **32a** (1.0 mL, 7.0 mmol) and of 2-(2-nitrovinyl)phenols **82** (83 mg, 0.5 mmol). After stirring the reaction mixture at 25 °C for 3 days, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure chiral products **126↔127↔128** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2b. ***General procedure for amino acid-catalyzed SMA reaction of acetone 32 with 2-(2-nitrovinyl)phenols 82:*** In an ordinary glass vial equipped with a magnetic stirring bar, to *S*-proline **34a** (6 mg, 0.05 mmol) in DMSO (2.0 mL), was added acetone **32a** (1.0 mL, 7.0 mmol) and of 2-(2-nitrovinyl)phenols **82** (83 mg, 0.5 mmol). After stirring the reaction mixture at 25 °C for 2 h, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude mixture was dissolved in alcohol **113** (2.5 mL) and cooled to 0 °C, and added *p*-TSA (19 mg, 20 mol %). The mixture was stirred at the same temperature for 30 min and then brought to room temperature and stirred for another 90 min. The crude reaction mixture was worked up with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure racemic products (±)-**129** and (±)-**130** were separated by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2c. ***General procedure for amine-catalyzed asymmetric SMA reaction of acetone 32 with 2-(2-nitrovinyl)phenols 82:*** In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of 9-amino-9-deoxyepiquinine **34x** (16 mg, 0.05 mmol) and diphenylacetic acid (11 mg, 0.05 mmol) in DCM (2.0 mL), was added acetone **32** (1.0 mL, 7.0 mmol) and of 2-(2-nitrovinyl)phenols **82** (83 mg, 0.5 mmol). After stirring the reaction mixture at 25 °C for 3 days, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude mixture was dissolved in alcohol **113** (2.5 mL) and cooled to 0 °C, and added *p*-TSA (19 mg, 20 mol %). The mixture was stirred at the same temperature for 30 min and then brought to room temperature and stirred for another 90 min. The crude reaction mixture was worked up with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure chiral products **129** and **130** were separated by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(2*S*)-4-(2-Hydroxy-phenyl)-5-nitro-pentan-2-one (126c), and (2*S*, 4*R*)-2-Methyl-4-nitromethylchroman-2-ol (127c): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The product **126c/127c/128c** was found to exist in rapid equilibrium with 1:1:1 ratio in solution. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 43.21 min (major), t_R = 58.4 min (minor). **$[\alpha]_D^{25}$ = +15.0°** (*c* = 0.3 g/100 mL, $CHCl_3$, **84% *ee***); IR (Neat): ν_{max} 3350 (O-*H*), 1708 (*C*=O), 1547 (NO_2), 1491, 1454, 1378, 1227, 1166, 1117, 891, 758 and 663 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1:1 mixture of δ-hydroxy ketone **126c** and lactols **127c/128c**) δ 7.21-7.16 (2H, m), 7.13-7.09 (3H, m), 7.06 (1H, d, *J* = 7.6 Hz), 6.96-6.92 (3H, m), 6.89-6.83 (2H, m), 6.78 (1H, d, *J* = 8.0 Hz), 6.37 (1H, s, Ar-O*H*), 5.07 (2H, dd, *J* = 12.8, 9.2 Hz), 4.95 (1H, dd, *J* = 12.2, 5.2 Hz), 4.72-4.66 (3H, m), 4.49 (1H, dd, *J* = 12.4, 9.2 Hz), 4.20 (1H, t, *J* = 6.8 Hz), 3.98-3.90 (1H, m), 3.72 (1H, dd, *J* = 14.6, 6.4 Hz), 3.01 (1H, d, *J* = 7.2 Hz), 2.84-2.80

(2H, m), 2.25-2.18 (3H, m), 2.13 (3H, s, CH_3), 2.08-2.02 (2H, m), 1.66 (3H, s, CH_3), 1.64 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 1:1:1 mixture of δ-hydroxy ketone **126c** and lactols **127c/128c**, DEPT-135) δ 207.6 (C, *C*=O), 153.5 (C), 152.1 (C), 152.0 (C), 128.94 (2 x CH), 128.91 (CH), 128.7 (CH), 128.6 (CH), 125.7 (CH), 125.1 (C), 121.4 (CH), 121.3 (CH), 119.9 (C), 119.4 (C), 117.9 (CH), 117.8 (2 x CH), 116.9 (CH), 96.4 (C), 95.8 (C), 80.2 (CH_2), 79.0 (CH_2), 77.8 (CH_2), 45.5 (CH_2), 35.6 (CH_2), 34.1 (CH), 33.0 (CH_2), 32.1 (CH_3), 30.2 (CH), 30.0 (CH), 29.5 (CH_3), 29.1 (CH_3); LRMS m/z 222.15 ($M - H^+$), calcd for $C_{11}H_{13}NO_4$ 223.0845; HRMS m/z 246.0740 (M + Na), calcd for $C_{11}H_{13}NO_4Na$ 246.0742; Anal. calcd for $C_{11}H_{13}NO_4$ (223.0845): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.25; H, 5.91; N, 6.23%.

(2*S*, 4*S*)-2-Methoxy-2-methyl-4-nitromethyl-chroman (129ca): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 99:1, flow rate 0.8 mL/min, λ = 254 nm), t_R = 14.10 min (major), t_R = 15.2 min (minor). Mp 46 °C; **$[\alpha]_D^{25}$ = +52.5°** (*c* = 0.25 g/100 mL, $CHCl_3$, **84% *ee***); IR (Neat): ν_{max} 2924, 1581, 1550 (NO_2), 1489, 1379, 1251, 1216, 1148, 1122, 1058, 877 and 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (1H, t, *J* = 7.6 Hz), 7.12 (1H, d, *J* = 7.6 Hz), 6.95 (1H, t, *J* = 7.6 Hz), 6.89 (1H, d, *J* = 8.0 Hz), 5.01 (1H, dd, *J* = 12.6, 8.8 Hz), 4.63 (1H, dd, *J* = 12.8, 5.6 Hz), 3.69 (1H, dd, *J* = 14.6, 6.8 Hz), 3.24 (3H, s, OC*H*$_3$), 2.20 (1H, d, *J* = 14.4 Hz), 2.07 (1H, dd, *J* = 14.4, 6.8 Hz), 1.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.8 (C), 128.9 (CH), 128.88 (CH), 121.5 (CH), 120.2 (C), 117.8 (CH), 98.5 (C), 80.7 (CH_2), 48.8 (CH_3, O*C*H$_3$), 34.0 (CH_2), 32.0 (CH), 23.0 (CH_3); LRMS m/z 236.00 ($M - H^+$), calcd for $C_{12}H_{15}NO_4$ 237.1001; HRMS m/z 260.0888 (M + Na), calcd for $C_{12}H_{15}NO_4Na$ 260.0899; Anal. calcd for $C_{12}H_{15}NO_4$ (237.1001): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.85; H, 6.35; N, 5.85%.

(2*S*, 4*R*)-2-Methoxy-2-methyl-4-nitromethyl-chroman (130ca): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 99:1, flow rate 0.8 mL/min, λ = 254 nm), t_R = 16.91 min (major),

t_R = 29.16 min (minor). Mp 58 °C; **$[\alpha]_D^{25}$ = −22.6°** (*c* = 0.50 g/100 mL, $CHCl_3$, **82% *ee***); IR (Neat): ν_{max} 2989, 1551 (NO_2), 1490, 1452, 1379, 1257, 1223, 1188, 1067, 882, 756 and 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (1H, t, *J* = 7.6 Hz), 7.10 (1H, d, *J* = 7.6 Hz), 6.95 (1H, t, *J* = 7.2 Hz), 6.89 (1H, d, *J* = 8.0 Hz), 4.94 (1H, dd, *J* = 12.0, 4.8 Hz), 4.46 (1H, dd, *J* = 12.4, 9.6 Hz), 3.97-3.89 (1H, m), 3.23 (3H, s, O*CH*$_3$), 2.22 (1H, dd, *J* = 13.2, 6.4 Hz), 1.81 (1H, t, *J* = 12.8 Hz), 1.57 (3H, s, *CH*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 152.1 (C), 128.6 (CH), 125.8 (CH), 121.3 (CH), 120.6 (C), 117.9 (CH), 98.0 (C), 79.2 (CH_2), 49.0 (CH_3, O*C*H$_3$), 36.6 (CH_2), 30.2 (CH), 22.9 (CH_3); LRMS m/z 236.00 ($M - H^+$), calcd for $C_{12}H_{15}NO_4$ 237.1001; HRMS m/z 260.0891 (M + Na), calcd for $C_{12}H_{15}NO_4Na$ 260.0899; Anal. calcd for $C_{12}H_{15}NO_4$ (237.1001): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.68; H, 6.32; N, 5.96%.

1d. ***General procedure for diamine-catalyzed asymmetric SMA reaction of acetone 32 with 2-(2-nitrovinyl)phenols 82:*** In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of (*S*)-(+)-1-(2-pyrrolidinylmethyl)-pyrrolidine **34j** (8 mg, 0.05 mmol) and diphenylacetic acid (11 mg, 0.05 mmol) in DCM (2.0 mL), was added acetone **32a** (1 mL, 7.0 mmol) and of 2-(2-nitrovinyl)phenol **82c** (83 mg, 0.5 mmol). After stirring the reaction mixture at 25 °C for 3 days, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude mixture was dissolved in alcohol **113a** (2.5 mL) and cooled to 0 °C and added *p*-TSA (19 mg, 20 mol-%). The mixture was stirred at the same temperature for 30 min and then brought to room temperature and stirred for another 90 min. The crude reaction mixture was worked up with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **129ca** and **130ca** were separated by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(2*R*, 4*R*)-2-Methoxy-2-methyl-4-nitromethyl-chroman (129ca): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 99:1, flow rate 0.8 mL/min, λ = 254 nm), t_R =

16.44 min (minor), t_R = 18.99 min (major). Mp 46 °C; **$[\alpha]_D^{25}$ = −17.4°** (*c* =0.42 g/100 mL, $CHCl_3$, **25% *ee***).

(2*R*, 4*S*)-2-Methoxy-2-methyl-4-nitromethyl-chroman (130ca): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 99:1, flow rate 0.8 mL/min, λ = 254 nm), t_R = 20.00 min (minor), t_R = 39.24 min (major). Mp 58 °C; **$[\alpha]_D^{25}$ = +10.8°** (*c* =0.53 g/100 mL, $CHCl_3$, **21% *ee***).

(1*S*, 3*S*)-3-Methyl-1-nitromethyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-ol (127d): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as solid. 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 = 13.69 min (minor), t_R = 16.42 min (major). Mp 116 °C; **$[\alpha]_D^{25}$ = +30.0°** (*c* = 0.38 g/100 mL, $CHCl_3$, **98% *ee*);** IR (Neat): ν_{max} 2796, 2758, 1621, 1544 (NO_2), 1514, 1438, 1403, 1382, 1341, 1229, 1160, 1106, 1053, 1023, 975, 892, 819, 782, 682 and 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (1H, d, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 8.0 Hz), 7.72 (1H, d, *J* = 8.0 Hz), 7.58 (1H, t, *J* = 8.0 Hz), 7.40 (1H, t, *J* = 8.0 Hz), 7.04 (1H, d, *J* = 8.0 Hz), 5.43 (1H, t, *J* = 12.0 Hz), 4.75 (1H, dd, *J* = 12.0, 4.0 Hz), 4.26 (1H, t, *J* = 4.0 Hz), 2.75 (1H, s), 2.45 (1H, d, *J* = 16.0 Hz), 2.08 (1H, dd, *J* = 14.0, 8.0 Hz), 1.73 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.3 (C), 131.4 (C), 129.9 (CH), 129.5 (C), 129.1 (CH), 127.5 (CH), 123.8 (CH), 121.0 (CH), 119.2 (CH), 110.0 (C), 96.6 (C), 76.9 (CH_2), 31.8 (CH_2), 30.2 (CH), 29.8 (CH_3); LRMS m/z 272.25 ($M-H^+$), calcd for $C_{15}H_{15}NO_4$ 273.1001; HRMS m/z 296.0898 (M + Na), calcd for $C_{15}H_{15}NO_4Na$ 296.0899; Anal. calcd for $C_{15}H_{15}NO_4$ (273.1001): C, 65.92, H; 5.53; N, 5.13. Found: C, 65.86; H, 5.49; N, 5.21%.

(1*S*, 3*S*)-3-Methoxy-3-methyl-1-nitromethyl-2,3-dihydro-1*H*-benzo[*f*]chromene (130da):

Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 84 °C; **$[\alpha]_D^{25}$ = +71.5°** (*c* = 0.23 g/100 mL, $CHCl_3$, **98% *ee***); IR (Neat): ν_{max} 3738, 1624, 1549 (NO_2), 1378, 1176, 1115, 1052 and 817 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87 (1H, d, *J* = 8.4 Hz), 7.78 (1H, d, *J* = 8.0 Hz), 7.70 (1H, d, *J* = 8.8 Hz), 7.55 (1H, t, *J* = 7.2 Hz), 7.38 (1H, t, *J* = 7.2 Hz), 7.08 (1H, d, *J* = 8.8 Hz), 5.33 (1H, dd, *J* = 12.8, 11.2 Hz), 4.71 (1H, dd, *J* = 13.2, 2.0 Hz), 4.19-4.15 (1H, m), 3.30 (3H, s, OCH_3), 2.41 (1H, d, *J* = 14.4 Hz), 2.05 (1H, dd, *J* = 14.8, 6.4 Hz), 1.60 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.1 (C), 131.4 (C), 129.8 (CH), 129.5 (C), 129.0 (CH), 127.4 (CH), 123.7 (CH), 121.1 (CH), 119.1 (CH), 110.7 (C), 98.7 (C), 77.3 (CH_2), 48.8 (CH_3, OCH_3), 32.8 (CH_2), 29.7 (CH), 23.2 (CH_3); LRMS m/z 286.00 ($M - H^+$), calcd for $C_{16}H_{17}NO_4$ 287.1158; HRMS m/z 310.0975 (M + Na), calcd for $C_{16}H_{17}NO_4Na$ 310.1055; Anal. calcd for $C_{16}H_{17}NO_4$ (287.1158): C, 66.89; H, 5.96; N, 4.88. Found: C, 66.83; H, 5.91; N, 4.92%.

(2*S*, 4*S*)-6-Fluoro-2-methoxy-2-methyl-4-nitromethyl-chroman (129ea): Prepared following the procedure **2c** 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 AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.00 min (major), t_R = 6.73 min (minor). **$[\alpha]_D^{25}$ = +11.5°** (*c* = 0.26 g/100 mL, $CHCl_3$, **82% *ee***); IR (Neat): ν_{max} 1530 (NO_2), 1492, 1427, 1379, 1248, 1195, 1145, 1120, 1056, 940, 877, 819 and 636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (1H, br dt, *J* = 9.0, 2.8 Hz), 6.86-6.82 (2H, m), 4.98 (1H, dd, *J* = 13.0, 8.8 Hz), 4.61 (1H, dd, *J* = 13.2, 5.6 Hz), 3.67 (1H, dd, *J* = 14.4, 6.8 Hz), 3.23 (3H, s, OCH_3), 2.18 (1H, d, *J* = 14.4 Hz), 2.04 (1H, dd, *J* = 14.6, 6.8 Hz), 1.55 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 157.1 (C, d, *J* = 238.4 Hz), 147.8 (C), 121.3 (C, d, *J* = 6.8 Hz), 118.8 (CH, d, *J* = 7.9 Hz), 115.8 (CH, d, *J* = 22.9 Hz), 114.8 (CH, d, *J* = 23.0 Hz), 98.6 (C), 80.5 (CH_2), 48.7 (CH_3, OCH_3), 33.8 (CH_2), 32.0 (CH), 22.8 (CH_3); LRMS m/z 254.00 ($M - H^+$), calcd for $C_{12}H_{14}FNO_4$ 255.0907; HRMS m/z 301.1362 (M + 2Na), calcd for $C_{12}H_{14}FNO_4Na_2$ 301.0703; Anal. calcd for $C_{12}H_{14}FNO_4$ (255.0907): C, 56.47; H, 5.53;N, 5.49. Found: C, 56.41; H, 5.54; N, 5.56%.

(2*S*, 4*R*)-6-Fluoro-2-methoxy-2-methyl-4-nitromethyl-chroman (130ea): Prepared following the procedure **2c** 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 = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.15 min (major), t_R = 10.75 min (minor). **$[\alpha]_D^{25}$ = −36.2°** (*c* = 0.26 g/100 mL, $CHCl_3$, **76% *ee***); IR (Neat): ν_{max} 2997, 1622, 1535 (NO_2), 1492, 1430, 1379, 1224, 1191, 1139, 1097, 1065, 883 and 802 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89 (1H, br dt, *J* = 8.8, 2.8 Hz), 6.85-6.81 (2H, m), 4.85 (1H, dd, *J* = 12.4, 4.8 Hz), 4.47 (1H, dd, *J* = 12.4, 9.2 Hz), 3.93-3.85 (1H, m), 3.21 (3H, s, OC*H*$_3$), 2.20 (1H, dd, *J* = 13.4, 6.0 Hz), 1.79 (1H, t, *J* = 12.8 Hz), 1.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 157.1 (C, d, *J* = 238.2 Hz), 148.1 (C), 121.7 (C, d, *J* = 6.8 Hz), 118.9 (CH, d, *J* = 8.0 Hz), 115.4 (CH, d, *J* = 22.8 Hz), 112.3 (CH, d, *J* = 23.7 Hz), 98.1 (C), 78.8 (CH_2), 49.0 (CH_3, O*C*H$_3$), 36.2 (CH_2), 30.4 (CH), 22.7 (CH_3); LRMS m/z 254.00 ($M - H^+$), calcd for $C_{12}H_{14}FNO_4$ 255.0907; HRMS m/z 278.0805 (M + Na), calcd for $C_{12}H_{14}FNO_4Na$ 278.0805; Anal. calcd for $C_{12}H_{14}FNO_4$ (255.0907): C, 56.47; H, 5.53; N, 5.49. Found: C, 56.44; H, 5.49; N, 5.56%.

(2*S*, 4*S*)-6-Chloro-2-methoxy-2-methyl-4-nitromethyl-chroman (129ba): Prepared following the procedure **2c** 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 AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 4.73 min (major), t_R = 5.50 min (minor). **$[\alpha]_D^{25}$ = +13.0°** (*c* = 0.20 g/100 mL, $CHCl_3$, **69% *ee***); IR (Neat): ν_{max} 2993, 2941, 1549 (NO_2), 1514, 1481, 1425, 1379, 1251, 1217, 1177, 1146, 1121, 1053, 877 and 821 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (1H, dd, *J* = 8.8, 2.4 Hz), 7.12 (1H, d, *J* = 2.4 Hz), 6.83 (1H, d, *J* = 8.8 Hz), 5.00 (1H, dd, *J* = 13.0, 9.2 Hz), 4.60 (1H, dd, *J* = 13.0, 5.2 Hz), 3.66 (1H, dd, *J* = 15.2, 6.4 Hz), 3.23 (3H, s, OC*H*$_3$), 2.19 (1H, dd, *J* = 14.6, 0.8 Hz), 2.04 (1H, dd, *J* = 14.8, 7.2 Hz), 1.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.5 (C), 128.9 (CH), 128.5 (CH), 126.1 (C), 121.8 (C), 119.2 (CH), 98.8 (C), 80.3 (CH_2), 48.8 (CH_3, O*C*H$_3$), 33.7 (CH_2), 31.8 (CH), 22.8 (CH_3); LRMS m/z 270.00 ($M - H^+$), calcd for $C_{12}H_{14}ClNO_4$ 271.0611; HRMS m/z 294.0511 (M + Na), calcd for $C_{12}H_{14}ClNO_4Na$ 294.0509;

Anal. calcd for $C_{12}H_{14}ClNO_4$ (271.0611): C, 53.05; H, 5.19; N, 5.16. Found: C, 53.12; H, 5.15, N, 5.22%.

(2*R*, 4*S*)-6-Chloro-2-methoxy-2-methyl-4-nitromethyl-chroman (130ba): Prepared following the procedure **2c** 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 AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 8.25 min (major), t_R = 8.84 min (minor). **$[\alpha]_D^{25}$ = −10.0°** (*c* = 0.18 g/100 mL, $CHCl_3$, **70% *ee***); IR (Neat): ν_{max} 2939, 2299, 1551 (NO_2), 1515, 1482, 1436, 1412, 1378, 1261, 1224, 1186, 1066, 881, 822, 680, 659 and 633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15-7.13 (1H, m), 7.09-7.08 (1H, m), 6.83 (1H, d, *J* = 8.8 Hz), 4.88 (1H, dd, *J* = 12.4, 4.8 Hz), 4.47 (1H, dd, *J* = 12.4, 9.2 Hz), 3.93-3.89 (1H, m), 3.22 (3H, s, OC*H*$_3$), 2.20 (1H, dd, *J* = 11.2, 6.0 Hz), 1.79 (1H, dd, *J* = 13.2, 12.4 Hz), 1.56 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.8 (C), 128.6 (CH), 126.1 (C), 125.8 (CH), 122.2 (C), 119.2 (CH), 98.3 (C), 78.7 (CH_2), 49.1 (CH_3, O*C*H$_3$), 36.2 (CH_2), 30.2 (CH), 22.6 (CH_3); LRMS m/z 270.00 ($M - H^+$), calcd for $C_{12}H_{14}ClNO_4$ 271.0611; HRMS m/z 294.0505 (M + Na), calcd for $C_{12}H_{14}ClNO_4Na$ 294.0509; Anal. calcd for $C_{12}H_{14}ClNO_4$ (271.0611): C, 53.05; H, 5.19; N, 5.16. Found: C, 53.10; H, 5.16; N, 5.23%.

(2*S*, 4*S*)-6-Bromo-2-methoxy-2-methyl-4-nitromethyl-chroman (129fa): Prepared following the procedure **2c** 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 AS-H column (hexane/2-propanol = 91:9, flow rate 1.0 mL/min, λ = 254 nm), t_R = 5.43 min (minor), t_R = 5.96 min (major). **$[\alpha]_D^{25}$ = +63.2°** (*c* = 0.23 g/100 mL, $CHCl_3$, **87% *ee***); IR (Neat): ν_{max} 1549 (NO_2), 1479, 1427, 1379, 1251, 1215, 1174, 1148, 1124, 1055, 877 and 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30-7.26 (2H, m), 6.78 (1H, d, *J* = 8.4 Hz), 5.00 (1H, dd, *J* = 13.2, 9.2 Hz), 4.60 (1H, dd, *J* = 13.0, 5.2 Hz), 3.69-3.64 (1H, m), 3.23 (3H, s, OC*H*$_3$), 2.19 (1H, dd, *J* = 14.8, 1.2 Hz), 2.03 (1H, dd, *J* = 14.6, 7.2 Hz), 1.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.1 (C), 131.8 (CH), 131.5 (CH), 122.4 (C), 119.6 (CH), 113.4 (C), 98.8 (C), 80.4 (CH_2), 48.8 (CH_3, O*C*H$_3$), 33.8 (CH_2),

31.7 (CH), 22.8 (CH_3); LRMS m/z 314.00 ($M - H^+$), calcd for $C_{12}H_{14}BrNO_4$ 315.0106; HRMS m/z 338.0012 (M + Na), calcd for $C_{12}H_{14}BrNO_4Na$ 338.0004; Anal. calcd for $C_{12}H_{14}BrNO_4$ (315.0106): C, 45.59; H, 4.46; N, 4.43. Found: C, 45.68; H, 4.39; N, 4.47%.

(2*S*, 4*R*)-6-Bromo-2-methoxy-2-methyl-4-nitromethyl-chroman (130fa): Prepared following the procedure **2c** 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 = 95:5, flow rate 0.8 mL/min, λ = 254 nm), t_R = 11.10 min (major), t_R = 14.47 min (minor). **$[\alpha]_D^{25}$ = −15.6°** (*c* = 0.18 g/100 mL, $CHCl_3$, **86% *ee***); IR (Neat): ν_{max} 1551 (NO_2), 1514, 1481, 1379, 1255, 1224, 1186, 1066 and 881 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29-7.26 (1H, m), 7.23-7.22 (1H, m), 6.77 (1H, d, *J* = 8.8 Hz), 4.89 (1H, dd, *J* = 12.4, 4.8 Hz), 4.46 (1H, dd, *J* = 12.0, 9.2 Hz), 3.94-3.86 (1H, m), 3.22 (3H, s, OC*H*$_3$), 2.21 (1H, dd, *J* = 13.2, 6.4 Hz), 1.78 (1H, dd, *J* = 13.0, 12.4 Hz), 1.56 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.3 (C), 131.6 (CH), 128.7 (CH), 122.8 (C), 119.7 (CH), 113.4 (C), 98.3 (C), 78.7 (CH_2), 49.1 (CH_3, O*C*H$_3$), 36.2 (CH_2), 30.1(CH), 22.7 (CH_3); LRMS m/z 314.00 ($M - H^+$), calcd for $C_{12}H_{14}BrNO_4$ 315.0106; HRMS m/z 338.0004 (M + Na), calcd for $C_{12}H_{14}BrNO_4Na$ 338.0004; Anal. calcd for $C_{12}H_{14}BrNO_4$ (315.0106): C, 45.59; H, 4.46; N, 4.43. Found: C, 45.65; H, 4.41; N, 4.51%.

(2*S*, 4*S*)-6,8-Dichloro-2-methoxy-2-methyl-4-nitromethyl-chroman (129ga): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.43 min (minor), t_R = 7.20 min (major). Mp 62 °C; **$[\alpha]_D^{25}$ = −7.6°** (*c* = 0.30 g/100 mL, $CHCl_3$, **88% *ee***); IR (Neat): ν_{max} 2962, 1548 (NO_2), 1450, 1380, 1235, 1177, 1090, 1050, 1024, 937, 882, 823 and 633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (1H, br d, *J* = 2.0 Hz), 7.05-7.04 (1H, m), 4.98 (1H, dd, *J* = 13.4, 9.2 Hz), 4.59 (1H, dd, *J* = 13.4, 5.2 Hz), 3.70 (1H, dd, *J* = 14.2, 6.8 Hz), 3.25 (3H, s, OC*H*$_3$), 2.22 (1H, br d, *J* = 14.8 Hz), 2.09 (1H, dd, *J* = 14.6, 7.2 Hz), 1.62 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 146.6 (C), 129.2 (CH), 127.0 (CH), 125.9 (C), 123.7 (C), 123.3 (C), 99.6 (C), 80.3 (CH_2), 49.1

(CH_3, O*C*H_3), 33.8 (CH_2), 31.9 (CH), 22.7 (CH_3); LRMS m/z 304.00 ($M - H^+$), calcd for $C_{12}H_{13}Cl_2NO_4$ 305.0222; HRMS m/z 328.0110 (M + Na), calcd for $C_{12}H_{13}Cl_2NO_4Na$ 328.0119.

(2*R*, 4*S*)-6,8-Dichloro-2-methoxy-2-methyl-4-nitromethyl-chroman (130ga): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.39 min (major), t_R = 11.34 min (minor). Mp 94 °C; **$[\alpha]_D^{25}$ = −64.6°** (*c* = 0.22 g/100 mL, $CHCl_3$, **91% *ee***); IR (Neat): ν_{max} 2963, 1557 (NO_2), 1455, 1382, 1278, 1239, 1181, 1082, 1051, 1026, 882, 678 and 636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29-7.28 (1H, m), 7.02-7.01 (1H, m), 4.85 (1H, dd, *J* = 12.6, 4.4 Hz), 4.50 (1H, dd, *J* = 12.8, 8.8 Hz), 3.94-3.86 (1H, m), 3.23 (3H, s, OC*H*$_3$), 2.25 (1H, dd, *J* = 13.2, 6.4 Hz), 1.86 (1H, t, *J* = 12.8 Hz), 1.63 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 146.9 (C), 128.9 (CH), 125.9 (C), 124.5 (CH), 123.8 (C), 123.7 (C), 99.2 (C), 78.5 (CH_2), 49.3 (CH_3, O*C*H_3), 36.2 (CH_2), 30.5 (CH), 22.5 (CH_3); LRMS m/z 306.30 ($M + H^+$), calcd for $C_{12}H_{13}Cl_2NO_4$ 305.0222; HRMS m/z 328.0110 (M + Na), calcd for $C_{12}H_{13}Cl_2NO_4Na$ 328.0119; Anal. calcd for $C_{12}H_{13}Cl_2NO_4$ (306.0222): C, 47.08; H, 4.28; N, 4.58. Found: C, 47.12; H, 4.23; N, 4.51%.

(2*S*, 4*S*)-2,8-Dimethoxy-2-methyl-4-nitromethyl-chroman (129ha): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.40 min (major), t_R = 8.38 min (minor). Mp 74 °C; **$[\alpha]_D^{25}$ = −43.1°** (*c* = 0.23 g/100 mL, $CHCl_3$, **79% *ee***); IR (Neat): ν_{max} 3729, 1584, 1546 (NO_2), 1479, 1378, 1262, 1212, 1086, 1053 and 661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (1H, t, *J* = 8.0 Hz), 6.81 (1H, dd, *J* = 8.2, 1.2 Hz), 6.74-6.72 (1H, m), 5.00 (1H, dd, *J* = 12.8, 9.2 Hz), 4.63 (1H, dd, *J* = 12.8, 5.2 Hz), 3.86 (3H, s, Ar-OC*H*$_3$), 3.72-3.66 (1H, m), 3.25 (3H, s, OC*H*$_3$), 2.19 (1H, dd, *J* = 14.6, 1.6 Hz), 2.08 (1H, dd, *J* = 14.8, 6.8 Hz), 1.62 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.0 (C), 141.3 (C), 121.0 (C), 120.9 (CH), 120.4 (CH), 110.6 (CH), 98.5 (C), 80.6 (CH_2), 55.9 (CH_3, O*C*H_3),

48.8 (CH_3, O*C*H_3), 33.8 (CH_2), 31.9 (CH), 23.0 (CH_3); LRMS m/z 268.00 (M + H^+), calcd for $C_{13}H_{17}NO_5$ 267.1107; HRMS m/z 290.1001 (M + Na), calcd for $C_{13}H_{17}NO_5Na$ 290.1004; Anal. calcd for $C_{13}H_{17}NO_5$ (267.1107): C, 58.42; H, 6.41; N; 5.24. Found: C, 58.36; H, 6.45; N; 5.28%.

(2*R*, 4*S*)-2,8-Dimethoxy-2-methyl-4-nitromethyl-chroman (130ha): Prepared following the procedure **2c** 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 AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.49 min (major), t_R = 12.27 min (minor). **$[\alpha]_D^{25}$ = −62.3°** (*c* = 0.14 g/100 mL, $CHCl_3$, **79% *ee***); IR (Neat): ν_{max} 2921, 2850, 1583, 1546 (NO_2), 1470, 1379, 1261, 1223, 1183, 1082, 1055, 1032, 906, 686 and 632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (1H, t, *J* = 8.0 Hz), 6.81 (1H, d, *J* = 7.6 Hz), 6.71 (1H, dt, *J* = 8.0, 1.2 Hz), 4.91 (1H, dd, *J* = 12.4, 4.8 Hz), 4.44 (1H, dd, *J* = 12.4, 9.6 Hz), 3.96-3.88 (1H, m), 3.86 (3H, s, Ar-OC*H*$_3$), 3.23 (3H, s, OC*H*$_3$), 2.22 (1H, dd, *J* = 13.4, 6.0 Hz), 1.84 (1H, dd, *J* = 13.2, 12.0 Hz), 1.63 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.1 (C), 141.5 (C), 121.5 (C), 120.8 (CH), 117.5 (CH), 110.6 (CH), 98.1 (C), 79.3 (CH_2), 56.0 (CH_3, O*C*H_3), 49.1 (CH_3, O*C*H_3), 36.5 (CH_2), 30.4 (CH), 22.9 (CH_3); LRMS m/z 268.00 (M + H^+), calcd for $C_{13}H_{17}NO_5$ 267.1107; HRMS m/z 290.1000 (M + Na), calcd for $C_{13}H_{17}NO_5Na$ 290.1004; Anal. calcd for $C_{13}H_{17}NO_5$ (267.1107): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.36; H, 6.44; N, 5.32%.

(2*S*, 4*S*)-2,6-Dimethoxy-2-methyl-4-nitromethyl-chroman (129ia): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.21 min (minor), t_R = 6.91 min (major). Mp 68 °C; **$[\alpha]_D^{25}$ = +20.7°** (*c* = 0.28 g/100 mL, $CHCl_3$, **79% *ee***); IR (Neat): ν_{max} 2956, 1727, 1550 (NO_2), 1495, 1426, 1380, 1251, 1207, 1147, 1107, 1049, 937, 874, 789, and 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83-6.76 (2H, m), 6.64 (1H, d, *J* = 2.0 Hz), 5.00 (1H, dd, *J* = 12.8, 9.2 Hz), 4.63 (1H, dd, *J* = 12.8, 5.6 Hz), 3.75 (3H, s, Ar-OC*H*$_3$), 3.65 (1H, dd, *J* = 14.2, 6.8 Hz), 3.22 (3H, s,

OC*H*$_3$), 2.16 (1H, d, *J* = 14.8 Hz), 2.04 (1H, dd, *J* = 14.4, 6.8 Hz), 1.53 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 154.0 (C), 145.6 (C), 120.7 (C), 118.4 (CH), 115.1 (CH), 113.1 (CH), 98.3 (C), 80.7 (CH_2), 55.6 (CH_3, O*C*H$_3$), 48.6 (CH_3, O*C*H$_3$), 33.9 (CH_2), 32.3 (CH), 22.9 (CH_3); LRMS m/z 266.00 ($M - H^+$), calcd for $C_{13}H_{17}NO_5$ 267.1107; HRMS m/z 290.0992 (M + Na), calcd for $C_{13}H_{17}NO_5Na$ 290.1004; Anal. calcd for $C_{13}H_{17}NO_5$ (267.1107): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.45; H, 6.38; N, 5.28%.

(2*R*, 4*S*)-2,6-Dimethoxy-2-methyl-4-nitromethyl-chroman (130ia): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.65 min (major), t_R = 11.11 min (minor). Mp 110 °C; **$[\alpha]_D^{25}$ = −47.6°** (*c* = 0.28 g/100 mL, $CHCl_3$, **79% *ee***); IR (Neat): ν_{max} 2940, 2340, 1546 (NO_2), 1499, 1379, 1281, 1251, 1220, 1150, 1106, 1068, 1037, 887, 821, 665 and 637 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.82 (1H, d, *J* = 8.8 Hz), 6.76 (1H, dd, *J* = 8.8, 2.4 Hz), 6.63 (1H, d, *J* = 2.0 Hz), 4.89 (1H, dd, *J* = 12.4, 4.8 Hz), 4.45 (1H, dd, *J* = 12.2, 9.2 Hz), 3.93-3.85 (1H, m), 3.75 (3H, s, Ar-OC*H*$_3$), 3.21 (3H, s, OC*H*$_3$), 2.19 (1H, dd, *J* = 13.2 , 6.0 Hz), 1.79 (1H, t, *J* = 12.4 Hz), 1.54 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 153.9 (C), 145.9 (C), 121.2 (C), 118.4 (CH), 114.1 (CH), 111.2 (CH), 97.8 (C), 79.2 (CH_2), 55.6 (CH_3, O*C*H$_3$), 48.9 (CH_3, O*C*H$_3$), 36.5 (CH_2), 30.6 (CH), 22.8 (CH_3); LRMS m/z 266.00 ($M - H^+$), calcd for $C_{13}H_{17}NO_5$ 267.1107; HRMS m/z 290.0975 (M + Na), calcd for $C_{13}H_{17}NO_5Na$ 290.1004; Anal. calcd for $C_{13}H_{17}NO_5$ (267.1107): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.32; H, 6.44; N, 5.28%.

(2*S*, 4*S*)-2,7-Dimethoxy-2-methyl-4-nitromethyl-chroman (129ja): Prepared following the procedure **2c** 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 AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.64 min (minor), t_R = 7.19 min (major). **$[\alpha]_D^{25}$ = −10.9°** (*c* = 0.18 g/100 mL, $CHCl_3$, **80% *ee***); IR (Neat): ν_{max} 2960, 1620, 1548 (NO_2), 1504, 1439, 1379, 1335, 1268, 1197, 1149, 1119, 1055, 979, 804, 648 and 625 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 7.01 (1H, d, *J* = 8.0 Hz), 6.54 (1H, dd, *J* = 8.0, 4.0 Hz), 6.45 (1H, d, *J* = 2.4, Hz), 4.95 (1H, dd, *J* = 12.0, 4.0 Hz), 4.60 (1H, dd, *J* = 12.0, 8.0 Hz), 3.78 (3H, s, Ar-OC*H*$_3$), 3.66-3.59 (1H, m), 3.26 (3H, s, OC*H*$_3$), 2.18 (1H, d, *J* = 16.0 Hz), 2.04 (1H, dd, *J* = 14.0, 8.0 Hz), 1.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.1 (C), 152.7 (C), 129.5 (CH), 112.2 (C), 108.3 (CH), 102.4 (CH), 98.6 (C), 80.8 (CH_2), 55.2 (CH_3, O*C*H$_3$), 48.8 (CH_3, O*C*H$_3$), 34.0 (CH_2), 31.5 (CH), 23.0 (CH_3); LRMS m/z 266.00 ($M - H^+$), calcd for $C_{13}H_{17}NO_5$ 267.1107; HRMS m/z 290.1003 (M + Na), calcd for $C_{13}H_{17}NO_5Na$ 290.1004; Anal. calcd for $C_{13}H_{17}NO_5$ (267.1107): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.50; H, 6.35; N, 5.21%.

(2*R*, 4*S*)-2,7-Dimethoxy-2-methyl-4-nitromethyl-chroman (130ja): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.60 min (major), t_R = 11.33 min (minor). Mp 76 °C; **$[\alpha]_D^{25}$ = −45.5°** (*c* = 0.18 g/100 mL, $CHCl_3$, **80% *ee***); IR (Neat): ν_{max} 2922, 2851, 1621, 1551 (NO_2), 1511, 1381, 1301, 1279, 1223, 1192, 1157, 1117, 1059, 1030, 859, 795, 675, and 649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.99 (1H, dd, *J* = 8.4, 0.8 Hz), 6.52 (1H, dd, *J* = 8.6, 2.4 Hz), 6.44 (1H, d, *J* = 4.8 Hz), 4.89 (1H, dd, *J* = 12.0, 4.8 Hz), 4.42 (1H, dd, *J* = 12.4, 9.2 Hz), 3.90-3.81 (1H, m), 3.76 (3H, s, Ar-OC*H*$_3$), 3.24 (3H, s, OC*H*$_3$), 2.19 (1H, dd, *J* = 13.2, 6.0 Hz), 1.76 (1H, dd, *J* = 13.0, 12.0 Hz), 1.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 159.8 (C), 153.1 (C), 126.4 (CH), 112.7 (C), 107.8 (CH), 102.7 (CH), 98.2 (C), 79.3 (CH_2), 55.2 (CH_3, O*C*H$_3$), 49.0 (CH_3, O*C*H$_3$), 36.7 (CH_2), 29.8 (CH), 22.8 (CH_3); LRMS m/z 266.00 ($M - H^+$), calcd for $C_{13}H_{17}NO_5$ 267.1107; HRMS m/z 290.1002 (M + Na), calcd for $C_{13}H_{17}NO_5Na$ 290.1004; Anal. calcd for $C_{13}H_{17}NO_5$ (267.1107): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.51; H, 6.38; N, 5.31%.

(2*S*, 4*S*)-2-Methoxy-2-methyl-4-nitromethyl-chroman-8-ol (129ka): Prepared following the procedure **2c** 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 = 98:2, flow rate 0.5 mL/min, λ = 254 nm), t_R = 59.74

min (minor), t_R = 64.77 min (major). **$[\alpha]_D^{25}$ = +14.2°** (*c* = 0.25 g/100 mL, $CHCl_3$, **83% *ee***); IR (Neat): ν_{max} 3509 (O*H*), 1596, 1547 (NO_2), 1474, 1426, 1378, 1239, 1202, 1148, 1119, 1058, 949, 863, 789, 731, 651, and 606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (2H, d, *J* = 3.5 Hz), 6.68 (1H, d, *J* = 4.0 Hz), 5.58 (1H, br s, Ar-O*H*), 4.99 (1H, dd, *J* = 12.2, 7.6 Hz), 4.63 (1H, dd, *J* = 12.7, 4.5 Hz), 3.71 (1H, d, *J* = 6.5 Hz), 3.24 (3H, s, OCH_3), 2.23 (1H, d, *J* = 14.5 Hz), 2.10 (1H, dd, *J* = 14.5, 7.0 Hz), 1.61 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 145.2 (C), 138.9 (C), 121.6 (CH), 120.5 (C), 119.7 (CH), 113.9 (CH), 99.6 (C), 80.4 (CH_2), 48.9 (CH_3), 34.2 (CH_2), 31.7 (CH), 23.0 (CH_3); LRMS m/z 252.15 (M– H^+), calcd for $C_{12}H_{15}NO_5$ 253.0950; HRMS m/z 276.0841 (M + Na), calcd for $C_{12}H_{15}NO_5Na$ 276.0848; Anal. calcd for $C_{12}H_{15}NO_5$ (253.0950): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.95; H, 5.88; N, 5.65%.

(2*R*, 4*S*)-2-Methoxy-2-methyl-4-nitromethyl-chroman-8-ol (130ka): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.93 min (major), t_R = 23.49 min (minor). Mp 92 °C; **$[\alpha]_D^{25}$ = −54.1°** (*c* = 0.27 g/100 mL, $CHCl_3$, **82% *ee***); IR (Neat): ν_{max} 3348 (O*H*), 2940, 1596, 1547 (NO_2), 1475, 1437, 1382, 1255, 1219, 1194, 1105, 1067, 1031, 954, 926, 864, 728, 651, 630, and 608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86-6.85 (2H, m), 6.66-6.64 (1H, m), 5.75 (1H, br s, Ar-O*H*), 4.93 (1H, dd, *J* = 12.2, 5.0 Hz), 4.46 (1H, dd, *J* = 12.2, 9.5 Hz), 3.96-3.90 (1H, m), 3.23 (3H, s, OCH_3), 2.25 (1H, dd, *J* = 13.5, 6.0 Hz), 1.85 (1H, dd, *J* = 13.5, 12.0 Hz), 1.62 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 145.3 (C), 139.0 (C), 121.5 (CH), 120.9 (C), 116.7 (CH), 113.8 (CH), 99.0 (C), 78.9 (CH_2), 49.2 (CH_3, OCH_3), 36.8 (CH_2), 30.1 (CH), 22.8 (CH_3); LRMS m/z 252.15 (M– H^+), calcd for $C_{12}H_{15}NO_5$ 253.0950; HRMS m/z 276.0843 (M + Na), calcd for $C_{12}H_{15}NO_5Na$ 276.0848; Anal. calcd for $C_{12}H_{15}NO_5$ (253.0950): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.95; H, 5.91; N, 5.49%.

(2*S*, 4*S*)-2-Methoxy-2,6-dimethyl-4-nitromethyl-chroman (129la): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was

determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 5.02 min (major), t_R = 5.70 min (minor). Mp 60 °C; **$[\alpha]_D^{25}$ = +16.0°** (*c* = 0.30 g/100 mL, $CHCl_3$, **92% *ee***); IR (Neat): ν_{max} 2951, 1547 (NO_2), 1498, 1378, 1251, 1213, 1153, 1123, 1056, 882 and 819 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.99 (1H, dd, *J* = 8.4, 2.0 Hz), 6.92 (1H, d, *J* = 1.6 Hz), 6.79 (1H, d, *J* = 8.0 Hz), 5.00 (1H, dd, *J* = 12.8, 9.6 Hz), 4.61 (1H, dd, *J* = 12.8, 5.6 Hz), 3.66-3.61 (1H, m), 3.22 (3H, s, OC*H*$_3$), 2.26 (3H, s, Ar-C*H*$_3$), 2.17 (1H, dd, *J* = 14.4, 1.2 Hz), 2.02 (1H, dd, *J* = 14.6, 6.8 Hz), 1.53 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.6 (C), 130.7 (C), 129.5 (CH), 129.1 (CH), 119.8 (C), 117.5 (CH), 98.4 (C), 80.7 (CH_2), 48.6 (CH_3, OC*H*$_3$), 33.9 (CH_2), 32.0 (CH), 23.0 (CH_3), 20.4 (CH_3); LRMS m/z 250.00 ($M - H^+$), calcd for $C_{13}H_{17}NO_4$ 251.1158; HRMS m/z 274.1050 (M + Na), calcd for $C_{13}H_{17}NO_4Na$ 274.1055; Anal. calcd for $C_{13}H_{17}NO_4$ (251.1158): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.21; H, 6.78; N, 5.61%.

(2*R*, 4*S*)-2-Methoxy-2,6-dimethyl-4-nitromethyl-chroman (130la): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.58 min (major), t_R = 7.07 min (minor). Mp 58 °C; **$[\alpha]_D^{25}$ = −42.5°** (*c* = 0.20 g/100 mL, $CHCl_3$, **89% *ee***); IR (Neat): ν_{max} 2990, 1551 (NO_2), 1498, 1435, 1378, 1284, 1228, 1179, 1067, 887, 820 and 639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.99-6.97 (1H, m), 6.89 (1H, br s), 6.78 (1H, d, *J* = 8.4 Hz), 4.92 (1H, dd, *J* = 12.4, 4.8 Hz), 4.42 (1H, dd, *J* = 12.2, 9.2 Hz), 3.92-3.84 (1H, m), 3.21 (3H, s, OC*H*$_3$), 2.26 (3H, s, Ar-C*H*$_3$), 2.19 (1H, dd, *J* = 13.2, 6.4 Hz), 1.78 (1H, dd, *J* = 13.2, 12.0 Hz), 1.54 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.8 (C), 130.5 (C), 129.2 (CH), 126.2 (CH), 120.2 (C), 117.6 (CH), 97.8 (C), 79.2 (CH_2), 48.9 (CH_3), 36.6 (CH_2), 30.2 (CH), 22.8 (CH_3), 20.6 (CH_3); LRMS m/z 250.00 ($M - H^+$), calcd for $C_{13}H_{17}NO_4$ 251.1158; HRMS m/z 274.1051 (M + Na), calcd for $C_{13}H_{17}NO_4Na$ 274.1055; Anal. calcd for $C_{13}H_{17}NO_4$ (251.1158): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.25; H, 6.88; N, 5.51%.

(2*S*, 4*S*)-2-Methoxy-2,6-dimethyl-4-nitromethyl-chroman-1,1,1,3,3-d5 (129la-d_5): Prepared following the procedure **2c** and purified by column chromatography

using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 5.17 min (major), t_R = 6.12 min (minor). Mp 56 °C; **$[\alpha]_D^{25}$ = +23.0°** (*c* = 0.27 g/100 mL, $CHCl_3$, **89% *ee***); IR (Neat): ν_{max} 2962, 1539 (NO_2), 1498, 1378, 1235, 1178, 1143, 1075, 1035 and 817 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.01 (1H, d, *J* = 8.0 Hz), 6.94 (1H, s), 6.81 (1H, d, *J* = 8.4 Hz), 5.00 (1H, d, *J* = 9.2 Hz, proton resolution is very poor), 4.61 (1H, s, proton resolution is very poor), 3.62 (1H, s), 3.24 (3H, s, OC*H*$_3$), 2.28 (3H, s, Ar-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.6 (C), 130.7 (C), 129.5 (CH), 129.1 (CH), 119.7 (C), 117.5 (CH), 98.3 (C), 80.7 (CH_2, peak resolution is very poor), 48.6 (CH_3, OC*H*$_3$), 33.9 (CH_2, peak resolution is very poor), 31.7 (CH), 23.0 (CH_3, peak resolution is very poor), 20.5 (CH_3); LRMS m/z 257.00 ($M + H^+$), calcd for $C_{13}H_{12}D_5NO_4$ 256.1466.

(2*R*, 4*S*)-2-Methoxy-2,6-dimethyl-4-nitromethyl-chroman-1,1,1,3,3-d5 (130la-d_5): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.84 min (major), t_R = 7.41 min (minor). Mp 66 °C; **$[\alpha]_D^{25}$ = −54.9°** (*c* = 0.37 g/100 mL, $CHCl_3$, **91% *ee***); IR (Neat): ν_{max} 2939, 1543 (NO_2), 1496, 1378, 1248, 1196, 1072, 1037, 820 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (1H, d, *J* = 8.0 Hz), 6.91 (1H, s), 6.80 (1H, d, *J* = 8.2 Hz), 4.92 (1H, s, proton resolution is very poor), 4.43 (1H, d, *J* = 9.6 Hz, proton resolution is very poor), 3.87 (1H, s), 3.23 (3H, s, OC*H*$_3$), 2.28 (3H, s, Ar-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.8 (C), 130.5 (C), 129.3 (CH), 126.2 (CH), 120.2 (C), 117.7 (CH), 97.7 (C), 79.0 (CH_2, peak resolution is very poor), 49.0 (CH_3, OC*H*$_3$), 36.0 (CH_2, peak resolution is very poor), 30.0 (CH), 22.1 (CH_3, peak resolution is very poor), 20.7 (CH_3); LRMS m/z 257.10 ($M + H^+$), calcd for $C_{13}H_{12}D_5NO_4$ 256.1466.

(2*S*, 4*S*)-2-Ethoxy-2-methyl-4-nitromethyl-chroman (129cb): Prepared following the procedure **2c** 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 = 5.12 min (minor), t_R = 5.52 min (major). **$[\alpha]_D^{25}$ = +74.8°** (*c* = 0.67 g/100 mL, $CHCl_3$, **80% *ee***); IR (Neat): ν_{max} 2974, 2937, 1582, 1550 (NO_2), 1488, 1454, 1379, 1247, 1156, 1126, 1101, 1057 and 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (1H, dt, *J* = 7.2, 1.0 Hz), 7.11 (1H, br d, *J* = 7.2 Hz), 6.94 (1H, br t, *J* = 7.2 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 5.06 (1H, dd, *J* = 13.0, 9.2 Hz), 4.65 (1H, dd, *J* = 12.8, 5.6 Hz), 3.69 (1H, q, *J* = 6.4 Hz), 3.59 (2H, q, *J* = 6.8 Hz, OCH_2CH_3), 2.22 (1H, d, *J* = 14.4 Hz), 2.04 (1H, dd, *J* = 14.4, 6.8 Hz), 1.56 (3H, s, CH_3), 1.03 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 152.0 (C), 128.9 (CH), 128.8 (CH), 121.3 (CH), 120.2 (C), 117.7 (CH), 98.4 (C), 80.9 (CH_2), 56.8 (CH_2, OCH_2CH_3), 34.2 (CH_2), 32.1 (CH), 23.7 (CH_3), 15.4 (CH_3, OCH_2CH_3); LRMS m/z 250.00 ($M - H^+$), calcd for $C_{13}H_{17}NO_4$ 251.1158; Anal. calcd for $C_{13}H_{17}NO_4$ (251.1158): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.25; H, 6.88; N, 5.61%.

(2*R*, 4*S*)-2-Ethoxy-2-methyl-4-nitromethyl-chroman (130cb): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. 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 = 5.72 min (major), t_R = 8.69 min (minor). Mp 60 °C; **$[\alpha]_D^{25}$ = −54.8°** (*c* = 0.83 g/100 mL, $CHCl_3$, **80% *ee***); IR (Neat): ν_{max} 2979, 1552 (NO_2), 1489, 1452, 1379, 1256, 1224, 1188, 1097, 1063, 938, 879, 756 and 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17 (1H, t, *J* = 7.6 Hz), 7.10 (1H, d, *J* = 7.6 Hz), 6.93 (1H, t, *J* = 7.2 Hz), 6.86 (1H, d, *J* = 8.0 Hz), 4.93 (1H, dd, *J* = 12.4, 4.8 Hz), 4.47 (1H, dd, *J* = 12.0, 9.2 Hz), 4.00-3.92 (1H, m), 3.64-3.47 (2H, m, OCH_2CH_3), 2.22 (1H, dd, *J* = 13.4, 6.0 Hz), 1.79 (1H, t, *J* = 12.8 Hz), 1.57 (3H, s, CH_3), 0.97 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 152.2 (C), 128.5 (CH), 125.7 (CH), 121.1 (CH), 120.6 (C), 117.8 (CH), 97.9 (C), 79.2 (CH_2), 56.8 (CH_2, OCH_2CH_3), 36.8 (CH_2), 30.3 (CH), 23.7 (CH_3), 15.3 (CH_3, OCH_2CH_3); LRMS m/z 250.00 ($M - H^+$), calcd for $C_{13}H_{17}NO_4$ 251.1158; HRMS m/z 274.1053 (M + Na), calcd for $C_{13}H_{17}NO_4Na$ 274.1055; Anal. calcd for $C_{13}H_{17}NO_4$ (251.1158): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.10; H, 6.88; N, 5.65%.

(2*S*, 4*S*)-6-Bromo-2-ethoxy-2-methyl-4-nitromethyl-chroman (129fb): Prepared following the procedure **2c** 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 AS-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 4.54 min (minor), t_R = 4.90 min (major). **$[\alpha]_D^{25}$ = +65.5°** (*c* = 0.83 g/100 mL, $CHCl_3$, **88% *ee***); IR (Neat): ν_{max} 2974, 2934, 2893, 1739, 1545 (NO_2), 1483, 1381, 1253, 1215, 1180, 1059, 951, 881, 818, 739, 681, 582 and 490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30-7.26 (2H, m), 6.76 (1H, d, *J* = 8.8 Hz), 5.07 (1H, dd, *J* = 13.2, 9.2 Hz), 4.61 (1H, dd, *J* = 13.0, 5.2 Hz), 3.70-3.61 (1H, m), 3.59-3.51 (2H, m, OC*H*$_2$$CH_3$), 2.20 (1H, dd, *J* = 14.8, 1.2 Hz), 2.01 (1H, dd, *J* = 14.6, 7.2 Hz), 1.56 (3H, s, C*H*$_3$), 1.03 (3H, t, *J* = 8.4 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.2 (C), 131.8 (CH), 131.5 (CH), 122.4 (C), 119.6 (CH), 113.3 (C), 98.6 (C), 80.5 (CH_2), 57.0 (CH_2, O*C*H_2CH_3), 33.9 (CH_2), 31.8 (CH), 23.6 (CH_3), 15.3 (CH_3, OCH_2*C*H_3); LRMS m/z 330.15 (M + H^+), calcd for $C_{13}H_{16}BrNO_4$ 329.0263; Anal. calcd for $C_{13}H_{16}BrNO_4$ (329.0263): C, 47.29; H, 4.88; N, 4.24. Found: C, 47.32; H, 4.84; N, 4.28%.

(2*R*, 4*S*)-6-Bromo-2-ethoxy-2-methyl-4-nitromethyl-chroman (130fb): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 5.34 min (major), t_R = 6.09 min (minor). Mp 70 °C; **$[\alpha]_D^{25}$ = −41.2°** (*c* = 0.83 g/100 mL, $CHCl_3$, **82% *ee***); IR (Neat): ν_{max} 2974, 2922, 1736, 1548 (NO_2), 1483, 1381, 1217, 1064, 939, 885, 814, 673 and 470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29-7.26 (1H, m), 7.23-7.22 (1H, m), 6.75 (1H, d, *J* = 8.8 Hz), 4.89 (1H, dd, *J* = 12.2, 4.4 Hz), 4.48 (1H, dd, *J* = 12.4, 9.2 Hz), 3.97-3.89 (1H, m), 3.68-3.44 (2H, m, OC*H*$_2$$CH_3$), 2.21 (1H, dd, *J* = 13.2, 6.0 Hz), 1.77 (1H, t, *J* = 12.4 Hz), 1.56 (3H, s, C*H*$_3$), 0.98 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.5 (C), 131.5 (CH), 128.7 (CH), 122.8 (C), 119.6 (CH), 113.2 (C), 98.2 (C), 78.8 (CH_2), 57.0 (CH_2, O*C*H_2CH_3), 36.4 (CH_2), 30.2 (CH), 23.5 (CH_3), 15.2 (CH_3,

OCH_2CH_3); LRMS m/z 330.15 ($M + H^+$), calcd for $C_{13}H_{16}BrNO_4$ 329.0263; Anal. calcd for $C_{13}H_{16}BrNO_4$ (329.0263): C, 47.29; H, 4.88; N, 4.24. Found: C, 47.32; H, 4.91; N, 4.31%.

(*S*)-4-(3-hydroxyphenyl)-5-nitropentan-2-one (131ca): Prepared following the procedure **2a** 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 = 7.50 min (major), t_R = 8.28 min (minor). **$[\alpha]_D^{25}$ = –6.5°** (*c* = 0.50 g/100 mL, CH_3OH, **67% *ee***); IR (KBr): ν_{max} 3347 (O*H*), 1706 (*C*=O), 1594, 1548, 1487, 1456, 1429, 1372, 1215, 1160, 1091, 957, 907, 872 and 786 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16-7.12 (1H, m), 6.72-6.70 (3H, m), 4.65-4.60 (1H, m), 4.56-4.51 (1H, m), 3.92 (1H, t, *J* = 6.8 Hz), 2.94-2.82 (2H, m), 2.09 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.5 (C, *C*=O), 156.2 (C), 140.3 (C), 130.1 (CH), 119.1 (CH), 114.9 (CH), 114.4 (CH), 79.3 (CH_2), 45.9 (CH_2), 38.8 (CH), 30.2 (CH_3); HRMS m/z 246.0743 (M + Na), calcd for $C_{11}H_{13}NO_4Na$ 246.0743.

(*S*)-4-(4-hydroxyphenyl)-5-nitropentan-2-one (131da): Prepared following the procedure **2a** 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 AS-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 18.77 min (major), t_R = 26.34 min (minor). **$[\alpha]_D^{25}$ = –10.4°** (*c* = 0.25 g/100 mL, CH_3OH, **67% *ee***); IR (KBr): ν_{max} 3465 (O*H*), 1708 (*C*=O), 1611, 1541, 1512, 1440, 1408, 1361, 1324, 1265, 1202, 1164, 1109, 950, 818 and 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (2H, d, *J* = 8.4 Hz), 6.77 (2H, d, *J* = 8.4 Hz), 5.16 (1H, br s, O*H*), 4.65 (1H, dd, *J* = 12.4, 6.8 Hz), 4.55 (1H, dd, *J* = 12.2, 8.0 Hz), 3.94 (1H, t, *J* = 7.6 Hz), 2.88 (2H, d, *J* = 6.8 Hz), 2.12 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.2 (C, *C*=O), 156.5 (C), 129.5 (C), 128.4 (2 x CH), 115.7 (2 x CH), 79.7 (CH_2), 46.2 (CH_2), 38.4 (CH), 30.3 (CH_3); HRMS m/z 246.0743 (M + Na), calcd for $C_{11}H_{13}NO_4Na$ 246.0743.

2e. ***Brønsted acid-catalyzed dehydration of SMA products:*** In an oven dried round bottom flask, to the Michael adduct **126c↔127c↔128c** (46 mg, 0.2 mmol), added toluene (2 mL), and

p-TSA.H_2O (7 mg, 20 mol%). After heating reaction mixture to 110 °C for 50 min, it was brought to 25 °C and the crude reaction mixture was worked up with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure chiral product **132c** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*S*)-2-Methyl-4-nitromethyl-4*H*-chromene (132c): Prepared following the procedure **2e** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 8.09 min (major), t_R = 8.74 min (minor). Mp 58 °C; **$[\alpha]_D^{25}$ = −15.5°** (*c* = 0.23 g/100 mL, $CHCl_3$, **81% *ee***); IR (Neat): ν_{max} 3623, 3602, 1688, 1544 (NO_2), 1485, 1380, 1314, 1263, 1227, 1193, 1105, 1069, 1022, 801 and 767 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (1H, t, *J* = 7.6 Hz), 7.11-7.05 (2H, m), 6.96 (1H, d, *J* = 8.4 Hz), 4.75 (1H, d, *J* = 3.6 Hz), 4.45 (1H, dd, *J* = 11.6, 5.6 Hz), 4.43-4.38 (1H, m), 4.27-4.26 (1H, m), 1.95 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.6 (C), 150.7 (C), 128.8 (CH), 128.0 (CH), 123.7 (CH), 118.2 (C), 116.9 (CH), 94.5 (CH), 82.0 (CH_2), 33.9 (CH), 19.3 (CH_3); LRMS m/z 204.00 ($M - H^+$), calcd for $C_{11}H_{11}NO_3$ 205.0739; Anal. calcd for $C_{11}H_{11}NO_3$ (205.0739): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.25; H, 5.46; N, 6.89%.

2f. ***Base-catalyzed protection of SMA products:*** To a solution of Michael adduct **126c↔127c↔128c** (44 mg, 0.2 mmol) in dry DCM (4 mL) were added successively *i*Pr_2NEt (0.13 mL, 0.8 mmol) and MOMCl (91 μL, 1.2 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 4 h. The reaction mixture was worked up with aqueous NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure product **133ca** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*S*)-4-(2-Methoxymethoxy-phenyl)-5-nitro-pentan-2-one (133ca): Prepared following the procedure **2f** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = −44.6°** (*c* = 0.20 g/100 mL, $CHCl_3$, **82% *ee***); IR (Neat): ν_{max} 2918, 2851, 1712 (*C*=O), 1550 (NO_2), 1489, 1375, 1232,

1151, 1078, 999 and 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (1H, dt, *J* = 7.2, 2.3 Hz), 7.15 (1H, dd, *J* = 7.6, 1.6 Hz), 7.11 (1H, br d, *J* = 7.6 Hz), 6.96 (1H, dt, *J* = 7.2, 1.6 Hz), 5.25 (2H, s), 4.74 (2H, d, *J* = 6.8 Hz), 4.30 (1H, quintet, *J* = 6.8 Hz), 3.52 (3H, s, OC*H*$_3$), 3.01 (2H, dABq, *J* = 17.6, 7.6 Hz), 2.14 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 205.9 (C, *C*=O), 154.8 (C), 129.0 (CH), 128.9 (CH), 126.9 (C), 122.0 (CH), 114.3 (CH), 94.4 (CH_2), 78.0 (CH_2), 56.3 (CH_3, O*C*H$_3$), 44.7 (CH_2), 34.7 (CH), 30.2 (CH_3); LRMS m/z 268.50 (M + H^+), calcd for $C_{13}H_{17}NO_5$ 267.1107; Anal. calcd for $C_{13}H_{17}NO_5$ (267.1107): C, 58.24; H, 6.41; N, 5.24. Found: C, 58.25; H, 6.44; N, 5.32%.

2g. ***Base-catalyzed protection of SMA products:*** To a solution of Michael adduct **126c↔127c↔128c** (44 mg, 0.2 mmol) in dry THF (2 mL) were added successively NaH (6 mg, 0.24 mmol) and MeI (74 μL, 1.2 mmol) at 0 °C. The resulting mixture was stirred at same temperature for 30 min and then brought to 25 °C and stirred for 4.5 h. The reaction mixture was worked up with aqueous NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure product (+)-**131ba** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*S*)-4-(2-Methoxy-phenyl)-5-nitro-pentan-2-one (131ba):♣ Prepared following the procedure **2g** 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 AS-H column (hexane/2-propanol = 60:40, flow rate 1.0 mL/min, λ = 210 nm), t_R = 10.62 min (major), t_R = 12.00 min (minor). **$[\alpha]_D^{25}$ = +33.2°** (*c* = 0.50 g/100 mL, $CHCl_3$, **80% *ee***); IR (Neat): ν_{max} 1716 (*C*=O), 1551 (NO_2), 1494, 1462, 1376, 1245, 1165, 1122, 1028, 910 and 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25-7.21 (1H, m), 7.12 (1H, d, *J* = 4.0 Hz), 6.90-6.86 (2H, m), 4.75-4.66 (2H, m), 4.20 (1H, quintet, *J* = 6.8 Hz), 3.84 (3H, s, OC*H*$_3$), 3.04-2.91 (2H, m), 2.10 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.1 (C, *C*=O), 156.9 (C), 129.1 (CH), 128.8 (CH), 126.2 (C), 120.6 (CH), 110.8 (CH), 77.6 (CH_2), 55.1 (CH_3, O*C*H$_3$), 44.3 (CH_2), 35.2 (CH), 30.0 (CH_3).

♣ The absolute configuration of chiral products **129ba-fb** and **130ba-fb** were also established by comparison of **(+)-131ba** with the chiral product synthesized from direct asymmetric Michael reaction (see Fei Xue et. al. *Adv. Synth. Catal.* **2008**, *350*, 2194-2198.)

2h. ***Methylenation of SMA products:*** In an oven dried round bottom flask, to triphenyl(bromomethyl)phosphonium bromide (457 mg, 1.28 mmol), in dry benzene (1 mL), under nitrogen, was added potassium *tert*-butoxide (134 mg, 1.28 mmol). After the mixture becomes deep yellow in colour, added the Michael adduct **126c↔127c↔128c** (46 mg, 0.2 mmol) in benzene (1 ml). After stirring the reaction mixture at 25 °C for 2h, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure product **134c** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(1*S*)-2-(3-Methyl-1-nitromethyl-but-3-enyl)-phenol (134c): Prepared following the procedure **2h** 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 AS-H column (hexane/2-propanol = 94:6, flow rate 0.8 mL/min, λ = 254 nm), t_R = 7.57 min (major), t_R = 8.75 min (minor). **$[\alpha]_D^{25} = -26.5°$** (*c* = 0.20 g/100 mL, $CHCl_3$, **82% *ee***); IR (Neat): ν_{max} 3518 (O*H*), 1600, 1550 (NO_2), 1454, 1378, 1260, 1105, 894, 755, 679, 646 and 601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13-7.10 (2H, m), 6.89 (1H, t, *J* = 7.2 Hz), 6.72 (1H, t, *J* = 8.0 Hz), 5.39 (1H, s, Ar-O*H*), 4.81-4.73 (3H, m), 4.67-4.62 (1H, m), 3.98 (1H, quintet, *J* = 6.8 Hz), 2.53-2.49 (2H, m), 1.75 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 153.5 (C), 142.1 (C), 129.1 (CH), 128.5 (CH), 125.5 (C), 121.1 (CH), 116.0 (CH), 113.5 (CH_2, C=*C*H_2), 78.6 (CH_2), 39.9 (CH_2), 37.6 (CH), 22.0 (CH_3); LRMS m/z 222.00 (M + H^+), calcd for $C_{12}H_{15}NO_3$ 221.1052; HRMS m/z 244.0945 (M + Na), calcd for $C_{12}H_{15}NO_3Na$ 244.0950; Anal. calcd for $C_{12}H_{15}NO_3$ (221.1052): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.25; H, 6.87; N, 6.42%.

2i. ***Iodine-catalyzed cyclization of olefin products:*** In an oven dried round bottom flask, was taken 2-(3-methyl-1-nitromethyl-but-3-enyl)-phenol (44 mg, 0.2 mmol) **134c** in DCM and it was cooled to 0 °C. To that added iodine (61 mg, 0.24 mmol) and stirred at same temperature for 15 min. The reaction mixture was worked up with aqueous sodium thiosulphate and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried

(Na_2SO_4), filtered and concentrated. Pure product **135c** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*S*)-2,2-Dimethyl-4-nitromethyl-chroman (135c): Prepared following the procedure **2i** 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 = 6.44 min (major), t_R = 8.15 min (minor). **$[\alpha]_D^{25}$ = −65.8°** (*c* = 0.57 g/100 mL, $CHCl_3$, **81% *ee***); IR (Neat): ν_{max} 2963, 2930, 2865, 1730, 1552 (NO_2), 1483, 1444, 1376, 1260, 1087, 1025, 800 and 651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17 (1H, t, *J* = 7.6 Hz), 7.08 (1H, d, *J* = 7.6 Hz), 6.89 (1H, t, *J* = 7.2 Hz), 6.84 (1H, d, *J* = 8.4 Hz), 4.95 (1H, dd, *J* = 12.0, 4.8 Hz), 4.40 (1H, t, *J* = 10.0 Hz), 3.78-3.73 (1H, m), 1.98 (1H, dd, *J* = 13.4, 6.4 Hz), 1.74 (1H, t, *J* = 11.6 Hz), 1.44 (3H, s, C*H*$_3$), 1.27 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 153.8 (C), 128.8 (CH), 126.3 (CH), 120.4 (CH), 118.7 (C), 118.4 (CH), 80.1 (CH_2), 73.9 (C), 37.5 (CH_2), 31.2 (CH), 29.5 (CH_3), 24.1 (CH_3); LRMS m/z 221.80 (M + H^+), calcd for $C_{12}H_{15}NO_3$ 221.1052; HRMS m/z 244.0942 (M + Na), calcd for $C_{12}H_{15}NO_3Na$ 244.0950; Anal. calcd for $C_{12}H_{15}NO_3$ (221.1052): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.08; H, 6.77; N, 6.25%.

2j. ***Hydrogenation followed by protection of nitro products:*** In an oven dried round bottom flask, was taken activated (10%) Pd/C (7 mg, 10 mol%), with compound **135c** or **130ca** dissolved in MeOH (4 mL) and stirred under H_2 atmosphere at 25 °C for 5 h. The reaction mixture was passed through a pad of celite and concentrated to dryness. The crude mixture was taken in a dry oven dried round bottom flask in dry DCM (2 mL) and added successively dry triethylamine (42 μL, 0.3 mmol) and di-*tert*-butyl carbonate (65 mg, 0.3 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 2 h and then worked up with aqueous NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure product **136c** or **137ca** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*S*)-(2,2-Dimethyl-chroman-4-ylmethyl)-carbamic acid *tert*-butyl ester (136c): Prepared following the procedure **2j** and purified by column chromatography using

EtOAc/hexane and isolated as solid. Mp 68 °C; **$[\alpha]_D^{25}$ = −24.7°** (*c* = 0.5 g/100 mL, $CHCl_3$, **81% *ee***); IR (Neat): ν_{max} 3350 (N*H*), 2982, 2924, 2492, 1678 (*C*=O), 1606, 1577, 1525 (NO_2), 1487, 1423, 1365, 1251, 1157, 1041, 935, 754, 638 and 403 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (1H, br d, *J* = 7.2 Hz), 7.12 (1H, t, *J* = 7.2 Hz), 6.88 (1H, t, *J* = 7.2 Hz), 6.81 (1H, dd, *J* = 7.2, 1.0 Hz), 4.50 (1H, s, N*H*), 3.82-3.77 (1H, m), 3.40-3.36 (1H, m), 3.09 (1H, m), 1.88 (1H, dd, *J* = 13.6, 6.0 Hz), 1.68 (1H, t, *J* = 12.8 Hz), 1.43 (12H, s, 4 x CH_3), 1.23 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 156.1 (C), 154.4 (C), 127.9 (CH), 126.7 (CH), 121.6 (C), 120.2 (CH), 117.8 (CH), 79.4 (C), 74.2 (C), 43.6 (CH_2), 37.3 (CH_2), 31.9 (CH), 30.0 (CH_3), 28.3 (3 x CH_3), 24.1 (CH_3); LRMS m/z 292.10 (M + H^+), calcd for $C_{17}H_{25}NO_3$ 291.1834; Anal. calcd for $C_{17}H_{25}NO_3$ (291.1834): C, 70.07; H, 8.65; N, 4.81. Found: C, 70.15; H, 8.61; N, 4.85%.

(*2R, 4S*)-(2-Methoxy-2-methyl-chroman-4-ylmethyl)-carbamic acid *tert*-butyl ester (137ca): Prepared following the procedure **2j** 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 = 94:6, flow rate 0.6 mL/min, λ = 254 nm), t_R = 9.83 min (major), t_R = 11.39 min (minor). **$[\alpha]_D^{25}$ = −44.5°** (*c* = 0.22 g/100 mL, $CHCl_3$, **81% *ee***); IR (Neat): ν_{max} 3627 (N*H*), 3361, 2977, 2936, 1704 (*C*=O), 1491, 1454, 1370, 1256, 1168, 1107, 1067 and 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (1H, d, *J* = 8.0 Hz), 7.15 (1H, t, *J* = 8.0 Hz), 6.94 (1H, dt, *J* = 8.0, 0.8 Hz), 6.86 (1H, dd, *J* = 8.2, 1.2 Hz), 4.44 (1H, s, N*H*), 3.80-3.73 (1H, m), 3.51-3.45 (1H, m), 3.29-3.22 (1H, m), 3.24 (3H, s, OC*H*$_3$), 2.13 (1H, dd, *J* = 13.4, 6.0 Hz), 1.75 (1H, t, *J* = 13.2 Hz), 1.56 (3H, s, C*H*$_3$), 1.47-1.41 (9H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 156.1 (C), 152.8 (C), 127.8 (CH), 126.2 (CH), 123.0 (C), 121.1 (CH), 117.4 (CH), 98.4 (C), 79.3 (C), 49.0 (CH_3, O*C*H_3), 42.4 (CH_2), 36.2 (CH_2), 31.0 (CH), 28.3 (3 x CH_3), 23.1 (CH_3); HRMS m/z 330.1682 (M + Na), calcd for $C_{17}H_{25}NO_4Na$ 330.1681; Anal. calcd for $C_{17}H_{25}NO_4$ (307.1784): C, 66.43; H, 8.20; N, 4.56. Found: C, 66.56; H, 8.25; N, 4.51%.

2k. ***Hydrogenation of nitro products:*** In an oven dried round bottom flask, was taken preactivated 10% Pd/C (3 mg, 5 mol%), with compound (+)-**131ba** (24 mg, 0.1 mmol) dissolved in dry ethyl acetate (1.0 mL) and stirred under H_2 atmosphere at 25 °C for 5 h. The reaction

mixture was passed through a pad of celite and the pure product (+)-**138cb** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*S*, 2*S*)-4-(2-Methoxy-phenyl)-2-methyl-pyrrolidine (*cis*-138cb) and (4*S*, 2*R*)-4-(2-Methoxy-phenyl)-2-methyl-pyrrolidine (*trans*-138cb): Prepared following the procedure **2k** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +31.0°** (*c* = 0.35 g/100 mL, $CHCl_3$, **80% *ee***); IR (Neat): ν_{max} 1598, 1493, 1459, 1243, 1095, 1026, 799, 641 and 605 cm^{-1}; ^1H NMR ($CDCl_3$, major *cis*-isomer) δ 7.22-7.09 (2H, m), 6.93-6.84 (2H, m), 3.82 (3H, s, OC*H*$_3$), 3.88-3.70 (1H, m), 3.64-3.56 (1H, m), 3.34-3.25 (1H, m), 2.99-2.95 (1H, m), 2.64-2.57 (1H, br s, N*H*), 2.32-2.23 (1H, m), 1.54-1.43 (1H, m), 1.27 (3H, d, *J* = 6.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major *cis*-isomer) δ 157.3 (C), 132.4 (C), 127.2 (CH), 127.1 (CH), 120.5 (CH), 110.4 (CH), 55.5 (CH), 55.3 (CH_3, O*C*H$_3$), 53.0 (CH_2), 41.5 (CH_2), 40.6 (CH), 21.0 (CH_3); LRMS m/z 192.15 (M + H^+), calcd for $C_{12}H_{17}NO$ 191.1310; Anal. calcd for $C_{12}H_{17}NO$ (191.1310): C, 75.35; H, 8.96; N, 7.32. Found: C, 75.48; H, 8.88; N, 7.42%.

2l. ***Protection of hydrogenated products:*** In an oven dried round bottom flask, were taken (+)-**138cb** (30 mg, 0.16 mmol) in chloroform (0.2 mL) and triethylamine (45 μL, 0.32 mmol). To that reaction mixture, *p*-toluenesulphonyl chloride (33 mg, 0.176 mmol) was added drop wise in 0.3 mL chloroform under N_2 atmosphere at 0 °C. After 30 min, it was brought to 25 °C and stirred for overnight. The reaction mixture was then worked up with aqueous NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure product (+)-**139cb** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4*S*, 2*S*)-4-(2-Methoxy-phenyl)-2-methyl-1-(toluene-4-sulfonyl)-pyrrolidine (*cis*-139cb) and (4*S*, 2*R*)-4-(2-Methoxy-phenyl)-2-methyl-1-(toluene-4-sulfonyl)-pyrrolidine (*trans*-139cb): Prepared following the procedure **2l** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +38.5°** (*c* = 0.33 g/100 mL, $CHCl_3$, **80% *ee***); IR (Neat): ν_{max} 1597, 1493, 1461, 1341, 1243, 1092, 1032, 817, 755, 724, 658, 642 and 625 cm^{-1}; ^1H NMR ($CDCl_3$, major *cis*-isomer) δ 7.82 (2H, d, *J* = 8.2 Hz), 7.36 (2H, d, *J* = 8.0 Hz), 7.24-7.19 (1H, m), 7.12-7.10 (1H, m), 6.93-6.89 (1H, m), 6.85-6.82 (1H, m), 3.96 (1H, ddd, *J* = 11.6, 7.4, 1.2 Hz), 3.79 (3H, s, Ar-OC*H*$_3$), 3.76-3.71 (1H, m), 3.27 (1H, t, *J* = 11.2 Hz), 2.97-2.87 (1H, m), 2.47 (3H, s, Ar-C*H*$_3$), 2.96-2.23 (1H, m), 1.82-1.74 (1H, m), 1.49 (3H, d, *J* = 6.2 Hz); ^1H NMR ($CDCl_3$, minor *trans*-isomer) δ 7.74 (2H, d, *J* = 8.2 Hz), 7.31 (2H, d, *J* = 8.0 Hz), 7.24-7.19 (1H, m), 7.12-7.10 (1H, m), 6.93-6.89 (1H, m), 6.85-6.82 (1H, m), 3.99-3.92 (1H, m), 3.79 (3H, s), 3.76-3.71 (1H, m), 3.27 (1H, t, *J* = 11.0 Hz), 2.97-2.87 (1H, m), 2.45 (3H, s), 2.96-2.23 (1H, m), 2.00-1.85 (1H, m), 1.44 (3H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major *cis*-isomer) δ 157.5 (C), 143.1 (C), 135.4 (C), 129.5 (2 x CH), 127.9 (CH), 127.7 (C), 127.6 (2 x CH), 126.6 (CH), 120.5 (CH), 110.3 (CH), 56.7 (CH), 55.2 (CH_3, O*C*H$_3$), 53.9 (CH_2), 39.9 (CH_2), 37.3 (CH), 22.8 (CH_3), 21.5 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, minor *trans*-isomer) δ 157.6 (C), 143.1 (C), 134.6 (C), 129.5 (2 x CH), 127.9 (CH), 127.6 (2 x CH), 127.5 (C), 126.6 (CH), 120.4 (CH), 110.36 (CH), 56.7 (CH), 55.7 (CH_3, O*C*H$_3$), 53.8 (CH_2), 37.9 (CH_2), 36.1 (CH), 23.4 (CH_3), 21.5 (CH_3); LRMS m/z 346.25 (M + H^+), calcd for $C_{19}H_{23}NO_3S$ 345.1399; Anal. calcd for $C_{19}H_{23}NO_3S$ (345.1399): C, 66.06; H, 6.71; N, 4.05. Found: C, 66.25; H, 6.62; N, 4.12%.

3. General experimental procedures for the asymmetric supramolecular catalysis.

3a. ***General procedure for asymmetric Michael reaction of cyclohexanone 32b with 2-(2-nitrovinyl)phenols 82 or (E)-β-nitrostyrene 92 through supramolecular-catalysis:*** In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of 9-amino-9-deoxyepiquinine thiourea **34i** (15 mg, 0.025 mmol) and D-proline *ent*-**34a** (3 mg, 0.025 mmol) in DCM (1.0 mL, 0.5 M), was added 2-(2-nitrovinyl)phenols **82** or (*E*)-β-nitrostyrene **92** (0.5

mmol). After stirring for 1 min, was added cyclohexanone **32b** (0.26 mL, 2.5 mmol) and the reaction mixture was stirred at 25 °C for 5-18 h. The crude reaction mixture was then worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **140** or **142** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

(9*R*,9a*S*)-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-4a-ol (140cb): Prepared following the procedure **3a** 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 OJ-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 13.39 min (minor), t_R = 16.73 min (major), t_R = 22.15 min (minor), t_R = 24.14 min (major); **$[\alpha]_D^{25}$ = +□29.0°** (*c* = 0.70 g/100 mL, $CHCl_3$, **97% *ee***); IR (Neat): ν_{max} 3526 (O*H*), 3034, 2939, 2862, 1697, 1610, 1556 (NO_2), 1489, 1454, 1377, 1234, 1130, 1076, 947, 864 and 756 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of 1:1 diastereomers) δ 7.17 (1H, br t, *J* = 7.0 Hz), 7.16 (1H, br t, *J* = 7.0 Hz), 7.00 (1H, dd, *J* = 7.6, 1.5 Hz), 6.96-6.87 (3H, m), 6.84 (1H, dd, *J* = 8.5, 1.0 Hz), 6.80 (1H, dd, *J* = 8.5, 1.0 Hz), 5.01-4.95 (2H, m), 4.67 (1H, dd, *J* = 13.2, 7.6 Hz), 4.54 (1H, dd, *J* = 12.4, 9.2 Hz), 4.31 (1H, m), 3.65 (1H, q, *J* = 6.0 Hz), 2.92 (1H, br s, O*H*), 2.50 (1H, br s, O*H*), 2.11-2.04 (2H, m), 1.97-1.83 (3H, m), 1.76-1.53 (10H, m), 1.38-1.20 (2H, m), 0.96 (1H, dq, *J* = 13.0, 2.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, mixture of 1:1 diastereomers) δ 151.4 (C), 151.2 (C), 129.0 (CH), 128.9 (CH), 128.5 (CH), 125.4 (CH), 122.4 (C), 121.3 (CH), 121.2 (CH), 119.4 (C), 117.45 (CH), 117.4 (CH), 97.7 (C, O-*C*-OH), 96.8 (C, O-*C*-OH), 78.7 (CH_2), 75.9 (CH_2), 40.9 (CH), 39.3 (CH_2), 39.0 (CH_2), 38.4 (CH), 36.4 (CH), 32.6 (CH), 25.82 (CH_2), 25.80 (CH_2), 24.3 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 22.5 (CH_2); LRMS m/z 263.95 (M + H^+), calcd for $C_{14}H_{17}NO_4$ 263.1158; HRMS m/z 286.1056 (M + Na), calcd for $C_{14}H_{17}NO_4Na$ 286.1055; Anal. calcd for $C_{14}H_{17}NO_4$ (263.1158): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.96; H, 6.61; N, 5.45%.

3b. ***General procedure for asymmetric Michael reaction of cyclohexanone 32 with 2-(2-nitrovinyl)phenols 82 through supramolecular catalysis followed by reductive etherification:*** In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of 9-amino-9-

deoxyepiquinine thiourea **34i** (15 mg, 0.025 mmol) and D-proline *ent*-**34a** (3 mg, 0.025mmol) in DCM (1.0 mL, 0.5 M), was added 2-(2-nitrovinyl)phenol **82** (0.5 mmol). After stirring for a minute, was added cyclohexanone **32** (2.5 mmol) and the reaction mixture was stirred at 25 °C for 5 to 24 h. The crude reaction mixture was then worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude mixture was filtered through a pad of silica eluting with EtOAc and hexanes. To the resulting dry lactol **140** in DCM at -10 °C, were added triethylsilane (0.24 mL, 1.5 mmol) and boron trifluoride diethyl etherate (0.12 mL, 1.0 mmol). The mixture was stirred at the same temperature for 30 min and then brought to room temperature and stirred for another 90 min. The crude reaction mixture was worked up with saturated $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **141** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4a*S*,9*R*,9a*S*)-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141cb): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 68 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 9.9 min (major), t_R = 11.8 min (minor); **$[\alpha]_D^{25}$ = −124.2°** (*c* = 0.40 g/100 mL, $CHCl_3$, **>99% *ee***); IR (KBr): ν_{max} 3069, 3038, 2934, 2860, 1605, 1580, 1549 (NO_2), 1489, 1450, 1381, 1356, 1340, 1288, 1238, 1186, 1155, 1128, 1072, 1041, 970, 939, 895, 860, 837, 794, 752, 694 and 648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18-7.14 (1H, m), 6.93 (1H, td, *J* = 8.0, 1.2 Hz), 6.88-6.84 (2H, m), 4.94 (1H, dd, *J* = 12.8, 5.6 Hz), 4.56 (1H, dd, *J* = 12.8, 10.0 Hz), 4.30 (1H, br s), 3.95 (1H, td, *J* = 10.0, 5.2 Hz), 2.14-2.09 (1H, m), 1.95-1.89 (1H, m), 1.79-1.75 (1H, m), 1.70-1.59 (1H, m), 1.56-1.51 (3H, m), 1.33-1.17 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 154.4 (C), 128.6 (CH), 125.5 (CH), 120.5 (CH), 118.7 (C), 117.1 (CH), 76.2 (CH_2), 73.9 (CH), 37.8 (CH), 34.9 (CH), 31.2 (CH_2), 24.8 (CH_2), 20.2 (CH_2), 19.6 (CH_2); LRMS m/z 248.35 (M + H^+), calcd for $C_{14}H_{17}NO_3$ 247.1208; HRMS m/z 270.1106 (M + Na), calcd for $C_{14}H_{17}NO_3Na$

270.1106; Anal. calcd for $C_{14}H_{17}NO_3$ (247.1208): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.12; H, 6.85; N, 5.71%.

(4a*S*,9*R*,9a*S*)-7-fluoro-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141eb): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 98 °C; 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 = 7.35 min (minor), t_R = 8.81 min (major); **$[\alpha]_D^{25}$ = –67.1°** (*c* = 0.40 g/100 mL, $CHCl_3$, **99% *ee***); IR (KBr): ν_{max} 2946, 2859, 1555 (NO_2), 1497, 1439, 1383, 1271, 1238, 1206, 1150, 1067, 959, 887, 781, 700 and 637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91-6.86 (1H, m), 6.81 (1H, dd, *J* = 8.0, 4.8 Hz), 6.67 (1H, ddd, *J* = 9.2, 2.8, 0.8 Hz), 4.86 (1H, dd, *J* = 12.8, 6.0 Hz), 4.57 (1H, dd, *J* = 12.8, 9.6 Hz), 4.28 (1H, br s), 3.94 (1H, td, *J* = 9.6, 5.2 Hz), 2.13-2.09 (1H, m), 1.95-1.90 (1H, m), 1.81-1.78 (1H, m), 1.69-1.52 (4H, m), 1.34-1.16 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 156.7 (C, d, *J* = 237.0 Hz), 150.4 (C, d, *J* = 2.0 Hz), 119.5 (C, d, *J* = 7.0 Hz), 118.0 (CH, d, *J* = 8.0 Hz), 115.3 (CH, d, *J* = 23.0 Hz), 112.0 (CH, d, *J* = 23.0 Hz), 75.9 (CH_2), 73.9 (CH), 37.8 (CH), 34.6 (CH), 31.1 (CH_2), 24.7 (CH_2), 20.2 (CH_2), 19.5 (CH_2); LRMS m/z 266.20 ($M + H^+$), calcd for $C_{14}H_{16}FNO_3$ 265.1114; HRMS m/z 288.1012 (M + Na), calcd for $C_{14}H_{16}FNO_3Na$ 288.1012; Anal. calcd for $C_{14}H_{16}FNO_3$ (265.1114): C, 63.39; H, 6.08; N, 5.28. Found: C, 63.45; H, 6.15; N, 5.21%.

(4a*S*,9*R*,9a*S*)-7-chloro-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141bb): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 76 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 97:3, flow rate 0.8 mL/min, λ = 254 nm), t_R = 9.67 min (minor), t_R = 10.70 min (major) [for major isomer], t_R = 12.67 min (minor), t_R = 17.60 min (major) [for minor isomer]; **$[\alpha]_D^{25}$ = –106.2°** (*c* = 0.40 g/100 mL, $CHCl_3$, **98% *ee***); IR (Neat): ν_{max} 2936, 1726, 1555 (NO_2), 1483, 1412, 1377, 1240, 1188, 1129, 970, 874, 820 and 747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (1H, ddd, *J* = 8.5, 2.5, 1.0 Hz), 6.91-6.90 (1H, m), 6.79 (1H, d, *J* = 8.5 Hz), 4.89 (1H, dd, *J* = 13.0, 5.5

Hz), 4.55 (1H, dd, *J* = 13.0, 10.0 Hz), 4.28 (1H, br s), 3.90 (1H, td, *J* = 10.0, 5.5 Hz), 2.12-2.08 (1H, m), 1.93-1.89 (1H, m), 1.79-1.76 (1H, m), 1.65-1.52 (4H, m), 1.32-1.25 (1H, m), 1.17-1.12 (1H m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 153.0 (C), 128.5 (CH), 125.5 (CH), 125.1 (C), 120.2 (C), 118.4 (CH), 75.7 (CH_2), 74.1 (CH), 37.6 (CH), 34.5 (CH), 31.0 (CH_2), 24.7 (CH_2), 20.1 (CH_2), 19.5 (CH_2); LRMS m/z 281.25 (M^+), calcd for $C_{14}H_{16}ClNO_3$ 281.0819; HRMS m/z 304.0717 (M + Na), calcd for $C_{14}H_{16}ClNO_3Na$ 304.0716; Anal. calcd for $C_{14}H_{16}ClNO_3$ (281.0819): C, 59.68; H, 5.72; N, 4.97. Found: C, 59.76; H, 5.65; N, 5.07%.

(4a*S*,9*R*,9a*S*)-7-bromo-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141fb): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 104 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 18.74 min (major), t_R = 21.71 min (minor); **$[\alpha]_D^{25}$ = −111.9°** (*c* = 0.35 g/100 mL, $CHCl_3$, **99% *ee***); IR (KBr): ν_{max} 2931, 2909, 2860, 1545 (NO_2), 1485, 1435, 1238, 964 and 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (1H, ddd, *J* = 8.8, 2.4, 0.8 Hz), 7.04 (1H, q, *J* = 1.2 Hz), 6.74 (1H, d, *J* = 8.8 Hz), 4.89 (1H, dd, *J* = 12.8, 5.6 Hz), 4.56 (1H, dd, *J* = 12.4, 10.0 Hz), 4.27 (1H, br s), 3.91 (1H, td, *J* = 9.6, 5.6 Hz), 2.12-2.06 (1H, m), 1.94-1.88 (1H, m), 1.80-1.75 (1H, m), 1.69-1.53 (4H, m), 1.30 (1H, tq, *J* = 12.8, 4.0 Hz), 1.14 (1H, dq, *J* = 12.8, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 153.5 (C), 131.5 (CH), 128.3 (CH), 120.8 (C), 118.9 (CH), 112.3 (C), 75.7 (CH_2), 74.1 (CH), 37.6 (CH), 34.5 (CH), 31.0 (CH_2), 24.6 (CH_2), 20.1 (CH_2), 19.5 (CH_2); LRMS m/z 325.15 (M^+), calcd for $C_{14}H_{16}BrNO_3$ 325.0314; HRMS m/z 348.0212 (M + Na), calcd for $C_{14}H_{16}BrNO_3Na$ 348.0211; Anal. calcd for $C_{14}H_{16}BrNO_3$ (325.0314): C, 51.55; H, 4.94; N, 4.29. Found: C, 51.65; H, 4.91; N, 4.35%.

(4a*S*,9*R*,9a*S*)-5-methoxy-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141hb): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid Mp 120 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.8 mL/min, λ

= 254 nm), t_R = 10.40 min (minor), t_R = 11.30 min (major); **$[\alpha]_D^{25}$ = –69.6°** (*c* = 0.40 g/100 mL, $CHCl_3$, **90% *ee***); IR (KBr): ν_{max} 3048, 2924, 2855, 1875, 1794, 1709, 1585, 1553 (NO_2), 1478, 1437, 1383, 1333, 1225, 1064, 1025, 968, 893, 849, 793, 768, 723, 694 and 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.82-6.81 (2H, m), 6.57-6.55 (1H, m), 4.93 (1H, dd, *J* = 12.8, 6.0 Hz), 4.57 (1H, dd, *J* = 12.4, 9.6 Hz), 4.33 (1H, br s), 3.97 (1H, td, *J* = 10.0, 5.6 Hz), 3.86 (3H, s, OC*H*$_3$), 2.29-2.26 (1H, m), 1.95-1.91 (1H, m), 1.80-1.70 (2H, m), 1.63-1.53 (3H, m) 1.37-1.21 (2H m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 148.6 (C), 144.0 (C), 120.0 (CH), 119.3 (C), 117.3 (CH), 110.8 (CH), 76.3 (CH_2), 74.2 (CH), 56.2 (CH_3, O*C*H$_3$), 37.8 (CH), 34.8 (CH), 31.1 (CH_2), 24.8 (CH_2), 20.2 (CH_2), 19.7 (CH_2); LRMS m/z 278.15 (M + H^+), calcd for $C_{15}H_{19}NO_4$ 277.1314; HRMS m/z 300.1212 (M + Na), calcd for $C_{15}H_{19}NO_4Na$ 300.1212; Anal. calcd for $C_{15}H_{19}NO_4$ (277.1314): C, 64.97; H, 6.91; N, 5.05. Found: C, 64.88; H, 6.85; N, 5.12%.

(4a*S*,9*R*,9a*S*)-7-methoxy-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141ib): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 84 °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 = 6.11 min (major), t_R = 7.58 min (minor); **$[\alpha]_D^{25}$ = –87.2°** (*c* = 0.40 g/100 mL, $CHCl_3$, **99% *ee***); IR (KBr): ν_{max} 2936, 2861, 1869, 1717, 1549 (NO_2), 1495, 1441, 1424, 1381, 1358, 1283, 1240, 1213, 1157, 1117, 1069, 1040, 974, 914, 882, 816, 772, 700, 639 and 598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (1H, d, *J* = 8.8 Hz), 6.75 (1H, dd, *J* = 8.8, 2.8 Hz), 6.49 (1H, d, *J* = 2.0 Hz), 4.90 (1H, dd, *J* = 12.8, 6.0 Hz), 4.57 (1H, dd, *J* = 12.4, 9.6 Hz), 4.24 (1H, br s), 3.93 (1H, td, *J* = 9.6, 5.6 Hz), 3.74 (3H, s, OC*H*$_3$), 2.11-2.05 (1H, m), 1.92-1.89 (1H, m), 1.79-1.76 (1H, m), 1.70-1.51 (4H, m), 1.35-1.19 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 153.4 (C), 148.3 (C), 119.2 (C), 117.6 (CH), 113.9 (CH), 111.3 (CH), 76.2 (CH_2), 73.7 (CH), 55.8 (CH_3, O*C*H$_3$), 37.9 (CH), 35.0 (CH), 31.2 (CH_2), 24.9 (CH_2), 20.2 (CH_2) 19.6 (CH_2); LRMS m/z 278.15 (M + H^+), calcd for $C_{15}H_{19}NO_4$ 277.1314; HRMS m/z 300.1211 (M + Na), calcd for $C_{15}H_{19}NO_4Na$ 300.1212; Anal. calcd for $C_{15}H_{19}NO_4$ (277.1314): C, 64.97; H, 6.91; N, 5.05. Found: C, 65.15; H, 6.85; N, 4.96%.

(4a*S*,9*R*,9a*S*)-6-methoxy-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141jb): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 106 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.32 min (major), t_R = 11.62 min (minor); **$[\alpha]_D^{25}$ = –62.1°** (*c* = 0.40 g/100 mL, $CHCl_3$, **99% *ee***); IR (KBr): ν_{max} 2932, 2855, 1616, 1551 (NO_2), 1501, 1441, 1288, 1162, 1129, 1025, 838, 800 and 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.82 (1H, dd, *J* = 8.4, 0.8 Hz), 6.47-6.42 (2H, m), 4.90 (1H, dd, *J* = 12.8, 5.6 Hz), 4.53 (1H, dd, *J* = 12.8, 10.0 Hz), 4.28 (1H, br s), 3.88 (1H, td, *J* = 10.0, 5.2 Hz), 3.78 (3H, s, OC*H*$_3$), 2.12-2.09 (1H, m), 1.92-1.87 (1H, m), 1.79-1.76 (1H, m), 1.69-1.50 (4H, m), 1.35-1.17 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 159.9 (C), 155.4 (C), 126.2 (CH), 110.8 (C), 107.4 (CH), 101.7 (CH), 76.3 (CH_2), 74.1 (CH), 55.3 (CH_3, O*C*H$_3$), 37.3 (CH), 35.0 (CH), 31.2 (CH_2), 24.8 (CH_2), 20.0 (CH_2), 19.6 (CH_2); LRMS m/z 278.10 (M + H^+), calcd for $C_{15}H_{19}NO_4$ 277.1314; HRMS m/z 278.1314 (M + H^+), calcd for $C_{15}H_{19}NO_4H$ 278.1392; Anal. calcd for $C_{15}H_{19}NO_4$ (277.1314): C, 64.97; H, 6.91; N, 5.05. Found: C, 64.85; H, 6.98; N, 4.95%.

(4a*S*,9*R*,9a*S*)-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-5-ol (141kb): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 96 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R =16.92 min (minor), t_R = 20.52 min (major); **$[\alpha]_D^{25}$ = −□83.9°** (*c* = 0.40 g/100 mL, $CHCl_3$, **97% *ee***); IR (KBr): ν_{max} 3485 (O*H*), 2932, 2849, 1589, 1540 (NO_2), 1469, 1370, 1206, 1112, 970, 773, 729, 696 and 636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.85 (1H, d, *J* = 7.6 Hz), 6.78 (1H, t, *J* = 8.0 Hz), 6.49 (1H, d, *J* = 8.0 Hz), 5.64 (1H, s, O*H*), 4.94 (1H, dd, *J* = 12.8, 5.6 Hz), 4.57 (1H, t, *J* = 10.8 Hz), 4.36 (1H, br s), 3.96 (1H, td, *J* = 10.0, 5.2 Hz), 2.17 (1H, br d, *J* = 8.0 Hz), 1.98-1.95 (1H, m), 1.79 (1H, br d, *J* = 12.4 Hz), 1.65-1.56 (4H, m), 1.40-1.18 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 144.9 (C), 141.1 (C), 120.8 (CH), 118.8 (C), 116.4 (CH), 113.6 (CH), 75.9 (CH_2), 74.8 (CH), 37.7 (CH), 35.0 (CH), 31.0 (CH_2), 24.7 (CH_2), 20.1 (CH_2), 19.6

(CH_2); LRMS m/z 263.95 ($M + H^+$), calcd for $C_{14}H_{17}NO_4$ 263.1158; HRMS m/z 286.1056 (M + Na), calcd for $C_{14}H_{17}NO_4Na$ 286.1056; Anal. calcd for $C_{14}H_{17}NO_4$ (263.1158): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.76; H, 6.55; N, 5.26%.

(4a*S*,9*R*,9a*S*)-7-methyl-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141lb): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 118 °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 = 6.58 min (major), t_R = 7.11 min (minor); **$[\alpha]_D^{25}$ = –95.1°** (*c* = 0.40 g/100 mL, $CHCl_3$, **97% *ee***); IR (KBr): ν_{max} 3036, 2938, 2861, 1906, 1744, 1615, 1553 (NO_2), 1530, 1501, 1460, 1439, 1377, 1358, 1310, 1283, 1237, 1190, 1152, 1132, 1073, 1040, 972, 885, 824, 796, 777 and 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (1H, br d, *J* = 6.8 Hz), 6.77 (1H, d, *J* = 6.8 Hz), 6.74 (1H, br s), 4.95 (1H, dd, *J* = 13.0, 6.0 Hz), 4.57 (1H, dd, *J* = 12.5, 10.0 Hz), 4.27 (1H, br s), 3.93 (1H, td, *J* = 10.0, 5.5 Hz), 2.26 (3H, s, C*H*$_3$), 2.13-2.09 (1H, m), 1.93-1.89 (1H, m), 1.80-1.77 (1H, m), 1.70-1.64 (1H, m), 1.60-1.53 (3H, m), 1.36-1.17 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 152.1 (C), 129.6 (C), 129.2 (CH), 125.9 (CH), 118.3 (C), 116.9 (CH), 76.2 (CH_2), 73.7 (CH), 37.7 (CH), 35.0 (CH), 31.2 (CH_2), 24.9 (CH_2), 20.7 (CH_3), 20.2 (CH_2), 19.6 (CH_2); LRMS m/z 262.25 ($M + H^+$), calcd for $C_{15}H_{19}NO_3$ 261.1365; HRMS m/z 284.1263 (M + Na), calcd for $C_{15}H_{19}NO_3Na$ 284.1263; Anal. calcd for $C_{15}H_{19}NO_3$ (261.1365): C, 68.94; H, 7.33; N, 5.36; Found: C, 68.85; H, 7.38; N, 5.27%.

(4a*S*,9*R*,9a*S*)-2-methyl-9-(nitromethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (141ce): Prepared following the procedure **3b** 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 OB-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 13.52 min (minor), t_R = 16.97 min (major) [for major isomer], t_R = 20.71 min (major), t_R = 24.30 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = −98.9°** (*c* = 0.40 g/100 mL, $CHCl_3$, **96% *ee***); IR (KBr): ν_{max} 2975, 2871, 2822, 1704, 1589, 1534 (NO_2), 1490, 1381, 1233, 1090 and 761 cm^{-1}; ^1H NMR ($CDCl_3$, Major isomer)

δ 7.19-7.14 (1H, m), 6.95-6.92 (1H, m), 6.88-6.84 (2H, m), 4.95 (1H, dd, *J* = 12.6, 6.0 Hz), 4.56 (1H, dd, *J* = 12.8, 10.0 Hz), 4.27 (1H, br s), 4.00-3.95 (1H, m), 2.15-2.09 (1H, m), 1.99-1.90 (2H, m), 1.62-1.29 (5H, m), 0.89 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$); ^{1}H NMR ($CDCl_3$, Minor isomer) δ 7.23-7.14 (1H, m), 6.99-6.90 (1H, m), 6.90-6.84 (2H, m), 4.93 (1H, dd, *J* = 12.6, 6.0 Hz), 4.53 (1H, dd, *J* = 12.4, 10.0 Hz), 4.27 (1H, br s), 4.00-3.95 (1H, m), 2.20-2.00 (1H, m), 2.00-1.80 (2H, m), 1.68-1.20 (5H, m), 1.03 (3H, d, *J* = 7.2 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, Major isomer) δ 154.3 (C), 128.6 (CH), 125.5 (CH), 120.5 (CH), 118.6 (C), 117.1 (CH), 76.17 (CH_2), 73.3 (CH), 37.5 (CH), 34.9 (CH), 31.0 (CH_2), 29.0 (CH), 28.6 (CH_2), 28.2 (CH_2), 22.4 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, Minor isomer) δ 154.5 (C), 128.5 (CH), 125.6 (CH), 120.4 (CH), 118.6 (C), 117.0 (CH), 76.21 (CH_2), 73.9 (CH), 37.3 (CH), 31.4 (CH), 26.1 (CH), 25.7 (CH_2), 25.5 (CH_2), 24.7 (CH_2), 17.4 (CH_3); LRMS m/z 262.25 (M + H^+), calcd for $C_{15}H_{19}NO_3$ 261.1365; HRMS m/z 284.1263 (M + Na), calcd for $C_{15}H_{19}NO_3Na$ 284.1263; Anal. calcd for $C_{15}H_{19}NO_3$ (261.1365): C, 68.94; H, 7.33; N, 5.36. Found: C, 68.85; H, 7.26; N, 5.41%.

(2*S*,4*R*)-2-methyl-4-(nitromethyl)chroman (141ca): Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 84 °C; 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 = 7.83 min (minor), t_R = 10.31 min (major); **$[\alpha]_D^{25}$ = −97.4°** (*c* = 0.47 g/100 mL, $CHCl_3$, **94% *ee***); IR (Neat): ν_{max} 2976, 2922, 1609, 1558 (NO_2), 1487, 1450, 1383, 1336, 1296, 1281, 1236, 1201, 1153, 1113, 1065, 1011, 958, 895, 866, 829, 756, 706, 650, 584 and 482 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.16 (1H, br t, *J* = 7.6 Hz), 7.06 (1H, br d, *J* = 7.6 Hz), 6.91-6.85 (2H, m), 4.91 (1H, dd, *J* = 12.0, 4.8 Hz), 4.35 (1H, dd, *J* = 12.4, 10.0 Hz), 4.15-4.09 (1H, m), 3.84-3.79 (1H, m), 2.12 (1H, ddd, *J* = 13.2, 6.4, 1.6 Hz), 1.64 (1H, br q, *J* = 11.2 Hz), 1.41 (1H, d, *J* = 6.0, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 155.4 (C), 128.7 (CH), 126.3 (CH), 120.8 (CH), 119.7 (C), 117.7 (CH), 80.1 (CH_2), 71.3 (CH), 34.4 (CH_2), 33.6 (CH), 21.3 (CH_3); LRMS m/z 208.00 (M + H^+), calcd for $C_{11}H_{13}NO_3$ 207.0895; HRMS m/z 230.0792 (M + Na), calcd for $C_{11}H_{13}NO_3Na$ 230.0793; Anal. calcd for $C_{11}H_{13}NO_3$ (207.0895): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.84; H, 6.26; N, 6.81%.

(4a*S*,10*R*,10a*R*)-10-(nitromethyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (141cf) and **(*S*)-10-(nitromethyl)-1,3,4,10-tetrahydropyrano[4,3-*b*]chromene (143cf):** Prepared following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 48.0 min (minor), t_R = 55.5 min (major) [for **143cf** product], t_R = 61.7 min (minor), t_R = 67.4 min (major) [for **141cf** product]; **$[\alpha]_D^{25}$ = −11.6°** (*c* = 0.50 g/100 mL, $CHCl_3$, **>99% *ee*** for **141cf** and **98% *ee*** for **143cf**); IR (Neat): ν_{max} 1710, 1549 (NO_2), 1535, 1487, 1454, 1429, 1378, 1290, 1230, 1137, 1092, 1046, 989, 962, 922, 898, 867, 843, 807 and 754 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of **141cf** and **143cf,** data for **141cf**) δ 7.22-7.17 (2H, m), 6.93-6.86 (2H, m), 4.90 (1H, dd, *J* = 14.0, 8.0 Hz), 4.44 (1H, dd, *J* = 12.0, 10.0 Hz), 4.10 (1H, br s), 4.06-3.96 (1H, m), 3.84-3.76 (3H, m), 3.42 (1H, t, *J* = 12.0 Hz), 2.34-2.28 (1H, m), 2.04-1.93 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of **141cf** and **143cf**, data for **141cf**) δ 153.8 (C), 128.8 (CH), 125.3 (CH), 120.9 (CH), 118.0 (C), 117.2 (CH), 75.8 (CH_2), 70.6 (CH), 62.4 (CH_2), 62.2 (CH_2), 35.4 (CH), 34.1 (CH), 31.5 (CH_2); ^1H NMR ($CDCl_3$, 1:1 mixture of **141cf** and **143cf,** data for **143cf**) δ 7.26 (1H, dt, *J* = 7.2, 2.0 Hz), 7.12-7.05 (2H, m), 7.00 (1H, dd, *J* = 8.4, 0.8 Hz), 4.49 (1H, dd, *J* = 11.8, 5.6 Hz), 4.41 (1H, dd, *J* = 11.8, 6.8 Hz), 4.26 (1H, td, *J* = 14.4, 2.4 Hz), 4.12-4.04 (2H, m), 4.03-3.99 (1H, m), 3.85-3.79 (1H, m), 2.49-2.41 (1H, m), 2.36-2.31 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of **141cf** and **143cf**, data for **143cf**) δ 151.4 (C), 145.8 (C), 128.9 (CH), 128.0 (CH), 124.0 (CH), 119.1 (C), 116.8 (CH), 103.0 (C), 80.3 (CH_2), 65.7 (CH_2), 64.6 (CH_2), 35.8 (CH), 26.9 (CH_2); HRMS for **141cf**: m/z 250.1046 ($M + H^+$), calcd for $C_{13}H_{15}NO_4H^+$ 250.1079.

3c. ***General procedure for the base-promoted protection of chiral Michael product:*** To a solution of chiral Michael product (+)-**140cb** (132 mg, 0.5 mmol) in dry DCM (1.6 mL) were added successively i-Pr_2NEt (0.44 mL, 2.5 mmol) and MeI (93 μL, 1.5 mmol) at 0 °C. The resulting mixture was stirred at same temperature for 30 min and then brought to 25 °C and stirred for 3.5 h. The reaction mixture was worked up with aqueous NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4),

filtered and concentrated. Pure product (-)-**142b** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(*S*)-2-((*R*)-1-(2-methoxyphenyl)-2-nitroethyl)cyclohexanone (142bb): Prepared following the procedure **3c** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 98 °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 = 11.66 min (minor), t_R = 15.49 min (major); **$[\alpha]_D^{25}$ = –36.7°** (*c* = 3.0 g/100 mL, $CHCl_3$, **97% *ee*** and **97% *de***); IR (KBr): ν_{max} 3381, 3078, 3005, 2949, 2864, 1703 (*C*=O), 1601, 1545 (NO_2), 1493, 1433, 1379, 1300, 1248, 1205, 1182, 1124, 1024, 937, 889, 837, 810, 758, 671, 638, 582, 521 and 490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (1H, t, *J* = 8.0 Hz), 7.07 (1H, d, *J* = 7.5 Hz), 6.87-6.85 (2H, m), 4.82 (2H, t, *J* = 4.0 Hz), 3.98-3.93 (1H, m), 3.81 (3H, s, Ar-OC*H*$_3$), 2.97 (1H, dt, *J* = 11.5, 5.0 Hz), 2.45-2.34 (2H, m), 2.06-2.03 (1H, m), 1.75-1.73 (1H, m), 1.67-1.52 (3H, m), 1.22-1.14 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.3 (C, *C*=O), 157.4 (C), 130.7 (CH), 128.7 (CH), 125.2 (C), 120.6 (CH), 110.8 (CH), 77.3 (CH_2), 55.1 (CH_3, Ar-O*C*H$_3$), 50.3 (CH), 42.5 (CH_2), 41.1 (CH), 33.0 (CH_2), 28.3 (CH_2), 24.9 (CH_2); LRMS m/z 278.15 (M + H^+), calcd for $C_{15}H_{19}NO_4$ 277.1314; HRMS m/z 300.1212 (M + Na), calcd for $C_{15}H_{19}NO_4Na$ 300.1212; Anal. calcd for $C_{15}H_{19}NO_4$ (277.1314): C, 64.97; H, 6.91; N, 5.05. Found: C, 65.07; H, 6.86; N, 5.12%.

(*S*)-2-((*R*)-1-(3-hydroxyphenyl)-2-nitroethyl)cyclohexanone (142cb): Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as 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 = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.88 min (minor), t_R = 32.83 min (major); **$[\alpha]_D^{25}$ = –8.2°** (*c* = 0.40 g/100 mL, $CHCl_3$, **39% *ee*** and **88% *de***); IR (KBr): ν_{max} 3272 (O*H*), 2951, 2867, 1684 (*C*=O), 1591, 1551 (NO_2), 1483, 1379, 1312, 1256, 1129, 1013, 907, 791 and 702 cm^{-1}; ^1H NMR ($CDCl_3$ + 1

drop MeOH-D_4) δ 7.15 (1H, t, *J* = 7.5 Hz), 6.74-6.72 (1H, m), 6.67-6.64 (2H, m), 4.91 (1H, dd, *J* = 12.5, 4.5 Hz), 4.60 (1H, dd, *J* = 12.5, 10.0 Hz), 3.69 (1H, dt, *J* = 10.0, 4.5 Hz), 2.66 (1H, dt, *J* = 11.5, 5.0 Hz), 2.55 (1H, br s, O*H*), 2.48-2.39 (2H, m), 2.10-2.05 (1H, m), 1.80-1.74 (2H, m), 1.70-1.55 (2H, m), 1.28-1.21 (1H, m); ^{13}C NMR ($CDCl_3$ + 1 drop MeOH-D_4, DEPT-135) δ 212.7 (C, *C*=O), 156.9 (C), 139.2 (C), 129.9 (CH), 119.4 (CH), 115.1 (CH), 114.7 (CH), 78.8 (CH_2), 52.4 (CH), 43.7 (CH), 42.6 (CH_2), 33.1 (CH_2), 28.5 (CH_2), 24.9 (CH_2); LRMS m/z 264.15 (M + H^+), calcd for $C_{14}H_{17}NO_4$ 263.1158; HRMS m/z 286.1056 (M + Na), calcd for $C_{14}H_{17}NO_4Na$ 286.1056; Anal. calcd for $C_{14}H_{17}NO_4$ (263.1158): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.79; H, 6.45; N, 5.26%.

(*S*)-2-((*R*)-1-(4-hydroxyphenyl)-2-nitroethyl)cyclohexanone (142db): Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 146 °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 = 13.89 min (minor), t_R = 23.73 min (major); **$[\alpha]_D^{25}$ = –18.3°** (*c* = 0.30 g/100 mL, $CHCl_3$, **65% *ee*** and **90% *de***); IR (Neat): ν_{max} 3439 (O*H*), 3022, 2941, 2864, 1879, 1707 (*C*=O), 1612, 1551 (NO_2), 1514, 1445, 1381, 1228, 1130, 833 and 739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.00 (2H, d, *J* = 8.5 Hz), 6.92 (1H, br s, O*H*), 6.77 (2H, d, *J* = 8.5 Hz), 4.90 (1H, dd, *J* = 12.5, 4.5 Hz), 4.56 (1H, dd, *J* = 12.2, 10.0 Hz), 3.70 (1H, dt, *J* = 10.0, 4.5 Hz), 2.65 (1H, dt, *J* = 11.5, 5.0 Hz), 2.46-2.34 (2H, m), 2.05-2.03 (1H, m), 1.77-1.72 (2H, m), 1.67-1.53 (2H, m), 1.20-1.17 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.2 (C, *C*=O), 155.3 (C), 129.1 (2 x CH), 128.8 (C), 115.6 (2 x CH), 78.9 (CH_2), 52.4 (CH), 43.0 (CH), 42.4 (CH_2), 32.9 (CH_2), 28.3 (CH_2), 24.6 (CH_2); LRMS m/z 263.95 (M + H^+), calcd for $C_{14}H_{17}NO_4$ 263.1158; HRMS m/z 286.1056 (M + Na), calcd for $C_{14}H_{17}NO_4Na$ 286.1055; Anal. calcd for $C_{14}H_{17}NO_4$ (263.1158): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.75; H, 6.56; N, 5.18%.

3d. ***General procedure for asymmetric Michael reaction of cyclohexanone 32 with 2-(2-nitrovinyl)phenols 82 through supramolecular-catalysis followed by dehydration:*** In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of 9-amino-9-deoxyepiquinine thiourea **34i** (15 mg, 0.025 mmol) and D-proline *ent*-**34a** (3 mg, 0.025 mmol) in

DCM (1.0 mL, 0.5 M), was added 2-(2-nitrovinyl)phenol **82** (0.5 mmol). After stirring for 1 min, was added cyclohexanone **32** (2.5 mmol) and the reaction mixture was stirred at 25 °C for 5 to 24 h. The crude reaction mixture was then worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude mixture was filtered through a pad of silica eluting with EtOAc and hexanes. To the resulting dry lactol **140** in DCM at 0 °C, was added boron trifluoride diethyl etherate (0.12 mL, 1.0 mmol). The mixture was stirred at the same temperature for 20 min and then brought to room temperature and stirred for another 10 min. The crude reaction mixture was worked up with saturated $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **143** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

(*R*)-9-(nitromethyl)-2,3,4,9-tetrahydro-1*H*-xanthene (143cb): Prepared following the procedure **3d** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 86 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 92:8, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.00 min (minor), t_R = 6.68 min (major); **$[\alpha]_D^{25}$ = −13.5°** (*c* = 0.23 g/100 mL, $CHCl_3$, **98% *ee***); IR (KBr): ν_{max} 2926, 2844, 1759, 1698, 1589, 1539 (NO_2), 1490, 1381, 1134 and 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (1H, dt, *J* = 7.2, 2.0 Hz), 7.07 (1H, dd, *J* = 7.6, 2.0 Hz), 7.02 (1H, dt, *J* = 7.2, 1.2 Hz), 6.96 (1H, dd, *J* = 8.8, 0.8 Hz), 4.50 (1H, dd, *J* = 11.6, 5.2 Hz), 4.38 (1H, dd, *J* = 11.4, 7.2 Hz), 4.00 (1H, t, *J* = 5.6 Hz), 2.31-2.15 (3H, m), 2.02-1.98 (1H, m), 1.85-1.73 (2H, m), 1.71-1.54 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.7 (C), 148.4 (C), 128.5 (CH), 127.8 (CH), 123.4 (CH), 120.0 (C), 116.4 (CH), 103.6 (C), 80.0 (CH_2), 39.4 (CH), 26.7 (2 x CH_2), 22.7 (CH_2), 22.4 (CH_2); LRMS m/z 246.15 (M + H^+), calcd for $C_{14}H_{15}NO_3$ 245.1052; HRMS m/z 268.0950 (M + Na), calcd for $C_{14}H_{15}NO_3Na$ 268.0950; Anal. calcd for $C_{14}H_{15}NO_3$ (245.1052): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.45; H, 6.09; N, 5.82%.

(*R*)-5,7-dichloro-9-(nitromethyl)-2,3,4,9-tetrahydro-1*H*-xanthene (143gb): Prepared following the procedure **3d** and purified by column

chromatography using EtOAc/hexane and isolated as solid. Mp 124 °C; 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 = 6.47 min (minor), t_R = 7.28 min (major); **$[\alpha]_D^{25}$ = –6.7°** (*c* = 0.28 g/100 mL, $CHCl_3$, **97% *ee***); IR (KBr): ν_{max} 3081, 2926, 2855, 1742, 1699, 1532 (NO_2), 1462, 1375, 1252, 1190, 1119, 1019, 876, 768, 627 and 563 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (1H, d, *J* = 2.5 Hz), 6.99 (1H, d, *J* = 2.5 Hz), 4.49 (1H, dd, *J* = 15.0, 6.0 Hz), 4.40 (1H, dd, *J* = 15.0, 9.5 Hz), 3.97 (1H, br t, *J* = 7.5 Hz), 2.39-2.21 (4H, m), 2.03-1.99 (1H, m), 1.81-1.58 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 148.8 (C), 146.6 (C), 129.0 (CH), 127.9 (C), 126.1 (CH), 122.8 (C), 122.6 (C), 104.0 (C), 79.3 (CH_2), 39.3 (CH), 26.5 (2 x CH_2), 22.5 (CH_2), 22.3 (CH_2); LRMS m/z 313.20 (M^+), calcd for $C_{14}H_{13}Cl_2NO_3$ 313.0272; HRMS m/z 336.0170 (M + Na), calcd for $C_{14}H_{13}Cl_2NO_3Na$ 336.0170; Anal. calcd for $C_{14}H_{13}Cl_2NO_3$ (313.0272); C, 53.52; H, 4.17; N, 4.46; Found: C, 53.45; H, 4.23; N, 4.51%.

(*S*)-10-(nitromethyl)-1,3,4,10-tetrahydropyrano[4,3-*b*]chromene (143cf): Prepared following the procedure **3d** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 98 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 53.53 min (minor), t_R = 55.42 min (major); **$[\alpha]_D^{25}$ = +7.4°** (*c* = 0.35 g/100 mL, $CHCl_3$, **98% *ee***); IR (KBr): ν_{max} 2981, 2865, 2822, 1704, 1583, 1529 (NO_2), 1485, 1381, 1233, 1085, 926, 866, 761, 625 and 493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (1H, dt, *J* = 7.2, 2.0 Hz), 7.12-7.05 (2H, m), 7.00 (1H, dd, *J* = 8.4, 0.8 Hz), 4.49 (1H, dd, *J* = 11.8, 5.6 Hz), 4.41 (1H, dd, *J* = 11.8, 6.8 Hz), 4.26 (1H, td, *J* = 14.4, 2.4 Hz), 4.12-4.04 (2H, m), 4.03-3.99 (1H, m), 3.85-3.79 (1H, m), 2.49-2.41 (1H, m), 2.36-2.31 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.4 (C), 145.8 (C), 128.9 (CH), 128.0 (CH), 124.0 (CH), 119.1 (C), 116.8 (CH), 103.0 (C), 80.3 (CH_2), 65.7 (CH_2), 64.6 (CH_2), 35.8 (CH), 26.9 (CH_2); LRMS m/z 248.35 ($M + H^+$), calcd for $C_{13}H_{13}NO_4$ 247.0845; HRMS m/z 270.0743 (M + Na), calcd for $C_{13}H_{13}NO_4Na$ 270.0742; Anal. calcd for $C_{13}H_{13}NO_4$ (247.0845): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.09; H, 5.26; N, 5.75%.

(*S*)-8-bromo-10-(nitromethyl)-1,3,4,10-tetrahydropyrano[4,3-*b*]chromene (143ff): Prepared following the procedure **3d** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 132 °C; 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 = 17.27 min (minor), t_R = 21.02 min (major); **$[\alpha]_D^{25}$ = −31.2°** (*c* = 0.17 g/100 mL, $CHCl_3$, **96% *ee***); IR (KBr): ν_{max} 2922, 2868, 1711, 1541 (NO_2), 1479, 1433, 1416, 1379, 1271, 1238, 1188, 1142, 1090, 1065, 1011, 926, 887, 870, 818, 787, 744, 629, 551 and 486 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (1H, dd, *J* = 8.8, 2.4 Hz), 7.26-7.25 (1H, m), 6.89 (1H, d, *J* = 8.8 Hz), 4.46 (2H, dABq, *J* = 12.0, 6.0 Hz), 4.25 (1H, td, *J* = 14.8, 2.0 Hz), 4.10-4.06 (1H, m), 4.04-3.99 (2H, m), 3.84-3.78 (1H, m), 2.48-2.40 (1H, m), 2.33-2.29 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 150.6 (C), 145.8 (C), 131.9 (CH), 130.6 (CH), 121.1 (C), 118.6 (CH), 116.0 (C), 102.7 (C), 79.9 (CH_2), 65.5 (CH_2), 64.5 (CH_2), 35.5 (CH), 26.8 (CH_2); LRMS m/z 326.25 (M + H^+), calcd for $C_{13}H_{12}BrNO_4$ 324.9950; HRMS m/z 347.9848 (M + Na), calcd for $C_{13}H_{12}BrNO_4Na$ 347.9847; Anal. calcd for $C_{13}H_{12}BrNO_4$ (324.9950): C, 47.87; H, 3.71; N, 4.29. Found: C, 47.76; H, 3.75; N, 4.36%.

(*S*)-10-(nitromethyl)-1,3,4,10-tetrahydrothiopyrano[4,3-*b*]chromene (143cg): Prepared following the procedure **3d** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 82 °C; 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 = 10.76 min (minor), t_R = 14.35 min (major); **$[\alpha]_D^{25}$ = –□37.1°** (*c* = 0.5 g/100 mL, $CHCl_3$, **96% *ee***); IR (KBr): ν_{max} 2924, 1695, 1589, 1537 (NO_2), 1487, 1460, 1427, 1375, 1290, 1261, 1234, 1173, 1146, 1120, 1093, 1032, 939, 914, 885, 841, 800, 754, 671, 625, 609, 497 and 413 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25-7.22 (1H, m), 7.09-7.03 (2H, m), 6.98 (1H, d, *J* = 8.0 Hz), 4.48 (1H, dd, *J* = 11.7, 5.0 Hz), 4.38 (1H, dd, *J* = 11.7, 7.5 Hz), 4.05 (1H, t, *J* = 6.5 Hz), 3.44 (1H, d, *J* = 16.0 Hz), 3.00 (1H, d, *J* = 16.0 Hz), 2.89-2.84 (1H, m), 2.82-2.78 (1H, m), 2.61-2.53 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.3 (C), 149.6 (C), 128.7 (CH), 127.6 (CH), 123.8 (CH), 119.9 (C), 116.3 (CH), 103.0 (C), 79.7 (CH_2), 39.8 (CH), 28.6 (CH_2), 27.4 (CH_2), 25.2 (CH_2); LRMS m/z 263.95 (M + H^+), calcd for $C_{13}H_{13}NO_3S$ 263.0616; HRMS

m/z 286.0514 (M + Na), calcd for $C_{13}H_{13}NO_3SNa$ 286.0514; Anal. calcd for $C_{13}H_{13}NO_3S$ (263.0616): C, 59.30; H, 4.98; N, 5.32. Found: C, 59.22; H, 4.91; N, 5.38%.

3e. ***General procedure for the reduction of Michael products 140::*** In an oven dried round bottom flask, to Michael adduct **140** (1.0 mmol) in MeOH (10 mL, 0.1 M) at 0 °C was added sodium borohydride (8 mg, 0.35 mmol) and stirred at 25 °C for 24 h. The crude reaction mixture was then worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure diols **144** were purified by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2-((1*R*)-1-((2*R*)-2-hydroxycyclohexyl)-2-nitroethyl)phenol (144cb): Prepared following the procedure **3e** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +37.1°** (*c* = 0.50 g/100 mL, $CHCl_3$, **99% *ee***); IR (Neat): ν_{max} 3289 (O*H*), 2931, 2858, 1705, 1595, 1547 (NO_2), 1502, 1453, 1378, 1263, 1233, 1194, 1095, 1044, 967, 887, 843, 817 and 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (1H, br s, O*H*), 7.07 (1H, dt, *J* = 8.6, 1.2 Hz), 7.02 (1H, dd, *J* = 7.6, 1.2 Hz), 6.82 (1H, t, *J* = 7.2 Hz), 6.77 (1H, d, *J* = 8.0 Hz), 4.95 (1H, dd, *J* = 11.8, 10.0 Hz), 4.86 (1H, dd, *J* = 12.4, 5.6 Hz), 4.09 (1H, br s), 3.86-3.80 (1H, m), 2.83 (1H, br s, O*H*), 1.95-1.83 (2H, m), 1.63-1.59 (2H, m), 1.53-1.42 (3H, m), 1.28-1.10 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 154.1 (C), 129.6 (C), 128.3 (CH), 124.8 (CH), 120.4 (CH), 116.2 (CH), 77.5 (CH_2), 67.6 (CH), 42.6 (CH), 41.7 (CH), 33.2 (CH_2), 25.5 (CH_2), 24.6 (CH_2), 19.4 (CH_2); LRMS m/z 266.25 (M + H^+), calcd for $C_{14}H_{19}NO_4$ 265.1314; HRMS m/z 288.1212 (M + Na), calcd for $C_{14}H_{19}NO_4Na$ 288.1212; Anal. calcd for $C_{14}H_{19}NO_4$ (265.1314): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.25; H, 7.29; N, 5.19%.

4-bromo-2-((1*R*)-1-((2*R*)-2-hydroxycyclohexyl)-2-nitroethyl)phenol (144fb): Prepared following the procedure **3e** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +7.9°** (*c* = 0.67 g/100 mL, $CHCl_3$, **99% *ee***); IR (Neat): ν_{max} 3360 (O*H*), 3098, 2928, 2858, 1697, 1609, 1547 (NO_2), 1504, 1456, 1383, 1236, 1138, 1105, 1066, 972, 756 and 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (1H, dd, *J* = 8.6, 2.4 Hz), 7.14

(1H, d, *J* = 2.4 Hz), 6.67 (1H, d, *J* = 8.8 Hz), 4.95-4.80 (2H, m), 4.07-4.05 (1H, m), 3.79 (1H, m), 2.27 (1H, br s, O*H*), 1.88-1.84 (2H, m), 1.67-1.63 (1H, m), 1.53-1.46 (3H, m), 1.24-1.16 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 153.5 (C), 132.1 (CH), 131.2 (CH), 127.5 (C), 118.2 (CH), 112.6 (C), 77.3 (CH_2), 67.6 (CH), 42.7 (CH), 41.5 (CH), 33.4 (CH_2), 25.5 (CH_2), 24.7 (CH_2), 19.4 (CH_2); LRMS m/z 344.20 (M + H^+), calcd for $C_{14}H_{18}BrNO_4$ 343.0419; HRMS m/z 366.0317 (M + Na), calcd for $C_{14}H_{18}BrNO_4Na$ 366.0317; Anal. calcd for $C_{14}H_{18}BrNO_4$ (343.0419): C, 48.85; H, 5.27; N, 4.07. Found: C, 48.91; H, 5.21; N, 4.12%.

3f. ***General procedure for the spiroetherification of diol 144:*** In an oven dried round bottom flask, to diol **144** (0.5 mmol) in DCM (5 mL) was added boron trifluoride diethyl etherate (0.12 mL, 1.0 mmol) and stirred at rt for 48 h. The crude reaction mixture was then worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure spiro compounds **145** were purified by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(*R*)-3-(nitromethyl)-3*H*-spiro[benzofuran-2,1'-cyclohexane] (145cb): Prepared following the **3f** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 64 °C; 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 = 6.41 min (minor), t_R = 7.22 min (major); **$[\alpha]_D^{25}$ = +71.7°** (*c* = 0.50 g/100 mL, $CHCl_3$, **98% *ee***); IR (Neat): ν_{max} 2933, 2859, 1595, 1550 (NO_2), 1478, 1460, 1452, 1376, 1328, 1269, 1239, 1189, 1134, 1068, 1018, 930, 908, 848, 817, 749 and 706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18 (1H, br t, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 7.2 Hz), 6.84 (1H, dt, *J* = 7.2, 0.8 Hz), 6.80 (1H, br d, *J* = 9.2 Hz), 4.64 (1H, dd, *J* = 13.4, 7.2 Hz), 4.41 (1H, dd, *J* = 13.2, 7.6 Hz), 3.82 (1H, t, *J* = 7.6 Hz), 1.95-1.40 (9H, m), 1.40-1.29 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 158.1 (C), 129.6 (CH), 126.2 (C), 124.9 (CH), 120.6 (CH), 110.5 (CH), 88.7 (C), 75.6 (CH_2), 48.5 (CH), 36.7 (CH_2), 31.0 (CH_2), 25.1 (CH_2), 22.4 (CH_2), 22.3 (CH_2); LRMS m/z 248.35 (M + H^+), calcd for $C_{14}H_{17}NO_3$ 247.1208; HRMS m/z 270.1106 (M + Na), calcd for $C_{14}H_{17}NO_3Na$ 270.1106; Anal. calcd for $C_{14}H_{17}NO_3$ (247.1208): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.26; H, 6.88; N, 5.71%.

(*R*)-5-bromo-3-(nitromethyl)-3*H*-spiro[benzofuran-2,1'-cyclohexane] (145fb): Prepared following the **3f** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 92 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 5.83 min (minor), t_R = 6.46 min (major); **$[\alpha]_D^{25}$ = +86.8°** (*c* = 0.26 g/100 mL, $CHCl_3$, **97% *ee***); IR (Neat): ν_{max} 2933, 2858, 1551 (NO_2), 1469, 1375, 1303, 1239, 1179, 1135, 1112, 1059, 934, 908, 811 and 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (1H, dd, *J* = 8.4, 2.0 Hz), 7.19-7.18 (1H, m), 6.69 (1H, d, *J* = 8.4 Hz), 4.64 (1H, dd, *J* = 13.6, 7.2 Hz), 4.40 (1H, dd, *J* = 13.6, 7.6 Hz), 3.82 (1H, t, *J* = 7.6 Hz), 1.91-1.84 (2H, m), 1.78-1.59 (4H, m), 1.55-1.41 (2H, m), 1.33-1.25 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 157.2 (C), 132.5 (CH), 128.6 (C), 127.9 (CH), 112.2 (C), 112.1 (CH), 89.7 (C), 75.2 (CH_2), 48.3 (CH), 36.6 (CH_2), 30.9 (CH_2), 25.0 (CH_2), 22.3 (CH_2), 22.1 (CH_2); LRMS m/z 325.30 (M^+), calcd for $C_{14}H_{16}BrNO_3$ 325.0314; HRMS m/z 348.0212 (M + Na), calcd for $C_{14}H_{16}BrNO_3Na$ 348.0211; Anal. calcd for $C_{14}H_{16}BrNO_3$ (325.0314): C, 51.55; H, 4.94; N, 4.29. Found: C, 51.45; H, 5.03; N, 4.21%.

3g. ***General procedure for the preparation of azide 146 from reductive etherification products 141:***

Step-1 (Nitro group reduction): The product **141cb** (245 mg, 1.0 mmol) and 10% Pd/C (106 mg, 10 mol%) in EtOAc (5 mL, 0.1 M) were stirred under H_2 atmosphere for 24 h. Then the reaction mixture was passed through a pad of celite and filtered with ethyl acetate. The compound was then evaporated to dryness and used for diazo transfer step without further purification.

Step-2 (Trifluoromethanesulfonyl azide was prepared fresh prior to reaction): Sodium azide (390 mg, 6 mmol) was dissolved in a minimum volume of water (1.0 mL) and cooled to 0 ºC. An equal volume of dichloromethane was added and trifluoromethanesulfonic anhydride (0.5 mL, 3 mmol) was slowly added to the vigorously stirring solution. The reaction was continued to stir at 0º C for 2h. Saturated sodium bicarbonate was carefully added while stirring was continued and the reaction contents were transferred to a separating funnel. The aqueous phase was washed

twice with dichloromethane, and the total volume of dichloromethane added, both in the reaction and for the extractions becomes approximately 2.5 times the amount of water used in the reaction. The solution was used for next reaction without further purification.

Step-3 (Diazo transfer reaction): The reduced product of **141cb** and zinc(II) chloride (1.4 mg, 1.0 mol%) were dissolved in 2.5 mL of water. Then added triethylamine (0.42 mL, 3 mmol) was added, followed by drop wise addition of methanol (7.5 mL). The dichloromethane solution of trifluoromethanesulfonyl azide was added at once with stirring. Reaction was stirred for 3 h at RT. The crude reaction mixture was worked up with saturated $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure azide **146cb** was separated by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(4a*S*,9*R*,9a*S*)-9-(azidomethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (146cb): Prepared following the procedure **3g** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –103.1°** (*c* = 0.50 g/100 mL, $CHCl_3$, **99% *ee***); IR (Neat): ν_{max} 2931, 2859, 2361, 2093 (N=N), 1580, 1487, 1452, 1363, 1154, 1126, 1040, 968, 893, 855 and 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14-7.11 (2H, m), 6.86-6.81 (2H, m), 4.27 (1H, br s), 3.95 (1H, dd, *J* = 12.0, 6.0 Hz), 3.41 (1H, dd, *J* = 12.0, 10.0 Hz), 3.26 (1H, td, *J* = 10.0, 5.5 Hz), 2.12-2.09 (1H, m), 2.04-2.01 (1H, m), 1.78-1.75 (1H, m), 1.69-1.54 (2H, m), 1.47-1.45 (1H, m), 1.38-1.28 (2H, m), 1.14-1.11 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 154.4 (C), 127.9 (CH), 126.1 (CH), 120.9 (C), 120.2 (CH), 116.6 (CH), 74.3 (CH), 51.7 (CH_2, CH_2N_3), 38.1 (CH), 35.1 (CH), 31.4 (CH_2), 25.0 (CH_2), 20.1 (CH_2), 19.8 (CH_2); LRMS m/z 243.65 ($M + H^+$), calcd for $C_{14}H_{17}N_3O$ 243.1372; HRMS m/z 266.1212 (M + Na), calcd for $C_{14}H_{17}N_3ONa$ 266.1269; Anal. calcd for $C_{14}H_{17}N_3O$ (243.1372): C, 69.11; H, 7.04; N, 17.27. Found: C, 69.05; H, 7.12; N, 17.32%.

3h. ***General procedure for the preparation of chiral triazole 147 from azide 146:*** To the pure azide **146cb** (121 mg, 0.5 mmol) in *t*BuOH (1.0 mL, 0.5 M), were added phenyl acetylene (0.05 mL, 0.5 mmol), $CuSO_4.5H_2O$ (25 mg, 20 mol%), Na-(+)-ascorbate (40 mg, 40 mol-%) and H_2O (1.0 mL) and stirred at 25 °C for 2 h. The crude reaction mixture was then worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The

combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure chiral triazole product **147cb** was purified by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(1-(((4a*S*,9*R*,9a*S*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-9-yl)methyl)-4-phenyl-1*H*-1,2,3-triazole (147cb): Prepared following the procedure **3h** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 148 °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 = 7.04 min (major), t_R = 7.85 min (minor); **$[\alpha]_D^{25}$ = –126.1°** (*c* = 0.50 g/100 mL, $CHCl_3$, **>99% *ee***); IR (Neat): ν_{max} 2933, 2859, 1608, 1579, 1488, 1452, 1365, 1289, 1252, 1232, 1189, 1157, 1127, 1076, 1044, 968, 909, 860, 802 and 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88-7.86 (2H, m), 7.85 (1H, s), 7.46-7.43 (2H, m), 7.35 (1H, tt, *J* = 7.5, 1.0 Hz), 7.20-7.14 (2H, m), 6.90-6.86 (2H, m), 5.00 (1H, dd, *J* = 14.0, 5.5 Hz), 4.53 (1H, dd, *J* = 13.5, 11.0 Hz), 4.23 (1H, br s), 3.78 (1H, td, *J* = 11.0, 5.0 Hz), 2.07-2.03 (1H, m), 1.75-1.60 (3H, m), 1.56-1.54 (1H, m), 1.51-1.43 (2H, m), 1.27-1.18 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 154.4 (C), 147.8 (C), 130.4 (C), 128.8 (2 x CH), 128.3 (CH), 128.2 (CH), 125.7 (2 x CH), 125.5 (CH), 120.3 (CH), 119.9 (C), 119.8 (CH), 116.8 (CH), 74.3 (CH), 49.9 (CH_2), 39.4 (CH), 34.1 (CH), 31.2 (CH_2), 24.7 (CH_2), 20.0 (CH_2), 19.7 (CH_2); LRMS m/z 346.15 (M + H^+), calcd for $C_{22}H_{23}N_3O$ 345.1841; HRMS m/z 368.1739 (M + Na), calcd for $C_{22}H_{23}N_3ONa$ 368.1739; Anal. calcd for $C_{22}H_{23}N_3O$ (345.1841): C, 76.49; H, 6.71; N, 12.16. Found: C, 76.32; H, 6.65; N, 12.25%.

4. General experimental procedures for mimicking human steroid 5β-reductase (AKR1D1) through organocatalysis.

4a. ***General procedure for organocatalytic Biomimetic hydrogenation*:** (*S*)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine **34j** (12 mg, 0.075 mmol) and D-Camphor sulphonic acid (17 mg, 0.075 mmol) in dry CH_3CN (3.0 mL, 0.1 M) were stirred at rt for 5 min, then added chiral enone **148** or **150** (0.3 mmol) and stirring was continued at the same temperature for another 5 min. To this, added Hantzsch ester **50a** (152 mg, 0.6 mmol) and refluxed for the time indicated in Tables

13 and 14. The crude reaction mixture was purified with or without aqueous work-up. Pure hydrogenated products **149** or **151** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4b. ***General procedure for Palladium/Charcoal catalyzed hydrogenation*****:** The mixture of 5% Pd/C (5 mol%), Hantzsch ester **50a** (152 mg, 0.9 mmol) and the enone **148** or **150** (0.2 mmol) in EtOH (2 mL, 0.1 M) was heated to 80 °C for the time indicated in Table 11 and 13. Crude mixture was then passed through a pad of celite. Pure hydrogenated products **149** or **151** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4c. ***General procedure for acyclic amine salt catalyzed hydrogenation*****:** The mixture of Acyclic amine salt **34af** (13 mg, 0.04 mmol), Hantzsch ester **50a** (101 mg, 0.4 mmol) and the enone **148** or **150** (0.2 mmol) in CH_3CN (0.1 M) was heated to 80 °C for 6-24 h. Then the crude reaction mixture was worked up with NH_4Cl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure hydrogenated products **149** or **151** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(5*R*,8*S*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyldecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,11,17(2*H*,4*H*,9*H*)-trione (149a): Prepared following the procedure **4c** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 176 °C; **$[\alpha]_D^{25}$ = +148.1°** (*c* = 0.5 g/100 mL, CH_3OH, **74% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2924, 2857, 1744 (*C*=O), 1705 (*C*=O), 1653 (*C*=O), 1462, 1377, 1163, 1014 and 723 cm^{-1}; ^1H NMR ($CDCl_3$, major *cis*-isomer) δ 2.77-2.73 (1H, m), 2.58-2.49 (2H, m), 2.46-2.23 (4H, m), 2.18-1.91 (6H, m), 1.81-1.63 (3H, m), 1.54-1.27 (4H, m), 1.25 (3H, s, C*H*$_3$), 0.85 (3H, s, C*H*$_3$); ^1H NMR ($CDCl_3$, minor *trans*-isomer) δ 2.77-2.73 (1H, m), 2.58-2.49 (2H, m), 2.46-2.23 (4H, m), 2.18-1.91 (6H, m), 1.81-1.63 (3H, m), 1.54-1.27 (4H, m), 1.23 (3H, s, C*H*$_3$), 0.85 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, major *cis*-isomer) δ 217.2 (C, *C*=O), 212.2 (C, *C*=O), 208.6 (C, *C*=O), 52.6 (CH), 50.5 (C), 50.4 (CH_2), 50.3 (CH), 44.7 (CH), 42.2 (CH_2), 37.4 (CH_2), 36.2 (CH_2), 36.2 (CH), 36.0 (CH_2), 34.5 (C), 25.8 (CH_2), 25.2 (CH_2), 22.5 (CH_3), 21.6 (CH_2), 14.7 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, minor *trans*-isomer) δ 217.2 (C, *C*=O), 211.1

(C, *C*=O), 208.6 (C, *C*=O), 64.3 (CH), 50.5 (C), 50.3 (CH), 50.3 (CH_2), 46.8 (CH), 44.2 (CH_2), 37.9 (CH_2), 36.9 (CH_2), 36.2 (CH), 36.0 (CH_2), 35.3 (C), 31.0 (CH_2), 27.9 (CH_2), 22.5 (CH_3), 21.6 (CH_2), 11.1 (CH_3); LRMS m/z 302.95 (M + H^+), calcd for $C_{19}H_{26}O_3$ 302.1882; HRMS m/z 325.1783 (M + Na), calcd for $C_{19}H_{26}O_3Na$ 325.1780; Anal. calcd for $C_{19}H_{26}O_3$ (302.1882): C, 75.46; H, 8.67. Found: C, 75.32; H, 8.61%.

(5*R*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (149b): Prepared following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 196 °C; **$[\alpha]_D^{25}$ = +61.5°** (*c* = 1.0 g/100 mL, CH_3OH, **72% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3449 (O*H*), 2924, 1722 (*C*=O), 1691 (*C*=O), 1462, 1373, 1257, 1090, 1034, 845, 794 and 744 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD (4 drops), major *cis*-isomer) δ 4.64 (1H, d, *J* = 16.0 Hz), 4.40-4.35 (1H, m), 4.27 (1H, d, *J* = 16.0 Hz), 2.70 (2H, t, *J* = 16.0 Hz), 2.34-2.23 (3H, m), 2.11-1.68 (9H, m), 1.62-1.38 (6H, m), 1.26 (3H, s, C*H*$_3$), 0.87 (3H, s, C*H*$_3$); ^1H NMR ($CDCl_3$ + CD_3OD (4 drops), minor *trans*-isomer) δ 4.63 (1H, d, *J* = 16.0 Hz), 4.40-4.35 (1H, m), 4.26 (1H, d, *J* = 16.0 Hz), 2.70 (2H, t, *J* = 16.0 Hz), 2.34-2.23 (3H, m), 2.11-1.68 (9H, m), 1.62-1.38 (6H, m), 1.23 (3H, s, C*H*$_3$), 0.87 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$ + CD_3OD (4 drops), DEPT-135, major *cis*-isomer) δ 214.4 (C, *C*=O), 212.2 (C, *C*=O), 88.7 (C), 67.6 (CH), 66.7 (CH_2), 52.2 (CH), 47.3 (C), 46.5 (CH), 43.3 (CH), 42.0 (CH_2), 39.4 (CH_2), 37.4 (CH_2), 36.5 (CH_2), 34.8 (C), 33.6 (CH_2), 31.1 (CH), 26.2 (CH_2), 25.5 (CH_3), 25.5 (CH_2), 23.5 (CH_2), 17.1 (CH_3); ^{13}C NMR ($CDCl_3$ + CD_3OD (4 drops), DEPT-135, minor *trans*-isomer) δ 213.5 (C, *C*=O), 212.2 (C, *C*=O), 88.7 (C), 67.7 (CH), 66.7 (CH_2), 56.8 (CH), 52.0 (CH), 47.6 (CH), 47.3 (C), 43.8 (CH_2), 39.2 (CH_2), 37.9 (CH_2), 37.7 (CH_2), 35.6 (C), 33.6 (CH_2), 32.0 (CH_2), 31.1 (CH), 28.1 (CH_2), 25.5 (CH_3), 25.5 (CH_2), 13.7 (CH_3); LRMS m/z 365.30 (M + H^+), calcd for $C_{21}H_{32}O_5$ 364.2250; HRMS m/z 387.2149 (M + Na), calcd for $C_{21}H_{32}O_5Na$ 387.2148; Anal. calcd for $C_{21}H_{32}O_5$ (364.2250): C, 69.20; H, 8.85. Found: C, 69.32; H, 8.76%.

(5*R*,8*S*,10*S*,13*S*,14*S*,17*R*)-17-hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-4,5,6,7,8,10,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (149c): Prepared following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 228 °C; **$[\alpha]_D^{25}$ = +59.2°** (*c* = 0.5 g/100 mL, CH_3OH, **87% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3449 (O*H*), 2924, 2857, 1693 (*C*=O), 1643, 1454, 1377, 1263, 1103 and 1039 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (4 drops)] δ 5.58 (1H, d, *J* = 4.8 Hz), 4.69 (1H, d, *J* = 19.6 Hz), 4.26 (1H, d, *J* = 19.6 Hz), 2.78-2.66 (2H, m), 2.56 (1H, dt, *J* = 14.4, 5.6 Hz), 2.45 (1H, t, *J* = 14.0 Hz), 2.35-2.30 (1H, m), 2.19-1.91 (7H, m), 1.76-1.73 (1H, m), 1.66-1.54 (3H, m), 1.40-1.23 (3H, m), 1.15 (3H, s, C*H*$_3$), 0.56 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$ + CD_3OD (4 drops), DEPT-135) δ 214.8 (C, *C*=O), 212.2 (C, *C*=O), 138.5 (C), 119.1 (CH), 88.5 (C), 66.4 (CH_2), 47.8 (CH), 46.3 (C), 44.4 (CH), 43.2 (CH_2), 38.5 (C), 37.7 (CH_2), 37.0 (CH_2), 36.2 (CH), 33.5 (CH_2), 31.8 (CH_2), 28.3 (CH_3), 26.2 (CH_2), 25.9 (CH_2), 24.0 (CH_2), 14.3 (CH_3); LRMS m/z 347.30 ($M + H^+$), calcd for $C_{21}H_{30}O_4$ 346.2144; HRMS m/z 369.2047 (M + Na), calcd for $C_{21}H_{30}O_4Na$ 369.2042; Anal. calcd for $C_{21}H_{30}O_4$ (346.2144): C, 72.80; H, 8.73. Found: C, 72.68; H, 8.81%.

2-((5*R*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-10,13-dimethyl-3-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-oxoethyl acetate (149d): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 214 °C; **$[\alpha]_D^{25}$ = +74.7°** (*c* = 0.67 g/100 mL, CH_3OH, **66% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3424 (O*H*), 2920, 2579, 1742 (*C*=O), 1722 (*C*=O), 1695 (*C*=O), 1454, 1375, 1227, 1153, 1039, 895, 846 and 785 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (4 drops)] δ 5.06 (1H, d, *J* = 16.0 Hz), 4.84 (1H, d, *J* = 16.0 Hz), 4.45-4.40 (1H, m), 2.78-2.60 (3H, m), 2.33-2.20 (3H, m), 2.18 (3H, s, C*H*$_3$), 2.15-1.91 (5H, m), 1.89-1.68 (5H, m), 1.60 (1H, dd, *J* = 12.0, 4.0 Hz), 1.54-1.30 (3H, m), 1.26 (3H, s, C*H*$_3$), 0.93 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$ + CD_3OD (4 drops), DEPT-135) δ 213.0 (C, *C*=O), 205.0 (C, *C*=O), 170.8 (C, O-*C*=O), 89.8 (C), 68.1 (CH), 67.9 (CH_2), 52.5 (CH), 47.7 (C), 46.5 (CH), 43.6 (CH), 42.3 (CH_2), 39.7 (CH_2), 37.7 (CH_2), 36.7 (CH_2), 35.0 (C), 34.6 (CH_2), 31.3 (CH), 26.5 (CH_2), 25.9 (CH_3), 25.7 (CH_2), 23.6 (CH_2),

20.5 (CH_3), 17.1 (CH_3); LRMS m/z 407.25 (M + H^+), calcd for $C_{23}H_{34}O_6$ 406.2355; HRMS m/z 429.2253 (M + Na), calcd for $C_{23}H_{34}O_6Na$ 429.2253; Anal. calcd for $C_{23}H_{34}O_6$ (406.2355): C, 67.96; H, 8.43. Found: C, 67.85; H, 8.51%.

2-((5*R*,8*S*,10*S*,13*S*,14*S*,17*R*)-17-hydroxy-10,13-dimethyl-3-oxo-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-oxoethyl acetate (*cis*-149e): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 216 °C; **$[\alpha]_D^{25}$ = +49.8°** (*c* = 0.7 g/100 mL, CH_3OH, **71% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3428 (O*H*), 2924, 2856, 1738 (*C*=O), 1715 (*C*=O), 1635, 1462, 1377, 1269, 1230, 1144, 1047, 777 and 731 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD (4 drops), major *cis*-isomer) δ 5.60 (1H, s, olefinic-H), 5.16 (1H, d, *J* = 15.0 Hz), 4.83 (1H, d, *J* = 19.0 Hz), 2.81 (1H, d, *J* = 15.0 Hz), 2.71 (1H, t, *J* = 10.0 Hz), 2.58 (1H, dt, *J* = 10.0, 2.0 Hz), 2.45 (1H, t, *J* = 15.0 Hz), 2.32 (1H, br d, *J* = 15.0 Hz), 2.18 (3H, s, C*H*$_3$), 2.05-1.73 (9H, m), 1.60-1.56 (2H, m), 1.35-1.24 (3H, m), 1.15 (3H, s, C*H*$_3$), 0.58 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$ + CD_3OD (4 drops), DEPT-135, major *cis*-isomer) δ 214.3 (C, *C*=O), 205.7 (C, *C*=O), 170.9 (C, O-*C*=O), 138.8 (C), 119.3 (CH), 89.3 (C), 67.9 (CH_2), 48.3 (CH), 46.6 (C), 44.5 (CH), 43.5 (CH_2), 38.7 (C), 38.0 (CH_2), 37.3 (CH_2), 36.5 (CH), 34.0 (CH_2), 31.9 (CH_2), 28.7 (CH_3), 26.5 (CH_2), 26.2 (CH_2), 24.2 (CH_2), 20.3 (CH_3), 14.3 (CH_3); LRMS m/z 389.35 (M + H^+), calcd for $C_{23}H_{32}O_5$ 388.2250; HRMS m/z 411.2148 (M + Na), calcd for $C_{23}H_{32}O_5Na$ 411.2148; Anal. calcd for $C_{23}H_{32}O_5$ (388.2250): C, 71.11; H, 8.30. Found: C, 71.23; H, 8.26%.

4d. ***General procedure for Pd/C catalyzed hydrogenation under hydrogen atmosphere:*** The mixture of 5% Pd/C (5 mol%) and the enone **148e** (0.2 mmol) in EtOH (0.1 M) was stirred at rt under hydrogen atmosphere for 2 h. Crude mixture was then passed through a pad of celite. The hydrogenated product *trans*-**149e** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2-((5*S*,8*S*,10*S*,13*S*,14*S*,17*R*)-17-hydroxy-10,13-dimethyl-3-oxo-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-oxoethyl acetate (*trans*-149e): Prepared following the procedure **4d** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 240 °C; **$[\alpha]_D^{25}$ = +60.6°** (*c* = 0.57 g/100 mL, CH_3OH, **41% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3428 (O*H*), 2924, 2856, 1738 (*C*=O), 1715 (*C*=O), 1635, 1462, 1377, 1269, 1230, 1144, 1047, 777 and 731 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD (4 drops), major *trans*-isomer) δ 5.35 (1H, d, *J* = 4.8 Hz), 5.02 (1H, d, *J* = 14.0 Hz), 4.77 (1H, d, *J* = 14.8 Hz), 2.73-2.61 (2H, m), 2.59-2.55 (1H, m), 2.53-2.37 (1H, m), 2.35-2.30 (1H, m), 2.25-2.20 (2H, m), 2.17-2.16 (1H, m), 2.10 (3H, s, *CH*$_3$), 2.05-1.73 (7H, m), 1.60-1.56 (2H, m), 1.35-1.24 (2H, m), 1.08 (3H, s, C*H*$_3$), 0.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$ + CD_3OD (4 drops), DEPT-135, major *trans*-isomer) δ 211.5 (C, *C*=O), 204.8 (C, *C*=O), 170.5 (C, O-*C*=O), 145.4 (C), 116.8 (CH), 89.9 (C), 67.7 (CH_2), 48.7 (CH), 47.0 (C), 45.0 (CH), 44.6 (CH_2), 38.1 (CH_2), 37.8 (C), 37.02 (CH), 37.0 (CH_2), 34.8 (CH_2), 32.8 (CH_2), 31.8 (CH_2), 28.7 (CH_2), 24.4 (CH_2), 20.5 (CH_3), 17.3 (CH_3), 14.2 (CH_3); LRMS m/z 389.35 (M + H^+), calcd for $C_{23}H_{32}O_5$ 388.2250; HRMS m/z 411.2148 (M + Na), calcd for $C_{23}H_{32}O_5Na$ 411.2148; Anal. calcd for $C_{23}H_{32}O_5$ (388.2250): C, 71.11; H, 8.30. Found: C, 71.23; H, 8.26%.

(5*R*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17(2*H*)-one (149f): Prepared following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 128 °C; **$[\alpha]_D^{25}$ = +96.2°** (*c* = 0.78 g/100 mL, $CHCl_3$, **99% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2924, 1745 (*C*=O), 1464, 1377, 1257, 1201, 1122, 1057, 1009, 831 and 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (1H, dd, *J* = 19.6, 8.0 Hz), 2.06 (1H, td, *J* = 18.0, 8.8 Hz), 1.93-1.88 (1H, m), 1.83-1.74 (2H, m), 1.66-1.63 (3H, m), 1.56-1.33 (4H, m), 1.30-1.15 (8H, m), 1.07-0.85 (3H, m), 0.83 (3H, s, C*H*$_3$), 0.78 (3H, s, C*H*$_3$), 0.73-0.69 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 221.4 (C, *C*=O), 54.8 (CH), 51.5 (CH), 47.7 (C), 46.9 (CH), 38.5 (CH_2), 36.3 (C), 35.8 (CH_2), 35.0 (CH), 31.5 (CH_2), 30.9 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 26.6 (CH_2), 22.0 (CH_2), 21.7 (CH_2), 20.0 (CH_2),

13.7 (CH_3), 12.1 (CH_3); LRMS m/z 275.00 ($M + H^+$), calcd for $C_{19}H_{30}O$ 274.2297; HRMS m/z 297.2195 (M + Na), calcd for $C_{19}H_{30}ONa$ 297.2195; Anal. calcd for $C_{19}H_{30}O$ (274.2297): C, 83.15; H, 11.02. Found: C, 83.25; H, 11.09%.

(3*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-acetyl-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (149g): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 190 °C**; $[\alpha]_D^{25}$ = +33.7°** (*c* = 0.68 g/100 mL, $CHCl_3$, **>99% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2924, 2855, 1728, 1708, 1454, 1373, 1219, 1105, 1032 and 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.36 (1H, d, *J* = 5.0 Hz), 4.64-4.57 (1H, m), 2.53 (1H, t, *J* = 9.0 Hz), 2.36-2.31 (2H, m), 2.21-2.15 (1H, m), 2.13 (3H, s, COC*H*$_3$), 2.04 (3H, s, COC*H*$_3$), 2.06-1.98 (2H, m), 1.91-1.85 (2H, m), 1.72-1.55 (5H, m), 1.50-1.45 (3H, m), 1.29-1.13 (3H, m), 1.05-0.95 (1H, m), 1.02 (3H, s, C*H*$_3$), 0.63 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.2 (C, *C*=O), 170.3 (C, O-*C*=O), 139.6 (C), 122.2 (CH), 73.7 (CH), 63.5 (CH), 56.7 (CH), 49.8 (CH), 43.8 (C), 38.7 (CH_2), 38.0 (CH_2), 36.9 (CH_2), 36.5 (C), 31.7 (CH), 31.6 (CH_2), 31.3 (CH_3), 27.6 (CH_2), 24.3 (CH_2), 22.7 (CH_2), 21.2 (CH_3), 20.9 (CH_2), 19.2 (CH_3), 13.1 (CH_3); LRMS m/z 358.55 (M^+), calcd for $C_{23}H_{34}O_3$ 358.2508; HRMS m/z 381.2400 (M + Na), calcd for $C_{23}H_{34}O_3Na$ 381.2406.

(8*R*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17(2*H*,6*H*)-dione (148i): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 176 °C; **$[\alpha]_D^{25}$ = +195.2°** (*c* = 0.25 g/100 mL, $CHCl_3$, **99% *ee***); IR (Nujol): ν_{max} 2924, 2858, 1724 (*C*=O), 1641, 1597, 1454, 1373, 1219, 1111, 1032 and 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.76 (1H, s, olefinic-*H*), 2.52-2.35 (5H, m), 2.14-1.97 (4H, m), 1.89-1.86 (1H, m), 1.77-1.70 (3H, m), 1.69-1.42 (2H, m), 1.33-1.27 (2H, m), 1.22 (3H, s, C*H*$_3$), 1.19-0.98 (2H,

m), 0.93 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 220.3 (C, *C*=O), 199.3 (C, *C*=O), 170.3 (C), 124.1 (CH), 53.8 (CH), 50.8 (CH), 47.5 (C), 38.6 (C), 35.7 (2 x CH_2), 35.1 (CH), 33.9 (CH_2), 32.5 (CH_2), 31.3 (CH_2), 30.7 (CH_2), 21.7 (CH_2) , 20.3 (CH_2), 17.4 (CH_3), 13.7 (CH_3); LRMS m/z 287.15 (M + H^+), calcd for $C_{19}H_{26}O_2$ 286.1933; HRMS m/z 287.2011 (M + H^+), calcd for $C_{19}H_{26}O_2H$ 287.2011; Anal. calcd for $C_{19}H_{26}O_2$ (286.1933): C, 79.68; H, 9.15. Found: C, 79.56; H, 9.21%.

(5*R*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyldodecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17(2*H*,4*H*)-dione (149h or **149i):** Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 134 °C; **$[\alpha]_D^{25}$ = +119.1°** (*c* = 0.75 g/100 mL, $CHCl_3$, **86% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2920, 2855, 1738 (*C*=O), 1707 (*C*=O), 1462, 1375 and 1014 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.67 (1H, t, *J* = 14.4 Hz), 2.50-2.43 (1H, m), 2.34-2.27 (1H, m), 2.23-2.14 (1H, m), 2.12-2.00 (2H, m), 1.98-1.84 (4H, m), 1.71-1.50 (4H, m), 1.49-1.18 (8H, m), 1.05 (3H, s, C*H*$_3$), 0.89 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 220.8 (C, *C*=O), 212.7 (C, *C*=O), 51.4 (CH), 47.8 (C), 44.1 (CH), 42.2 (CH_2), 41.0 (CH), 37.1 (CH_2), 36.9 (CH_2), 35.8 (CH_2), 35.1 (CH), 35.0 (C), 31.6 (CH_2), 26.3 (CH_2), 24.7 (CH_2), 22.6 (CH_3), 21.7 (CH_2), 20.4 (CH_2), 13.8 (CH_3); LRMS m/z 289.20 (M + H^+), calcd for $C_{19}H_{28}O_2$ 288.2089; HRMS m/z 311.1987 (M + Na), calcd for $C_{19}H_{28}O_2Na$ 311.1987; Anal. calcd for $C_{19}H_{28}O_2$ (288.2089): C, 79.12; H, 9.78. Found: C, 79.26; H, 9.65%.

(5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-6,10,13-trimethyldodecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17(2*H*,4*H*)-dione (149j or **149l):** Prepared following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 144 °C; **$[\alpha]_D^{25}$ = +69.2°** (*c* = 0.33 g/100 mL, $CHCl_3$, **59% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2924, 2860, 1730, 1713, 1454, 1377, 1246, 1055 and 1014 cm^{-1}; ^{1}H NMR ($CDCl_3$, major isomer) δ 2.61 (1H, t, *J* = 14.5 Hz), 2.46 (1H, dd, *J* = 19.5, 9.0 Hz), 2.37 (1H, dd, *J* = 14.5, 6.0 Hz), 2.32-2.30 (1H, m), 2.13-1.94 (5H, m), 1.86-1.69 (6H, m), 1.57-1.22 (6H, m),1.22 (3H, s, C*H*$_3$), 0.96 (3H, d, *J* = 7.5 Hz, CHC*H*$_3$), 0.92 (3H, s, C*H*$_3$); ^{1}H NMR ($CDCl_3$, minor isomer) δ

2.61 (1H, t, *J* = 14.5 Hz), 2.46 (1H, dd, *J* = 19.5, 9.0 Hz), 2.39-2.35 (1H, m), 2.32-2.30 (1H, m), 2.13-1.94 (5H, m), 1.86-1.69 (6H, m), 1.57-1.22 (6H, m),1.05 (3H, s, C*H*$_3$), 0.89 (3H, s, C*H*$_3$), 0.82 (3H, d, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 220.7 (C, *C*=O), 212.1 (C, *C*=O), 54.5 (CH), 51.0 (CH), 48.4 (CH), 47.7 (C), 43.3 (CH_2), 41.1 (CH_2), 38.1 (CH_2), 37.7 (CH_2), 36.3 (C), 35.8 (CH_2), 32.9 (CH), 31.5 (CH_2), 30.2 (CH), 21.9 (CH_2), 20.6 (CH_2), 15.7 (CH_3), 14.9 (CH_3), 13.8 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 220.5 (C, *C*=O), 212.7 (C, *C*=O), 51.3 (CH), 49.6 (CH), 47.8 (C), 43.3 (CH_2), 40.7 (CH), 37.01 (CH_2), 36.98 (C), 36.7 (CH_2), 35.8 (CH_2), 35.2 (CH), 32.7 (CH_2), 31.7 (CH_2), 29.4 (CH), 22.7 (CH_3), 21.7 (CH_2), 20.5 (CH_2), 19.2 (CH_3), 13.8 (CH_3); LRMS m/z 302.95 ($M + H^+$), calcd for $C_{20}H_{30}O_2$ 302.2246; HRMS m/z 303.2324 ($M + H^+$), calcd for $C_{20}H_{30}O_2H$ 303.2324; Anal. calcd for $C_{20}H_{30}O_2$ (302.2246): C, 79.42; H, 10.00; Found: C, 79.32; H, 10.11%.

(8*R*,9*S*,10*R*,13*S*,14*S*)-6,10,13-trimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17(2*H*,6*H*)-dione (148k): Prepared following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 198 °C; **$[\alpha]_D^{25}$ = +114.2°** (*c* = 0.13 g/100 mL, $CHCl_3$, **18-23% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2924, 2862, 1738, 1666, 1604, 1462, 1377, 1265, 1190, 1093, 1016, 812 and 715 cm^{-1}; ^{1}H NMR ($CDCl_3$, major isomer) δ 5.78 (1H, br s, olefinic-H), 2.74-2.68 (1H, m), 2.54-2.32 (3H, m), 2.17-2.02 (3H, m), 2.01-1.93 (1H, m), 1.92-1.85 (2H, m), 1.82-1.79 (1H, m), 1.76-1.69 (4H, m), 1.63-1.36 (3H, m), 1.29 (3H, s, C*H*$_3$), 1.27 (3H, d, *J* = 7.6 Hz, C*H*$_3$), 0.94 (3H, s, C*H*$_3$); ^{1}H NMR ($CDCl_3$, minor isomer) δ 5.81 (1H, d, *J* = 1.25 Hz, olefinic-H), 2.74-2.68 (1H, m), 2.54-2.32 (3H, m), 2.17-2.02 (3H, m), 2.01-1.93 (1H, m), 1.92-1.85 (2H, m), 1.82-1.79 (1H, m), 1.76-1.69 (4H, m), 1.63-1.36 (3H, m), 1.21 (3H, s, C*H*$_3$), 1.10 (3H, d, *J* = 6.5 Hz, C*H*$_3$), 0.92 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 220.2 (C, *C*=O), 199.6 (C, *C*=O), 173.4 (C), 121.5 (CH), 53.4 (CH), 51.0 (CH), 47.5 (C), 38.9 (C), 38.1 (CH), 37.7 (CH_2), 36.3 (CH_2), 35.7 (CH_2), 34.0 (CH_2), 33.7 (CH), 31.3 (CH_2), 23.0 (CH_3), 21.8 (CH_2), 20.4 (CH_2), 18.3 (CH_3), 13.8 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 220.1 (C, *C*=O), 199.5 (C, *C*=O), 174.5 (C), 125.4 (CH), 54.1 (CH), 50.7 (CH), 47.5 (C), 39.7 (CH_2), 38.4 (C), 38.1 (CH), 35.9 (CH_2), 35.0 (CH_2), 33.6 (CH_2), 31.3 (CH_2), 30.0 (CH), 23.0 (CH_3), 21.7 (CH_2),

20.5 (CH_2), 18.3 (CH_3), 13.7 (CH_3); LRMS m/z 301.20 (M + H^+), calcd for $C_{20}H_{28}O_2$ 300.2089; Anal. calcd for $C_{20}H_{28}O_2$ (300.2089): C, 79.96; H, 9.39; Found: C, 79.85; H, 9.28%.

(5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (149m): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 62 °C; **$[\alpha]_D^{25}$ = +38.2°** (*c* = 1.0 g/100 mL, $CHCl_3$, **86% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2918, 2727, 1716 (*C*=O), 1464, 1379, 1263 and 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (1H, t, *J* = 14.5 Hz), 2.34 (1H, dt, *J* = 15.0, 5.5 Hz), 2.16 (1H, qd, *J* = 14.5, 4.0 Hz), 2.06-2.00 (3H, m), 1.92-1.79 (3H, m), 1.61-1.59 (1H, m), 1.54-1.44 (5H, m), 1.42-1.32 (6H, m), 1.28-1.20 (3H, m), 1.18-1.05 (7H, m), 1.02 (3H, s, C*H*$_3$), 0.92 (3H, d, *J* = 10.0 Hz, CHC*H*$_3$), 0.87 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 0.87 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 0.69 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.2 (C, *C*=O), 56.5 (CH), 56.3 (CH), 44.3 (CH), 42.7 (C), 42.3 (CH_2), 40.8 (CH), 40.1 (CH_2), 39.5 (CH_2), 37.1 (CH_2), 37.0 (CH_2), 36.1 (CH_2), 35.7 (CH), 35.5 (CH), 34.8 (C), 28.2 (CH_2), 27.9 (CH), 26.6 (CH_2), 25.8 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.7 (CH_3), 22.6 (CH_3), 22.5 (CH_3), 21.2 (CH_2), 18.6 (CH_3), 12.0 (CH_3); LRMS m/z 387.30 (M + H^+), calcd for $C_{27}H_{46}OH$ 387.3549; HRMS m/z 409.3444 (M + Na), calcd for $C_{27}H_{46}ONa$ 409.3447; Anal. calcd for $C_{27}H_{46}O$ (386.3549): C, 83.87; H, 11.99. Found: C, 83.75; H, 11.89%.

(5*R*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-hydroxy-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (149n): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 140 °C; **$[\alpha]_D^{25}$ = +32.1°** (*c* = 0.6 g/100 mL, CH_3OH, **94% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3420 (O*H*), 2924, 2858, 1705 (*C*=O), 1635, 1446, 1375, 1261, 1128 and 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (1H, t, *J* = 8.5 Hz), 2.68 (1H, t, *J* = 14.0 Hz), 2.35-2.29 (1H, m), 2.19-2.15 (1H, m), 2.14-2.00 (3H, m), 1.92-1.80 (4H, m), 1.74-1.72 (1H, m), 1.65-1.58 (1H, m), 1.56-1.41 (4H, m), 1.40-1.34 (2H, m), 1.33-1.22 (3H, m), 1.16-1.04 (2H, m), 1.03 (3H, s, C*H*$_3$), 0.76 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.1 (C, *C*=O), 81.8 (CH), 51.0 (CH), 44.2

(CH), 43.1 (C), 42.2 (CH_2), 40.9 (CH), 37.1 (CH_2), 37.0 (CH_2), 36.8 (CH_2), 35.6 (CH), 34.9 (C), 30.5 (CH_2), 26.4 (CH_2), 25.3 (CH_2), 23.3 (CH_2), 22.6 (CH_3), 20.7 (CH_2), 11.1 (CH_3); LRMS m/z 291.00 (M + H^+), calcd for $C_{19}H_{30}O_2$ 290.2246; HRMS m/z 313.2147 (M + Na), calcd for $C_{19}H_{30}O_2Na$ 313.2144; Anal. calcd for $C_{19}H_{30}O_2$ (290.2246): C, 78.57; H, 10.41. Found: C, 78.45; H, 10.48%.

(+)-(5*R*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-acetyl-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (149o): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 116 °C; **$[\alpha]_D^{25}$ = +96.1°** (*c* = 0.47 g/100 mL, $CHCl_3$, **86% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2924, 2858, 1728 (*C*=O), 1709, 1462, 1377, 1261, 1101, 1049, 1016, 821 and 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.69 (1H, t, *J* = 14.0 Hz), 2.55 (1H, t, *J* = 9.5 Hz), 2.34 (1H, dt, *J* = 15.0, 5.0 Hz), 2.21-2.16 (2H, m), 2.13 (3H, s, COC*H*$_3$), 2.09-2.02 (3H, m), 1.95-1.81 (2H, m), 1.73-1.65 (2H, m), 1.58-1.46 (5H, m), 1.47-1.37 (2H, m), 1.32-1.22 (4H, m), 1.03 (3H, s, C*H*$_3$), 0.64 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.9 (C, *C*=O), 209.3 (C, *C*=O), 63.7 (CH), 56.6 (CH), 44.2 (C), 44.1 (CH), 42.3 (CH_2), 40.8 (CH), 39.1 (CH_2), 37.1 (CH_2), 36.9 (CH_2), 35.5 (CH), 34.9 (C), 31.5 (CH_3), 26.5 (CH_2), 25.7 (CH_2), 24.4 (CH_2), 22.9 (CH_2), 22.6 (CH_3), 21.2 (CH_2), 13.4 (CH_3); LRMS m/z 314.75 (M - H^+), calcd for $C_{21}H_{32}O_2$ 316.2402; HRMS m/z 339.2305 (M + Na), calcd for $C_{21}H_{32}O_2Na$ 339.2300; Anal. calcd for $C_{21}H_{32}O_2$ (316.2402): C, 79.70; H, 10.19. Found: C, 79.65; H, 10.24%.

(5*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-10-(hydroxymethyl)-13-methyldodecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17(2*H*,4*H*)-dione (149p): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 202 °C; **$[\alpha]_D^{25}$ = +108.7°** (*c* = 0.68 g/100 mL, CH_3OH, **79% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3453 (O*H*), 2924, 2855, 1730 (*C*=O), 1693 (*C*=O), 1462, 1377, 1261, 1092, 1043, 1014, 802 and 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (1H, d, *J* = 11.0 Hz), 3.68 (1H, d, *J* = 10.5 Hz), 2.66 (1H, t, *J* = 14.5 Hz), 2.47 (1H, dd, *J* = 19.2, 8.5 Hz), 2.39-2.29 (3H, m), 2.14-

2.02 (3H, m), 2.00-1.86 (5H, m), 1.74-1.50 (5H, m), 1.47-1.16 (5H, m), 0.88 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 220.6 (C, *C*=O), 212.7 (C, *C*=O), 64.6 (CH_2), 51.8 (CH), 47.7 (C), 41.9 (CH_2), 41.3 (CH), 39.1 (C), 36.7 (CH_2), 36.2 (CH), 35.8 (CH_2), 35.0 (CH), 32.1 (CH_2), 30.7 (CH_2), 25.9 (CH_2), 24.4 (CH_2), 21.7 (CH_2), 20.5 (CH_2), 13.8 (CH_3); LRMS m/z 305.25 (M + H^+), calcd for $C_{19}H_{28}O_3$ 304.2038; HRMS m/z 327.1939 (M + Na), calcd for $C_{19}H_{28}O_3Na$ 327.1936; Anal. calcd for $C_{19}H_{28}O_3$ (304.2038): C, 74.96; H, 9.27. Found: C, 74.85; H, 9.21%.

(5*R*,8*R*,9*R*,10*S*,13*S*,14*S*,17*S*)-17-hydroxy-13-methyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (149q): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 110 °C; **$[\alpha]_D^{25}$ = +28.3°** (*c* = 0.67 g/100 mL, $CHCl_3$, **82% *de*** and **99% *ee***); IR (Neat): ν_{max} 3500 (O*H*), 2926, 2855, 1709 (*C*=O), 1462, 1377 and 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.68 (1H, t, *J* = 8.5 Hz), 2.59 (1H, t, *J* = 14.0 Hz), 2.28-2.16 (4H, m), 2.10-2.05 (2H, m), 1.88-1.85 (1H, m), 1.78-1.59 (6H, m), 1.53-1.42 (3H, m), 1.35-1.07 (7H, m), 0.79 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.8 (C, *C*=O), 81.9 (CH), 50.0 (CH), 43.2 (C), 42.9 (CH_2), 41.5 (CH), 39.8 (CH), 38.5 (CH), 38.3 (CH), 36.7 (CH_2), 36.4 (CH_2), 30.55 (CH_2), 30.51 (CH_2), 27.7 (CH_2), 25.5 (CH_2), 25.0 (CH_2), 23.2 (CH_2), 11.0 (CH_3); LRMS m/z 277.15 (M + H^+), calcd for $C_{18}H_{28}O_2$ 276.2089; HRMS m/z 299.1988 (M + Na), calcd for $C_{18}H_{28}O_2Na$ 299.1987; Anal. calcd for $C_{18}H_{28}O_2$ (276.2089): C, 78.21; H, 10.21. Found: C, 78.15; H, 10.26%.

(5*R*,8*R*,9*R*,10*S*,13*S*,14*S*,17*S*)-13-methyl-3-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl acetate (149r or **149s):** Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 130 °C; **$[\alpha]_D^{25}$ = +50.6°** (*c* = 0.83 g/100 mL, $CHCl_3$, **96% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2930, 2849, 1740 (*C*=O), 1703 (*C*=O), 1454, 1373, 1238, 1099 and 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.62 (1H, t, *J* = 8.0 Hz), 2.59 (1H, t, *J* = 14.0 Hz), 2.27-2.09 (6H, m), 2.04 (3H, s, COC*H*$_3$), 1.81-1.58 (6H, m), 1.55-1.46 (3H, m), 1.37-1.28 (2H, m), 1.25-1.10 (5H, m), 0.83 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.7 (C, *C*=O), 171.1 (C, O-*C*=O), 82.8 (CH), 49.7 (CH), 42.9 (CH_2), 42.8 (C),

41.2 (CH), 39.8 (CH), 38.32 (CH), 38.3 (CH), 36.8 (CH_2), 36.4 (CH_2), 30.5 (CH_2), 27.7 (CH_2), 27.5 (CH_2), 25.4 (CH_2), 25.0 (CH_2), 23.3 (CH_2), 21.1 (CH_3), 12.1 (CH_3); LRMS m/z 319.15 (M + H^+), calcd for $C_{20}H_{30}O_3$ 318.2195; HRMS m/z 341.2093 (M + Na), calcd for $C_{20}H_{30}O_3Na$ 341.2093; Anal. calcd for $C_{20}H_{30}O_3$ (318.2195): C, 75.43; H, 9.50. Found: C, 75.28; H, 9.41%.

4e. ***General procedure for oxidation of hydrogenated products:*** To the pure hydrogenated product **149b** or **149c** (0.1 mmol) in DCM (0.05 M) was added pyridinium dichromate (526 mg, 1.4 mmol) under nitrogen atmosphere and the reaction mixture was stirred at rt for 48 h. Then the crude reaction mixture was worked up with 1N HCl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to obtain the oxidized product *cis*-(+)-**149a** or (+)-**149t** respectively as solids.

(5*R*,8*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-5,6,7,8,10,12,13,14,15,16-decahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17(2*H*,4*H*)-dione (149t): Prepared following the procedure **4e** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 144 °C; **$[\alpha]_D^{25}$ = +139.1°** (*c* = 0.4 g/100 mL, CH_3OH, **>99% *de*** and **99% *ee***); IR (Nujol): ν_{max} 2924, 2855, 1736 (*C*=O), 1707 (*C*=O), 1462, 1377, 1267, 1205, 1072, 1034, 1010, 914, 819 and 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.61 (1H, d, *J* = 5.5 Hz), 2.55-2.44 (2H, m), 2.42-2.35 (1H, m), 2.34-2.24 (2H, m), 2.20-2.14 (2H, m), 2.12-2.05 (4H, m), 1.99-1.93 (2H, m), 1.87-1.84 (1H, m), 1.63-1.56 (3H, m), 1.41-1.37 (1H, m), 1.27 (1H, dq, *J* = 8.25, 4.5 Hz), 1.18 (3H, s, C*H*$_3$), 0.85 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 221.3 (C, *C*=O), 212.7 (C, *C*=O), 140.3 (C), 118.6 (CH), 48.6 (CH), 46.0 (C), 44.4 (CH), 43.6 (CH_2), 39.2 (C), 38.1 (CH_2), 37.4 (CH_2), 36.2 (CH_2), 35.9 (CH), 33.5 (CH_2), 28.9 (CH_3), 26.1 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 14.0 (CH_3); LRMS m/z 287.05 (M + H^+), calcd for $C_{19}H_{26}O_2$ 286.1933; HRMS m/z 309.1833 (M + Na), calcd for $C_{19}H_{26}O_2Na$ 309.1831; Anal. calcd for $C_{19}H_{26}O_2$ (286.1933): C, 79.68; H, 9.15. Found: C, 79.55; H, 9.23%.

(4a*R*,8a*S*)-8a-methylhexahydronaphthalene-1,6(2*H*,7*H*)-dione (151a): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane

and isolated as solid. Mp 48 °C; **$[\alpha]_D^{25}$ = +6.9°** (*c* = 0.27 g/100 mL, C_6H_6, **>99% *de*** and **99% *ee***); IR (Neat): ν_{max} 2940, 2869, 1697 (*C*=O), 1652, 1454, 1310, 1259, 1216, 1176, 1102 and 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65-2.35 (4H, m), 2.35-2.25 (4H, m), 2.20-2.05 (1H, m), 2.05-1.89 (2H, m), 1.60-1.50 (1H, m), 1.50-1.38 (1H, m), 1.36 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 214.1 (C, *C*=O), 211.2 (C, *C*=O), 48.5 (C), 46.0 (CH), 43.7 (CH_2), 38.3 (CH_2), 37.4 (CH_2), 33.6 (CH_2), 26.6 (CH_2), 23.9 (CH_3), 22.9 (CH_2); LRMS m/z 181.00 (M + H^+), calcd for $C_{11}H_{16}O_2$ 180.1150; HRMS m/z 203.1048 (M + Na), calcd for $C_{11}H_{16}O_2Na$ 203.1048; Anal. calcd for $C_{11}H_{16}O_2$ (180.1150): C, 73.30; H, 8.95. Found: C, 73.274; H, 8.984%.

(4a*S*,8a*R*)-8a-methylhexahydronaphthalene-1,6(2*H*,7*H*)-dione (*ent*-151a): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 48 °C; **$[\alpha]_D^{25}$ = –5.6°** (*c* = 0.33 g/100 mL, C_6H_6, **>99% *de*** and **99% *ee*)**.

(4a*R*,8a*R*)-8a-allylhexahydronaphthalene-1,6(2*H*,7*H*)-dione (151b): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as a gummy solid. **$[\alpha]_D^{25}$ = –42.4°** (*c* = 0.4 g/100 mL, $CHCl_3$, **84% *de*** and **95% *ee***); IR (Neat): ν_{max} 2952, 2922, 1712 (*C*=O), 1638, 1438, 1357, 1312, 1286, 1257, 1236, 1210, 1161, 1131, 1086, 997, 918, 868, 807, 789, 760, 675 and 606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68-5.59 (1H, m, RC*H*=CH_2), 5.13-5.08 (2H, m, RCH=C*H*$_2$), 2.69 (1H, dd, *J* = 14.0, 7.6 Hz), 2.57-2.48 (3H, m), 2.48-2.34 (3H, m), 2.31-2.16 (4H, m), 1.99-1.94 (2H, m), 1.52-1.41 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.1 (C, *C*=O), 211.4 (C, *C*=O), 132.3 (CH, R*C*H=CH_2), 118.8 (CH_2, RCH=*C*H_2), 51.9 (C), 43.5 (CH), 43.4 (CH_2), 41.0 (CH_2), 38.1 (CH_2), 38.0 (CH_2), 31.4 (CH_2), 26.0 (CH_2), 22.5 (CH_2); LRMS m/z 207.05 (M + H^+), calcd for $C_{13}H_{18}O_2$ 206.1307; HRMS m/z 229.1202 (M + Na), calcd for $C_{13}H_{18}O_2Na$ 229.1204; Anal. calcd for $C_{13}H_{18}O_2$ (206.1307): C, 75.69; H, 8.80. Found: C, 75.58, H, 8.86%.

(4a*R*,8a*R*)-8a-benzylhexahydronaphthalene-1,6(2*H*,7*H*)-dione (151c): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –36.0°** (*c* = 0.27 g/100 mL, $CHCl_3$, **>99% *de*** and **90% *ee***); IR (Neat): ν_{max} 2952, 2876, 1708 (*C*=O), 1652, 1497, 1450, 1277, 1255, 1190, 1157, 1113, 1067, 759, 706, 634

and 621 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21-7.16 (3H, m), 6.99 (2H, d, *J* = 6.8 Hz) [Ph-*H*]; 3.15 (1H, d, *J* = 14.0 Hz), 2.95 (1H, d, *J* = 13.6 Hz) [PhCH_2]; 2.80-2.72 (1H, m), 2.43-2.14 (8H, m), 1.98-1.94 (2H, m), 1.49-1.30 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.2 (C, *C*=O), 211.3 (C, *C*=O), 136.1 (C), 129.9 (2 x CH), 128.3 (2 x CH), 127.0 (CH), 52.9 (C), 43.53 (CH), 43.47 (CH_2), 42.8 (CH_2), 38.2 (CH_2), 38.1 (CH_2), 31.6 (CH_2), 26.0 (CH_2), 22.2 (CH_2); LRMS m/z 257.00 (M + H^+), calcd for $C_{17}H_{20}O_2$ 256.1463; HRMS m/z 279.1361 (M + Na), calcd for $C_{17}H_{20}O_2Na$ 279.1361; Anal. calcd for $C_{17}H_{20}O_2$ (256.1463): C, 79.65; H, 7.86. Found: C, 79.676; H, 7.840%.

(4a*R*,8a*R*)-8a-(prop-2-yn-1-yl)hexahydronaphthalene-1,6(2*H*,7*H*)-dione (151d): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 76 °C; **$[\alpha]_D^{25}$ = –17.1°** (*c* = 0.63 g/100 mL, $CHCl_3$, **>99% *de*** and **90% *ee***); IR (Neat): ν_{max} 2930, 2856, 1697(*C*=O), 1666, 1452, 1254, 1234, 1197, 1175, 1101, 1047, 713, 701, 690 and 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.71 (2H, q, *J* = 2.7 Hz), 2.67-2.63 (1H, m), 2.58-2.50 (3H, m), 2.48-2.41 (1H, m), 2.37-2.32 (3H, m), 2.08 (1H, t, *J* = 2.7 Hz), 2.05-1.90 (3H, m), 1.72-1.54 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 211.6 (C, *C*=O), 210.4 (C, *C*=O), 79.0 (C, *C*≡CH), 72.1 (CH, C≡*C*H), 51.3 (C), 43.3 (CH_2), 42.6 (CH), 37.9 (CH_2), 37.5 (CH_2), 30.9 (CH_2), 26.4 (CH_2), 25.7 (CH_2), 22.8 (CH_2); LRMS m/z 203.10 (M – H^+), calcd for $C_{13}H_{16}O_2$ 204.1150; HRMS m/z 227.1048 (M + Na), calcd for $C_{13}H_{16}O_2Na$ 227.1048; Anal. calcd for $C_{13}H_{16}O_2$ (204.1150): C, 76.44; H, 7.90. Found: C, 76.58; H, 7.85%.

(4a*R*,8a*S*)-8a-phenylhexahydronaphthalene-1,6(2*H*,7*H*)-dione (151e): Prepared following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –42.7°** (*c* = 0.28 g/100 mL, $CHCl_3$, **>99% *de*** and **62% *ee***); IR (Neat): ν_{max} 3401, 3059, 2949, 1958, 1713 (*C*=O), 1597, 1495, 1446, 1342, 1311, 1271, 1207, 1157, 1107, 1078, 1036, 993, 872, 760, 702 and 646 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40-7.35 (2H, m), 7.29 (1H, tt, *J* = 8.0, 4.0 Hz), 7.20-7.18 (2H, m), 3.26 (1H, qd, *J* = 13.2, 3.2 Hz), 2.84-2.75 (1H, m), 2.63-2.57 (1H, m), 2.56-2.45 (2H, m), 2.40-2.35 (1H, m), 2.32-2.24 (2H, m), 2.23-2.16 (1H, m), 2.02-1.94 (1H, m), 1.92-1.88

(1H, m), 1.57-1.48 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.6 (C, *C*=O), 211.1 (C, *C*=O), 142.1 (C), 129.3 (2 x CH), 127.2 (CH), 125.9 (2 x CH), 57.4 (C), 43.2 (CH_2), 41.9 (CH), 39.3 (CH_2), 39.2 (CH_2), 37.8 (CH_2), 26.3 (CH_2), 22.5 (CH_2); LRMS m/z 243.10 (M + H^+), calcd for $C_{16}H_{18}O_2$ 242.1307; Anal. calcd for $C_{16}H_{18}O_2$ (242.1307): C, 79.31; H, 7.49. Found: C, 79.23; H, 7.41%.

(4a*S*,5*S*,8a*R*)-5-hydroxy-4a-methyloctahydronaphthalen-2(1*H*)-one (151f): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. Relative and absolute stereochemistry of the product (+)-**151f** was established through oxidation and X-ray crystallography on the resulting product (+)-**151a** as shown in eq. A-13, Annexure-IV. **$[\alpha]_D^{25}$ = +18.8°** (*c* = 0.7 g/100 mL, $CHCl_3$, **83% *de*** and **99% *ee***); IR (Neat): ν_{max} 3485 (O*H*), 2936, 2866, 1709 (*C*=O), 1445, 1319, 1258, 1169, 1117, 1056, 1001, 964, 806, 757, 690, 663, 632 and 625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (1H, m, C*H*-OH), 2.44-2.31 (4H, m), 2.27-2.22 (1H, m), 2.06-2.04 (1H, m), 1.84-1.80 (1H, m), 1.72-1.55 (5H, m), 1.45-1.38 (1H, m), 1.16 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.6 (C, *C*=O), 70.8 (CH), 43.2 (CH_2), 41.2 (CH), 37.4 (CH_2), 36.9 (C), 32.9 (CH_2), 29.8 (CH_2), 27.4 (CH_2), 20.9 (CH_3), 19.8 (CH_2); LRMS m/z 183.15 (M + H^+), calcd for $C_{11}H_{18}O_2$ 182.1307; HRMS m/z 205.1205 (M + Na), calcd for $C_{11}H_{18}O_2Na$ 205.1205; Anal. calcd for $C_{11}H_{18}O_2$ (182.1307): C, 72.49; H, 9.95. Found: C, 72.35; H, 9.91%.

(4a*S*,5*S*,8a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4a-methyloctahydronaphthalen-2(1*H*)-one (151g): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +9.4°** (*c* = 0.77 g/100 mL, $CHCl_3$, **53% *de*** and **74% *ee***); IR (Neat): ν_{max} 2932, 2860, 1713 (*C*=O), 1470, 1365, 1254, 1169, 1088, 983, 835, 771 and 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, major *cis*-isomer) δ 3.68 (1H, d, *J* = 4.0 Hz), 2.39-2.30 (3H, m), 2.23-2.12 (2H, m), 2.06-2.01 (1H, m), 1.70-1.64 (2H, m), 1.58-1.45 (3H, m), 1.34-1.30 (1H, m), 1.25-1.23 (1H, m), 1.10 (3H, s, CH_3), 0.89 (9H, s, C(CH_3)$_3$), 0.04 (6H, s, Si(CH_3)$_2$); ^{1}H NMR ($CDCl_3$, minor *trans*-isomer) δ 3.19 (1H, dd, *J* = 10.7, 4.5 Hz), 2.39-2.30 (3H, m), 2.23-2.12 (2H, m), 2.06-2.01 (1H, m), 1.70-1.64 (2H, m), 1.58-

1.45 (3H, m), 1.34-1.30 (1H, m), 1.25-1.23 (1H, m), 0.99 (3H, s, C*H*$_3$), 0.86 (9H, s, C(C*H*$_3$)$_3$), 0.02 (6H, s, Si(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135, major *cis*-isomer) δ 212.6 (C, *C*=O), 79.2 (CH), 44.0 (CH), 43.6 (CH_2), 37.64 (CH_2), 37.61 (C), 32.5 (CH_2), 29.8 (CH_2), 27.8 (CH_2), 25.8 (3 x CH_3), 19.8 (CH_2), 18.1 (C), 9.3 (CH_3), –4.0 (CH_3), –4.9 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, minor *trans*-isomer) δ 211.7 (C, *C*=O), 72.3 (CH), 44.1 (CH_2), 40.6 (CH), 39.0 (C), 38.1 (CH_2), 37.8 (CH_2), 30.8 (CH_2), 28.2 (CH_2), 24.1 (CH_2), 21.8 (3 x CH_3), 18.0 (C), 9.3 (CH_3), –3.9 (CH_3), –4.9 (CH_3); LRMS m/z 297.15 (M + H^+), calcd for $C_{17}H_{32}O_2Si$ 296.2172; HRMS m/z 319.2068 (M + Na), calcd for $C_{17}H_{32}O_2SiNa$ 319.2070; Anal. calcd for $C_{17}H_{32}O_2Si$ (296.2172): C, 68.86; H, 10.88. Found: C, 68.75; H, 10.81%.

(3a*R*,7a*S*)-7a-methylhexahydro-1*H*-indene-1,5(6*H*)-dione (151h): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 68°C; **$[\alpha]_D^{25}$ = +89.6°** (*c* = 0.25 g/100 mL, $CHCl_3$, **>99% *de*** and **99% *ee***); IR (Neat): ν_{max} 2951, 2914, 2877, 1737 (*C*=O), 1730 (*C*=O), 1707, 1423, 1344, 1253, 1223, 1151, 1098, 1057, 827 and 634 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60 (1H, dd, *J* = 15.0, 6.2 Hz), 2.50-2.00 (6H, m), 2.20-1.95 (2H, m), 1.70-1.55 (2H, m), 1.25 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 220.2 (C, *C*=O), 210.6 (C, *C*=O), 47.2 (C), 44.5 (CH), 41.8 (CH_2), 37.0 (CH_2), 35.1 (CH_2), 29.8 (CH_2), 25.1 (CH_2), 20.6 (CH_3); LRMS (MALDI-TOF) m/z 167.026 (M + H^+), calcd for $C_{10}H_{14}O_2$ 166.0994; Anal. calcd for $C_{10}H_{14}O_2$ (166.0994): C, 72.26; H, 8.49. Found: C, 72.25, H, 8.49%.

(3a*R*,7a*S*)-7a-propylhexahydro-1*H*-indene-1,5(6*H*)-dione (151i): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –38.5°** (*c* = 0.4 g/100 mL, $CHCl_3$, **59% *de*** and **88% *ee***); IR (Neat): ν_{max} 2958, 1732 (*C*=O), 1540, 1463, 1414, 1343, 1237, 1105, 843, 807, 760, 686, 654, 640 and 628 cm^{-1}; ^{1}H NMR ($CDCl_3$, major *cis*-isomer) δ 2.64-2.50 (2H, m), 2.44-2.26 (3H, m), 2.24-2.10 (2H, m), 2.07-2.00 (1H, m), 1.72-1.50 (4H, m), 1.41-1.15 (3H, m), 0.93 (3H, t, *J* = 7.2 Hz, C*H*$_3$); ^{1}H NMR ($CDCl_3$, minor *trans*-isomer) δ 2.64-2.50 (2H, m), 2.44-2.26 (3H, m), 2.24-2.10 (2H, m), 2.07-2.00 (1H, m), 1.72-1.50 (4H, m), 1.41-1.15 (3H, m), 0.94 (3H, t, *J* = 6.8 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, major *cis*-isomer) δ 220.4 (C, *C*=O), 211.2 (C, *C*=O), 50.8 (C), 42.1 (CH_2), 40.5

(CH), 37.0 (CH_2), 36.9 (CH_2), 36.3 (CH_2), 29.0 (CH_2), 25.4 (CH_2), 17.6 (CH_2), 14.5 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, minor *trans*-isomer) δ 216.9 (C, *C*=O), 209.6 (C, *C*=O), 49.5 (C), 45.3 (CH_2), 40.5 (CH), 36.6 (CH_2), 36.1 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 23.1 (CH_2), 16.4 (CH_2), 14.6 (CH_3); LRMS m/z 195.25 (M + H^+), calcd for $C_{12}H_{18}O_2$ 194.1307; HRMS m/z 217.1205 (M + Na), calcd for $C_{12}H_{18}O_2Na$ 217.1205; Anal. calcd for $C_{12}H_{18}O_2$ (194.1307): C, 74.19; H, 9.34. Found: C, 74.25; H, 9.28%.

(3a*R*,7a*S*)-7a-butylhexahydro-1*H*-indene-1,5(6*H*)-dione (151j): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –41.6°** (*c* = 0.32 g/100 mL, $CHCl_3$, **24% *de*** and **89% *ee***); IR (Neat): ν_{max} 2957, 2867, 1732 (*C*=O), 1715 (*C*=O), 1672, 1540, 1463, 1414, 1342, 1256, 1233, 1191, 1154, 1103, 1047, 831, 803, 686, 659 and 636 cm^{-1}; ^{1}H NMR ($CDCl_3$, major *cis*-isomer) δ 2.65-2.50 (2H, m), 2.45-2.26 (3H, m), 2.24-2.10 (2H, m), 2.07-1.80 (1H, m), 1.74-1.59 (4H, m), 1.58-1.50 (1H, m), 1.43-1.14 (4H, m), 0.90 (3H, t, *J* = 7.0 Hz, C*H*$_3$); ^{1}H NMR ($CDCl_3$, minor *trans*-isomer) δ 2.65-2.50 (2H, m), 2.45-2.26 (3H, m), 2.24-2.10 (2H, m), 2.07-1.80 (1H, m), 1.74-1.59 (4H, m), 1.58-1.50 (1H, m), 1.43-1.14 (4H, m), 0.91 (3H, t, *J* = 7.2 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, major *cis*-isomer) δ 220.4 (C, *C*=O), 211.1 (C, *C*=O), 50.7 (C), 42.1 (CH_2), 40.5 (CH), 37.1 (CH_2), 36.2 (CH_2), 34.4 (CH_2), 29.0 (CH_2), 26.4 (CH_2), 25.2 (CH_2), 23.2 (CH_2) 14.0 (CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, minor *trans*-isomer) δ 216.9 (C, *C*=O), 209.6 (C, *C*=O), 49.5 (C), 45.3 (CH), 42.1 (CH_2), 36.6 (CH_2), 36.1 (CH_2), 26.0 (CH_2), 24.9 (CH_2), 23.5 (CH_2), 23.3 (CH_2), 23.1 (CH_2), 14.0 (CH_3); LRMS m/z 209.15 (M + H^+), calcd for $C_{13}H_{20}O_2$ 208.1463; HRMS m/z 231.1361 (M + Na), calcd for $C_{13}H_{20}O_2Na$ 231.1361; Anal. calcd for $C_{13}H_{20}O_2$ (208.1463): C, 74.96; H, 9.68. Found: C, 74.85; H, 9.76%.

(4a*S*,9a*R*)-9a-(prop-2-yn-1-yl)-4,4a-dihydro-1*H*-fluorene-3,9(2*H*,9a*H*)-dione (151k): Prepared following the procedure **4c** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +169.7°** (*c* = 0.21 g/100 mL, $CHCl_3$, **>99% *de*** and **69% *ee***); IR (Neat): ν_{max} 3397, 2926, 2857, 1693, 1641, 1456, 1377, 1165, 1103 and 1014 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80 (1H, d, *J* = 7.5 Hz), 7.69 (1H, dt, *J* = 7.0, 1.0 Hz), 7.51 (1H, d, *J* = 7.5 Hz), 7.45 (1H, t, *J* = 7.5 Hz),

3.87 (1H, dd, *J* = 6.5, 3.0 Hz), 3.12 (1H, dd, *J* = 16.0, 6.5 Hz), 2.92 (1H, dd, *J* = 16.5, 3.0 Hz), 2.67 (1H, dd, *J* = 16.5, 2.5 Hz), 2.53 (1H, dd, *J* = 16.5, 2.5 Hz), 2.32-2.26 (2H, m), 2.22-2.19 (1H, m), 1.99 (1H, t, *J* = 2.5 Hz), 1.68-1.63 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.8 (C, *C*=O), 208.0 (C, *C*=O), 155.4 (C), 136.24 (C), 136.2 (CH), 128.5 (CH), 125.4 (CH), 124.1 (CH), 80.0 (C, *C*≡CH), 70.7 (CH, C≡*C*H), 50.6 (C), 42.4 (CH_2), 41.9 (CH), 35.7 (CH_2), 28.7 (CH_2), 26.9 (CH_2); LRMS m/z 239.10 (M + H^+), calcd for $C_{16}H_{14}O_2$ 238.0994; HRMS m/z 261.0891 (M + Na), calcd for $C_{16}H_{14}O_2Na$ 261.0892; Anal. calcd for $C_{16}H_{14}O_2$ (238.0994): C, 80.65; H, 5.92. Found: C, 80.54; H, 5.85%.

(1*S*,3a*R*,7a*S*)-1-hydroxy-7a-methylhexahydro-1*H*-inden-5(6*H*)-one (151l): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +21.9°** (*c* = 0.53 g/100 mL, $CHCl_3$, **82% *de*** and **99% *ee***); IR (Neat): ν_{max} 3419 (O*H*). 2956. 2872, 1709 (***C***=O), 1450, 1420, 1258, 1142, 1099, 1056, 989, 757, 697, 658, 634, 621 and 603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (1H, dd, *J* = 8.0, 4.0 Hz, C*H*-OH), 2.49-2.38 (2H, m), 2.29-2.22 (3H, m), 2.17-2.12 (1H, m), 1.97-1.92 (1H, m), 1.74-1.57 (3H, m), 1.31-1.21 (1H, m), 1.19 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.9 (C, *C*=O), 79.9 (CH), 43.8 (CH), 43.1 (C), 41.9 (CH_2), 36.8 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 28.3 (CH_2), 19.3 (CH_3); LRMS m/z 167.15 (M – H^+), calcd for $C_{10}H_{16}O_2$ 168.1150; HRMS m/z 191.1047 (M + Na), calcd for $C_{10}H_{16}O_2Na$ 191.1048; Anal. calcd for $C_{10}H_{16}O_2$ (168.1150): C, 71.39; H, 9.59. Found: C, 71.48; H, 9.51%.

(4a*R*,8a*S*)-4a-methyloctahydronaphthalen-2(1*H*)-one (151m): Prepared following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –7.7°** (*c* = 0.9 g/100 mL, $CHCl_3$, **70% *de*** and **88% *ee***); IR (Neat): ν_{max} 2922, 2854, 1717 (*C*=O), 1652, 1540, 1515, 1456, 1266, 1119, 1078, 1019 and 802 cm^{-1}; ^{1}H NMR ($CDCl_3$, major *cis*-isomer) δ 2.61 (1H, dd, *J* = 14.0, 8.0 Hz), 2.49-2.40 (1H, m), 2.33-2.26 (1H, m), 2.21-2.08 (3H, m), 1.75-1.64 (2H, m), 1.61-1.45 (4H, m), 1.44-1.33 (1H, m), 1.31-1.21 (2H, m), 1.19 (3H, s, C*H*$_3$); ^{1}H NMR ($CDCl_3$, minor *trans*-isomer) δ 2.61 (1H, dd, *J* = 14.0, 8.0 Hz), 2.49-2.40 (1H, m), 2.33-2.26 (1H, m), 2.21-2.08 (3H, m), 1.75-1.64 (2H, m), 1.61-1.45 (4H, m), 1.44-1.33 (1H, m), 1.31-1.21 (2H, m), 1.04 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, major *cis* isomer) δ 212.7 (C,

C=O), 44.2 (CH_2), 43.9 (CH), 37.7 (CH_2), 37.0 (CH_2), 32.9 (CH_2), 32.5 (C), 28.8 (CH_2), 27.1 (CH_3), 24.9 (CH_2), 21.5 (CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135, minor *trans* isomer) δ 211.1 (C, *C*=O), 45.0 (CH_2), 44.6 (CH), 41.0 (CH_2), 40.3 (CH_2), 38.2 (CH_2), 32.9 (C), 28.9 (CH_2), 26.0 (CH_2), 21.5 (CH_2), 14.9 (CH_3); LRMS m/z 167.05 (M + H^+), calcd for $C_{11}H_{18}O$ 166.1358; HRMS m/z 189.1256 (M + Na), calcd for $C_{11}H_{18}ONa$ 189.1256; Anal. calcd for $C_{11}H_{18}O$ (166.1358): C, 79.46; H, 10.91. Found: C, 79.58; H, 10.86%.

4f. ***General procedure for reduction of hydrogenated product*:** To the pure hydrogenated product **149m** (38 mg, 0.1 mmol) in ethanol (0.04 M), was added sodium borohydride (6 mg, 0.15 mmol) at 0 °C under nitrogen atmosphere and the reaction mixture was stirred at same temperature for 5 min. Then the crude reaction mixture was worked up with 1N HCl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure alcohol (+)-**152m** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (152m): Prepared following the procedure **4f** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 110 °C; **$[\alpha]_D^{25}$ = +29.5°** (*c* = 0.45 g/100 mL, $CHCl_3$, **78% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3244 (O*H*), 2924, 2855, 1643, 1462, 1377, 1261, 1163, 1082, 1045, 800 and 723 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.62 (1H, tt, *J* = 12.0, 4.0 Hz), 1.97 (1H, td, *J* = 12.0, 7.0 Hz), 1.85-1.72 (4H, m), 1.72-1.64 (1H, m), 1.58-1.48 (5H, m), 1.43-1.32 (8H, m), 1.27-1.21 (4H, m), 1.17-1.07 (6H, m), 1.05-0.99 (2H, m), 0.92 (3H, s, C*H*$_3$), 0.90 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 0.87 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 0.86 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 0.64 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 71.9 (CH), 56.5 (CH), 56.4 (CH), 42.7 (C), 42.1 (CH), 40.5 (CH), 40.2 (CH_2), 39.5 (CH_2), 36.5 (CH_2), 36.2 (CH_2), 35.9 (CH), 35.8 (CH), 35.4 (CH_2), 34.6 (C), 30.6 (CH_2), 28.3 (CH_2), 28.0 (CH), 27.2 (CH_2), 26.4 (CH_2), 24.2 (CH_2), 23.8 (CH_2), 23.4 (CH_3), 22.8 (CH_3), 22.5 (CH_3), 20.8 (CH_2), 18.7 (CH_3), 12.0 (CH_3); LRMS m/z 389.35 (M

+ H^+), calcd for $C_{27}H_{48}O$ 388.3705; HRMS m/z 411.3604 (M + Na), calcd for $C_{27}H_{48}ONa$ 411.3603; Anal. calcd for $C_{27}H_{48}O$ (388.3705): C, 83.44; H, 12.45. Found: C, 83.28; H, 12.41%.

4g. ***General procedure for deacetylation of hydrogenated product:*** To the mixture of hydrogenated product **149g** and pyridine byproduct (50 mg, 0.1 mmol) was added 2 mL of 20% methanolic KOH and the mixture was stirred at rt for 2 h. Then the crude reaction mixture was worked up with 1N HCl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The mixture was then purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to obtain pure deacetylated product (+)-**152g**.

1-((3*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)ethanone (152g): Prepared following the procedure **4g** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 190 °C; **$[\alpha]_D^{25}$ = +26.6°** (*c* = 0.46 g/100 mL, $CHCl_3$, **>99% *de*** and **99% *ee***); IR (Nujol): ν_{max} 3501 (O*H*), 2924, 2855, 1682 (*C*=O), 1462, 1377, 1165, 1053, 1016, 949, 800 and 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.35 (1H, d, *J* = 5.0 Hz), 3.53 (1H, tt, *J* = 11.0, 4.5 Hz), 2.53 (1H, t, *J* = 9.5 Hz), 2.30-2.23 (1H, m), 2.19-2.17 (2H, m), 2.12 (3H, s, COC*H*$_3$), 2.06-1.97 (2H, m), 1.87-1.84 (2H, m), 1.70-1.61 (5H, m), 1.54-1.44 (4H, m), 1.30-0.95 (4H, m), 1.01 (3H, s, C*H*$_3$), 0.63 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.4 (C, *C*=O), 140.8 (C), 121.3 (CH), 71.6 (CH), 63.7 (CH), 56.9 (CH), 50.0 (CH), 43.9 (C), 42.2 (CH_2), 38.8 (CH_2), 37.2 (CH_2), 36.5 (C), 31.8 (CH_3), 31.7 (CH_2), 31.6 (CH_2), 31.4 (CH), 24.4 (CH_2), 22.8 (CH_2), 21.0 (CH_2), 19.3 (CH_3), 13.2 (CH_3); LRMS m/z 317.25 (M + H^+), calcd for $C_{21}H_{32}O_2$ 316.2402; HRMS m/z 339.2299 (M + Na), calcd for $C_{21}H_{32}O_2Na$ 339.2300; Anal. calcd for $C_{21}H_{32}O_2$ (316.2402): C, 79.70; H, 10.19. Found: C, 79.58; H, 10.25%.

4h. ***General procedure for the synthesis of tricyclic core from bicyclic diketone*:**

Step 1: A solution of bicyclic ketone **151a** (360 mg, 2.0 mmol) in dry THF (20 mL, 0.1 M) at -78 °C, was added to LDA (6.0 mmol, prepared freshly from diisopropyl amine (606 mg, 6 mmol) and *n*BuLi (6 mmol) in dry THF (20 mL, 0.1 M)) dropwise under N_2 atmosphere. After 1

h of stirring at -78 °C, TMSCl (0.8 mL, 6.3 mmol) was added and the mixture was brought to rt in 1 h time period. Then mixture was quenched with 2 mL of water. The solvent was then evaporated and reaction mixture was then worked up by extracting with diethyl ether (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude viscous oil containing regio isomers of silyl enol ethers. The crude mixture was then used in the succeeding step as such without any further purification.

Step 2: To the above crude viscous oil in THF (20 mL, 0.1 M) was added crystallized NBS (1.07 g, 6.0 mmol) and the mixture was stirred at rt under N_2 atmosphere for 3 h. The solvent was then evaporated and added diethyl ether and the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude viscous oil containing mixture of dibromides, which was then used in the next step as such without any further purification.

Step 3: To the above obtained crude mixture of dibromides in dry THF (20 mL, 0.1 M), was added DBU (912 mg, 6.0 mmol) and the reaction mixture was refluxed at 65 °C under N_2 atmosphere for 16 h. The reaction mixture was then quenched with water and solvent was evaporated. The oil was then dissolved in DCM and then neutralized with 1M HCl and the organic layer was then extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The mixture was then purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to obtain pure tricyclic ketone **153a**.

(4*S*)-1-bromo-4-methylhexahydro-1*H*-1,4-methanoindene-7,8(7a*H*)-dione (153a): Prepared following the procedure **4h** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –109.4°** (*c* = 0.3 g/100 mL, $CHCl_3$, **>99% *de*** and **70% *ee***); IR (Neat): ν_{max} 1763 (*C*=O), 1711 (*C*=O), 1449, 1420, 1378, 1321, 1273, 1219, 1188, 1167, 1150, 1130, 1044, 1021, 993, 949, 913, 879, 831, 806, 770, and 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (1H, br s), 2.53 (1H, m), 2.44 (1H, dd, *J* = 17.8, 6.0 Hz), 2.23-2.16 (2H, m), 2.05-1.93 (4H, m), 1.75 (1H, dt, *J* = 14.0, 6.4 Hz), 1.23 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.9 (C, *C*=O), 207.1 (C, *C*=O), 68.5 (C), 66.2 (CH), 50.0 (C), 49.1 (CH), 36.5 (CH_2), 35.7 (CH_2), 34.7 (CH_2), 24.5 (CH_2), 17.0 (CH_3); HRMS m/z 278.9997 (M + Na), calcd for $C_{11}H_{13}BrO_2Na$ 278.9997.

(4*R*)-1-bromo-4-methylhexahydro-1*H*-1,4-methanoindene-7,8(7a*H*)-dione (*ent*-153a): Prepared following the procedure **4h** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +156.8°** (*c* = 0.35 g/100 mL, $CHCl_3$, **>99% *de*** and **97% *ee***).

4i ***General procedure for the synthesis of tricyclic alcohol from bicyclic diketone:*** To the solution of tricyclic ketone **153a** (256 mg, 1.0 mmol) in dry THF (20 mL, 0.05 M) at -78 °C, was added isopropenyl magnesium bromide (prepared freshly from magnesium turinings (194 mg, 8.0 mmol) and 2-propenyl bromide (0.71 mL, 8.0 mmol) in 8 mL THF) in 8 mL dry THF, dropwise under N_2 atmosphere. The reaction mixture was stirred at -50 °C for 4 h and then slowly brought to rt and then quenched with saturated NH_4Cl solution. The crude mixture was then extracted with ether (3 x 30 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The mixture was then purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to obtain pure tricyclic alcohol **154a**.

(4*S*,7*R*)-1-bromo-7-hydroxy-4-methyl-7-(prop-1-en-2-yl)octahydro-1*H*-1,4-methanoinden-8-one (154a): Prepared following the procedure **4i** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = −71.5°** (*c* = 0.6 g/100 mL, $CHCl_3$, **>99% *de*** and **70% *ee***); IR (Neat): ν_{max} 2956 (O*H*), 1756 (*C*=O), 1644, 1448, 1371, 1260, 1025, 992 and 904 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.06 (2H, s), 2.76 (1H, t, *J* = 1.5 Hz), 2.60 (1H, s), 2.34-2.29 (2H, m), 2.09 (1H, d, *J* = 4.0 Hz), 2.00-1.94 (1H, m), 1.91 (3H, t, *J* = 1.0 Hz, CH_3), 1.89-1.83 (1H, m), 1.77-1.63 (3H, m), 1.57 (1H, dt, *J* = 12.5, 5.0 Hz), 1.09 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.9 (C, *C*=O), 146.1 (C, *C*=CH_2), 112.7 (CH_2, C=*C*H_2), 74.5 (C), 68.8 (C), 57.2 (CH), 50.3 (C), 46.1 (CH), 37.8 (CH_2), 35.0 (CH_2), 32.3 (CH_2), 23.3 (CH_2), 18.5 (CH_3), 16.8 (CH_3); HRMS m/z 321.0466 (M + Na), calcd for $C_{14}H_{19}BrO_2Na$ 321.0466.

4j ***General procedure for the synthesis of aryl substituted Wieland-Miescher ketone 150e:***

Step. 1: To cyclohexane 1,3-dione (200 mg, 1.78 mmol) in DMSO (0.25 M), were added CuI (17 mg, 0.09 mmol), potassium carbonate (491 mg, 3.56 mmol), L-proline (41 mg, 0.36 mmol) and iodo benzene (0.5 mL, 1.78 mmol) successively. The mixture was stirred at 90 °C for 24 h and then worked up with aqueous 1N HCl. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure coupling product (180 mg, 56% yield) was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Step. 2: The mixture of coupling product (180 mg, 0.96 mmol), triethylamine (0.01 mL, 0.096 mmol) and methyl vinyl ketone (0.24 mL, 2.88 mmol) was stirred at rt under neat conditions for 0.5 h. Then the crude reaction mixture was worked up with 1N HCl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The mixture was then purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to obtain the Micheal adduct (119 mg, 48% yield).

Step. 3: The mixture of Michael adduct (105 mg, 0.4 mmol), L-Proline (9 mg, 0.08 mmol) in DMSO (0.3 M) was stirred at rt for 24 h and then added a pinch of *p*-TSA and stirred for another 1 h at rt. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure enone **150e** (75 mg, 78% yield, 60% ee) was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate) (see eq. A-6 and eq. A-8, Annexure-IV).

4k. ***General procedure for synthesis of testosterone 148n:*** To the pure Androstan-4-ene-3,17-dione **148i** (143 mg, 0.5 mmol) in methanol (0.3 M), was added sodium borohydride (7 mg, 0.17 mmol) at 0 °C under nitrogen atmosphere and the reaction mixture was stirred at same temperature for 5 min. Then the crude reaction mixture was worked up with 1N HCl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure testosterone **148n** (112 mg, 78% yield, >99% de) was isolated as a solid through column chromatography (silica gel, mixture of hexane/ethyl acetate) (see eq. A-11, Annexure-IV).

4l. ***General procedure for synthesis of dehydroprogesterone 148o:***

Step. 1: The mixture of 16-dehydro Pregnenolone-3-acetate **148g** (122 mg, 0.4 mmol) and 10 mL of 20% methanolic KOH was stirred for 0.5 h at rt. Then the crude reaction mixture was worked up with 1N HCl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure deacetylated product (82 mg, 78% yield) was isolated by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Step. 2: To the deacetylated product (100 mg, 0.38 mmol), was added pyridinium chlorochromate (488 mg, 1.9 mmol) over SiO_2 (500 mg) in DCM (0.1 M) and the mixture was stirred at rt for 0.5 h. Then the crude reaction mixture was worked up with 1N HCl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure oxidized product (77 mg, 77% yield) was isolated by column chromatography (silica gel, mixture of hexane/ethyl acetate)

Step 3: To the oxidized product (77 mg, 0.29 mmol), was added $^{t}BuO^{-}K^{+}$ (32 mg, 0.29 mmol) and dry benzene (0.1 M) and refluxed for 2 h, then the crude reaction mixture was worked up with 1N HCl solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure dienone product **148o** was isolated as a solid by column chromatography (silica gel, mixture of hexane/ethyl acetate) (see eq. A-12, Annexure-IV).

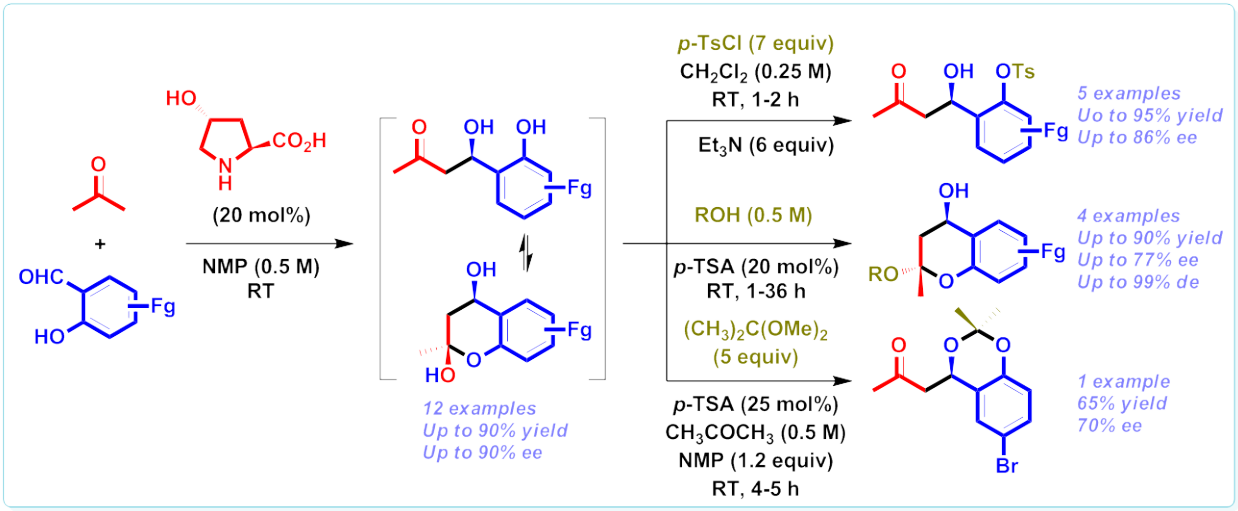
(*S,Z*)-1-((*S*)-4a-methyl-5-oxo-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-ylidene)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-ium (I): **hexahydronaphthalen-2(3*H*)-ylidene)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-ium (I):** ^{1}H NMR (CD_3CN) δ 5.85 (1H, s, olefinic-H), 4.01-3.94 (1H, m), 3.82-3.71 (3H, m), 3.65-3.63 (1H, m), 3.59-3.51 (1H, m), 3.46-3.40 (3H, m), 3.20-3.09 (3H, m), 2.84-2.74 (2H, m), 2.58-2.49 (2H, m), 2.40-2.30 (4H, m), 2.20-1.92 (5H, m), 1.84-1.77 (1H, m), 1.69-1.58 (1H, m), 1.42 (3H, s, C*H*$_3$); ^{13}C NMR (CD_3CN, DEPT-135) δ 213.2 (C, *C*=O), 202.3 (C, *C*=N), 171.7 (C),

125.2 (CH), 57.8 (CH), 56.5 (CH_2), 56.3 (CH_2), 55.7 (CH_2), 51.6 (C), 48.1 (CH_2), 38.1 (CH_2), 33.8 (CH_2), 32.3 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 23.7 (CH_2), 23.56 (CH_3), 23.52 (2 x CH_2), 23.2 (CH_2); HRMS m/z 315.2436 (M^+), calcd for $C_{20}H_{31}N_2O$ 315.2436.

(*S*,*Z*)-1-((8*R*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*,6*H*,10*H*)-ylidene)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-ium (II): ^{1}H NMR (CD_3CN) δ 5.86 (1H, s, olefinic-H), 4.00-3.99 (1H, m), 3.83-3.64 (3H, m), 3.57-3.43 (3H, m), 3.27-3.10 (2H, m), 2.61-2.35 (6H, m), 2.14-1.89 (11H, m), 1.83-1.81 (2H, m), 1.72-1.55 (4H, m), 1.47-1.29 (2H, m), 1.20 (3H, s, C*H*$_3$), 1.09-0.98 (2H, m), 0.88 (3H, s, C*H*$_3$); ^{13}C NMR (CD_3CN, DEPT-135) δ 224.7 (C, *C*=O), 205.7 (C, *C*=N), 181.8 (C, *C*=CH), 123.0 (CH, C=*C*H), 57.9 (CH), 56.6 (CH_2), 56.3 (CH_2), 55.7 (CH_2), 54.3 (CH), 51.1 (CH), 48.6 (C), 48.2 (CH_2), 40.1 (C), 36.4 (CH_2), 35.3 (CH), 35.3 (CH_2), 33.7 (CH_2), 33.4 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 23.7 (CH_2), 23.5 (2 x CH_2), 22.2 (CH_2), 20.9 (CH_2), 17.5 (CH_3), 14.0 (CH_3); HRMS m/z 423.3375 (M^+), calcd for $C_{28}H_{43}N_2O$ 423.3375.

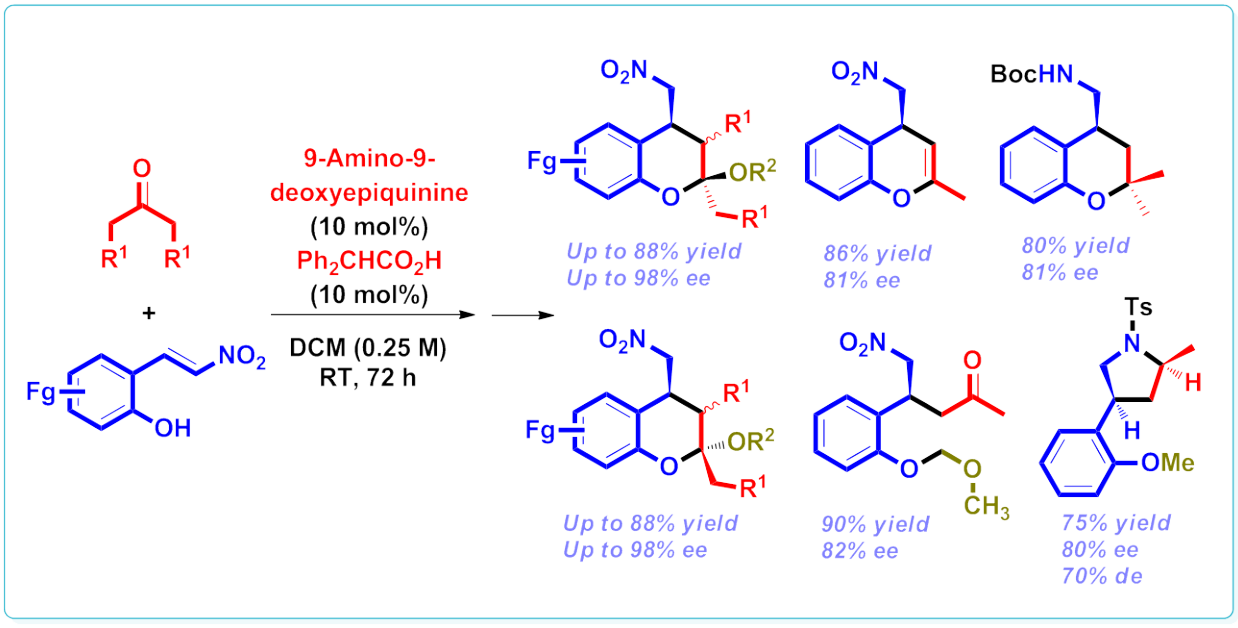
(*S*)-8a-phenyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (150e): Prepared following the procedure **4j** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), *t*R = 23.80 min (minor), *t*R = 25.82 min (major). **$[\alpha]_D^{25}$ = –64.2°** (*c* = 0.3 g/100 mL, $CHCl_3$, **60% *ee***); IR (Neat): ν_{max} 2957, 2926, 1713 (*C*=O), 1676 (*C*=O), 1616, 1493, 1337, 1223, 1030 and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (2H, d, *J* = 7.2 Hz), 7.33 (1H, t, *J* = 6.8 Hz), 7.17 (2H, d, *J* = 7.6 Hz), 6.24 (1H, s, olefinic-H), 2.73-2.69 (1H, m), 2.63-2.59 (1H, m), 2.52-2.48 (3H, m), 2.34-2.23 (3H, m), 2.09-2.01 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (*C*=O), 198.7 (*C*=O), 162.7 (C, HC=*C*), 137.7 (C), 129.5 (CH, H*C*=C), 129.4 (2 x CH), 127.9 (CH), 126.8 (2 x CH), 60.5 (C), 39.0 (CH_2), 33.4 (CH_2), 32.9 (CH_2), 32.7 (CH_2), 23.5 (CH_2); LRMS m/z 241.05 (M + H^+), calcd for $C_{16}H_{16}O_2H$ 241.1150. Anal. calcd for $C_{16}H_{16}O_2$ (240.1150): C, 79.97; H, 6.71. Found: C, 79.65; H, 6.75%.

1. Direct Catalytic Asymmetric Synthesis of Highly Functionalized 2-Methylchroman-2,4-diols via Barbas–List Aldol Reaction.



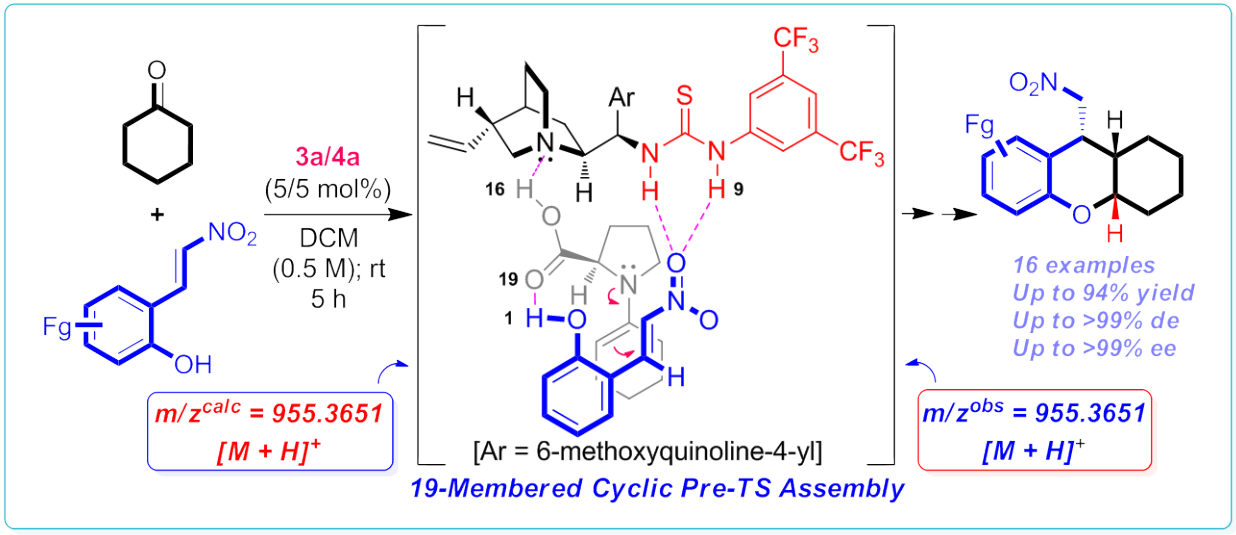
Chem. Eur. J. **2009**, *15*, 4516–4522.

2. Sequential Combination of Michael and Acetalization Reactions: Direct Catalytic Asymmetric Synthesis of Functionalized 4-Nitromethyl-chromans as Drug Intermediates.



Org. Biomol. Chem. **2010**, *8*, 4259–4265.

3. Asymmetric Supramolecular Catalysis: A Bio-inspired Tool for the High Asymmetric Induction in the Enamine Based Michael Reactions.



Chem. Eur. J. **2012**, *18*, 8008–8012.

4. Mimicking Human Steroid 5β-Reductase (AKR1D1) through Organocatalysis: A Facile Route to Stereoselective Synthesis of Chiral 5β-Dihydrosteroids, 5β-Dihydro-Wieland-Miescher Ketones and 5β-Dihydro-Hajos-Parrish Ketones.

Org. Biomol. Chem. **2008**, *6*, 2488–2492.; and full paper *communicated.*

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27. X-ray crystal data of **109aj**: $C_{10}H_{11}NO_5$; MW = 225.06, Triclinic, space group P-1, with a = 6.732(2) Å, b = 7.855(3) Å, c = 10.996(3) Å, α = 79.085°, β = 84.319°, γ = 64.645°. CCDC-710264 contains the supplementary crystallographic data for this crystal structure.
28. X-ray crystal data of **116ahd**: $C_{18}H_{19}O_3Br$; MW = 362.05, Monoclinic, space group P 21/c, with a = 5.7045(9) Å, b = 14.498(2) Å, c = 19.360(3) Å, α = 90°, β = 97.695°, γ = 90°. CCDC-710265 contains the supplementary crystallographic data for this crystal structure.
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37. X-ray crystal data of **129ha**: $C_{13}H_{17}NO_5$; MW = 267.11, Monoclinic, space group P 21/c, with a = 11.2657(18) Å, b = 6.0004(10)Å, c = 19.842(3)Å, α = 90, β = 94.626°, γ = 90. CCDC-765267 contains the supplementary crystallographic data for this crystal structure.
38. X-ray crystal data of **130ia**: $C_{13}H_{17}NO_5$; MW = 267.11, Monoclinic, space group P 21/c, with a = 8.850(3)Å, b = 6.326(2)Å, c = 23.884(9)Å, α = 90, β = 95.201°, γ = 90°. CCDC - 765268 contains the supplementary crystallographic data for this crystal structure.
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