# High-yielding Stereoselective Asymmetric Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions

A Thesis
Submitted for the Degree of

*Doctor of Philosophy*

By

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SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD-500 046, INDIA

December-2014


DEDICATED TO MY BELOVED
NANNA
(PANYALA NARSIMHAREDDY)
AND
MAMAYYA
(MUTHYALA VENKATREDDY)
For All Your Love, Support and Encouragement that
Enabled Me to Achieve My Dreams

# *DECLARATION*

*I hereby declare that the entire work embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the guidance of* ***Prof. D. 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*

*I hereby certify that the entire work embodied in this thesis has been carried out by Mr.* ***Srinivasareddy Panyala*** *under my guidance in the School of Chemistry, University of Hyderabad and that no part of it has been submitted elsewhere for any degree or diploma.*

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

***Dean***
***School of Chemistry***
***University of Hyderabad***

# *CONTENTS*

# ACKNOWLEDGEMENTS

*I am greatly indebted to **Prof. D. B. Ramachary**, my research supervisor, for his inspiring guidance and constant encouragement throughout the course of the present investigations. It has been a great privilege and honor to be associated with him.*

*I thank present and former Dean of School of Chemistry, Prof. M. Durga Prasad, Prof. D. Basavaiah and Prof M. Periasamy and all the faculty members of the School of Chemistry for their timely help and cooperation during my Ph. D. program.*

*It is great privilege to express my heartfelt regards to all my teachers during the entire tenure of my educational carrier.*

*It gives me great pleasure to thank all my labmates, especially Dr. Ramakumar, Dr. Kishore, Dr. Narayana, Dr. Rumpa Mondal, Dr. Vijay, Dr. Sakthidevi, Dr. Venkaiah, Dr. Shiva Prasad, Shashank, Madhavachary, Murali, Shruthi, Karthik, Prabhakar reddy Shashi kumar and Surendranath reddy for their friendly cooperation in the lab.*

*I am so thankful to Dr. Swamy, Sathish, Ramavath and Krishna for their help in crystal solving. Dr. Ramesh Reddy, Dr. Phanipavan, Dr. M. Ramu, Dr. Ramasuresh, Dr. S. Sateesh, Dr. T. K. Chaitanya, Dr. Anji, Dr. Sekhar Reddy, Dr. Nagaraju, Dr. Nagarjuna reddy, Dr. Ashoka vardhan reddy, Dr. Guru Brahmam, Dr. RamuYadav, Dr.Nayanghosh, Dr.Thirupathireddy, Dr. Naveen, Dr. Srinu and Dr. vijji for their help in throughout the course.*

*I am very thankful to all friends in School of Chemistry, Dr. Aravindu, Dr. D. K. Dr. Satpal Singh, Dr. Arindham, Dr. Sivaranjan, Dr. Arunbabu, Dr. Nagaraju, Dr. Swamy, Dr. Mallesh, Dr. Laxman, Dr. Sanjeev, Dr. Venu, Dr. Ramesh, Dr. Nagarjuna, Dr. Satish, Dr. Rambabu, Dr. G. Durgaprasad, Dr. Bharat, Dr. Kishore, Dr. Naba, Dr. Ravikumar, Dr. Ramesh, Rajesh, Dr. Gupta, Dr. Hari, Dr. Venu, Dr. Seshadri, Dr. Suresh, Dr. Sekhar Reddy, Dr. Kishore, Dr. Anand, Dr. K. Srinivas, Dr. Ganesh, Dr. Ravindrababu, Dr. Vanaja, Dr. Naveen, Veeraraghavaiah, Dr. Mallikarjuna, Dr. Lenin Babu, Praveen, Dr. Aneesh, Dr. Karunakar, Dr. Srinu, and Nandakishore, Ashok, , Uday, chandresekharreddy, Lings, Allu Srinu, Sudheer, Sivaramakrishna, Chandrasekar, Ramavath babu, Ramana. I am very thankful to all friends in HCU, Narendharreddy, Srinivasareddy, Venky, Anji, Paramesh, Sunkanna, Shyam, Suseel and Sai for making me to attract into politics.*

*I am thankful to my M. Sc. classmates Madhu, Arun, Madhusudhanreddy, Chtyala madhu, Ashok, Prabhakar, Lavanya, Dhinesh, Vinod, Swamy, Subhadeep, Shamimuel, Sravani, Jharna, Nagalaxmi, Balija srinu, Janardhan, Singuru Ramakrishna, Vamshi, Thirupathi, Amarendhar, Visveswar, Appa rao, Ramu. Bharath, Lavanya, Sai, Laxminarasimha, Vinod, Naveen and Rajendra for their heartily support throughout my M. Sc. Carrier.*

*I am thankful to my well-wishers and friends particularly, Dr. Mahendhareddy, Janardhanreddy, Vijayendhareddy, Nagaraju, Praveen, Mallareddy, Haribabu, Santhosh-Vasavi, Naresh, Sai, Sampathreddy, Srinivas, Mahi, Srinivasreddy, Kanakayya, Ravi, Prasad, Sathish and my Siddipet friends for their heartily support throughout my carrier.*

*I acknowledge the help and support provided by the technical and non-teaching staff of the School of Chemistry. I also thank Dr. P. Raghavaiah, Satyanarayana, M. Shetty, Bhaskara Rao, Venkataramana, Asia Perwej, Vijaya Laxmi, A. R. Setty, Jayaram, Prasad and Durgesh for their timely help.*

*National Single Crystal X-ray Facility, funded by DST (New Delhi) in School of Chemistry is highly acknowledged. I am thankful to IGM library for providing excellent books and journals. Financial assistance by UGC (New Delhi) is gratefully acknowledged.*

*I am thankful to my family members Late. Sathya reddy, Late. Ramavva, Narayanareddy, Gopavva, Prabhakarreddy, Padma, Pranay, Pallavi, Kavitha, Sathyanarayanareddy, Vishnavi, Jhahnavi, Lavanya, Chandrareddy, Sujana, Praneeth, Chandrareddy, Sathavva, Krishna, Madavi, Akshitha, , Suresh, Soujanya, Junior Suresh, Rajitha, Raju, Nandini, Viswas, Sarala, Anil, Akhil, Rajireddy, Manavva, Jaanaki, Laxmareddy, Swaroopa, Sridhar, Maanasa, Sripal, Navatha, Lingareddy, Sujatha, Gopi, Sravanthi, Nagarani, Vignan, Nihal, Sathish, Dharmareddy, Shankareddy, Late. Lingareddy, Rajavva, Sathyavathi, Laxmareddy, Vedavathi, Priya, Srimathi, Mallareddy, Mounika, Saikrishnareddy, Aruna, Rajireddy, Vijayendharreddy, Pranitha, Vishnuvardhan reddy, Varshini, Neelima, Jithendharreddy, Harshitha for their heartily support throughout in my carrier.*

*I am thankful to my family members Late Narayana reddy, Late. Vajramma, Bhucchamma, Swapna, Narayanareddy, Santhosh, Srinivasreddy, Dayakar reddy, Adulla Pochireddy, Late. Satthvaa, Sulochana, Ramreddy, Thirupathireddy, Kavitha, Sai, Vamshi, Mallareddy, Sudha, Abhi, junior ramreddy, Vasantha, Srinivasareddy, Suma, Thirupathireddy, Junior thirupathireddy, Sama, Hema, Rajireddy, Atthamma, Naveen, Nandini, Saireddy, Jemuna, Prathap reddy, Swapna, Srinivasreddy, Saritha, Chennareddy, Sandhya, Thara, Rajireddy, Laddu, Rani, Mahendhar reddy, Shantha, Padma reddy, Harshavardhan, Chinna for their heartily support from childwood days onwards.*

*Most importantly, none of this would have been possible without the love and patience of my family. My great-grand father, who offered his encouragement in my childwood days and gave me a wonderful life. With his own brand of humor and dare Panyala Gopal Reddy has been kind and supportive to me. I am also grateful to my sisters and their family Kavitha, Narsimhareddy, Manoj, Saikethan and Madavi, Srinivasareddy, Thrivarna reddy, Ammulu for their help in throughout the career. I am also grateful to my uncle Muthyala Venkat reddy and aunt Vijaya for helping me tremendously during hectic days of my career. I thank my lovely junior Gopal Reddy, for his sweet smile and understanding. Above all I would like to thank Sindhupriya for her love, constant support for all the peaks and valleys. Thank you for being my muse, editor, proofreader and sounding board. But most of all, thank you for being my best friend. I owe you everything.*

*Last but not the least, I would like to thank my parents it would be an understatement to say that, as a family, we have experienced some ups and downs in the past fifteen years. Every time I was ready to quit, you did not let me and I am forever grateful. This dissertation stands as a testament to your unconditional love and encouragement. My immediate family, to whom this dissertation is dedicated to, has been a constant source of love, concern, support and strength all these years. I would like to express my heart-felt gratitude to my family. My extended family has aided and encouraged me throughout this endeavor.*

*Srinivasareddy Panyala*

# *PREFACE*

*Nature is the inspiration to develop a new area of catalysis like "organocatalysis" to synthesize stereochemically complex chiral molecules with high selectivity. Over the last decade chemists have adopted fundamental principles of biosynthesis like organocatalyzed cascade reactions for the synthesis of bioactive molecules. Organocatalyzed multi-component cascade (MCC) reactions to deliver highly functionalized molecules are the objective of the present scenario. The thesis entitled "High-yielding Stereoselective Asymmetric Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions" by Mr. Srinivasa Reddy Panyala describes MCC reactions for the synthesis of highly functionalized chiral molecules of pharmaceutical and biological importance based on the organocatalyzed reductive coupling (OrgRC), asymmetric Michael and aldol reactions platform. The present thesis entitled "**High-yielding Stereoselective Asymmetric Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions**" describes the further applications of Hantzsch ester in cascade reactions and its pharmaceutical applications as well as mechanistic insights. 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.*

*To begin with, we have developed a metal-free simple one-pot cascade synthesis of highly substituted 2-alkyl-CH-acids and chiral Wieland-Mischer ketone (WMK) analogues from simple starting materials via organocatalyzed reductive coupling (OrgRC) and Robinson annulation (R-A) reactions under amino acid catalysis. We have reported the OrgRC of highly reactive CH acids (tetronic acid, cyclohexane-1,3-dione, cyclopentane-1,3-dione and dimedone) with phthalamidoacetaldehyde and Hantzsch ester without bis-product formation under amino acid catalysis. This OrgRC reaction delivers the corresponding product in good yields with high chemo- and regioselectivity using only 10 mol% of amino acid as the catalyst. Furthermore, we have demonstrated the application of OrgRC products into WMK analogues and GABA analogues which are pharmaceutically useful molecules and synthons for many natural products. We*

*demonstrated the two-carbon homologation of aldehyde via OrgRC and decarboxylation reactions with high yields of GABA analogues which are important pharmaceuticals. Presently developed combination of cascade OrgRC and R-A reactions will be suitable to synthesize library of herbicides, the total synthesis of biologically important natural products and their analogues. These reactions can be performed on a multi-gram scale under operationally simple and environmentally safe conditions.*

*In continuation to the development of OrgRC reactions for the synthesis of highly substituted chiral building blocks (chiral 2-alkyl-CH-acids), we have developed the high-yielding alkylation of variety of CH-acids with chiral aldehydes like (R)-glyceraldehyde acetonide/(S)-Garner aldehyde and Hantzsch ester through amino acid-catalyzed OrgRC reactions without racemization at α-position to carbonyl. We have developed the L-proline catalyzed diastereoselective Michael and aldol reaction of OrgRC products with alkyl vinyl ketone at the ambient conditions. The diastereoselective aldol reaction proceeds in good yields with high diastereoselectivity using L-proline as the catalyst through dynamic kinetic resolution (DKR). Furthermore, we have demonstrated the mechanism of Michael, aldol and retro-Michael reaction. We have isolated two intermediates, which are giving a strong support to our proposed mechanism.*

*In continuation to the development of OrgRC reactions, we explored the synthesis of highly functionalized 2-alkyl-CH-acids which are having a broad application scope. Herein, we have successfully utilized the OrgRC products in the domino Michael and intramolecular aldol reaction with good yields, enantio- and diastereostereoselectivities. We have found that bridged bicyclic skeletons containing highly functional groups can be constructed in diastereoselective and enantioselective fashion using asymmetric Michael-aldol (M-A) reaction of 2-alkyl CH-acids, α, β-unsaturated ketones and organocatalyst. This novel asymmetric M-A reaction proceeds in good yield with high enantioselectivity and diasterioselectivity, producing the bridged bicylic compounds with two quaternary and three chiral centers derived in one-pot. Furthermore, we demonstrated the application of chiral M-A product in the synthesis of highly functionalized cyclohexanone.*

*In continuation to the synthesis of bioactive molecules through asymmetric organocatalytic Michael, aldol reactions platform, we demonstrated the utilization of neighboring ortho-hydroxy group participation in the pre-transition state of enamine- and iminium-based triple domino reactions for high reactions rates and asymmetric*

*induction. Enantiomerically pure, drug-like chromanes and tetrahydro-6H-benzo[c]-chromenes having three to four contiguous stereocenters are synthesized through triple domino Michael/aldol/oxa-Michael reactions catalyzed by (R)-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine followed by Wittig and Michael/Wittig–Horner reactions from simple precursors under mild conditions.*

# *LIST OF ABBREVIATIONS*

| | |
|---|---|
| Ac | acetyl |
| ACE | angiotensin converting enzyme |
| AcOH | acetic acid |
| $Ac_2O$ | acetic anhydride |
| Anal. | analysis |
| aq. | aqueous |
| Ar | aryl |
| Bn | benzyl |
| Boc | butyloxy carbonyl |
| Bp | boiling point |
| br | broad |
| Bu | butyl |
| *t*Bu or $^t$Bu | *tertiar*y-butyl |
| *n*-BuLi | *n*-butyl lithium |
| calcd. | calculated |
| cat. | Catalytic |
| Cbz | Benzyloxy carbamate |
| cm | centimeter |
| CPD | 1,3-cyclopenatanedione |
| dABq | doublet of AB quartet |
| 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 |
| DFT | density functional theory |
| DIBAL-H | Diisobutylaluminium hydride |
| DMAP | dimethylaminopyridine |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| 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 |
| HIV | human immunodeficiency virus |
| HMPT | hexamethylphosphorous triamide |
| HPLC | high-performance liquid chromatography |
| H-P ketone | Hajos-Parrish ketone |
| $^i$Pr | isopropyl |
| IR | infrared |
| lit. | literature |
| liq | liquid |
| LN | Lithium naphthalenide |

| | |
|---|---|
| m | multiplet |
| M-A | Michael-Aldol |
| *m*-CPBA | *m*-chloro perbenzoic acid |
| M | molarity |
| Mp. | melting point |
| Me | methyl |
| mg | milligram (s) |
| mL | milliliter |
| mmol | millimole |
| MVK | methyl vinyl ketone |
| NMR | nuclear magnetic resonance |
| NMP | *N*-methylpyrrolidine |
| 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 |
| RA | Robinson Annulation |
| s | singlet |
| sec | secondary |
| t | triplet |
| TBS | *tert*-Butyldimethylsilyl |
| TBDPS | *tert*-Butyldiphenylsilyl |
| td | triplet of doublet |
| tert | tertiary |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| TsCl | toluenesulphonyl chloride |
| UV | ultraviolate |
| W-M ketone | Wieland-Miescher ketone |
| H-P ketone | Hajos-Parrish ketone |
| TCA | trichloro aceticacid |
| GABA | gamma amino butyric acid |
| OrgRC | organocatalyzed reductive coupling |

# *High-yielding Stereoselective Asymmetric Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions*

## 1. ABSTRACT

To begin with, in the first chapter, we have developed a metal-free simple one-pot cascade synthesis of highly substituted 2-alkyl-CH-acids and chiral Wieland-Mischer ketone (WMK) analogues from simple starting materials *via* organocatalyzed reductive coupling (OrgRC) and Robinson annulation (R-A) reactions under amino acid catalysis. We have reported the OrgRC of highly reactive CH acids (tetronic acid, cyclohexane-1,3-dione, cyclopentane-1,3-dione and dimedone) with phthalamidoacetaldehyde and Hantzsch ester without *bis*-product formation under amino acid catalysis. This OrgRC reaction delivers the corresponding product in good yields with high chemo- and regio-selectivity using only 10 mol% of amino acid as the catalyst. Furthermore, we have demonstrated the application of OrgRC products into WMK analogues and GABA analogues which are pharmaceutically useful molecules and synthons for many natural products. We demonstrated the two-carbon homologation of aldehyde *via* OrgRC and decarboxylation reactions with high yields of GABA analogues which are important pharmaceuticals. Presently developed combination of cascade OrgRC and R-A reactions will be suitable to synthesize library of herbicides, the total synthesis of biologically important natural products and their analogues. These reactions can be performed on a multi-gram scale under operationally simple and environmentally safe conditions.

In continuation to the development of OrgRC reactions for the synthesis of highly substituted chiral building blocks (chiral 2-alkyl-CH-acids), in second chapter, we have developed the high-yielding alkylation of variety of CH-acids with chiral aldehydes like (*R*)-glyceraldehyde acetonide/(*S*)-Garner aldehyde and Hantzsch ester through amino acid-catalyzed OrgRC reactions without racemization at α-position to carbonyl. We have developed the L-proline catalyzed diastereoselective Michael and aldol reaction of OrgRC products with alkyl vinyl ketone at the ambient conditions. The asymmetric aldol reaction proceeds in good yields with high diastereoselectivity using L-proline as the catalyst through dynamic kinetic resolution (DKR). Furthermore, we have demonstrated the mechanism of Michael, aldol and *retro*-Michael reaction. We have isolated two

intermediates, which are giving a strong support to our proposed mechanism. For the first time we showed the DKR with the proof of intermediate.

In continuation to the development of OrgRC reactions, in the third chapter, we explored the synthesis of highly functionalized 2-alkyl CH-acids which are having a broad application scope. Herein, we have successfully utilized the OrgRC products in the domino Michael and intramolecular aldol reaction with good yields, enantio- and diastereostereoselectivities. We have found that bridged bicyclic skeletons containing highly functional groups can be constructed in diastereoselective and enantioselective fashion using asymmetric Michael-aldol (M-A) reaction of 2-alkyl CH-acids, α, β-unsaturated ketones and organocatalyst. This novel asymmetric M-A reaction proceeds in good yield with high enantioselectivity and diasterioselectivity, producing the bridged bicylic compounds with two quaternary and three chiral centers derived in one pot. Furthermore, we demonstrated the application of chiral M-A product in the synthesis of highly functionalized cyclohexanone.

In continuation to the synthesis of bioactive molecules through asymmetric organocatalytic Michael, aldol reactions platform, in the fourth chapter, we demonstrated the utilization of neighboring *ortho*-hydroxy group participation in the pre-transition state of enamine- and iminium-based triple domino reactions for high reactions rates and asymmetric induction. Enantiomerically pure, drug-like chromanes and tetrahydro-6*H*-benzo[*c*]-chromenes having three to four contiguous stereocenters are synthesized through triple domino Michael/aldol/oxa-Michael reactions catalyzed by (*R*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine followed by Wittig and Michael/Wittig–Horner reactions from simple precursors under mild conditions.[1]

## 2. INTRODUCTION

The development of the science and technology and new trends of catalysis has opened up new vistas for the swift and careful production of required chemical molecules. In order to achieve this development, it is necessary to develop a number of innovative materials and to evolve ways and means for their rapid and cheap production in large quantities. Nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) are central metabolic cofactors mediating an impressive variety of redox processes in living organisms and as such regulates a wealth of metabolic transformations. Hydrogenation is the reductive removal of the double bond

functional group and it has long been the preserve of the transition metal catalyst. Finely divided metals, such as palladium, platinum and nickel are among the most widely used hydrogenation catalysts. In general, olefinic hydrogenations often involve the use of high pressure hydrogen gas with expensive and even toxic organometallic catalysts or stoichiometric amounts of metal hydrides. To overcome these drawbacks, one of the best alternatives is to apply organoreductants that possess excellent reproducibility and environmental safety. Inspired by the nature, as reduction reactions are routine in biological processes, catalysed by enzymes, chemists have recently begun to develop synthetic dihydropyridine NADH analogues as the hydride source with impressive results. The first synthesis of dihydropyridines was reported by Arthur Rudolf Hantzsch in 1881 and involved the condensation between an aldehyde, ammonia and two molecules of *β*-ketoester in one pot.[2a] Hantzsch syntheses of dihydropyridines and common Hantzsch ester **1a** crystallizes in yellow needles with green fluorescence, mp 183–185 °C and is commercially available [$C_{13}H_{19}NO_4$, CAS: 1149-23-1]. Hantzsch ester **1a** can also be easily prepared from a combination of paraformaldehyde, ethyl acetoacetate and ammonium acetate under mild and solvent-free conditions with good yield within 3-4 h.[2b] Hantzsch ester **1a** also known as Ethidine, is a well-known organoreductant that has found many applications in organic transformations. In recent years, Hantzsch esters **1a** and their related organic hydride donors have been widely utilized by synthetic chemists in bio mimetic reduction of olefins,[3] carbonyl compounds[4] and imine functionalities[5] by transfer hydrogenation reaction with high yields. Along with the conjugate hydride and proton transfer, Hantzsch ester **1a** is usually subsequently oxidized to the Hantzsch pyridine.

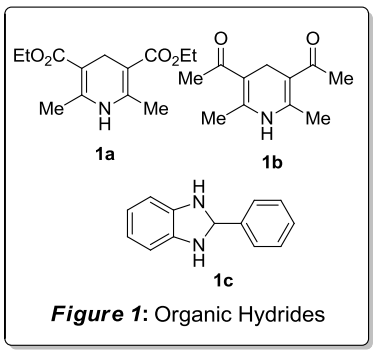



***Figure 1***: Organic Hydrides

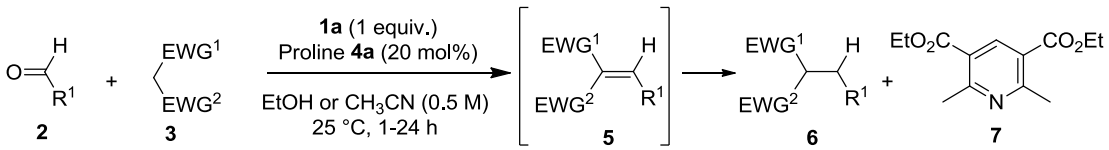
In addition, dihydropyridine-mediated reductions can be easily implemented in asymmetric or normal cascade processes using one or more catalysts by which there are many possibilities to develop cascade reaction as well as multi component catalysis (*MCC*) reaction is also possible.[6] The versatility of these catalytic protocols has been demonstrated by their application to the synthesis of a variety of biologically active compounds by decreasing number of steps. 1, 4-Dihydropyridines (symmetric or asymmetric) find many important applications in

medicinal chemistry like calcium channel blockers and their biological activity has been thoroughly studied over the last decades.[7]

Numerous reducing agents were developed such as Na-$(OAc)_3BH$,[8] $NaBH_3CN$,[9] the borane−amine complex,[9] triethylammonium formate,[11] hydrogen, 2-phenylimidazoline,[12] 2-phenylthiazoline,[13] diethyl amine/Pd/C-$H_2$[14] and the Hantzsch ester[15] for the reduction of Knoevenagel products. While several of these reducing agents Hantzsch ester **1a**, **1b, 1c** are the best protocols over the all in terms of yield, time, number of steps, reaction conditions and substrate scope. Additionally, the borane−amine complex posed safety, cost and sourcing issues.

The C=C reduction of activated olefin compounds is a useful but challenging transformation. Because both 1,2- and 1,4-reductions willingly occur, low selectivity for either of the two pathways is common and functional groups that are sensitive to hydrogenation conditions such as the ester, nitro, other olefins, alkynes, some protecting groups and nitrile groups are usually not tolerated. Clearly mild, catalytic, one-pot, chemoselective and green variants of this reaction are highly advantageous. Such a process would comprise an one-pot metal-free green hydrogenation similar to bio-transformations. We reasoned that the amino acid catalysis strategy might be applicable to the *in-situ* generation and conjugate reduction of chemically activated olefin compounds if a suitable hydride donor could be identified. Such a process would comprise an onepot metal-free green hydrogenation similar to bio-transformations.

In 2006, we found that the amino acid, proline **4a** readily catalyzes the Knoevenagel condensation of aliphatic or aromatic aldehyde **2** with active methylene **3** to furnish the active olefin **5**, which on *in-situ* treatment with Hantzsch ester **1a** produces the transfer hydrogenated product **6** with very good yield after 1-24 h in EtOH or $CH_3CN$ at 25 °C as shown in eq.1.[151]

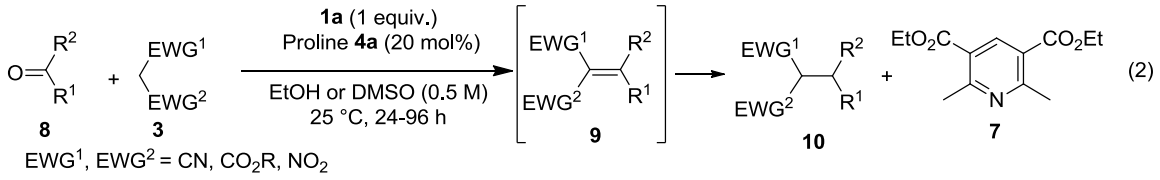



(1)

$EWG^1$, $EWG^2$ = CN, $CO_2R$, $NO_2$

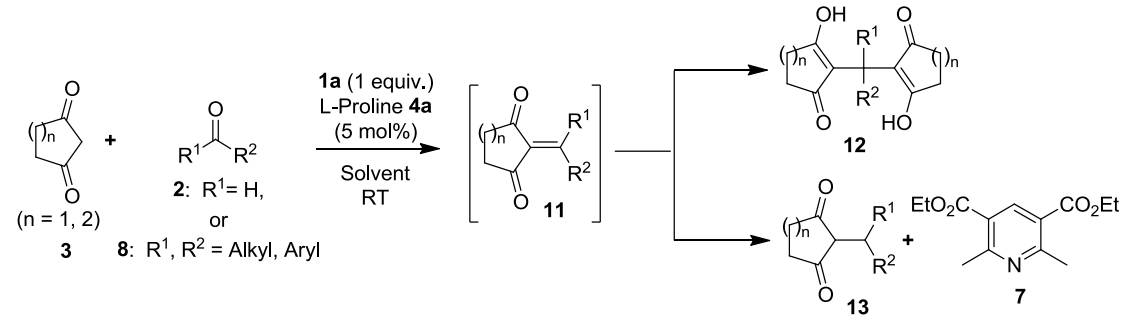
In the same year we discovered that the amino acid proline **4a** readily catalyzes the Knoevenagel condensation of cyclic and acyclic ketones **8** with the active methylenes **3** to furnish the active olefin **9**, which on *in-situ* treatment with Hantzsch ester **1a**

produces the transfer hydrogenated or OrgRC product **10** with very good yield after 24-96 h in EtOH or DMSO at 25 °C as shown in eq.2.[15k]




(2)

The reduction of C=C of activated olefins from cyclic active methylene compounds is a highly useful but challenging transformation. Because metal mediated C-alkylation of cyclic CH-acids by using bases like sodium hydride is also did not give more than 20-30% yields in the literature and instead of C-alkylation, O-alkylation product or double alkylated product has formed with alkyl halides. Surprisingly, there is no direct method for the synthesis of useful 2-alkyl-cycloalkane-1,3-diones **13** and only two-step methods are known to prepare them.[16, 17] Paquette *et al.* developed the two-step synthesis of 2-alkyl-cycloalkane-1,3-diones **13** in moderate to good yields *via* an *in-situ* trapping and desulfurization sequence on 2-alkylidene-1,3-diones **11** with thiophenol and raney nickel, respectively.[16] As shown in Scheme 1, the well-recognized fact is the inability to arrest olefination reactions involving CH acids **3** (cycloalkane-1,3-diones) and aliphatic, aromatic aldehydes **2** and ketones **8** at the monoaddition stage.[18, 19] Very few Knovengal products have been isolated with very poor yield.[18, 20, 21] This is because the olefination products **11** are highly reactive Michael acceptors capable of engaging the reactant CH acid in kinetically rapid 1,4-addition to give *bis*-adducts such as **12**. To overcome these draw back more reactive Michael donor (hydride donor) should be readily available. Nucleophilicity of Hantzsch ester (Hydride donor ability) is more compared to nucleophilicity of CH-acids.




***Scheme 1***: Reductive *C*-Alkylation of Active Methylenes through an OrgRC Reaction.

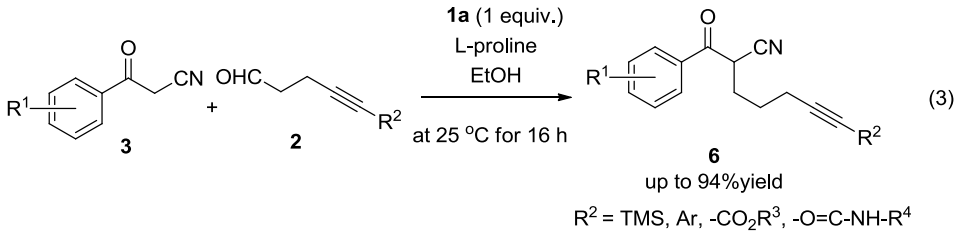
In 2007, we found that the amino acid proline **4a** readily catalyzes the Knoevenagel condensation of aliphatic or aromatic aldehyde **2** and cyclic or acyclic ketones **8** with the cyclic CH acid **3** to furnish the active olefin **11**, which on *in-situ* treatment with highly reactive hydride donor Hantzsch ester **1a** produces the OrgRC product **13** with very good yield as shown in Scheme 1.[15]

As the research work described in this thesis deals with the amino acid-catalyzed biomimetic hydrogenations, a brief overview on proline-catalyzed hydrogenations using Hantzsch ester and analogues as hydrogen source are presented below.

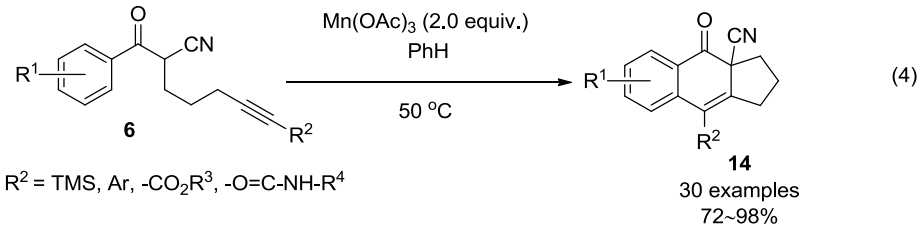
Over the past few years there have been significant developments in this area.[8, 15, 22-34] An overview of organocatalyzed transfer hydrogenations using OrgRC reaction, highlighting their applications in the synthesis of biologically relevant molecules, new synthetic methodologies, total synthesis of natural products and medicinal compounds are presented below.

## *2.1. Applications in New Methodology Development*

In 2014, Kak-Shan Shia *et al.*[22] have developed a convenient and general approach for cyclopenta[*b*]naphthalene **14** derivatives containing a structurally diverse functionality at C-4 position by using Manganese (III) acetate, which plays a key role to facilitate the tandem 5-*exo*-dig and 6-*exo*/*endo* cyclization in an efficient manner from designed substrates **6**. Various functional groups like trimethyl silyl, aryl, ester, ketone, secondary/tertiary amide, phosphonate and halogen capped on the terminal acetylenic unit are well accepted under optimal reaction conditions. It is highly feasible that this novel [6.6.5] framework formation procedure may have wide synthetic utility in light of its operational simplicity and high yields. For this reaction $\alpha$-cyano $\alpha$-TMS/aryl-capped alkynyl aryl ketones were easily prepared using our OrgRC strategy as a basic reaction in good yields with high substrate scope (eq. 3).

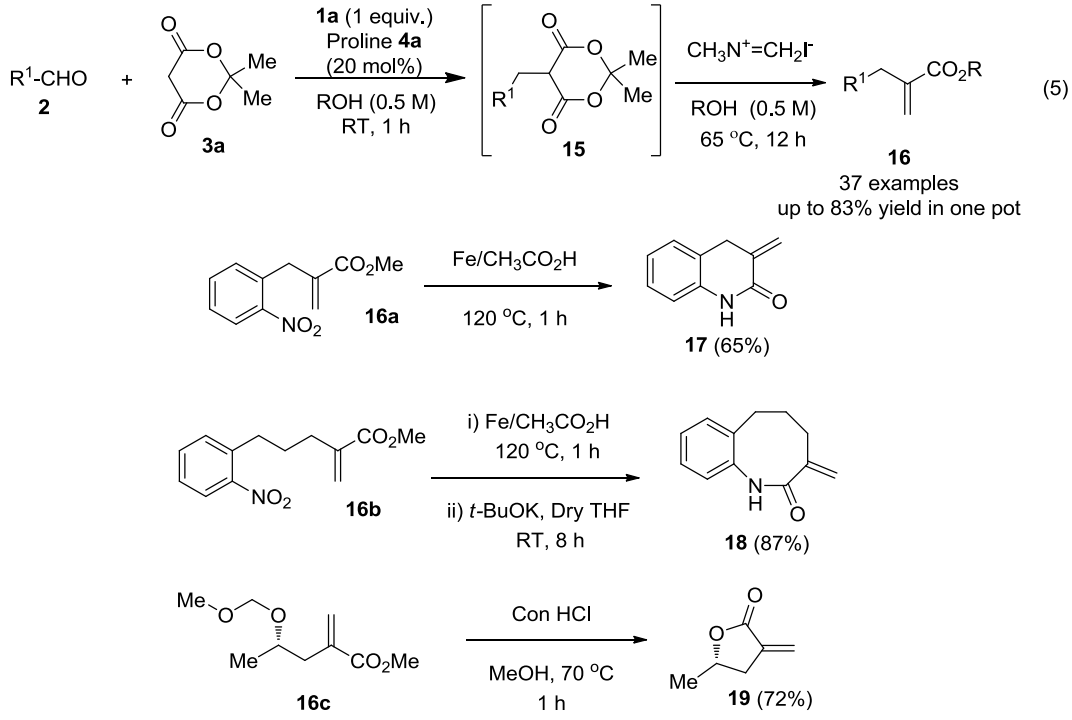



(3)




(4)

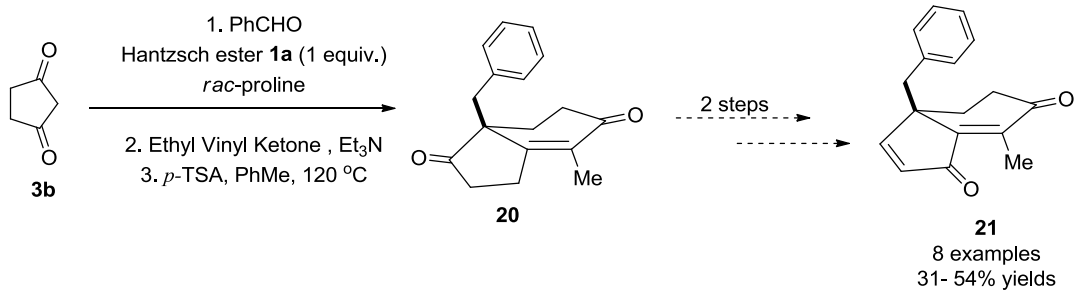
In 2014, our group[15m] developed OrgRC reaction of Meldrum's acid **3a**, aldehydes (chiral and achiral) and Hantzsch ester catalyzed by L-proline, followed by methylenation with Eschenmoser's salt in getting chiral and achiral $\alpha$-substituted acrylates in an alcoholic media in one pot with 50-80% yields (eq. 5). Further chiral/achiral $\alpha$-substituted acrylates converted to very good intermediates, for the pharmaceuticals and natural products synthesis.




(5)

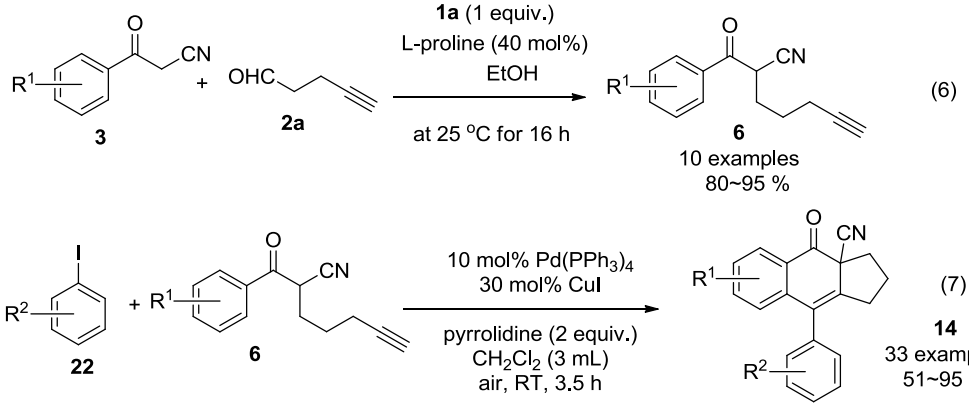
In 2014, De Paolis *et al.*[23] reported a metal-free procedure for the aerobic and complete C–H methylene oxidation of Hajos–Parrish enones to versatile dihydroindenediones and further they converted to highly substituted indanes after an intramolecular Friedel–Craft's conjugate addition. Aerobic oxidation reaction of the dienolate of Hajos–Parrish's enones, proceeds with medium efficiency (31–54%) but remains useful in the view of multiple transformations, including deprotonation, oxygenation, rearrangement and elimination are taking place in a single step (Scheme 2). The process led to the complete oxidation of the C–H ethylene and is compatible with substrates sensitive to radicals. Further synthetic transformations of the oxidised products

include their conversion into indanes displaying a highly substituted carbon network. A variety of Hajos-Parrish Ketones (HPK) **20** prepared by our lab by using OrgRC reaction and R-A reaction with very good yields.[15f] Further HPKs were used to synthesize substituted indanes by this method.



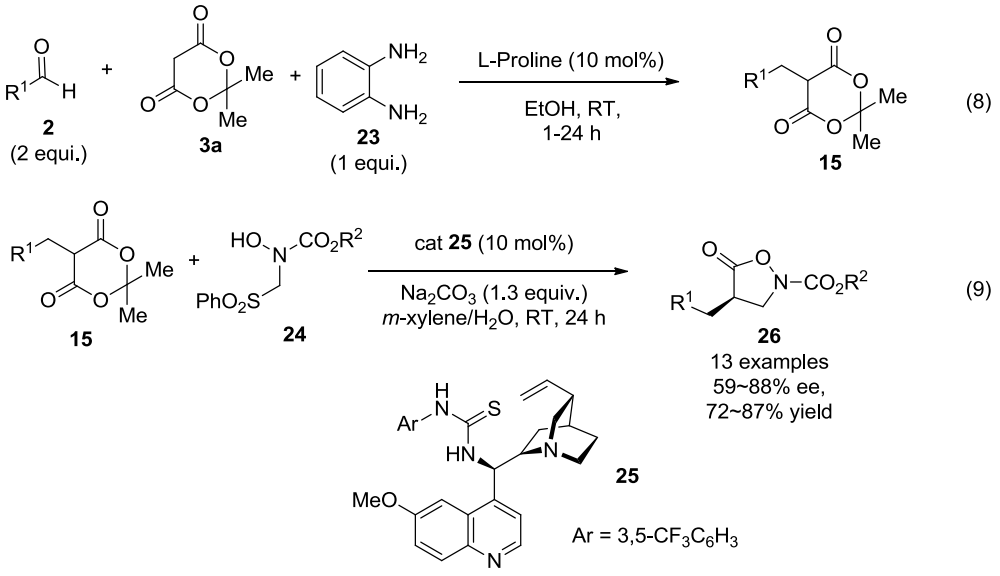

***Scheme 2***: Conversion of OrgRC Products to Indanes by De Paolis *et al.* Group.

In 2013, Kak-Shan Shia *et al.*[24] developed a novel and general approach to achieve a facile access to benzo[*b*]fluorene and cyclopenta[*b*]naphthalene derivatives *via* sequential Pd(0)/Cu(I)-catalyzed radical cyclization of the aryl 1-cyanoalk-5-ynyl ketone systems **6** in a very good manner (eq. 7). Aryl 1-cyanoalk-5-ynyl ketones **6** are prepared easily using our OrgRC strategy with more than 90% yields (eq. 6). Copper (I)-catalyzed aerobic oxidation is the key step in this tandem reactions, which allows for activation of two successive intramolecular cycloadditions immediately after the Sonogashira coupling reaction has occurred.

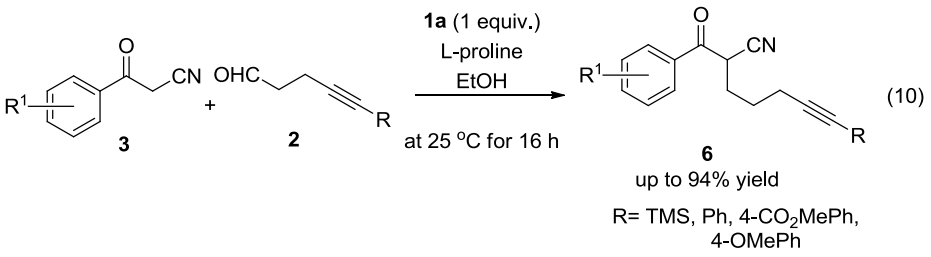


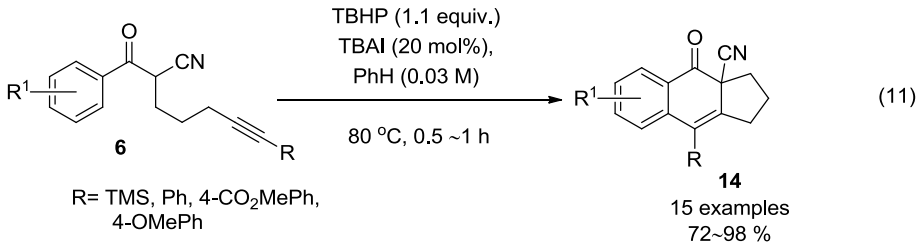

In 2013, Jean-Francois Briere *et al.*[25] reported an asymmetric organocatalysed decarboxylative protonation reaction allowing a straightforward synthesis of *α*-substituted isoxazolidin- 5-ones **26** from readily available 5-substituted Meldrum's acids (eq. 9). This 5-substituted Meldrum's acids **15** are prepared easily through our OrgRC reaction starting from Meldrum's acid with more than 90% yield (eq. 8) by using *in-situ* generated organic hydride **1c**. This reaction is initiated by an anionic formal (3+2)

cycloaddition– fragmentation, generated *in-situ* from a sulfone-amide **24** precursor which also served as an original latent source of hydrogen. Then, they explored the scope of this asymmetric protonation reaction with 10% of 9-*epi*-QDU catalyst **25**/$Na_2CO_3$ in order to give various $\alpha$-substituted isoxazoldin-5-ones **26** with high ennantioselectivity and high yields. This substituted isoxazolidin-5-ones further converted into $\beta^2$-amino acid precursors by a ring opening hydrogenolysis reaction, with high enantioselectivity.



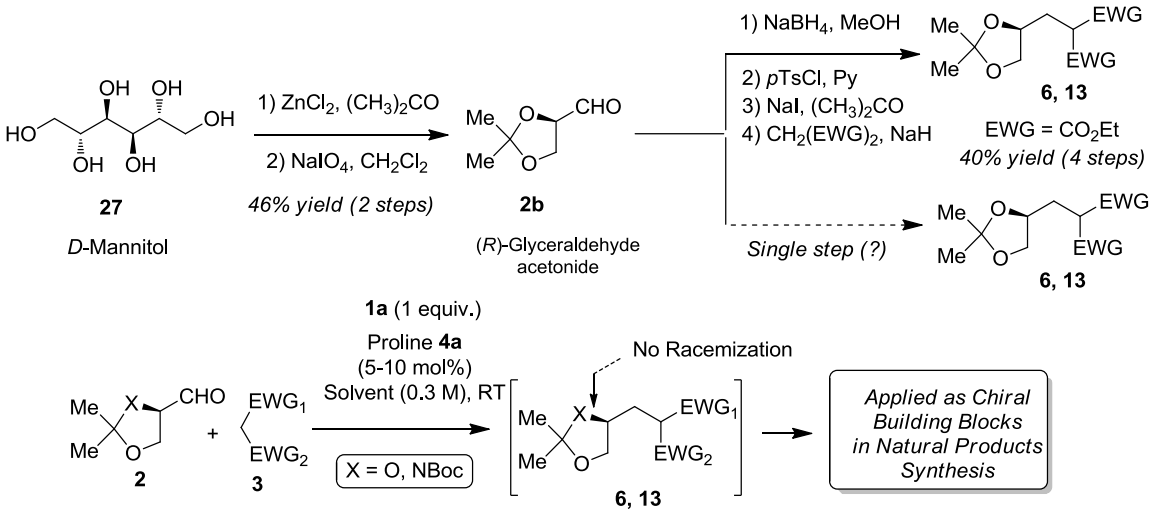

In 2012, Kak-Shan Shia *et al.*[26] developed an intramolecular radical cascade protocol of the $\alpha$-cyano $\alpha$-TMS/aryl-capped alkynyl aryl ketones **6** promoted by *tert*-butyl hydroperoxide (TBHP) as oxidant under catalysis with tetrabutylammonium iodide (TBAI) in refluxing benzene for 1 h, leading to the construction of a variety of highly functionalized [6,6,5] tricyclic frameworks **14** with excellent yields (eq. 11). This $\alpha$-cyano $\alpha$-TMS/aryl-capped alkynyl aryl ketones were easily prepared using our OrgRC strategy in good yields with high substrate scope (eq. 10).

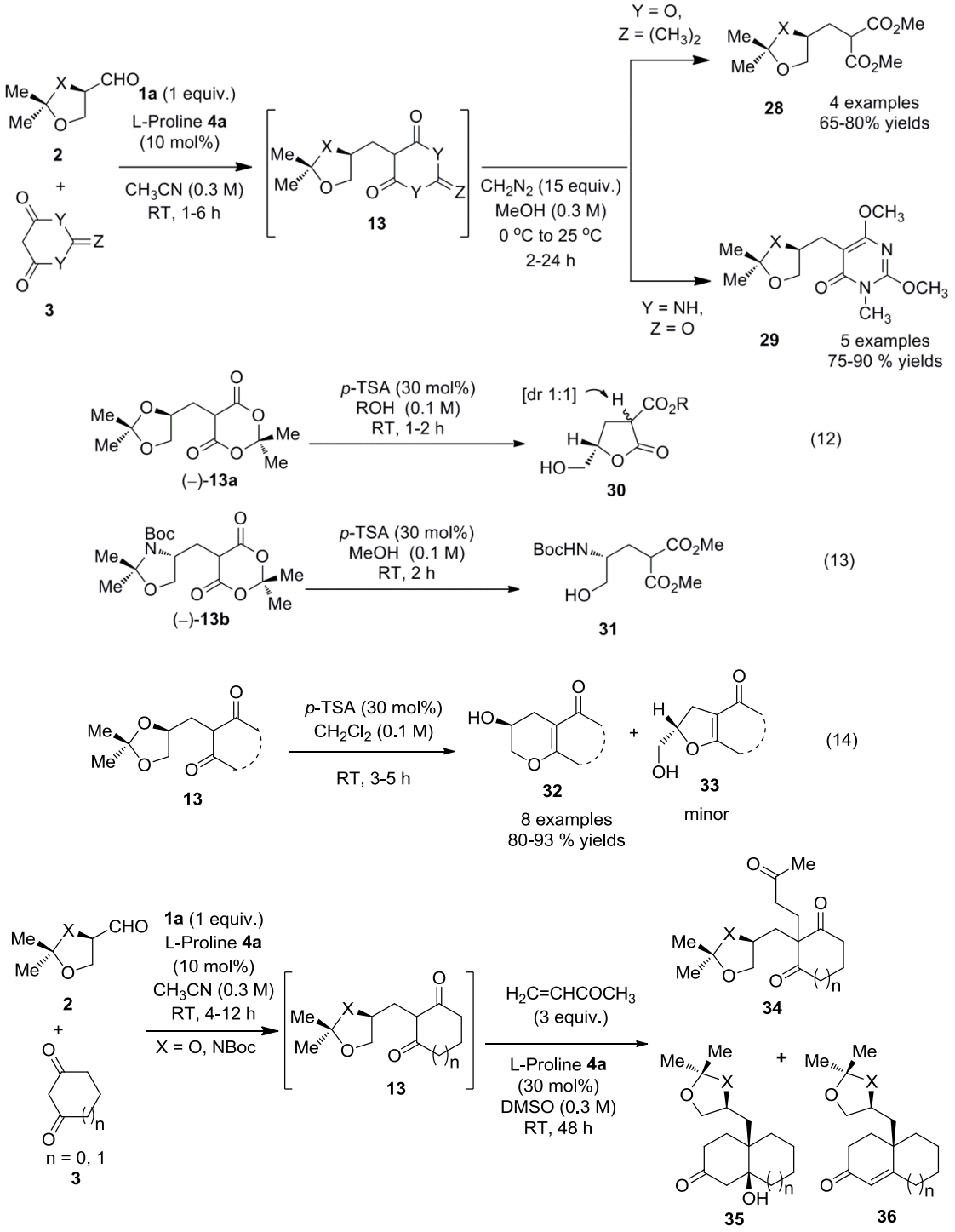





(11)

In 2010, our group[15b] developed Hantzch ester mediate *MCC* process for the asymmetric synthesis of highly useful chiral building blocks (2-alkyl-CH-acids, H-P ketone analogs and some more applications shown in below Scheme and equations) based on the OrgRC platform by using with (*R*)-glyceraldehyde acetonide (**2b**)/(*S*)-Garner aldehyde (**2c**) and CH-acids, without racemisation in very good yields. Direct combination of *L*-proline-catalyzed OrgRC reaction with chiral aldehydes, CH-acids, Hantzsch ester, diazomethane and methyl vinyl ketone, in combination of other reactions like alkylation/ketenization/esterification/alkylation, alkylation/ketenization/esterification, Robinson annulation of CH-acids, hydrolysis/lactonization/esterification, hydrolysis/esterification and hydrolysis/oxy-Michael/dehydration furnished the highly functionalized chiral building blocks with good to high yields and with excellent diastereoselectivities. Many pharmaceutically and academically useful chiral building blocks were prepared through OrgRC reaction.

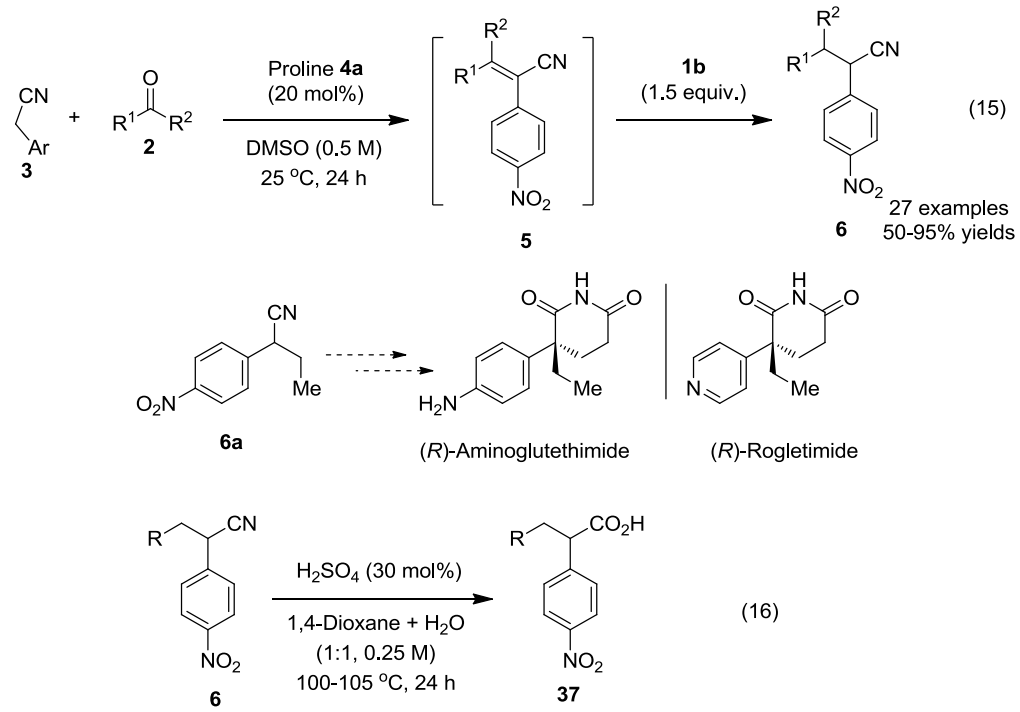




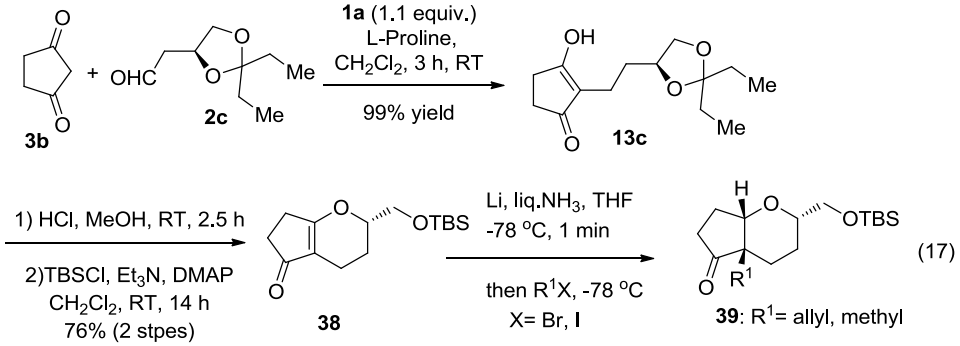

***Scheme 3***: Simple Chiral Aldehydes to Natural Products through an OrgRC Reaction.

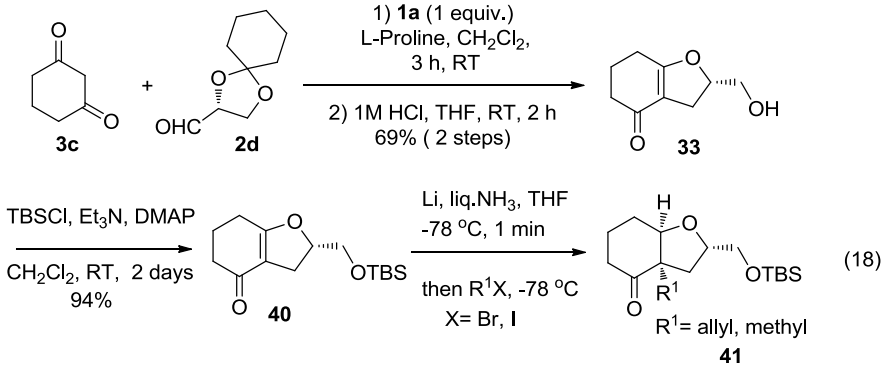
In 2010, our group[15c] showed that a direct amino acid-/self-catalyzed cascade OrgRC reactions of unactive methylene arylacetonitriles **3** containing electron withdrawing groups with aldehydes **2** and organic-hydride **1b** furnished the OrgRC products **6** with 50-95% yields (eq. 15). The OrgRC products are direct applications in

agricultural and pharmaceutical chemistry like ibuprofen, flurbiprofen, (R)-aminoglutethimide and (R)-rogletimide analogues. OrgRC products have converted to 2-arylpropionic acids **37** with very good yields, which are useful as non-steroidal anti-inflammatory drugs (eq. 16).



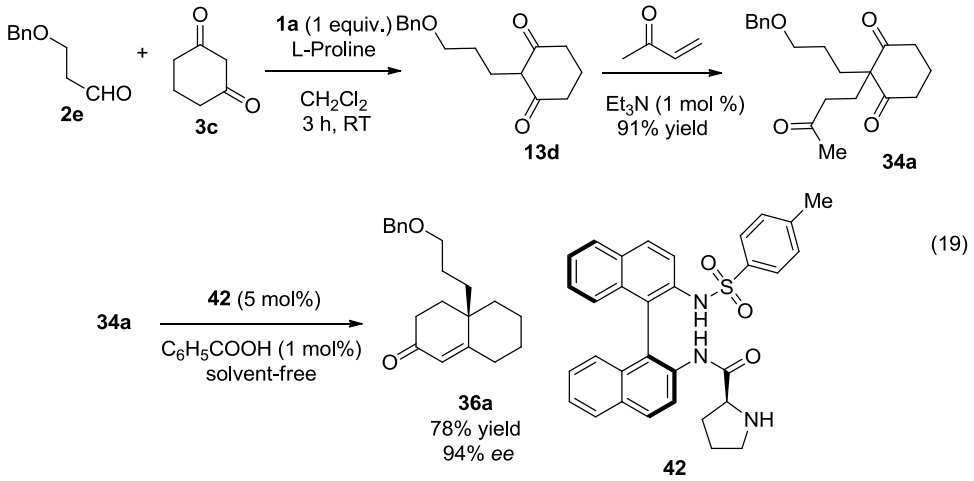

In 2009, Kou Hiroya *et al.*[27] reported diastereoselective Birch reduction-alkylation reactions of bicyclic $\beta$-alkoxy-$\alpha$, $\beta$-unsaturated carbonyl compounds with moderate yields (eq. 17 and eq. 18). Although the stereoselectivity of the product was altered according to the structure of the starting material **38** and **40**, stereoselectivity of the reaction could be accounted by similar reaction pathways. The stereochemistry at the $\beta$ position of $\beta$-alkoxy-$\alpha$, $\beta$-unsaturated carbonyl compounds is controlled by the stereochemistry of the TBS-oxymethyl group and that at the $\alpha$ position is controlled as *cis* to the $\beta$ position for all starting materials. The starting materials **38** and **40** for this reaction were easily prepared through our OrgRC reaction in two steps.






***Scheme 4***: New Compounds Synthesis from Chiral OrgRC Products.

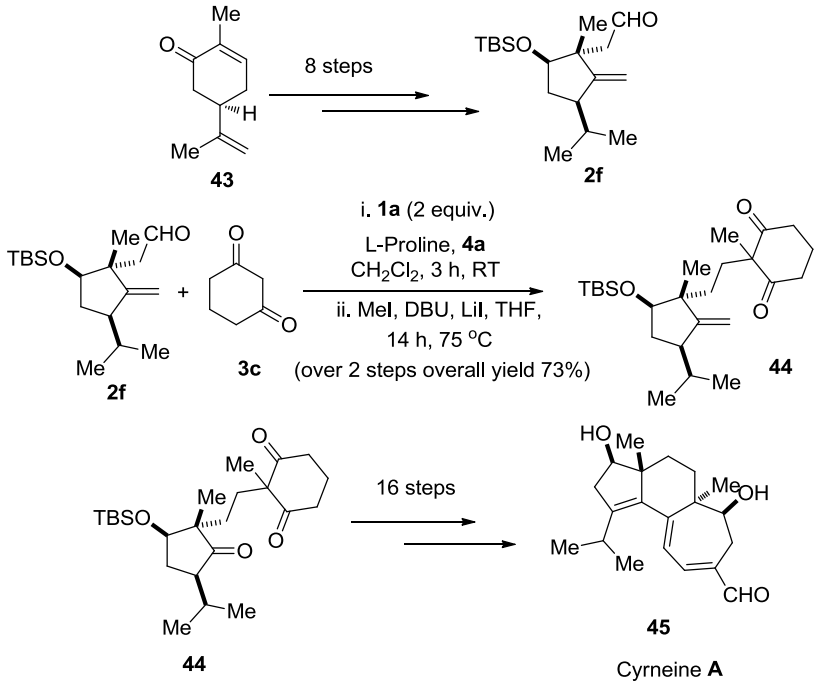
In 2009, Josep Bonjoch *et al.*[28] developed a simple organocatalytic procedure for the synthesis of the Wieland–Miescher ketone (10-g scale) and its analogues incorporating several side-chains at C-8 position starting with triketones in neat condition, in high yields with high enantioselectivities by using *N*-tosyl-(*S*a)-binam-prolinamide as a catalyst (eq. 19). High enantioselectivities of up to 97% were obtained under solvent-free conditions with low catalyst loadings. They have reported a very good method to prepare the triketone from 2-alkyl-1, 3-cyclohexanedione and MVK using triethylamine as a base. In this protocol also, starting materials 2-alkyl-1,3-cyclohexanediones were prepared easily by utilizing our OrgRC reaction as shown in eq.19.




## *2.2 Applications in Total Synthesis of Natural Products*

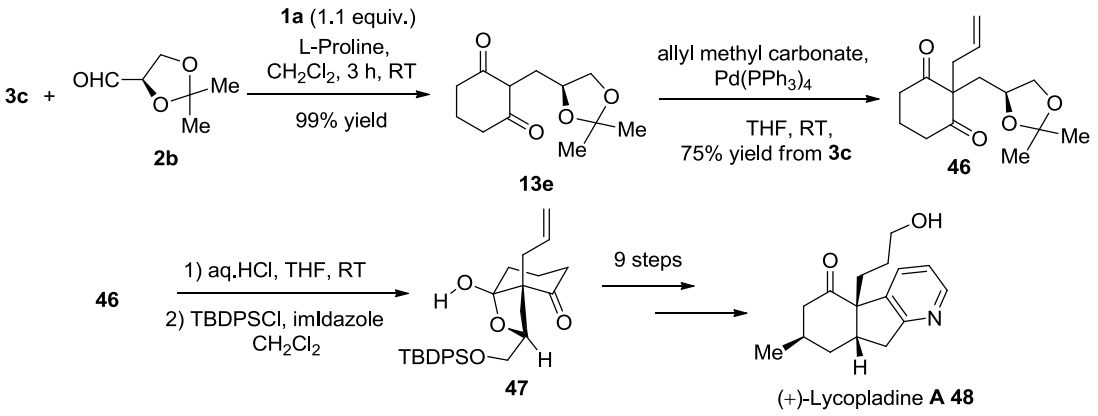
In 2012, Karl Gademann *et al.*[29] reported the first total synthesis of cyrneine A **45**, which enhances neurite outgrowth in pheochromocytoma cells as shown in Scheme 5. The total synthesis of cyrneine A **45** started with (−)-carvone. From this (−)-carvone they obtained the five-membered building block with overall 55% yield in 8 steps. The

Knoevenagel condensation of the aldehyde **2f** with cyclohexa-1, 3-dione was readily carried out in the presence of L-proline as the catalyst and the intermediate was reduced *in-situ* by the Hantzsch ester **1a** to prevent *bis*-product with 100% yield. The less stable intermediate was alkylated immediately with methyl iodide and DBU to give **44** in 73% yield. The triketone was reduced diastereoselectively under Luche conditions, with high regioselectivity. The transformation of alcohol to the corresponding mesylate was achieved in high yield. Elimination to the cyclohexenone followed by reduction and protection, later Heck reaction followed by ring expansion through carbene rearrangement and finally reductive palladium-catalyzed carbonylation strategy they prepared **45,** in 25 reactions starting from (−)-carvone.



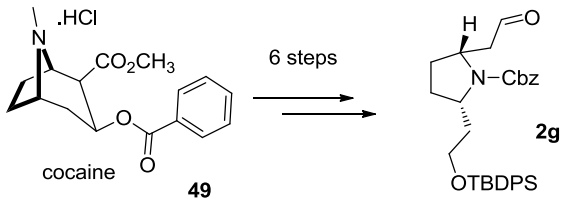

***Scheme 5***: Karl Gademann Synthesis of Cyrneine A through an OrgRC Reaction.

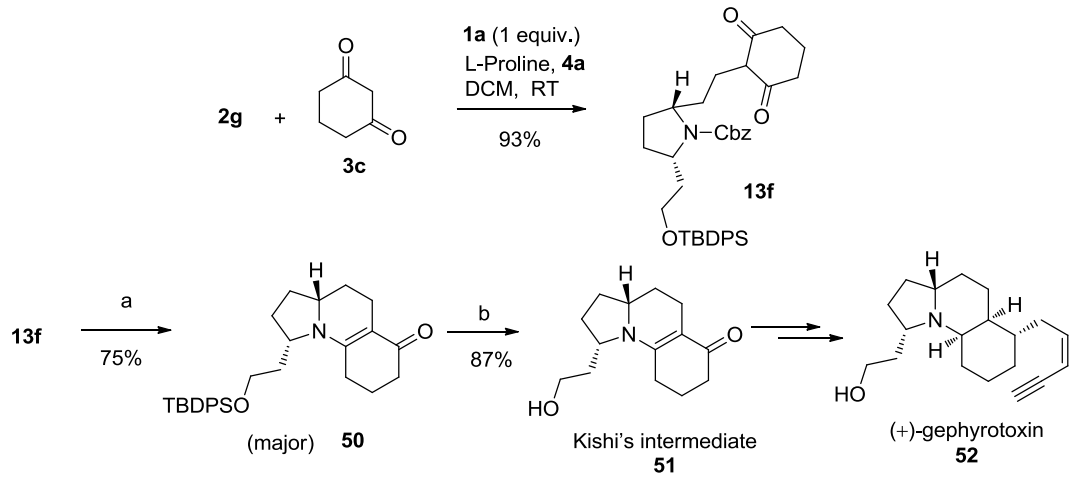
In 2011, Kou Hiroya *et al.*[30] reported the synthesis of both enantiomers of common intermediate using **13e** for the total synthesis of natural (+)-lycopladine **A** [(+)-**48**] and unnatural (−)-lycopladine **A** [(−)-**48**] as shown in Scheme 6. One of the enantiomer of common intermediate is prepared from **13e** in five steps and another is prepared from **13e** in six steps. They reported the total synthesis of natural (+)-lycopladine **A** [(+)-**48**] from the common intermediate and the formal synthesis of unnatural (−)-lycopladine **A** [(−)-**48**] from common intermediate in nine steps. The starting material **13e** were prepared easily by using OrgRC method with 1,3-cyclohexane-dione, acetonide glyceraldehyde and Hantzch ester in one-pot with good yield.[15b]




***Scheme 6***: Total Synthesis of (+)-Lycopladine **A** through Chiral OrgRC Products.

In 2010, Mark L. Trudell *et al.*[31] reported the tricyclic skeleton of the gephyrotoxin amphibian alkaloids by an enantioselective manner involving fifteen discrete steps that furnished Kishi's intermediate **51** in 22% overall yield starting from cocaine. They synthesized (1R)-2-tropinone derivative by degradation of cocaine, with 60-80% yield. A core *cis*-2, 5-disubstituted pyrrolidine ring was obtained from tropinone in four steps and further it was converted to aldehyde **2g** in four steps. The final stages of the synthesis of **13f** were completed by coupling the aldehyde **2g** with 1,3-cyclohexanedione (**3c**) using our OrgRC strategy. This step significantly streamlined the overall synthetic approach with 93% yield, by avoiding the tedious multistep functional group manipulations employed in earlier syntheses to construct similar dione precursors. Subsequent hydrogenolysis of the diketone **13f** catalyzed by 10% Pd/C furnished the tricyclic amine as a mixture of diastereoisomers **50** (9:1) in 75% yield *via* sequential Cbz removal, cyclization/ enamine formation. Mixture **50** with Tetrabutylammonium fluoride hydrate (TBAF) gave a separable mixture of diastereoisomers and furnished Kishi's intermediate **51** in 87% yield in enantiopure form (Scheme 7).

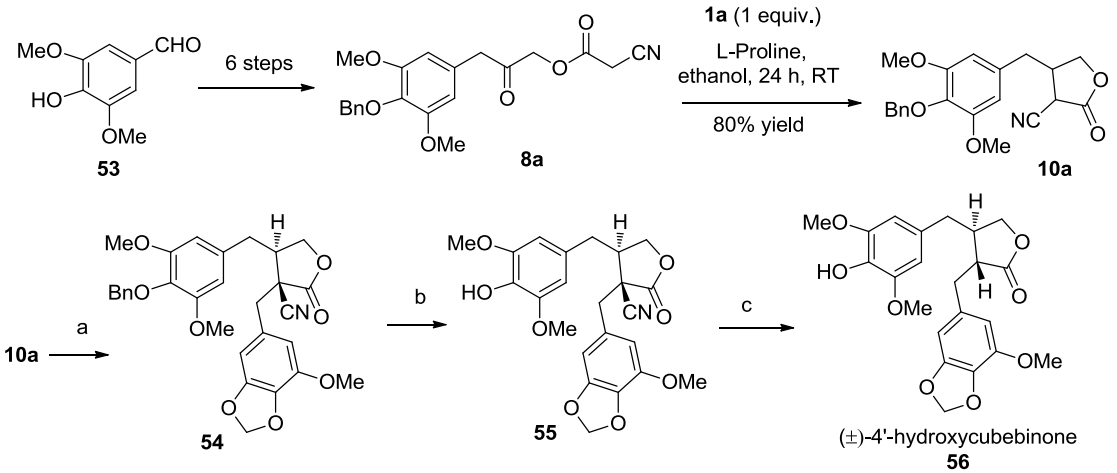





Reagents and conditions:(a) $H_2$ (1 atm), 10% Pd/C, $CH_3OH$, r.t. (b) TBAF, THF, r.t

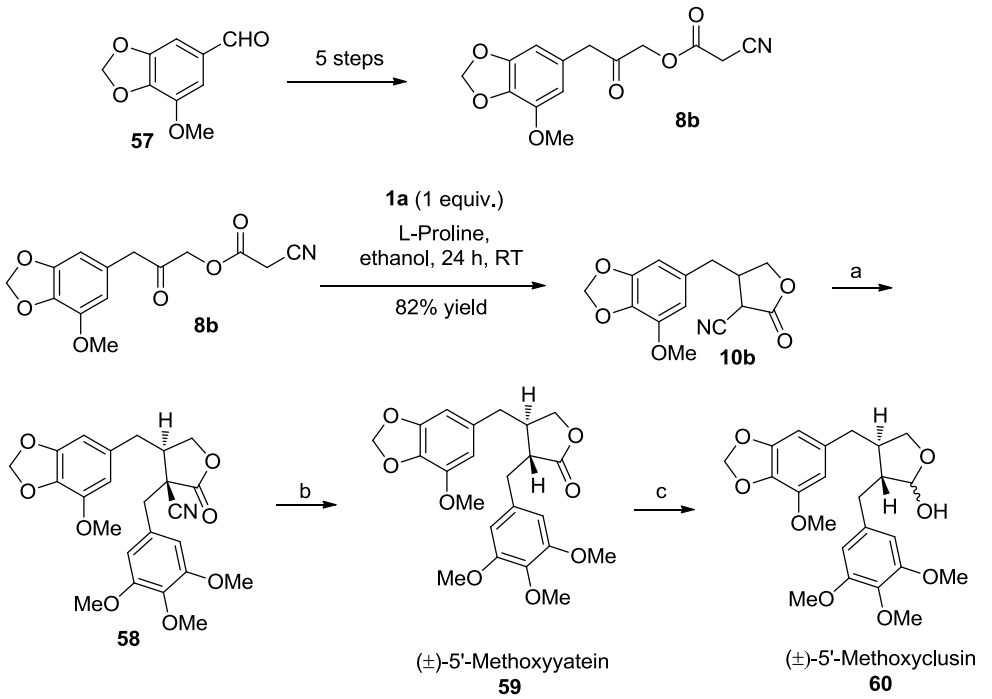
***Scheme 7***: Total Synthesis towards (+)-Gephyrotoxin through Chiral OrgRC Products.

In 2010, Kak-Shan Shia *et al.*[32] reported the total synthesis of natural lignans 5´-methoxyyatein **59**, 5´-methoxyclusin **60** and 4´-hydroxycubebinone **56**, in racemic form, in which they used our OrgRC strategy as key operation to build a five membered ring by tandem Knoevenagel condensation formed internally with active methylene and keto group and *in-situ* hydrogenated with Hantzsch ester **1a** in 92% yield. Compound **10a** and **10b** was subsequently treated with 5-methoxypipernoyl bromide and 3, 4, 5- trimethoxy benzyl bromide under basic conditions respectively with 80-82% yield and with decyanation to give desired *trans*-dibenzylbutyrolactone. Same procedure followed for the preparation 5´-methoxyyatein **59**, 5´-methoxyclusin **60** and 4´-hydroxycubebinone **56** as shown in Schemes 8 and 9**.**




Reaction conditions: a) 5-methoxypiperonyl bromide, $K_2CO_3$, THF, RT, 24 h, 82%; (b) $H_2$, Pd/C (10% w/w), methanol, RT, 10 min, 98%; (c) LN (3.5 equi.), THF, –45 °C, 30 min then $NH_4Cl$ (aq.), –45 °C to RT, 95%.

***Scheme 8***: Total Synthesis of 4´-Hydroxycubebinone through an OrgRC Reaction.



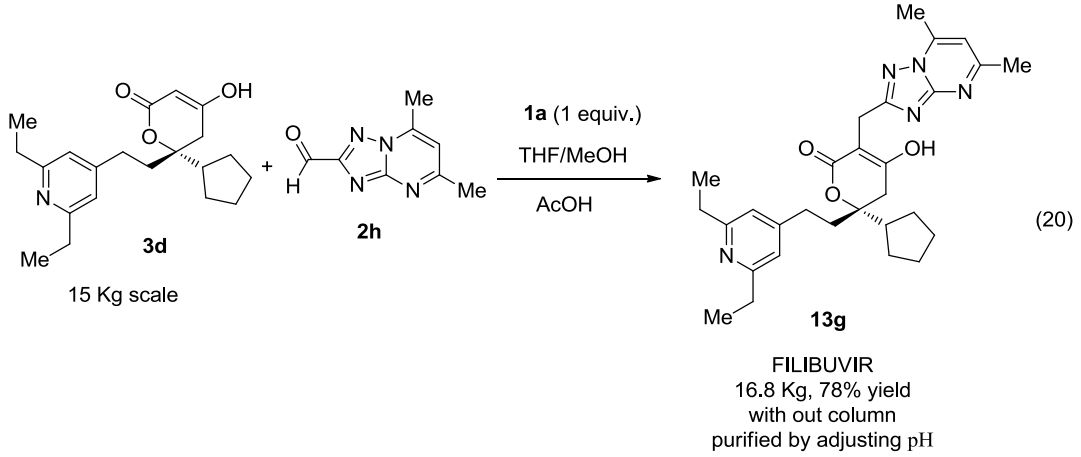

Reaction conditions: a) 3,4,5-trimethoxybenzyl bromide, $K_2CO_3$, THF, RT, 24 h, 80%; (b) LN (3.5 equi.), THF, –45 °C, 30 min then $NH_4Cl$ (aq.), –45 °C to RT, 95%; (c) DIBAL, toluene, –78 °C, 2 h, 72%.

***Scheme 9***: Total Synthesis of Lignans through an OrgRC Reaction.

## 2.3 Applications in Industry:-

In 2014, Nathan and Ragan *et al.*[8] developed the large scale method for the synthesis of Filibuvir through OrgRC as main reaction. Hepatitis C virus (HCV) is the leading cause of liver transplantation and infects over 170 million people worldwide (over 3% of the world population) and still there is no proper medicine for HCV. Development of small-molecule HCV therapies (Filibuvir) is a promising approach to improve this clinical situation. The initial manufacturing methods of pharmaceutical ingredient **13g**, using a borane−amine-mediated reductive coupling was not that much effective and provided poor yield (17%) and a subsequent recrystallization was required. Additionally, the borane−amine complex posed safety, cost and sourcing issues. These drawbacks led them to seek an alternative reductive coupling protocol. They developed a reductive coupling of a *β*-keto-lactone and an aldehyde to give active pharmaceutical ingredient (API) in good yield without any *bis*-product in which the Hantzsch ester serves as an inexpensive and convenient reducing agent in normal condition (eq. 20) and without any decomposition of the product. Structural features in the *β*-keto-lactone rendered standard reductive coupling protocol ineffective, requiring development of a specific addition and temperature protocol to obtain good yield and avoiding all the drawbacks (*bis*-product formation and decomposition of **13g** *via* elimination and decarboxylation). They

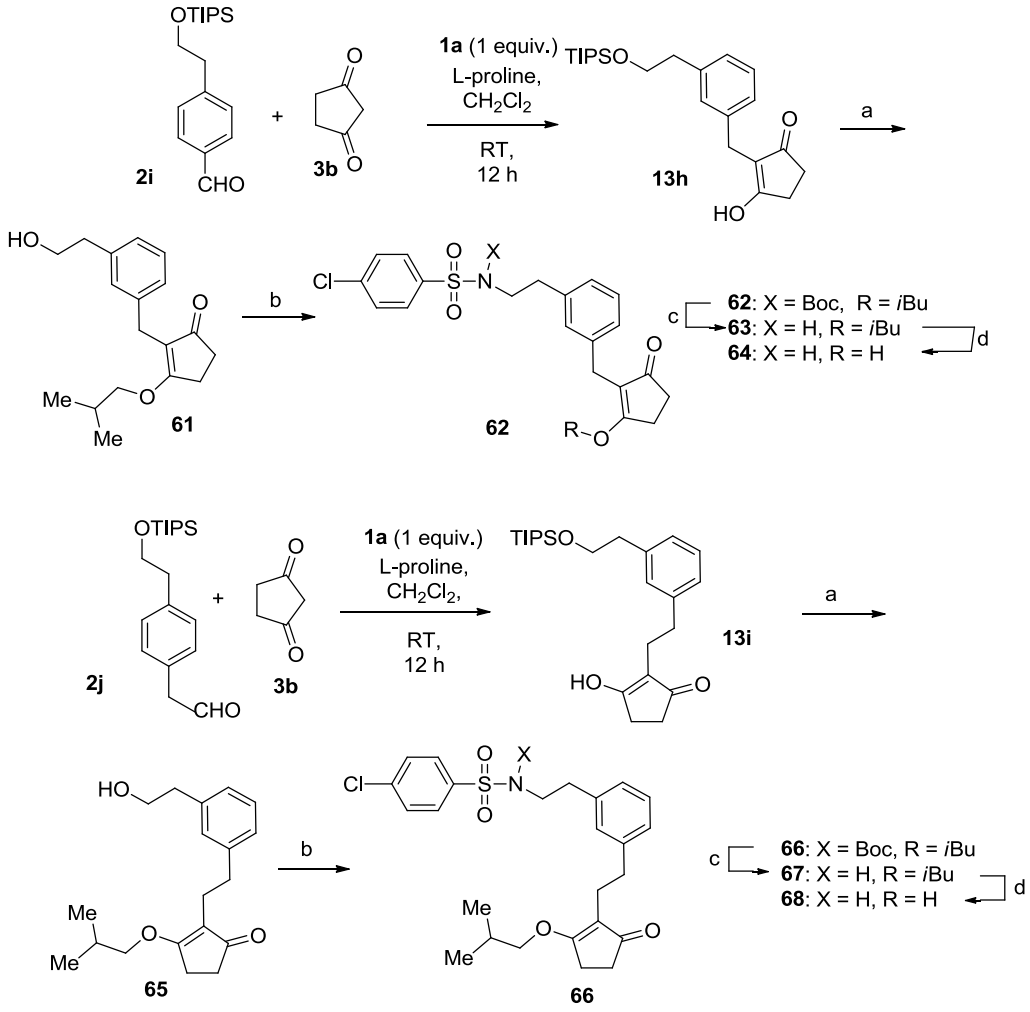
minimized the Ames positive aldehyde **2h** in the final API even on multikilogram scale to meet single digit ppm specifications. Identification of one of the reactants as Ames positive required a single-digit parts per million control strategy for this impurity in the final active pharmaceutical ingredient **13g**. They went up to 15 kg scale with this method and they obtained 78% yield without column purification and the starting material $\beta$-keto-lactone was prepared in two ways, reported in consecutive papers.




(20)

## 2.4 Applications in Medicinal Chemistry

In 2011, Carlo Ballatore and Amos B. Smith III *et al.*[33] studied that the cyclopentane-1,3-diones (CPD) fragment will comprise a viable new surrogate for the carboxylic acid moiety with potential applications in drug design, as $pK_a$ values of cyclopentane-1,3-diones are known to exhibit typically in the range of carboxylic acids and the ability to establish H-bonds. In addition to the significant intrinsic acidity and the ability to form salt bridges, they found that the CPD moiety may permit substantial structural differentiation of the acidic residue and this characteristic property may be particularly highly useful when attempting to modulate drug target/off-target interactions and/or physical, chemical properties of biologically active compounds. The lipophilicity of CPD compounds is also either equal or higher than acids and tetrazoles. By these results, the CPD would appear to be a valuable addition to the existing palette of carboxylic acid isosteres. In their studies they proved that steric hindrance at the C-2 position would be relatively well accepted and they can easily prepared as shown in Scheme **10**. This characteristic property may be exploited to design analogues with increased complementarities with the receptor and/or to modify the physical chemical properties (e.g., lipophilicity) of the compound. Happy to mention that, a variety of library at C-2 position of CPD were synthesized using OrgRC reaction.




Reagents and reaction conditions: (a) *p*-toluenesulfonic acid (cat.), *i*-butanol/benzene, reflux, 16 h; (b) *tert*-butyl (4-chlorophenyl)sulfonylcarbamate, $PPh_3$, diethyl azodicarboxylate, THF, RT, 4 h; (c) 2,2,2-trifluoroacetic acid, DCM, RT, 2 h; (d) 2 N hydrochloric acid, acetone, RT, 12 h.

***Scheme 10***: Medicinal Use of OrgRC Products.

The examples described in the above unambiguously show that metal-free transfer hydrogenation of olefins with Hantzsch ester plays a key role and has quickly become a powerful methodology for the synthesis of difficult conversions and has found widespread applications in the preparation of various medicinally relevant molecules as well as in the total synthesis of natural and bioactive products. Importantly, inspired by the nature stepwise addition of hydride, Hantzsch ester-mediated transfer hydrogenation process is compatible with various functional groups and different organocatalysts and has therefore been implemented in multi-step cascade or domino-reactions allowing the fast construction of complex chiral molecules of structural complexity and targets possessing various biological activities in one pot operations. On the other hand, the combination of this mild and tolerant process with other metal catalytic reactions (cascade or domino reactions) by using multi components, which has been successfully

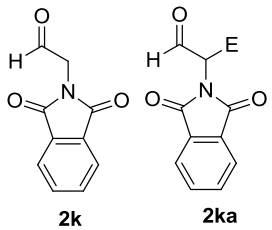
demonstrated in some remarkable cascade processes over the past eight years, offers a variety of possibilities which still have to be fully explored. The reaction conditions with Hantzsch esters mediated OrgRC reactions are usually performed under mild conditions (at room temperature or slightly heating) and easy to handle because no special apparatus or techniques for high pressure process, dry or air-free conditions are needed whereas, the transition metal-catalyzed hydrogenations show high reactivity and poor selectivity, most of them still suffer with significant drawbacks including inadequate substrate generality, difficulty in catalyst removal and recovering as well as the handling high pressure of flammable hydrogen gas. These things made metal-free transfer hydrogenation of Hantzsch ester regarded as a superiority in contrast to most transition metal-catalyzed hydrogenations. Additionally, transfer hydrogenations with Hantzsch esters gave the desired products free of *bis* product and metallic by-products which are often difficult to remove. All these developments make this biomimetic reductive process very attractive in modern organic synthesis. The by-product (Hantzsch ester pyridine) coming from OrgRC reaction will be easily separated through column or without column even if it is bulk scale.[8]

The OrgRC applications discussed in the above have confidently motivated us for further approaches in developing OrgRC reaction to superior heights with a broad range of applications and understandings in synthetic organic chemistry. In continuation of synthesis of highly functionalized molecules starting from the simple materials in one-pot, research work has been carried out on the synthesis of drugs and drug-like molecules in a single step and the results are presented in this thesis.

# 3. Phthalamidoacetaldehyde in Organocatalytic Reductive Couplings: Synthesis of Highly Useful Synthons for the Natural Products, GABA Drug Anlogues and Wieland-Mischer Ketones

## 3.1 INTRODUCTION

Synthesis of drug-like compounds from simple substrates through cascade or domino reactions is one of the rising areas in present synthetic organic chemistry, even though there are already several well known organic reactions for the construction of C-C, C-N, C-O, C-S and C-X (X = halogen) bonds in structurally diverse natural and unnatural products by conventional methods. More characteristically, many of these well known reactions and reaction strategies are not perfect in comparison with biological reactions in terms of conversion or chemo-, regio-, diastereo- and enantio-selectivity. From the synthetic organic chemist's point of view, in an ideal chemical reaction, the quantity of reactants equals the quantity of all products generated in the reaction without wastage of molecules and it poses a formation of multiple carbon-carbon and carbon-hetero atom bonds, formed in a single step from simple, readily available materials through a series of reactions. In multi-component catalysis (*MCC*) and cascade reactions three or more readily available reactants are mixed together in one pot to give a highly functionalized desired product showing features of all inputs; therefore, the reactions offer greater promise for molecular diversity per step with less reaction time, solvents and work.[6] As a result, great concentration has been paid to the expansion of cascade or domino reactions, because of their high levels of atom economy and their applications in synthetic organic chemistry as well as diversity-oriented synthesis.[6,15] Even though a great research has took place on cascade chemistry for the synthesis of stereochemically complex compounds,[6,15,35] still a lot of research has to be done in this area. A key to many motivating cascade reactions is the incorporation of biomimetic olefination and hydrogenation reaction sequences to build structurally diversified compounds in a completely stereoselective manner.[15]



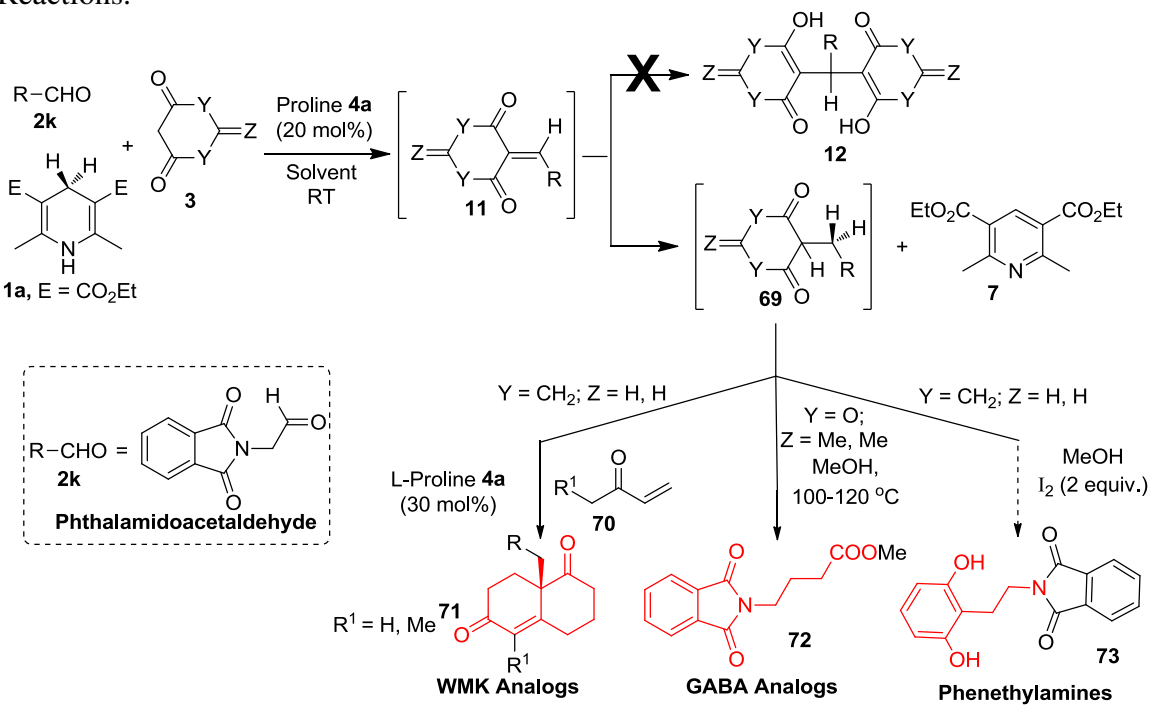

**2k** **2ka**

Figure **2**

Phthalamidoacetaldehyde[36] **2k** is an amine protected glycine aldehyde (Figure 2). Until now, very few reports are there in literature on this amino aldehyde. For first time

Barbas *et al.* used phthalamidoacetaldehyde **2k** in organocatlysis for the preparation of *β*-hydroxy-α-amino acid derivatives which are having wide-range biological properties. There are some more reports for the successful utilization of phthalamidoacetaldehyde **2k** as nucleophile to furnish *β*-substituted amino aldehyde **2ka**.[36] With *β*-substituted amino aldehyde **2ka** in hand, one can prepare so many natural, unnatural amino acids and natural products. With this background on phthalamidoacetaldehyde, we want to use this aldehyde for building natural products, pharmaceuticals and synthetic application purpose.

***Scheme 11***. Direct Organocatalytic Reductive Alkylation, RA, Decarboxylation Reactions.

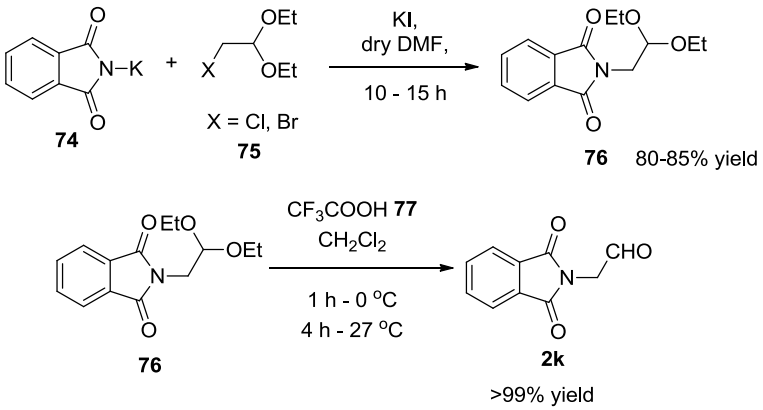



Recently, we have established the chemoselective C-alkylation of 1,3-diketones with a variety of aldehydes and organic hydrides under amino acid-catalysis through an OrgRC.[15] From the time when we reported this metal-free reductive coupling or OrgRC reaction, many synthetic chemists used this powerful OrgRC reaction in their method development[22-28] or total synthesis.[29-32] Biologists in drug developments[33] and industrialists in the bulk scale synthesis of medicines[8] had utilized as a crucial and key step in alkylation of active methylene. As part of our study to develop direct amino acid-catalyzed tandem, multi-component or organo-click reactions,[15,35] herein we reported organocatalyzed reductive coupling (OrgRC), reductive coupling –Robinson annulation

(OrgRC–RA) and reductive coupling–decraboxylation (OrgRC–D) reactions that construct, 2-alkyl-CH-acids **69**, Wieland-Miescher (W-M) ketone analogues **71,** GABA analogues **72** and synthons to phenethylamines **73** from phthalamidoacetaldehyde **2k**, CH-acids **3**, Hantzsch ester **1a**, alkyl vinyl ketone **70** and amino acid **4a** as shown in Scheme 11.

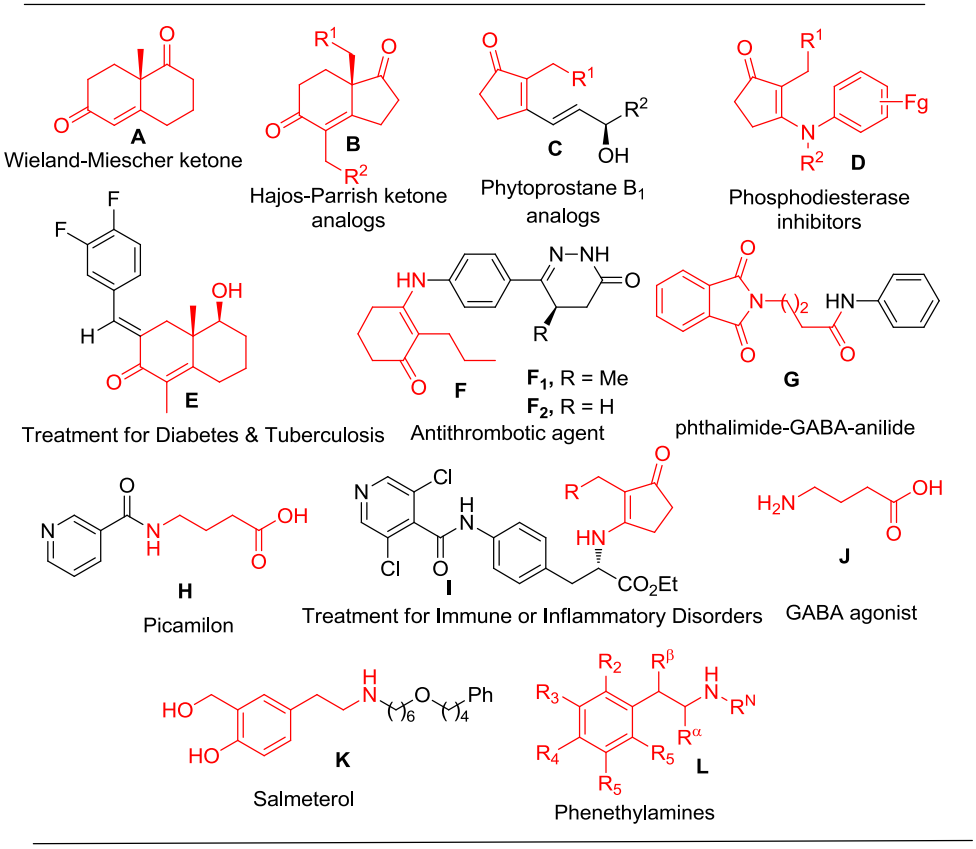
Phthalamidoacetaldehyde **2k** can be prepared in two steps with readily available starting materials. A mixture of potassium phthalimide, bromo or chloroacetaldehyde diethylacetal and potassium iodide in DMF refluxed for 10-15 h and then cooled to room temperature. The precipitate of KBr or KCl was separated; the filtrate was evaporated and purified to give the compound **76** in 80-85% yield. The compound **76** further treated with trifluoroacetic acid in $CH_2Cl_2$ for 5 h and solvent was evaporated to give the phthalamidoacetaldehyde **2k** in >99% yield.

***Scheme 12***: Preparation of **2k**.




W-M ketone analogues **71** are attractive intermediates in the synthesis of natural products and in medicinal chemistry,[37] while 2-alkyl-cyclohexane-1, 3-diones[38] **69** have a broad utility in pharmaceutical chemistry and are excellent starting materials in the natural product synthesis as shown in Chart 1. Hence, their preparation has continued to attract considerable synthetic interest in developing new methods for their synthesis. 2-Alkyl-cyclopentane-1,3-diones[39] **69** and H–P ketone analogues[40] **B** are attractive intermediates in the synthesis of natural products and in medicinal chemistry.

***Chart 1***. Natural and Unnatural Products Library Generated from OrgRC Products.



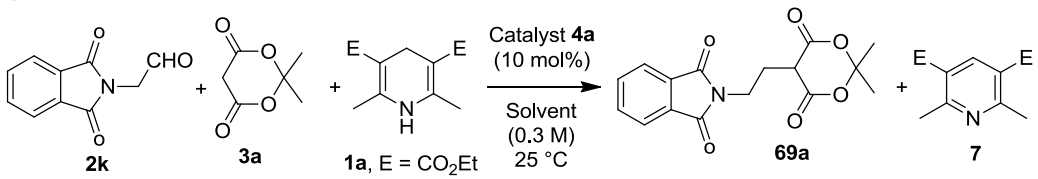

## 3.2 RESULTS AND DISCUSSION

### 3.2.1 Amino Acid Catalyzed OrgRC Reaction with Phthalamidoacetaldehyde: Reaction Optimization

First we focused on the optimization for high-yielding synthesis of 2-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl)isoindoline-1,3-dione **69a** from **1a**, **2k**, and **3a** through amino acid **4a** catalysis at room temperature, by studying the solvent effect in the designed OrgRC reactions. We studied solvents like $CH_2Cl_2$, $CH_3CN$, EtOH and DMSO. Interestingly, in all solvents we obtained good yield of the OrgRC product without solvent effect on the proline catalyzed cascade reductive coupling of **1a**, **2k**, and **3a** in three different type of solvents (protic polar, aprotic polar and aprotic non-polar) as shown in Table 1, entries 1-5. In $CH_2Cl_2$ the OrgRC reaction completed with less reaction time in good yield and the solvent was chosen for the optimised condition. The optimum conditions involved the use of 10 mol% catalyst **4a** and one equi. of phthalamidoacetaldehyde **2k**, one equi. of CH-acid **3** with respect to Hantzch ester **1a** with solvent as $CH_2Cl_2$ at room temperature, in cascade OrgRC reaction. With an

efficient organocatalytic cascade OrgRC protocol in hand, the scope of the proline-catalyzed cascade reductive coupling reactions was investigated with aldehyde **2k** and CH-acids **3** through the generation of highly useful diversity-oriented library. OrgRC product **69a** found in many natural and medicinal chemistry, which is highlighting the value of this OrgRC approach to the pharmaceuticals. This interesting result represents a novel methodology for the preparation of 2-alkyl-CH-acids **69a**.

***Table 1*:** Optimization of the Direct Organocatalytic Reductive Alkylation Reactions of **1a**, **2k** and **3a**.[a]




| Entry | Solvent | Time [h] | Yield [%][b] |
|---|---|---|---|
| 1 | $CH_3CN$ | 2 | 70 |
| 2 | $CH_3CN$ | 3 | 76 |
| **3** | **$CH_2Cl_2$** | **15** | **98** |
| 4 | DMSO | 18 | 98 |
| 5 | EtOH | 36 | 89 |

[a] see experimental section. [b] Determined by coloumn purified product.

### *3.2.2 Diversity-Oriented Synthesis of Reductive Coupling Products 69*

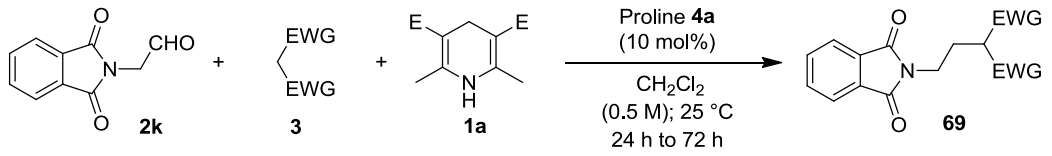
With the optimized reaction conditions in hand, the scope of the OrgRC reactions was investigated with CH-acids **3**, aldehyde **2k** and Hantzsch ester **1a** as shown in Table 2. A series of cyclic and acyclic CH-acids **3a-m** were reacted with phthalamidoacetaldehyde **2k** and Hantzsch ester **1a** catalyzed by 10 mol% of proline at 25 °C in $CH_2Cl_2$ (Table 2).

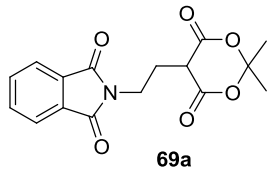
Interestingly cascade reaction with phthalamidoacetaldehyde **2k**, dimidone **3e** and **1a** furnished the reductive alkylation product **69b** in 97% yield after 48 h at 25 °C (Table 2). 2-(2-(2,6-Dioxocyclohexyl)ethyl)isoindoline-1,3-dione **69c** was obtained in 90% yield within 48 h by using the optimized condition. The cascade reaction of cyclopentane-1, 3-dione **3b** with phthalamidoacetaldehyde **2k** and **1a** furnished the reductive alkylation product 2-(2-(2,5-dioxocyclopentyl)ethyl)isoindoline-1,3-dione **69d** in 98% yield after 24 h at 25 °C (Table 2). OrgRC reaction of phthalamidoacetaldehyde **2k**, tetronic acid **3f** and **1a** furnished the reductive alkylation product **69e** in 95% yield after 48 h at 25 °C same as 1,3-cyclopentanedione case (Table 2). Interestingly cascade reaction with

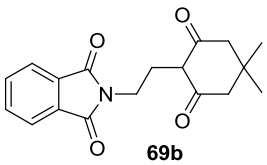
phthalamidoacetaldehyde **2k**, indanedione **3g** and **1a** furnished the reductive alkylation product **69f** with 95% yield after 48 h at 25 °C same as 1,3-cyclopentanedione case (Table 2). The product 2-(2-(2,6-dioxo-4-phenylcyclohexyl)ethyl)isoindoline-1,3-dione **69g** was obtained with 99% yield by mixing 5-phenyl-1,3-cyclohexanedione **3h**, **2k**, **1a** and proline as catalyst in 48 h. This result is also similar compared to 1,3-cyclohexanedione case. Keeping utility of spiro systems in biological compounds, we tested spiro CH-acids in OrgRC reaction and all of them reacted smoothly in OrgRC reaction. Spiro[4.5]decane-7,9-dione **3i** and spiro[5.5]undecane-2,4-dione **3j** reacted with phthalamidoacetaldehyde **2k** and Hantzch ester **1a** under proline catalysis to furnish the products **69h** and **69i** in 81% and 85% yield respectively. We also used benzo fused CH-acids in the OrgRC reaction with phthalamidoacetaldehyde. The product 2-(2-(2,4-dioxochroman-3-yl)ethyl)isoindoline-1,3-dione **69j** was obtained with 98% yield within 48 h by the OrgRC reaction of phthalamidoacetaldehyde **2k**, 4-hydroxycoumarin **3k** and **1a**. Interestingly cascade reaction with phthalamidoacetaldehyde **2k**, 2-hydroxy-1,4-naphthoquinone **3l** and **1a** furnished the reductive alkylation product **69k** with 99% yield after 48 h at 25 °C same as 4-hydroxycoumarin **3k** case (Table 2). Then we want to check OrgRC applicability with acyclic CH-acids. Unfortunately the cascade reaction of malononitrile **3m** with phthalamidoacetaldehyde **2k** and **1a** furnished the reductive alkylation product 2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)malononitrile **69l** with 60% yield only, after 48 h at 25 °C with $CH_2Cl_2$ as solvent (Table 2). Then we changed the solvent to EtOH and interestingly we isolated **69l** in 98% yield with reaction time 48 h.

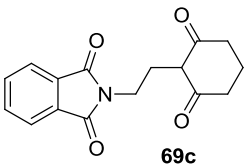
Interestingly, many of the 2-alkyl-CH-acids exist in the enol form in solution state, which may be due to the strong intermolecular hydrogen bonding. Also, this characteristic is observed in many other 1,3-diketones.[16,17] The chemical shifts of the carbonyl carbons and α-to the carbonyl carbon atoms in the isolated, non-hydrogen-bonded enol forms of 2-(2-(2,5-dioxocyclopentyl)ethyl)isoindoline-1,3-dione **69d** can be determined hardly in solution, due to the rapid keto–enol and enol–enol tautomerism.[17] This property of enolic nature is highly useful in medicinal chemistry. Carlo Ballatore and Amos B. Smith III *et al.*[33] studied that the 2-alkylcyclopentane-1,3-diones were comprised a viable new surrogate for the carboxylic acid moiety with potential applications in drug design, as $pK_a$ values of cyclopentane-1,3-diones are known to exhibit typically in the range of carboxylic acids and the ability to establish H-bonds. OrgRC products 2-alkyl-cyclic CH-acids can also be used as carboxylic acid isosteres.

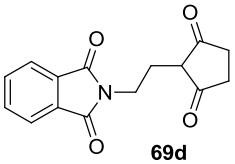
***Table 2***: Synthesis of Reductive Alkylation Library from **3** and Aldehyde **2k**.[a]

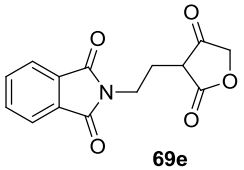


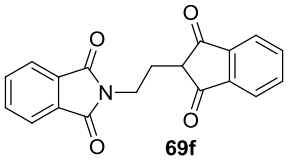


**69a**
15 h, 98% yield

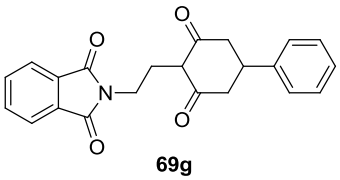

**69b**
48 h, 97% yield

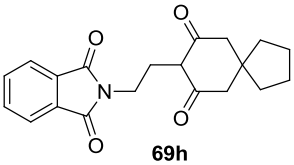

**69c**
48 h, 90% yield

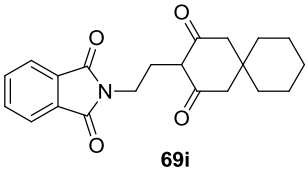

**69d**
24 h, 98% yield

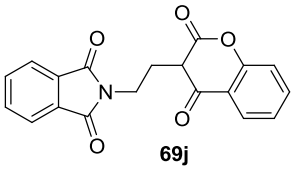

**69e**
48 h, 95% yield

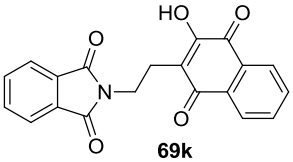

**69f**
48 h, 95% yield

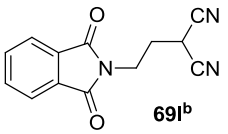

**69g**
48 h, 99% yield


**69h**
60 h, 81% yield


**69i**
60 h, 85% yield


**69j**
48 h, 98% yield


**69k**
48 h, 99% yield


**69l**[b]
48 h, 98% yield

[a] Yield refers to the column purified product. [b] EtOH used as solvent.

## *3.2.3 Applications of OrgRC Products*

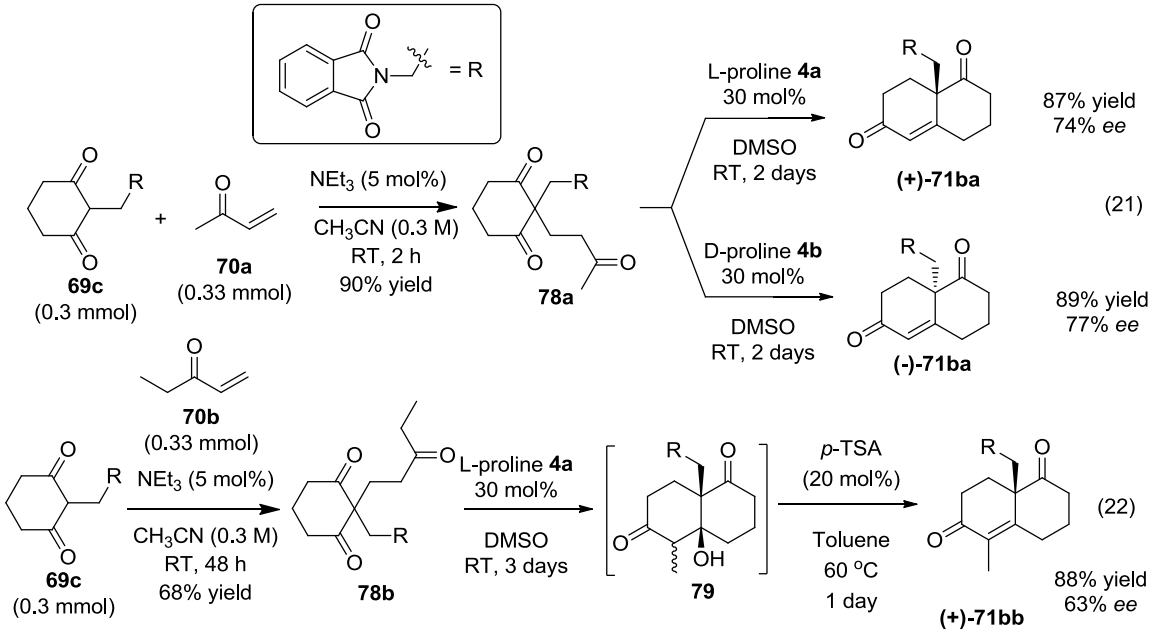
Based on the demand of pharmaceutical applications, we further extended the OrgRC products **69** into more useful intermediates.

### *3.2.3.1 Direct Amino Acid Catalyzed Robinson Annulation of 69c with 70*

W-M ketone analogs **71** and H–P ketone analogues **B** are very good starting materials for the synthesis of steroids.[40,41] Ali Amjad *et al*. showed in their patent[37,42] that W-M ketone analogue **71** and higher alkyl H–P ketone analogues **B** are very good intermediates for the preparation of pharmaceutically suitable salts or hydrates of spiro-heterocycles, which are disclosed as selective glucocorticoid receptor modulators for curing a variety of autoimmune and inflammatory conditions or diseases.[37,42] With

pharmaceutical applications and natural products synthesis in mind, we further extended the OrgRC products in the asymmetric synthesis of functionalized W-M ketone analogs under proline catalysis as shown in equation 21 & 22. All expected chiral W-M ketone analogs were furnished in good yields with good to moderate *ee*'s starting from OrgRC compounds.

**Scheme 13:** Direct Amino Acid Catalyzed Robinson Annulation of **69** with **70**.




We were pleased to find that the triethylamine catalyzed Michael reaction of 2-(2-(2,6-dioxocyclohexyl)ethyl)isoindoline-1,3-dione **69c** with 1.1 equiv of freshly distilled methyl vinyl ketone **70a** in $CH_3CN$ furnished the expected Michael product **78a** in 90% yield in 2 h. Direct L-proline-catalyzed RA reaction of **78a** in DMSO solvent furnished the W-M ketone analog (+)-7**1ba** with 87% yield with 74% *ee*. The D-proline-catalyzed RA reaction of **78a** furnished the opposite enantiomer of the W-M ketone analogue (–)-7**1ba** in 89% yield with 77% *ee* (eq. 21). The triethylamine catalyzed Michael reaction of 2-(2-(2,6-dioxocyclohexyl)ethyl)isoindoline-1,3-dione **69c** with 1.1 equiv of freshly distilled ethyl vinyl ketone **70b** in $CH_3CN$ furnished the expected Michael product **78b** in moderate yield (68%) in 48 h. Direct L-proline-catalyzed RA reaction of **78b** in DMSO solvent furnished the hydroxy product **79** and *in-situ* dehydrolised to furnish the product (+)-**71bb** with moderate *ee* values as shown in equation 22. Stereochemistry of the products **71** are assigned with the correlation of previous work.[15i]

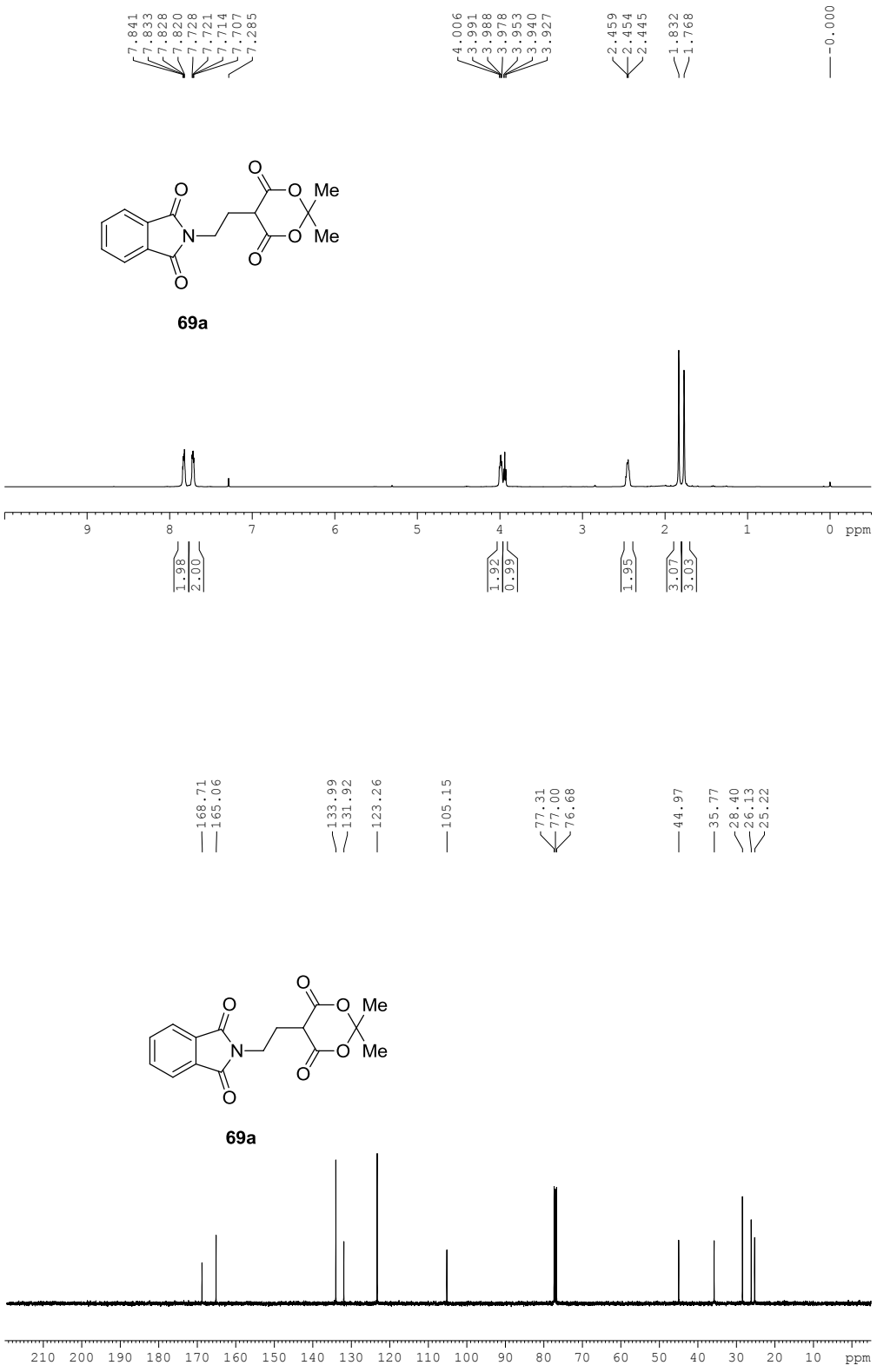



***Figure-N1:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **69a**.

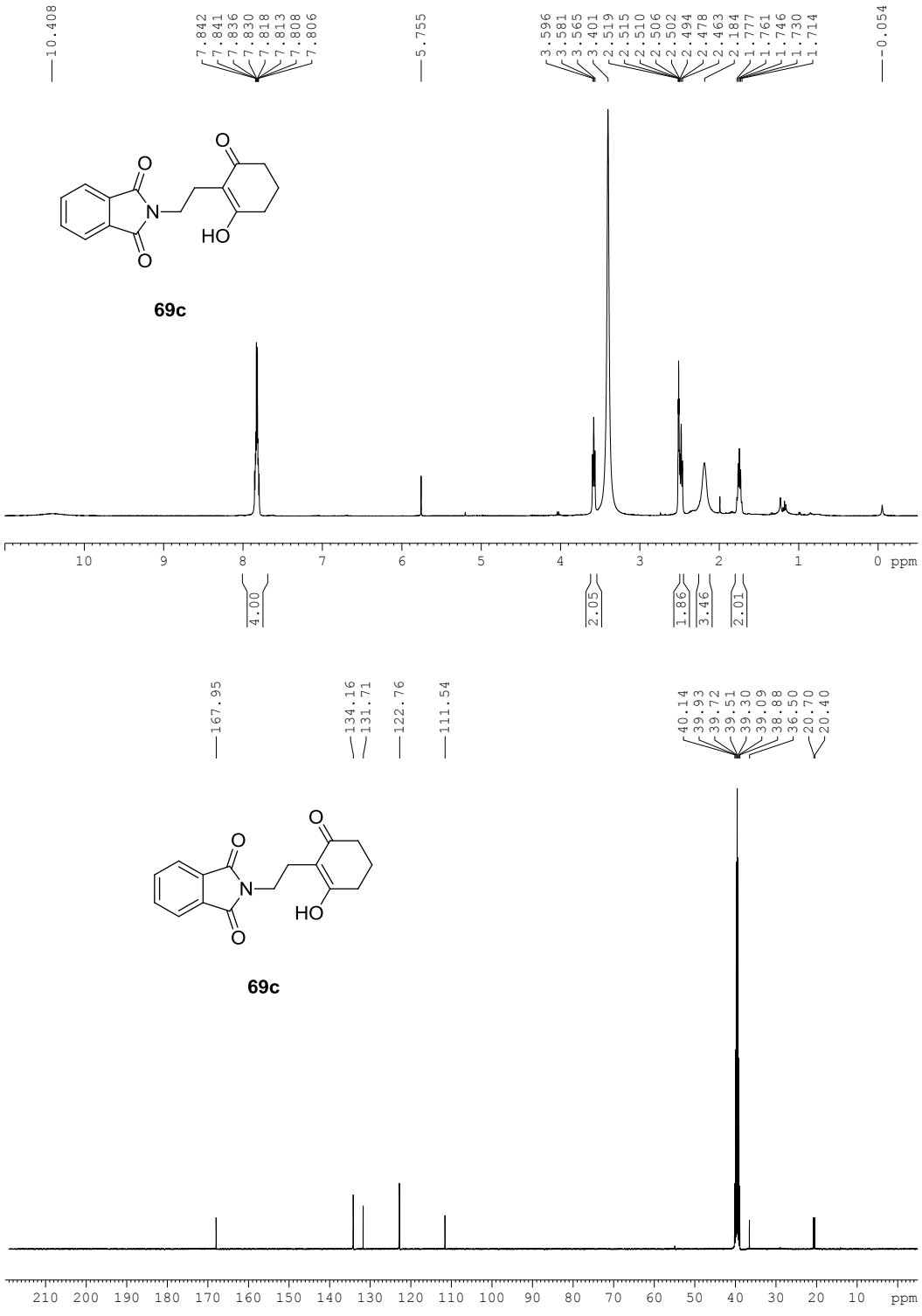



***Figure-N2:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **69c**.

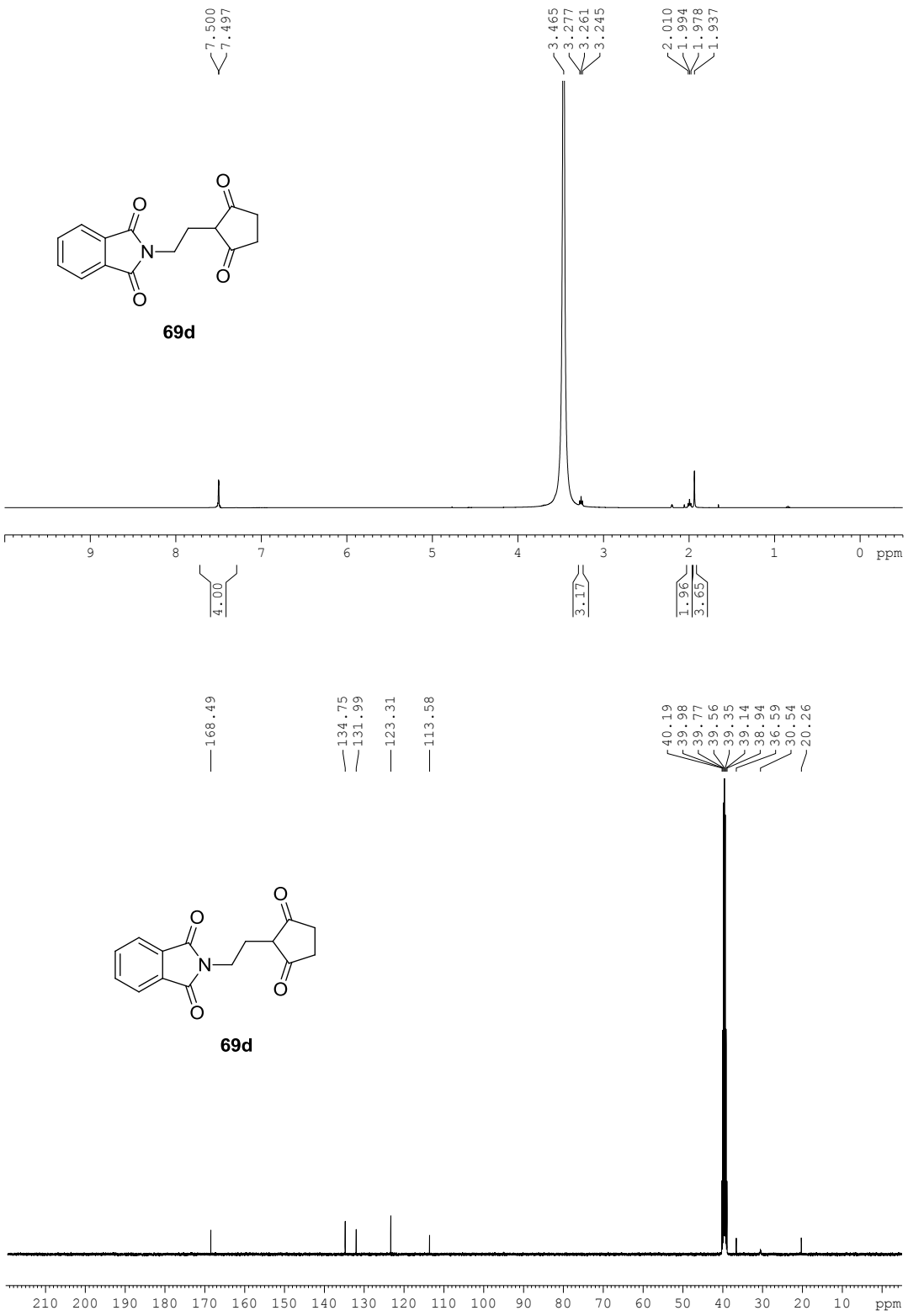



***Figure-N3:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **69d**.

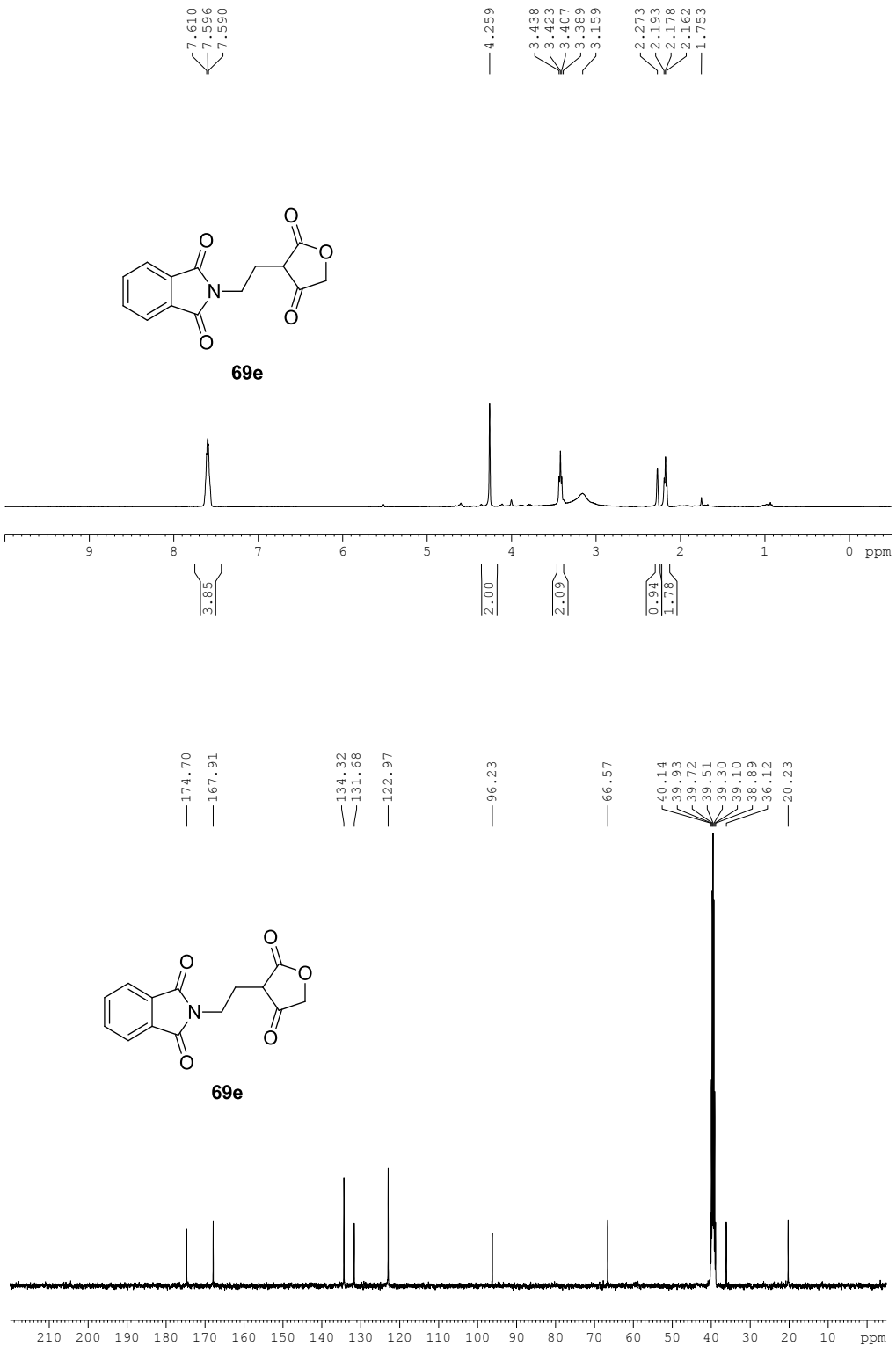



***Figure-N4:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **69e**.

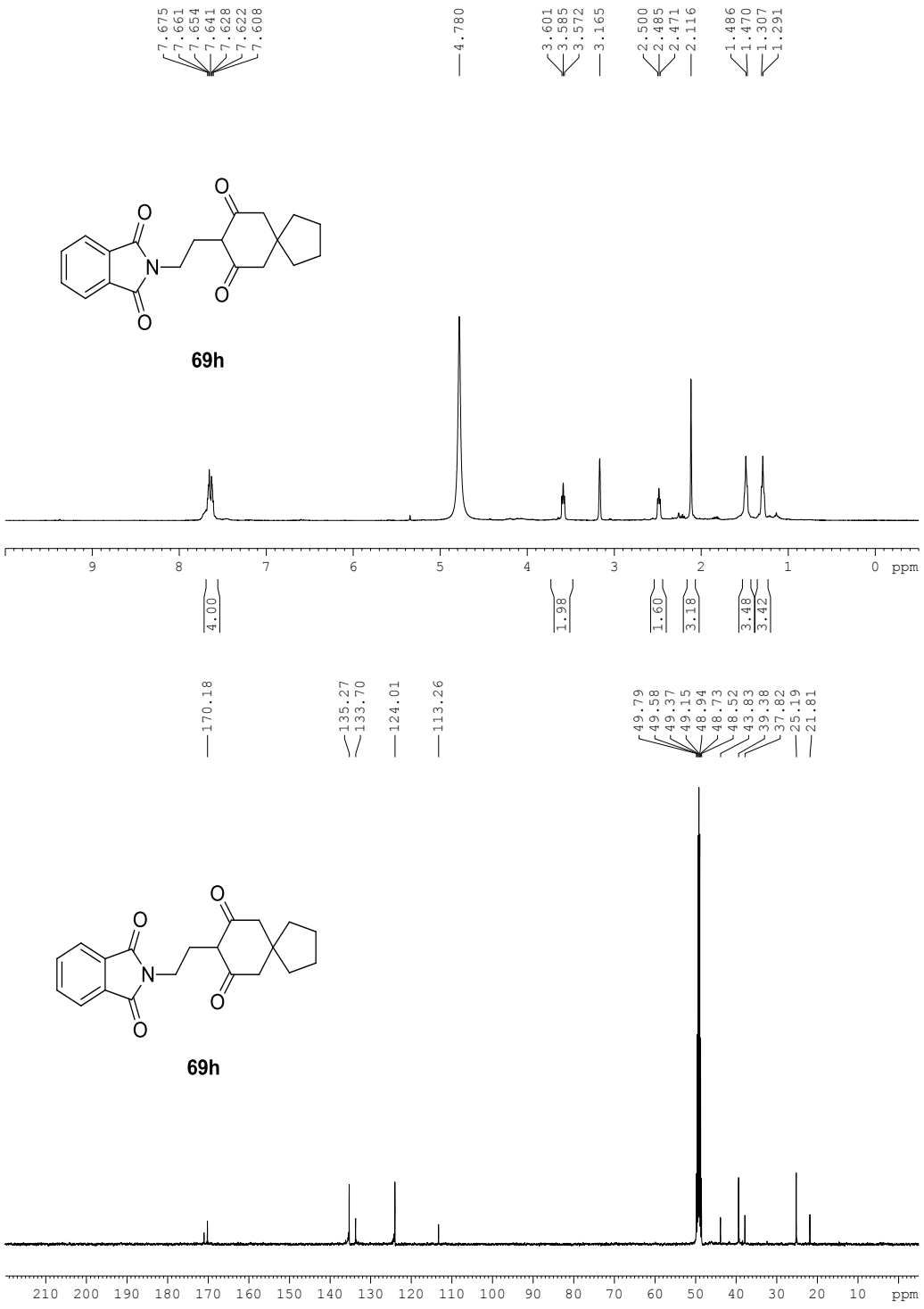



***Figure-N5:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **69h**.

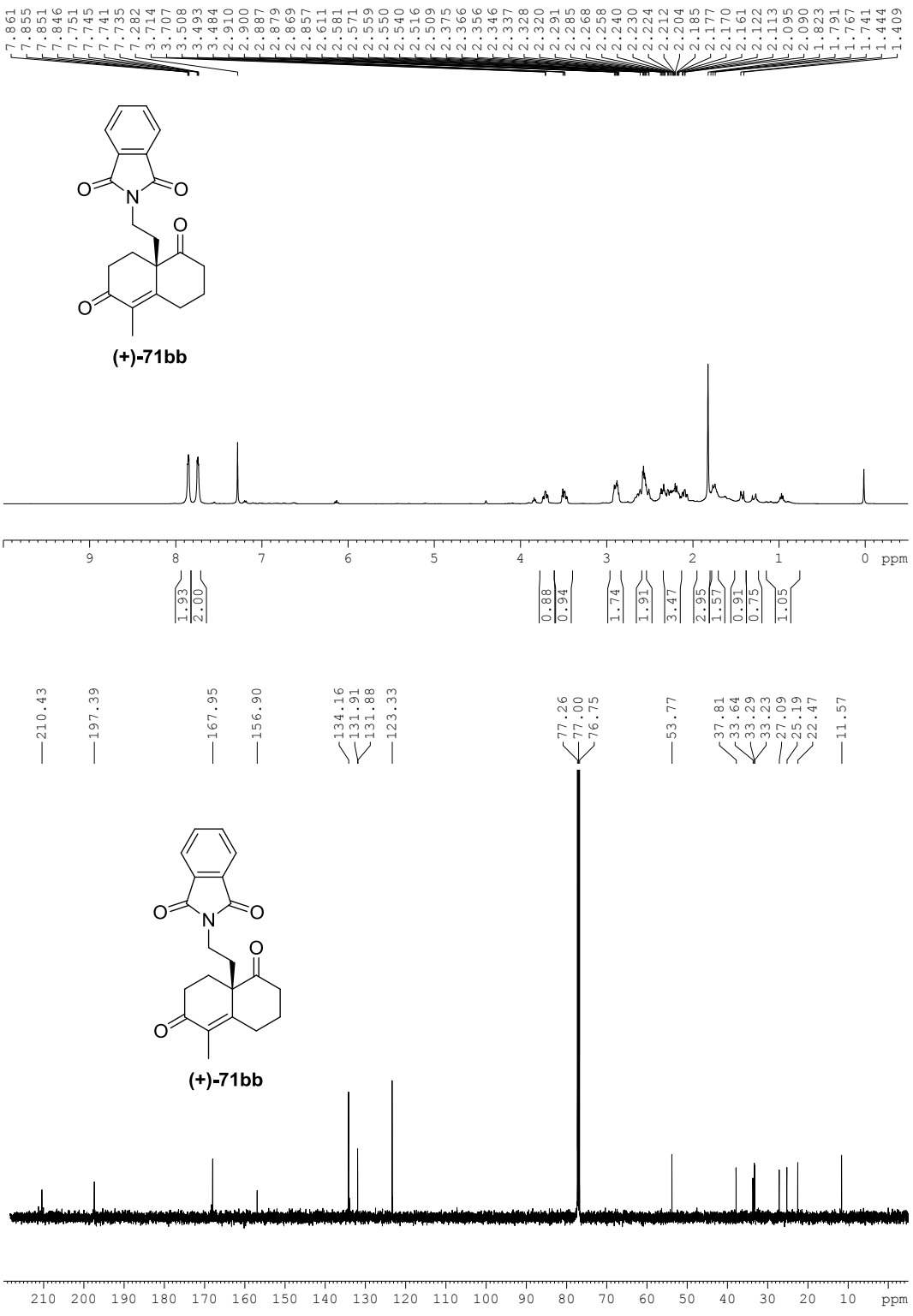
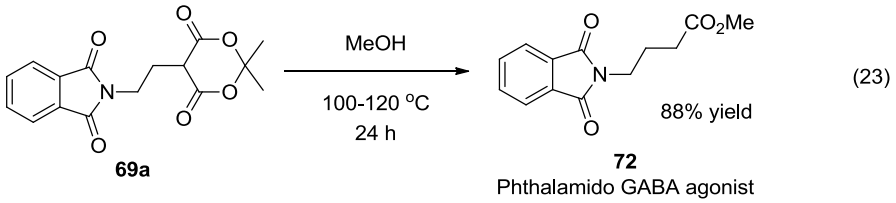



***Figure-N6:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **(+)-71bb**.

### *3.2.3.2 Synthesis of GABA-Analogue*

When brain experiences a lot of tension and stress, it may be caused by an excess of norepinephrine or epinephrine (adrenaline). To deactivate this extra adrenaline, the brain releases neurotransmitters, one of which is Gamma-Amino Butyric acid (GABA),[43] that contain inhibitory property upon the nervous system. GABA is an amino acid which acts as a neurotransmitter in the central nervous system and directly responsible for the regulation of muscle tone. It inhibits nerve transmission in the brain, calming nervous activity. More than 75,000 papers have come regarding the studies on GABA, which shows the importance of the molecule. Low levels of GABA and anxiety are related but a deficiency in GABA may also lead to insomnia, depression, mood disorders, excessive stress, hypertension, atherosclerosis, motion sickness, low levels of digestive enzymes, ADHD, epileptic seizures, panic disorders Tourette's syndrome, bronchitis and low growth hormone levels. Some of the GABA analogues had shown here. (Chart 1**, G, H, J, K)**

The phthalamido group attached to GABA will increase the lipophilicity and it will be easily dissolved in lipids, oils and fats, emphasizing the value of this reductive two carbons homologation approach of the OrgRC product.[44] Phthalamido-GABA **72** is the starting material for the many natural products and medicines. Interestingly, the cascade reductive coupling product 2-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl)isoindoline-1,3-dione **69a** was converted into two-carbon homologated ester methyl 4-(1,3-dioxoisoindolin-2-yl)butanoate **72** by heating 100-120 $^{o}$C in methanol solvent as shown in equation 23. More GABA analogues can be prepared by attaching electrophile to the phthalamidoacetaldehyde **2k** to get **2ka** type derivatives and adding Meldrum's acid using OrgRC protocol.




**69a** → **72** Phthalamido GABA agonist (23)

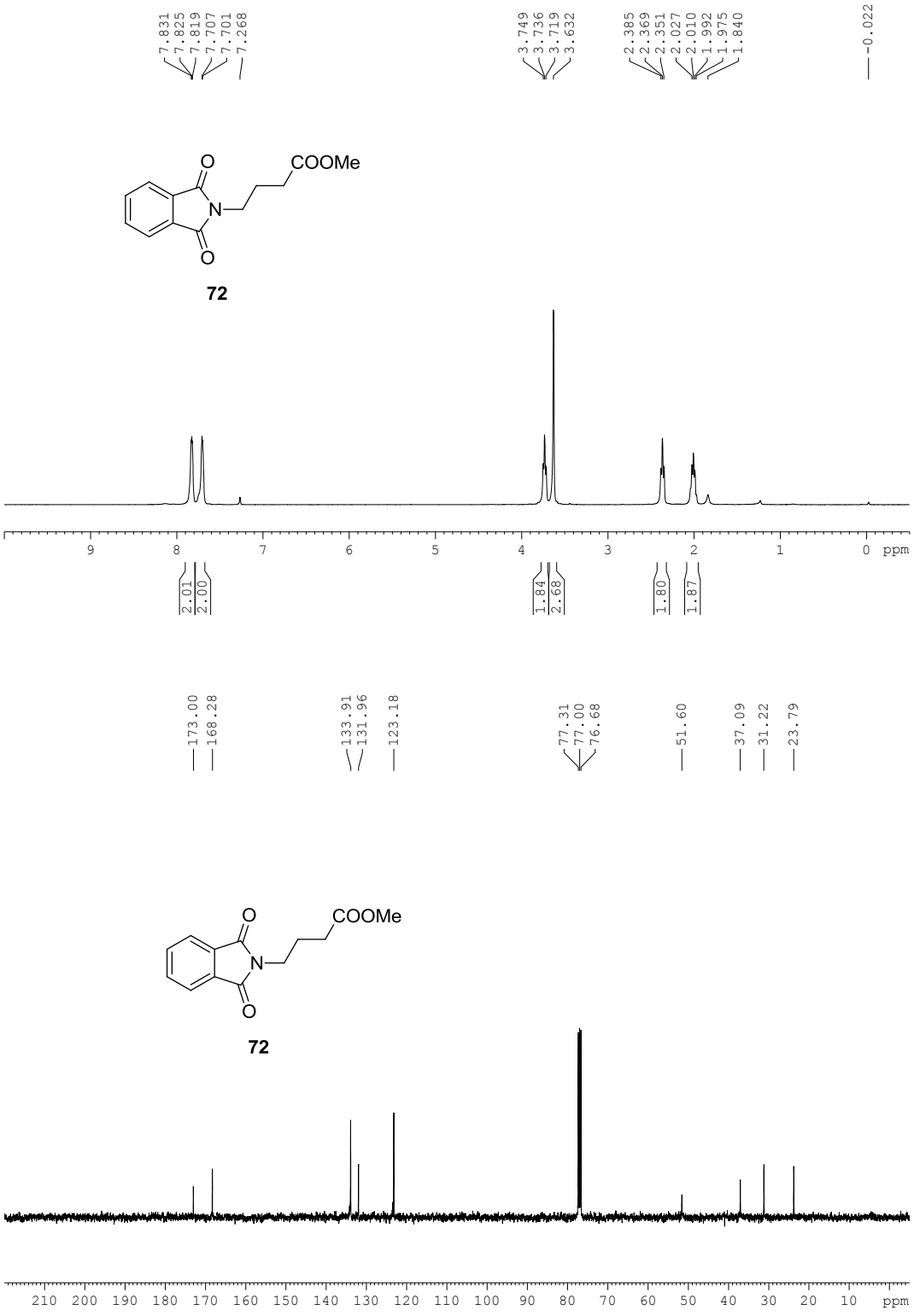
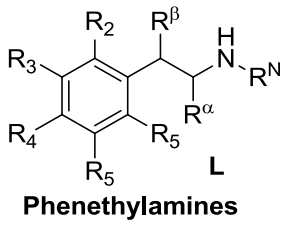


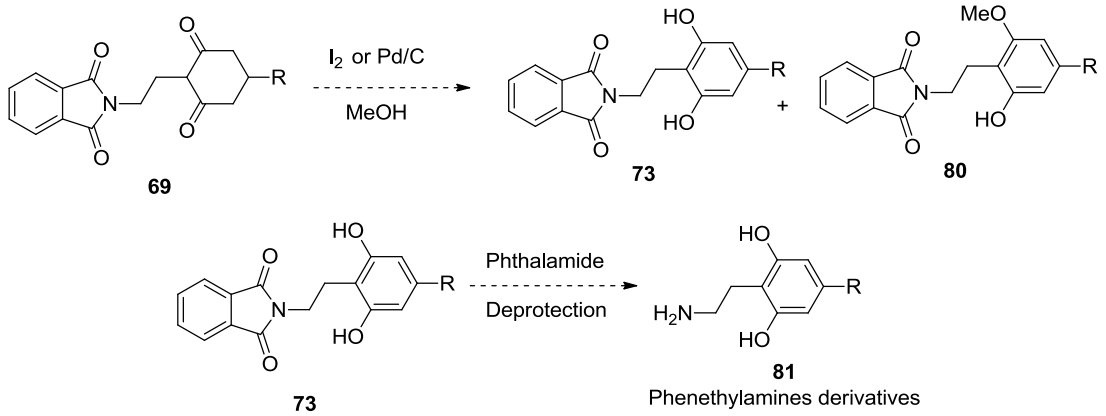

***Figure-N7:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **72**.

### *3.2.3.3 Diversity-Oriented Synthesis of Substituted Phenethylanimes*

Phenethylanimes are the class of drugs with hallucinogenic, physical, mental, emotional effects and entactogens, which exhibit their effects mainly through the monoamine neurotransmitter systems modulation. Others, such as epinephrine and dopamine function as neurotransmitters. A large group of alkaloids like benzylisoquinolines, tetrahydroisoquinolines, protoberberines, morphinans, protopines, narcotine and aporphines are derivatives of phenethylamines. Phenethylamines include a wide range of drug classes like psychotropic drugs, central nervous system stimulants (amphetamine), appetite depressants (phentermine), vasoconstrictors (levomethamphetamine and pseudoephedrine), antidepressants (phenelzine, bupropion and tranylcypromine), bronchodilators, vasodilators, calcium channel blockers (prenylamine and verapamil), neuroprotective agents, cardiotonic agents, antiparkinson agents, adrenergic agents (methamphetamine, methoxyphenamine and mephentermine), antilipemic agents (benfluorex), dopamine agents (bupropion), serotonin agents (2,5-dimethoxy-4-bromoamphetamine and fenfluramine) and monoamine oxidase inhibitors (selegiline). Many of these phenethylamines can be prepared easily using the Scheme 14 as shown below through OrgRC compounds **69**.[45, 46, 15i, 15n]




***Scheme 14***:- Aromatization of 2-Alkyl-cyclohexane-1,3-diones.




## *3.3 CONCLUSIONS*

In summary, we have developed a metal-free simple one-pot cascade synthesis of highly substituted 2-alkyl-CH-acids **69** and chiral W-M ketone analogues **71** from simple starting materials *via* cascade reductive coupling, RA reactions under amino acid

catalysis. We have reported the reductive alkylation of highly reactive CH acids (tetronic acid, cyclohexane-1,3-dione, cyclopentane-1,3-dione and dimedone) with aldehyde and Hantzsch ester without *bis*-product formation under amino acid catalysis. This three component reductive alkylation strategy or cascade reductive coupling reaction delivers the corresponding product in good yields with high chemo- and regio-selectivity using only 10 mol% of amino acid as the catalyst. Furthermore, we have demonstrated the application of OrgRC and M-A reactions in the synthesis of pharmaceutically useful molecules and natural products. We also demonstrated the two-carbon homologation of aldehyde *via* organo-catalyzed reductive coupling and decarboxylation reactions with high yields of GABA analogues which are important pharmaceuticals. Presently developed combination of cascade OrgRC and M-A reactions will be suitable to synthesize library of the total synthesis of biologically important natural products and their analogues. These reactions can be performed on a multi-gram scale under operationally simple and environmentally safe conditions.

# 4. Dynamic Kinetic Resolution through Proline-catalyzed Robinson Annulation Reactions

## 4.1 INTRODUCTION

The value of chirality is well recognised, mainly in relationship with the fact that almost all natural products are chiral and their pharmacological or physiological functions depend on their recognition with chiral receptors, which will do interactions only with the desired chiral molecules. Indeed, the synthesis of chiral molecules is a significant and demanding area of modern synthetic organic chemistry.[47] The broad utility of synthetic chiral molecules as single enantiomer medicines[48] has made asymmetric synthesis a prominent area of investigation.

Although magnificent progress has been made in asymmetric synthesis, either catalytically induced or substrate driven, kinetic resolution of racemates is still the most important method in industries for the synthesis of chiral compounds with high enantiopurity.[49,50] If the kinetic resolution method is used, one of the enantiomer from the racemic mixture is picked up to the required product while the other is remained fruitless and finally having a maximum theoretical yield of 50%.

In dynamic kinetic resolution (DKR),[50,51] one can obtain a quantitative yield of required enantiomer with high enantiopurity. Successfully, DKR combines the resolution step of kinetic resolution, with an *in-situ* equilibration of the chirally-labile reactnants (Figure 3). In DKR, the two enantiomers of a racemic reactant are forced to equilibrate at a rate that is faster than the reaction rate of the slow-reactant enantiomer to the product (Curtin–Hammett kinetics). Racemization of the reactants can be performed either catalytically, chemically or even spontaneously and at the same time conditions must be chosen to avoid the product racemisation. Among the most important achievements of DKR, organocatalyzed DKRs play a vital role in the synthetic scope of this process. A significant number of chiral organocatalysts are now available that afford excellent levels of stereocontrol which have been used in DKR.[51]

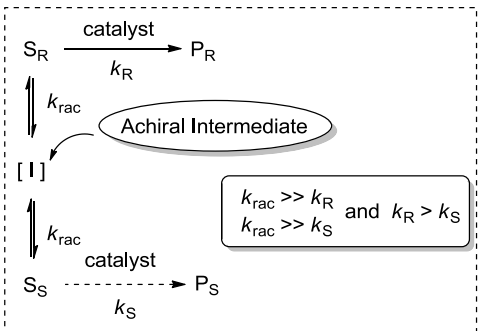



***Figure 3*** : Dynamic Kinetic Resolution

The Robinson annulation is an organic reaction utilized to convert an α, β-unsaturated ketone and a ketone to a carbocyclic molecule using base. Robinson annulation reactions are having a distinct place in asymmetric organic chemistry because of their ability to form a four-carbon chain in a single step leading to chiral six membered ring systems. Special concentration was shown to the organocatalytic high enantioselective preparation of both Hajos–Parrish ketones (HPK) and Wieland–Miescher ketones (WMK) starting from 2-alkylated 1,3-cyclopentanedione and 1,3-cyclohexanedione, respectively.[52] A lot of catalysts have been developed, including amine derivatives,[53] peptide derivatives,[54] α-amino acids derivatives,[55] β-amino acids derivatives[56] and proline derivatives[57] to prepare high enantioselective annulated products. The reaction triggers by deprotonation with the base of the α-hydrogen of the ketone to generate an enolate. The enolate then undergoes a 1,4- addition (Michael reaction) and then abstracts a proton from $H_2O$ to form a Michael product. Base abstracts other α-hydrogen and generates another enolate which then undergoes intramolecular aldol reaction with the ketone group to give a cyclic alkoxy intermediate. Dehydration of cyclic alkoxy intermediate leads to the stable α, β-unsaturated ketone. These products are significant systems in various biological products, for example within steriods.[58] The Robinson annulation reaction has long been employed as a convenient route to fused ring ketones.[52]

Hajos *et al.* in 1974,[53a] Agami *et al.*[59] in 1984, Swaminathan *et al.*[60] in 1999, Houk *et al.*[61] in 2001 and List *et al.*[62] in 2004 have developed independently the mechanism of Robinson annulation (Figure 4). All of them had proposed the mechanism based on prochiral substrate.

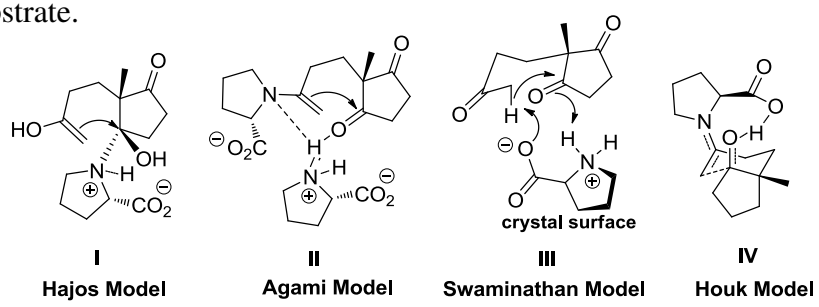


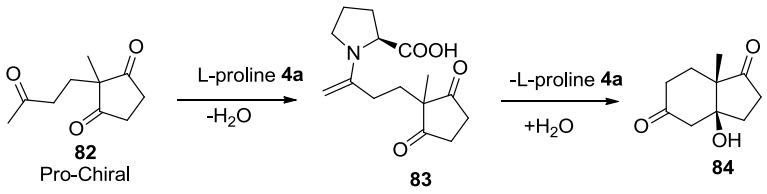

***Figure 4***: Proposed Transition States for Robinson Annulation Reaction through Asymmetric Desymmetrization.

The mechanism of the proline-catalyzed aldol reaction has been proposed at least five different ways. Experimentally, List *et al.* disclosed proline-catalyzed intramolecular

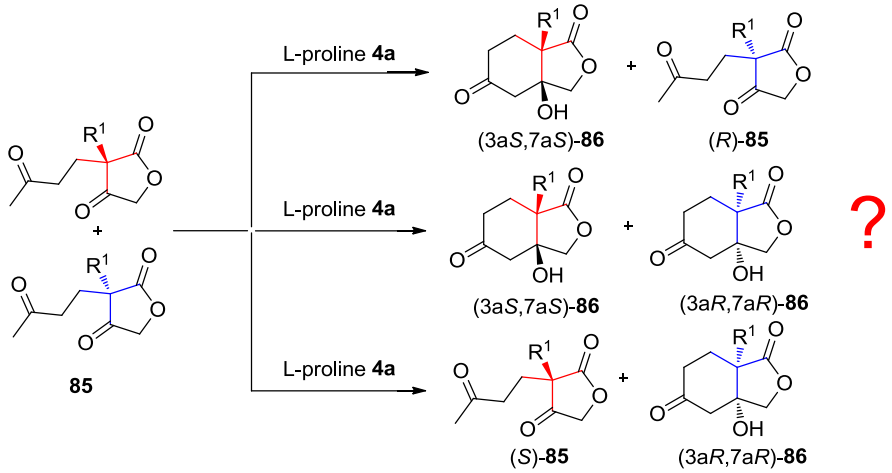
aldol reaction mechanism and provided further evidence for the involvement of enamine intermediates.

***Scheme 15:*** Direct Diastereoselective Intramolecular Aldol Reactions.

a) Houk-List Proposed Mechanism.




b) Present Work–I.




Eventhough the Robinson annulation mechanism of Hajos-Parish ketones and Wileand-Miesher ketones has well established but still there is no proper mechanism for other Robinson annulation reactions of unsymmetrical diketones **85** as shown in Scheme 15. When racemic compound-**85** undergoes an intramolecular aldol reaction under L-proline catalysis there are three possibilities of product formation. Among them

i) Cyclised product (3a*S*, 7a*S*)-**86** from (*S*)-**85** + left over starting material (*R*)-**85**.

ii) Racemic cyclised product **86**.

iii) Cyclised product (3a*R*, 7a*R*)-**86** from (*R*)-**85** + left over starting material (*S*)-**85**.

And also when enolizable tetronic acid derivative **87** undergoes Michael addition there also three types of products are possible.

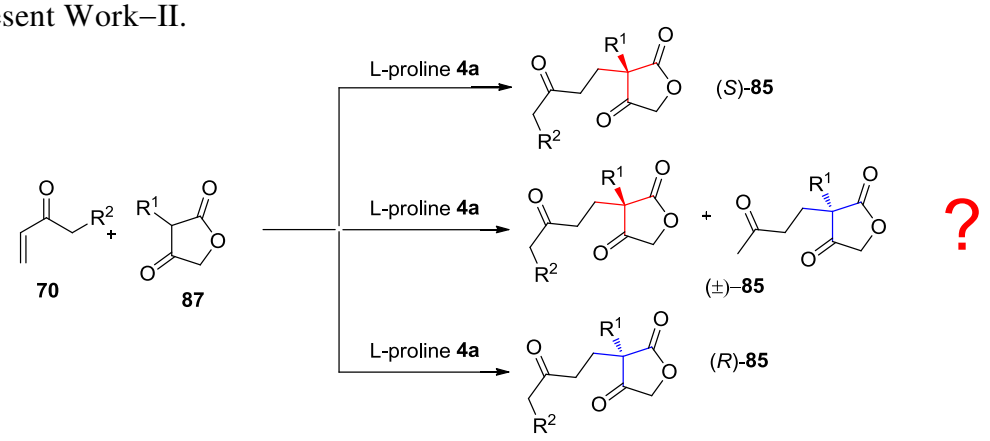
iv) Michael adduct (*R*)-**85**.

v) Racemic Michael adducts **85**.

vi) Michael adduct (*S*)-**85**.

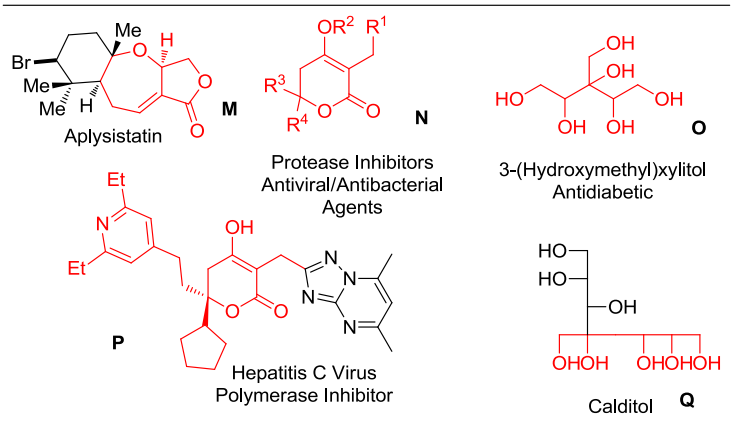
***Scheme 16:*** Chiral Catalyst Catalyzed Diastereoselective Michael Reactions.

c) Present Work–II.




In order to answer all these questions we started working on 2-alkyl tetronic acid derivatives. From last ten years, we are developing the chemoselective C-alkylation of 1,3-dicarbonyls with a variety of organic hydrides and aldehydes through OrgRC reaction under amino acid-catalysis.[15] With well developed report of this metal-free reductive coupling or OrgRC reaction, many synthetic chemists in their method development[22-28] or total synthesis[29-32], biologists in drug developments[33] and industrialists in the bulk scale synthesis of medicines[8] had utilized this powerful OrgRC reaction as a crucial and key step in alkylation of active methylenes. Herein, we envisioned that the OrgRC reaction of tetronic acid **3f**, organic hydrides **1a** and aldehyde **2** in the presence of a catalytic amount of L-proline **4a** would provide the reductive alkylation products **87** at 25 °C, which on further used as nucleophiles in Michael addition with alkyl vinyl ketones **70** to give Michael adducts **85**. These Michael adducts were treated with L-proline **4a** to provide bicylic alcohol **86**. Some of the applications of OrgRC and M-A products have shown in Chart 2.

***Chart 2:*** Applications of OrgRC products.



## 4.2 RESULTS AND DISCUSSIONS

### 4.2.1 Three-Component Reductive Alkylation (OrgRC) of Chiral Aldehydes: Reaction Optimization

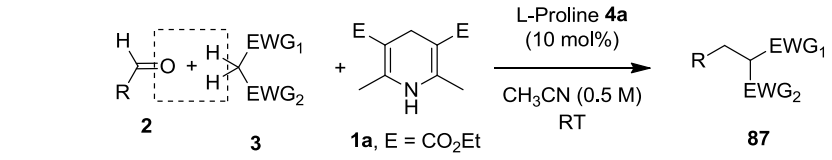
We initiated our preliminary studies of the OrgRC reactions by screening two solvents for the reductive coupling of (*R*)-glyceraldehyde acetonide **2b** with tetronic acid **3f** and Hantzsch ester **1a** under L-proline **4a**-catalysis and some representative results are shown in Table 3. Interestingly, reaction of (*R*)-**2b** (>98% ee) with each 1 equiv. of **3f** and **1a** in $CH_2Cl_2$ under 10 mol% of **4a**-catalysis furnished the OrgRC product **87a** ($[\alpha]^{25}_D = -34.4$) in 95% yield without racemisation. Same reaction in $CH_3CN$ under 10 mol% of L-proline **4a**-catalysis furnished the OrgRC product **87a** with increased yield (98%) and similar optical rotation value after 12 h. In the final, solvent $CH_3CN$ was chosen as optimized reaction condition.

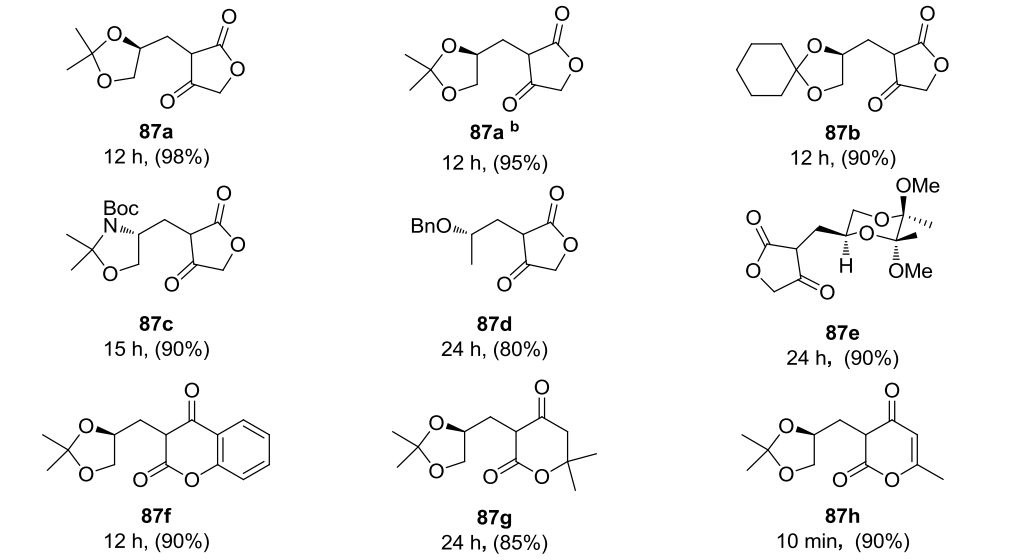
### 4.2.2 Diversity-Oriented Synthesis of OrgRC Products 87

With the optimized OrgRC reaction conditions in hand, the scope of the L-proline-catalyzed cascade OrgRC reactions were investigated with different chiral aldehydes **2**, various CH-acids **3** and Hantzsch ester **1a** as shown in Table 3. Reaction of chiral aldehyde **2d** with tetronic acid **3f** and Hantzsch ester **1a** in $CH_3CN$ at 25 °C for 12 h under L-proline-catalysis furnished the OrgRC products **87b** as single enantiomer in 90% yield respectively (Table 3). The reaction of (*S*)-Garner aldehyde **2l** with tetronic acid **3f** and Hantzsch ester **1a** under L-proline-catalysis furnished the OrgRC product **87c** as single enantiomer in 90% yield at 25 °C (Table 3). In similar manner, the reaction of **2m** with tetronic acid **3f** and Hantzsch ester **1a** under L-proline-catalysis furnished the OrgRC product **87d** as single enantiomer in 80% yield at 25 °C (Table 3). Protected (*R*)-glyceraldehyde **2n** on reaction with tetronic acid **3f** and Hantzsch ester **1a** in $CH_3CN$ at 25 °C for 24 h under L-proline-catalysis furnished the OrgRC products **87e** as single enantiomers in 90% yield respectively (Table 3). Similarly **3k** and **3n** on reaction with **2b,** Hantzsch ester **1a** in $CH_3CN$ at 25 °C for 12 h and 24 h under L-proline-catalysis furnished the OrgRC products **87f** and **87g** as single enantiomers in 90% and 85% yield respectively (Table 3). Interestingly, Reaction of chiral aldehyde **2b** with CH-acid **3o** and Hantzsch ester **1a** in $CH_3CN$ at 25 °C under L-proline-catalysis furnished the OrgRC products **87h** with in 10 min as single enantiomers in 90% yield respectively (Table 3). The results in Table 3 demonstrate the broad scope of this reductive methodology

covering a structurally diverse group of chiral aldehydes **2** with many of the yields obtained being very good and without racemisation of the reduced products.

***Table 3***: Diversity-Oriented Synthesis of Chiral OrgRC Products **87a-h**.[a]




[a] Yield refers to the column purified product. [b] $CH_2Cl_2$ used as solvent.

### *4.2.3 Effect of Chiral Catalyst (L-Proline) on Michael Addition*

After 2-alkyl-tetronic acids in hand, we want to know the asymmetric induction effect of proline in Michael Reaction. We initiated our preliminary studies of the diastereoselective Micahel reaction on the OrgRC product **87a** with freshly distilled methyl vinyl ketone (MVK) (3 equiv.) under L-Proline catalysis in dry DMSO. After stirring for 9 h, interestingly we isolated the Michael adduct **85aa** in 80% yield with 1:1 diasteremeric ratio. With this preliminary reaction in hand, we want to perform this reaction on some more OrgRC products **87** for generality purpose. The OrgRC product **87b** on reaction with MVK under L-proline catalysis in DMSO furnished the product **85ba** in 1:1 diastereomeric ratio. The OrgRC product **87c** and **87d** on reaction with MVK under L-proline catalysis in DMSO furnished the product **85ca** and **85da** in 1:1 and 1:1.2 diastereomeric ratios respectively. The OrgRC product **87e** and **87g** on reaction with MVK under L-proline catalysis in DMSO furnished the product **85ea** and **85ga** in 1:1.3 and 1:1 diastereomeric ratios, respectively as shown in Table 4. The OrgRC product **87a** on reaction with ethyl vinyl ketone **70b** under L-proline catalysis in DMSO furnished the product **85ab** in 1:1 diastereomeric ratio.

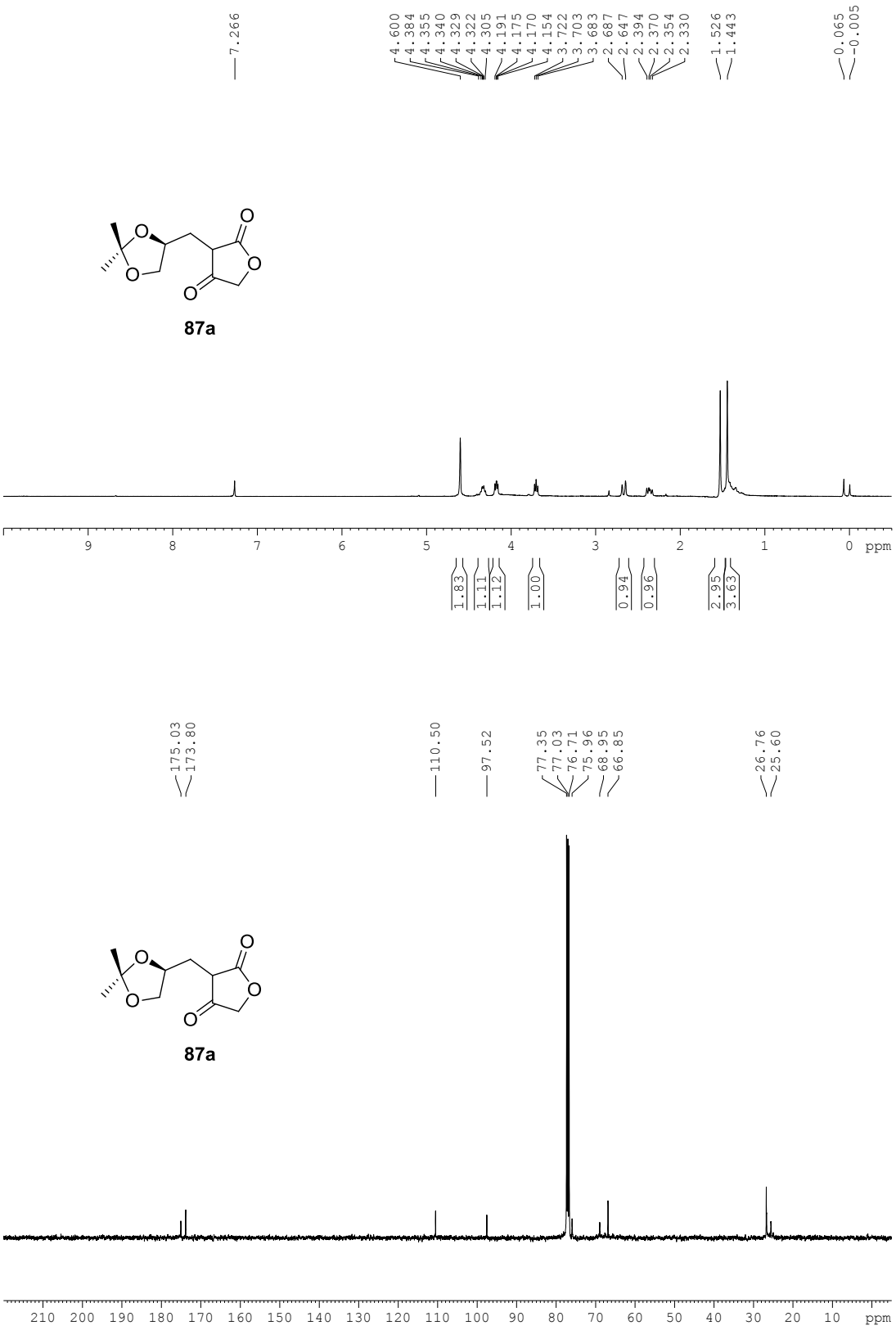



***Figure-N8:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **87a**.

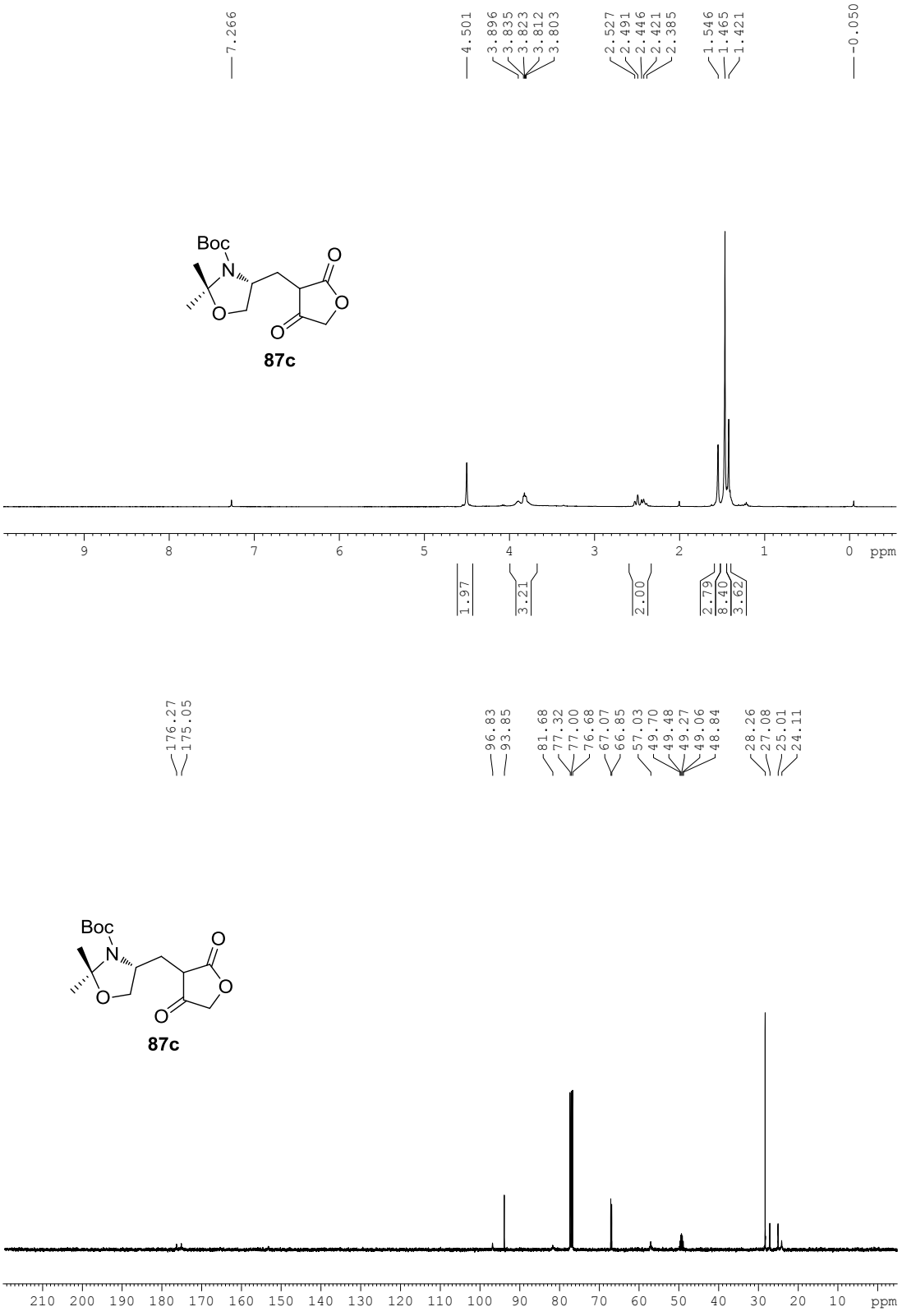



***Figure-N9:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **87c**.

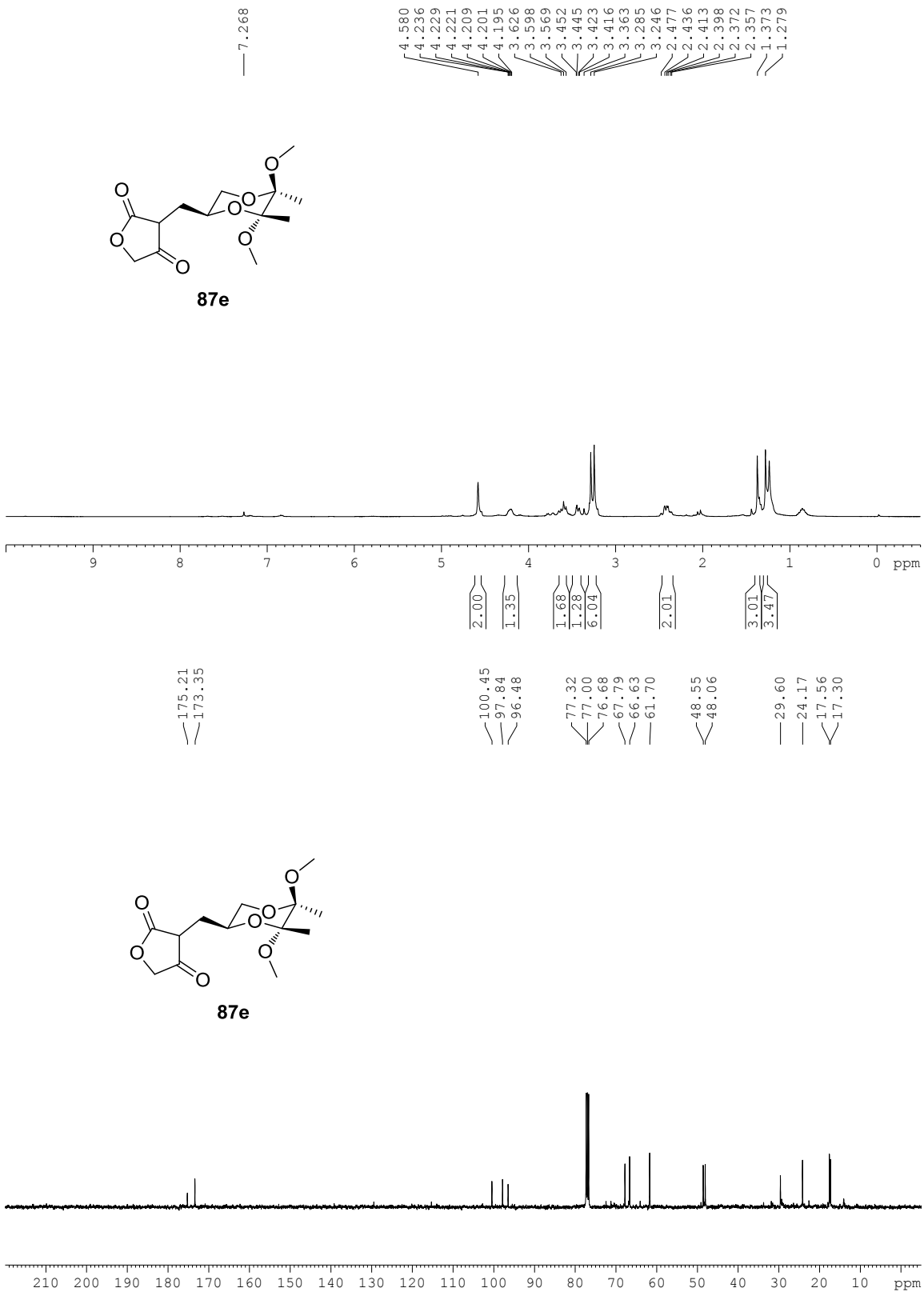



***Figure-N10:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **87e**.

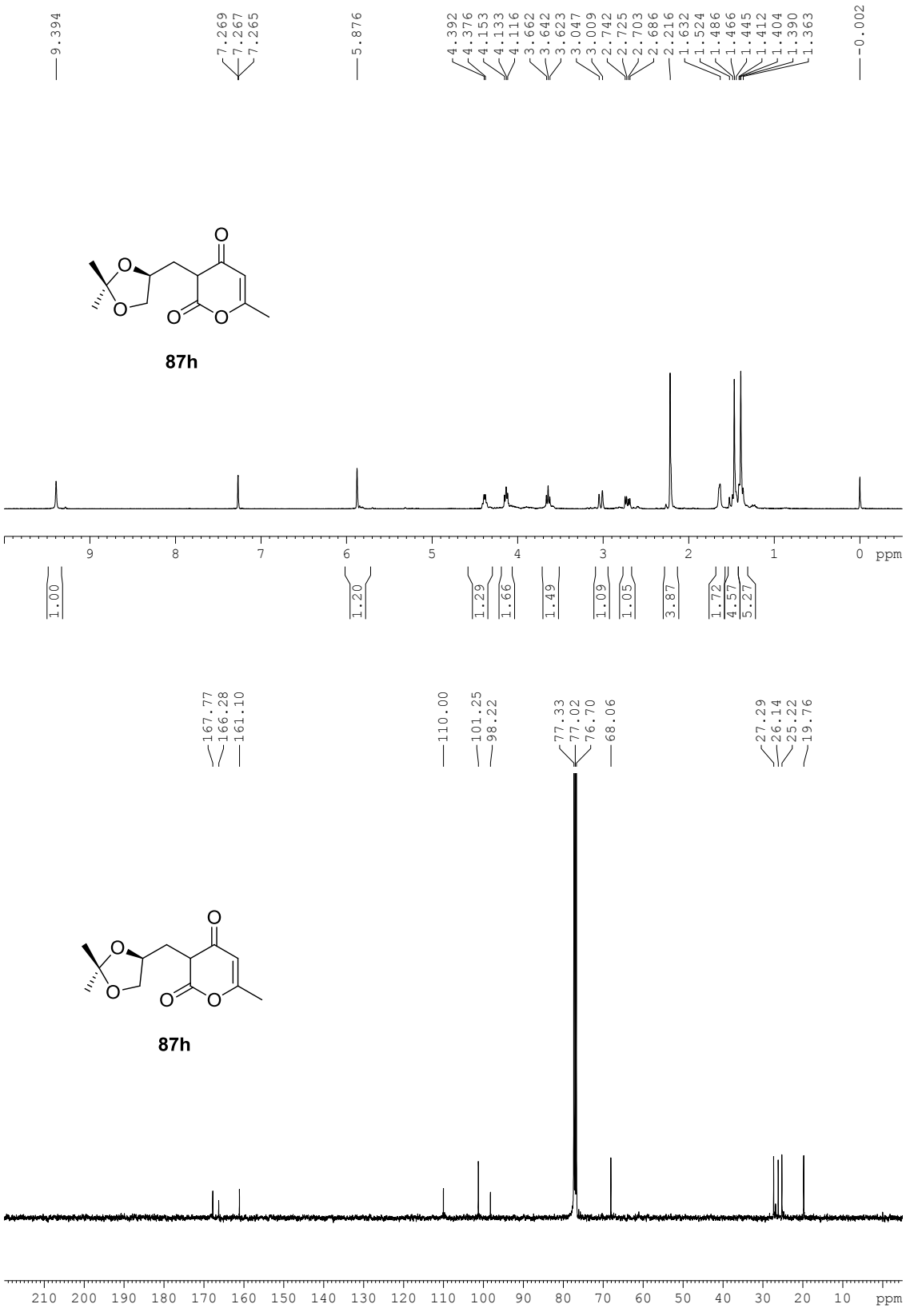
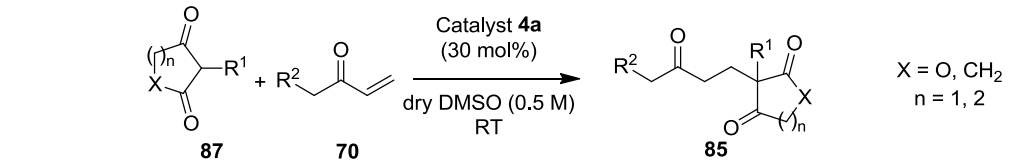
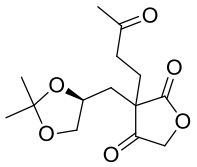


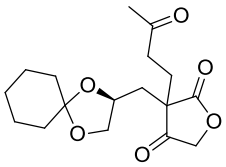

***Figure-N11:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **87h**.

***Table 4***: Diversity-Oriented Synthesis of Michael Adducts **85**.[a, b, c]

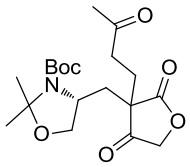


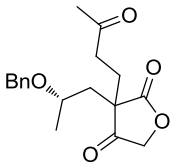
**85aa**
9 h, 78%
*dr* = 1:1



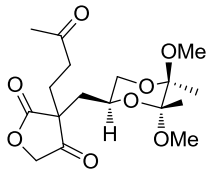
**85ba**
6 h, 62%
*dr* = 1:1



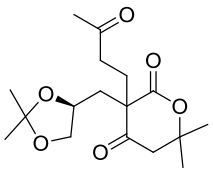

**85ca**
3 h, 68%
*dr* = 1:1



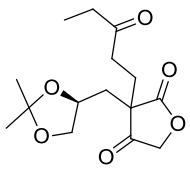

**85da**
6 h, 60%
*dr* = 1:1.2



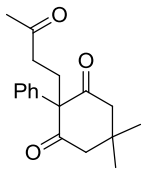

**85ea**
4 h, 80%
*dr* = 1:1.3



**85ga**
2 h, 58%
*dr* = 1:1



**85ab**[d]
6 h, 80%
*dr* = 1:1




**85x**[e]
4 h, 82%

[a] Reactions were carried out in solvent (0.5 M) with 3.0 equiv. of freshly distilled methyl vinyl ketone **70a** in the presence of 30 mol% of Catalyst. [b] Yield refers to the column purified product. [c] *dr* based on NMR analysis. [d] Ethyl vinyl ketone **70b** was used. [e] Triethyl amine (10 mol%) used as the catalyst under neat condition.

### *4.2.4 Diastereoselective Aldol Reaction with Chiral Michael Adducts 85 through DKR: Reaction Optimization*

After successful synthesis of 1:1 diastereomeric chiral Michael aduucts **85,** next we focussed on organocatalyst effect on diastereoselective aldol cyclisation through DKR. We initiated our preliminary studies of the aldol reaction by screening a number of known and novel organocatalysts for the aldolization of **85aa** with different conditions and some representative results are shown in Table 5. Interestingly, aldol reaction of 1:1 diastereotropic **85aa** in DMSO under 30 mol% of L-proline **4a**-catalysis furnished the aldol product (3a*S*,7a*R*)-**86aa** in 90% yield with 10:1 diasteremeric ratio at 25 °C for 2 days (Table 5, entry 1). Same reaction in DMSO under 30 mol% of DL-proline **4b**- catalysis furnished the aldol product **86aa** with 1:1 diastereomeric ratio in 88% yield at 25 °C for 2 days (Table 5, entry 2). Interestigly, same reaction in DMSO under 30 mol% of D-proline **4c**-catalysis furnished other isomer of the aldol product (3a*R*,7a*S*)-**86aa** in 80% yield with 7:1 diastereomeric ratio at 25 °C for 2 days (Table 5, entry 3).

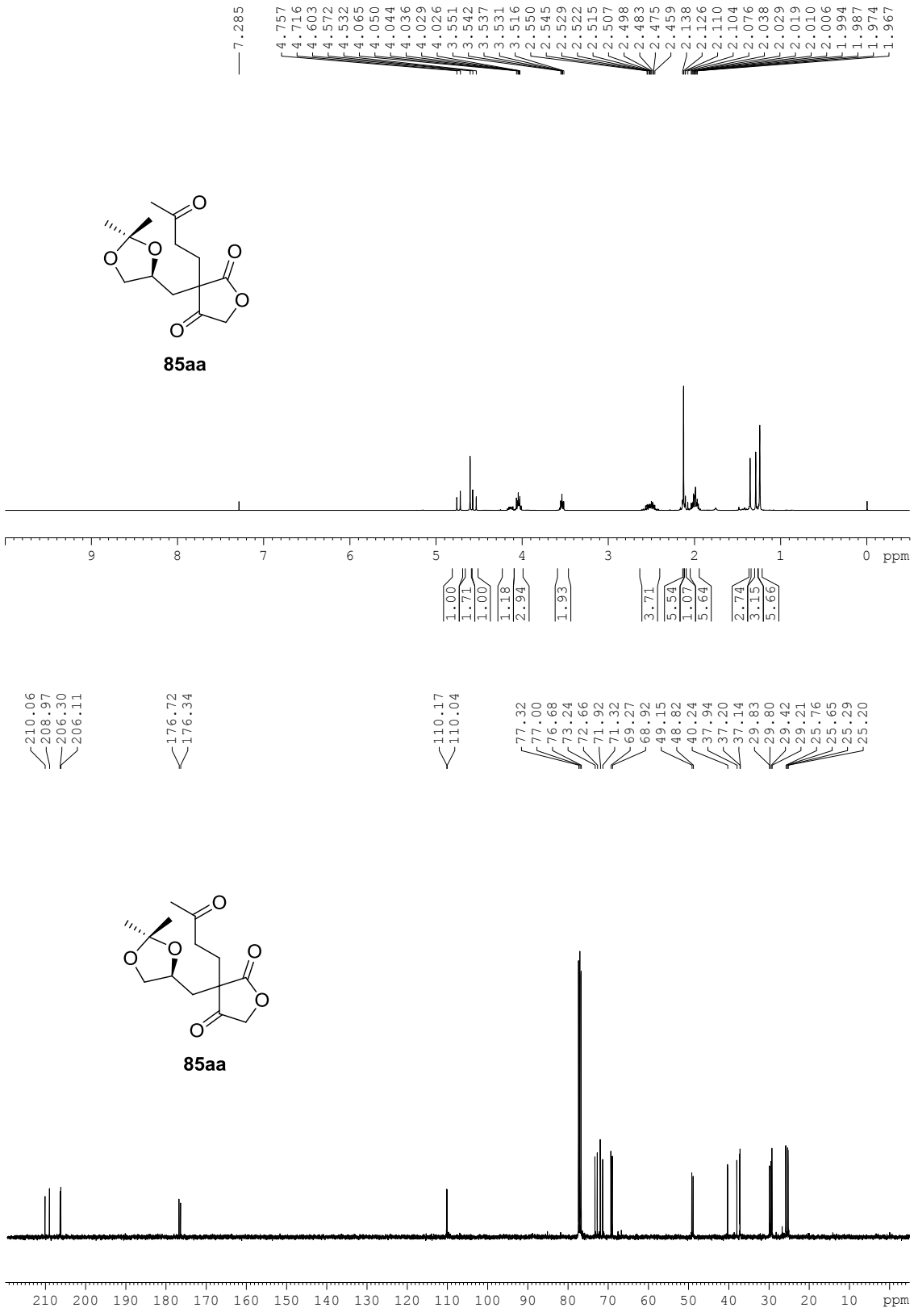



***Figure-N12:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **85aa**.

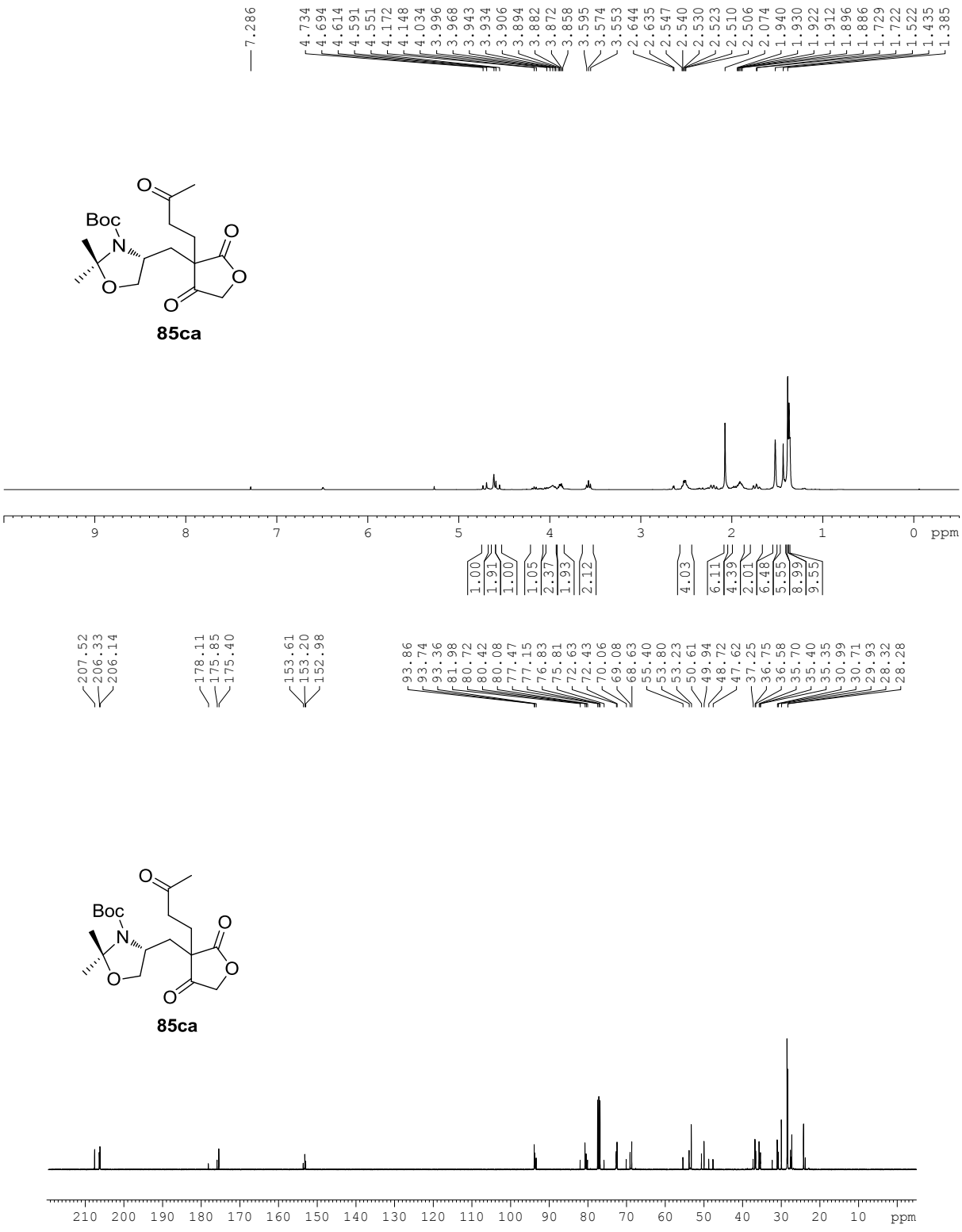



***Figure-N13:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **85ca**.

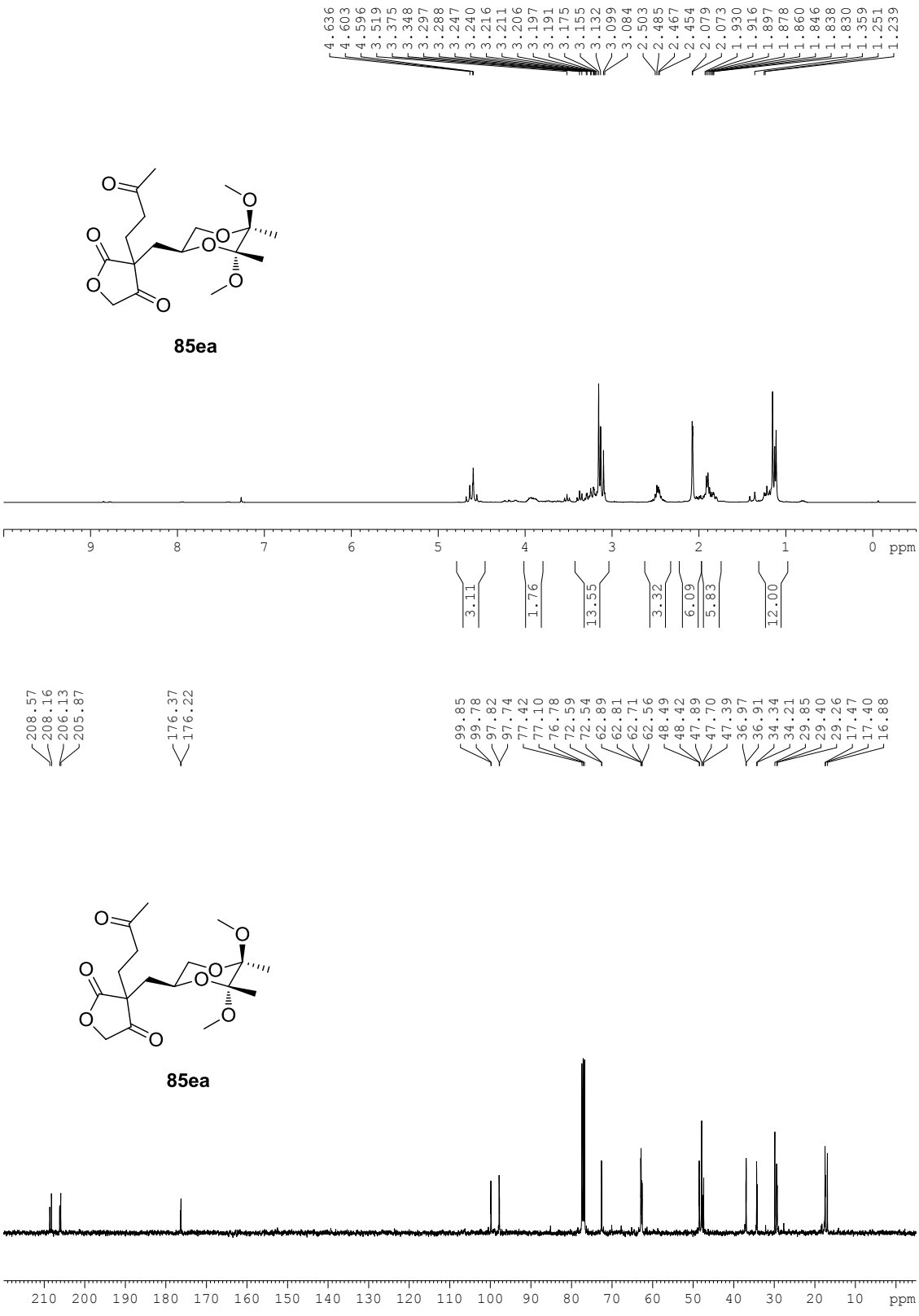
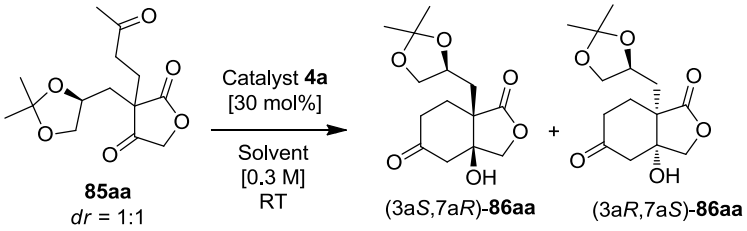



***Figure-N14:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **85ea**.

***Table 5***: Reaction Optimization-Diastereoselective Aldol Reaction.[a, b]

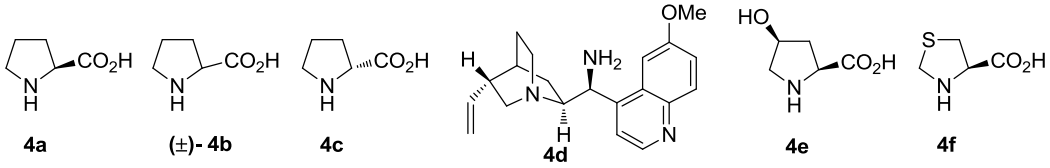



**85aa**
*dr* = 1:1

(3a*S*,7a*R*)-**86aa** + (3a*R*,7a*S*)-**86aa**

| Entry | Catalyst | Solvent | Time [days] | **86aa** Yield [%][a] | **86aa** *dr*[b] |
|---|---|---|---|---|---|
| **1** | **4a** | **DMSO** | **2** | **90** | **10:1** |
| **2** | **4b** | **DMSO** | **2** | **88** | **1:1** |
| **3** | **4c** | **DMSO** | **2** | **80** | **1:7** |
| 4 | **4a** | DMSO+$D_2O$ (2:1) | 2 | 20 | --- |
| 5[c] | **4a** | DMSO+$D_2O$ (2:1) | 1 | 75 | 1:1 |
| 6 | **4a** | THF | 3 | 31 | --- |
| 7 | **4a** | $CH_3CN$ | 3 | 50 | 3:1 |
| 8[d] | **4d/TCA** | THF | 2 | 20 | --- |
| 9 | **4e** | DMSO | 2 | 75 | 3:1 |
| 10 | **4f** | DMSO | 3 | 72 | 2:1 |
| 11 | **4a** | MeOH | 3 | 50 | 1:1 |
| 12 | **4a** | DMF | 2 | 85 | 3:1 |
| 10[e] | **4a** | DMF | 3 | 62 | 1.5:1 |

[a] Yield refers to the column purified product. [b] Based on NMR analysis. [c] Reaction heating at 50-60 °C. [d] 10 mol% of **4d** catalyst, 20 mol% of trichloro acetic acid (TCA) as cocatalyst was used. [e] Reaction performed at -10 °C.




**4a** (±)- **4b** **4c** **4d** **4e** **4f**

To further improve the *dr*/yield of aldol product **86aa**, we also tested number of amino acids, cinchona alkaloid Q-$NH_2$ **4d**/TCA for the diastereoselective aldol reaction of **85aa** with different solvents and temperature as demonstrated in Table 5. Among these catalysts **4a-f** tested for aldol reaction, L-Proline **4a** showed better results compared to other catalysts (Table 5, entry 1). We envisioned the optimized condition to be 25 °C in DMSO under 30 mol% L-proline **4a**-catalysis to furnish

major diastereomer of highly substituted product **86aa** in 90% yield with 10:1 *dr* through DKR. The absolute configuration of products **86aa** were assigned under L-/D-proline-catalysis was established by comparison with the related crystal structure.

After obtaining interesting results with high diastereomeric **86aa**, then we want to examine on different substrates.

### *4.2.5 Diversity-Oriented Diastereoselective Synthesis of Chiral Aldol Products 86*

Interestingly, aldol reaction of 1:1 diastereotropic **85ba** in DMSO under 30 mol% of L-proline **4a**-catalysis furnished the aldol product **86ba** in 80% yield with 6:1 diasteremeric ratio at 25 °C for 1.5 days (Table 6). Aldol reaction of 1:1 diastereotropic **85ca** in DMSO under 30 mol% of L-proline **4a**-catalysis furnished the aldol product **86ca** in 80% yield with 5:1 diasteremeric ratio at 25 °C for 3 days (Table 6). Interestingly, aldol reaction of 1:1.2 diastereotropic **85da** in DMSO under 30 mol% of L-proline **4a**-catalysis furnished the aldol product **86da** in 60% yield with 2:1 diasteremeric ratio at 25 °C for 1.5 days (Table 6). Interestingly, aldol reaction of 1:1.3 diastereotropic **85ea** in DMSO under 30 mol% of L-proline **4a**-catalysis furnished the aldol product (3a*S*,7a*R*)-**86ea** in 90% yield with 8:1 diasteremeric ratio at 25 °C for 3 days (Table 6). Same reaction of 1:1.3 diastereotropic **85ea** in DMSO under 30 mol% of D-proline **4c**-catalysis furnished the aldol product (3a*R*,7a*S*)-**86ea** in 82% yield with 5:1 diastereomeric ratio at 25 °C for 3 days (Table 6). All expected chiral aldol products **86** were furnished in good yields with good *dr*'s from the reaction of **85** under **4a** catalysis (see Table 6). Interestingly, aldol reaction of 1:1 diastereotropic **85ab** in DMSO under 30 mol% of L-proline **4a**-catalysis furnished the aldol product **86ab** in 50% yield with >10:1 diasteremeric ratio and 2.5:1 diasteremeric ratio of the sec-methyl (Table 6) and left over starting material *dr* increased to 1:3 indicating that one of the enantiomer is reacting fastly and other one is reacting slowly.


***Figure-N15:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **86aa**.

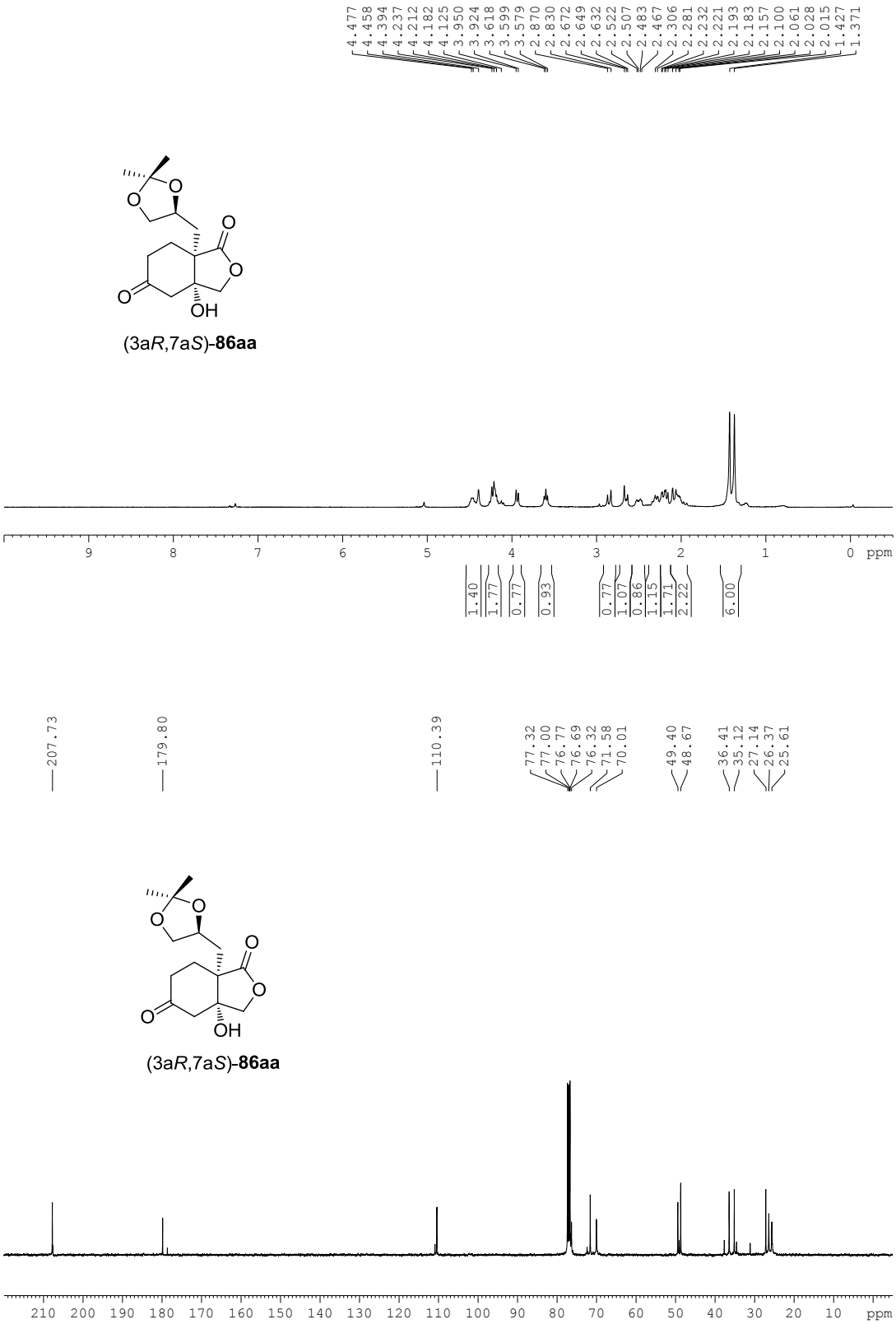
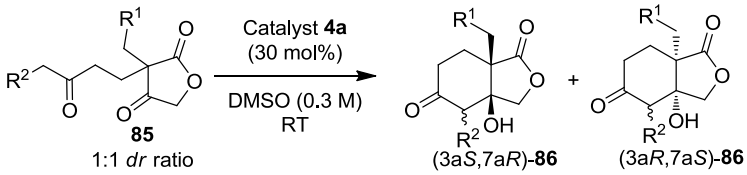
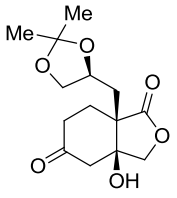
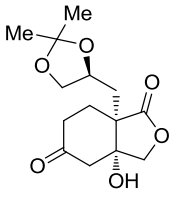
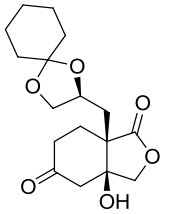
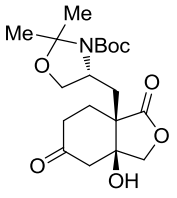
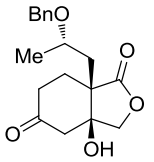
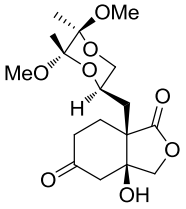
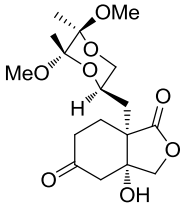
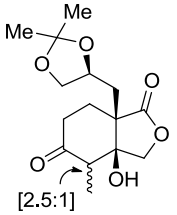



***Figure-N16:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **86aa**.

***Table 6:*** Synthesis of Chiral Bicyclic-ketones **86**.[a, b]

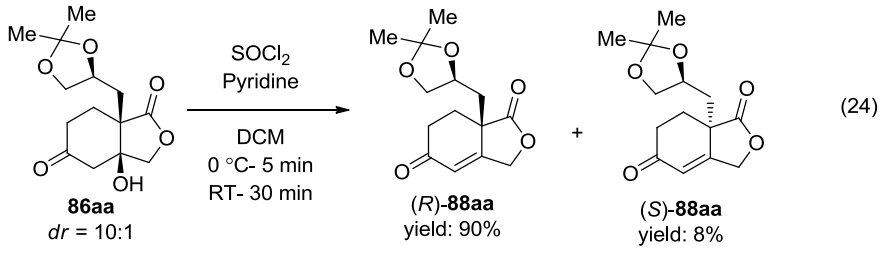



| | | | |
|---|---|---|---|
|  |  |  |  |
| (3a*S*,7a*R*)-**86aa**<br>2 days, yield: 90%<br>*dr* = 10:1 | (3a*R*,7a*S*)-**86aa**[c]<br>2 days, yield:80%<br>*dr* = 7:1 | **86ba**<br>1.5 days, yield: 80%<br>*dr* = 6:1 | **86ca**<br>3 days, yield: 80%<br>*dr* = 5:1 |
|  |  |  |  |
| **86da**[d]<br>1.5 days, yield: 60%<br>*dr* = 2:1 | (3a*S*,7a*R*)-**86ea**[e]<br>3 days, yield: 90%<br>*dr* = 8:1 | (3a*R*,7a*S*)-**86ea**[c,e]<br>3 days, yield: 82%<br>*dr* = 5:1 | **86ab**<br>5 days, yield: 50%<br>*dr* = >10:1 |

[a] Yield refers to the column-purified product. [b] *dr* determined by NMR analysis. [c] D-proline **4c** used as the catalyst. [d] reactant **85da** (*dr* = 1:1.2) [e] reactant **85ea** (*dr* = 1:1.3)

Bicyclic-alcohol **86aa** on treating with $SOCl_2$/pyridine in DCM at 0 $^oC$ for 5 minutes and at rt for 30 minutes furnished the expected diastereomeric bicyclic-enone (*R*)-**88aa** in 90% yield and another diastereomeric bicyclic-enone (*S*)-**88aa** with 8% yield as shown in eq.24. Same procedure followed for the dehydration of bicyclic-alcohol **86ab** to bicyclic-enone (*R*)-**88ab** as shown in eq.25.

***Scheme 17***: Dehydration of Hydroxy Compounds **86**.



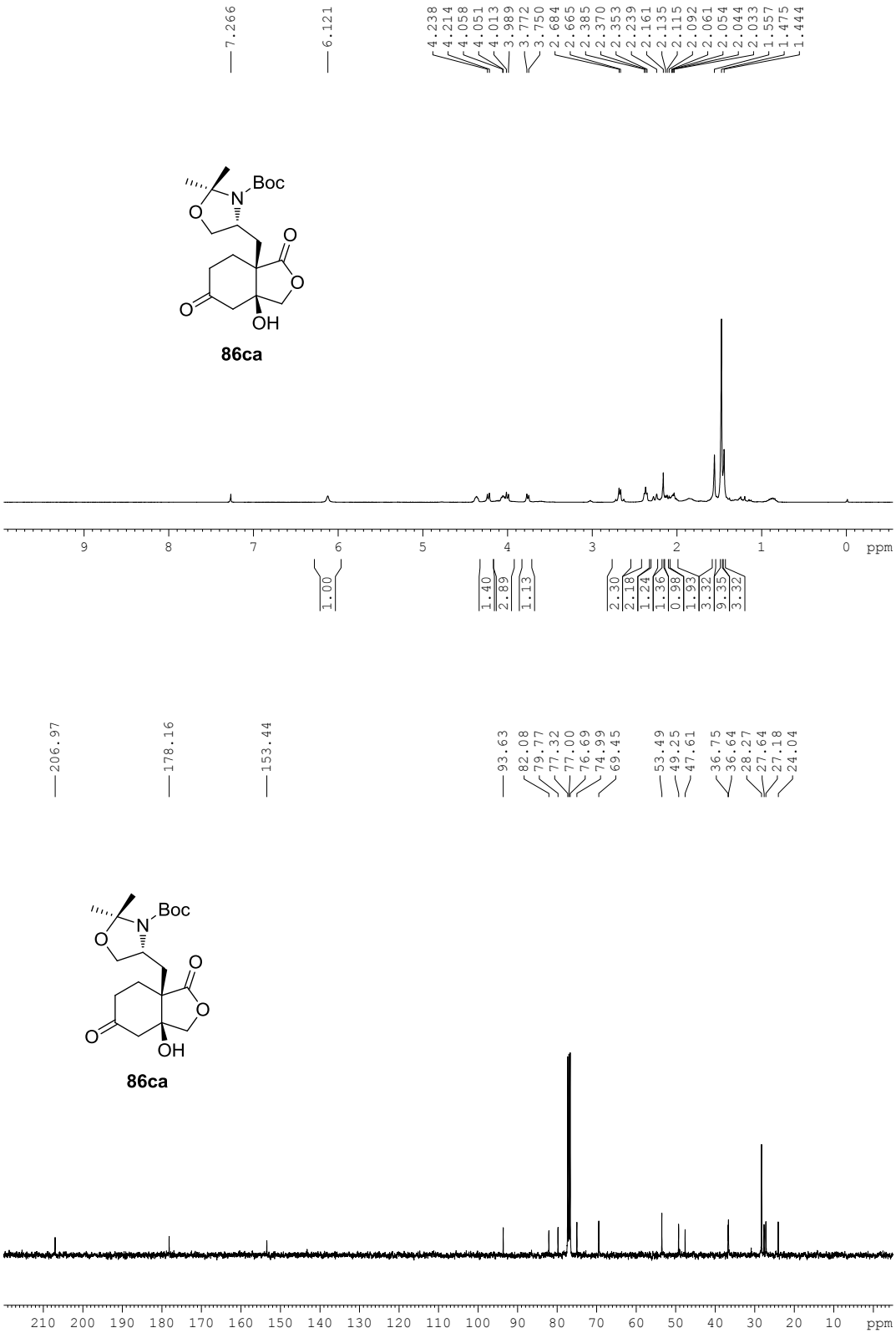



***Figure-N17:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **86ca**.

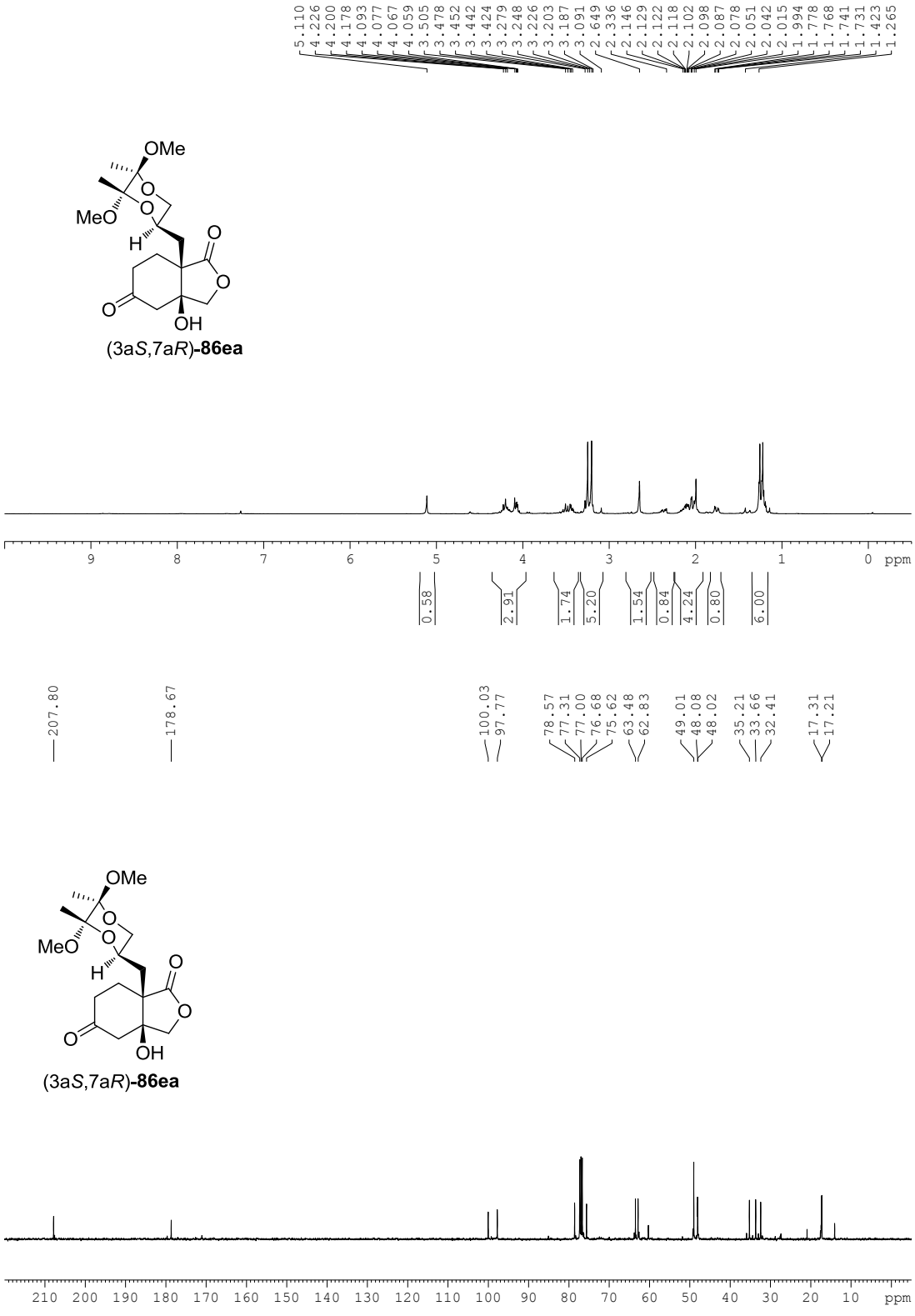



***Figure-N18:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **86ea**.

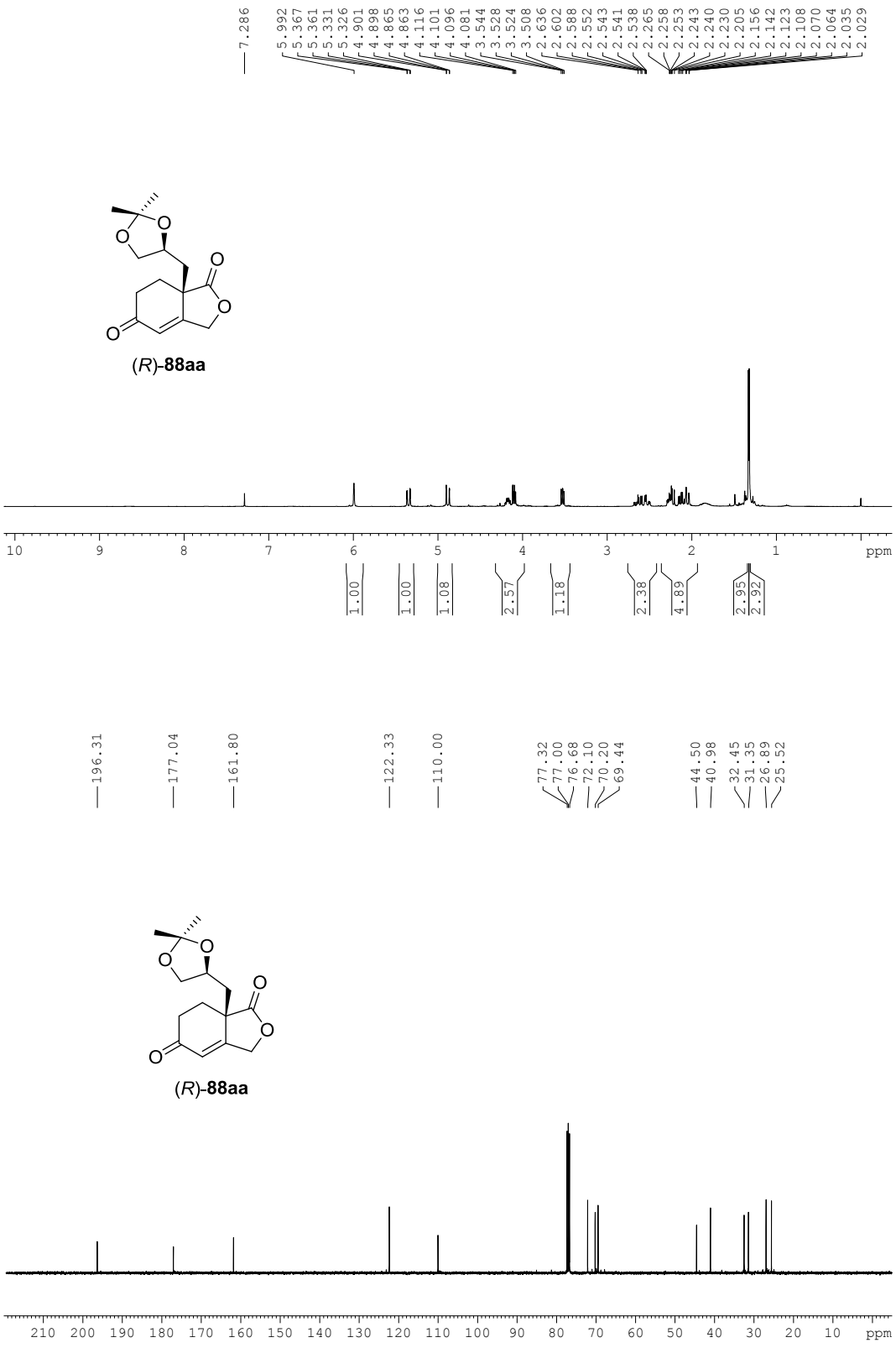



***Figure-N19:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **88aa**.

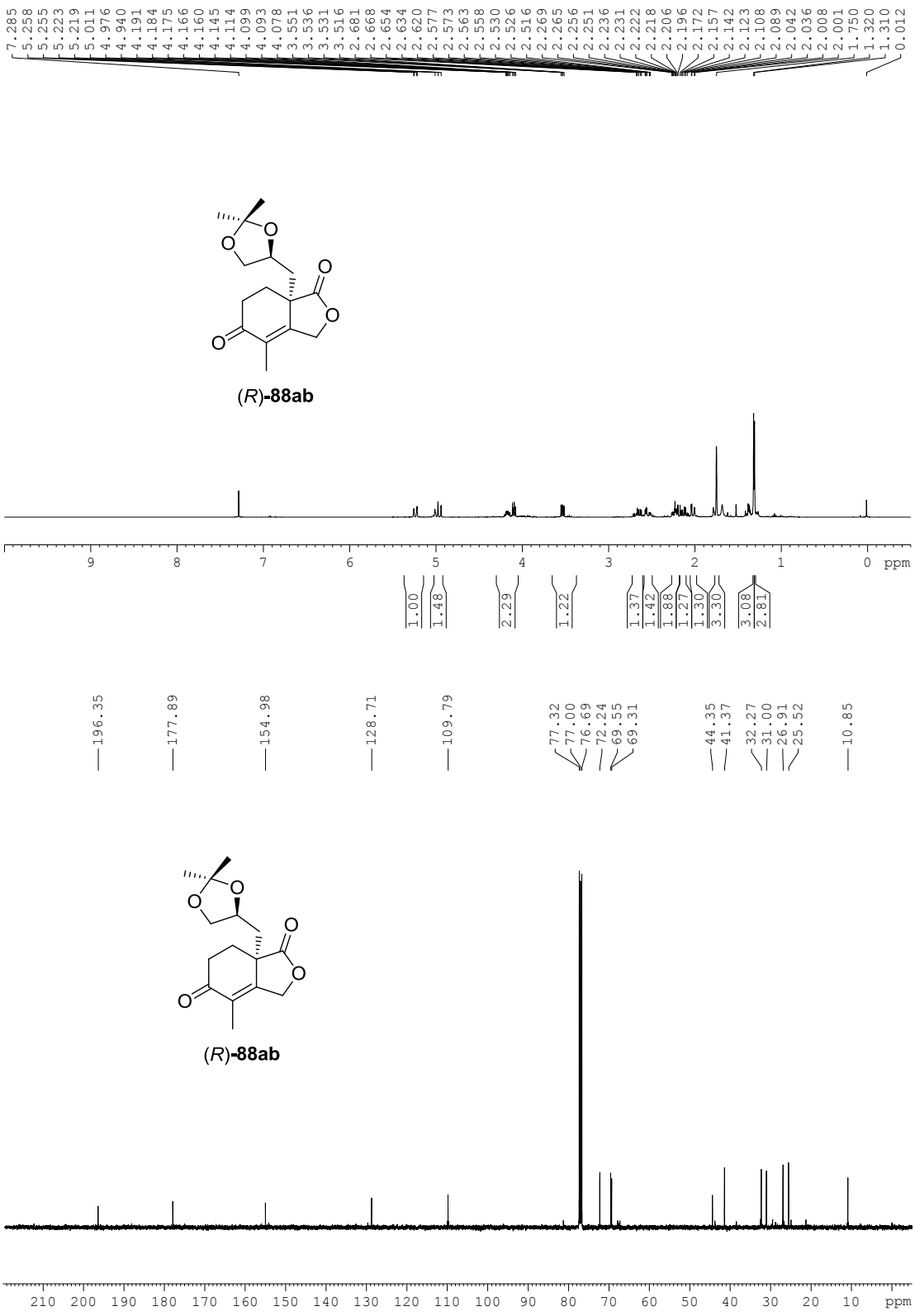
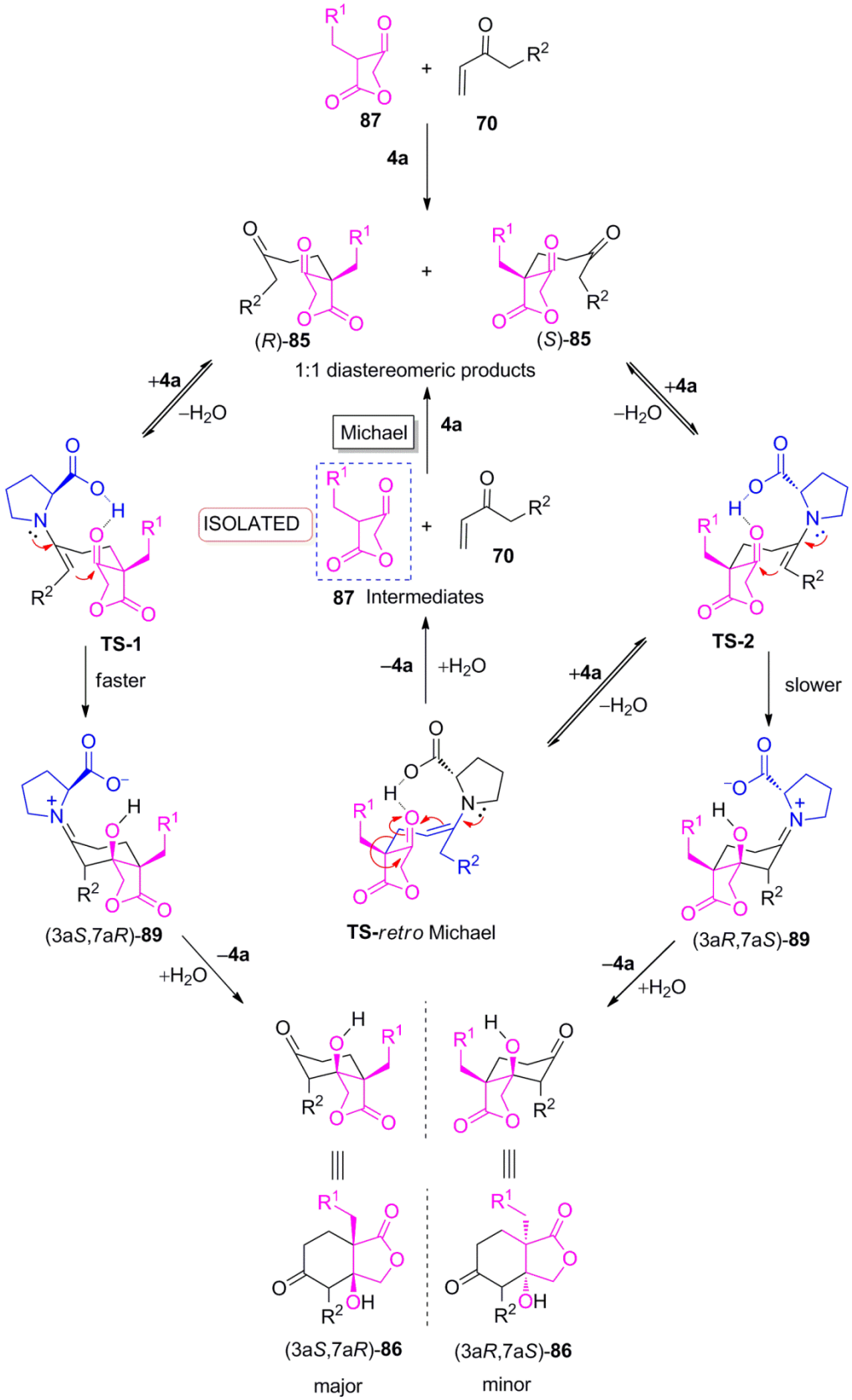



***Figure-N20:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **88ab**.

### *4.2.6 Mechanistic Insights*

***Scheme 18***: Proposed Mechanism for the DKR in Diastereoselective Aldol Reactions.



Michael addition of **87** with alkyl vinyl ketone **70** is most likely *via* iminium ion activation leads to the formation of Michael adduct **85** with less diastereoselective fashion as we obtained 1:1 ratio of the products. The possible mechanism for L-proline catalyzed diastereoselective synthesis of the diastereoselective intramolecular aldol condensation of **85** *via* enamine catalysis and *dr*'s of the desired bicyclic-alcohols **86** were obtained through dynamic kinetic resolution (DKR). In order to give strong support to DKR, we have done controlled experiments as shown in Schemes 18 and 19.

The observed high diastereoselectivity in aldol **86** products through DKR can be explained as illustrated in Scheme 18. L-Proline **4a**-catalyzed Michael addition of **87** with alkyl vinyl ketone **70** furnished the Michael adducts (*R*)-**85** and (*S*)-**85** with 1:1 disteremeric ratio, which on further reaction of the catalyst amino acid (*S*)-**4a** with both diketones (*R*)-**85** and (*S*)-**85** generate the enamines with almost similar rates as shown in Scheme 18. Intramolecular aldol condensation of enamine generated from diketone (*R*)-**85** will be a faster compared to aldol condensation of enamine generated from (*S*)-**85** as shown in **TS-1** and **TS-2** based on the strong/weak hydrogen bonding interactions, respectively (see Scheme 18). As the hydrogen bond does not support to cyclise the Michael adduct (*S*)-**85**, then it changes its regioselectivity in enamine formation and causing to break C-C bond by *retro*-Michael (*r*-M) Reaction producing OrgRC products **87** and alkyl vinyl ketones **70**. This *in-situ* generated products **87** and **70** again undergo Michael adiition to form 1:1 diastereomeric product. Over all diketone, (*S*)-**85** is again converting into Michael adducts (*R*)-**85** and (*S*)-**85** with 1:1 disteremeric ratio.

*In situ* hydrolysis of imines generated from **TS-1** and **TS-2** with $H_2O$ furnished the bicyclic-alcohols (3a*S*,7a*R*)-**86** and (3a*R*,7a*S*)-**86** respectively and observed high *dr* values of (3a*S*,7a*R*)-**86** is directly due to the faster reaction rate in **TS-1** and DKR.

### *4.2.7 Conditional Experiments for the Support of Proposed Mechanism*

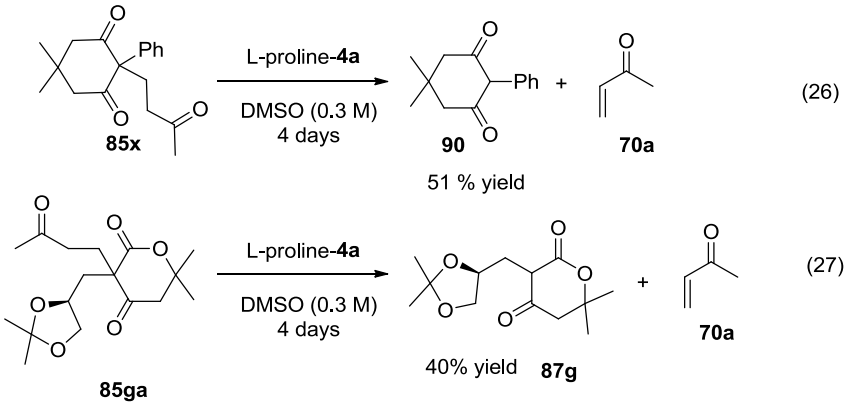
Surprisingly, there is no certified mechanism for the Robinson annulations of unsymmetrical ketones. The *r*-M reaction is well-known to occur readily under biological conditions.[63] On the other hand, only a few *r*-M reactions have taken place in laboratory syntheses.[64] Furthermore, studies on the scope of *r*-M reactions, particularly those linking 1,5-carbonyl compounds are rare, though the *r*-M reaction is known to take place for

several aromatic 1,5-diketones during mass spectral fragmentation.[65] Albrecht and coworkers[66] reported the *r*-M reaction of selected 1,5-diketones and proved that the reaction could be enhanced by using steam distillation in the presence of sodium hydroxide adsorbed on glass wool as catalyst. Li and Wang[67] reported steam-mediated *r*-M reaction for some 1,5-dicarbonyls present in steroid-type molecules. Until now there is no report on *r*-M reaction in Robinson Annulation.

***1) retro-Michael Reaction:-*** Here we keenly focused on the molecule desiging in order to observe *retro*-Michael reaction either by stabilising the intermediate or completely stoping the aldol reaction by increasing steric hindrance on the molecule.

Interestingly, aldol reaction of triketone **85x** in DMSO under 30 mol% of L-proline **4a**-catalysis did not furnish the expected aldol product at 25 °C for 4 days also (eq. 26). However, surprisingly, the major products formed in the reaction are the *retro*-Michael product, 5,5-dimethyl-2-phenylcyclohexane-1,3-dione **90** and methylvinyl ketone **70a** (51% yield; eq. 26). The expected aldol product was not formed in trace amount also. Interestingly, aldol reaction of 1:1 diastereomeric diketone **85ga** in DMSO under 30 mol% of L-proline **4a**-catalysis did not furnish the expected aldol product at 25 °C for 4 days also (eq. 27). However, surprisingly, the major products formed in the reaction are the *retro*-Michael product, 3-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6,6-dimethyldihydro-2H-pyran-2,4(3H)-dione **87g** and methyl vinyl ketone **70a** (40% yield; eq. 27). With these two isolated *retro*-Micheal intermediates, we can conclude that *retro*-Michael is responsible for the observed DKR in this compounds.

***Scheme 19:*** Isolation of Proposed Transition State Intermediates in the Diastereoselective Aldol Reactions.



We have recently reported evidence for the involvement of kinetic resolution of the C–C-bond forming step of proline-catalyzed intramolecular aldol reactions.[15d] Here we build on these findings and provided the evidence for DKR intermediates. We have shown that high *dr* values of aldol reaction, conducted in the presence of L-proline are due to DKR, a requirement of the proposed enamine mechanism. In addition, intermediates formed in *retro*-Michael reaction of ketones with proline have been detected and characterized by $^{1}$H NMR and $^{13}$C NMR and **86ca** further conformed by X-ray analysis.

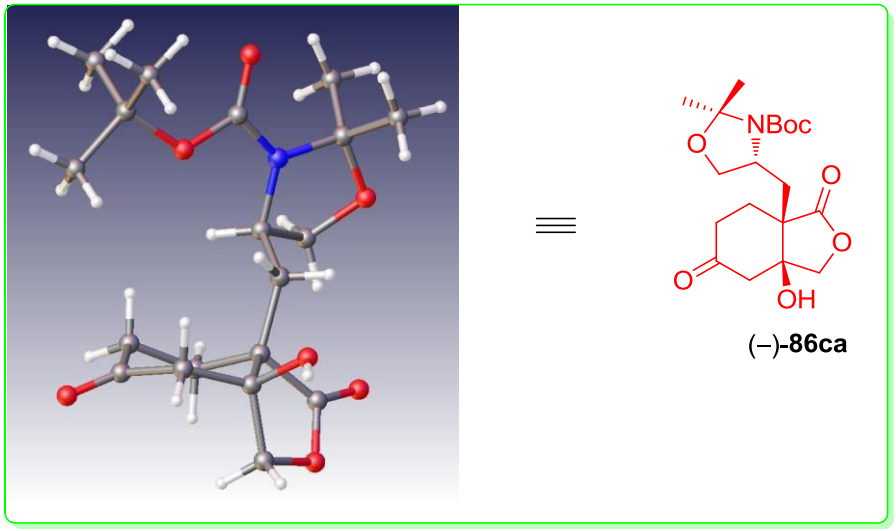



***FIGURE 5.*** X-Ray Crystal Structure of (*R*)-*tert*-Butyl 4-((7a-hydroxy-3,6-dioxooctahydroisobenzofuran-3a-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate **(-)-86ca.**

## *4.3 CONCLUSIONS*

In summary, first time we have developed the L-proline **4a**-catalyzed diastereoselective M-A reaction of OrgRC adducts **87** with alkyl vinyl ketone **70** at the ambient conditions. The diastereoselective M-A reactions proceed in good yields with high selectivities using L-proline as the catalyst through dynamic kinetic resolution (DKR). Furthermore, we have demonstrated the mechanism of Michael, aldol and *retro*-Michael reaction. We have isolated two intermediates which are giving a strong support to our proposed mechanism. For the first time we showed the DKR with the proof of intermidiate.

# 5. A General Approach to Chiral 8-Hydroxy-2-thiabicyclo[3.3.1]nonane-4,9-diones via Direct Amine-catalyzed Cascade Reductive Couplings and Robinson Annulations

## 5.1 INTRODUCTION

The Robinson annulation is an organic reaction utilized to convert an α, β-unsaturated ketone and a ketone to a carbocyclic molecule using base. Robinson annulation reactions are having a distinct place in asymmetric organic chemistry because of their ability to form a four-carbon chain in a single step leading to chiral six membered ring systems. Special concentration was shown to the organocatalytic high enantioselective preparation of both Hajos–Parrish ketones (HPK) and Wieland–Miescher ketones (WMK) starting from 2-alkylated 1,3-cyclopentanedione and 1,3-cyclohexanedione, respectively.[52] A lot of catalysts have been developed, including amine derivatives,[53] peptide derivatives,[54] α-amino acids derivatives,[55] β-amino acids derivatives[56] and proline derivatives[57] to prepare high enantioselective annulated products. The reaction triggers by deprotonation with the base of the α-hydrogen of the ketone to generate an enolate. The enolate then undergoes a 1,4- addition (Michael reaction) and then abstracts a proton from $H_2O$ to form a Michael product. Base abstracts other α-hydrogen and generates another enolate which then undergoes intramolecular aldol reaction with the ketone group to give a cyclic alkoxy intermediate. Dehydration of cyclic alkoxy intermediate leads to the stable α,β-unsaturated ketone. These products are significant systems in various biological products, for example within steriods.[58] The Robinson annulation reaction has long been employed as a convenient route to fused ring

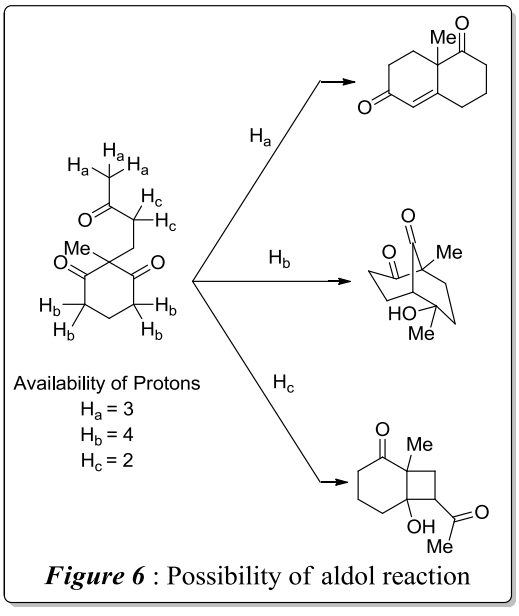



***Figure 6*** : Possibility of aldol reaction

ketones.[52] As shown in Figure 6 there are three types of α-hydrogens and there is a chance to get three types of cyclised products.

Asymmetric aldol reactions give an atom-economic approach to construct a C–C bond with β-hydroxyl carbonyls as the products and are widely applied in industry either in fine or in bulk pharmaceutical target production or chemical manufacture.[68] Recently, important developments have been made with regards to the asymmetric aldol reactions catalyzed either by transition metal complexes,[69] biocatalysts[70] or organocatalysts.[71-72] Despite of recent advances in the area of direct asymmetric aldol reaction,[73] in most cases aldol donors are simple ketones and few catalytic aldol reactions are with α-substituted unsymmetrical ketones[74] by hetero-atoms such as sulfur,[74a] oxygen,[74d] fluorine[74b] and chlorine[74c]. The reactions of α-hetero-atom substituted ketones have received less importance with the exception of those of α-hydroxyketones. Furthermore, in almost all the intermolecular organocatalyzed direct asymmetric aldol reactions, mostly aldehydes are used as acceptors or electrophiles[74] and in some cases very highly active non enolizable ketones[75] carrying an electron-withdrawing group adjacent to the carbonyl carbon are used as acceptors.

Most intensively emerging areas in modern organic chemistry is the improvement of methods for the synthesis and functionalization of molecules having important pharmacological properties and the view of subsequent use as bioactive pharmaceutical substrates. Sulfones belong to a major class of organosulfur compounds, that have been extensively used in applications of organic synthesis.[76] Among other derivatives of sulfones, a special attention of synthetic chemists is drawn to cyclic β-keto sulfones bearing carbonyl function in the β-position to sulfonyl group.[76a] They are versatile synthetic intermediates used for the preparation of diverse classes of organic compounds as a structural feature of the target substrate and synthesis of natural products.[76b] In addition, certain cyclic β-keto sulfones are known to exhibit a broad spectrum of biological activity.

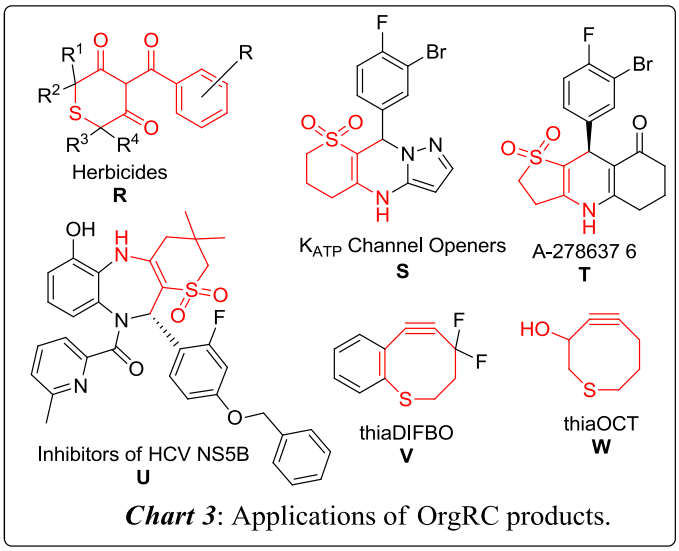



***Chart 3***: Applications of OrgRC products.

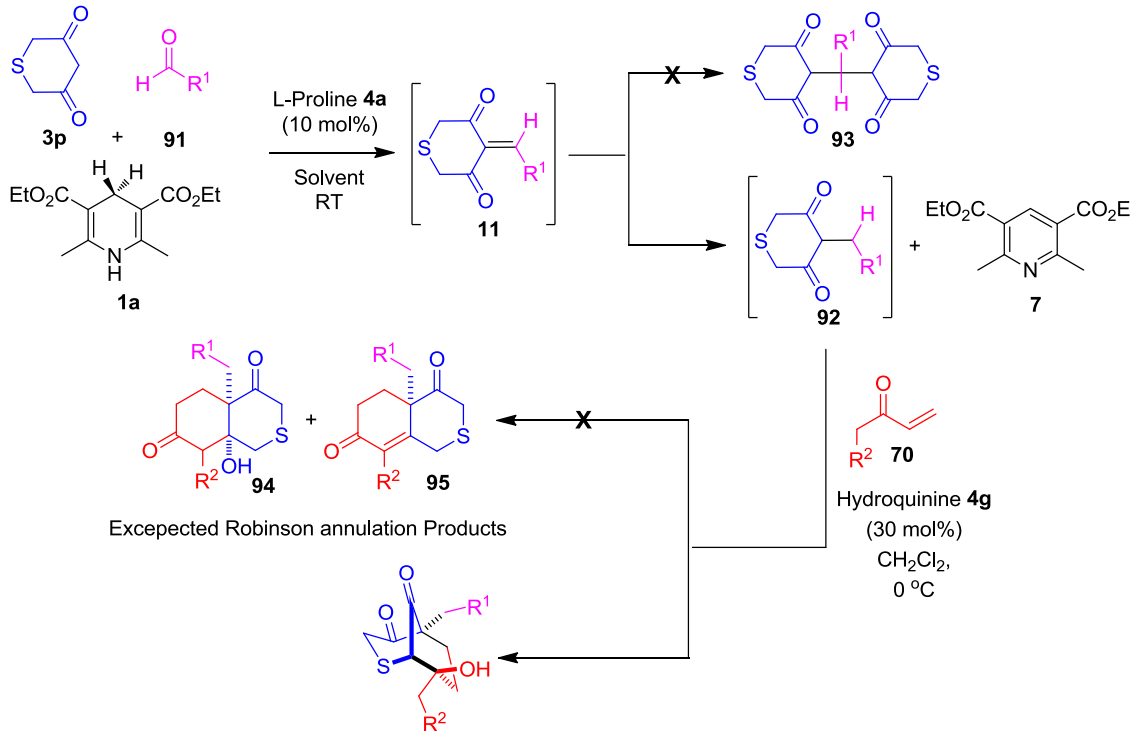
Cyclic β-keto sulfones have found with antiviral,[76c-d] antibacterial,[76e] antiinflammatory,[76f] bronchodilatory[76g] properties, antitumor,[76h] potassium channel agonists,[76i] calcium channel antagonists,[77] DNA gyrase inhibitors[76e] and compounds useful in the treatment of osteoporosis.[76f] At the same time development in medicinal chemistry depends basically on the accessibility of wide range of new structures for clinical trials. Sulfones prepared by the construction of the corresponding cyclic sulfides from appropriately functionalized precursors, followed by oxidation of the sulfides to sulfones.

A growing area of chemical biology strives to probe biomolecules in living systems by using bioorthogonal chemical reactions. Particularly, the strain-promoted azide-alkyne cycloadditions have proved mainly promising as cytocompatible ligation methods. Due to their high reactivity towards addition reactions, strained cyclooctynes have a high importance in click chemistry as bioorthogonal reactions.[78] In addition, some molecules for strain-promoted reactions with azides have recently been developed including biarylazacyclooctynone, (aza-)dibenzocyclooctynes, biarylazacyclooctynone and thiacyclooct-5-ynes which exhibit similar utility.[79] Hence, their preparation has continued to attract considerable synthetic interest in developing new methods for their synthesis.

Recently, we have established the chemoselective C-alkylation of 1,3-dicarbonyls with a variety of aldehydes and organic hydrides under amino acid-catalysis through OrgRC reaction.[15] From the time when we reported this metal-free reductive coupling or OrgRC reaction, many synthetic chemists used this powerful OrgRC reaction in their method development[22-28] or total synthesis.[29-32] Biologists in drug developments[33] and industrialists in the bulk scale synthesis of medicines[8] had utilized as a crucial and key step in alkylation of active methylene. As part of our study to develop direct amino acid-catalyzed tandem, multi-component or organo-click reactions,[15, 35] herein we reported organocatalytic chemo-selective direct cascade reductive alkylation, Robinson annulation (RA) to build structural complex molecule. Keeping the mechanism of RA and regiocontrolled aldol reactions in mind, we developed a novel cascade reaction by using OrgRC products and α, β- unsaturated ketones for the construction of highly functionalized chiral bridged [3, 3, 1] bicylic compounds. OrgRC products and annulated products are very good intermediates to prepare biologically important β-keto sulfones and thiacyclooctynes respectively.

Interestingly, there is no direct methodology for the synthesis of useful 4-alkyl-2H-thiopyran-3,5(4H,6H)-dione **92**. We consequently set out to develop an organo-catalyzed asymmetric cascade synthesis of higher alkyl analogues of annulated products **96** from simple starting materials, which have not been prepared in the past. Here, we present the development and application of the amino acid-catalyzed reductive alkylation of 2*H*-thiopyran-3,5(4*H*,6*H*)-dione **92** through cascade OrgRC reaction of reactive 2*H*-thiopyran-3,5(4*H*,6*H*)-dione **3p**, aldehydes **91** and Hantzsch ester **1a** as shown in Scheme 20.

***Scheme 20**:* Direct Organocatalytic Reductive Alkylations and M/A Reactions.




## 5.2 RESULTS AND DISCUSSION

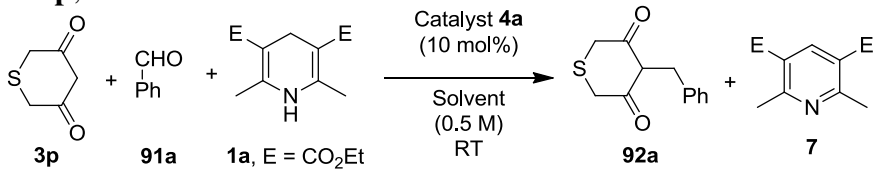
### 5.2.1 Direct Amino Acid-Catalyzed Cascade Reductive Alkylation of 2H-Thiopyran-3,5(4H,6H)-dione 3p: Reaction Optimization

First we focused on the optimization for high-yielding synthesis of 4-benzyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione **92a** from **3p**, **91a** and **1a** through amino acid **4a** catalysis at room temperature, by studying the solvent and reaction time in the designed OrgRC reactions. We tested solvens like $CH_2Cl_2$, $CH_3CN$, MeOH and DMSO. There is a large amount of solvent effect on the direct proline-catalyzed reductive coupling of **3p**, **91a** and **1a** as shown in Table 7. Proline-catalyzed cascade

OrgRC reactions can be performed in three types of solvents (protic polar, aprotic polar and aprotic non-polar) with moderate to good yields as shown in Table 7. Surprisingly, the cascade OrgRC reaction of **3p**, **91a** and **1a** in $CH_3CN$ furnished the expected hydrogenated product **92a** in 51% yield after 5 h at 25 °C (Table 7, entry 1). The same cascade reaction, under proline-catalysis in $CH_3CN$ furnished the expected product **92a** in 91% yield after 12 h at 25 °C (Table 7, entry 2). Unfortunately we are unable to isolate the OrgRC product **92a** with same reaction conditions in DMSO, instead of OrgRC product **92a** a *bis* type product **93** is formed and it is not pure enough to analyze through NMR analysis (Table 7, entry 3). Surprisingly, the cascade OrgRC reaction of **3p**, **91a** and **1a** in $CH_2Cl_2$ and MeOH furnished the expected hydrogenated product **92a** in 60% and 47% yield after 24 h and 5 h respectively at 25 °C (Table 7, entry 4 and 5).We envisioned the optimized conditions to be mixing the 1 equiv. of benzaldehyde **91a** with CH-acid **3p** and Hantzsch ester **1a** at 25 °C in $CH_3CN$ under 10 mol% of proline-catalysis to furnish the hydrogenated product **92a** in 91% yield (Table 7, entry 2). The product structure was confirmed by $^{1}H$ and $^{13}C$ NMR and mass analysis.

With an efficient organocatalytic cascade OrgRC protocol in hand, the scope of the proline-catalyzed cascade reductive alkylation reactions was investigated with aldehydes **91** and CH-acid **3p** through the generation of highly useful diversity-oriented library.

***Table 7***: Optimization of the Direct Organocatalytic Cascade Reductive Alkylation Reactions of **3p**, **91a** and **1a**.[a]




**3p** **91a** **1a**, E = $CO_2Et$ **92a**

| entry | solvent (0.5 M) | time (h) | yield (%)[b] **92a** |
|---|---|---|---|
| 1 | $CH_3CN$ | 5 | 51 |
| **2** | **$CH_3CN$** | **12** | **91** |
| 3[c] | DMSO | 48 | --- |
| 4 | $CH_2Cl_2$ | 24 | 60 |
| 5 | MeOH | 5 | 47 |

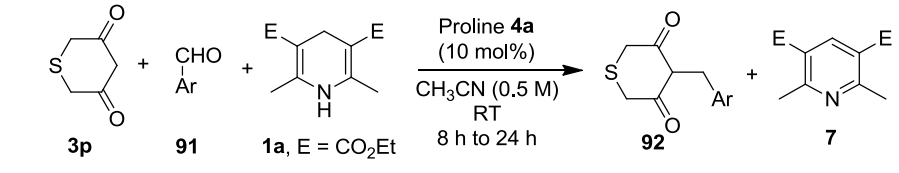
[a] Reactions were carried out in solvent (0.5 M) with 1.0 equiv. of **91a** and 1.0 equiv. of **3p** relative to the **1a** (0.5 mmol) in the presence of 10 mol% of catalyst **4a**. [b] Yield refers to the column purified product.[c] CH-acid **3p** decomposed.

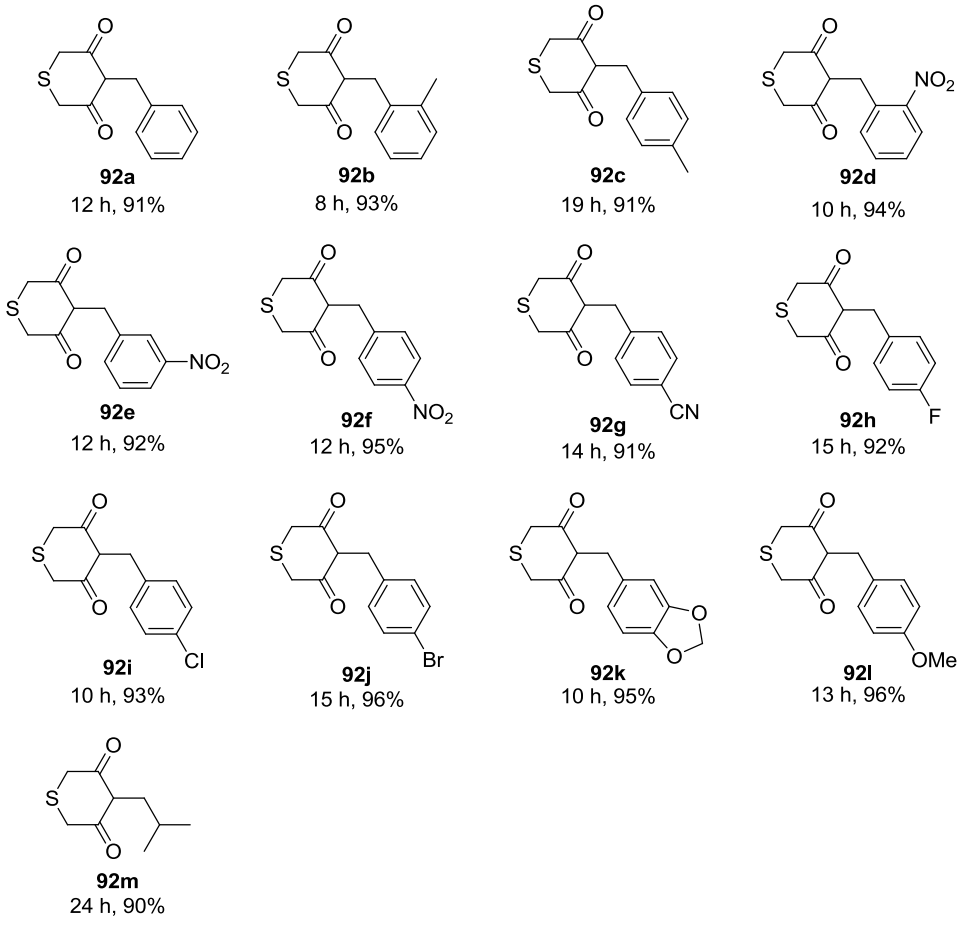

***Figure-N21:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **92a**.

### 5.2.2 Diversity-Oriented Synthesis of Reductive Alkylation Products 92

The scope of the proline catalyzed reductive alkylation reactions was investigated with 2*H*-thiopyran-3,5(4*H*,6*H*)-dione **3p**, various aldehydes **91** and Hantzsch ester **1a** as shown in Table 8. A series of aromatic aldehydes including electron withdrawing, electron releasing & neutral substitutions at various positions on benzene ring and aliphatic aldehydes **91** (1 equiv.) were reacted with 2*H*-thiopyran-3,5(4*H*,6*H*)-dione **3p** and Hantzsch ester **1a** catalyzed by 10 mol% of proline at 25 °C in $CH_3CN$ (Table 8).

***Table 8:*** Synthesis of Compounds **92** *via* OrgRC Reactions from 2*H*-Thiopyran-3,5(4*H*,6*H*)-dione **3p** and Aldehydes **91**.[a]




[a] Yield refers to the column purified product.

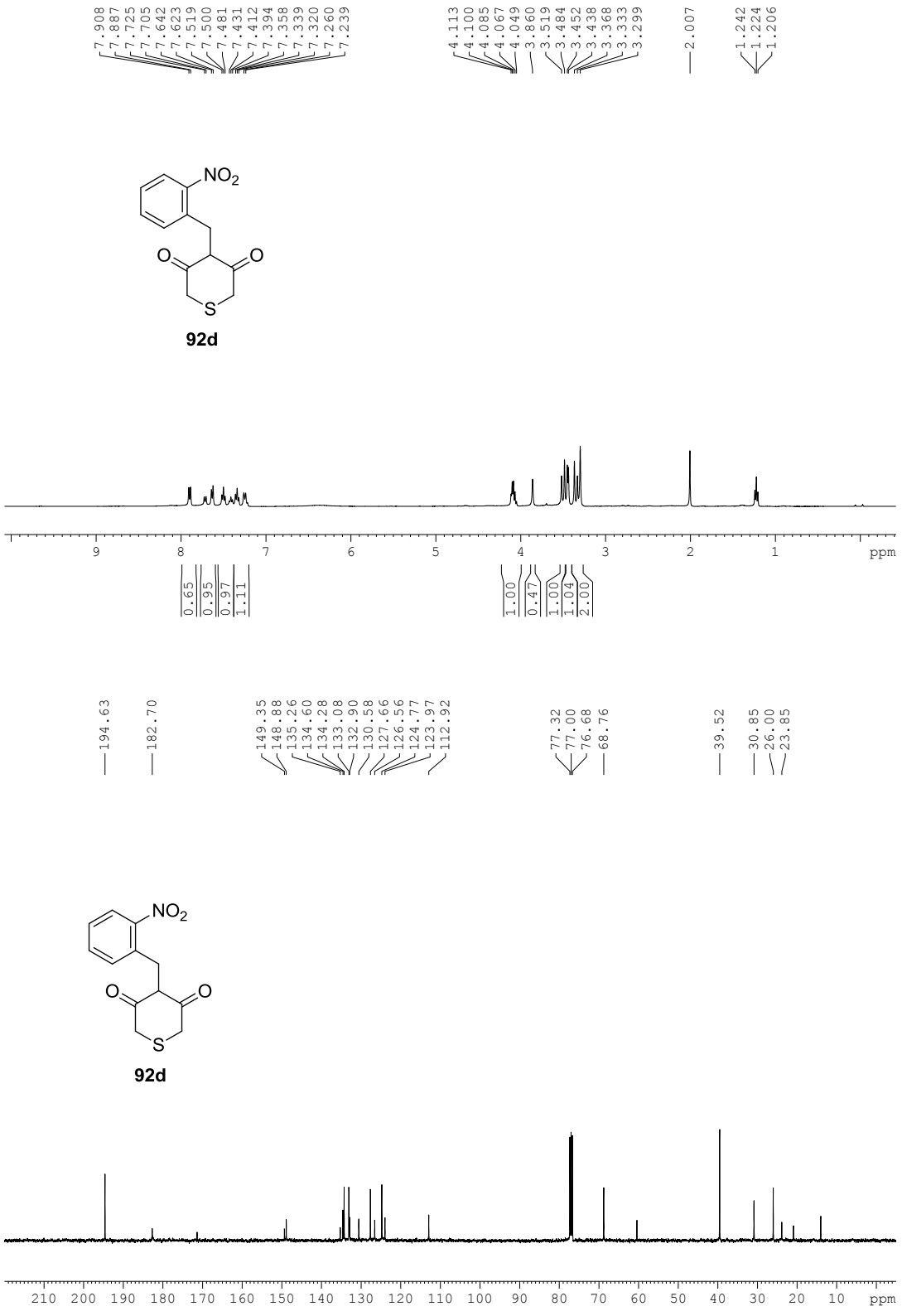



***Figure-N22:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **92d**.

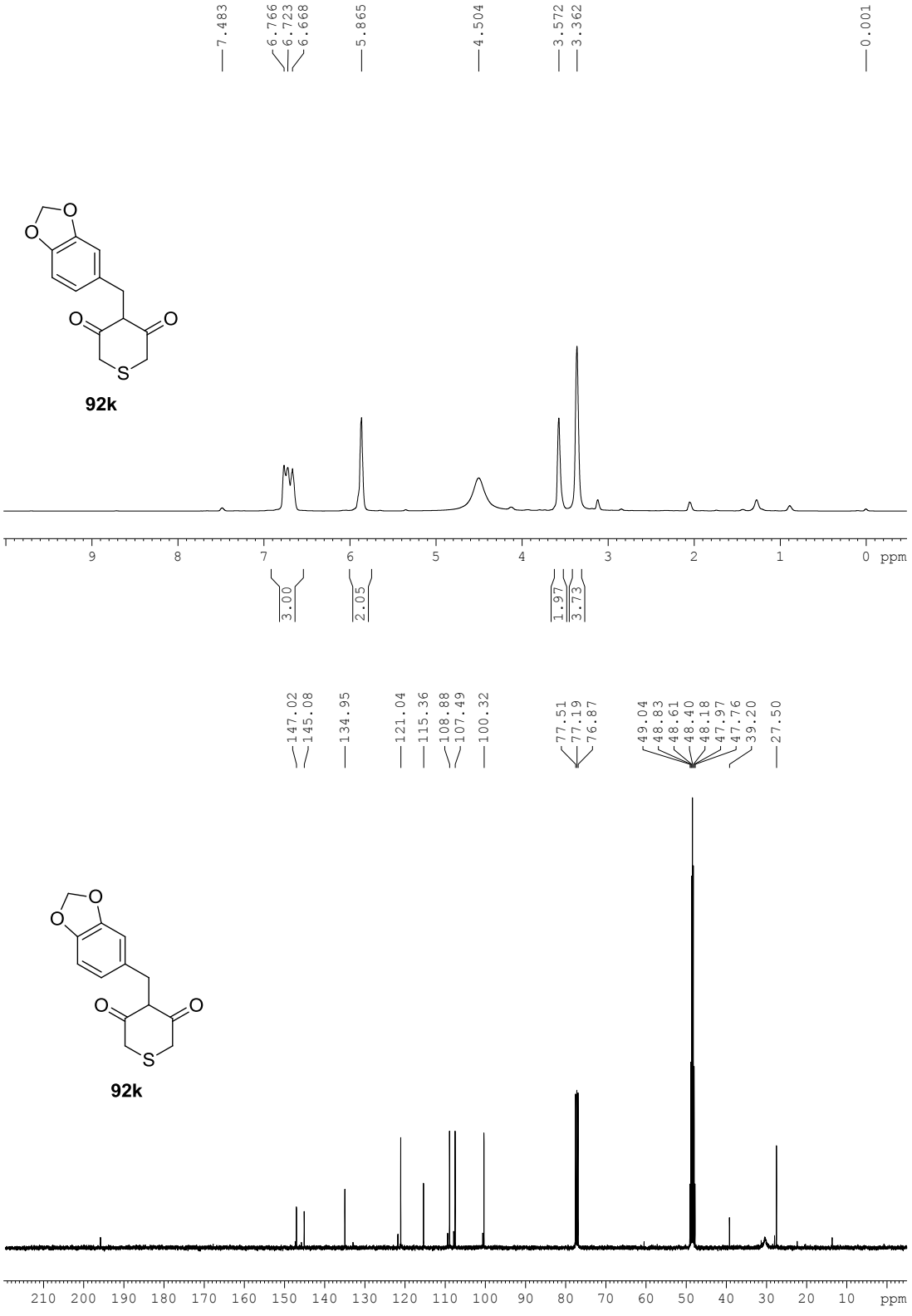



***Figure-N23:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **92k**.

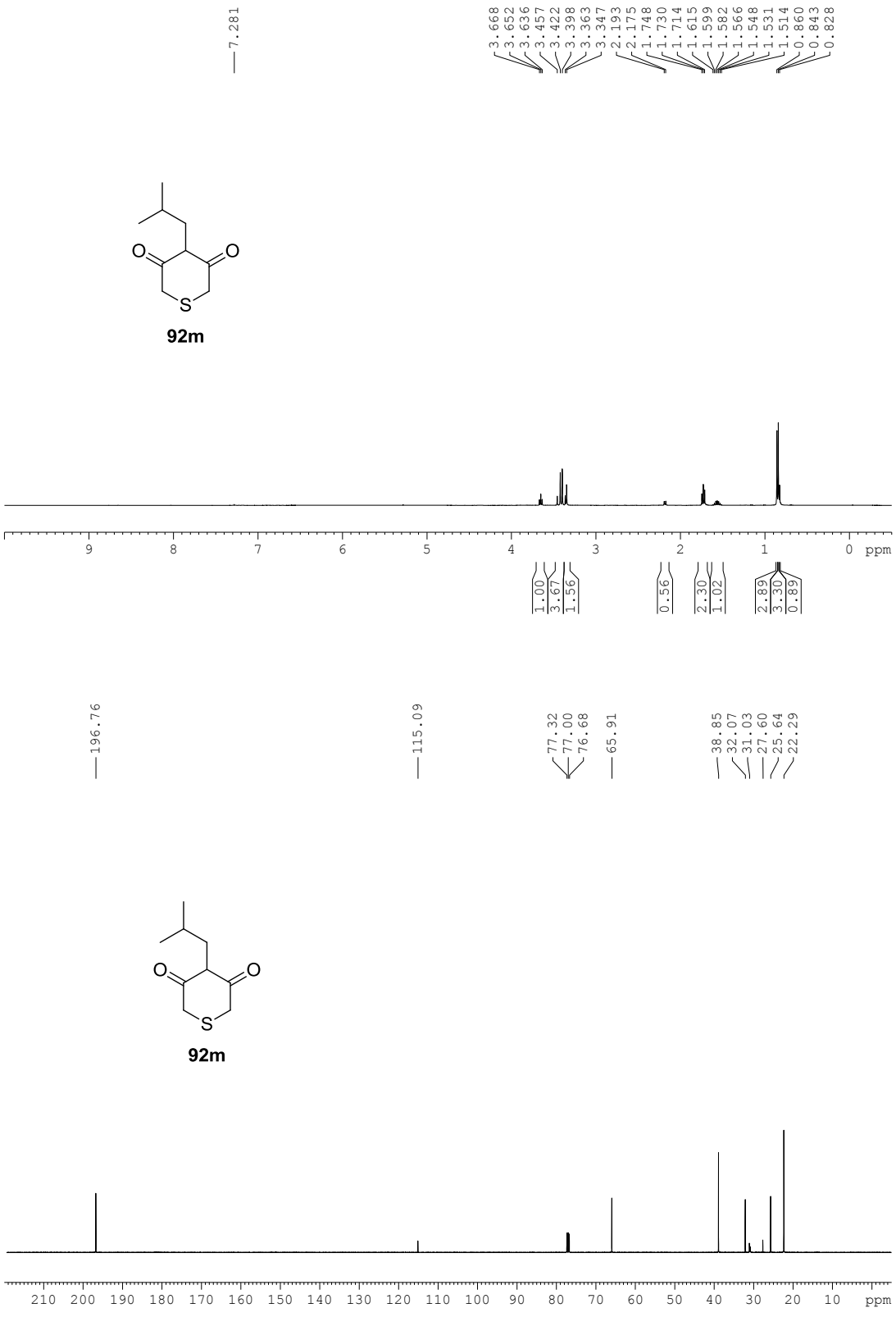



***Figure-N24:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **92m**.

The cascade reaction of thiopyran-3,5(4*H*,6*H*)-dione **3p** with 2-tolualdehyde **91b** and **1a** furnished the reductive alkylation product **92b** in 93% yield after 8 h at 25 °C (Table 8). Interestingly, OrgRC reaction of 4-tolualdehyde **91c** with **3p** and **1a** under **4a**-catalysis furnished the **92c** as major product with 91% yield (Table 8) in 19 h. The cascade reaction of thiopyran-3,5(4*H*,6*H*)-dione **3p** with 2-nitrobenzaldehyde **91d** and **1a** furnished the reductive alkylation product **92d** in 94% yield after 10 h at 25 °C (Table 8). Reaction of **3p** with **91e** and **1a** under **4a**-catalysis furnished the expected 4-(3-nitrobenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione **92e** with good yields as shown in Table 8 with in 12 h. The cascade reaction of thiopyran-3,5(4*H*,6*H*)-dione **3p** with 4-nitrobenzaldehyde **91f** and **1a** furnished the reductive alkylation product **92f** in 95% yield after 12 h at 25 °C (Table 8). Interestingly, OrgRC reaction of 4-cyanobenzaldehyde **91g** with **3p** and **1a** under **4a**-catalysis furnished the **92g** as major product with 91% yield (Table 8) in 14 h. Interestingly, OrgRC reaction of 4-fluorobenzaldehyde **91h** with **3p** and **1a** under **4a**-catalysis furnished the **92h** as major product with 92% yield (Table 8) in 15 h. OrgRC reaction of 4-chlorobenzaldehyde **91i** with **3p** and **1a** under **4a**-catalysis furnished the **92i** as major product with 93% yield (Table 8) in 10 h. The cascade reaction of thiopyran-3,5(4*H*,6*H*)-dione **3p** with 4-bromobenzaldehyde **91j** and **1a** furnished the reductive alkylation product **92j** in 96% yield after 15 h at room temperature (Table 8). The cascade reaction of thiopyran-3,5(4*H*,6*H*)-dione **3p**, **1a** with **91k** and **91l** furnished the reductive alkylation product **92k** and **92l** in 95% and 96% yield after 10 h and 13 h at 25 °C respectively (Table 8). Proline-catalyzed cascade reductive alkylation of thiopyran-3,5(4*H*,6*H*)-dione **3p** was further extended with aliphatic aldehydes also as shown in Table 8. Interestingly, OrgRC reaction of *iso*-butyraldehyde **91m** with **3p** and **1a** under **4a**-catalysis furnished the **92m** as the major product with 90% yield (Table 8) in 24 h. The structure and regiochemistry of 4-alkyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones **92a-m** were confirmed by $^{1}$H NMR,$^{13}$C NMR and mass analysis.

### *5.2.3 Asymmetric Cascade Michael-Aldol (M-A) Reaction with 4-Benzyl-2H-thiopyran-3,5(4H,6H)-dione: Reaction Optimization*

After successful synthesis of 4-alkyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione **92**, we shown interest to study the asymmetric cascade M-A reactions of **92** with α, β-unsaturated compounds **70** through organocatalysis. As part of our investigations in the area of Robinson annulation,[15b, 15d, 15f, 15i] the ability of regioselectivity in enolate formation to promote the bridged cyclisation of *in-situ* generated triketone (Michael

adduct) **103** was examined. When 2-alkyl-CH-acid reacted with α, β-unsaturated compounds **70**, in presence organocatalyst **4**, M-A cascade reaction taken place to give bridged bicyclic compounds **96** instead of compounds **94** and **95**. It is apparent that the incorporation of hetero atom sulfur within the ring framework completely changes reaction pattern; therefore enolate regioselectivity can be obtained differently. Notably, the Michael reaction of CH-acid **92** and 2 equiv. of ethyl vinyl ketone **70b** and further intramolecular cyclization of Michael adduct with L-proline in DMSO proceeded with a remarkable rate enhancement (100% conversion, 4 h) in one-pot with comparison to the common Robinson annulated products observed in previous papers and with a remarkable change in product distribution, giving only the racemic bicyclic species (Table 9, entry 1). Even though Hajos *et al.*[58b] and Shibasaki *et al.*[69c] had reported this type of cyclization with less yield, poor enantio- and diastereoselectivity using inorganic bases. Organocatalytically there are two reports on one molecule regarding this type of cyclization in racemic manner in 20-30% yield.[56c, 15d]

Interestingly, cascade M-A reaction of **92a** with 2 equiv. of ethyl vinyl ketone **70b** in DMSO under 30 mol% of L-proline **4a**-catalysis furnished the Michael-aldol product **96ab** in 89% yield with only 0% *ee*. Same reaction in $CH_3CN$ under 30 mol% of L-proline **4a-**catalysis also furnished the racemc mixcture of Michael-aldol product **96ab** in 91% yield. (Table 9, entry 2). After obtaining poor results with L-proline, we changed the catalyst to get further improvement of *ee*/yield of cascade products **96ab.** We tested a number of cinchona alkaloids like hydroquinine (HQ) **4g,** quinine (Q) **4h,** quinidine (QD) **4i,** OH-Q-OBn **4j,** Q-OBn **4k,** Q-NH-thiourea catalyst **4l** and OH-Q-O-*i*-amyl **4m** as catalysts for the cascade asymmetric M-A reaction of **92a** with **70b** in different solvents as demonstrated in Table 9. Among these catalysts **4** tested for cascade asymmetric M-A reaction, 30 mol% of hydroquinine **4g** or quinine **4h** in $CH_2Cl_2$ solvent showed better results compared to other catalysts (Table 9, entry 3 and 8). Cascade M-A reaction of **92a** and **70b** in $CH_2Cl_2$ under 30 mol% of quinidine **4i-**catalysis furnished the opposite enantiomer of M-A product **(+)-96ab** in 90% yield with -61% *ee* (Table 9, entry 9). We envisioned the optimized condition to be 0 °C in $CH_2Cl_2$ under 30 mol% of hydroquinine **4g** or quinine **4h** to furnish the highly substituted M-A product **(–)-96ab** in 92-95% yield with 72-74% *ee* respectively (Table 9).

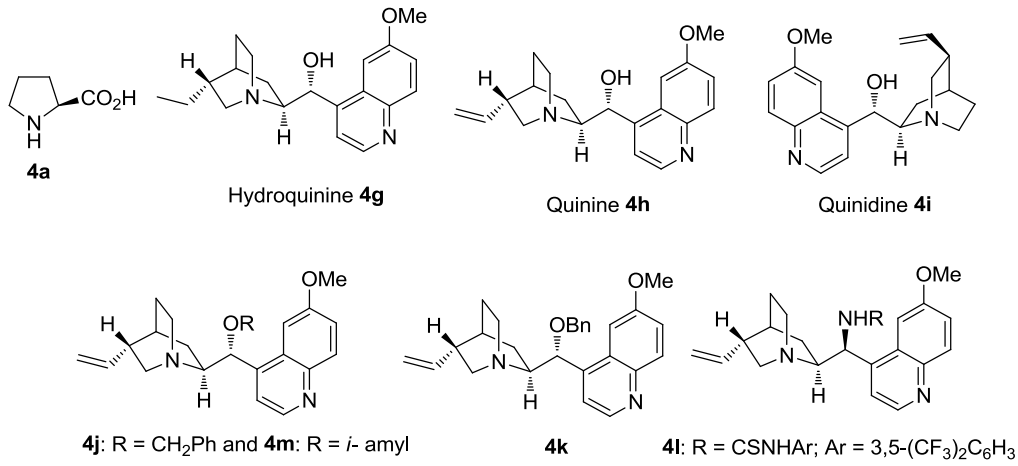
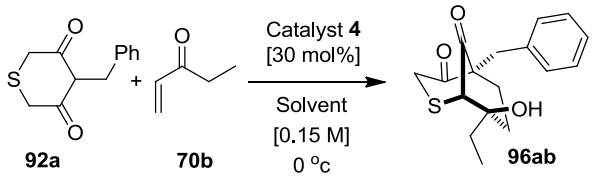



***Figure 7:*** Catalysts Screened for the Asymmetric Michael-Aldol Reaction.

***Table 9:*** Effect of Solvent and Catalyst on the Direct Organocatalyzed Asymmetric Cascade M-A Reaction of **92a** and **70b**.[a]

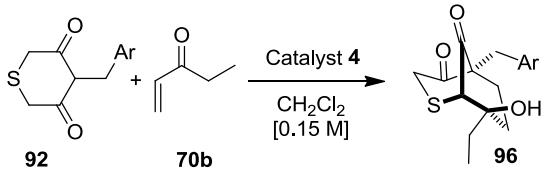



| Entry | Catalyst | Solvent | Time [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **4a** | DMSO | 4 | 89 | 0 |
| 2 | **4a** | $CH_3CN$ | 6 | 91 | 0 |
| **3** | **4g** | **$CH_2Cl_2$** | **12** | **95** | **72** |
| 4 | **4g** | DCE | 60 | 87 | 59 |
| 5 | **4g** | DCB | 15 | 92 | 63 |
| 6 | **4g** | Toluene | 24 | 89 | 55 |
| 7 | **4g** | THF | 15 | 95 | 65 |
| **8** | **4h** | **$CH_2Cl_2$** | **12** | **92** | **74** |
| 9 | **4i** | $CH_2Cl_2$ | 18 | 90 | -61 |
| 10 | **4j** | $CH_2Cl_2$ | 12 | 96 | 50 |
| 11 | **4k** | $CH_2Cl_2$ | 72 | 90 | 1 |
| 12 | **4l** | $CH_2Cl_2$ | 48 | 92 | 6 |
| 13 | **4m** | $CH_2Cl_2$ | 24 | 92 | 1 |

[a] Reactions were carried out in solvent [0.15 M] with 2.0 equiv. of freshly distilled **70b** in the presence of 30 mol% of catalyst **4.** [b] Yield refers to the column purified product. [c] *ee* determined by HPLC analysis.

After preliminary understanding of catalyst effect on M-A reaction of **92a** and **70b** then we focused on the temperature and catalyst loading effect with different substrates. As hydroquinine **4g** or quinine **4h** has showed similar result, we checked both catalysts for temperature and catalyst loading effect. Interestingly there is a lot of effect with the reaction temperature and catalyst loading. With 30 mol-% of catalyst **4g** at room temperature furnished the product **96ab** with 28% *ee* and 97% yield as shown in Table 10 (entry 5). Then we performed the reaction at –30 $^{o}$C temperature with 30 mol% of quinine **4h** as catalyst and $CH_2Cl_2$ as solvent, surprisingly we isolated the product **96ab** with decreased *ee* (68% *ee)* in 92% yield after 60 h. There is no much difference between the reaction preformed at 0 °C and that at -30 $^{o}$C as shown in Table 10 (entry 4) and we finalized that temperature 0 °C is the best optimized condition to perform the reaction.

***Table 10:*** Effect of Temperature and Catalyst Loading on the Direct Organocatayzed Asymmetric Cascade M-A Reaction of **92** and **70b**.[a]




**92** **70b** **96**

**92a**: Ar = Ph; **92b**: Ar = *o*-Tolyl; **92d**: Ar = 2-nitro phenyl

| Entry | Reactant | Catalyst | Temperature ($^{o}$C) | mol % | Time [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | **92a** | **4h** | 0 | 15 | 36 | 89 | 6 |
| **2** | **92a** | **4h** | **0** | **30** | **12** | **92** | **74** |
| 3 | **92a** | **4h** | 0 | 50 | 7 | 95 | 75 |
| 4 | **92a** | **4h** | -30 | 30 | 60 | 92 | 68 |
| 5 | **92a** | **4g** | 27 | 30 | 6 | 97 | 28 |
| 6 | **92b** | **4h** | 0 | 5 | 36 | 90 | 14 |
| 7 | **92b** | **4h** | 0 | 30 | 15 | 96 | 44 |
| 8 | **92b** | **4g** | 0 | 30 | 18 | 90 | 62 |
| 9 | **92d** | **4h** | 0 | 3 | 60 | 70 | 2 |
| 10 | **92d** | **4h** | 0 | 30 | 16 | 90 | 58 |
| 11 | **92d** | **4g** | 0 | 30 | 15 | 93 | 62 |

[a] Reactions were carried out in solvent [0.15 M] with 2.0 equiv. of freshly distilled **70b** in the presence of 30 mol% of catalyst **4.** [b] Yield refers to the column purified product. [c] *ee* determined by HPLC analysis.

Then we interested the catalyst loading on enantioselectivity. Interestingly there is a lot of effect on catalyst loading. In 5-15% catalyst loading we achieved the product with poor *ee* values.

Significantly *ee* was increased upon increasing the catalyst loading up to 50 mol% (Table 10, entry 3), which is clearly indicating that catalyst loading should not be below 30 mol%. Lower catalyst loading effect on decreasing enantioselectivity is also proved in the case of **92b** and **92d** (Table 10, entry 6 and 9). As we performed the reaction with two different catalysts on three different substrates, which are showed equal results but slightly good results in case of hydroquinine. Final optimization condition for the M-A reaction of **92** and **70** is 30 mol% of catalyst **4g** with 1 equiv. of 2-alkyl-CH-acid **92**, 2 equiv. of α, β-unsaturated ketone **70** and solvent as $CH_2Cl_2$ at 0 $^oC$. The pronounced regio-controlled aldol reaction with good yield, enantio-and diastereoselectivity observed in the Robinson annulation reaction inspired us to study the asymmetric cascade Michael-aldol annulation reaction with variety of 2-alkyl-CH-acids **92.**

### *5.2.4 Applications of OrgRC products*

#### *5.2.4.1 Diversity-Oriented Asymmetric Synthesis of Cascade M-A Products 96ab-96ed:*

With natural products synthesis and pharmaceutical applications in mind, we further extended the utilization of OrgRC products in the asymmetric synthesis of functionalized chiral-5-alkyl-8-hydroxy-8-alkyl-2-thiabicyclo[3.3.1]nonane-4,9-diones **96** *via* asymmetric cascade M-A reactions of various 4-alkyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones **92** with different α, β-unsaturated ketones **70** under **4g** catalysis in one-pot as shown in Table 11.A series of 4-alkyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones **92** were reacted with 2.0 equiv. of α, β-unsaturated ketones **70** catalyzed by 30 mol% of hydroquinine **4g** at 0 °C in $CH_2Cl_2$ for 9-48 h (Table 11). All expected chiral 5-alkyl-8-hydroxy-8-alkyl-2-thiabicyclo[3.3.1]nonane-4,9-diones analogues **96ab-96ed** were obtained in 90-98% yields with up to 94% *ee* as shown in Table 11. Interestingly, in these reactions, no trace amount of Robinson annulated bicyclic alcohols **94,** enones **95** and/or Michael adducts **103** were isolated.

The chiral 5-alkyl-8-hydroxy-8-alkyl-2-thiabicyclo[3.3.1]nonane-4,9-diones 96ab-96ed were obtained in good yields and excellent *ee*'s with variety of substitutions on benzene ring containing neutral, electron-donating, electron-withdrawing and halogenated

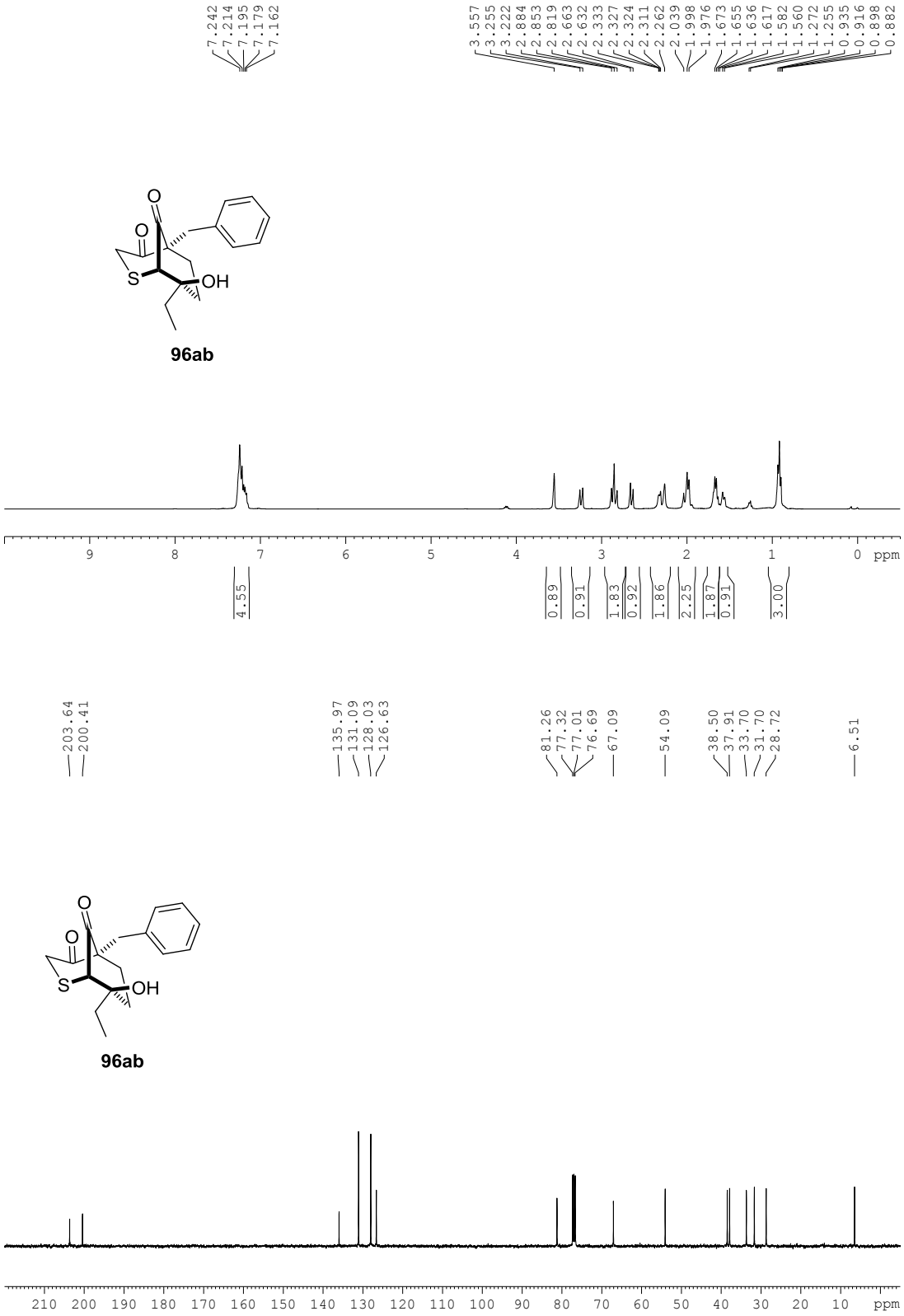
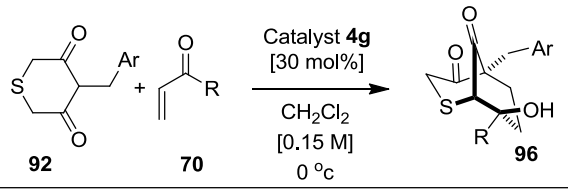


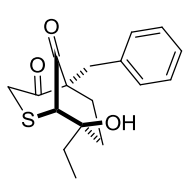

***Figure-N25:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **96ab**.

groups on 4-alkyl-2*H*-thiopyran-3,5(4*H*,6*H*)-diones **92a-l** and enones containing aromatic and aliphatic substitution **70a-d** from the asymmetric M-A reaction (Table 11). Surprisingly, the M-A reaction of aromatic enone 1-phenylprop-2-en-1-one **70d** with **92a** and **92e** under the catalysis of **4g** furnished the M-A product **96ad** and **96ed** in 92% and 94% yield with 47% and 79% *ee* respectively (Table 11).

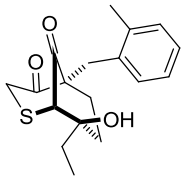
***Table 11:*** Asymmetric Synthesis of Chiral Cascade M-A Products **96**.[a, b]



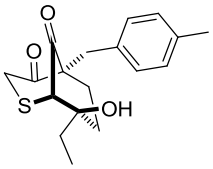

92 70 96



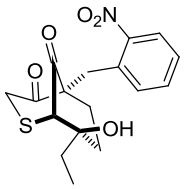
**96ab**[c]
12 h, yield: 95%
*ee*: 74%



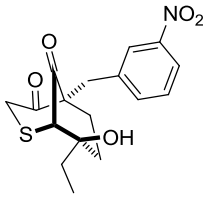
**96bb**
18 h, yield: 90%
*ee*: 62%



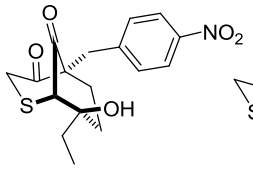
**96cb**
19 h, yield: 91%
*ee*: 73%



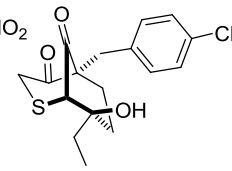
**96db**
48 h, yield: 90%
*ee*: 62%



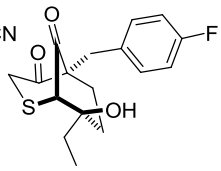
**96eb**
15 h, yield: 95%
*ee*: 87%



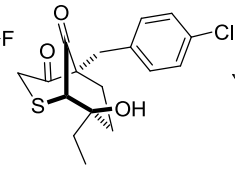
**96fb**
15 h, yield: 96%
*ee*: 78%



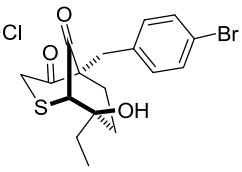
**96gb**
20 h, yield: 92%
*ee*: 73%



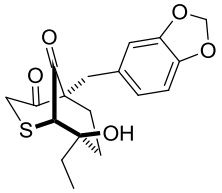
**96hb**
16 h, yield: 91%
*ee*: 64%



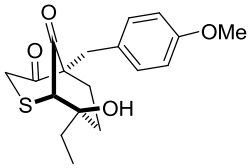
**96ib**
14 h, yield: 92%
*ee*: 69%



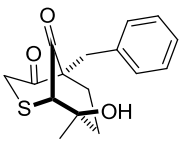
**96jb**
21 h, yield: 98%
*ee*: 71%



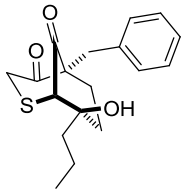
**96kb**
20 h, yield: 95%
*ee*: 75%



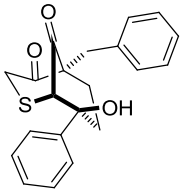
**96lb**
17 h, yield: 95%
*ee*: 73%



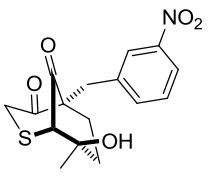
**96aa**
9 h, yield: 92%
*ee*: 46%



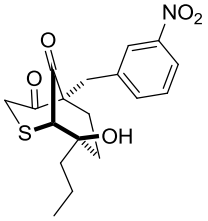
**96ac**
18 h, yield: 92%
*ee*: 70%



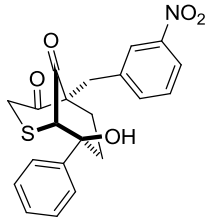
**96ad**
18 h, yield: 92%
*ee*: 47%



**96ea**
20 h, yield: 94%
*ee*: 83%



**96ec**
15 h, yield: 95%
*ee*: 94%



**96ed**
24 h, yield: 94%
*ee*: 79%

[a] Yield refers to the column-purified product. [b] *ee* determined by CSP HPLC analysis. [c] **4h** used as the catalyst.

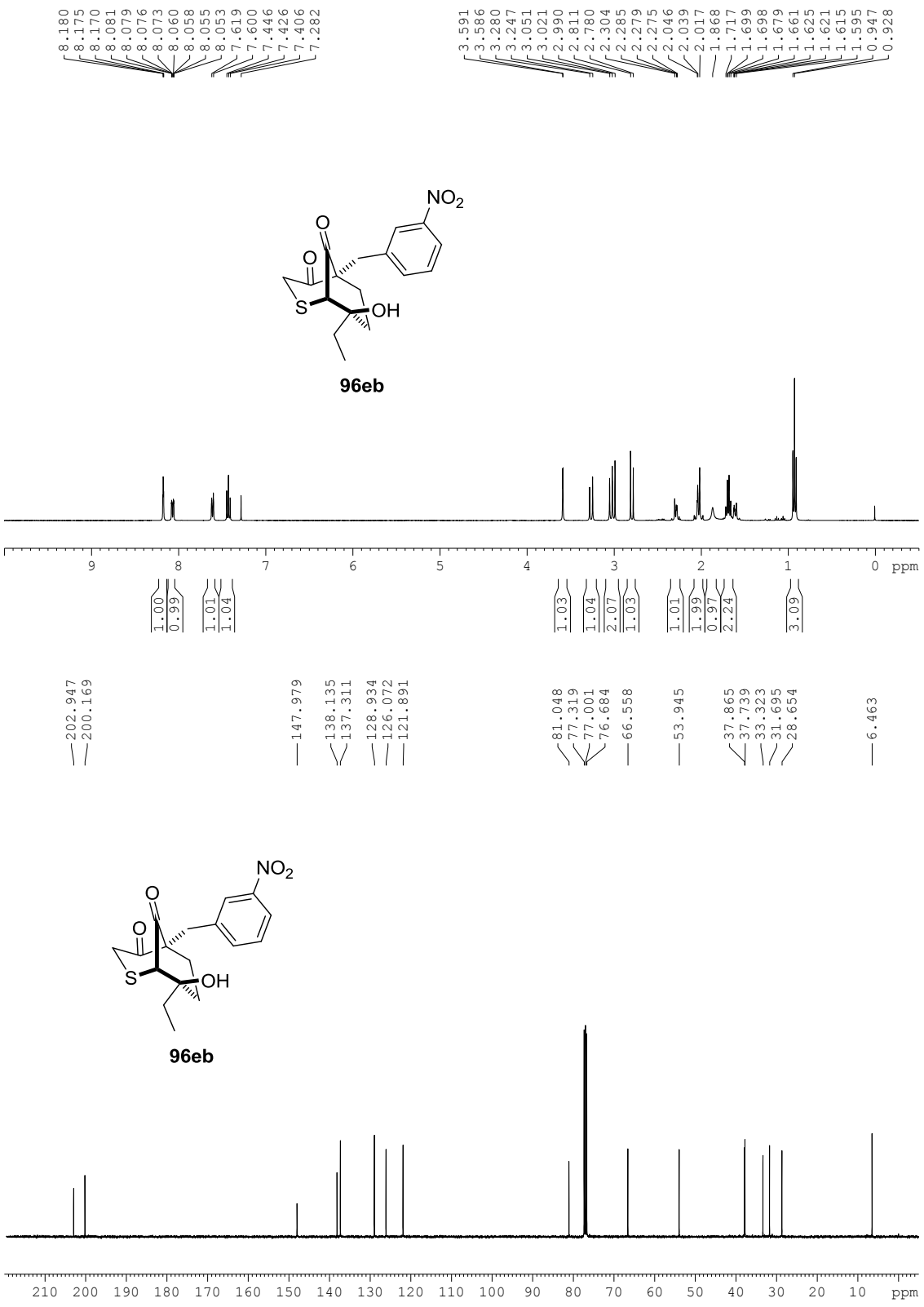



***Figure-N26:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **96eb**.

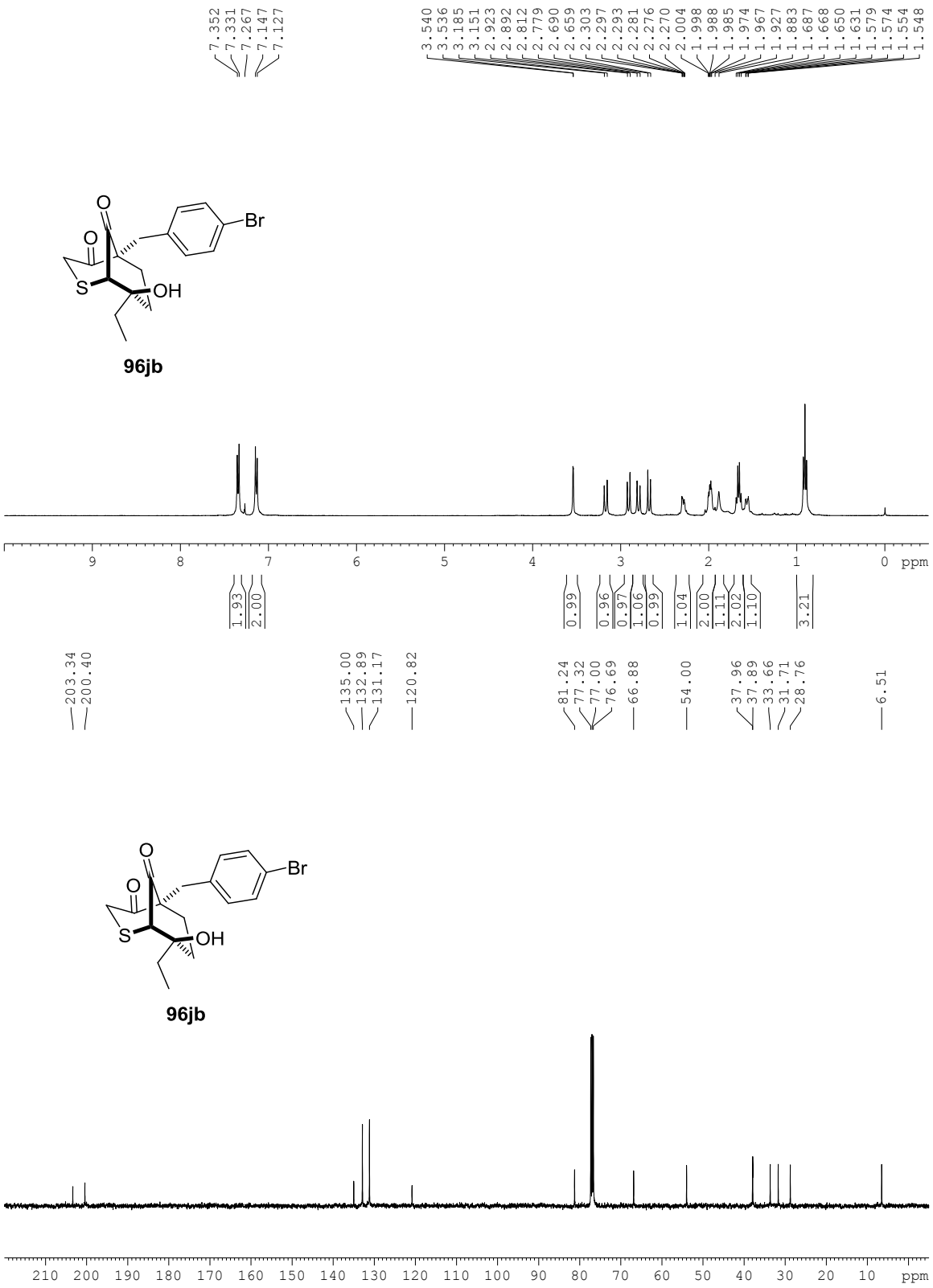



***Figure-N27:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **96jb**.

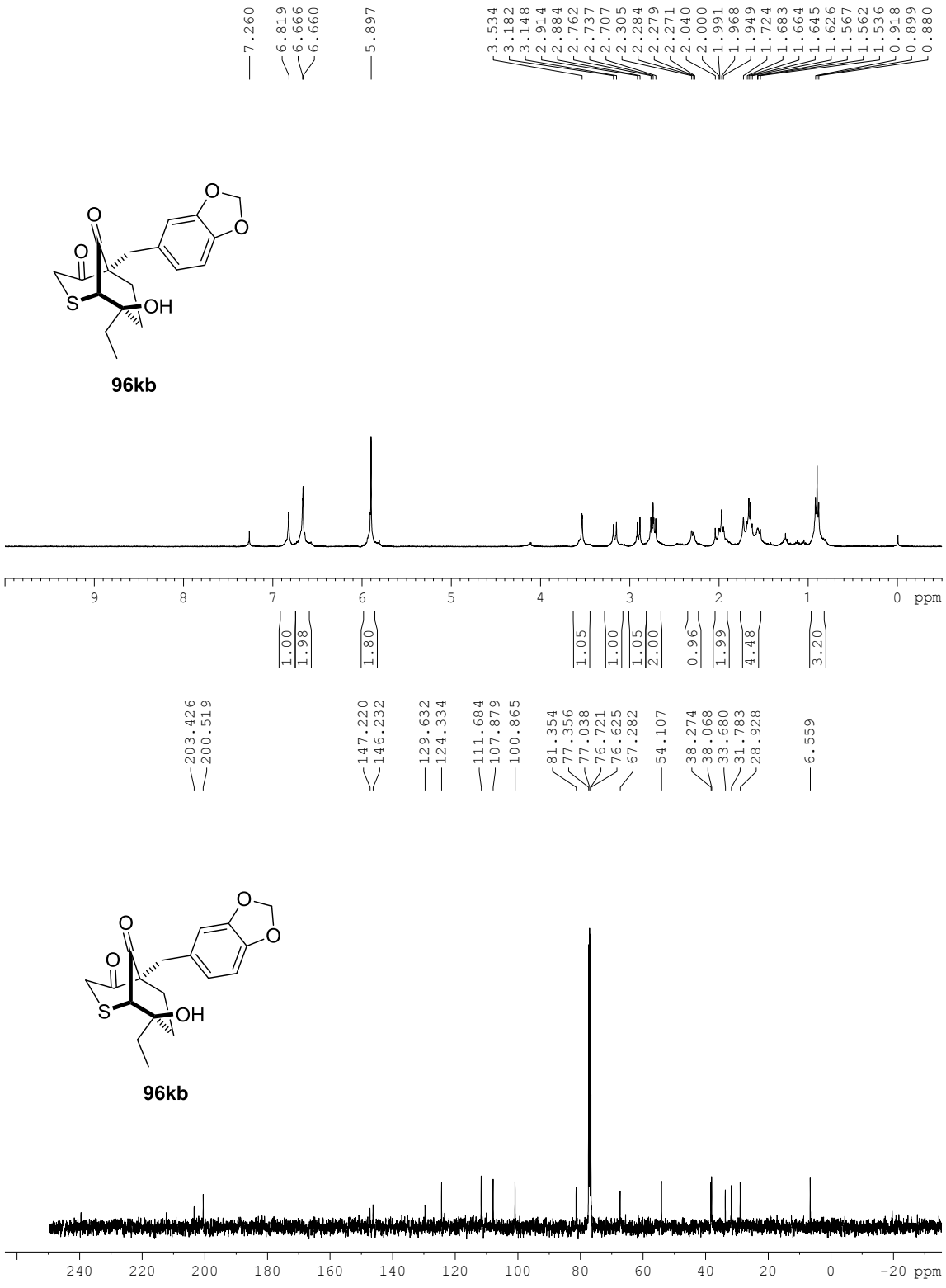



***Figure-N28:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **96kb**.

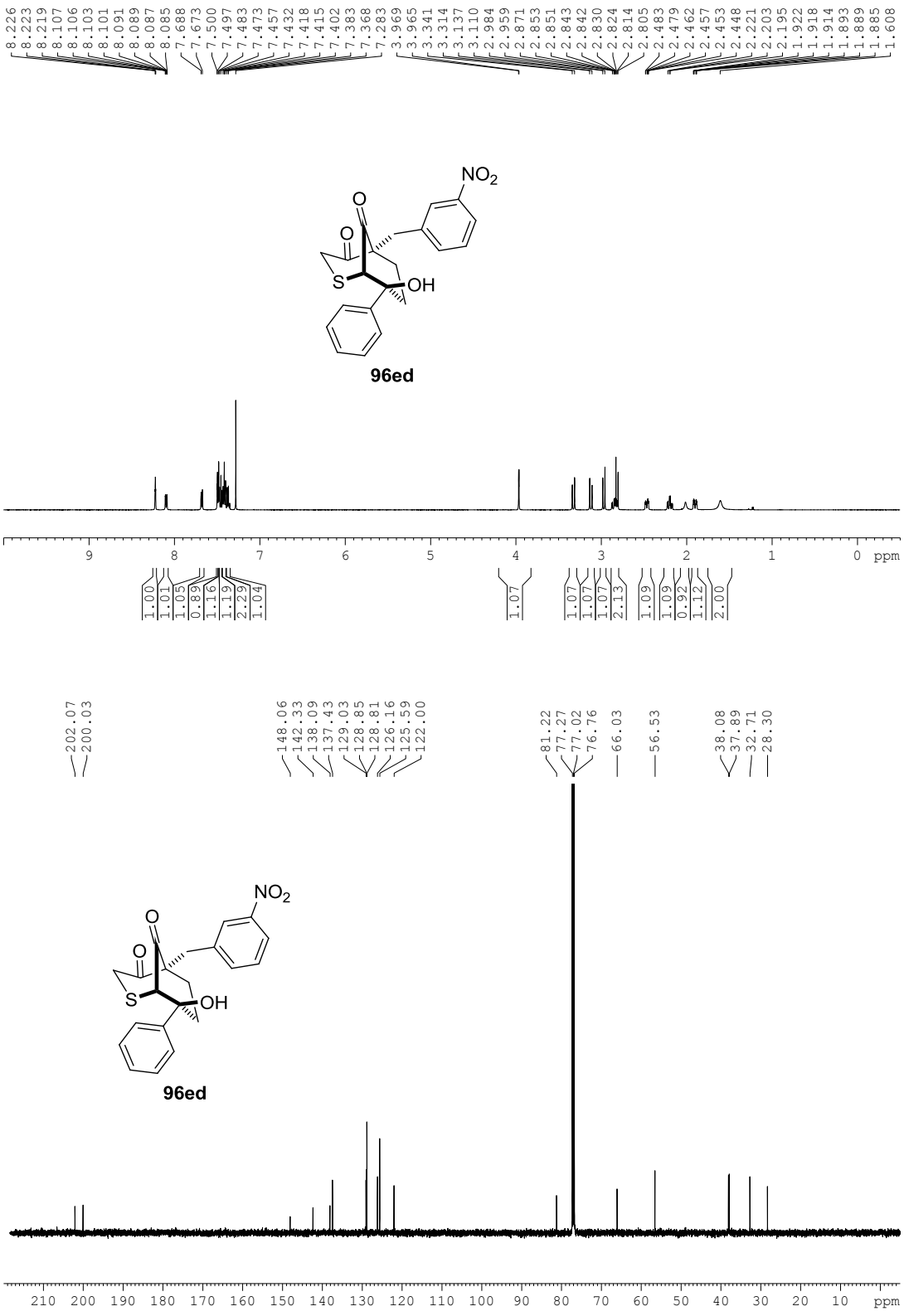
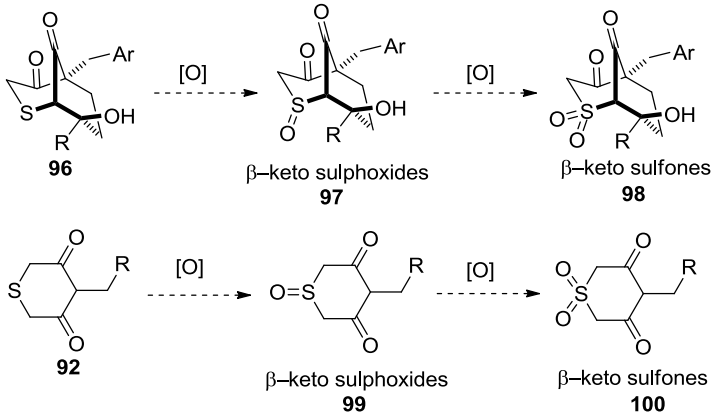



***Figure-N29:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **96ed**.

### 5.2.4.2 Synthesis of β-Keto Sulfoxides and β-Keto Sulfones:

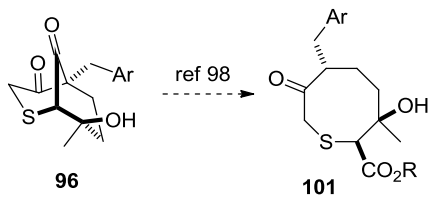
Oxidation of sulfides is the simplest method for the production of sulfoxides and sulfones, both of which are important commodity chemicals as well as pharmaceuticals. Conventional oxidants are mainly $NaBO_3$,[80] NaClO,[81] $Ca(ClO)_2$,[82] $H_5IO_6$,[83] $KHSO_5$,[84] $HNO_3$,[85] $(NH_4)_2Ce(NO_3)_6$,[86] $NaIO_4$,[87] $MnO_2$,[88] $KMnO_4$,[89] $RuO_4$,[90] $CF_3CO_3H$,[91] dimethyldioxirane,[92] *t*-$C_4H_9O_2H$,[93] 4-methylmorpholine oxide with $OsO_4$,[94] 3-$ClC_6H_4CO_3H$[95, 96] and hydrogen peroxide ($H_2O_2$)[97]. With well established oxidation of sulfides to sulphoxides and sulfones, the OrgRC products and M-A products can be converted easily to the respective sulphoxides and sulfones as shown Scheme 21.




***Scheme 21***. Oxidation of **92** and **96** Products.

### 5.2.4.3 Applications Towards CycloOctane Derivatives:

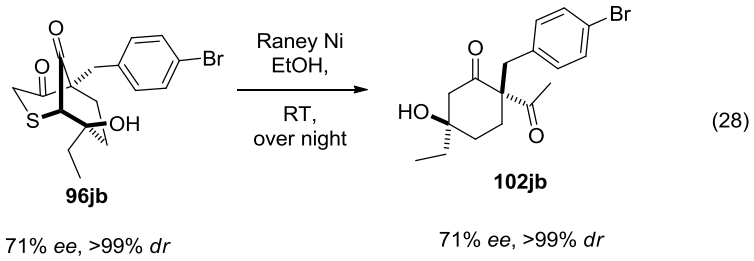
Strained cyclooctynes have a high importance in click chemistry and bioorthogonal reactions. The M-A reaction of the functionalized OrgRC products **92a-l** with **70a-d** will form bicyclic octane-dione derivatives with one keto group at bridging position. The bridging keto group will be easily converted into ester group by base mediated reaction leading to an eight-member ring opened product with different functional groups.[98] With few functional group transformations, one can prepare chiral octyne rings from substituted chiral compounds **96** as shown in Scheme 22.




***Scheme 22*:** Ring Opening by Using Bases.

### 5.2.4.4 Synthesis of Highly Functionalized Cyclohexanone:

Development of new and highly efficient cascade approaches for the synthesis of complex functionalized cyclohexanes is highly significant.[99] The M-A product **96jb** treated with raney nickel in presence of ethanol as solvent furnished the cyclohexanone derivative with >99% diastereoselectivity and 71% *ee,* by complete desulfurization of the ring by stirring for overnight as shown in eq. 28.

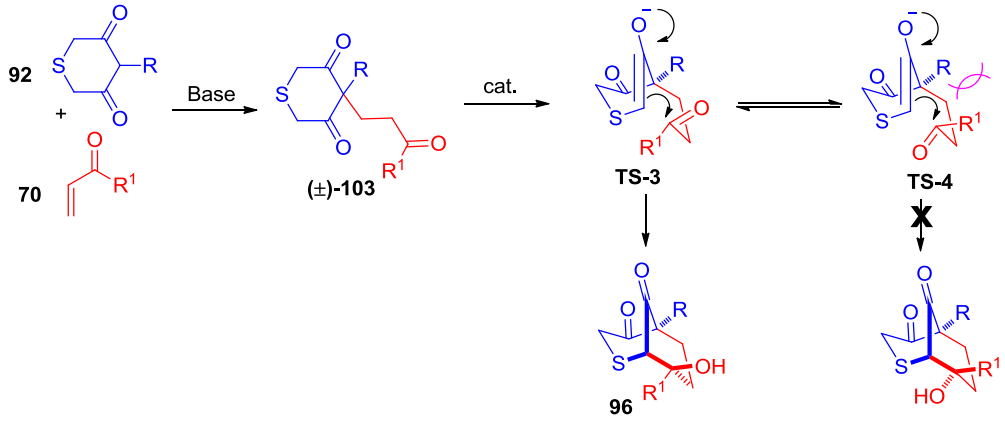



(28)

### 5.2.5 Mechanistic Insights:

The formation of the bicyclic compound **96** from the triketone **103** is the result of fast enolization of the six-membered ring ketone under basic condition and bond formation *via* nucleophilic attack of the enolate on the keto group of the side chain. Preferential enolization of cyclic ketone over aliphatic monoketone is well known from the literature.[100] The reaction may be considered to proceed *via* **TS-3** and **TS-5**, as there is no steric repulsions between alkyl/aryl group attached to side chain keto group and aromatic ring of hydroquinine leading to the product with *endo*-alkyl and *exo*-OH. Whereas there will be high steric hindrance between R & $R^1$, troubling enolate to undergo nucleophilic addition with side chain keto group as shown in **TS-4**. The crystal structure is also in well agreement with this statement. Dione **96** possesses two quaternary stereocentres with defined relative configuration (*endo*-alkyl, *exo*-OH, as shown in proposed mechanism).

***Scheme 23*:** Proposed Mechanism.



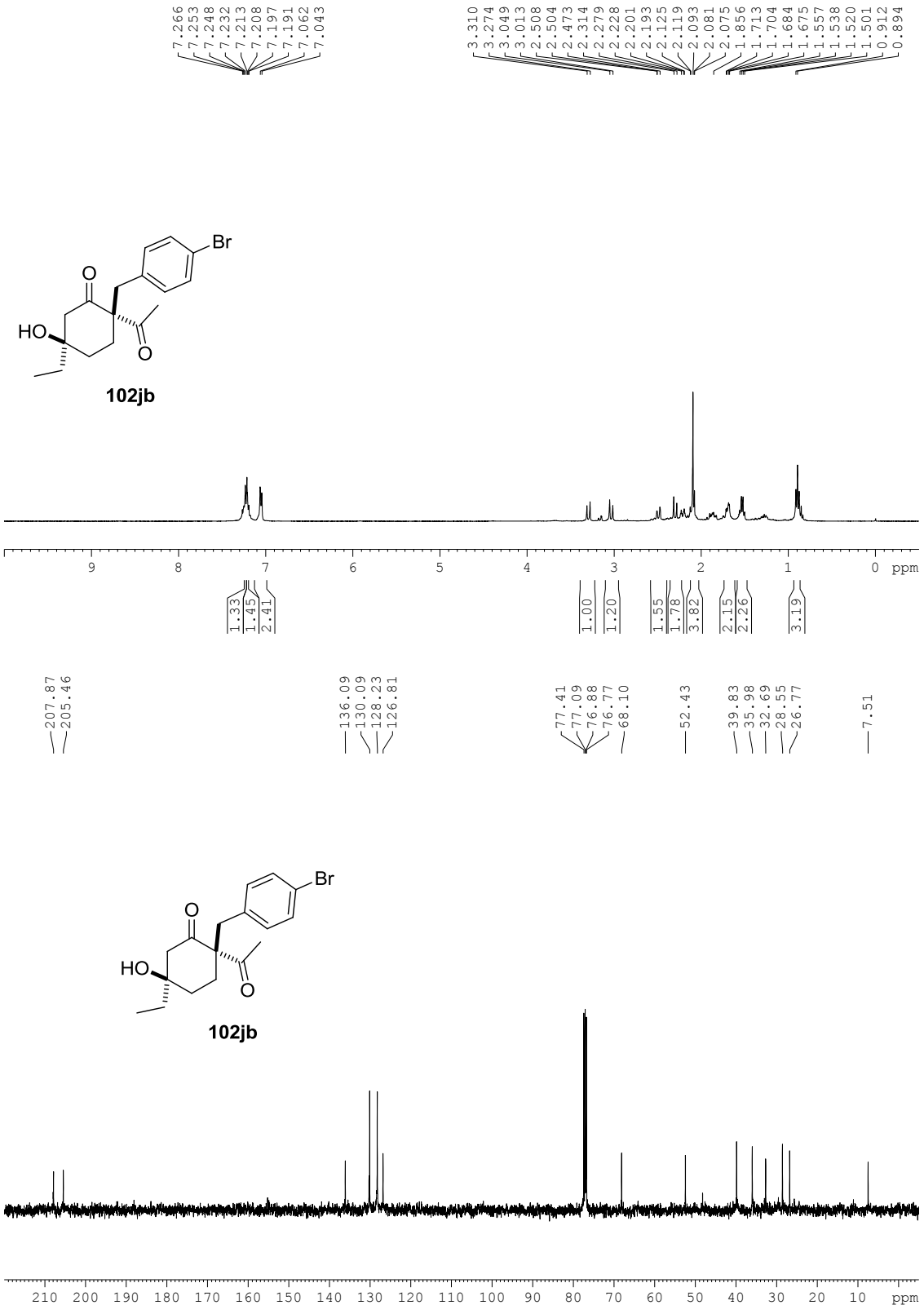



***Figure-N30:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **102jb**.

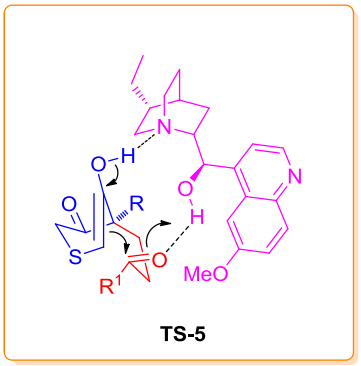



***Figure 8***: Proposed Transition State.

The results in Table 11 are clearly indicating that the regioselectivity in aldol reaction of Michael adducts **103** is controlled by the hetero atom introduced in the ring system to generate the reactive cyclic enolate and which is responsible for six-membered bridged bicylic M-A product instead of fused bicylic M-A product formation. The structure of the products **92**, **96**, **102jb** were confirmed by NMR analysis and also relative stereochemistry of the products **96** and **102jb** were assigned by product **96eb** X-ray structure analysis (Figure 9).

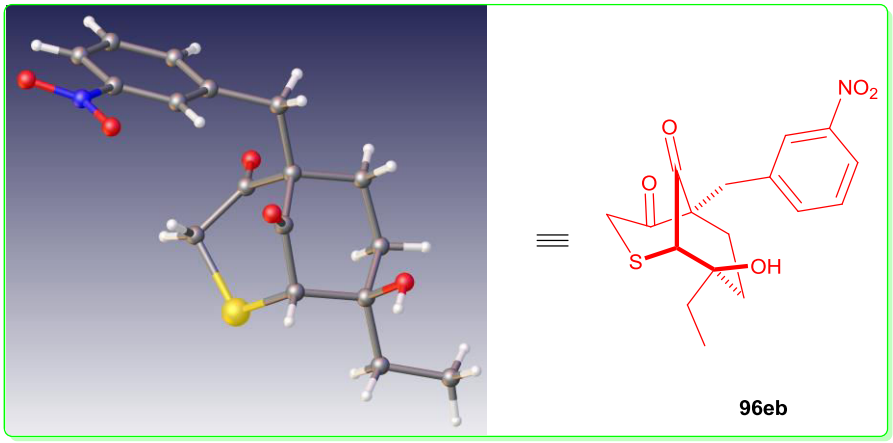



***Figure 9:*** Crystal Structure of (1*SR*,5*RS*,8*RS*)-8-Ethyl-8-hydroxy-5-(3-nitrobenzyl)-2-thiabicyclo [3.3.1] nonane-4,9-dione **96eb**.

## *5.3 CONCLUSIONS*

In summary, we have successfully utilized the concept of hetero-atom induced regioselevtivity in aldol reaction. Further we explored the synthesis of highly useful 2-alkyl CH-acids which are having a broad application scope. Here we described the hydroquinine catalyzed asymmetric Michael-aldol reactions of 2-alkyl CH-acids **92** with

α, β-unsaturated ketones **70** at ambient conditions. This novel asymmetric Michael-aldol reaction proceeds in good yields with high enantioselectivity and diasterioselectivity, producing the bridged bicylic compounds **96** with two quaternary centers derived in one pot. Furthermore, we demonstrated the application of chiral Michael-aldol products in the synthesis of highly functionalized cyclohexanones. We have found that fused bicyclic skeletons containing highly functional groups can be constructed in diastereoselective and enantioselective fashion using simple organic substrates and catalytic amount of hydroquinine.

# 6. Neighboring Ortho-Hydroxyl Group Directed Catalytic Asymmetric Triple Domino Reactions of Acetaldehyde with (E)-2-(2-Nitrovinyl)Phenols

## 6.1 INTRODUCTION

The discovery of amino acid-catalyzed double domino *asymmetric three-component Diels-Alder* (*ATCDA*) reaction (2003) initiated a new era in the asymmetric synthesis through a combination of multi-component and multi-domino catalysis.[6n] There has been a considerable range of multi-component and multi-domino reactions effectively catalyzed by chiral amines or amino acids since the last one decade. However it possesses some limitations from the substrate scope and reactivity/selectivity point of view.[101-103] Although the design and synthesis of natural products and drug-like chiral molecules have been synthesized through a combination of multi-component and multi-domino reactions,[104] these domino reactions still have some limitations. To elucidate, when the well defined catalytic conditions are applied to the substrates with additional functionality in known domino reactions, they fail to give the similar product with the desired selectivity.[105]

The development of efficient cellular-type organocatalytic domino reactions from simple substrates to form complex drug-like chiral molecules is a significantly challenging task. Carbon–carbon bond forming reactions with acetaldehyde provide access to synthetically useful compounds. Many research groups have tried to utilize the simplest enolizable carbonyl compound of acetaldehyde as a nucleophile into aldol, Michael or Mannich reactions using organocatalysis.[106] The first organocatalytic Michael reaction of acetaldehyde with simple β-nitrostyrenes was reported in 2008 by List and Hayashi groups (see eq. 29 and 30, Figure 10).[106g,106i] Following their protocols, Enders and co-workers reported a quadruple domino reaction of acetaldehyde with simple β-nitrostyrenes to furnish the trisubstituted cyclohexene carbaldehydes (eq. 31, Figure 10).[106o] In the above three reactions, List and Hayashi groups utilized five to ten equivalents of acetaldehyde at 0-25 °C for longer reaction times to furnish the expected Michael adducts in good yields and *ee*'s; but Enders domino reaction used ten equivalents of acetaldehyde under the trivial conditions to furnish the chiral compounds in moderate

yields with good *ee*'s and moderate *dr*'s (eq. 29-31, Figure 10). Inspired by the acetaldehyde reactivity pattern, herein, we describe the neighboring *ortho*-hydroxyl group directed[107] asymmetric organocatalytic multi-component, domino reaction for the synthesis of drug-like chiral chromanes[108] and tetrahydro-6*H*-benzo[c]chromenes[108] from acetaldehyde and 2-(2-nitrovinyl)phenols by using triple domino Michael/aldol/oxa-Michael reactions followed by a sequential one-pot Wittig, Michael/Wittig-Horner or reduction reactions.

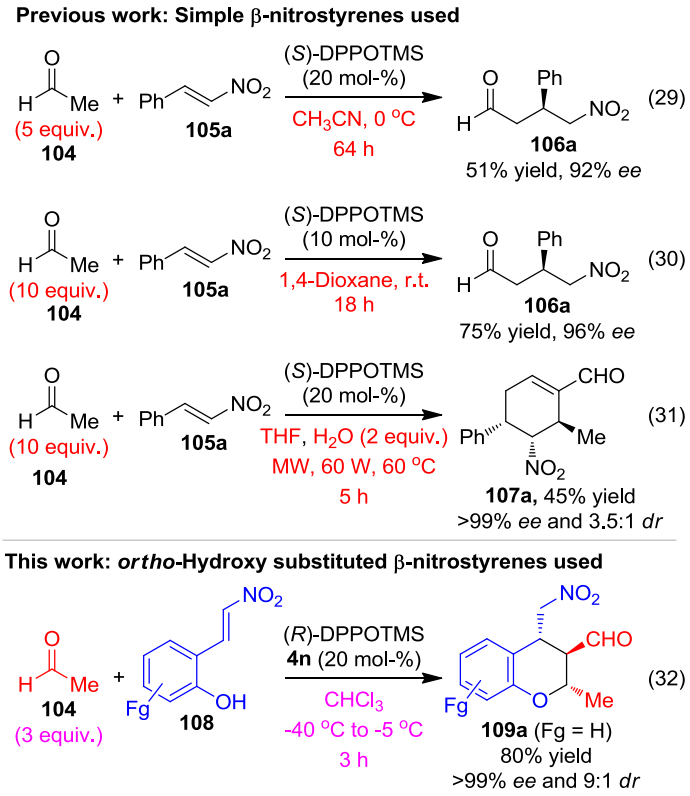



***Figure 10*:** Proposal for asymmetric triple domino-catalysis.

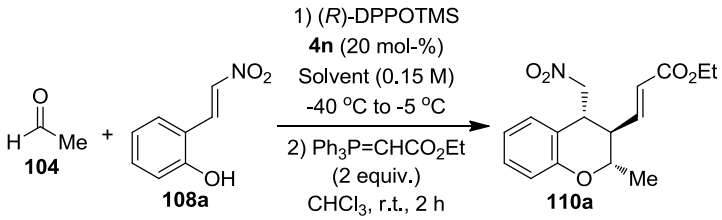
## 6.2 RESULTS AND DISCUSSION

### 6.2.1 Reaction Optimization

To investigate our hypothesis of directing high rate and asymmetric induction through neighboring *ortho*-hydroxyl group participation, we performed the Michael reaction of 2-(2-nitrovinyl)phenol **108a** with only three equivalents of acetaldehyde **104** in the presence of 20 mol% of (*R*)-DPPOTMS **4n** in $CHCl_3$ at –40 to –5 °C. Surprisingly, within 3 h, the reaction yielded chromane product **109a** in 80% yield with >99% *ee* and 9:1 *dr* (Figure 10, eq. 32). For clear understanding of the reaction selectivity and also for clean HPLC separation, we then subjected the *in situ* reaction mixture of **109a** to Wittig

conditions with two equivalents of $Ph_3P{=}CHCO_2Et$ at 25 °C for 2 h. To our delight, the sequential one-pot Wittig product (–)-**110a** was isolated in 80% yield with >17:1 *dr* and >99% *ee* (Table 12, entry 1). This result sugested that there was neighboring *ortho*-hydroxyl group participation through hydrogen bonding in the double domino Michael/aldol reactions pre-transition states, which was responsible for the highest reactivity and enantioselectivity. Interestingly, the chromane **109a** was isolated in 9:1 *dr* at the triple domino Michael/aldol/oxa-Michael reaction stage, but were enriched to >17:1 *dr* after the Wittig reaction may be due to the epimerization or decomposition of minor isomer of chromane **109a**.

***Table 12*:** Reaction Optimization.[a]




| Entry | **1** [equiv.] | Solvent [0.15 M] | *t* [h] | Yield [%][b] **110a** | *dr*[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| **1** | **3** | **$CHCl_3$** | **3** | **80** | **>17:1** | **>99** |
| 2 | 5 | $CHCl_3$ | 3 | 45 | >17:1 | >99 |
| 3 | 1 | $CHCl_3$ | 3 | 25 | 10:1 | >99 |
| 4[e] | 3 | $CHCl_3$ | 3 | 61 | >17:1 | >99 |
| 5[f] | 3 | $CHCl_3$ | 3 | 51 | >17:1 | 98 |
| 6[g] | 3 | $CHCl_3$ | 6 | 67 | >17:1 | >99 |
| 7[h] | 3 | $CHCl_3$ | 9 | 64 | >17:1 | >99 |
| 8[i] | 3 | $CHCl_3$ | 3 | 61 | 15:1 | >99 |
| 9 | 3 | DCM | 5 | 54 | >17:1 | >99 |
| 10 | 3 | DCE | 7 | 66 | >17:1 | >99 |
| 11 | 3 | $CH_3CN$ | 12 | 53 | >17:1 | >99 |
| 12 | 3 | $CH_3C_6H_5$ | 12 | 47 | 10:1 | >99 |
| 13 | 3 | 1,4-dioxane | 24 | 31 | 5:1 | >99 |

[a] Reactions were carried out in solvent (0.15 M) with 1 to 5 equiv. of **104** relative to the**108a** (0.3 mmol) in the presence of 20 mol-% of (*R*)-**4n** followed by one-pot Wittig reaction in $CHCl_3$ (0.15 M). [b] Yield refers to the column-purified product after 2 steps. [c] *dr* was determined based on $^1$H NMR or HPLC analysis. [d] *ee* was determined by CSP HPLC analysis. [e] 20 mol-% of $CH_3CO_2H$ was used as co-catalyst. [f] 20 mol-% of $PhCO_2H$ was used as co-catalyst. [g] 10 mol-% of (*R*)-**4n** was used. [h] 5 mol-% of (*R*)-**4n** was used. [i] Reaction performed at 25 °C.

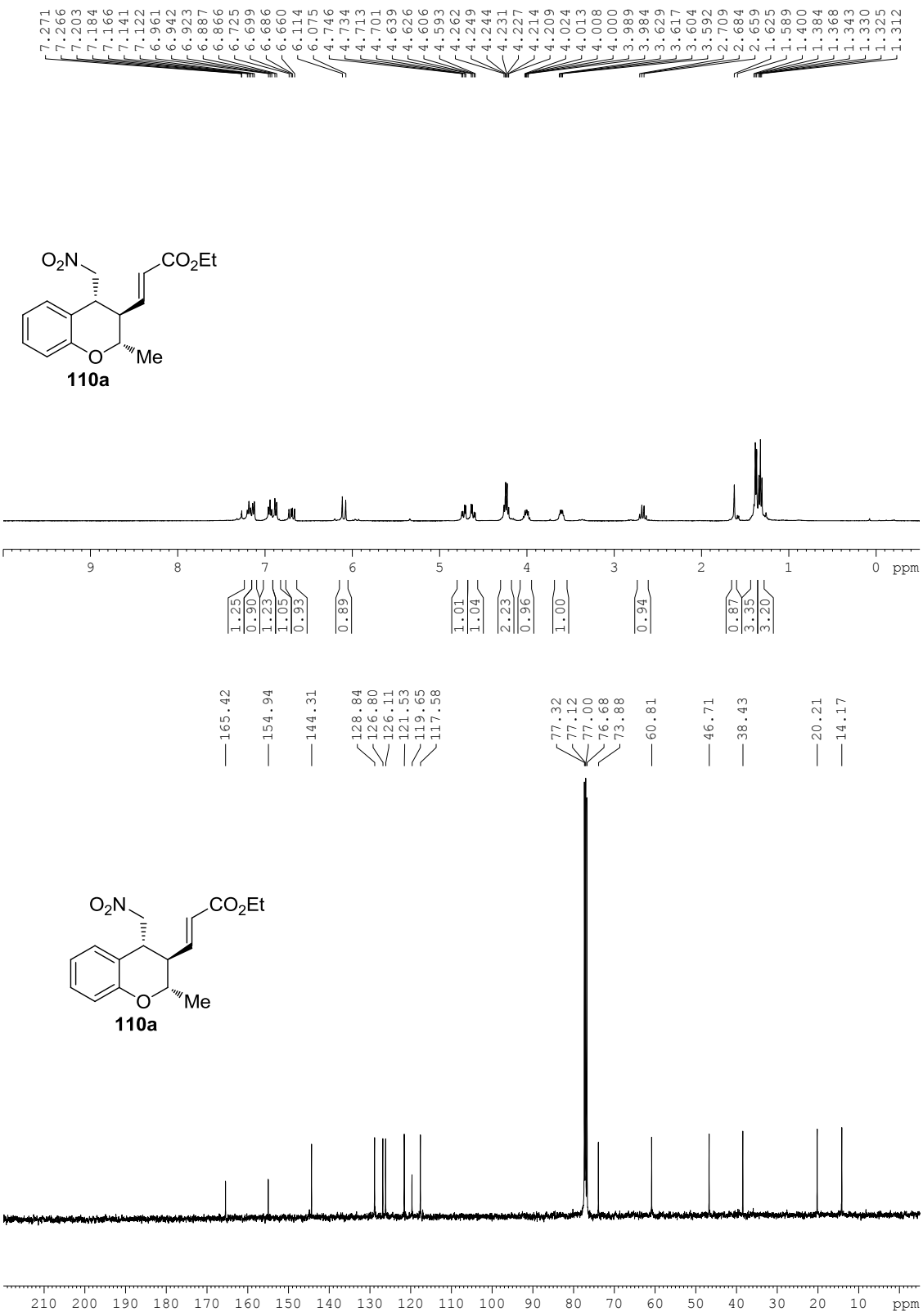



***Figure-N31:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **110a**.

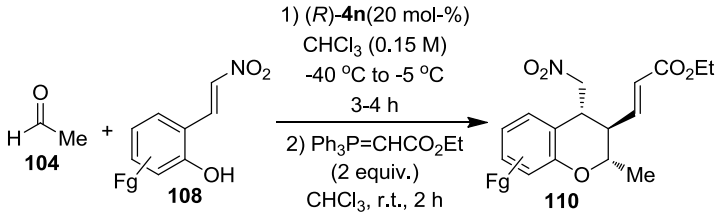
We further investigated the above triple domino reaction to see the improvement in yield and *dr*. However, the same reaction with five or one equivalent of acetaldehyde **104** at −40 to −5 °C for 3 h followed by the Wittig reaction in sequential one-pot manner furnished the (−)-**110a** in reduced (45% or 25%) yield with >17:1 or 10:1 *dr* and >99% *ee*, respectively (Table 12, entries 2 and 3). After thorough investigation of (*R*)-**4n**-catalyzed asymmetric triple domino Michael/aldol/oxa-Michael reaction followed by a sequential one-pot Wittig reaction, we found that the solvent, co-catalyst, catalyst loading and reaction temperature have significant effects on the *dr*/*ee*'s and yields. In the final optimization, asymmetric *triple domino* reaction of **104** and **108a** through (*R*)-**4n**-catalysis in chloroform (0.15 M) at −40 to −5 °C for 3 h followed by Wittig reaction with two equivalents of $Ph_3P{=}CHCO_2Et$ in a sequential one-pot manner at 25 °C for 2 h in chloroform (0.15 M) furnished the isomerically pure chiral chromane (−)-**110a** in 80% yield with 99% *ee* and >17:1 *dr* (Table 12, entry 1).

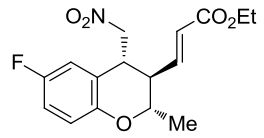
### *6.2.2 Diversity Oriented Synthesis of Chromanes:*

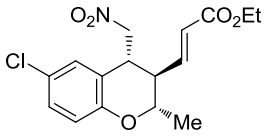
The generality of the asymmetric triple domino-catalysis was further supported by reacting a series of functionalized 2-(2-nitrovinyl)phenols **108b–k** with three equivalents of acetaldehyde **104** catalyzed by 20 mol% of (*R*)-**4n** at −40 to −5 °C in $CHCl_3$ (0.15 M) for 3-4 h followed by the Wittig reaction in a sequential one-pot manner with two equivalents of $Ph_3P{=}CHCO_2Et$ at 25 °C for 2 h (Table 13). The chiral chromane products **110b-k** were isolated in excellent yields, *dr's* and *ee*'s, tolerating the electronic and steric influence of the substrates. Herein, a variety of 2-(2-nitrovinyl)phenols **108a-k** were used as dual Michael acceptors and donors to trap the *in situ* generated "*simplest enamine*" and functionalized "*iminium ions*" from the *triple domino* reaction of **104**, **108** and (*R*)-**4n** to furnish the functionalized chiral chromanes **110a-k** with up to >99% *ee* and >25:1 *dr* in excellent yields (Table 13). Furthermore to understand the complex chiral molecules synthesis from the triple domino reaction and also for the structural importance of chromene moiety in medicinal chemistry,[108] the domino products **109** were treated *in situ* with the ethyl 2-(diethoxyphosphoryl)acrylate **111**[104h] to furnish a series of tricyclic chromenes **112a-j** in excellent yields with good *dr* and *ee* values (Table 14). When *in situ* formed triple domino chromane **109a** was used in the sequential one-pot Michael/Wittig-Horner reactions with two equivalents **111** at 25 °C for 2 h, the tricyclic chromene (−)-**112a** was furnished in 75% yield with >99:1 *dr* and >99% *ee* (Table 14). In a similar manner, isomerically and optically pure three more chiral tricyclic chromenes **112** were

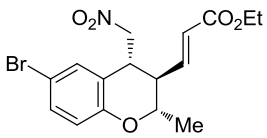
synthesized in very good yields from functionalized 2-(2-nitrovinyl)phenols **108** without any side reactions (Table 14).

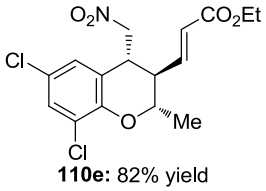
***Table 13*:** Scope of the Asymmetric Triple Domino-Catalysis.[a-c]

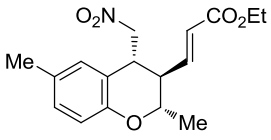


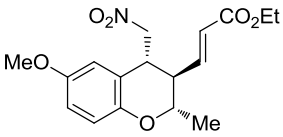


**110b:** 82% yield
24:1 *dr* and >99% *ee*

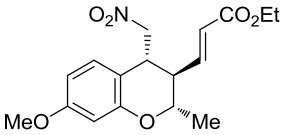

**110c:** 82% yield
>25:1 *dr* and >99% *ee*

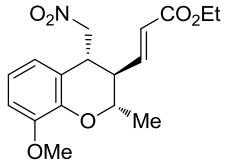

**110d:** 83% yield
18:1 *dr* and >99% *ee*

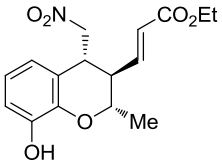

**110e:** 82% yield
18:1 *dr* and >99% *ee*

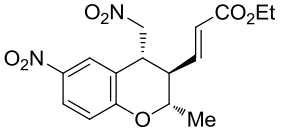

**110f:** 87% yield
15:1 *dr* and >99% *ee*


**110g:** 82% yield
24:1 *dr* and >99% *ee*


**110h:** 80% yield
24:1 *dr* and >99% *ee*


**110i:** 75% yield
24:1 *dr* and >99% *ee*


**110j:** 75% yield
16:1 *dr* and >99% *ee*


**110k:** 80% yield
15:1 *dr* and >99% *ee*

[a] Yield refers to the column-purified product after 2 steps. [b] *dr* was determined based on $^1$H NMR or HPLC analysis. [c] *ee* was determined by CSP HPLC analysis.

The structure and absolute stereochemistry of the triple domino products **109**, **110** and tricyclic chromenes **112** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (–)-**110a** as shown in Figure-11 .[109]

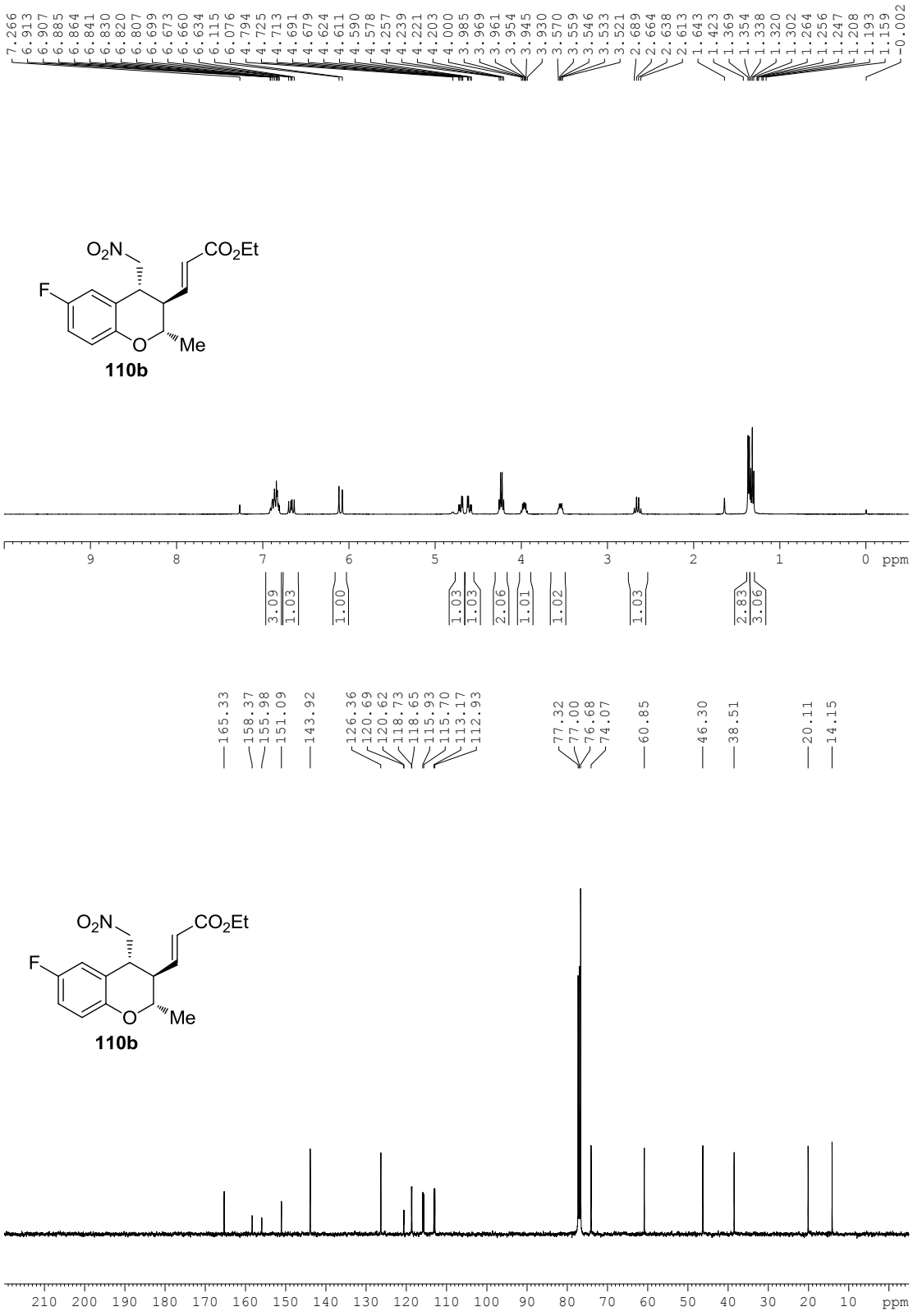



***Figure-N32:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **110b**.

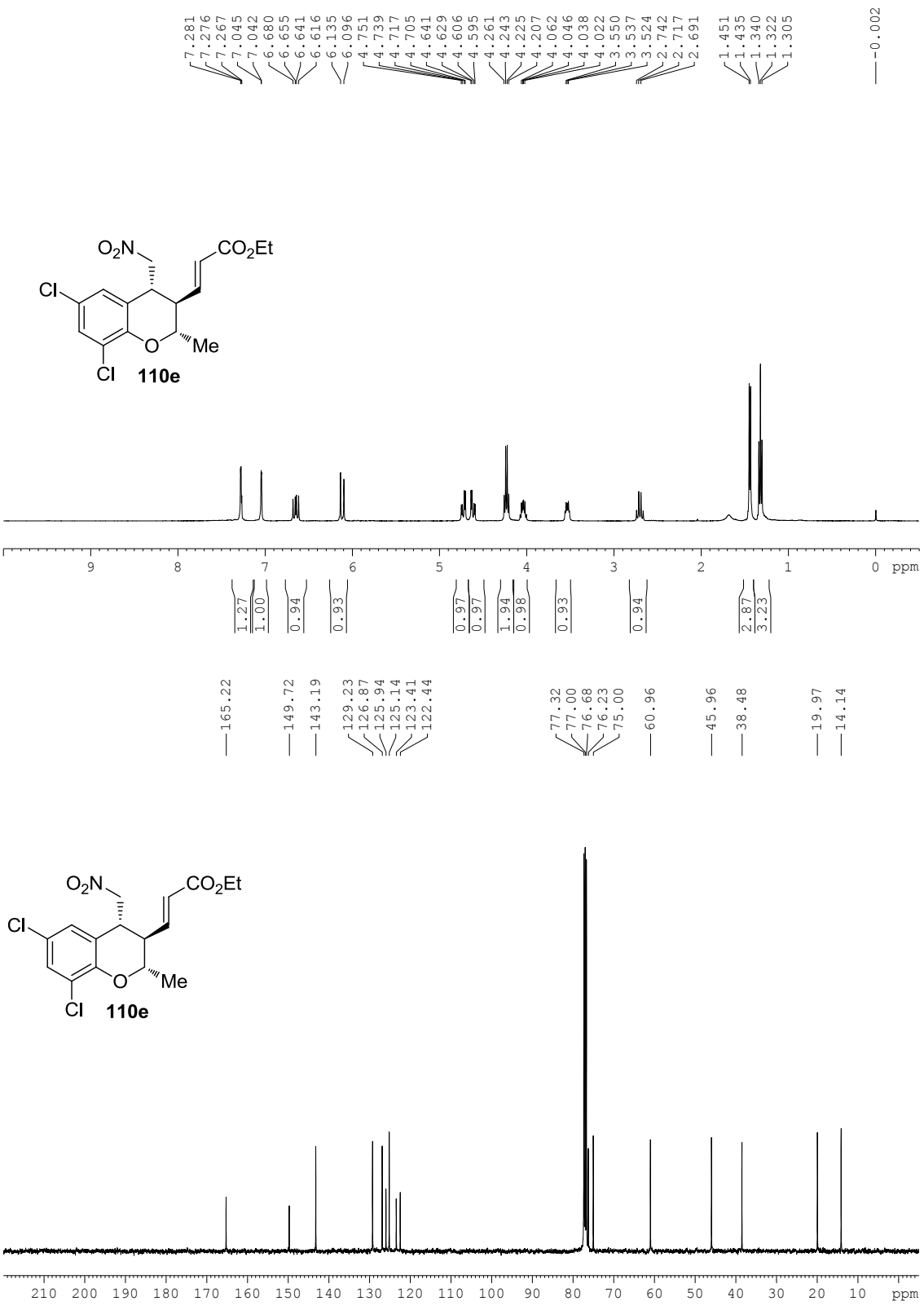



***Figure-N33:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **110e**.

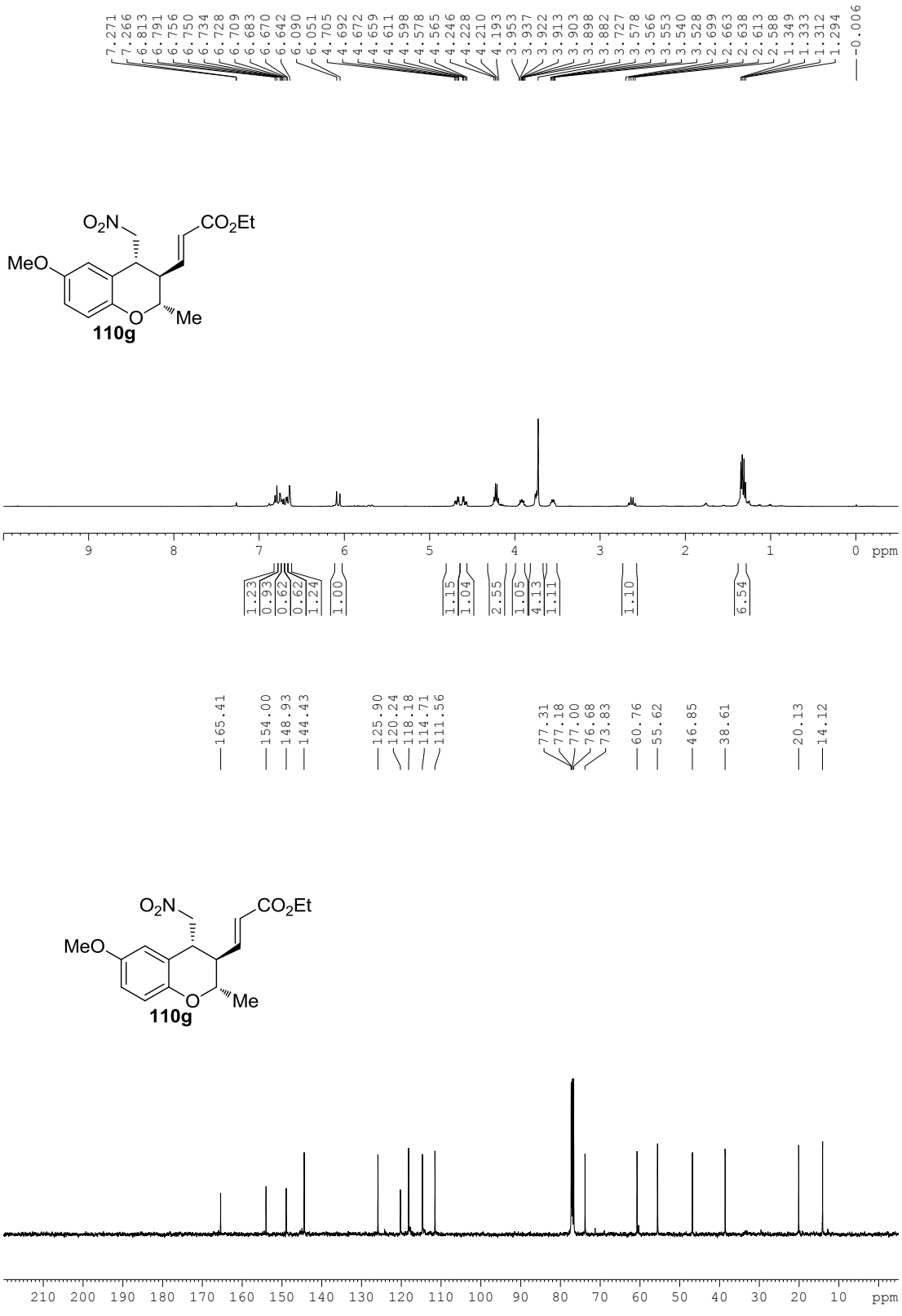



***Figure-N34:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **110g**.

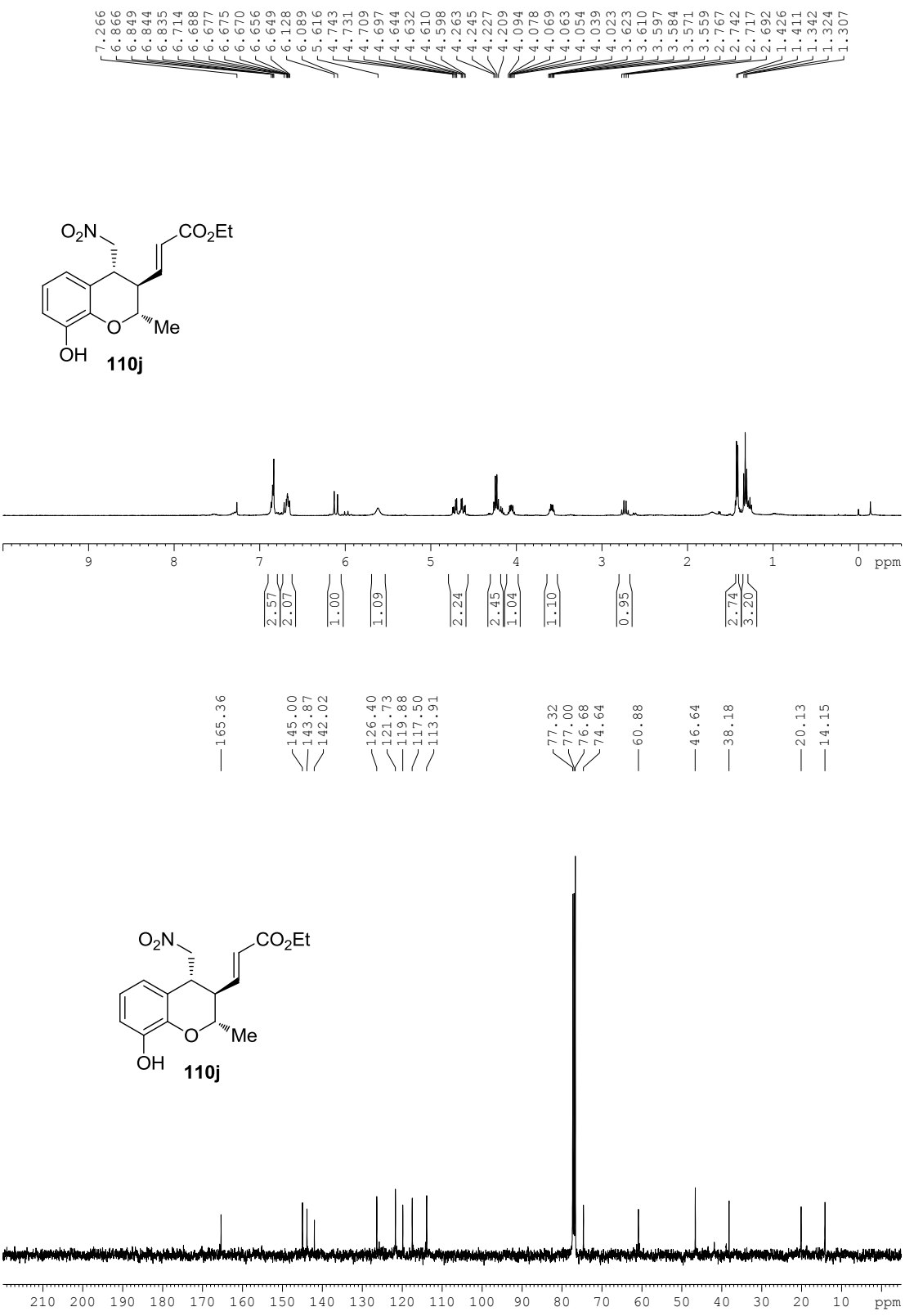



***Figure-N35:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **110j**.

***Figure 11*: X-ray Crystal Structure of Chiral (*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110a).**

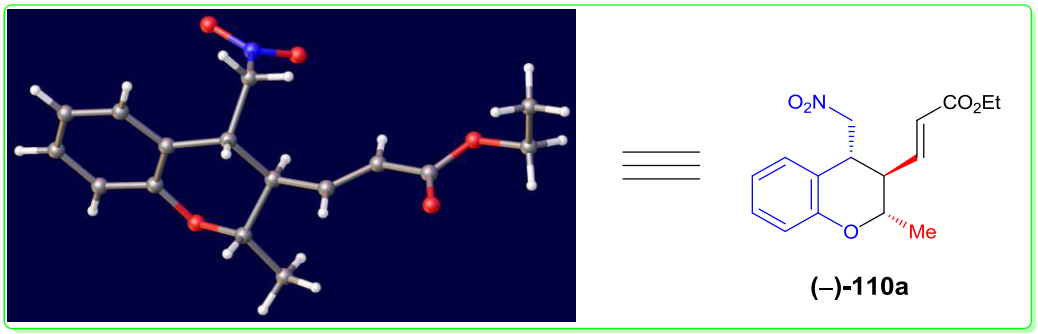
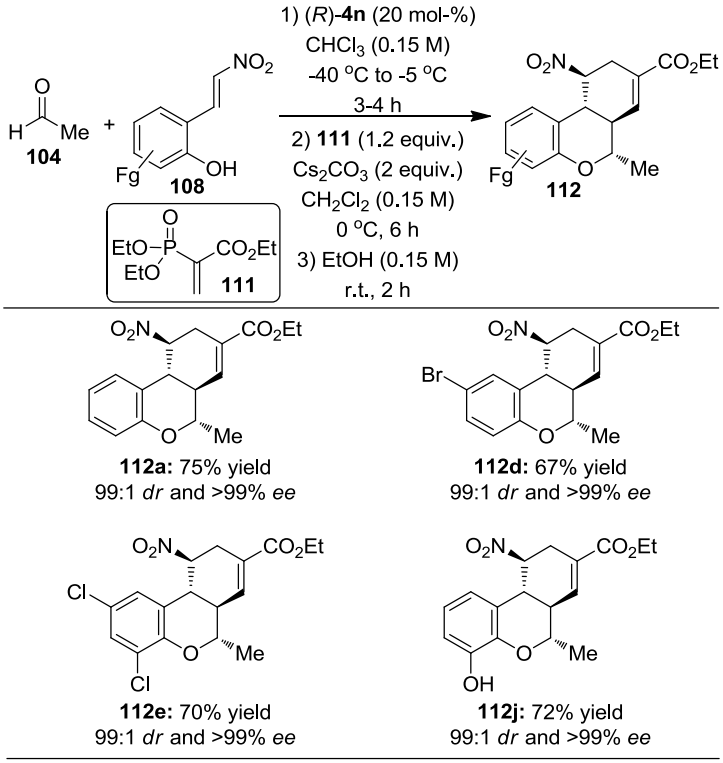



***Table 14*: Scope of the Asymmetric Sequential One-pot Reactions.[a-c]**




[a] Yield refers to the column-purified product after 3 steps. [b] *dr* was determined based on $^1$H NMR or HPLC analysis. [c] *ee* was determined by CSP HPLC analysis.

To explore the utility of the chiral (2*S*,3*R*,4*R*)-2-methyl-4-(nitromethyl)chroman-3-carbaldehydes **109**, we subjected them to simple reduction protocol to furnish the ((2*S*,3*S*,4*R*)-2-methyl-4-(nitromethyl)chroman-3-yl)methanols (eq. 33). Moreover, the *in situ* sodium borohydride mediated reduction on the chiral triple domino product **109a**

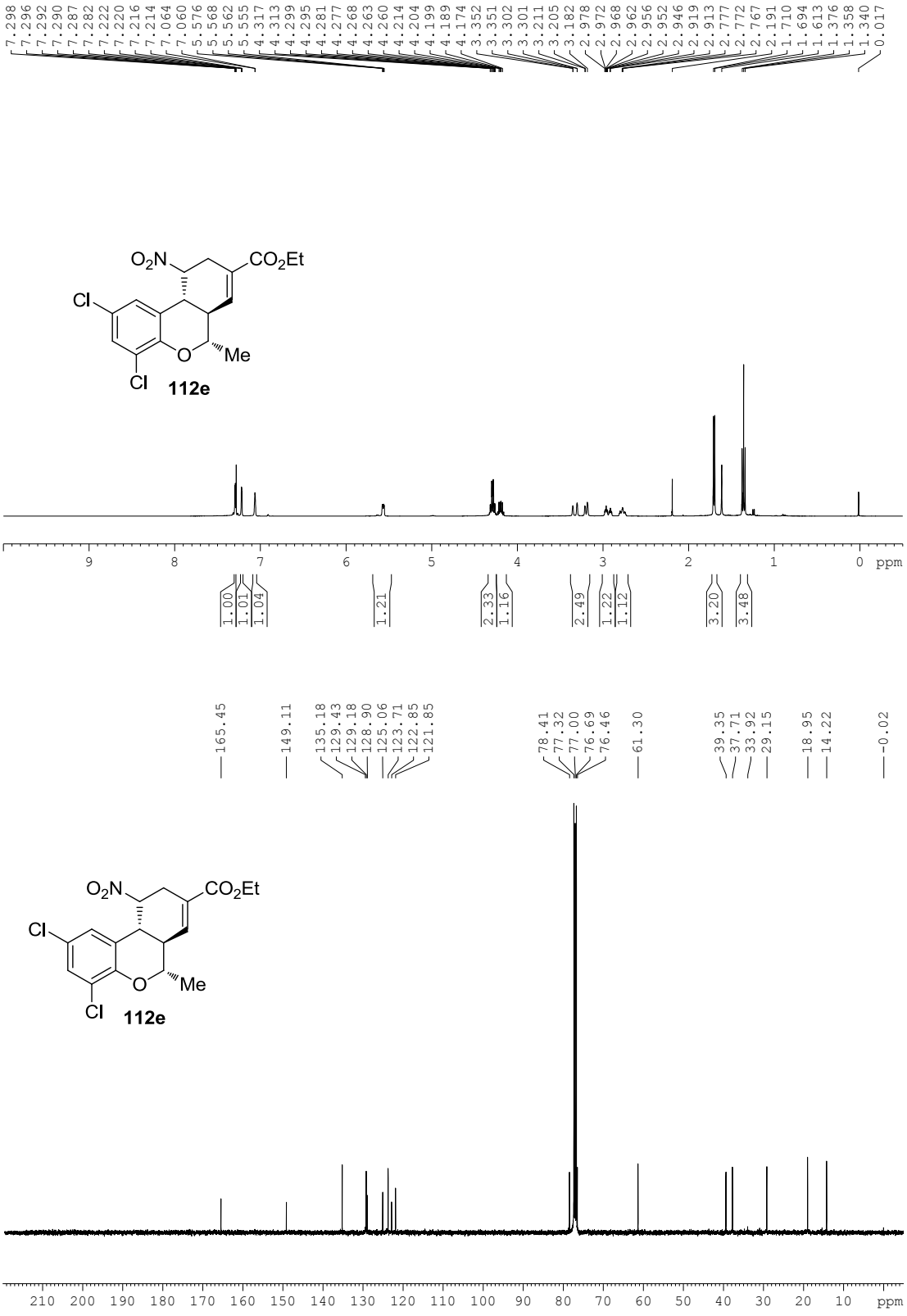
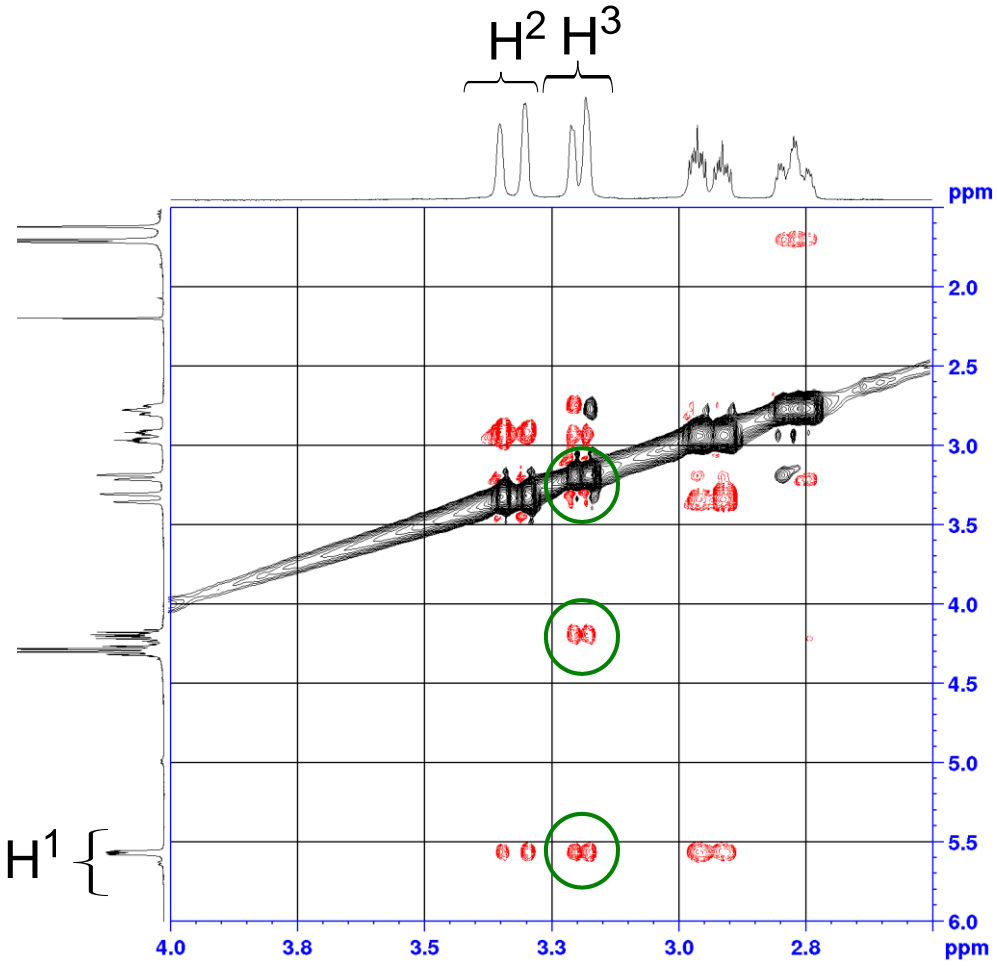



***Figure-N36:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **112e**.


***Figure-N37:*** $^{1}$H NMR and $^{13}$C NMR Spectrum of Product **112j**.



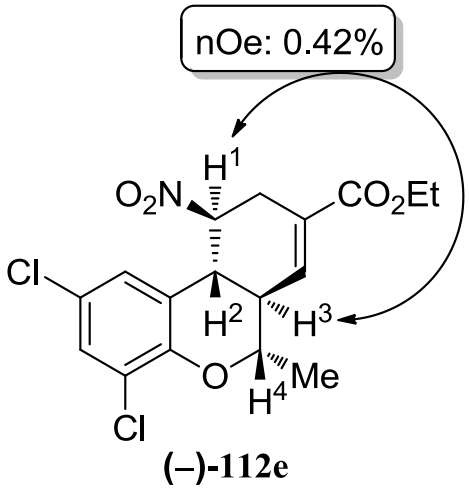
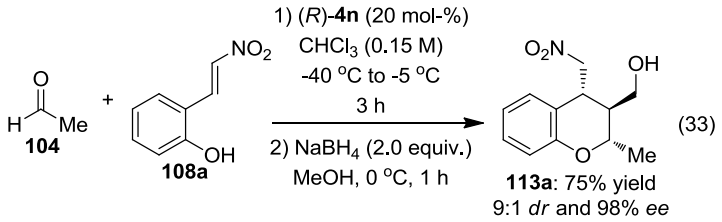



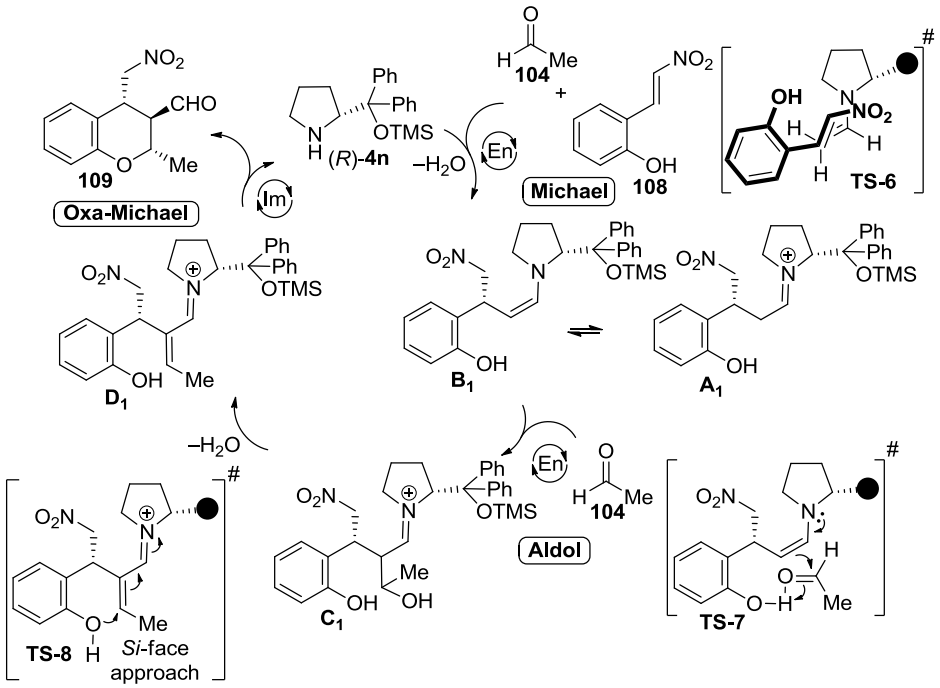

***Figure-N38:*** $^{1}$H-$^{1}$H NOESY NMR Spectrum of the Product **112e**.

furnished the compound (–)-**113a** in 75% yield with 98% *ee* and 9:1 *dr*. Perhaps, this observed less diastereoselectivity of (–)-**113a** may be due to the possibility of very slow epimerization of minor isomer of **109a** at these conditions. The observation of less diastereoselectivity in reduction strategy was further supported by the same selectivity observed in the previous step of triple domino-catalysis (eq. 32 and 33).




## *6.2.3 Mechanistic Insights*

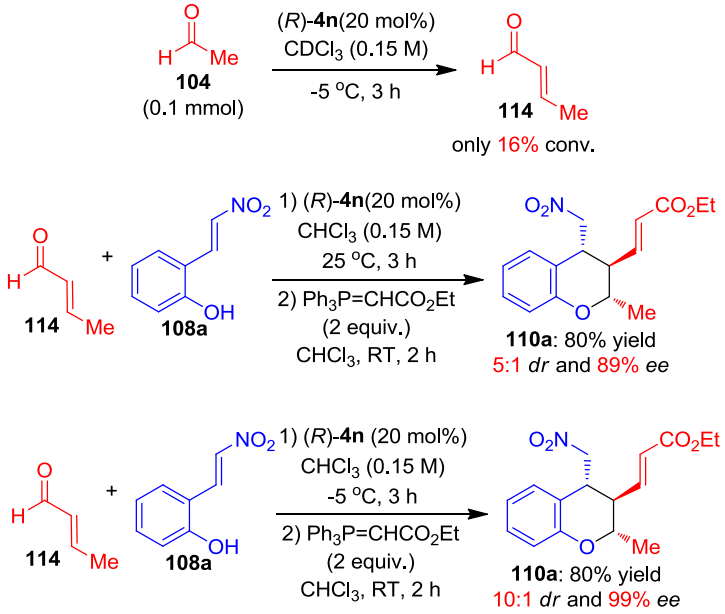
***Figure 12:*** Proposed Reaction Mechanism for the Triple Domino Catalysis.




Even though further studies are needed to securely elucidate the mechanism of triple domino reactions through (*R*)-**4n**-catalysis, the reaction proceeds in a stepwise domino manner between the *in situ* generated "*simplest enamine*" from **104** and (*R*)-**4n** and the olefins **108** (Figure 12). In the first step of Michael addition, based on the crystal structure studies we can rationalize the observed high stereoselectivity through an allowed transition state where the *re*-face of *ortho*-hydroxy olefin **108** approaches the *in situ* generated "*simplest enamine*" from **104** and (*R*)-**4n** due to the less steric hindrance/electrostatic repulsion as shown in **TS-6**. In the second aldol condensation step,

formation of the "*iminium ion*" **$D_1$** can be explained by the model **TS-7**, in which the newly generated "*enamine*" **$B_1$** approaches the activated acetaldehyde **104** through intermolecular hydrogen bonding with *ortho*-OH group followed by water elimination from intermediate **$C_1$**, which is also induced by *ortho*-OH group through intramolecular hydrogen bonding (Figure 12). In the third *oxa*-Michael step, on the basis of crystal structure studies we conclude that the observed high stereoselectivity through an allowed transition state where the *si*-face of "*iminium ion*" **$D_1$** undergoes intramolecular *oxa*-Michael addition with *ortho*-Ar-OH group followed by hydrolysis as shown in **TS-8**.

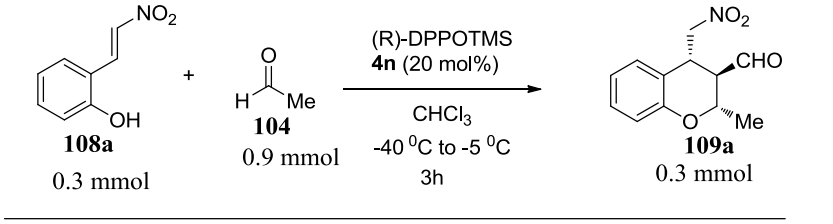
Alternative pathway for domino products **109** formations can be possible through aldol condensation/oxa-Michael/Michael sequence, which will be triggered by *in situ* crotonaldehyde formation.[103a] But this pathway is overruled by performing few controlled experiments and also detecting key intermediates of an on-going reaction using ESI-HRMS analysis (Scheme 24 and Figure 13). Rate of the *in situ* crotonaldehyde **114** formation from the acetaldehyde **104** under the identical conditions was very poor, compared to Michael addition with olefin **108a**. Reaction of crotonaldehyde **114** with olefin **108a** under the (*R*)-**4n** catalysis at -5 or 25 °C followed by sequential one-pot addition with $Ph_3P{=}CHCO_2Et$ furnished the domino product **110a** in good yield/*ee*, but with moderate *dr*. These two controlled experiments suggesting that the reaction pathway will be the domino Michael/aldol condensation/oxa-Michael instead of aldol condensation/oxa-Michael/Michael sequence.

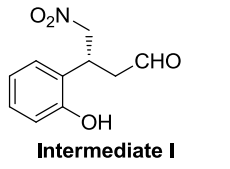



***Scheme 24***: Controlled Experiments to Investigate the Reaction Mechanism.

As evidence, the proposed reaction pathway and the formation of the important catalytic species of "*iminium ions*" $\mathbf{C_1}$ and $\mathbf{D_1}$ were confirmed through the electrospray ionization with high resolution mass spectrometry (ESI-HRMS) analysis of the on-going reaction between 0.9 mmol of **104**, 0.3 mmol of **108a** and 20 mol-% of (*R*)-**4n** in $CHCl_3$ at –40 °C to –5 °C for 3 h and also shown by the structural requirement in the olefins **108** to increase the triple domino reaction rate through controlled experiments (Scheme 24). The ESI-HRMS spectrum of an on-going reaction of **104** (3 equiv.) and **108a** in the presence of (*R*)-**4n** (20 mol-%) in the $CHCl_3$ at –40 °C to –5 °C for 3 h reveals the presence of mono Michael product+$H^+$ (*m*/*z* 210.0769), Michael-aldol product·$Na^+$ (*m*/*z* 276.0847), Michael-aldol condensation product·$Na^+$ (*m*/*z* 258.0746) and also the formation of the key catalytic intermediates $\mathbf{C_1}^+$ (*m*/*z* 561.2786) and $\mathbf{D_1}^+$ (*m*/*z* 543.2680). Nevertheless, the key catalytic intermediate ions $\mathbf{C_1}^+$ and $\mathbf{D_1}^+$ are observed from the first moments of reaction (Figure-13).[107]

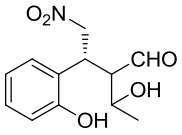
***Figure-13:*** The Complete Information on the ESI-HRMS Spectrum of an On-going Reaction of **104** and **108a** in the Presence of **4n.**



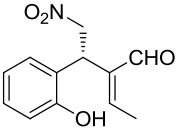

**Intermediate I**

Formula: $C_{10}H_{11}NO_4$
Exact Mass: 209.0688



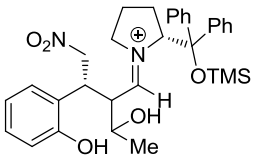

**Intermediate II**

Formula: $C_{12}H_{15}NO_5$
Exact Mass: 253.0950



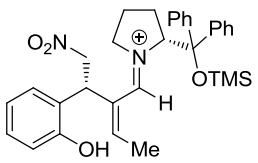

**Intermediate III**

Formula: $C_{12}H_{13}NO_4$
Exact Mass: 235.0845




**Intermediate $\mathbf{C_1}$**

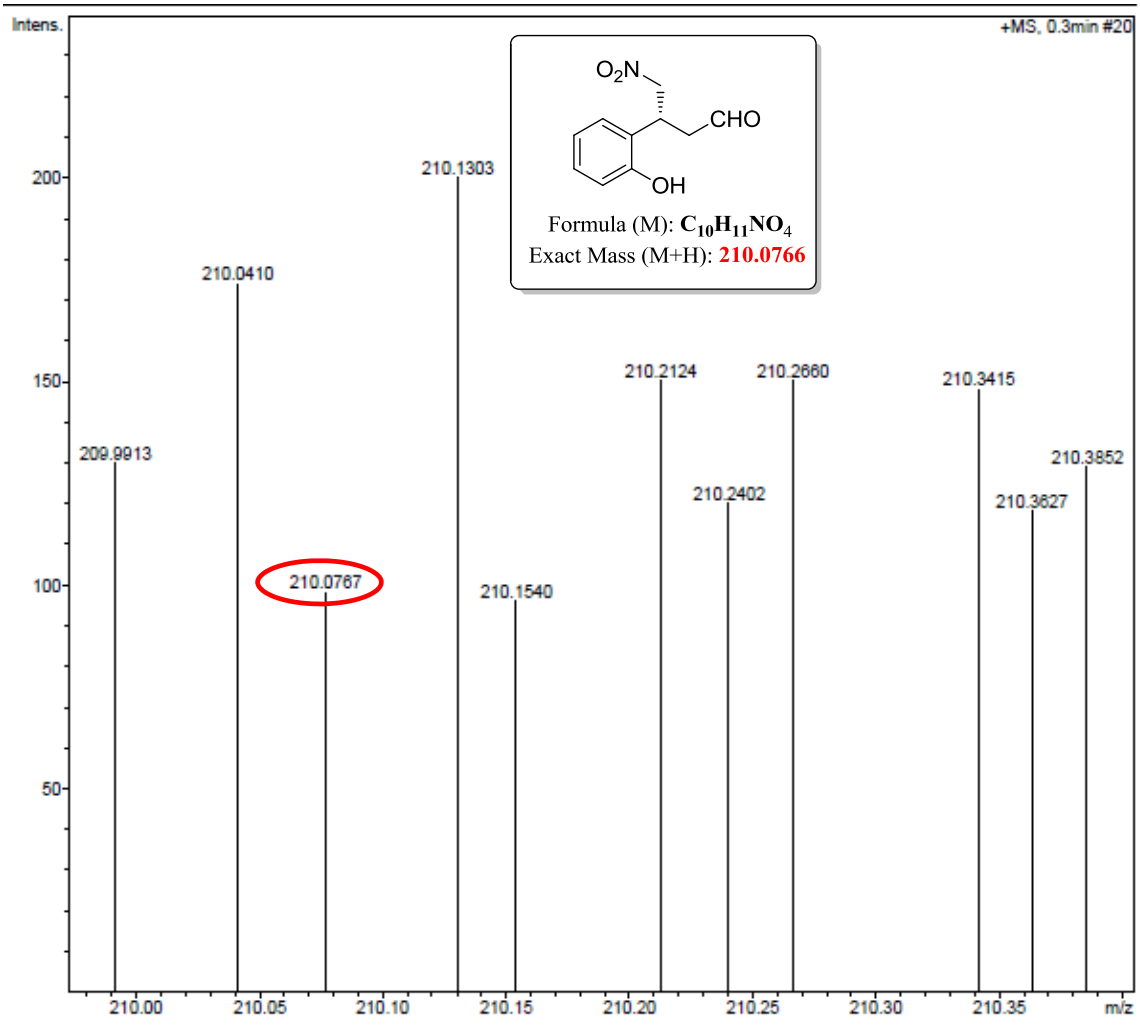
Formula: $C_{32}H_{41}N_2O_5Si^+$
Exact Mass: 561.2785



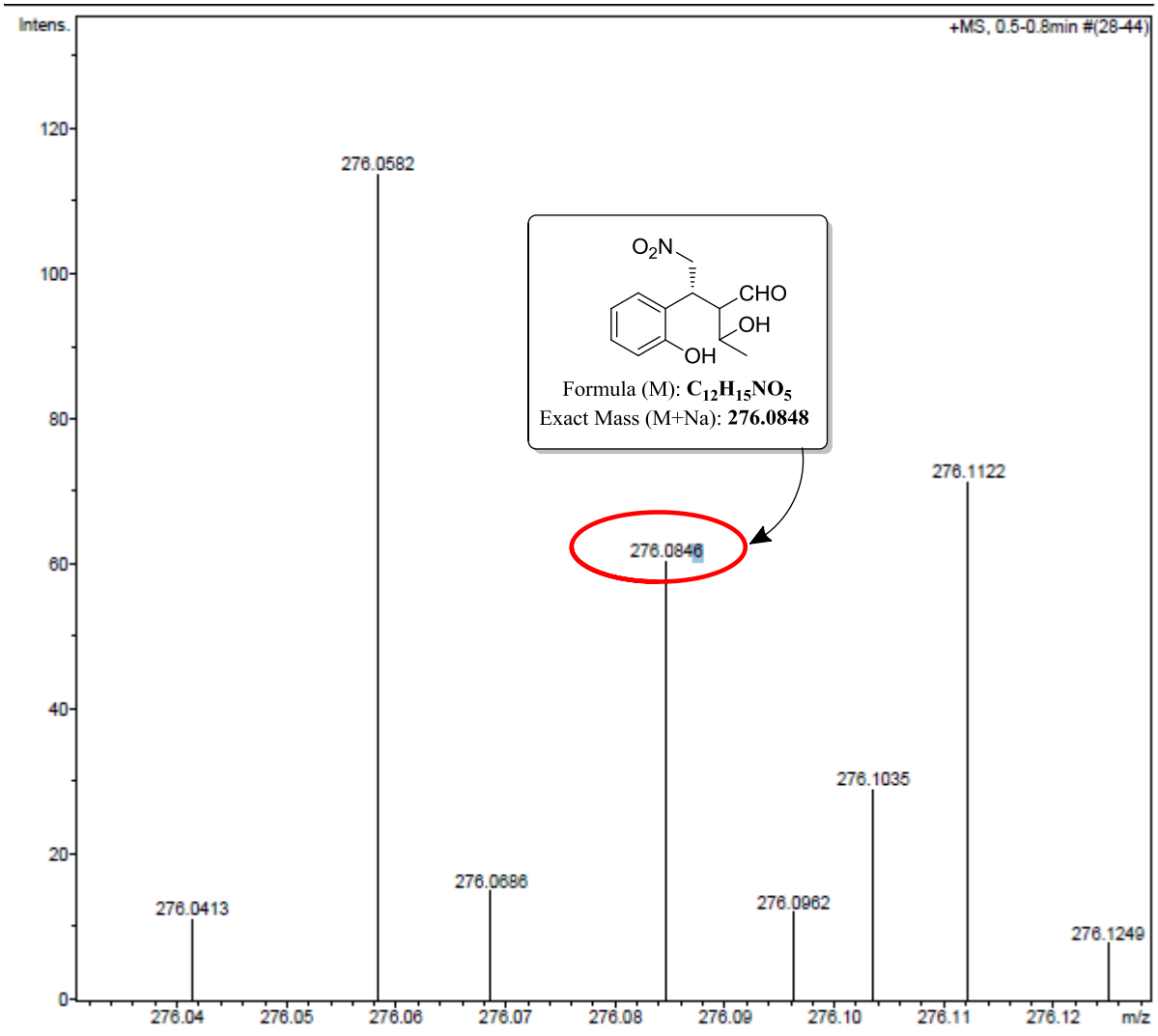

**Intermediate $\mathbf{D_2}$**

Formula: $C_{32}H_{39}N_2O_4Si^+$
Exact Mass: 543.2679

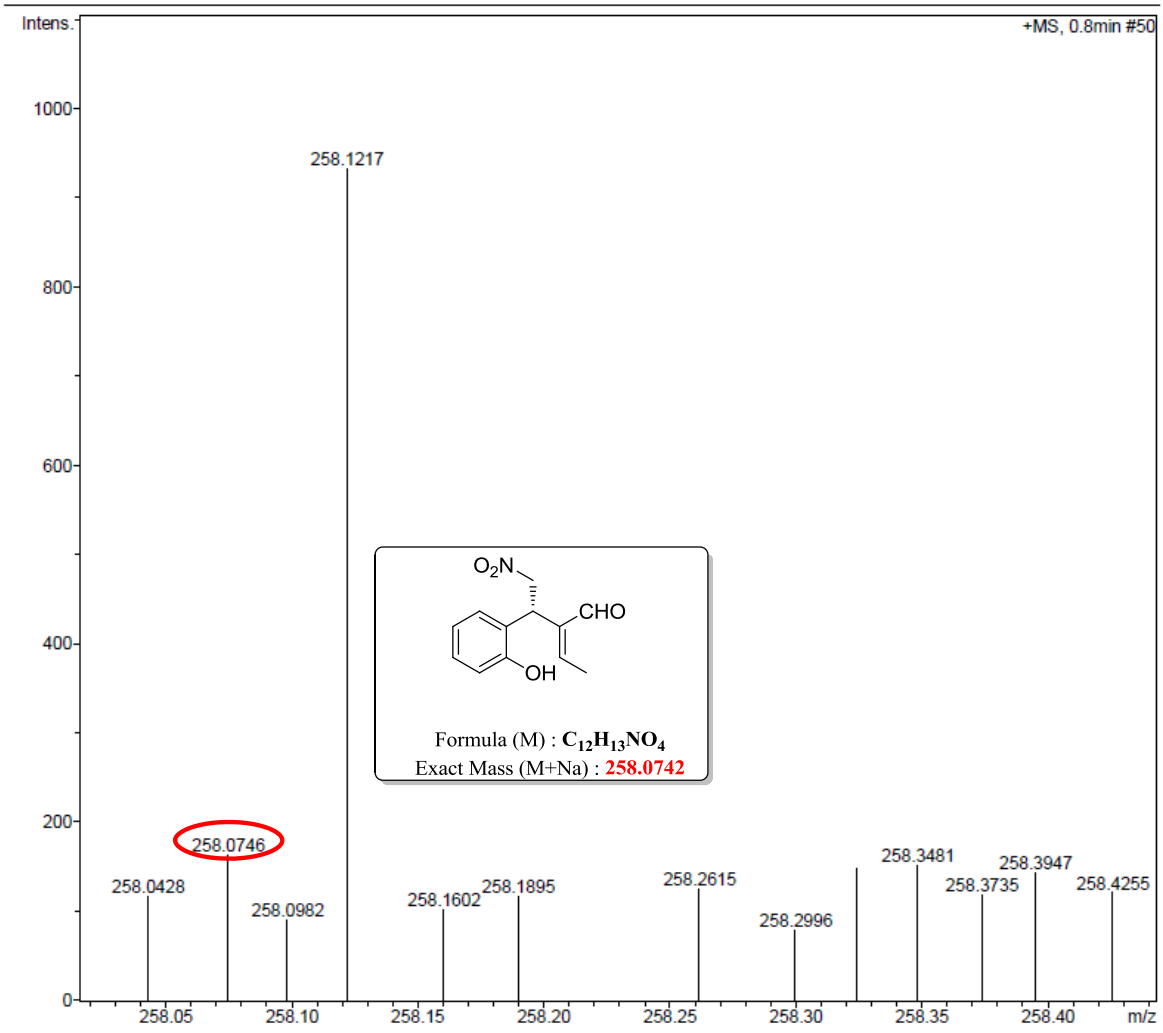
Experimentally Observed **Intermediate-I** on the ESI-HRMS Spectrum of an On-going Reaction of **104** and **108a** in the Presence of **4n**.



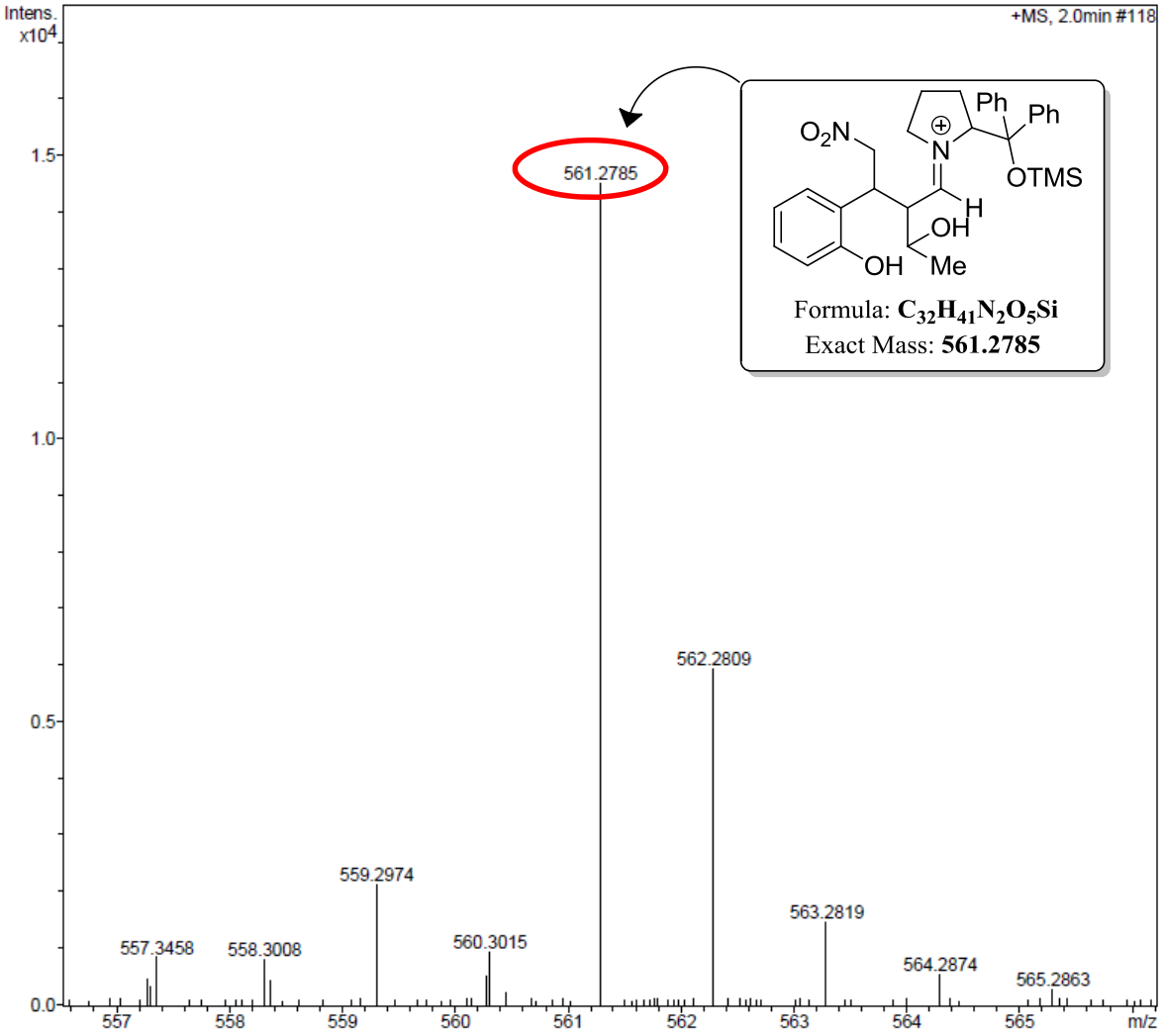
Experimentally Observed **Intermediate-II** on the ESI-HRMS Spectrum of an On-going Reaction of **104** and **108a** in the Presence of **4n**.



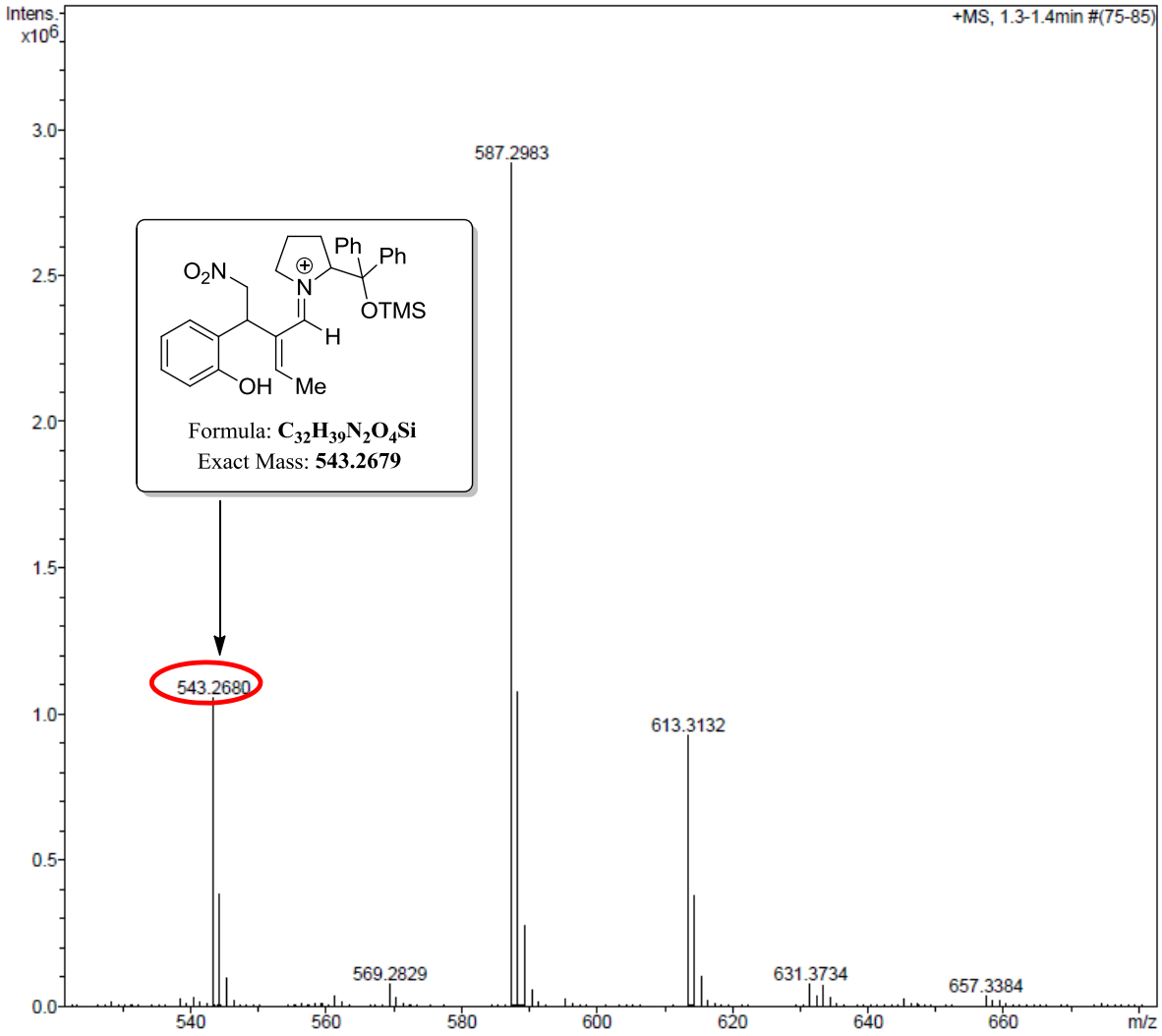
Experimentally Observed **Intermediate-III** on the ESI-HRMS Spectrum of an On-going Reaction of **104** and **108a** in the Presence of **4n**.



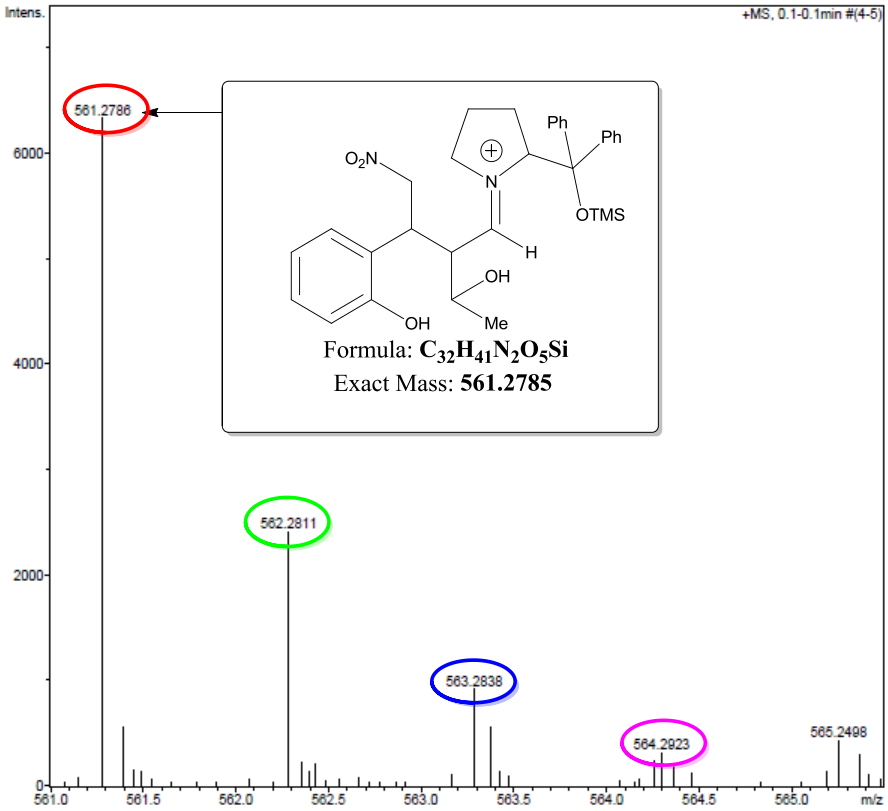
Experimentally Observed **Intermediate-$C_1$** on the ESI-HRMS Spectrum of an On-going Reaction of **104** and **108a** in the Presence of **4n**.



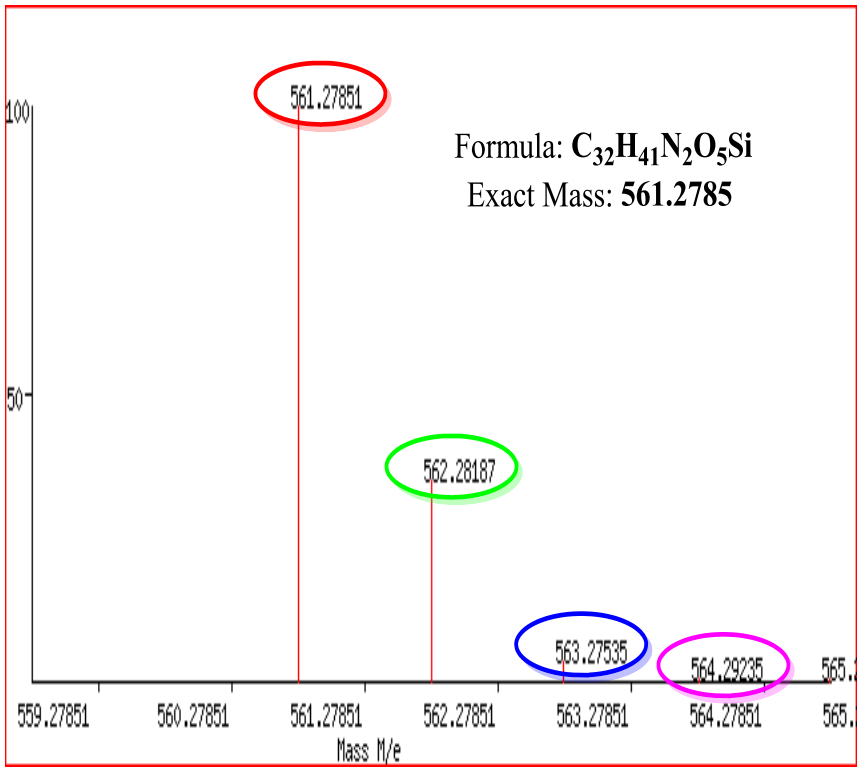
Experimentally Observed **Intermediate-$D_1$** on the ESI-HRMS Spectrum of an On-going Reaction of **104** and **108a** in the Presence of **4n**.



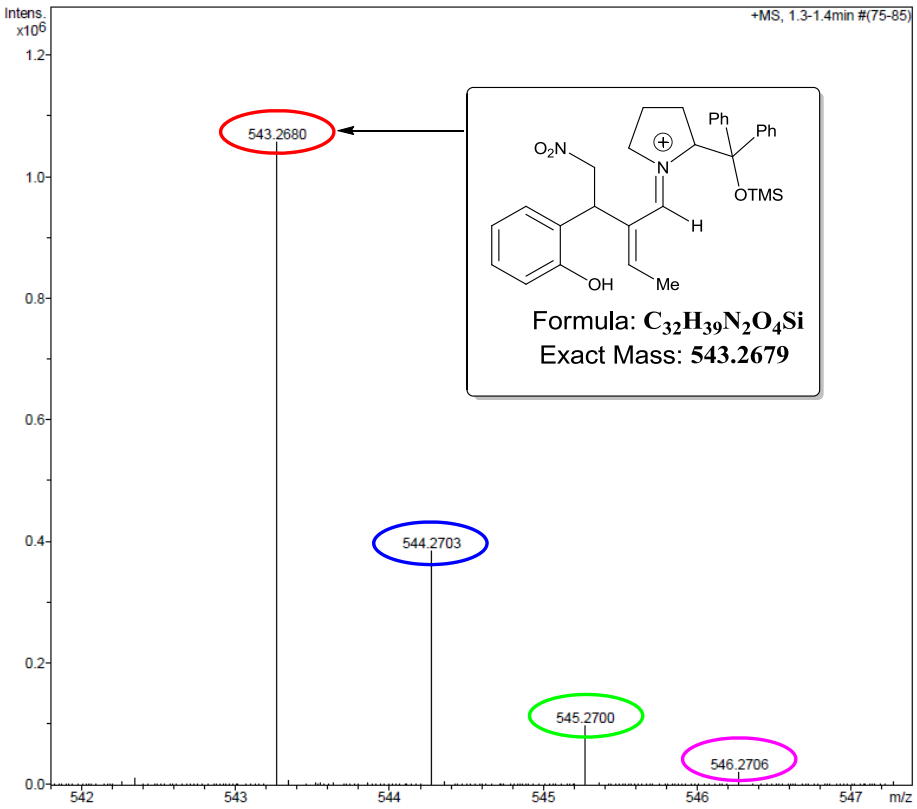
Experimentally Observed Isotopic Pattern of the **Intermediate [$C_1$]**.



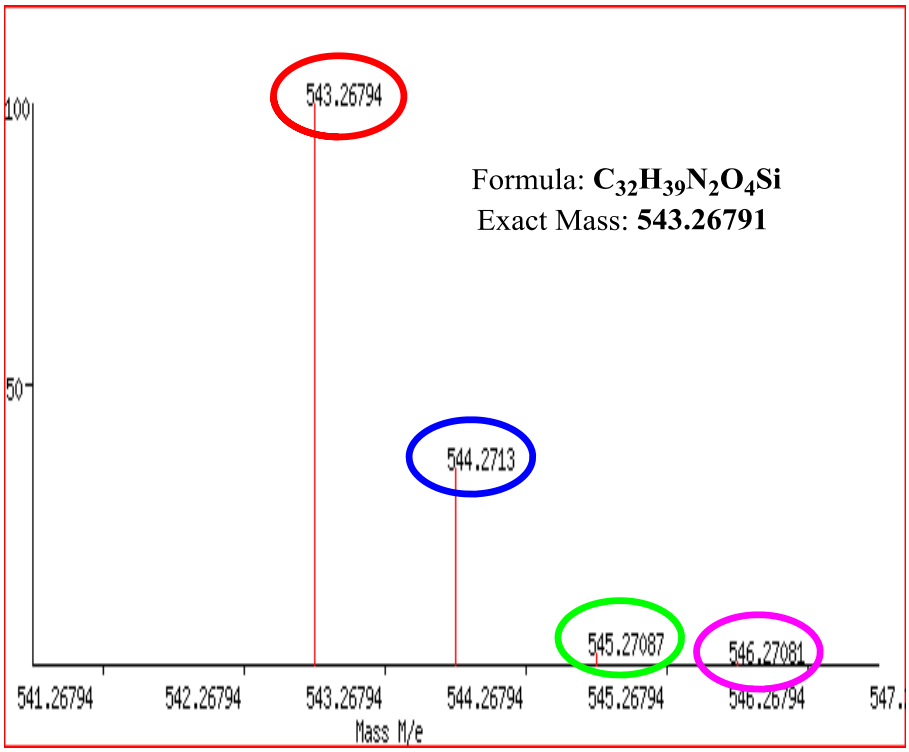

Theoretically Calculated Isotopic Pattern of the **Intermediate [$C_1$].**



Experimentally Observed Isotopic Pattern of the **Intermediate [$D_1$].**

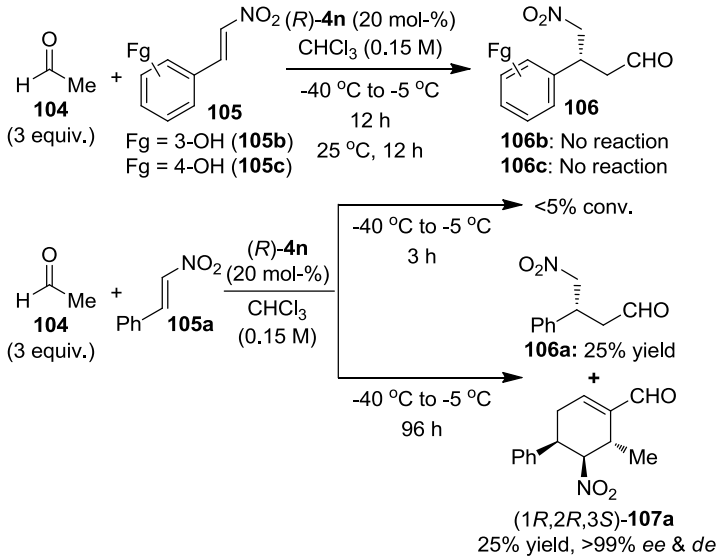



Theoretically Calculated Isotopic Pattern of the **Intermediate [$D_1$].**



However, there is no reaction observed between either (*E*)-3-(2-nitrovinyl)phenol **105b** or (*E*)-4-(2-nitrovinyl)phenol **105c** with acetaldehyde **104** *via* (R)-**4n**-catalysis in $CHCl_3$ at −40 °C to −5 °C for 12 h and 25 °C for 12 h as shown in Scheme 25. In a similar manner, only <5% conversion was observed for the domino reaction between **104** and simple β-nitrostyrene **105a** *via* (R)-**4n**-catalysis in $CHCl_3$ at −40 °C to −5 °C for 3 h. But the same reaction took a long time (96 h) to furnish the Michael product **106a** in 25% yield and quadruple domino product **107a** in 25% yield with >99% *ee* and *de* (Scheme 25).[110] Enders reported the same quadruple domino reaction to furnish the opposite enantiomer of (1*R*,2*R*,3*S*)**-107a** in 45% yield with >99% *ee* and 3.5:1 *dr* from the ten equivalents of **104** with **105a** in THF/$H_2O$ at 60 °C [MW, 60 W] for 5 h under the (*S*)-**4n** catalysis.[106o]

The observed poor reactivity of these reactions could be explained due to the lack of neighboring *ortho*-hydroxyl group participation through hydrogen bonding or creation of the meta-stable electronic structures in the transition states. This phenomenon is sufficient to control the observed high reactivity and selectivity in other substrates like **108a-k**.




***Scheme 25*:** Controlled Experiments to See the Neighboring *ortho*-Hydroxyl Group Participation in Triple Domino-Catalysis.

## *6.3 CONCLUSIONS*

In conclusion, we have designed a novel and efficient triple domino Michael/aldol/*oxa*-Michael followed by a sequential one-pot Wittig, Michael/Wittig-Horner or reduction reactions of acetaldehyde **104** with 2-(2-nitrovinyl)phenols **108** under

the (*R*)-**4n**-catalysis followed by the addition of $Ph_3P{=}CHCO_2Et$, **111** or $NaBH_4$ to furnish the functionalized chromanes **110** or chromenes **112** with high yield, *ee* and *de* values. With the help of ESI-HRMS technique, we have given strong evidence to the reaction pathway through triple domino-catalysis by detecting key catalytic intermediate ions.[110] The catalytic asymmetric triple domino reactions would become a promising tool for the synthesis of functionalized chiral heterocycles and the examination of the potential medicinal applications of these molecules would certainly show the importance of this novel protocol.

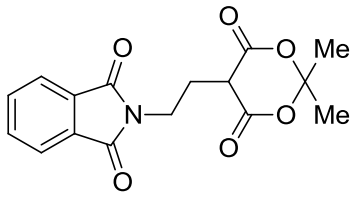
# 7. EXPERIMENTAL SECTION

**General Methods:** The $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta$ = 0) for $^{1}H$ NMR and relative to the central $CDCl_3$, ($\delta$ = 77.0), DMSO-$d_6$, ($\delta$ = 39.5) or MeOH-$d_4$ ($\delta$ = 49.1) resonance for $^{13}C$ NMR. *In the $^{13}C$ NMR spectra, the nature of the carbons (C, CH, $CH_2$ or $CH_3$) was determined by recording the DEPT-135 experiment, and is given in parentheses.* The coupling constants *J* are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063-0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-K$\alpha$ ($\lambda$ = 0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K$\alpha$ fine-focus sealed tube ($\lambda$ = 0.71073 Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. $H_2SO_4$ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

**General Experimental Procedures for the Cascade Reactions:**

**Procedure A: Amino Acid-Catalyzed Reductive Alkylation Reactions with Phthalamidoacetaldehyde:** In an ordinary glass vial equipped with a magnetic stirring bar, 0.5 mmol of the aldehyde **2k**, 0.5 mmol of CH-acid **3** and 0.5 mmol of Hantzsch ester **1a** was added 1.0 mL of solvent and then the catalyst amino acid **4a** (0.05 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1and 2. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure cascade products **69** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

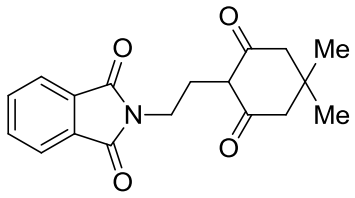
**2-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl)isoindoline-1,3-dione (69a):**



**69a**

Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 112°C. IR (Neat): $\nu_{max}$ 1736, 1700, 1345, 1206 and 1027 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.84-7.82 (2H, m), 7.73-7.71 (2H, m), 4.01-3.98 (2H, m), 3.94 (1H, t, *J* = 5.2 Hz), 2.46-2.45 (2H, m), 1.83 (3H, s), 1.77 (3H, s); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 168.7 (2xC, *C*=O), 165.1 (2xC, *C*=O), 134.0 (2xCH), 131.9 (2xC), 123.3 (2xCH), 105.2 (C), 45.0 (CH), 35.8 ($CH_2$), 28.4 ($CH_3$), 26.1 ($CH_3$), 25.2 ($CH_2$); LRMS m/z 318.15 ($M+H^+$), calcd $C_{16}H_{15}NO_6$ (317.09); Anal. Calcd. for $C_{16}H_{15}NO_6$ (317.0899): C, 60.57; H, 4.77; N, 4.41. Found: C, 60.45; H, 4.82; N, 4.51.

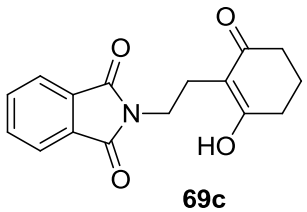
**2-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl)isoindoline-1,3-dione (69b):**



**69b**

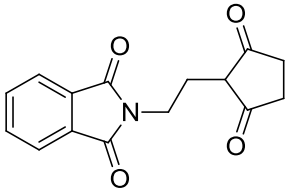
Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 153°C. IR (Neat): $\nu_{max}$ 2947, 1713, 1606, 1561, 1472, 1349 and 1119 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 7.81-7.79 (4H, m), 3.57 (2H, t, *J* = 5.6 Hz), 2.47 (2H, t, *J* = 6.4 Hz), 2.12 (1H, bs, -O*H*), 2.08 (4H, s, 2x$CH_2$C=O), 0.90 (6H, s); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 168.5 (2xC, *C*=O), 134.7 (2xCH), 132.0 (2xC), 123.2 (2xCH), 110.6 (C), 36.9 ($CH_2$), 31.6 (C), 28.3 (2x$CH_3$), 20.9 ($CH_2$); LRMS m/z 314.15 ($M+H^+$), calcd $C_{18}H_{19}NO_4$ (313.13); Anal. Calcd. for $C_{18}H_{19}NO_4$ (313.1314): C, 68.99; H, 6.11; N, 4.47. Found: C, 68.87; H, 6.11; N, 4.47.

**2-(2-(2,6-dioxocyclohexyl)ethyl)isoindoline-1,3-dione** (**69c**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 147°C. IR (Neat): $\nu_{max}$ 2928, 2856, 1711, 1569, 1385, 1120 and 751 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 7.85-7.80 (4H, m), 3.58 (2H, t, *J* = 6.0 Hz), 2.51 (2H, t, *J* = 2.0 Hz), 2.48 (2H, t, *J* = 6.0 Hz), 2.19 (1H, bs, -OH), 1.75 (2H, quin, *J* = 6.4 Hz); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 168.0 (2xC, *C*=O), 134.2 (2xCH), 131.7 (2xC), 122.8 (2xCH), 111.5 (C), 36.5 ($CH_2$), 20.7 ($CH_2$), 20.4 ($CH_2$); LCMS: m/z 286.50 (M + H), calcd for $C_{16}H_{15}NO_4$ 285.10; Anal. calcd for $C_{16}H_{15}NO_4$ (285.10): C, 67.36; H, 5.30; N, 4.91. Found: C, 67.36; H, 5.30; N, 4.99%.



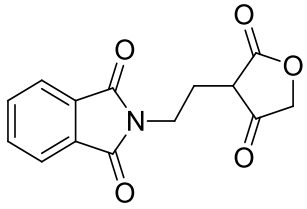
**69c**

**2-(2-(2,5-dioxocyclopentyl)ethyl)isoindoline-1,3-dione** (**69d**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 117°C. IR (Neat): $\nu_{max}$ 3441, 1707, 1554, 1399, 1360, 1251, 1120 and 714 $cm^{-1}$; $^{1}H$ NMR (DMSO-$d_6$) δ 7.50 (4H, bs), 3.26 (3H, t, *J* = 6.4 Hz), 1.99 (2H, t, *J* = 6.8 Hz), 1.94 (4H, bs, 2x$CH_2$C=O); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 168.5 (2xC, *C*=O), 134.8 (2xCH), 132.0 (2xC), 123.3 (2xCH), 113.6 (C), 36.6 ($CH_2$), 20.3 ($CH_2$); LCMS: m/z 272.20 (M + H), calcd for $C_{15}H_{13}NO_4$ 271.08; Anal. calcd for $C_{15}H_{13}NO_4$ (271.0845): C, 66.41; H, 4.83; N, 5.16. Found: C, 66.48; H, 4.76; N, 5.09%.



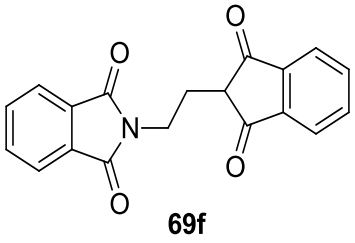
**69d**

**2-(2-(2,4-dioxotetrahydrofuran-3-yl)ethyl)isoindoline-1,3-dione** (**69e**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 132°C. IR (Neat): $\nu_{max}$ 3429, 2928, 1766, 1706, 1659, 1602, 1462, 1390, 1125 and 954 $cm^{-1}$; $^{1}H$ NMR (DMSO-$d_6$) δ 7.61-7.59 (4H, m), 4.26 (2H, s), 3.40 (2H, t, *J* = 6.0 Hz), 2.27 (1H, s), 2.18 (2H, t, *J* = 6.0 Hz); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 174.7 (C, *C*=O), 167.9 (2xC, *C*=O), 134.3 (2xCH), 131.7 (2xC), 123.0 (2xCH), 96.2 (C), 66.6 ($CH_2$), 36.1 ($CH_2$), 20.2 ($CH_2$); LCMS: m/z 272.20 (M - H), calcd for $C_{14}H_{11}NO_5$ 273.06; Anal. calcd for $C_{14}H_{11}NO_5$ 273.0637: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.68; H, 4.12; N, 5.09%.



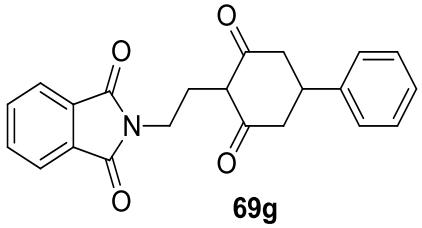
**69e**

**2-(2-(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)ethyl)isoindoline-1,3-dione** (**69f**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 172°C. IR (Neat): $\nu_{max}$ 1776, 1707, 1407, 1382, 1014, 875 and 716 $cm^{-1}$; $^{1}H$ NMR (DMSO-$d_6$) δ 7.90 (2H, s), 7.87 (2H, s), 7.78 (4H, bs), 3.76 (2H, t, *J* = 8.0 Hz), 3.39 (1H, bs, -OH), 2.19-2.15 (2H, m); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 200.3 (2xC, *C*=O), 168.2 (2xC, *C*=O), 142.1 (2xC), 136.3 (2xCH), 134.7 (2xCH), 132.0 (2xC), 123.4 (2xCH), 123.2 (2xCH), 52.1 (CH), 35.8 ($CH_2$), 24.5 ($CH_2$); LCMS: m/z 320.10 (M + H), calcd for $C_{19}H_{13}NO_4$ 319.08; Anal. calcd for $C_{19}H_{13}NO_4$ 319.0845: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.35; H, 4.22; N, 4.31%



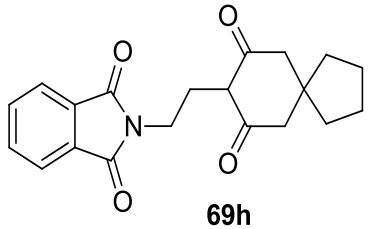
**69f**

**2-(2-(2,6-dioxo-4-phenylcyclohexyl)ethyl)isoindoline-1,3-dione** (**69g**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 147°C. IR (Neat): $\nu_{max}$ 3469, 1774, 1720, 1714, 1466, 1411 and 1015 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 7.85-7.78 (4H, m), 7.32-7.19 (5H, m), 3.61 (2H, t, $J$ = 6.0 Hz), 3.43 (1H, bs, -OH), 3.21-3.13 (1H, m), 2.54-2.47 (4H, m), 2.40-2.37 (2H, m); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 168.5 (2xC, *C*=O), 143.9 (C), 134.6 (2xCH), 132.2 (2xC), 129.0 (2xCH), 127.2 (2xCH), 127.1 (CH), 123.3 (2xCH), 111.7 (C), 38.8 (CH), 36.9 ($CH_2$), 21.3 ($CH_2$); LCMS: m/z 362.20 (M + H), calcd for $C_{22}H_{19}NO_4$ 361.13; Anal. calcd for $C_{22}H_{19}NO_4$ (361.1314): C, 73.12; H, 5.30; N, 3.88. Found: C, 73.05; H, 5.36; N, 3.81%.



**69g**

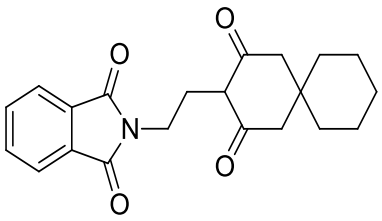
**2-(2-(7,9-dioxospiro[4.5]decan-8-yl)ethyl)isoindoline-1,3-dione** (**69h**):



**69h**

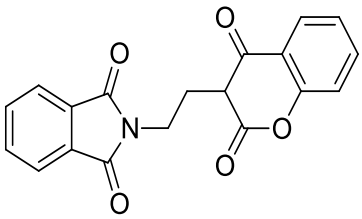
Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 135°C. IR (Neat): $\nu_{max}$ 1708, 1603, 1463, 1429, 1391, 1122, 1040 and 720 $cm^{-1}$; $^1H$ NMR (MeOH-$d_4$) δ 7.68-7.60 (4H, m), 3.60 (2H, t, $J$ = 6.4 Hz), 3.17 (2H, s), 2.49 (2H, t, $J$ = 6.0 Hz), 2.12 (3H, s), 1.49-1.47 (3H, m), 1.31-1.29 (3H, m); $^{13}C$ NMR (MeOH-$d_4$, DEPT-135) δ 168.6 (2xC, *C*=O), 133.7 (2xCH), 132.1 (2xC), 122.5 (2xCH), 111.7 (C), 42.3 (C), 37.8 (2x$CH_2$), 36.3 ($CH_2$), 23.7 (2x$CH_2$), 20.3 ($CH_2$); LCMS: m/z 340.25 (M + H), calcd for $C_{20}H_{21}NO_4$ 339.15; Anal. calcd for $C_{20}H_{21}NO_4$ 339.1471: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.15; H, 6.12; N, 4.22%.

**2-(2-(2,4-dioxospiro[5.5]undecan-3-yl)ethyl)isoindoline-1,3-dione** (**69i**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 127°C. IR (Neat): $\nu_{max}$ 2931, 2858, 1730, 1697, 1603, 1502, 1343, 1293, 1259 and 1147 $cm^{-1}$; $^1H$ NMR (MeOH-$d_4$) δ 7.17-7.12 (4H, m), 3.08 (2H, t, $J$ = 5.6 Hz), 1.98 (2H, t, $J$ = 6.0 Hz), 1.60 (4H, s), 0.78 (6H, bs), 0.75 (4H, bs); $^{13}C$ NMR (MeOH-$d_4$, DEPT-135) δ 170.1 (2xC, *C*=O), 135.3 (2xCH), 133.6 (2xC), 124.0 (2xCH), 112.6 (C), 42.3 (C), 37.8 ($CH_2$), 37.6 (2x$CH_2$), 35.6 ($CH_2$), 27.4 ($CH_2$), 22.8 (2x$CH_2$), 21.7 ($CH_2$); LCMS: m/z 354.25 (M + H), calcd for $C_{21}H_{23}NO_4$ 353.17; Anal. calcd for $C_{21}H_{23}NO_4$ (353.1627): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.45; H, 6.51; N, 3.92%.



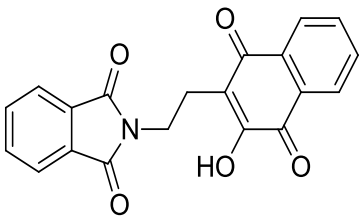
**69i**

**2-(2-(2,4-dioxochroman-3-yl)ethyl)isoindoline-1,3-dione** (**69j**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 115°C. IR (Neat): $\nu_{max}$ 3421, 1695, 1609, 1566, 1401, 123774, 1186 and 722 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 7.86 (1H, d, *J* = 7.6 Hz), 7.78 (4H, bs), 7.57 (1H, t, *J* = 7.6 Hz), 7.32-7.28 (2H, m), 3.79 (2H, t, *J* = 5.6 Hz), 3.36 (1H, bs), 2.86 (2H, t, *J* = 5.6 Hz); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 168.4 (2xC, *C*=O), 163.5 (C, *C*=O), 161.5 (C), 152.4 (C), 134.7 (2xCH), 132.3 (2xC), 132.0 (CH), 124.3 (CH), 123.5 (CH), 123.4 (2xCH), 116.7 (CH), 116.4 (C), 103.0 (C), 36.7 ($CH_2$), 23.5 ($CH_2$); LCMS: m/z 336.25 (M + H), calcd for $C_{19}H_{13}NO_5$ 335.08; Anal. calcd for $C_{19}H_{13}NO_5$ (335.0794): C, 68.06; H, 3.91; N, 4.18. Found: C, 68.22; H, 3.96; N, 4.11%.



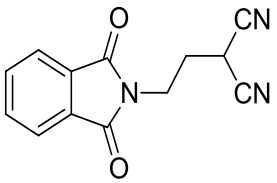
**69j**

**2-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)isoindoline-1,3-dione** (**69k**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 168°C. IR (Neat): $\nu_{max}$ 3289, 1697, 1669, 1642, 1405, 1269, 1107 and 718 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 7.93 (1H, d, *J* = 7.2 Hz), 7.89 (1H, d, *J* = 7.2 Hz), 7.81-7.41 (6H, m), 3.77 (2H, t, *J* = 6.0 Hz), 3.37 (1H, bs), 2.80 (2H, t, *J* = 6.4 Hz); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 184.7 (C, *C*=O), 181.1 (C, *C*=O), 168.3 (2xC, *C*=O), 156.8 (C), 135.0 (CH), 134.8 (2xCH), 133.7 (CH), 132.3 (C), 132.0 (2xC), 130.4 (C), 126.2 (2xCH), 123.4 (2xCH), 121.2 (C), 36.5 ($CH_2$), 22.7 ($CH_2$); LCMS: m/z 346.15 (M - H), calcd for $C_{20}H_{13}NO_5$ 347.08; Anal. calcd for $C_{20}H_{13}NO_5$ 347.0794: C, 69.16; H, 3.77; N, 4.03. Found: C, 69.32; H, 3.74; N, 4.12%.



**69k**

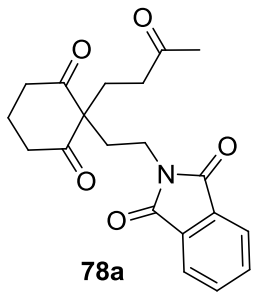
**2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)malononitrile** (**69l**): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 105°C. IR (Neat): $\nu_{max}$ 3555, 2937, 2209, 1774, 1719, 1650, 1379, 1106 and 718 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 7.89-7.82 (4H, m), 4.81 (1H, t, *J* = 6.8 Hz), 3.77 (2H, t, *J* = 12.4 Hz), 2.36 (2H, t, *J* = 6.0 Hz); $^{13}C$ NMR (DMSO-$d_6$, DEPT-135) δ 168.4 (2xC, *C*=O), 134.9 (2xCH), 132.2 (2xC), 123.6 (2xCH), 114.4 (2xC, -CN), 34.8 ($CH_2$), 29.0 ($CH_2$), 20.9 (CH); LCMS: m/z 240.05 (M + H), calcd for $C_{13}H_9N_3O_2$ 239.0695; Anal. calcd for $C_{13}H_9N_3O_2$ 239.0695: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.12; H, 3.82; N, 17.45%.



**69l**

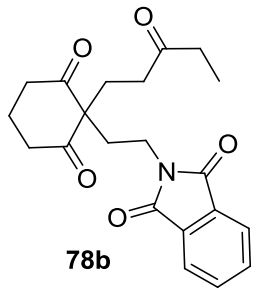
**Procedure B: Preparation for Racemic Michael Products 78a & 78b with Triethylamine-Catalysis:** In an ordinary glass vial equipped with a magnetic stirring bar, 0.3 mmol of **69c** and 0.9 mmol of alkyl vinyl ketone **70** with a catalytic amount of triethylamine (5 mol%) in 1.0 mL of $CH_3CN$ solvent mixture was stirred at 25 °C for 2-48 h. 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 products **78a & 78b** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**2-(2-(2,6-dioxo-1-(3-oxobutyl)cyclohexyl)ethyl)isoindoline-1,3-dione (78a):** Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a gummy solid. The enantiomeric excess (*ee*) was determined by chiral stationary phase IR (Neat): $\nu_{max}$ 2953, 1775, 1715, 1666, 1397, 1151 and 877 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.83-7.81 (2H, m), 7.72-7.70 (2H, m), 3.62 (2H, t, *J* = 6.4 Hz), 2.76-2.59 (5H, m), 2.40 (2H, t, *J* = 6.8 Hz), 2.17 (2H, t, *J* = 6.4 Hz), 2.10 (4H, s), 2.03 (2H, t, *J* = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 209.4 (2xC, O–*C*=O), 206.9 (C, O–*C*=O), 168.4 (2xC, O–*C*=O), 133.9 (2xCH), 132.1 (2xC), 123.2 (2xCH), 66.9 (C), 37.8 (2x$CH_2$), 37.5 ($CH_2$), 34.05 ($CH_2$), 30.05 ($CH_2$), 29.9 ($CH_3$), 29.8 ($CH_2$), 17.2 ($CH_2$); LCMS: m/z 356.10 (M + H), calcd for $C_{20}H_{21}NO_5$ 355.14; Anal. calcd for $C_{20}H_{21}NO_5$ (355.1420): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.48; H, 5.91; N, 3.86%.



**78a**

**2-(2-(2,6-dioxo-1-(3-oxopentyl)cyclohexyl)ethyl)isoindoline-1,3-dione (78b):** Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a gummy solid. Mp 90°C. IR (Neat): $\nu_{max}$ 2926, 1759, 1715, 1457, 1370, 1233, 1233 and 1041$cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.83-7.80 (2H, m), 7.71-7.69 (2H, m), 3.62 (2H, t, *J* = 6.4 Hz), 2.76-2.58 (4H, m), 2.40-2.35 (4H, m), 2.16 (2H, t, *J* = 6.4 Hz), 2.12-2.07 (1H, m), 2.03 (2H, t, *J* = 6.8 Hz), 1.74-1.73 (1H, m), 1.01 (3H, t, *J* = 7.2 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 209.8 (C, O–*C*=O), 209.4 (2xC, O–*C*=O), 168.4 (2xC, O–*C*=O), 133.9 (2xCH), 132.1 (2xC), 123.2 (2xCH), 66.9 (C), 37.8 (2x$CH_2$), 36.1 ($CH_2$), 36.0 ($CH_2$), 34.07 ($CH_2$), 30.09 ($CH_2$), 29.7 ($CH_2$), 17.2 ($CH_2$), 7.7 ($CH_3$); LCMS: m/z 368.20 (M - H), calcd for $C_{21}H_{23}NO_5$ 369.1576; Anal. calcd for $C_{21}H_{23}NO_5$ (369.1576): C, 68.28; H, 6.28; N, 3.79. Found: C, 68.16; H, 6.35; N, 3.71%.



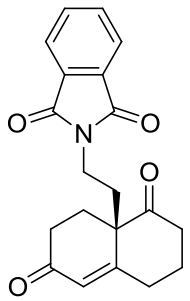
**78b**

**Procedure C: Amino Acid-Catalyzed Asymmetric Aldol Reactions:**

**i) Synthesis of (+)-71ba and (-)-71ba:** In an ordinary glass vial equipped with a magnetic stirring bar, 0.3 mmol of Michael adduct **78** was added to 1.0 mL of DMSO solvent with the catalyst proline **4** (0.09 mmol) and the reaction mixture was stirred at 25 °C for 2 days. 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 to afford (+)-**71ba** and (-)-**71ba.**

**ii) Synthesis of (+)-71bb:-** In an ordinary glass vial equipped with a magnetic stirring bar, 0.3 mmol of Michael adduct **78b** was added to 1.0 mL of DMSO solvent and then the catalyst L-proline **4a** (0.09 mmol) was added and the reaction mixture was stirred at 25 °C for 2 days. 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 ($Na_2SO_4$) and concentrated. To the crude mixture *p*-TSA (20 mol %) was added and heated to 60°C for 12 h and directly loaded on to the silicagel to get (+)-**71bb**.

**(*R*)-2-(2-(4,7-dioxo-1,2,3,4,4a,5,6,7-octahydronaphthalen-4a-yl)ethyl)isoindoline-1,3-dione**

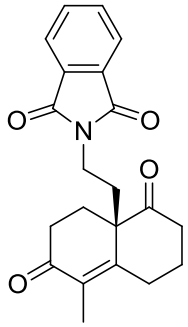


**(+)-71ba**

**(+)-71ba**: Prepared by following the procedure **C(i)** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 91°C. 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), $t_R$ = 7.293 min (minor), $t_R$ = 8.864 min (major). **$[\alpha]_D^{25}$ = +45.87° (*c* = 0.2 g/100 mL, $CHCl_3$, 74% *ee*)**; IR (Neat): $\nu_{max}$ 2937, 1770, 1704, 1660, 1611, 1403, 1375, 1156 and 718 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.85-7.83 (2H, m), 7.74-7.72 (2H, m), 5.89 (1H, s), 3.74-3.67 (1H, m), 3.49-3.40 (1H, m), 2.93-2.76 (2H, m), 2.58-2.50 (4H, m), 2.40-2.27 (2H, m), 2.20-2.03 (3H, m), 1.73-1.69 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 209.6 (C, O–*C*=O), 197.8 (C, *C*=O), 167.9 (2xC, O–*C*=O), 164.4 (C), 134.1 (2xCH), 131.9 (2xC), 126.7 (CH), 123.3 (2xCH), 53.6 (C), 38.1 ($CH_2$), 33.5 ($CH_2$), 33.4 ($CH_2$), 32.6 ($CH_2$), 31.6 ($CH_2$), 25.3 ($CH_2$), 23.5 ($CH_2$); LCMS: m/z 338.45 (M + H), calcd for $C_{20}H_{19}NO_4$ 337.13; Anal. calcd for $C_{20}H_{19}NO_4$ (337.1314): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.32; H, 5.61; N, 4.23%.

**(*R*)-2-(2-(8-methyl-4,7-dioxo-1,2,3,4,4a,5,6,7-octahydronaphthalen-4a-yl)ethyl)isoindoline-1,3-dione (+)-71bb:** Prepared by following the procedure **C(ii)** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 101°C. 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 = 220 nm), $t_R$ = 14.496 min (minor), $t_R$ =

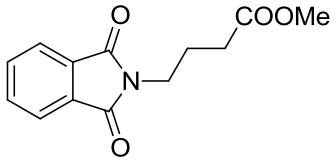
18.716 min (major). **$[\alpha]_D^{25}$ = +40.06° (*c* = 0.4 g/100 mL, $CHCl_3$, 63% *ee*)** ;IR (Neat): $\nu_{max}$ 2942, 1775, 1715, 1660, 1397, 1370, 1052 and 718 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.86-7.85 (2H, m), 7.75-7.73 (2H, m), 3.71 (1H, td, *J* = 10.8, 4.0 Hz), 3.52-3.46 (1H, m), 2.91-2.86 (2H, m), 2.64-2.55 (4H, m), 2.39-2.06 (5H, m), 1.82 (3H, s), 1.79-1.74 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 210.5 (C, *C*=O), 197.4 (C, *C*=O), 168.0 (2xC, *C*=O), 156.9 (C), 134.2 (2xCH), 134.0 (C), 131.9 (2xC), 123.4 (2xCH), 53.8 (C), 37.8 ($CH_2$), 33.7 ($CH_2$), 33.32 ($CH_2$), 33.26 ($CH_2$), 27.1 ($CH_2$), 25.2 ($CH_2$), 22.5 ($CH_2$), 11.6 ($CH_3$); LCMS: m/z 352.10 (M + H), calcd for $C_{21}H_{21}NO_4$ 351.15; Anal. calcd for $C_{21}H_{21}NO_4$ 351.1471: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.65; H, 6.12; N, 4.07%.



**(+)-71bb**

**Procedure D:** In a seal tube **69a** (0.5 mmol) and 2 mL of Methanol was added heated to 100-120 °C for 24 h time and the crude reaction mixture was purified by column to get **80** in 88% yield.

**Methyl 4-(1,3-dioxoisoindolin-2-yl)butanoate (72):**

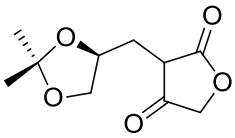


**72**

Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 93°C. IR (Neat): $\nu_{max}$ 2975, 1758, 1710, 1436, 1375, 1227, 1047 and 822 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.83-7.82 (2H, m), 7.71-7.70 (2H, m), 3.74 (2H, t, *J* = 5.2 Hz), 3.63 (3H, s), 2.37 (2H, t, *J* = 6.4 Hz), 2.01 (2H, t, *J* = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 173.0 (C, *C*=O), 168.3 (2xC, *C*=O), 133.9 (2xCH), 132.0 (2xC), 123.2 (2xCH), 51.6 ($CH_3$), 37.1 ($CH_2$), 31.2 ($CH_2$), 23.8 ($CH_2$); LCMS: m/z 248.35 (M + H), calcd for $C_{13}H_{13}NO_5$ 247.08; Anal. calcd for $C_{13}H_{13}NO_5$ (247.0845): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.21; H, 5.36; N, 5.58%.

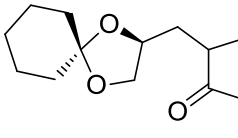
**Procedure E: General Procedure for the Amino Acid-Catalyzed Reductive Coupling Reactions with Cyclic β-keto-Lactones:** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde **2**, 0.5 mmol of CH acid **3**, 0.5 mmol of Hantzsch ester **1a**, 1.0 mL of $CH_3CN$ solvent and then the catalyst amino acid **4a** (0.05 mmol) was added. The reaction mixture was stirred at 25 °C for the time indicated in Tables 3. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup and pure cascade products **87a-h** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**3-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-furan-2,4-dione (87a):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as colorless oil; **$[\alpha]_D^{25}$ = −34.4° (*c* = 2.00 g/100 mL, MeOH);** IR (neat): $\nu_{max}$ 1733, 1655 (C=O and O-C=O), 1410, 1375, 1044, 614 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.61 (2H, s), 4.34-4.33 (1H, m), 4.16 (1H, dd, *J* = 8.4, 6.0 Hz), 3.71 (1H, t, *J* = 7.2 Hz), 2.67 (1H, d, *J* = 16.0 Hz), 2.38 (1H, dd, *J* = 16.0, 9.6 Hz), 1.53 (3H, s), 1.45 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 175.0 (C, O-C=C), 173.8 (C, C=O), 110.5 (C), 97.5 (C, -C=C), 75.9 (CH, O-CH), 68.9 ($CH_2$, O-$CH_2$), 66.8 ($CH_2$, O-$CH_2$), 26.7 ($CH_3$, $CH_2$), 25.6 ($CH_3$); LRMS m/z 213.10 ($M-H^+$), calcd $C_{10}H_{14}O_5$ 214.08; Anal. Calcd. for $C_{10}H_{14}O_5$ (214.08): C, 56.07; H, 6.59. Found: C, 56.12; H, 6.52%.



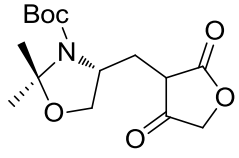
**87a**

**3-(1,4-Dioxa-spiro[4.5]dec-2-ylmethyl)-furan-2,4-dione (87b):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as colorless oil; **$[\alpha]_D^{25}$ = −35.1 (*c* = 0.2 g/100 mL, MeOH)**; IR (neat): $\nu_{max}$ 1734, 1656 (C=O and O-C=O), 1417, 1318, 1044, 650, 618 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.61 (2H, s), 4.36-4.30 (1H, m), 4.18 (1H, dd, *J* = 8.4, 6.0 Hz), 3.70 (1H, t, *J* = 7.2 Hz), 2.67 (1H, dd, *J* = 16.0, 1.6 Hz), 2.35 (1H, dd, *J* = 16.0, 9.6 Hz), 1.74-1.45 (10H, m); $^{13}$C NMR ($CDCl_3$) δ 175.0 (C, O-C=C), 173.7 (C, C=O), 111.3 (C), 97.5 (C, -C=C), 75.6 (CH, O-CH), 68.6 ($CH_2$, O-$CH_2$), 66.8 ($CH_2$, O-$CH_2$), 36.1 ($CH_2$), 34.8 ($CH_2$), 26.8 ($CH_2$), 24.7 ($CH_2$), 23.9 ($CH_2$), 23.7 ($CH_2$); LRMS m/z 255.15 ($M-H^+$), calcd $C_{13}H_{18}O_5$ 254.12; Anal. calcd for $C_{13}H_{18}O_5$ (255.15): C, 61.40; H, 7.14. Found: C, 61.55; H, 7.09%.



**87b**

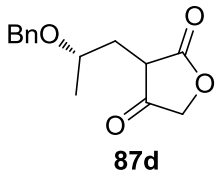
**4-(2,4-Dioxo-tetrahydro-furan-3-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (87c):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as a white Solid. Mp 118 °C; **$[\alpha]_D^{25}$ = +22.8° (*c* = 5.0 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2980, 1688 (C=O), 1399, 1369, 1254, 1171, 1106, 1047, 649, 621, 604 $cm^{-1}$; $^1$H NMR ($CDCl_3$ + one drop of MeOH-$d_4$) at RT δ 4.55 (2H, s), 3.93-3.87 (3H, m), 2.57-2.44 (2H, m), 1.59 (3H, s), 1.52 (9H, s), 1.47 (3H, s); $^{13}$C NMR ($CDCl_3$ + one drop of MeOH-$d_4$) at RT δ 176.3 (C=O), 175.1 (O-C=C), 96.8 (C), 93.9 (C), 81.7 (C), 67.1 ($CH_2$, O-$CH_2$), 66.9 ($CH_2$, O-$CH_2$), 57.0 (CH, N-CH), 28.3 (3x$CH_3$), 27.1 ($CH_3$), 25.0 ($CH_2$), 24.1 ($CH_3$); $^1$H NMR ($CDCl_3$ + one drop of MeOH-$d_4$) at 50 °C RT δ 4.54 (2H, s), 3.92-3.86 (3H, m), 2.54 (2H, d, *J* = 8.0 Hz), 1.58 (3H, s), 1.52 (9H, s), 1.47 (3H, s); $^{13}$C NMR ($CDCl_3$ + one drop of



**87c**

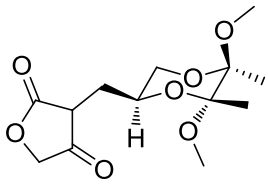
MeOH-$d_4$) at 50 °C δ 175.9 (C=O), 175.0 (O-C=C), 153.3 (C, N-C=O), 97.3 (C), 93.9 (C), 81.7 (C), 67.3 ($CH_2$, O-$CH_2$), 67.0 ($CH_2$, O-$CH_2$), 57.2 (CH, N-CH), 28.3 (3x$CH_3$), 27.0 ($CH_3$), 25.0 ($CH_2$), 24.2 ($CH_3$); LRMS m/z 312.15 ($M-H^+$), calcd $C_{15}H_{23}NO_6$ 313.15; Anal. calcd for $C_{15}H_{23}NO_6$ (313.15): C, 57.50; H, 7.40; N, 4.47. Found: C, 57.65; H, 7.35, N=4.41%.

3-**(2-Benzyloxy-propyl)-furan-2,4-dione (87d):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as a yellow gummy oil; **$[\alpha]_D^{25}$ = +21.3° (*c* = 5.0 g/100 mL, $CHCl_3$)**; IR (neat): $\nu_{max}$ 1732 (O-C=O), 1653 (C=O), 1376, 1269, 1045, 754, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.39-7.35 (5H, m), 4.72 (1H, d, *J* = 11.2 Hz), 4.57 (1H, s), 4.54 (2H, s), 4.05-4.01 (1H, m), 2.62 (1H, d, *J* = 16.0 Hz), 2.44 (1H, dd, *J* = 16.0, 4.8 Hz), 1.27 (3H, d, *J* = 6.0 Hz); $^{13}C$ NMR ($CDCl_3$) δ 175.6 (C, O-C=O), 173.4 (C, -O-C=C), 135.9 (C), 128.7 (2xCH), 128.6 (1xCH), 128.2 (2xCH), 96.8 (C, -C=C), 75.3 (CH, O-CH), 71.0 ($CH_2$, O-$CH_2$), 66.6 ($CH_2$), 29.1 ($CH_2$), 18.0 ($CH_3$); LRMS m/z 247.05 ($M-H^+$), calcd $C_{14}H_{16}O_4$ 248.10; Anal. calcd for $C_{14}H_{16}O_4$ (248.10): C, 67.73; H, 6.50. Found: C, 67.66; H, 6.57 %.



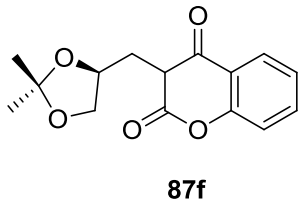
**87d**

**3-(5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxan-2-ylmethyl)-furan-2,4-dione (87e):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as a white Solid. Mp 78 °C; **$[\alpha]_D^{25}$ = –43.3° (*c* = 0.8 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 1735 (O-C=O), 1659 (C=O), 1444, 1123, 1040, 880, 654, 604 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.60 (2H, s), 4.26-4.22 (1H, m), 3.62 (1H, t, *J* = 11.6 Hz), 3.46 (1H, dd, *J* = 12.0, 3.2 Hz), 3.31 (3H, s), 3.27 (3H, s), 2.50-2.38 (2H, m), 1.40 (3H, s), 1.30 (3H, s); $^{13}C$ NMR ($CDCl_3$) δ 175.2 (C, O-C=O), 173.4 (C, O-C=C), 100.5 (C), 97.8 (C, -C=C), 96.5 (C), 67.8 (CH, O-CH), 66.6 ($CH_2$, O-$CH_2$), 61.7 ($CH_2$, O-$CH_2$ ), 48.6 ($CH_3$, O-$CH_3$ ), 48.1 ($CH_3$, O-$CH_3$ ), 24.2 ($CH_2$), 17.6 ($CH_3$), 17.3 ($CH_3$); LRMS m/z 287.05 ($M-H^+$), calcd $C_{13}H_{20}O_7$ 288.12; Anal. calcd for $C_{13}H_{20}O_7$ (288.12): C, 54.16; H, 6.99. Found: C, 56.26; H, 6.91%.



**87e**

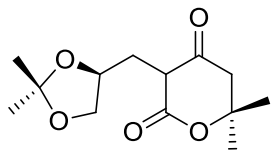
**3-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-chroman-2,4-dione (87f):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as a white powder. Mp 80 °C; **$[\alpha]_D^{25}$ = –3.2° (*c* = 2.0 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 1686 (C=O), 1629 (C=O), 1498, 1383, 1213, 1046, 863, 652, 617 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 9.91 (1H, s, -OH), 7.89 (1H, d, *J* = 7.2 Hz), 7.54 (1H, t, *J* = 7.2 Hz), 7.33-7.30 (2H, m), 4.47 (1H, d, *J* = 6.0 Hz), 4.18 (1H, t, *J* = 7.6 Hz), 3.71 (1H, t, *J* = 7.6 Hz), 3.21 (1H, d, *J* = 15.6 Hz), 2.87 (1H, dd, *J* = 15.6, 7.2 Hz), 1.52 (3H, s), 1.42 (3H, s); $^{13}C$ NMR ($CDCl_3$)



**87f**

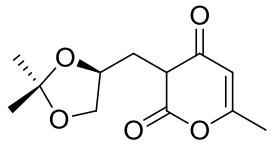
δ 164.3 (C, O-C=O), 163.2 (C, O-C=C), 152.6 (C), 132.0 (CH), 123.9 (CH), 123.4 (CH), 116.3 (CH), 110.2 (C), 100.9 (C, -C=C), 76.8 (CH, O-CH), 68.1 ($CH_2$, O-$CH_2$), 27.9 ($CH_2$), 26.1 ($CH_3$), 25.2 ($CH_3$); LRMS m/z 276.15 (M-$H^+$), calcd $C_{15}H_{16}O_5$ 276.10; Anal. calcd for $C_{15}H_{16}O_5$ (276.15): C, 65.21; H, 5.84. Found: C, 65.55; H, 5.91%.

**3-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-6,6-dimethyl-dihydro-pyran-2,4-dione (87g):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow gummy Solid; **$[\alpha]_D^{25}$ = –2.6° (*c* = 1.1 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2926, 1712 (C=O), 1651 (C=C), 1458, 1386, 1263, 1065, 739 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.35 (1H, q, *J* = 5.2 Hz), 4.11 (1H, q, *J* = 6.4 Hz), 3.63 (1H, t, *J* = 8.0 Hz), 2.90 (1H, d, *J* = 15.6 Hz), 2.63-2.57 (1H, m), 2.55 (2H, d, *J* = 3.2 Hz), 1.47 (3H, s), 1.46 (6H, s), 1.39 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 168.2 (C, O-C=O), 167.2 (C, -C=C), 109.8 (C), 99.1 (C, C=C-O), 77.1 (CH, O-CH), 68.0 ($CH_2$, O-$CH_2$), 39.3 ($CH_2$), 27.6 ($CH_3$), 27.5 ($CH_3$), 27.2 ($CH_2$), 26.2 ($CH_3$), 25.2 ($CH_3$); LRMS m/z 255.10 (M-$H^+$), calcd $C_{13}H_{20}O_5$ 256.13; Anal. calcd for $C_{13}H_{20}O_5$ (256.13): C, 60.92; H, 7.87. Found: C, 60.88; H, 7.82%.



**87g**

**3-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-6-methyl-pyran-2,4-dione (87h):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as a white Solid. Mp 85 °C; **$[\alpha]_D^{25}$ = +14.7° (*c* = 0.15 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2987, 1680 (O-C=O), 1585 (C=C), 1409, 1266, 1063, 648 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 9.40 (1H, s, O-*H*), 5.88 (1H, s, olefinic-*H*), 4.39 (1H, dd, *J* = 12.4, 6.0 Hz), 4.13 (1H, t, *J* = 8.4 Hz), 3.64 (1H, t, *J* = 8.0 Hz), 3.03 (1H, d, *J* = 15.6 Hz), 2.72 (1H, dd, *J* = 15.6, 6.8 Hz), 2.22 (3H, s), 1.47 (3H, s), 1.39 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 167.8 (C), 166.3 (C, O-C=O), 161.1 (C), 110.0 (C), 101.2 (CH, -C=CH), 98.2 (C), 77.2 (CH, O-CH), 68.1 ($CH_2$, O-$CH_2$), 27.3 ($CH_2$), 26.1 ($CH_3$), 25.2 ($CH_3$), 19.7 ($CH_3$); LRMS m/z 240.95 (M-$H^+$), calcd $C_{13}H_{18}O_5$ 240.10; Anal. calcd for $C_{12}H_{16}O_5$ (240.10): C, 59.99; H, 6.7. Found: C, 59.88; H, 7.79%.



**87h**

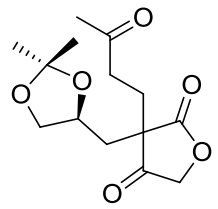
**Procedure F: Preparation of Michael Products 85**

**(i) with L-Proline-Catalysis**: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **87** and 1.5 mmol of alkyl vinyl ketone **70** with a catalytic amount of L-proline in 1.0 mL of DMSO solvent and the reaction mixture was stirred at 25 °C for 2-9 h. 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 products **85** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

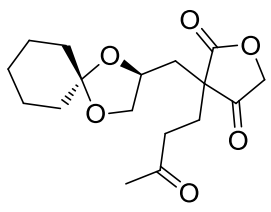
**(ii) with Triethylamine-Catalysis:** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of **87** or 5,5-dimethyl-2-phenylcyclohexane-1,3-dione **90** and 0.36 mmol of alkyl vinyl ketone **70** with a catalytic amount of triethylamine (10 mol%) in 1.0 mL of THF solvent and the reaction mixture was stirred at 25 °C for 30 min-4 h. 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 products **85** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**3-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-3-(3-oxo-butyl)-furan-2,4-dione (85aa):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane and isolated as colorless viscous liquid; **$[\alpha]_D^{25} = -86.0°$ (*c* = 0.2g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2927, 1771 (C=O), 1720 (O-C=O), 1378, 1216, 1063, 678 $cm^{-1}$; $^1$H NMR ($CDCl_3$) (1:1 diastereomeric mixture) δ 4.74 (1H, d, *J* = 16.4 Hz), 4.61 (2H, s), 4.56 (1H, d, *J* = 16.0 Hz), 4.18-4.03 (4H, m), 3.56-3.52 (2H, m), 2.57-2.46 (4H, m), 2.17-2.14 (1H, m), 2.13 (6H, s), 2.12-2.10 (1H, m), 2.04-1.95 (6H, m), 1.36 (3H, s), 1.29 (3H, s), 1.25 (6H, s); $^{13}$C NMR ($CDCl_3$) (1:1 diastereomeric mixture) δ 210.1 (C=O), 209.0 (C=O), 206.3 (C=O), 206.1 (C=O), 176.7 (C, O-C=O), 176.3 (C, O-C=O), 110.2 (C), 110.0 (C), 73.2 ($CH_2$, O-$CH_2$), 72.7 ($CH_2$, O-$CH_2$), 71.9 (CH, O-CH), 71.3 (CH, O-CH), 69.3 ($CH_2$, O-$CH_2$), 68.9 ($CH_2$, O-$CH_2$), 49.2 (C), 48.8 (C), 40.2 ($CH_2$), 37.9 ($CH_2$), 37.2 ($CH_2$), 37.1 ($CH_2$), 29.83 ($CH_3$), 29.80 ($CH_3$), 29.4 ($CH_2$), 29.2 ($CH_2$), 25.8 ($CH_3$), 25.6 ($CH_3$), 25.3 ($CH_3$), 25.2 ($CH_3$); LRMS m/z 285.10 ($M+H^+$), calcd $C_{14}H_{20}O_6$ 284.13; Anal. calcd for $C_{14}H_{20}O_6$( 284.13);C, 59.14; H, 7.09; Found: C, 59.23, H, 6.98%.



**85aa**

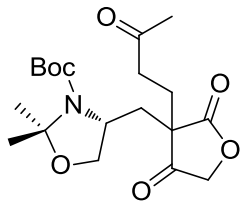
**3-(1,4-Dioxa-spiro[4.5]dec-2-ylmethyl)-3-(3-oxo-butyl)-furan-2,4-dione (85ba):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oil; **$[\alpha]_D^{25} = -76.6°$ (*c* = 0.15 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2935, 1756 (C=O), 1717 (O-C=O), 1364, 1229, 1165, 1098, 1045, 930, 651 $cm^{-1}$; $^1$H NMR ($CDCl_3$) (1:1 diastereomeric mixture) δ 4.79 (1H, d, *J* = 16.4 Hz), 4.63 (2H, s), 4.59 (1H, d, *J* = 16.4 Hz), 4.18-3.96 (4H, m), 3.53-3.50 (2H, m), 2.58-2.48 (4H, m), 2.13 (6H, s), 2.10-1.96 (8H, m), 1.60-1.38 (20H, m); $^{13}$C NMR ($CDCl_3$) (1:1 diastereomeric mixture) δ 210.0 (C=O), 208.7 (C=O), 206.2 (C=O), 206.1 (C=O), 176.6 (C, O-C=O), 176.2 (C, O-C=O), 110.9 (C), 110.7 (C), 73.2 ($CH_2$, O-$CH_2$), 72.6 ($CH_2$, O-$CH_2$), 71.6



**85ba**

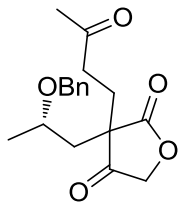
(CH, O-CH), 71.0 (CH, O-CH), 68.9 ($CH_2$, O-$CH_2$), 68.6 ($CH_2$, O-$CH_2$), 49.2 (C), 48.8 (C), 40.1 ($CH_2$), 38.2 ($CH_2$), 37.13 ($CH_2$), 37.08 ($CH_2$), 35.7 ($CH_2$), 35.5 ($CH_2$), 34.6 ($CH_2$), 34.5 ($CH_2$), 29.7 (2x$CH_3$), 29.4 ($CH_2$), 29.2 ($CH_2$), 24.9 ($CH_2$), 24.84 ($CH_2$), 24.77 ($CH_2$), 23.9 ($CH_2$), 23.74 ($CH_2$), 23.67 ($CH_2$); LRMS m/z 325.00 ($M+H^+$), calcd $C_{17}H_{24}O_6$ 324.16; Anal. calcd for $C_{17}H_{24}O_6$(324.16);C, 62.95; H, 7.46; Found: C, 62.88, H, 7.51%.

**4-[2,4-Dioxo-3-(3-oxo-butyl)-tetrahydro-furan-3-ylmethyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (85ca):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane and isolated as a Solid. Mp 102 °C; **$[\alpha]_D^{25}$ = −18.7° (*c* = 1.5 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2978, 1756 (O-C=O), 1717 (C=O), 1675 (C=O), 1402, 1370, 1172, 1104, 851, 638. $cm^{-1}$; $^1$H NMR ($CDCl_3$) (1:1 diastereomeric mixture) δ 4.78 (1H, d, *J* = 16.0 Hz), 4.68 (2H, s), 4.63 (1H, d, *J* = 15.6 Hz), 4.24 (1H, t, *J* = 9.6 Hz), 4.06-3.97 (3H, m), 3.96-3.92 (2H, m), 3.64 (2H, t, *J* = 8.0 Hz), 2.61-2.57 (4H, m), 2.14 (6H, s), 2.00-1.95 (4H, m), 1.83-1.76 (2H, m), 1.59 (6H, s), 1.50 (6H, s), 1.45 (9H, s), 1.43 (9H, s); $^{13}$C NMR ($CDCl_3$) (1:1 diastereomeric mixture) δ 207.4 (C, C=O), 206.2 (C, C=O), 206.0 (2 x C, C=O), 175.7 (C, O-C=O), 175.3 (C, O-C=O), 153.1 (C, N-C=O), 152.8 (C, N-C=O), 93.7 (C), 93.6 (C), 80.6 (C), 80.3 (C), 72.5 ($CH_2$, O-$CH_2$), 72.3 ($CH_2$, O-$CH_2$), 68.9 ($CH_2$, O-$CH_2$), 68.5 ($CH_2$, O-$CH_2$), 53.7 (CH, N-CH), 53.1 (CH, N-CH), 49.8 (C), 50.5 (C), 37.1 ($CH_2$), 36.4 ($CH_2$), 35.6 ($CH_2$), 35.2 ($CH_2$), 30.9 ($CH_2$), 30.6 ($CH_2$), 29.8 ($CH_3$), 28.3 (3x$CH_3$), 28.2 (3x$CH_3$), 28.1 ($CH_3$), 27.5 ($CH_3$), 27.1 ($CH_3$), 24.1 ($CH_3$), 23.6 ($CH_3$); LRMS m/z 384.05 ($M+H^+$), calcd $C_{19}H_{29}NO_7$ 383.19; Anal. calcd for $C_{19}H_{29}NO_7$ (383.19): C, 59.92; H, 7.62; N, 3.65. Found: C, 59.45; H, 7.62, N=3.71%.



**85ca**

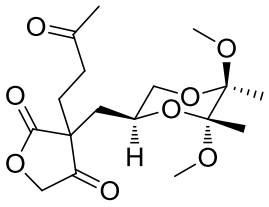
**3-(2-Benzyloxy-propyl)-3-(3-oxo-butyl)-furan-2,4-dione (85da):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane and isolated as a liquid; **$[\alpha]_D^{25}$ = +21.5° (*c* = 1.5 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2927, 1768 (O-C=O), 1718 (C=O), 1377, 1098, 1029, 696, 637. $cm^{-1}$; $^1$H NMR ($CDCl_3$) (1:1.2 diastereomeric mixture) δ 7.36-7.23 (10H, m), 4.59-4.55 (2H, m), 4.32 (1H, d, *J* = 16.8 Hz), 4.23 (1H, d, *J* = 16.4 Hz), 4.08 (2H, t, *J* = 10.8 Hz), 3.84 (1H, d, *J* = 16.8 Hz), 3.79 (1H, d, *J* = 16.4 Hz), 3.70-3.54 (2H, m), 2.60-2.40 (4H, m), 2.22-2.19 (1H, m), 2.16-2.15 (1H, m), 2.12 (6H, s), 2.01-1.90 (5H, m), 1.73 (1H, s), 1.22 (3H, s), 1.20 (3H, s); $^{13}$C NMR ($CDCl_3$) (1:1.7 diastereomeric mixture) δ 209.4 (C=O), 208.3 (C=O), 206.2 (C=O), 206.0 (C=O), 177.1 (C, O-C=O), 176.6 (C, O-C=O), 137.0 (C), 136.9 (C), 128.40 (2xCH), 128.35 (2xCH), 127.93 (2xCH), 127.88 (1xCH), 127.7 (1xCH), 127.3 (2xCH), 72.6 ($CH_2$, O-$CH_2$), 72.1 ($CH_2$, O-$CH_2$), 71.5 (CH, O-CH), 70.9 ($CH_2$, O-$CH_2$), 70.6 (CH, O-CH),



**85da**

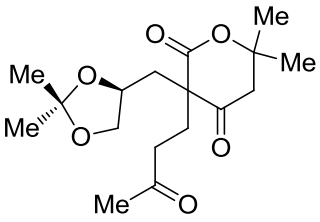
70.4 ($CH_2$, O-$CH_2$), 48.6 (C), 48.4 (C), 41.9 ($CH_2$), 41.2 ($CH_2$), 37.13 ($CH_2$), 37.07 ($CH_2$), 29.9 (2x$CH_3$), 29.3 ($CH_2$), 28.9 ($CH_2$), 18.8 ($CH_3$), 18.6 ($CH_3$); LRMS m/z 319.20 ($M+H^+$), calcd $C_{18}H_{22}O_5$ 318.25; Anal. calcd for $C_{18}H_{22}O_5$ 318.25;C, 67.91; H, 6.97; Found: C, 67.98, H, 6.92%.

**3-(5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxan-2-ylmethyl)-3-(3-oxo-butyl)-furan-2,4-dione (85ea):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane and isolated as colorless viscous oil. Mp 54 °C Mp 46 °C; **$[\alpha]_D^{25}$ = –99.4° (*c* = 1.5 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2945, 1801 (O-C=O), 1757 (C=O), 1717 (C=O), 1439, 1374 , 1141, 1118, 1042, 737, 657. $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (1:1.3 diastereomeric mixture) δ 4.74-4.61 (4H, m), 4.01-3.95 (2H, m), 3.58 (1H, t, *J* = 11.0 Hz), 3.44 (1H, t, *J* = 11.2 Hz), 3.35 (1H, d, *J* = 2.4 Hz), 3.33-3.31 (1H, m), 3.22-3.16 (12H, m), 2.59-2.47 (4H, m), 2.14 (6H, s), 2.01-1.87 (8H, m), 1.22-1.18 (12H, m); $^{13}C$ NMR ($CDCl_3$) (1:1.3 diastereomeric mixture) δ 208.5 (1xC, C=O), 208.1 (1xC, C=O), 206.0 (1xC, C=O), 205.8 (1xC, C=O), 176.3 (C, O-C=O), 176.1 (C, O-C=O), 99.8 (C), 99.7 (C), 97.7 (C), 97.6 (C), 72.5 ($CH_2$, O-$CH_2$), 72.4 ($CH_2$, O-$CH_2$), 62.8 ($CH_2$, O-$CH_2$), 62.7 (CH, O-CH), 62.6 (CH, O-CH), 62.5 ($CH_2$, O-$CH_2$), 48.4 ($CH_3$, O-$CH_3$), 48.3 ($CH_3$, O-$CH_3$), 47.8 (2xC), 47.6 ($CH_3$, O-$CH_3$), 47.3 ($CH_3$, O-$CH_3$), 36.9 ($CH_2$), 36.8 ($CH_2$), 34.2 ($CH_2$), 34.1 ($CH_2$), 29.7 (2x$CH_3$), 29.3 ($CH_2$), 29.2 ($CH_2$), 17.4 ($CH_3$), 17.3 ($CH_3$), 16.81 ($CH_3$), 16.78 ($CH_3$); LRMS m/z 359.25 ($M+H^+$), calcd $C_{17}H_{26}O_8$ 358.16; Anal. calcd for $C_{17}H_{26}O_8$ (358.16): C, 56.97; H, 7.31; Found: C, 56.88; H, 7.36%.



**85ea**

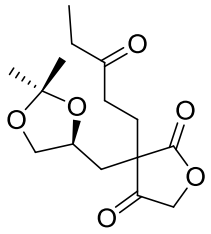
**3-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-6,6-dimethyl-3-(3-oxo-butyl)-dihydro-pyran-2,4-dione (85ga):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil; **$[\alpha]_D^{25}$ = –2.2° (*c* = 5.0 g/100 mL, $CHCl_3$)**; IR (neat): $\nu_{max}$ 2981, 1712 (O-C=O), 1375, 1324, 1219, 1163, 1064, 677, 650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (1:1 diastereomeric mixture) δ 4.08-4.06 (4H, m), 3.51-3.49 (1H, m), 3.00 (1H, d, *J* = 15.2 Hz), 2.87 (1H, d, *J* = 7.2 Hz), 2.80-2.77 (1H, m), 2.59-2.47 (4H, m), 2.27-2.24 (2H, m), 2.16-2.13 (7H, m), 2.05-1.92 (3H, m), 1.53-1.26 (28H, m); $^{13}C$ NMR ($CDCl_3$) (1:1 diastereomeric mixture) δ 206.6 (2xC, C=O), 205.9 (C=O), 205.6 (C=O), 172.9 (2xC, O-C=O), 109.8 (C), 109.7 (C), 79.0 (C), 78.5 (C), 72.4 (CH, O-CH), 71.5 (CH, O-CH), 69.6 ($CH_2$, O-$CH_2$), 69.4 ($CH_2$, O-$CH_2$), 56.6 (C), 56.1 (C), 49.4 ($CH_2$), 49.2 ($CH_2$), 40.4 ($CH_2$), 39.7 ($CH_2$), 38.0 ($CH_2$), 37.8 ($CH_2$), 31.6 ($CH_2$), 31.1 ($CH_2$), 29.9 ($CH_3$), 29.6 ($CH_3$), 29.1 ($CH_3$), 28.9 ($CH_3$), 26.7 ($CH_3$), 26.4 ($CH_3$), 26.2 ($CH_3$), 25.53 ($CH_3$), 25.48 ($CH_3$), 25.1



**85ga**

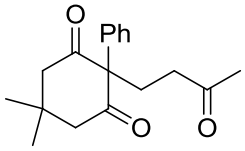
($CH_3$); LRMS m/z 327.00 ($M+H^+$), calcd $C_{17}H_{26}O_6$ 326.17; Anal. calcd for $C_{17}H_{26}O_6$ (326.17): C, 62.56; H, 8.03; Found: C, 62.45; H, 8.12%.

**3-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-3-(3-oxo-pentyl)-furan-2,4-dione (85ab):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oil; **$[\alpha]_D^{25}$ = –36.5° (*c* = 3.7 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2985`, 1800, 1756, 1714, 1376, 1223, 1156, 1052. $cm^{-1}$; $^1$H NMR (500MHz, $CDCl_3$) (1:1 diastereomeric mixture) δ 4.73 (1H, d, *J* =16.4 Hz), 4.60 (2H, s), 4.55 (1H, d, *J* = 16.0 Hz), 4.18-4.09 (1H, m), 4.06-4.02 (3H, m), 3.54-3.52 (2H, m), 2.56-2.44 (2H, m), 2.43-2.39 (5H, m), 2.16 (1H, s), 2.12-2.07 (2H, m), 2.01-1.98 (6H, m), 1.35 (3H, s), 1.28 (3H, s), 1.24 (6H, s), 1.02 (6H, t, *J* = 7.0 Hz); $^{13}$C NMR (125MHz, $CDCl_3$) (1:1 diastereomeric mixture) δ 210.0 (C=O), 209.1 (C=O), 209.0 (C=O), 208.9 (C=O), 176.7 (C, O-C=O), 176.3 (C, O-C=O), 110.2 (C), 110.0 (C), 73.3 ($CH_2$, O-$CH_2$), 72.7 ($CH_2$, O-$CH_2$), 72.0 (CH, O-CH), 71.4 (CH, O-CH), 69.4 ($CH_2$, O-$CH_2$), 69.0 ($CH_2$, O-$CH_2$), 49.3 (C), 49.0 (C), 40.4 ($CH_2$), 38.1 ($CH_2$), 35.91 ($CH_2$), 35.86 ($CH_2$), 35.84 ($CH_2$), 35.82 ($CH_2$), 29.6 ($CH_2$), 29.4 ($CH_2$), 25.8 ($CH_3$), 25.7 ($CH_3$), 25.4 ($CH_3$), 25.3 ($CH_3$), 7.6 (2x$CH_3$); LRMS m/z 299.20 ($M+H^+$), calcd $C_{15}H_{22}O_6$ 298.14; Anal. calcd for $C_{15}H_{22}O_6$(298.14);C, 60.39; H, 7.43; Found: C, 60.25, H, 7.51%.



**85ab**

**5,5-Dimethyl-2-(3-oxo-butyl)-2-phenyl-cyclohexane-1,3-dione (85x):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow Oil; IR (neat): $\nu_{max}$ 2957, 1711 (C=O), 1691 (C=O), 1494, 1371, 1240, 762, 702. $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.35-7.27 (3H, m), 6.96-6.93 (2H, m), 2.72 (2H, d, *J* = 13.6 Hz), 2.42-2.33 (4H, m), 2.17-2.13 (2H, m), 2.05 (3H, s), 1.03 (3H, s), 0.86 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 208.0 (C=O), 207.2 (2xC=O), 138.8 (C), 129.6 (2xCH), 127.9 (1xCH), 126.4 (2xCH), 73.5 (C), 52.8 (2x$CH_2$), 39.8 ($CH_2$), 31.1 (C), 30.4 ($CH_3$), 29.7 ($CH_3$), 28.8 ($CH_2$), 26.2 ($CH_3$); LRMS m/z 287.05 ($M+H^+$), calcd $C_{18}H_{22}O_3$ 286.16; Anal. calcd for $C_{18}H_{22}O_3$ (286.16);C, 75.50; H, 7.74; Found: C, 75.46, H, 7.71%.



**85x**

**Procedure G: Amino Acid-Catalyzed Diastereoselective Aldol Reactions: Synthesis of 86:**

In an ordinary glass vial equipped with a magnetic stirring bar, 0.3 mmol of Michael adduct **85** was added to 1.0 mL of solvent with the catalyst **4** (0.09 mmol) and the reaction mixture was stirred at 25 °C for the time indicated in the Table 5 and Table 6. 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 to afford **86.**

**(3a*S*,7a*R*)-7a-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3a-hydroxytetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione [(3a*S*,7a*R*)-86aa]:**

Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oil; **$[\alpha]_D^{25} = -17.3°$ (*c* = 0.9 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 3390, 2984, 1773 (C=O), 1721 (C=O), 1420, 1377, 1218, 1106, 1056,, 1029, 651 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.06 (1H, -OH, s), 4.30-4.13 (4H, m), 3.66-3.59 (1H, m), 2.73-2.65 (2H, m), 2.57-2.41 (1H, m), 2.34-2.29 (1H, m), 2.28-2.23 (1H, m), 2.15-2.02 (2H, m), 1.98 (1H, d, *J* = 14.8 Hz), 1.47 (3H, s), 1.39 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 207.2 (C=O), 178.5 (C, O-C=O), 111.0 (C), 76.6 ($CH_2$, O-$CH_2$), 76.5 (C), 72.5 (CH, O-CH), 70.1 ($CH_2$, O-$CH_2$), 49.2 ($CH_2$), 48.9 (C), 37.8 ($CH_2$), 35.4 ($CH_2$), 31.3 ($CH_2$), 26.5 ($CH_3$), 25.5 ($CH_3$); LRMS m/z 285.10 ($M+H^+$), calcd $C_{14}H_{20}O_6$ 284.13; Anal. calcd for $C_{14}H_{20}O_6$ (284.13);C, 59.14; H, 7.09; Found: C, 59.22, H, 7.13%.

(3a*S*,7a*R*)-**86aa**

**(3a*R*,7a*S*)-7a-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3a-hydroxytetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione [(3a*R*,7a*S*)-86aa]:** Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oil; **$[\alpha]_D^{25} = -102.6°$ (*c* = 0.2 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 3429, 1772 (C=O), 1722 (C=O), 1218, 1027, 734, 648, 621. $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.48-4.39 (1H, m), 4.24-4.13 (2H, m), 3.94 (1H, d, *J* = 10.4 Hz), 3.60 (1H, t, *J* = 7.6 Hz), 2.85 (1H, d, *J* = 16.0 Hz), 2.67-2.63 (1H, m), 2.52-2.47 (1H, m), 2.31-2.28 (1H, m), 2.23-2.16 (2H, m), 2.10-2.02 (2H, m), 1.43 (3H, s), 1.37 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 207.7 (C=O), 179.8 (C, O-C=O), 110.4 (C), 76.8 ($CH_2$, O-$CH_2$), 76.3 (C), 71.6 (CH, O-CH), 70.0 ($CH_2$, O-$CH_2$), 49.4 ($CH_2$), 48.7 (C), 36.4 ($CH_2$), 35.1 ($CH_2$), 27.1 ($CH_2$), 26.4 ($CH_3$), 25.6 ($CH_3$).

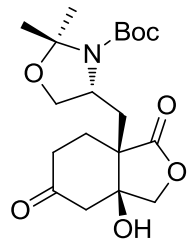
(3a*R*,7a*S*)-**86aa**

**(3a*S*,7a*R*)-7a-((*S*)-1,4-dioxaspiro[4.5]decan-2-ylmethyl)-3a-hydroxytetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione [(3a*S*,7a*R*)-86ba]:** Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oil; **$[\alpha]_D^{25} = -62.5°$ (*c* = 0.15 g/100 mL, $CHCl_3$)**; IR (neat): $\nu_{max}$ 3370, 2934, 1768 (C=O), 1721 (C=O), 1368, 1162, 1026, 928, 653, 611 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ

**86ba**

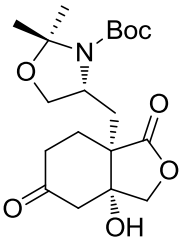
5.21 (1H, s), 4.33-4.15 (4H, m), 3.61-3.59 (1H, m), 2.70 (2H, s), 2.48-2.41 (1H, m), 2.32-2.24 (2H, m), 2.14-1.96 (3H, m), 1.68 (3H, s), 1.62 (3H, s), 1.49-1.39 (4H, m); $^{13}$C NMR ($CDCl_3$) δ 207.4 (C=O), 178.6 (C, O-C=O), 111.8 (C), 76.5 ($CH_2$, O-$CH_2$), 72.1 (CH, O-CH), 69.6 ($CH_2$, O-$CH_2$), 49.2 (C), 48.9 (C), 37.7 ($CH_2$), 36.0 ($CH_2$), 34.7 ($CH_2$), 34.6 ($CH_2$), 31.2 ($CH_2$), 24.7 ($CH_2$), 23.9 ($CH_2$), 23.83 ($CH_2$), 23.75 ($CH_2$); LRMS m/z 325.00 ($M+H^+$), calcd $C_{17}H_{24}O_6$ 324.16; Anal. calcd for $C_{17}H_{24}O_6$ (324.16);C, 62.95; H, 7.46; Found: C, 62.85, H, 7.51%.

**(*R*)-tert-butyl 4-(((3a*R*,7a*S*)-7a-hydroxy-3,6-dioxooctahydroisobenzofuran-3a-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate [(3a*R*,7a*S*)-86ca]:** Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a white Solid. Mp 122 °C; **$[\alpha]_D^{25}$ = −16.1° (*c* = 0.15 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 2981, 1775 (C=O), 1695 (O-C=O), 1655, 1411, 1371, 1259, 1110, 644; $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 6.60 (1H, -OH), 4.25 (2H, t, *J* = 9.6 Hz), 4.17-4.15 (1H, m), 4.09 (2H, d, *J* = 8.8 Hz), 2.71 (2H, s), 2.42-2.35 (3H, m), 2.18 (1H, bs), 2.04-1.93 (2H, m), 1.58 (3H, s), 1.49 (9H, s), 1.40 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 206.2 (C=O), 178.2 (C, O-C=O), 153.7 (C, N-C=O), 93.4 (C), 82.1 (C), 80.1 (C), 75.9 ($CH_2$, O-$CH_2$), 70.2 ($CH_2$, O-$CH_2$), 55.5 (CH, N-CH), 48.8 ($CH_2$), 47.7 (C), 37.4 ($CH_2$), 35.5 ($CH_2$), 32.4 ($CH_2$), 28.3 (3x$CH_3$), 27.4 ($CH_3$), 23.8 ($CH_3$); LRMS m/z 384.05 ($M+H^+$), calcd $C_{19}H_{29}NO_7$ 383.19; Anal. calcd for $C_{19}H_{29}NO_7$ (383.19);C, 59.52; H, 7.62; N,3.65; Found: C, 59.45; H, 7.70; N, 3.61%.



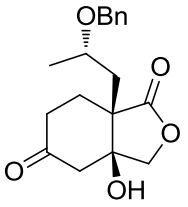
(3a*R*,7a*S*)-**86ca**

**(*R*)-tert-butyl 4-(((3a*S*,7a*R*)-7a-hydroxy-3,6-dioxooctahydroisobenzofuran-3a-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate [(3a*S*,7a*R*)-86ca]:** Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a white Solid. Mp 110 °C; **$[\alpha]_D^{25}$ = −5.2° (*c* = 0.5 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 3445, 2981, 1774 (C=O), 1693 (C=O), 1394, 1371, 1253, 1174, 1101, 644; $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 6.13 (1H, s, -OH), 4.24 (1H, d, *J* = 8.0 Hz), 4.07 (1H, q, *J* = 4.0 Hz), 4.02 (1H, d, *J* = 12.0 Hz), 3.77 (1H, d, *J* = 8.0 Hz), 2.71 (2H, ABq, *J* = 12.0 Hz), 2.38 (2H, t, *J* = 8.0 Hz), 2.26 (1H, d, *J* = 16.0 Hz), 2.17 (1H, s), 2.15-2.09 (1H, m), 2.07-2.02 (2H, m), 1.57 (3H, s), 1.49 (9H, s), 1.46 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 207.0 (C=O), 178.2 (C, O-C=O), 153.4 (C, N-C=O), 93.6 (C), 82.1 (C), 79.8 (C), 75.0 ($CH_2$, O-$CH_2$), 69.4 ($CH_2$, O-$CH_2$), 53.5 (CH, N-CH), 49.2 ($CH_2$), 47.6 (C), 36.8 ($CH_2$), 36.6 ($CH_2$), 28.3 (3x$CH_3$), 27.6 ($CH_2$), 27.2 ($CH_3$), 24.0 ($CH_3$); LRMS m/z 384.05 ($M+H^+$), calcd $C_{19}H_{29}NO_7$ 383.19; Anal. calcd for $C_{19}H_{29}NO_7$ (383.19); C, 59.52; H, 7.62; N,3.65; Found: C, 59.65; H, 7.58; N, 3.61%.



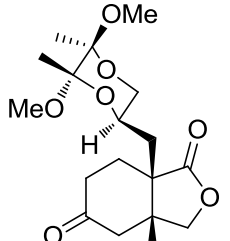
(3a*S*,7a*R*)-**86ca**

**(3a*S*,7a*R*)-7a-((*S*)-2-(benzyloxy)propyl)-3a-hydroxytetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione (86da):** Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a white Solid. Mp 79 °C; **$[\alpha]_D^{25}$ = +67.7° (*c* = 0.6 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 3369, 2926, 1759 (C=O), 1717 (O-C=O), 1418, 1212, 1105, 1059, 697, 656;$cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.37-7.34 (3H, m), 7.29-7.28 (2H, m), 4.75 (1H, t, *J* = 3.2 Hz), 4.35 (1H, d, *J* = 10.8 Hz), 4.16 (1H, d, *J* = 10.4 Hz), 4.05-3.97 (1H, m), 3.90 (1H, d, *J* = 10.0 Hz), 3.84 (1H, d, *J* = 10.4 Hz), 2.57 (2H, s), 2.49-2.31 (3H, m), 2.07-2.01 (3H, m), 1.38-1.32 (3H, m); $^{13}$C NMR ($CDCl_3$) δ 208.2 (C=O), 180.5 (C, O-C=O), 135.9 (C), 128.9 (CH), 128.7 (CH), 128.53 (CH), 128.49 (2xCH), 76.9 ($CH_2$, O-$CH_2$), 75.8 (C), 71.1 (CH, O-CH), 70.9 ($CH_2$, O-$CH_2$), 49.8 ($CH_2$), 48.8 (C), 39.2 ($CH_2$), 36.2 ($CH_2$), 26.6 ($CH_2$), 19.3 ($CH_3$); HRMS m/z 341.1365 (M+Na), calcd $C_{18}H_{22}O_5Na$ 341.1365.



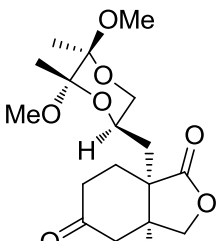
**86da**

**(3a*S*,7a*R*)-7a-(((2*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)-3a-hydroxytetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione [(3a*S*,7a*R*)-86ea]:** Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a light gummy yellow Solid; **$[\alpha]_D^{25}$ = −72.0° (*c* = 0.8 g/100 mL, $CHCl_3$)**; IR (neat): $\nu_{max}$ 3424, 2924, 1767 (C=O), 1721 (O-C=O), 1377, 1033, 938, 662. $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.16 (1H, s), 4.28-4.22 (2H, m), 4.14-4.09 (1H, m), 3.56-3.49 (2H, m), 3.30 (3H, s), 3.25 (3H, s), 2.70 (2H, s), 2.44-2.39 (1H, m), 2.22-2.09 (4H, m), 1.81 (1H, dd, *J* = 14.8, 4.4 Hz), 1.31 (3H, s), 1.27 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 207.8 (C, C=O), 178.7 (C, O-C=O), 100.0 (C), 97.8 (C), 78.6 ( $CH_2$, O-$CH_2$), 75.6 (C), 63.5 (CH, O-CH), 62.8 ($CH_2$, O-$CH_2$), 49.14 ($CH_3$, O-$CH_3$), 49.12 ($CH_2$), 48.1 ($CH_3$, O-$CH_3$), 48.0 (C), 35.2 ($CH_2$), 33.7 ($CH_2$), 32.4 ($CH_2$), 17.3 ($CH_3$), 17.2 ($CH_3$); LRMS m/z 359.00 ($M+H^+$), calcd $C_{17}H_{26}O_8$ 358.16; Anal. calcd for $C_{17}H_{26}O_8$ (358.16): C, 56.97; H, 7.31; Found: C, 56.88; H, 7.36%.



(3a*S*,7a*R*)-**86ea**

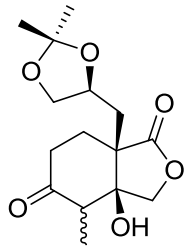
**(3a*R*,7a*S*)-7a-(((2*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)-3a-hydroxytetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione [(3a*R*,7a*S*)-86ea]:** Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow gummy Solid; **$[\alpha]_D^{25}$ = −109.6° (*c* = 1.3 g/100 mL, $CHCl_3$);** IR (neat): $\nu_{max}$ 3424, 2924, 1767 (C=O), 1721 (O-C=O), 1377, 1033, 938, 662 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.66 (1H, s), 4.35-4.31 (2H, m), 3.98 (1H, d, *J* = 10.4



(3a*R*,7a*S*)-**86ea**

Hz), 3.63 (1H, t, *J* = 11.2 Hz), 3.47 (1H, dd, *J* = 11.6, 3.6 Hz), 3.33 (3H, s), 3.26 (3H, s), 2.84-2.67 (2H, m), 2.52-2.47 (1H, m), 2.23-2.08 (4H, m), 1.91 (1H, dd, *J* = 15.2, 2.8 Hz), 1.32 (3H, s), 1.28 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 207.6 (C, C=O), 179.8 (C, O-C=O), 100.1 (C), 97.9 (C), 76.5 ($CH_2$, O-$CH_2$), 76.3 (C), 63.9 (CH, O-CH), 62.6 ($CH_2$, O-$CH_2$), 49.4 (C), 49.3 ($CH_2$, $CH_3$, O-$CH_3$), 48.1 ($CH_3$, O-$CH_3$), 36.0 ($CH_2$), 33.3 ($CH_2$), 22.5 ($CH_2$), 17.6 ($CH_3$), 17.5 ($CH_3$); LRMS m/z 359.25 ($M+H^+$), calcd $C_{17}H_{26}O_8$ 358.16; Anal. calcd for $C_{17}H_{26}O_8$ (358.16): C, 56.97; H, 7.31; Found: C, 56.88; H, 7.36%.

**(3a*S*,7a*R*)-7a-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3a-hydroxy-4-methyltetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione [(3a*S*,7a*R*)-86ab]:**



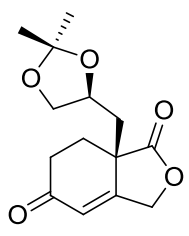
**86ab**

Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oil; **$[\alpha]_D^{25}$ = +36.8° (*c* = 0.25 g/100 mL, $CHCl_3$)**; IR (neat): $\nu_{max}$ 3432, 2982, 1756 (C=O), 1713 (C=O), 1439, 1376, 1223, 1053, 652 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.20 (1H, -OH, s), 4.32-4.14 (2H, m), 4.09 (1H, s), 3.60 (1H, t, *J* = 8.0 Hz), 2.81-2.66 (1H, m), 2.53-2.40 (2H, m), 2.36-2.23 (2H, m), 2.16-1.94 (2H, m), 1.83-1.75 (1H, m), 1.48-1.38 (6H, m), 1.22-1.17 (3H, m); $^{13}$C NMR ($CDCl_3$) δ 208.5 (C=O), 178.3 (C, O-C=O), 110.6 (C), 79.8 (C), 74.0 ($CH_2$, O-$CH_2$), 72.6 (CH, O-CH), 70.0 ($CH_2$, O-$CH_2$), 50.7 (C), 50.6 (CH), 36.4 ($CH_2$), 35.9 ($CH_2$), 30.9 ($CH_2$), 26.6 ($CH_3$), 25.5 ($CH_3$), 7.1 ($CH_3$); LRMS m/z 299.20 ($M+H^+$), calcd $C_{15}H_{22}O_6$ 298.14; Anal. calcd for $C_{15}H_{22}O_6$ (298.14);C, 60.39; H, 7.43; Found: C, 60.28, H, 7.46%.

**Procedure H: General Procedure for Dehydration of 86:**

To a solution of alcohol compound **86aa** or **86ab** (0.3 mmol) in dry DCM (2 mL) and dry pyridine (1 mL) at 0 °C, $SOCl_2$ (5 equiv.) was added drop wise and stirred at 0 °C for 5 minutes. After removal of cooling, the reaction mixture was stirred at room temperature for 30 minutes and washed with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered concentrated. Pure products **88aa** or **88ab** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**(*R*)-7a-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-7,7a-dihydroisobenzofuran-1,5(3*H*,6*H*)-dione [(*R*)-88aa]:**

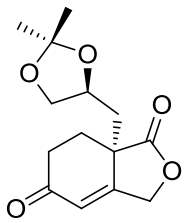


(*R*)-**88aa**

Prepared by following the procedure **H** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow sticky Solid; **$[\alpha]_D^{25}$ = +266.3° (*c* = 0.4 g/100 mL, $CHCl_3$)**; IR (neat): $\nu_{max}$ 3327, 2929, 1780 (C=O), 1672 (C=O), 1374, 1216, 1061, 1014, 664, 603. $cm^{-1}$;

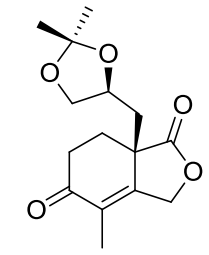
$^1$H NMR ($CDCl_3$) δ 5.99 (1H, s, olefinic), 5.35 (1H, dd, *J* = 14.4, 2.4 Hz), 4.88 (1H, dd, *J* = 14.4, 1.2 Hz), 4.21-4.14 (1H, m), 4.11 (1H, dd, *J* = 8.0, 6.0 Hz), 3.53 (1H, dd, *J* = 8.0, 6.4 Hz), 2.64-2.54 (2H, m), 2.27-2.03 (4H, m), 1.33 (3H, s), 1.32 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 196.3 (C=O), 177.0 (C, O-C=O), 161.8 (C, -C=C), 122.3 (CH, -C=CH), 110.0 (C), 72.1 (CH, O-CH), 70.2 ($CH_2$, O-$CH_2$), 69.4 ($CH_2$, O-$CH_2$), 44.5 (C), 41.0 ($CH_2$), 32.5 ($CH_2$), 31.4 ($CH_2$), 26.9 ($CH_3$), 25.5 ($CH_3$); LRMS m/z 265.20 (M-H$^+$), calcd $C_{14}H_{18}O_5$ 266.12; Anal. calcd for $C_{14}H_{18}O_5$ (266.12);C, 63.15; H, 6.81; Found: C, 63.22, H, 6.85%.

**(*S*)-7a-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-7,7a-dihydroisobenzofuran-1,5(3*H*,6*H*)-dione [(*S*)-88aa]:** Prepared by following the procedure **H** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow gummy Solid; **$[\alpha]_D^{25}$ = –65.5° (*c* = 1.5 g/100 mL, $CHCl_3$)**; $^1$H NMR ($CDCl_3$) δ 6.04 (1H, s, olefinic), 5.13 (1H, dd, *J* = 14.4, 2.4 Hz), 4.90 (1H, dd, *J* = 14.4, 1.2 Hz), 4.15-4.08 (2H, m), 3.52 (1H, dd, *J* = 8.4, 6.8 Hz), 2.69-2.54 (2H, m), 2.18-1.96 (4H, m), 1.41 (3H, s), 1.35 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 196.6 (C=O), 176.8 (C, O-C=O), 161.0 (C, -C=C), 123.1 (CH, -C=CH), 110.1 (C), 72.1 (CH, O-CH), 69.5 ($CH_2$, O-$CH_2$), 68.7 ($CH_2$, O-$CH_2$), 43.7 (C), 38.7 ($CH_2$), 32.6 ($CH_2$), 28.5 ($CH_2$), 26.7 ($CH_3$), 25.6 ($CH_3$).



(*S*)-**88aa**

**(*R*)-7a-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-methyl-7,7a-dihydroisobenzofuran-1,5(3*H*,6*H*)-dione [(*R*)-88ab]:** Prepared by following the procedure **H** and purified by column chromatography using EtOAc/hexane and isolated as a colorless sticky Solid; **$[\alpha]_D^{25}$ = +100.7° (*c* = 0.25 g/100 mL, $CHCl_3$)**; IR (neat): $\nu_{max}$ 2938, 1768 (C=O), 1661 (C=O), 1376, 1222, 1162, 1123, 1061, 1019, 831, 667 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.23 (1H, dd, *J* = 14.0, 1.6 Hz), 4.96 (1H, t, *J* = 14.0 Hz), 4.18-4.13 (1H, m), 4.08 (1H, dd, *J* = 10.4, 2.0 Hz), 3.53 (1H, dd, *J* = 8.0, 6.0 Hz), 2.66-2.61 (1H, m), 2.57-2.55 (1H, m), 2.22-2.18 (2H, m), 2.16-2.10 (1H, m), 2.01 (1H, dd, *J* = 13.6, 2.4 Hz), 1.74 (3H, s), 1.31 (3H, s), 1.30 (3H, s); $^{13}$C NMR ($CDCl_3$) δ 196.3 (C=O), 177.9 (C, O-C=O), 155.0 (C, -C=C), 128.7 (C, -C=C), 109.8 (C), 72.2 (CH, O-CH), 69.6 ($CH_2$, O-$CH_2$), 69.3 ($CH_2$, O-$CH_2$), 44.4 (C), 41.4 ($CH_2$), 32.3 ($CH_2$), 31.0 ($CH_2$), 26.9 ($CH_3$), 25.5 ($CH_3$), 10.9 ($CH_3$); LRMS m/z 281.25 (M+H$^+$), calcd $C_{15}H_{20}O_5$ 280.13; Anal. calcd for $C_{15}H_{20}O_5$(280.13);C, 64.27; H, 7.19; Found: C, 64.21, H, 7.22%.

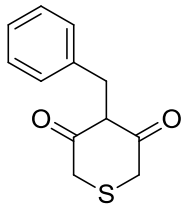


(*R*)-**88ab**

**Procedure I: Amino Acid-Catalyzed Reductive Alkylation Reactions with 3p:** In an ordinary glass vial equipped with a magnetic stirring bar, 0.5 mmol of the aldehyde **91**, 0.5 mmol of CH-acid **3p** and 0.5 mmol of Hantzsch ester **1a** was added 1.0 mL of solvent, and then the catalyst

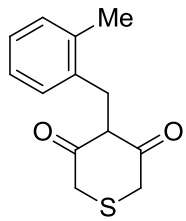
amino acid **4a** (0.05 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 8. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure cascade products **92** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**4-benzyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92a):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 57°C. IR (Neat): $\nu_{max}$ 2922, 2853, 1744, 1630,1460, 1159 and 1029 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.29-7.20 (5H, m), 3.93 (1H, t, *J* = 6.0 Hz), 3.47-3.36 (4H, m), 3.25 (2H, d, *J* = 6.0 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 195.5 (2xC, *C*=O), 139.5 (C), 129.2 (2xCH), 128.5 (2xCH), 126.4 (CH), 70.0 (CH), 39.6 ($2xCH_2$), 28.5 ($CH_2$); HRMS m/z 221.0618 (M + H), calcd for $C_{12}H_{12}O_2SH$ 221.0636.



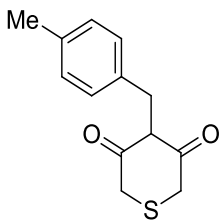
**92a**

**4-(2-methylbenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92b):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 93°C. IR (Neat): $\nu_{max}$ 2925, 1704, 1598, 1373, 1264, 1218 and 1024 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.19-7.09 (4H, m), 3.91 (1H, t, *J* = 5.6 Hz), 3.47-3.37 (4H, m), 3.25 (2H, d, *J* = 5.6 Hz), 2.31 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 195.4 (2xC, *C*=O), 137.5 (C), 136.2 (C), 130.3 (CH), 129.5 (CH), 126.5 (CH), 125.9 (CH), 68.7 (CH), 39.5 ($2xCH_2$), 25.2 ($CH_2$), 19.5 ($CH_3$); HRMS m/z 257.0612 (M + Na), calcd for $C_{13}H_{14}O_2SNa$ 257.0612.



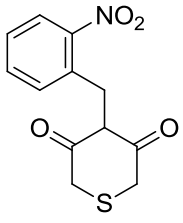
**92b**

**4-(4-methylbenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92c):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 91°C. IR (Neat): $\nu_{max}$ 2921, 1603, 1372, 1265, 183, 1027 and 809 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$) δ 7.13-7.00 (4H, m), 3.61 (1H, s), 3.39 (3H, q, *J* = 14.0 Hz), 3.13 (1H, s), 3.16 (1H, s), 2.27 (2H, s), 2.25 (1H, s); $^{13}C$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$, DEPT-135) δ 195.6 (2xC, *C*=O), 136.1 (C), 135.9 (C), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 39.5 ($2xCH_2$), 28.1 ($CH_2$), 27.6 (CH), 20.9 ($CH_3$); HRMS m/z 235.0740 (M + H), calcd for $C_{13}H_{14}O_2SH$ 235.0793.



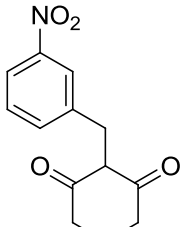
**92c**

**4-(2-nitrobenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92d):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 72°C. IR (Neat): $\nu_{max}$ 1558, 1521, 1355, 1226, 1133, 1034 and 847 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.90 (1H, d, *J* = 8.4 Hz), 7.73-7.24 (3H, m), 4.11-4.05 (1H, m), 3.86 (1H, s), 3.52-3.44 (3H, m), 3.37-3.30 (2H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 194.6 (2xC, *C*=O), 148.9 (C), 134.3 (CH), 133.1 (CH), 127.7 (CH), 124.8 (CH), 112.9 (C), 68.8 (CH), 39.5 (2x$CH_2$), 30.9 ($CH_2$); HRMS m/z 266.0486 (M + H), calcd for $C_{12}H_{11}NO_4SH$ 266.0487.



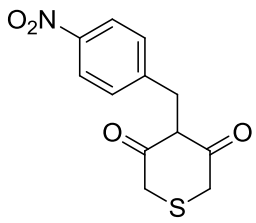
**92d**

**4-(3-nitrobenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92e):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 60°C. ;IR (Neat): $\nu_{max}$ 2927, 1721, 1598, 1526, 1348, 1220, 1102 and 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$) δ 8.12 (1H, s), 7.99 (1H, d, *J* = 8.0Hz), 7.63 (1H, d, *J* = 7.6 Hz), 7.39 (1H, t, *J* = 8.0 Hz), 3.76 (2H, s), 3.38 (4H, s); $^{13}C$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$, DEPT-135) δ 147.9 (C), 143.4 (C), 135.0 (CH), 128.6 (CH), 123.3 (CH), 120.5 (CH), 114.2 (C), 39.3 (2x$CH_2$), 27.8 ($CH_2$); HRMS m/z 288.0308 (M + Na), calcd for $C_{12}H_{11}NO_4SNa$ 288.0306.



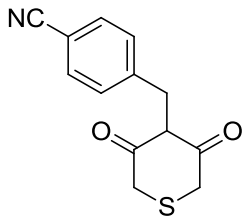
**92e**

**4-(4-nitrobenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92f):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 98°C. IR (Neat): $\nu_{max}$ 2922, 2362, 1703, 1599, 1514, 1342 and 854 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+2 drops of MeOH-$d_4$) δ 7.76-7.73 (2H, m), 7.11-7.08 (2H, m), 3.42 (2H, bs), 3.07 (4H, bs); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 195.1 (2xC,*C*=O), 138.5 (C), 131.5 (2xCH), 131.0 (2xCH), 120.3 (C), 69.8 (CH), 39.7 (2x$CH_2$), 27.8 ($CH_2$); HRMS m/z 288.0307 (M + Na), calcd for $C_{12}H_{11}NO_4SNa$ 288.0306.



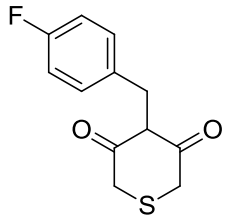
**92f**

**4-((3,5-dioxotetrahydro-2*H*-thiopyran-4-yl)methyl)benzonitrile (92g):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 123°C. IR (Neat): $\nu_{max}$ 3379, 2925, 1711, 1605, 1368, 1265, 1113 and 734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$) δ 7.42 (2H, d, *J* = 7.6 Hz), 7.28 (2H, d, *J* = 7.6 Hz), 3.61 (2H, s), 3.29 (4H, s); $^{13}C$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$, DEPT-135) δ 147.0 (C), 131.2 (2xCH), 128.8 (2xCH), 118.6 (C), 113.4 (C), 108.1 (C), 39.0 (2x$CH_2$), 27.8 ($CH_2$); HRMS m/z 268.0409 (M + Na), calcd for $C_{13}H_{11}NO_2SNa$ 268.0408.



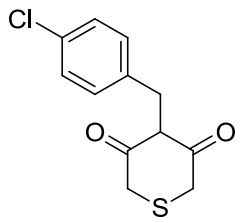
**92g**

**4-(4-fluorobenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92h):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 101°C. ;IR (Neat): $\nu_{max}$ 3056, 1703, 1601, 1508, 1220, 1157 and 830 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$) δ 7.23-7.20 (2H, m), 6.94-6.87 (2H, m), 3.62 (2H, bs), 3.35 (4H, bs), 3.19 (1H, s); $^{13}C$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$) δ 195.5 (2xC, *C*=O), 160.9 (C, d, *J* = 240.0 Hz), 136.7 (C), 129.7 (2xCH, d, *J* = 7.6 Hz), 115.3 (C), 114.4 (2xCH, d, *J* = 21.0 Hz), 39.4 (2x$CH_2$), 27.1 ($CH_2$); HRMS m/z 239.0540 (M + H), calcd for $C_{12}H_{11}FO_2SH$ 239.0542.



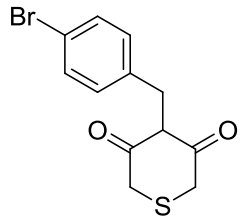
**92h**

**4-(4-chlorobenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92i):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 105°C. ;IR (Neat): $\nu_{max}$ 3055, 1706, 1595, 1491, 1366, 1264, 1089, 1015 and 805 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$) δ 7.52 (2H, d, *J* = 8.0 Hz), 7.38 (2H, d, *J* = 8.0 Hz), 3.71 (2H, s), 3.37 (4H, s); $^{13}C$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$, DEPT-135) δ 147.3 (C), 131.6 (2xCH), 129.2 (2xCH), 119.0 (C), 113.9 (C), 108.4 (C), 28.9 ($CH_2$); HRMS m/z 253.0096 (M-H) calcd for $C_{12}H_{11}ClO_2S$ 254.0618 (M).



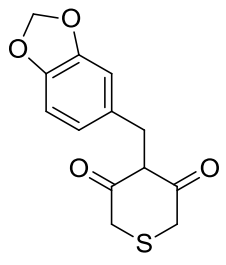
**92i**

**4-(4-bromobenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92j):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 90°C.**;** IR (Neat): $\nu_{max}$ 3141, 2926, 1591, 1483, 1298, 1013 and 748 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.39 (2H, d, *J* = 8.0 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 3.87 (1H, t, *J* =6.0 Hz), 3.43 (4H, q, *J* = 14.0 Hz), 3.19 (2H, d, *J* = 6.0 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 195.1 (2xC, *C*=O), 138.5 (C), 131.5 (2xCH), 131.0 (2xCH), 120.3 (C), 69.8 (CH), 39.7 (2x$CH_2$), 27.8 ($CH_2$); HRMS m/z 320.9561 (M + Na), calcd for $C_{12}H_{11}BrO_2SNa$ 320.9561.



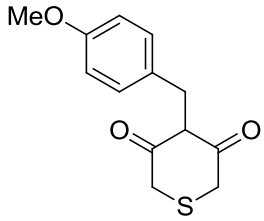
**92j**

**4-(benzo[d][1,3]dioxol-5-ylmethyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92k):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 85°C. IR (Neat): $\nu_{max}$ 3182, 2895, 1717, 1594, 1483, 1367, 1245, 1070 and 919 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$) δ 6.77-6.65 (3H, m), 5.87 (2H, s), 3.57 (2H, s), 3.36 (4H, s); $^{13}C$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$, DEPT-135) δ 146.9 (C), 144.9 (C), 134.8 (C), 120.9 (CH), 115.3 (C), 108.8 (CH), 107.4 (CH), 100.2 ($CH_2$), 39.1 (2x$CH_2$), 27.4 ($CH_2$); HRMS m/z 287.0366 (M + Na), calcd for $C_{13}H_{12}O_4SNa$ 287.0354.



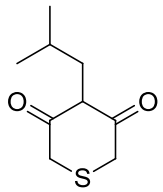
**92k**

**4-(4-methoxybenzyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92l):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 87°C.;IR (Neat): $\nu_{max}$ 2931, 2837, 1701, 1606, 1510, 1243, 1176, 1029, 825 and 732 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$) δ 7.18 (2H, d, *J* =8.4 Hz), 6.77 (2H, d, *J* = 8.4 Hz), 3.78 (1H, s), 3.76 (2H, s), 3.60 (2H, s), 3.35 (3H, s, OC$H_3$); $^{13}C$ NMR ($CDCl_3$ +2 drops of MeOH-$d_4$, DEPT-135) δ 195.8 (C), 157.2 (C), 133.3 (C), 129.2 (2xCH), 115.6 (C), 113.2 (2xCH), 55.0 ($CH_3$, O$CH_3$), 39.3 (2x$CH_2$), 27.0 ($CH_2$); HRMS m/z 251.0741 (M + H), calcd for $C_{13}H_{14}O_3SH$ 251.0742.



**92l**

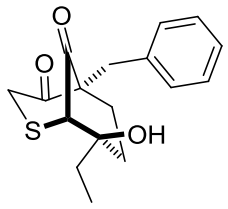
**4-isobutyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (92m):** Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 77°C.;IR (Neat): $\nu_{max}$ 2956, 1702, 1588, 1370, 1233, 1117 and 991 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.65 (1H, t, *J* = 6.4 Hz), 3.41 (4H, q, *J* = 9.6 Hz), 3.35 (2H, s), 1.62-1.51 (1H, m), 0.85 (6H, d, *J* = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 196.8 (2xC), 65.9 (CH), 38.9 (2x$CH_2$), 32.1 ($CH_2$), 25.6 (CH), 22.3 (2x$CH_3$); HRMS m/z 187.0793 (M + H), calcd for $C_9H_{14}O_2SH$ 187.0793.



**92m**

**Procedure J: Organocatalyzed Asymmetric Cascade Michael-Aldol Reaction:** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-alkyl-cyclohexane-1,3-dione **92** and 0.6 mmol of α,β-unsaturated ketone **70** was added 2.0 mL of solvent and then the hydroquinine **4g** (30 mol%) was added and the reaction mixture was stirred 0 °C for the time indicated in Tables 11. The crude reaction mixture was directly loaded on to the silica gel (mixture of hexane/ethyl acetate) to give **96**.

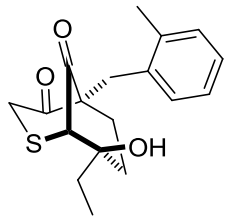
**(–)-5-benzyl-8-ethyl-8-hydroxy-2-thiabicyclo[3.3.1]nonane-4,9-dione (96ab):** Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 96°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.056 min (major), $t_R$ = 11.972 min (minor). **$[\alpha]_D^{25}$ = –68.1° (*c* = 0.20 g/100 mL, $CHCl_3$, 74% *ee*);** IR (Neat): $\nu_{max}$ 3433, 2930, 1731, 1698, 1446, 1268, 959 and 737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.24-7.16 (5H, m), 3.56 (1H, s), 3.24 (1H, d, *J* = 13.2 Hz), 2.85 (2H, t, *J* = 12.4 Hz), 2.65 (1H, d, *J* = 12.4 Hz), 2.33-2.26 (2H, m), 2.00 (2H, t, *J* = 16.4 Hz), 1.65 (2H, q, *J* = 7.2 Hz), 1.57 (1H, d, *J* = 8.8 Hz), 0.92 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 203.6 (C, *C*=O), 200.4 (C, *C*=O), 136.0 (C), 131.1 (2xCH), 128.0 (2xCH), 126.6 (CH), 81.3 (C), 67.1 (C), 54.1 (CH), 38.5 ($CH_2$), 37.9 ($CH_2$), 33.7 ($CH_2$),



**96ab**

31.7 ($CH_2$), 28.7 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 327.1031 (M + Na), calcd for $C_{17}H_{20}O_3SNa$ 327.1031.

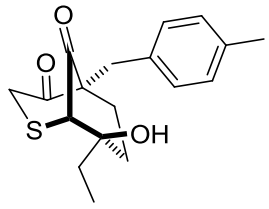
**(–)-8-ethyl-8-hydroxy-5-(2-methylbenzyl)-2-thiabicyclo[3.3.1]nonane-4,9-dione (96bb):**




**96bb**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 102°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), $t_R$ = 7.167 min (major), $t_R$ = 8.710 min (minor); **$[\alpha]_D^{25}$ = –196.1° (*c* = 0.20 g/100 mL, $CHCl_3$, 62% *ee*);** IR (Neat): $\nu_{max}$ 2932, 1706, 1667, 1580, 1455, 1417, 1269, 1134 and 820 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.28-7.26 (1H, m), 7.11-7.08 (3H, m), 3.63 (1H, s), 3.26 (1H, d, *J* = 14.0 Hz), 3.03-2.94 (3H, m), 2.34-2.31 (1H, m), 2.28 (3H, s), 2.00-1.93 (3H, m), 1.66 (2H, q, *J* = 7.2 Hz) 1.57-1.54 (1H,m), 0.92 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 203.6 (C, *C*=O), 199.4 (C, *C*=O), 137.4 (C), 134.7 (C), 131.0 (CH), 130.7 (CH), 126.9 (CH), 125.7 (CH), 81.2 (C), 66.9 (C), 54.2 (CH), 37.9 ($CH_2$), 33.5 ($CH_2$), 33.2 ($CH_2$), 31.8 ($CH_2$), 28.9 ($CH_2$), 20.3 ($CH_3$), 6.6 ($CH_3$); HRMS m/z 341.1187 (M + Na), calcd for $C_{18}H_{22}O_3SNa$ 341.1187.

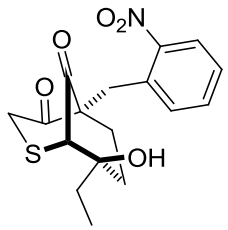
**(–)-8-ethyl-8-hydroxy-5-(4-methylbenzyl)-2-thiabicyclo[3.3.1]nonane-4,9-dione (96cb):**




**96cb**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 111°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol **=** 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 6.875 min (major), $t_R$ = 13.386 min (minor). **$[\alpha]_D^{25}$ = –311.60° (*c* = 0.50 g/100 mL, $CHCl_3$, 73% *ee*);** IR (Neat): $\nu_{max}$ 3433, 2926, 1731, 1698, 1514, 1442, 1275 and 964 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.14 (2H, d, *J* = 8.0 Hz), 7.03 (2H, d, *J* = 7.6 Hz), 3.53 (1H, s), 3.21 (1H, d, *J* = 13.2 Hz), 2.87 (1H, d, *J* = 12.4 Hz), 2.80 (1H, d, *J* = 13.2 Hz), 2.67 (1H, d, *J* = 12.0 Hz), 2.33-2.30 (1H, m), 2.28 (3H, s), 2.00-1.97 (3H, m), 1.65 (2H, q, *J* = 7.2 Hz), 1.57-1.54 (1H, m), 0.90 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 203.3 (C, *C*=O), 200.5 (C, *C*=O), 136.2 (C), 132.9 (C), 131.0 (2xCH), 128.8 (2xCH), 81.3 (C), 67.2 (C), 54.1 (CH), 38.2 ($CH_2$), 38.1 ($CH_2$), 33.7 ($CH_2$), 31.8 ($CH_2$), 29.0 ($CH_2$), 21.0 ($CH_3$), 6.5 ($CH_3$); HRMS m/z 341.1188 (M + Na), calcd for $C_{18}H_{22}O_3SNa$ 341.1187.

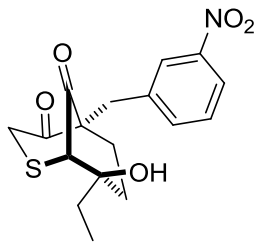
**(–)-8-ethyl-8-hydroxy-5-(2-nitrobenzyl)-2-thiabicyclo[3.3.1]nonane-4,9-dione (96db):**



**96db**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 113°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 16.283 min (major), $t_R$ = 17.847 min (minor). **$[\alpha]_D^{25}$ = –148.3° (*c* = 0.20 g/100 mL, $CHCl_3$, 62% *ee*);** IR (Neat): $\nu_{max}$ 3503, 2931, 1733, 1699, 1610, 1522, 1341, 1267, 965 and 788 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.05 (1H, d, *J* = 8.0 Hz), 7.55 (1H, t, *J* = 7.2 Hz), 7.43 (1H, t, *J* = 7.6 Hz), 7.32 (1H, d, *J* = 7.6 Hz), 3.98 (1H, d, *J* = 14.0 Hz), 3.65 (1H, s), 3.44 (1H, d, *J* = 12.4 Hz), 3.10 (1H, d, *J* = 12.4 Hz), 2.94 (1H, d, *J* = 14.0 Hz), 2.44-2.42 (1H, m), 2.26-2.23 (1H, m), 2.01-1.83 (3H, m), 1.65 (2H, q, *J* = 7.2 Hz), 0.91 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 202.6 (C, *C*=O), 197.8 (C, *C*=O), 149.2 (C), 133.7 (CH), 132.8 (CH), 131.9 (C), 128.2 (CH), 125.6 (CH), 80.9 (C), 64.8 (C), 54.1 (CH), 37.6 ($CH_2$), 35.2 ($CH_2$), 32.4 ($CH_2$), 31.7 ($CH_2$), 28.3 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 350.1063 (M + H), calcd for $C_{17}H_{19}NO_5SH$ 350.1062.

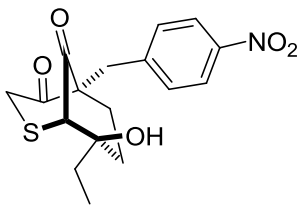
**(–)-8-ethyl-8-hydroxy-5-(3-nitrobenzyl)-2-thiabicyclo[3.3.1]nonane-4,9-dione (96eb):**



**96eb**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 156°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 13.428 min (major), $t_R$ = 32.078 min (minor). **$[\alpha]_D^{25}$ = –182.9° (*c* = 0.30 g/100 mL, $CHCl_3$, 87% *ee*);** IR (Neat): $\nu_{max}$ 2930, 1701, 1601, 1517, 1344, 1270, 1108 and 858 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.16 (1H, s), 8.05 (1H, d, *J* = 7.6 Hz), 7.59 (1H, d, *J* = 7.6 Hz), 7.41 (1H, t, *J* = 8.0 Hz), 3.57 (1H, s), 3.25 (1H, d, *J* = 13.6 Hz), 3.00 (2H, t, *J* = 12.4 Hz), 2.77 (1H, d, *J* = 12.4 Hz), 2.49-2.41 (1H, m), 2.28 (1H, d, *J* = 7.6 Hz), 2.01 (2H, q, *J* = 12.0 Hz), 1.90 (1H, s), 1.67 (2H, q, *J* = 7.2, Hz), 0.91 (3H, t, *J* = 7.2 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 203.0 (C, *C*=O), 200.2 (C, *C*=O), 148.0 (C), 138.1 (C), 137.3 (CH), 128.9 (CH), 126.1 (CH), 121.9 (CH), 81.1 (C), 66.6 (C), 53.9 (CH), 37.9 ($CH_2$), 37.7 ($CH_2$), 33.3 ($CH_2$), 31.7 ($CH_2$), 28.7 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 350.1063 (M + H), calcd for $C_{17}H_{19}NO_5SH$ 350.1062.

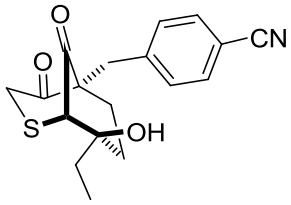
**(–)-8-ethyl-8-hydroxy-5-(4-nitrobenzyl)-2-thiabicyclo[3.3.1]nonane-4,9-dione (96fb):**




**96fb**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 138°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 13.942 min (major), $t_R$ = 39.388 min (minor). **$[\alpha]_D^{25}$ = –203.2° (*c* = 0.20 g/100 mL, $CHCl_3$, 78% *ee*);** IR (Neat): $\nu_{max}$ 3418, 2929, 1733, 1700, 1488, 1439, 1265, 1105, 1012 and 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.10 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.4 Hz), 3.57 (1H, s), 3.28 (1H, d, *J* = 13.2 Hz), 2.97 (2H, dd, *J* = 13.2, 9.6 Hz), 2.73 (1H, d, *J* = 12.4 Hz), 2.30-2.29 (1H, m), 2.02 (2H, d, *J* = 6.8 Hz), 1.74 (1H, s), 1.68 (2H, q, *J* = 7.6 Hz), 1.62-1.58 (1H, m), 0.91 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 202.7 (C, *C*=O), 200.2 (C, *C*=O), 146.8 (C), 143.9 (C), 132.1 (2xCH), 123.2 (2xCH), 81.1 (C), 66.8 (C), 53.9 (CH), 38.2 ($CH_2$), 37.8 ($CH_2$), 33.6 ($CH_2$), 31.7 ($CH_2$), 28.8 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 372.0882 (M + Na), calcd for $C_{17}H_{19}NO_5SNa$ 372.0882.

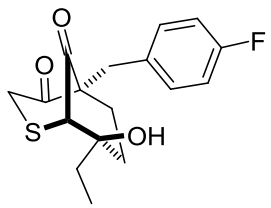
**(–)-4-((8-ethyl-8-hydroxy-4,9-dioxo-2-thiabicyclo[3.3.1]nonan-5-yl)methyl)benzonitrile**




**96gb**

**(96gb):** Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 144°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 210 nm), $t_R$ = 10.841 min (major), $t_R$ = 20.119 min (minor). **$[\alpha]_D^{25}$ = –176.5° (*c* = 0.20 g/100 mL, $CHCl_3$, 73% *ee*);** IR (Neat): $\nu_{max}$ 3417, 2966, 2360, 1734, 1699, 1488, 1236, 1012, 969 and 773 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.55 (2H, d, *J* = 8.0 Hz), 7.41 (2H, d, *J* = 8.0 Hz), 3.57 (1H, s), 3.25 (1H, d, *J* = 13.2 Hz), 2.95 (2H, dd, *J* = 12.4, 6.4 Hz), 2.71 (1H, d, *J* = 12.4 Hz), 2.31-2.26 (1H, m), 2.08-1.96 (1H, m), 1.71-1.58 (4H, m), 1.60-1.58 (1H, m), 0.92 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 202.7 (C, *C*=O), 200.2 (C, *C*=O), 141.8 (C), 132.0 (2xCH), 131.8 (2xCH), 118.7 (C), 110.7 (C), 81.1 (C), 66.8 (C), 53.9 (CH), 38.5 ($CH_2$), 37.8 ($CH_2$), 33.6 ($CH_2$), 31.7 ($CH_2$), 28.8 ($CH_2$), 6.5($CH_3$); HRMS m/z 352.0983 (M + Na), calcd for $C_{18}H_{19}NO_3SNa$ 352.0983.

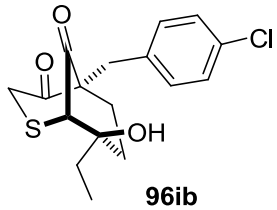
**(–)-8-ethyl-5-(4-fluorobenzyl)-8-hydroxy-2-thiabicyclo[3.3.1]nonane-4,9-dione (96hb):**




**96hb**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 112°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.311 min (major), $t_R$ = 12.216 min (minor). **$[\alpha]_D^{25}$ = –168.5° (*c* = 0.20 g/100 mL, $CHCl_3$, 64% *ee*);** IR (Neat): $\nu_{max}$ 3433, 2928, 1731, 1699, 1492, 1442, 1409, 1235, 1096 and 964 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.28-7.24 (2H, m), 6.95-6.91 (2H, m), 3.56 (1H, d, *J* = 1.6 Hz), 3.23 (1H, d, *J* = 10.8 Hz), 2.90 (1H, d, *J* = 10.0 Hz), 2.83 (1H, d, *J* = 10.8 Hz), 2.66 (1H, d, *J* = 10.0 Hz), 2.38-2.26 (1H, m), 2.06-1.96 (2H, m), 1.68 (3H, q, *J* = 6.0 Hz), 1.66-1.57 (1H, m), 0.92 (3H, t, *J* = 6.0 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 203.3 (C, *C*=O), 200.5 (C, *C*=O), 158.5 (C, d, *J* = 264.8 Hz), 132.8 (2xCH, d, *J* = 8.0 Hz), 131.7 (C), 114.9 (2xCH, d, *J* = 20.7 Hz), 81.3 (C), 67.1 (C), 54.0 (CH), 37.9 ($CH_2$), 37.7 ($CH_2$), 33.7 ($CH_2$), 31.7 ($CH_2$), 28.9 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 345.0937 (M + Na), calcd for $C_{17}H_{19}FO_3SNa$ 345.0937.

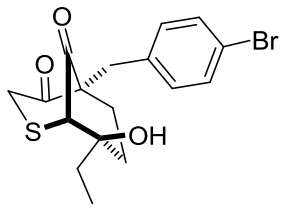
**(–)-5-(4-chlorobenzyl)-8-ethyl-8-hydroxy-2-thiabicyclo[3.3.1]nonane-4,9-dione (96ib):**




**96ib**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 138°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.762 min (major), $t_R$ = 13.178 min (minor). **$[\alpha]_D^{25}$ = –324.9° (*c* = 0.30 g/100 mL, $CHCl_3$, 69% *ee*);** IR (Neat): $\nu_{max}$ 3467, 2929, 1696, 1492, 1441, 1271, 1094, 964 and 826 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.25-7.13 (4H, m), 3.53 (1H, s), 3.18 (1H, d, *J* = 13.2 Hz), 2.83 (2H, q, *J* = 11.6 Hz), 2.66 (1H, d, *J* = 12.4 Hz), 2.30-2.28 (1H, m), 2.00 (2H, s), 1.79-1.51 (4H, m), 0.90 (3H, t, *J* = 5.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 203.3 (C, *C*=O), 200.4 (C, *C*=O), 134.5 (C), 132.5 (1xC, 2xCH), 128.2 (2xCH), 81.3 (C), 67.0 (C), 54.0 (CH), 38.0 ($CH_2$), 37.8 ($CH_2$), 33.7 ($CH_2$), 31.7 ($CH_2$), 28.8 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 361.0641 (M + Na), calcd for $C_{17}H_{19}ClO_3SNa$ 361.0641.

**(–)-5-(4-bromobenzyl)-8-ethyl-8-hydroxy-2-thiabicyclo[3.3.1]nonane-4,9-dione (96jb):**

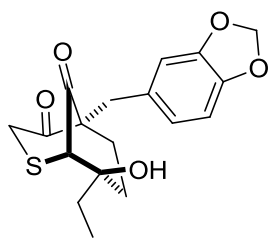



**96jb**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 158°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ =

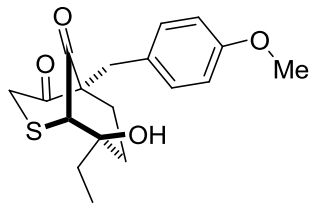
8.109 min (major), $t_R$ = 13.762 min (minor). **$[\alpha]_D^{25}$ = –497.5° (*c* = 0.20 g/100 mL, $CHCl_3$, 71% *ee*);** IR (Neat): $\nu_{max}$ 3374, 2965, 2928, 1731, 1694, 1487, 1105, 1013 and 844 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.34 (2H, d, *J* = 8.0 Hz), 7.14 (2H, d, *J* = 8.4 Hz), 3.54 (1H, s), 3.17 (1H, d, *J* = 13.6 Hz), 2.91 (1H, d, *J* = 12.4 Hz), 2.80 (1H, d, *J* = 13.2 Hz), 2.67 (1H, d, *J* = 12.4 Hz), 2.30-2.27 (1H, m), 2.00-1.97 (2H, m), 1.88 (1H, s), 1.66 (2H, q, *J* = 7.6 Hz), 1.58-1.55 (1H, m), 0.91 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 203.3 (C, *C*=O), 200.4(C, *C*=O), 135.0 (C), 132.9 (2xCH), 131.2 (2xCH), 120.8 (C), 81.2 (C), 66.9 (C), 54.0 (CH), 38.0 ($CH_2$), 37.9 ($CH_2$), 33.7 ($CH_2$), 31.7 ($CH_2$), 28.8 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 405.0137 (M + Na), calcd for $C_{17}H_{19}BrO_3SNa$ 405.0136.

**(–)-5-(benzo[d][1,3]dioxol-5-ylmethyl)-8-ethyl-8-hydroxy-2-thiabicyclo[3.3.1]nonane-4,9-dione (96kb):** Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 139°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 9.911 min (major), $t_R$ = 21.032 min (minor). **$[\alpha]_D^{25}$ = –164.6° (*c* = 0.20 g/100 mL, $CHCl_3$, 75% *ee*);** IR (Neat): $\nu_{max}$ 3459, 2928, 1731, 1698, 1487, 1441, 1243, 1037, 927 and 735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 6.82 (1H, S), 6.67-6.64 (2H, m), 5.90 (2H, s), 3.53 (1H, s), 3.17 (1H, d, *J* = 13.6 Hz), 2.90 (1H, d, *J* = 12.4 Hz), 2.76-2.71(2H, m), 2.31-2.27(1H, m), 2.04-1.91 (2H, m), 1.73-1.54 (4H, m), 0.90 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 200.3 (C, *C*=O), 200.5 (C, *C*=O), 147.2 (C), 146.2 (C), 129.6 (C), 124.3 (CH), 111.7 (CH), 107.9 (CH), 100.8 ($CH_2$), 81.4 (C), 67.3 (C), 54.1 (CH), 38.2 ($CH_2$), 38.1 ($CH_2$), 33.7 ($CH_2$), 31.8 ($CH_2$), 28.9 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 371.0929 (M + Na), calcd for $C_{18}H_{20}O_5SNa$ 371.0929.



**96kb**

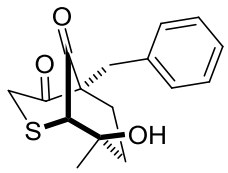
**(–)-8-ethyl-8-hydroxy-5-(4-methoxybenzyl)-2-thiabicyclo[3.3.1]nonane-4,9-dione (96lb):** Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 123°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 8.895 min (major), $t_R$ = 21.825 min (minor). **$[\alpha]_D^{25}$ = –148.8° (*c* = 0.30 g/100 mL, $CHCl_3$, 73% *ee*);** IR (Neat): $\nu_{max}$ 2930, 1731, 1698, 1512, 1244, 1178, 1033, 961 and 735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.18 (2H, d, *J* = 8.4 Hz), 6.76 (2H, d, *J* = 8.4 Hz), 3.76 (3H, s), 3.53 (1H, s), 3.20 (1H, d, *J* = 13.2 Hz), 2.86 (1H, d, *J* = 12.0 Hz), 2.77 (1H, d, *J* = 13.6 Hz), 2.64 (1H, d, *J* = 12.4 Hz), 2.32-2.30 (1H, m), 2.01-1.96 (2H, m), 1.70-1.63 (4H, m), 0.90 (3H, t, *J* =



**96lb**

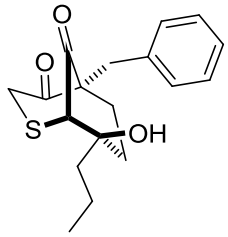
7.6 Hz); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 203.5 (C, *C*=O), 200.6 (C, *C*=O), 158.2 (C), 132.2 (2xCH), 128.0 (C), 113.4 (2xCH), 81.3 (C), 67.3 (C), 55.1 ($CH_3$), 54.1 (CH), 38.0 ($CH_2$), 37.8 ($CH_2$), 33.6 ($CH_2$), 31.8 ($CH_2$), 28.9 ($CH_2$), 6.5 ($CH_3$); HRMS m/z 357.1137 (M + Na), calcd for $C_{18}H_{22}O_4SNa$ 357.1136.

**(–)-5-benzyl-8-hydroxy-8-methyl-2-thiabicyclo[3.3.1]nonane-4,9-dione (96aa):** Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 112°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 6.300 min (major), $t_R$ = 11.197 min (minor). **$[\alpha]_D^{25}$ = –98.2° (*c* = 0.20 g/100 mL, $CHCl_3$, 46% *ee*);** IR (Neat): $\nu_{max}$ 3396, 2929, 1783, 1696, 1215, 1147 and 703 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.25-7.17 (5H, m), 3.50 (1H, s), 3.24 (1H, d, *J* = 13.2 Hz), 2.86 (2H, q, *J* = 16.0, 12.0 Hz), 2.66 (1H, d, *J* = 12.0 Hz), 2.32 (1H, d, *J* = 12.4 Hz), 2.10-1.99 (2H, m), 1.72 (1H, s), 1.53 (1H, d, *J* = 14.4 Hz), 1.35 (3H, s); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 203.4 (C, *C*=O), 200.4 (C, *C*=O), 136.0 (C), 131.2 (2xCH), 128.1 (2xCH), 126.7 (CH), 79.4 (C), 66.6 (C), 56.5 (CH), 38.5 ($CH_2$), 38.1 ($CH_2$), 33.8 ($CH_2$), 30.3 ($CH_2$), 27.4 ($CH_3$); HRMS m/z 313.0876 (M + Na), calcd for $C_{16}H_{18}O_3SNa$ 313.0874.



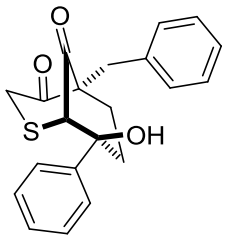
**96aa**

**(–)-5-benzyl-8-hydroxy-8-propyl-2-thiabicyclo[3.3.1]nonane-4,9-dione (96ac):** Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 102°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 = 230 nm), $t_R$ = 4.936 min (minor), $t_R$ = 9.179 min (major). **$[\alpha]_D^{25}$ = –54.1° (*c* = 1.00 g/100 mL, $CHCl_3$, 70% *ee*);** IR (Neat): $\nu_{max}$ 3417, 2959, 1732, 1697, 1443, 1237, 985 and 741 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.27-7.17 (5H, m), 3.55 (1H, s), 3.24 (1H, d, *J* = 13.2 Hz), 2.85 (2H, q, *J* = 14.4, 12.0 Hz), 2.64 (1H, d, *J* = 12.4 Hz), 2.33-2.31 (1H, m), 2.31-2.00 (3H, m), 1.65-1.60 (3H, m), 1.44-1.33 (2H, m), 0.95 (3H, t, *J* = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 203.6 (C, *C*=O), 200.4 (C, *C*=O), 136.0 (C), 131.1 (2xCH), 128.1 (2xCH), 126.7 (CH), 81.3 (C), 67.1 (C), 54.6 (CH), 41.5 ($CH_2$), 38.5 ($CH_2$), 38.0 ($CH_2$), 33.7 ($CH_2$), 29.1 ($CH_2$), 15.6 ($CH_2$), 14.2 ($CH_3$); HRMS m/z 341.1188 (M + Na), calcd for $C_{18}H_{22}O_3SNa$ z 341.1187.



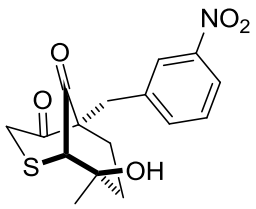
**96ac**

**(–)-5-benzyl-8-hydroxy-8-phenyl-2-thiabicyclo[3.3.1]nonane-4,9-dione (96ad):** Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 108°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 12.026 min (minor), $t_R$ = 16.004 min (major). **$[\alpha]_D^{25}$ = –126.3° (*c* = 0.20 g/100 mL, $CHCl_3$, 47% *ee*);** IR (Neat): $\nu_{max}$ 3447, 2929, 1734, 1699, 1265, 1219, 1070 and 969 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.21 (1H, s), 8.08 (1H, dd, *J* = 8.4, 1.2 Hz), 7.66 (1H, d, *J* = 7.6 Hz), 7.50-7.28 (7H, m), 3.95 (1H, d, *J* = 1.6 Hz), 3.31 (1H, d, *J* = 13.6 Hz), 3.11 (1H, d, *J* = 13.6 Hz), 2.96 (1H, d, *J* = 12.8 Hz), 2.83 (1H, s), 2.79 (1H, s), 2.48-2.43 (1H, m), 2.18 (1H, td, *J* = 12.8, 4.0 Hz), 1.91-1.87 (1H, m), 1.61 (1H, bs, -OH); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 202.5 (C, *C*=O), 200.3 (C, *C*=O), 142.6 (C), 135.9 (C), 131.2 (2xCH), 128.6 (2xCH), 128.6 (CH), 128.1 (2xCH), 126.7 (CH), 125.6 (2xCH), 81.3 (C), 66.5 (C), 56.6 (CH), 38.4 ($CH_2$), 38.2 ($CH_2$), 33.0 ($CH_2$), 28.3 ($CH_2$); HRMS m/z 375.1031 (M + Na), calcd for $C_{21}H_{20}O_3SNa$ 375.1031.



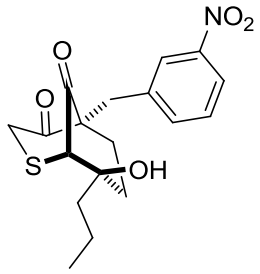
**96ad**

**(–)-8-hydroxy-8-methyl-5-(3-nitrobenzyl)-2-thiabicyclo[3.3.1]nonane-4,9-dione (96ea):** Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 152°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 9.499 min (major), $t_R$ = 20.752 min (minor). **$[\alpha]_D^{25}$ = –201.1° (*c* = 0.20 g/100 mL, $CHCl_3$, 83% *ee*);** IR (Neat): $\nu_{max}$ 3419, 2925, 1733, 1701, 1375, 1350, 1221, 1102, 1083, 809 and 739 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.17 (1H, s), 8.06 (1H, d, *J* = 7.6 Hz), 7.60 (1H, d, *J* = 7.2 Hz), 7.41 (1H, t, *J* = 8.0 Hz), 3.53 (1H, s), 3.25 (1H, d, *J* = 13.6 Hz), 3.01 (2H, dd, *J* = 13.6, 8.8 Hz), 2.79 (1H, d, *J* = 12.4 Hz), 2.27 (1H, d, *J* = 13.2 Hz), 2.13-2.02 (2H, m), 1.79 (1H, s), 1.56 (1H, d, *J* = 14.0 Hz), 1.37 (3H, s); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 202.7 (C, *C*=O), 200.1 (C, *C*=O), 148.0 (C), 138.1 (C), 137.3 (CH), 128.9 (CH), 126.1 (CH), 121.9 (CH), 79.1 (C), 66.1 (C), 56.3 (CH), 37.89 ($CH_2$), 37.84 ($CH_2$), 33.4 ($CH_2$), 30.2 ($CH_2$), 27.5 ($CH_3$); HRMS m/z 336.0905 (M + H), calcd for $C_{16}H_{17}NO_5SH$ 336.0906.



**96ea**

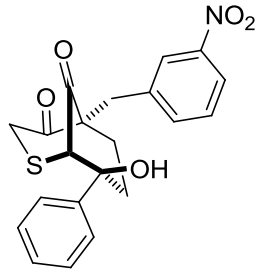
**(–)-8-hydroxy-5-(3-nitrobenzyl)-8-propyl-2-thiabicyclo[3.3.1]nonane-4,9-dione (96ec):**



**96ec**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 143°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 12.694 min (major), $t_R$ = 45.060 min (minor). **$[\alpha]_D^{25}$ = –128.1° (*c* = 0.20 g/100 mL, $CHCl_3$, 94% *ee*);** IR (Neat): $\nu_{max}$ 3419, 2925, 1706, 1530, 1350, 1286, 1234, 1105, 1042 and 773; $^1$H NMR ($CDCl_3$) δ 8.16 (1H, s), 8.06 (1H, d, *J* = 8.0 Hz), 7.60 (1H, d, *J* = 7.2 Hz), 7.41 (1H, t, *J* = 8.0 Hz), 3.57 (1H, s), 3.25 (1H, d, *J* = 13.6 Hz), 3.00 (2H, dd, *J* = 13.6, 10.0 Hz), 2.77 (1H, d, *J* = 12.4 Hz), 2.28-2.26 (1H, m), 2.07-2.00 (2H, m), 1.81(1H, s), 1.72 (1H, s), 1.60 (2H, t, *J* = 8.4 Hz), 1.43-1.25 (2H, m), 0.94 (3H, t, *J* = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 202.9 (C, *C*=O), 200.2 (C, *C*=O), 148.0 (C), 138.1 (C), 137.3 (CH), 128.9 (CH), 126.1 (CH), 121.9 (CH), 81.0 (C), 66.5 (C), 54.3 (CH), 41.4 ($CH_2$), 37.9 ($CH_2$), 37.8 ($CH_2$), 33.3 ($CH_2$), 28.9 ($CH_2$), 15.6 ($CH_2$), 14.3 ($CH_3$); HRMS m/z 386.1038 (M + Na), calcd for $C_{18}H_{21}NO_5SNa$ 386.1038.

**(–)-8-hydroxy-5-(3-nitrobenzyl)-8-phenyl-2-thiabicyclo[3.3.1]nonane-4,9-dione (96ed):**

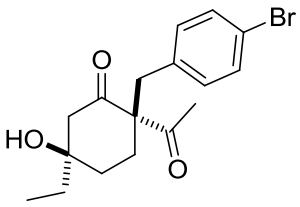


**96ed**

Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 125°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 16.559 min (major), $t_R$ = 32.328 min (minor). **$[\alpha]_D^{25}$ = –308.3° (*c* = 0.20 g/100 mL, $CHCl_3$, 79% *ee*);** IR (Neat): $\nu_{max}$ 3420, 2928, 1733, 1698, 1591, 1488, 1439, 1351, 1012, 839 and 735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 8.13 (1H, s), 8.01 (1H, d, *J* = 6.0 Hz), 7.59 (1H, d, *J* = 6.0 Hz), 7.41-7.37 (2H, m), 7.35-7.26 (3H, m), 7.19 (1H, s), 3.88 (1H, s), 3.24 (1H, d, *J* = 10.8 Hz), 3.03 (1H, d, *J* = 10.8 Hz), 2.88 (1H, d, *J* = 10.0 Hz), 2.76-2.71 (2H, m), 2.38 (1H, d, *J* = 9.2 Hz), 2.11 (1H, dt, *J* = 10.4, 2.8 Hz), 1.81 (1H, d, *J* = 11.6 Hz), 1.52 (1H, s); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 202.1 (C, *C*=O), 200.0 (C, *C*=O), 148.0 (C), 142.3 (C), 138.1 (C), 137.4 (CH), 129.0 (CH), 128.83 (CH), 128.79 (2xCH), 126.1 (CH) , 125.6 (2xCH), 122.0 (CH), 81.2 (C), 66.0 (C), 56.5 (CH), 38.1 ($CH_2$), 37.9 ($CH_2$), 32.7 ($CH_2$), 28.3 ($CH_2$); HRMS m/z 420.0881 (M + Na), calcd for $C_{21}H_{19}NO_5SNa$ 420.0882.

**Procedure K: Synthesis of Cyclohexanones by desulfurization of annulated compound 96jb:** To a solution of compound **96jb** (0.3 mmol) in EtOH (10 mL) at room temperature was added activated raney nickel (0.6 g). The mixture was stirred at room temperature for 12 h and then passed through a Celite pad. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (Hexane and EtOAc) to give compound **102jb** as a white solid in in 93% yield.

**(–)-2-acetyl-2-(4-bromobenzyl)-5-ethyl-5-hydroxycyclohexanone (102jb):** Prepared by following the procedure **K** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 102°C. **$[\alpha]_D^{25}$ = –37.5° (*c* = 0.10 g/100 mL, $CHCl_3$, 71% *ee*, >99 *dr*);** IR (Neat): $\nu_{max}$ 2932, 1770, 1710, 1397, 1370 and 1112 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 7.27-7.20 (2H, m), 7.05 (2H, m), 3.29 (1H, d, *J* = 16.0 Hz), 3.03 (1H, d, *J* = 16.0 Hz), 2.49 (1H, d, *J* = 12.0 Hz), 2.30 (2H, d, *J* = 12.0 Hz), 2.09 (3H, s), 2.08 (1H, s), 1.71-1.68 (2H, m), 1.53 (2H, q, *J* = 8.0 Hz), 0.88 (3H, t, *J* = 8.0 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 207.9 (C, *C*=O), 205.5(C, *C*=O), 136.1 (C), 130.1 (2xCH), 128.2 (2xCH), 126.8 (C), 76.9 (C), 68.1 (C), 52.4 ($CH_2$), 39.8 ($CH_2$), 36.0 ($CH_2$), 32.7 ($CH_2$), 28.6 ($CH_2$), 26.8 ($CH_3$), 7.5 ($CH_3$); LCMS: m/z 353.30 (M + H), calcd for $C_{17}H_{21}BrO_3$ 352.0674; Anal. calcd for $C_{17}H_{21}BrO_3$ (352.0674): C, 57.80; H, 5.99; Found: C, 57.72; H, 5.91.

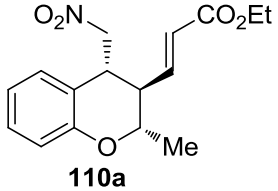


**102jb**

**Procedure L: General procedure for amine-catalyzed asymmetric triple domino reaction of acetaldehyde 104 with 2-(2-nitrovinyl)phenols 108a-k followed by one-pot Wittig reaction:**

(*E*)-2-(2-Nitrovinyl)phenol **108a-k** (0.3 mmol) was added to a solution of (*R*)-diphenylprolinol trimethylsilyl ether **4n** (19.5 mg, 0.06 mmol) in $CHCl_3$ (1.0 mL), taken in an ordinary glass vial equipped with a magnetic stirring bar and it was cooled to –40 °C. Acetaldehyde **104** (49.8 μL, 0.9 mmol, 3 equiv.) dissolved in $CHCl_3$ (1.0 mL) in another glass vial, was cooled to –40 °C and this cooled solution was added to the reaction mixture at the same temperature, over 15 minutes time. Then the reaction mixture was warmed to –5 °C and was stirred for 3-4 h. After addition of (carbethoxymethylene)triphenylphosphorane (2 equiv.) to the reaction mixture, it was stirred for 2 h at room temperature. Then the crude mixture was loaded directly onto the silica gel column and eluted with EtOAc/*n*-hexane and concentrated under reduced pressure to afford chiral products **110a-k**.

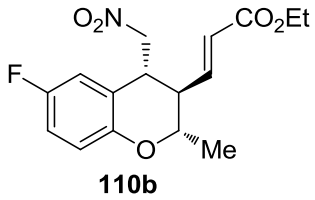
**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110a):** Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 57 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase



**110a**

HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 16.78 min (minor), $t_R$ = 26.02 min (major). **$[\alpha]_D^{25}$ = –105.7° (*c* = 0.15 g/100 mL, $CHCl_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 2981, 1721, 1650, 1556, 1485, 1452, 1381, 1321, 1041 and 761 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.19 (1H, t, *J* = 7.6 Hz), 7.13 (1H, d, *J* = 7.6 Hz), 6.95 (1H, t, *J* = 7.6 Hz), 6.88 (1H, d, *J* = 8.4 Hz), 6.71 (1H, dd, *J* = 15.6, 10.4 Hz, olefinic-H), 6.09 (1H, d, *J* = 15.6 Hz, olefinic-H), 4.73 (2H, dABq, *J* = 13.6, 5.2 Hz, C*H*$_2$NO$_2$), 4.24 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 4.05-3.97 (1H, m, OC*H*), 3.61 (1H, quin, *J* = 5.2 Hz), 2.66 (1H, q, *J* = 10.0 Hz), 1.38 (3H, d, *J* = 6.0 Hz, OCHC*H*$_3$), 1.33 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.4 (C, O–*C*=O), 154.9 (C), 144.3 (CH), 128.8 (CH), 126.8 (CH), 126.1 (CH), 121.5 (CH), 119.6 (C), 117.6 (CH), 77.1 (CH$_2$, *C*H$_2$NO$_2$), 73.9 (CH, O*C*H), 60.8 (CH$_2$, O*C*H$_2$CH$_3$), 46.7 (CH), 38.4 (CH), 20.0 (CH$_3$), 14.1 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 328.1155 (M + Na), calcd for $C_{16}H_{19}NO_5Na$ 328.1161.

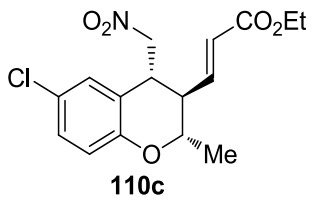
**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-6-fluoro-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110b):**



**110b**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 93°C. 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 = 220 nm), $t_R$ = 10.39 min (minor), $t_R$ = 12.87 min (major). **$[\alpha]_D^{25}$ = –51.8° (*c* = 0.4 g/100 mL, $CHCl_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 2986, 1721, 1655, 1551, 1496, 1425, 1375, 1266, 1216, 986 and 827 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 6.91-6.81 (3H, m, Ar-*H*), 6.68 (1H, dd, *J* = 15.6, 10.4 Hz, olefinic-H), 6.10 (1H, d, *J* = 15.6 Hz, olefinic-H), 4.65 (2H, dABq, *J* = 13.2, 4.8 Hz, C*H*$_2$NO$_2$), 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.00-3.93 (1H, m, OC*H*), 3.55 (1H, quin, *J* = 5.2 Hz), 2.68 (1H, q, *J* = 10.4 Hz), 1.36 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.32 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.3 (C, O–*C*=O), 157.2 (C, d, *J* = 239.0 Hz, *C*-F), 151.1 (C), 143.9 (CH), 126.4 (CH), 120.7 (C, d, *J* = 7.0 Hz), 118.7 (CH, d, *J* = 8.0 Hz), 115.8 (CH, d, *J* = 23.0 Hz), 113.1 (CH, d, *J* = 24.0 Hz), 76.7 (CH$_2$, *C*H$_2$NO$_2$), 74.1 (CH, O*C*H), 60.9 (CH$_2$, O*C*H$_2$CH$_3$), 46.3 (CH), 38.5 (CH), 20.1 (CH$_3$), 14.2 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 324.1245 (M + H), calcd for $C_{16}H_{18}FNO_5H$ 324.1247.

**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-6-chloro-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110c):**

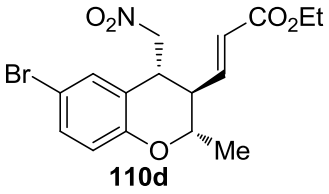


**110c**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 72°C. 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 = 220 nm), $t_R$ = 10.28 min (minor), $t_R$ = 11.80 min (major). **$[\alpha]_D^{25}$ = –85.1° (*c* = 0.2 g/100 mL, $CHCl_3$, >99% *ee*);**

IR (Neat): $\nu_{max}$ 2980, 1715, 1655, 1561, 1490, 1370, 1283, 1205 and 1036 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.15-7.12 (2H, m), 6.82 (1H, d, *J* = 8.4 Hz), 6.67 (1H, dd, *J* = 15.6, 10.0 Hz, olefinic-H), 6.10 (1H, d, *J* = 16.0 Hz, olefinic-H), 4.67 (2H, dABq, *J* = 13.6, 4.8 Hz, C*H*$_2$NO$_2$), 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.00-3.97 (1H, m, OC*H*), 3.55 (1H, quin, *J* = 6.4 Hz), 2.68 (1H, q, *J* = 10.0 Hz), 1.37 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$), 1.33 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.3 (C, O–*C*=O), 153.6 (C), 143.8 (CH), 129.0 (CH), 126.6 (CH), 126.5 (CH), 126.3 (C), 121.1 (C), 119.0 (CH), 76.5 (CH$_2$, *C*H$_2$NO$_2$), 74.1 (CH, O*C*H), 60.9 (CH$_2$, O*C*H$_2$CH$_3$), 46.2 (CH), 38.3 (CH), 20.1 (CH$_3$), 14.2 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 340.0951 (M + H), calcd for $C_{16}H_{18}ClNO_5H$ 340.0952.

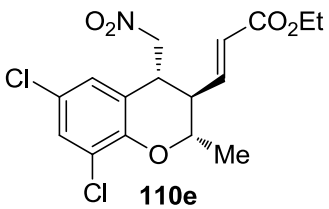
**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-6-bromo-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110d):**



**110d**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 98°C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel ChiralPak AD-H column (hexane/ethanol = 80:20, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 15.11 min (minor), $t_R$ = 34.21 min (major). **$[\alpha]_D^{25}$ = –122.8° (*c* = 0.15 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): $\nu_{max}$ 2975, 1721, 1655, 1556, 1479, 1370, 1276, 1178, 992 and 822 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.29 (1H, br s), 7.26 (1H, br s), 6.76 (1H, d, *J* = 8.4 Hz), 6.67 (1H, dd, *J* = 15.6, 10.4 Hz, olefinic-H), 6.10 (1H, d, *J* = 16.0 Hz, olefinic-H), 4.67 (2H, dABq, *J* = 13.6, 5.2 Hz, C*H*$_2$NO$_2$), 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.00-3.96 (1H, m, OC*H*), 3.54 (1H, quin, *J* = 8.0 Hz), 2.66 (1H, q, *J* = 10.4 Hz), 1.39 (3H, d, *J* = 7.6 Hz, CHC*H*$_3$), 1.32 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.3 (C, O–*C*=O), 154.1 (C), 143.7 (CH), 131.8 (CH), 129.5 (CH), 126.5 (CH), 121.6 (C), 119.4 (CH), 113.5 (C), 76.5 (CH$_2$, *C*H$_2$NO$_2$), 74.1 (CH, O*C*H), 60.9 (CH$_2$, O*C*H$_2$CH$_3$), 46.2 (CH), 38.2 (CH), 20.1 (CH$_3$), 14.2 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 384.0445 (M + H), calcd for $C_{16}H_{18}BrNO_5H$ 384.0447.

**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-6,8-dichloro-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110e):**

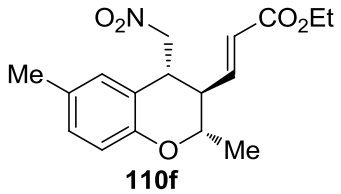


**110e**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 90 °C. 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 = 200 nm), $t_R$ = 13.58 min (major), $t_R$ = 26.37 min (minor). **$[\alpha]_D^{25}$ = –90.1° (*c* = 0.2 g/100 mL, $CHCl_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 2975, 1715, 1655, 1551, 1463, 1370, 1205 and 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.28 (1H, br s), 7.04 (1H, br s), 6.66 (1H, dd, *J* = 15.6, 10.0 Hz, olefinic-H), 6.12 (1H, d, *J* = 15.6 Hz, olefinic-H), 4.67 (2H, dABq, *J* = 13.6, 4.8 Hz, C*H*$_2$NO$_2$), 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$),

4.06-4.02 (1H, m, OC*H*), 3.54 (1H, quin, *J* = 5.2 Hz), 2.73 (1H, q, *J* = 10.0 Hz), 1.44 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.32 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); $^{13}$C NMR (CDCl$_3$, DEPT-135) δ 165.2 (C, O–*C*=O), 149.7 (C), 143.2 (CH), 129.2 (CH), 126.9 (CH), 125.9 (C), 125.1 (CH), 123.4 (C), 122.4 (C), 76.2 (CH$_2$, *C*H$_2$NO$_2$), 75.0 (CH, O*C*H), 61.0 (CH$_2$, O*C*H$_2$CH$_3$), 46.0 (CH), 38.5 (CH), 20.0 (CH$_3$), 14.1 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 374.0561 (M + H), calcd for $C_{16}H_{17}Cl_2NO_5H$ 374.0562.

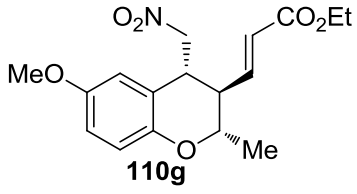
**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-2,6-dimethyl-4-(nitromethyl)chroman-3-yl)acrylate (110f):** Prepared



**110f**

by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 91 °C. 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 = 220 nm), $t_R$ = 7.29 min (minor), $t_R$ = 8.86 min (major). **$[\alpha]_D^{25}$ = –85.9° (*c* = 0.4 g/100 mL, CHCl$_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 2986, 1715, 1649, 1556,1496, 1375, 1255 and 816 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 6.98 (1H, d, *J* = 8.4 Hz), 6.91 (1H, br s), 6.77 (1H, d, *J* = 8.4 Hz), 6.70 (1H, dd, *J* = 15.6, 10.0 Hz, olefinic-H), 6.08 (1H, d, *J* = 15.6 Hz, olefinic-H), 4.65 (2H, dABq, *J* = 13.2, 5.2 Hz, C*H*$_2$NO$_2$), 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.99-3.92 (1H, m, OC*H*), 3.57 (1H, quin, *J* = 5.4 Hz), 2.65 (1H, q, *J* = 10.0 Hz), 2.27 (3H, s, Ar-C*H*$_3$), 1.36 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.32 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$); $^{13}$C NMR (CDCl$_3$, DEPT-135) δ 165.5 (C, O–*C*=O), 152.8 (C), 144.5 (CH), 130.8 (CH), 129.5 (CH), 127.0 (CH), 125.9 (C), 119.3 (C), 117.3 (CH), 77.3 (CH$_2$, *C*H$_2$NO$_2$), 73.8 (CH, O*C*H), 60.8 (CH$_2$, O*C*H$_2$CH$_3$), 46.9 (CH), 38.4 (CH), 20.7 (CH$_3$), 20.2 (CH$_3$), 14.2 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 320.1494 (M + H), calcd for $C_{17}H_{21}NO_5H$ 320.1498.

**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-6-methoxy-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110g):**

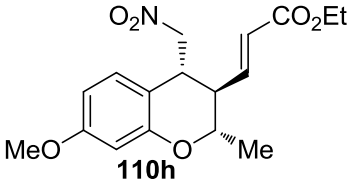


**110g**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 101 °C. 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 = 224 nm), $t_R$ = 10.66 min (minor), $t_R$ = 13.60 min (major). **$[\alpha]_D^{25}$ = –44.1° (*c* = 0.4 g/100 mL, CHCl$_3$, >99% *ee*)**; IR (Neat): $\nu_{max}$ 2975, 1715, 1649, 1545, 1496, 1370, 1227, 1162, 1036 and 997 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 6.91-6.71 (2H, m), 6.68 (1H, dd, *J* = 15.6, 10.0 Hz, olefinic-H), 6.64 (1H, br s), 6.07 (1H, d, *J* = 15.6, olefinic-H), 4.64 (2H, dABq, *J* = 13.2, 5.2 Hz, C*H*$_2$NO$_2$), 4.22 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.95-3.88 (1H, m, OC*H*), 3.73 (3H, s, OC*H*$_3$), 3.55 (1H, quin, *J* = 5.2 Hz), 2.63 (1H, q, *J* = 10.0 Hz), 1.33 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$), 1.31 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); $^{13}$C NMR (CDCl$_3$, DEPT-135) δ 165.4 (C, O–*C*=O), 154.0 (C), 148.9 (C), 144.4 (CH), 125.9

(CH), 120.2 (C), 118.2 (CH), 114.7 (CH), 111.6 (CH), 77.2 ($CH_2$, $CH_2NO_2$), 73.8 (CH, OCH), 60.8 ($CH_2$, $OCH_2CH_3$), 55.6 ($CH_3$, $OCH_3$), 46.9 (CH), 38.6 (CH), 20.1 ($CH_3$), 14.1 ($CH_3$, $OCH_2CH_3$); HRMS m/z 336.1444 (M + H), calcd for $C_{17}H_{21}NO_6H$ 336.1447.

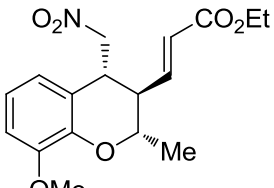
**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-7-methoxy-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110h):**



**110h**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 105 °C. 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 = 220 nm), $t_R$ = 9.34 min (minor), $t_R$ = 11.44 min (major). **$[\alpha]_D^{25}$ = –57.1° (*c* = 0.3 g/100 mL, $CHCl_3$, >99% *ee*)**; IR (Neat): $\nu_{max}$ 2980, 1726, 1655, 1616, 1556, 1512, 1375, 1331, 1200, 1161, 1036 and 992 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.02 (1H, d, *J* = 8.4 Hz), 6.70 (1H, dd, *J* = 15.6, 10.4 Hz, olefinic-H), 6.53 (1H, dd, *J* = 8.8, 2.4 Hz), 6.43 (1H, d, *J* = 2.4 Hz), 6.09 (1H, d, *J* = 15.6 Hz, olefinic-H), 4.64 (2H, dABq, *J* = 13.2, 4.8 Hz, $CH_2NO_2$), 4.23 (2H, q, *J* = 7.2 Hz, $OCH_2CH_3$), 4.03-3.96 (1H, m, OCH), 3.76 (3H, s, $OCH_3$), 3.54 (1H, quin, *J* = 5.2 Hz), 2.64 (1H, q, *J* = 10.0 Hz), 1.37 (3H, d, *J* = 6.0 Hz, $CHCH_3$), 1.32 (3H, t, *J* = 7.2 Hz, $OCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.5 (C, $O^-C$=O), 160.0 (C), 155.9 (C), 144.4 (CH), 127.5 (CH), 126.1 (CH), 111.6 (C), 108.7 (CH), 102.1 (CH), 77.2 ($CH_2$, $CH_2NO_2$), 74.0 (CH, OCH), 60.8 ($CH_2$, $OCH_2CH_3$), 55.3 ($CH_3$, $OCH_3$), 46.7 (CH), 38.1 (CH), 20.2 ($CH_3$), 14.2 ($CH_3$, $OCH_2CH_3$); HRMS m/z 336.1447 (M + H), calcd for $C_{17}H_{21}NO_6H$ 336.1447.

**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-8-methoxy-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110i):**

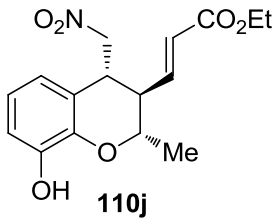


**110i**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 87 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.6 mL/min, λ = 220 nm), $t_R$ = 39.37 min (minor), $t_R$ = 42.82 min (major). **$[\alpha]_D^{25}$ = –35.5° (*c* = 0.20 g/100 mL, $CHCl_3$, >99% *ee*)**; IR (Neat): $\nu_{max}$ 2975, 1715, 1649, 1589, 1545, 1479, 1331, 1260, 1173, and 986 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 6.90 (1H, t, *J* = 8.0 Hz), 6.80 (1H, d, *J* = 7.6 Hz), 6.73 (1H, d, *J* = 6.8 Hz), 6.69 (1H, dd, *J* = 15.6, 10.0 Hz, olefinic-H), 6.09 (1H, d, *J* = 15.6 Hz, olefinic-H), 4.65 (2H, dABq, *J* = 13.6, 5.2 Hz, $CH_2NO_2$), 4.23 (2H, q, *J* = 7.2 Hz, $OCH_2CH_3$), 4.06-3.99 (1H, m, OCH), 3.86 (3H, s, $OCH_3$), 3.62 (1H, quin, *J* = 4.8 Hz), 2.69 (1H, q, *J* = 10.0 Hz), 1.45 (3H, d, *J* = 6.4 Hz, $CHCH_3$), 1.32 (3H, t, *J* = 7.2 Hz, $OCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.4 (C, $O^-C$=O), 148.7 (C), 144.6 (C), 144.3 (CH), 126.1 (CH), 121.1 (CH), 120.5 (C), 118.4 (CH), 110.5 (CH), 77.2 ($CH_2$, $CH_2NO_2$), 74.2

(CH, O*C*H), 60.8 ($CH_2$, O*C*$H_2CH_3$), 55.9 ($CH_3$, O*C*$H_3$), 46.6 (CH), 38.4 (CH), 20.2 ($CH_3$), 14.2 ($CH_3$, $OCH_2$*C*$H_3$); HRMS m/z 336.1445 (M + H), calcd for $C_{17}H_{21}NO_6H$ 336.1447.

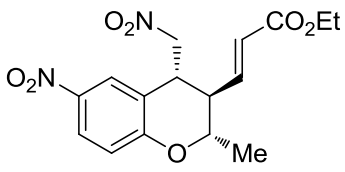
**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-8-hydroxy-2-methyl-4-(nitromethyl)chroman-3-yl)acrylate (110j):**



**110j**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 60 °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), $t_R$ = 39.77 min (minor), $t_R$ = 77.06 min (major). **$[\alpha]_D^{25}$ = –26.0° (*c* = 0.10 g/100 mL, $CHCl_3$, >99% *ee*)**; IR (Neat): $\nu_{max}$ 3420 (O-H), 2975, 1715, 1649, 1589, 1545, 1474, 1375, 1211 and 1041 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 6.87-6.84 (2H, m), 6.71-6.65 (2H, m), 6.11 (1H, d, *J* = 15.6 Hz, olefinic-H), 5.62 (1H, br s, Ar-O*H*), 4.67 (2H, dABq, *J* = 13.2, 4.8 Hz, C*H*$_2NO_2$), 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2CH_3$), 4.09-4.02 (1H, m, OC*H*), 3.58 (1H, quin, *J* = 5.2Hz), 2.73 (1H, q, *J* = 10.0 Hz), 1.42 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.33 (3H, t, *J* = 7.2 Hz, $OCH_2$C*H*$_3$); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 165.4 (C, O–*C*=O), 145.0 (C), 143.9 (CH), 142.0 (C), 126.4 (CH), 121.7 (CH), 119.9 (C), 117.5 (CH), 113.9 (CH), 76.7 ($CH_2$, *C*$H_2NO_2$), 74.7 (CH, O*C*H), 60.9 ($CH_2$, O*C*$H_2CH_3$), 46.6 (CH), 38.2 (CH), 20.1 ($CH_3$), 14.2 ($CH_3$, $OCH_2$*C*$H_3$); HRMS m/z 322.1287 (M + H), calcd for $C_{16}H_{19}NO_6H$ 322.1291.

**(*E*)-Ethyl 3-((2*S*,3*R*,4*R*)-2-methyl-6-nitro-4-(nitromethyl)chroman-3-yl)acrylate (110k):**



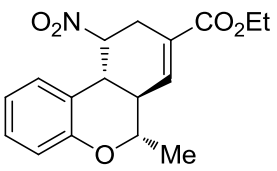
**110k**

Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 85 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5U Amylose-2 column (hexane/2-propanol = 70:30, flow rate 1.0 mL/min, λ = 200 nm), $t_R$ = 37.17 min (minor), $t_R$ = 45.70 min (major). **$[\alpha]_D^{25}$ = –214.2° (*c* = 0.25 g/100 mL, $CHCl_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 2980, 1715, 1655, 1556, 1518, 1342, 1266, 1030 and 756 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 8.17 (1H, br s), 8.10 (1H, dd, *J* = 8.8, 2.4 Hz), 6.97 (1H, d, *J* = 9.2 Hz), 6.67 (1H, dd, *J* = 15.6, 10.4 Hz, olefinic-H), 6.17 (1H, d, *J* = 15.6 Hz, olefinic-H), 4.91 (1H, dd, *J* = 13.6, 4.4 Hz), 4.73 (1H, dd, *J* = 13.6, 4.4 Hz), 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2CH_3$), 4.16-4.12 (1H, m, OC*H*), 3.57-3.54 (1H, m), 2.78 (1H, q, *J* = 10.0 Hz), 1.43 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.34 (3H, t, *J* = 7.2 Hz, $OCH_2$C*H*$_3$); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 165.2 (C, O–*C*=O), 160.2 (C), 142.7 (CH), 141.7 (C), 127.3 (CH), 124.8 (CH), 123.3 (CH), 119.8 (C), 118.3 (CH), 75.3 ($CH_2$, *C*$H_2NO_2$), 75.0 (CH, O*C*H), 61.0 ($CH_2$, O*C*$H_2CH_3$), 45.2 (CH), 38.4 (CH), 20.0 ($CH_3$), 14.2 ($CH_3$, $OCH_2$*C*$H_3$); HRMS m/z 351.1191 (M + H), calcd for $C_{16}H_{18}N_2O_7H$ 351.1192.

**Procedure M: General procedure for amine-catalyzed asymmetric triple domino reaction of acetaldehyde 104 with 2-(2-nitrovinyl)phenols 108a-j followed by one-pot Wittig-Horner reaction:**

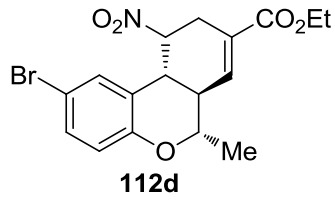
(*E*)-2-(2-Nitrovinyl)phenol **108a-j** (0.3 mmol) was added to a solution of (*R*)-diphenylprolinol trimethylsilyl ether **4n** (19.5 mg, 0.06 mmol) in $CHCl_3$ (1.0 mL), taken in an ordinary glass vial equipped with a magnetic stirring bar and it was cooled to –40 °C. Acetaldehyde **104** (49.8 μL, 0.9 mmol, 3 equiv.) dissolved in $CHCl_3$ (1.0 mL) in another glass vial, was cooled to –40 °C and this cooled solution was added to the reaction mixture at same temperature over 15 minutes time. Then the reaction mixture was warmed to –5 °C and was stirred for 3-4 h before removing excess of acetaldehyde and solvent under the reduced pressure. Ethyl 2-(diethoxyphosphoryl)acrylate **111** (85.0 mg, 0.36 mmol) and $Cs_2CO_3$ (195.5 mg, 0.6 mmol) were added to a solution of the crude material in $CH_2Cl_2$ (2.0 mL) at 0 °C under argon atmosphere. The resulting reaction mixture was stirred for 6 h at 0 °C before addition of EtOH (2 mL) at same temperature. The resulting mixture was stirred for additional 2 h at room temperature before being quenched with saturated aqueous NH4Cl solution. The aqueous layer was extracted three times with $CHCl_3$ dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The crude was filtered through silica gel column by using EtOAc/*n*-hexane as eluents and concentrated under reduced pressure to afford chiral products **112a-j**.

**(6*S*,6a*R*,10*S*,10a*R*)-Ethyl 6-methyl-10-nitro-6a,9,10,10a-tetrahydro-6*H*-benzo[c]chromene-8-carboxylate (112a):** Prepared by following the procedure **M** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 123 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 290 nm), $t_R$ = 21.34 min (major), $t_R$ = 22.97 min (minor). **$[\alpha]_D^{25}$ = –282.6° (*c* = 0.25 g/100 mL, $CHCl_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 2975, 1715, 1551, 1496, 1452, 1260, 1238, 1052 and 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.32 (1H, d, *J* = 7.6 Hz), 7.18 (1H, t, *J* = 7.6 Hz), 7.09 (1H, s, olefinic-*H*), 6.93 (1H, t, *J* = 7.2 Hz), 6.85 (1H, d, *J* = 8.0 Hz), 5.66 (1H, dd, *J* = 6.0, 2.8 Hz, C*H*$NO_2$), 4.27 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 4.12 (1H, sextet, *J* = 3.6 Hz, OC*H*), 3.26-3.19 (2H, m), 2.96-2.88 (1H, m), 2.78-2.74 (1H, m), 1.62 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.34 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.7 (C, O–*C*=O), 154.5 (C), 136.2 (CH), 128.8 (CH), 128.6 (C), 125.1 (CH), 120.4 (CH), 118.9 (C), 117.1 (CH), 78.8 (CH, *C*H$NO_2$), 75.3 (CH, O*C*H), 61.2 ($CH_2$, O*C*H$_2$CH$_3$), 39.4 (CH), 38.1 (CH), 29.1 ($CH_2$), 19.1 ($CH_3$), 14.2 ($CH_3$, OCH$_2$*C*H$_3$); HRMS m/z 340.1161 (M + Na), calcd for $C_{17}H_{19}NO_5Na$ 340.1161.



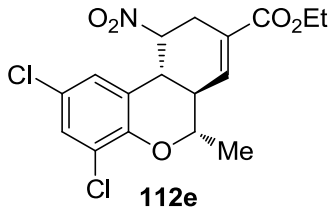
**112a**

**(6*S*,6a*R*,10*S*,10a*R*)-Ethyl 2-bromo-6-methyl-10-nitro-6a,9,10,10a-tetrahydro-6*H*-benzo[c]chromene-8-carboxylate (112d):** Prepared by following the procedure **M** and purified by column chromatography using EtOAc/hexane and isolated as a 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 = 290 nm), $t_R$ = 30.36 min (minor), $t_R$ = 36.80 min (major). **$[\alpha]_D^{25}$ = –311.6° (*c* = 0.50 g/100 mL, $CHCl_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 2980, 1710, 1551, 1474, 1266, 1233, 1057 and 817 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.43 (1H, br s), 7.28-7.25 (1H, m), 7.05 (1H, br s, olefinic-*H*), 6.73 (1H, d, *J* = 8.8 Hz), 5.57 (1H, dd, *J* = 5.6, 2.4 Hz, C*H*$NO_2$), 4.27 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 4.09 (1H, sextet, *J* = 3.6 Hz, OC*H*), 3.28 (1H, br d, *J* = 19.6 Hz), 3.17 (1H, br d, *J* = 12.0 Hz), 2.95-2.87 (1H, m), 2.74-2.68 (1H, m), 1.61 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.34 (3H, t, *J* = 7.2 Hz, $OCH_2C$*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.6 (C, O–*C*=O), 153.6 (C), 135.7 (CH), 131.7 (CH), 128.8 (C), 128.1 (CH), 121.1 (C), 118.9 (CH), 112.6 (C), 78.8 (CH, *C*H$NO_2$), 75.5 (CH, O*C*H), 61.2 ($CH_2$, O*C*H$_2$$CH_3$), 39.3 (CH), 37.8 (CH), 29.1 ($CH_2$), 19.0 ($CH_3$), 14.2 ($CH_3$, $OCH_2$*C*H$_3$); HRMS m/z 418.0263 (M + Na), calcd for $C_{17}H_{18}BrNO_5Na$ 418.0266.



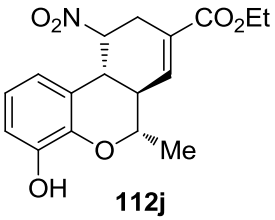
**112d**

**(6*S*,6a*R*,10*S*,10a*R*)-Ethyl 2,4-dichloro-6-methyl-10-nitro-6a,9,10,10a-tetrahydro-6*H*-benzo[c]chromene-8-carboxylate (112e):** Prepared by following the procedure **M** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 125 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5U Amylose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 290 nm), $t_R$ = 17.24 min (major), $t_R$ = 26.50 min (minor). **$[\alpha]_D^{25}$ = –101.8° (*c* = 0.25 g/100 mL, $CHCl_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 2981, 1704, 1649, 1551, 1463, 1260, 1184, 1058 and 871 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.27 (1H, br s), 7.21 (1H, br s), 7.05 (1H, br s, olefinic-*H*), 5.56 (1H, dd, *J* = 3.6, 2.0 Hz, C*H*$NO_2$), 4.28 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 4.18 (1H, sextet, *J* = 4.0 Hz, OC*H*), 3.31 (1H, d, *J* = 19.6 Hz), 3.18 (1H, d, *J* = 10.4 Hz), 2.97-2.89 (1H, m), 2.76 (1H, br t, *J* = 11.6 Hz), 1.69 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.35 (3H, t, *J* = 6.8 Hz, $OCH_2C$*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 165.5 (C, O–*C*=O), 149.2 (C), 135.2 (CH), 129.2 (CH), 128.9 (C), 125.0 (C), 123.7 (CH), 122.9 (C), 121.9 (C), 78.4 (CH, *C*H$NO_2$), 76.5 (CH, O*C*H), 61.3 ($CH_2$, O*C*H$_2$$CH_3$), 39.4 (CH), 37.7 (CH), 29.2 ($CH_2$), 18.9 ($CH_3$), 14.2 ($CH_3$, $OCH_2$*C*H$_3$); HRMS m/z 408.0382 (M + Na), calcd for $C_{17}H_{17}Cl_2NO_5Na$ 408.0381.



**112e**

**(6*S*,6a*R*,10*S*,10a*R*)-Ethyl 4-hydroxy-6-methyl-10-nitro-6a,9,10,10a-tetrahydro-6*H*-benzo[c]chromene-8-carboxylate (112j):** Prepared by following the procedure **M** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp: 112 °C. 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 = 220 nm), $t_R$ = 29.53 min (major), $t_R$ = 43.96 min (minor). **$[\alpha]_D^{25}$ = –260.5° (*c* = 0.10 g/100 mL, $CHCl_3$, >99% *ee*);** IR (Neat): $\nu_{max}$ 3414 (O-H), 2981, 2921, 1721, 1688, 1562, 1496, 1458, 1375, 1238 and 752 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.10 (1H, s), 6.87 (3H, s), 5.64 (1H, dd, *J* = 6.0, 2.8 Hz, C*H*$NO_2$), 5.50 (1H, s, O-*H*), 4.32-4.26 (2H, m, OC*H*$_2$$CH_3$), 4.22-4.18 (1H, m, OC*H*), 3.35-3.20 (2H, m), 3.00-2.91 (1H, m), 2.90-2.84 (1H, m), 1.69 (3H, d, *J* = 6.0 Hz, CHC*H*$_3$), 1.34 (3H, t, *J* = 7.2 Hz, $OCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) 165.7 (C, O–*C*=O), 144.8 (C), 141.5 (C), 135.7 (CH), 128.8 (C), 120.8 (CH), 119.3 (C), 116.0 (CH), 114.0 (CH), 78.7 (CH, *C*H$NO_2$), 76.1 (CH, O*C*H), 61.2 ($CH_2$, O*C*H$_2$$CH_3$), 39.2 (CH), 38.3 (CH), 29.2 ($CH_2$), 19.1 ($CH_3$), 14.2 ($CH_3$, $OCH_2CH_3$); HRMS m/z 356.1107 (M + Na), calcd for $C_{17}H_{19}NO_6Na$ 356.1110.

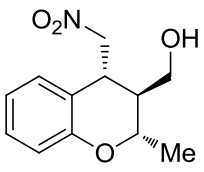


**112j**

**Procedure N: General procedure for amine-catalyzed asymmetric triple domino reaction of acetaldehyde 104 with 2-(2-nitrovinyl)phenol 108a followed by one-pot reduction reaction:**

(*E*)-2-(2-Nitrovinyl)phenol **108a** (49.5 mg, 0.3 mmol) was added to a solution of (*R*)-diphenylprolinol trimethylsilyl ether **4n** (19.5 mg, 0.06 mmol) in $CHCl_3$ (1.0 mL), taken in an ordinary glass vial equipped with a magnetic stirring bar and it was cooled to –40 °C. Acetaldehyde **104** (49.8 μL, 0.9 mmol, 3 equiv.), dissolved in $CHCl_3$ (1 mL) in another vial, was cooled to –40 °C and this cooled solution was added to the reaction mixture at the same temperature over 15 minutes time. Then the reaction mixture was warmed to –5 °C and was stirred for 3 h. To the reaction mixture, MeOH (2.0 mL) and $NaBH_4$ (22.7 mg, 0.6 mmol) was added and stirred at 0 °C for 1 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 over anhydrous $Na_2SO_4$ and concentrated. Pure alcohol **113a** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**((2*S*,3*S*,4*R*)-2-Methyl-4-(nitromethyl)chroman-3-yl)methanol (113a):** Prepared by following the procedure **N** and purified by column chromatography using EtOAc/hexane and isolated as a yellow gummy liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5U Cellulose-1 column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 290 nm), $t_R$ = 32.86 min (minor), $t_R$ = 46.10 min (major). **$[\alpha]_D^{25}$ = –24.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 98.7% *ee*);** IR (Neat): $\nu_{max}$ 3392 (O-H), 2981, 2200, 1611, 1578, 1556, 1485, 1458, 1381,

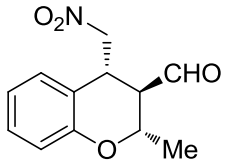


**113a**

1238 and 762 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.20-7.16 (2H, m), 6.95 (1H, t, *J* = 7.2 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 4.73-4.68 (2H, m, C*H*$_2$NO$_2$), 4.09 (1H, quin, *J* = 7.2 Hz, OC*H*), 3.79-3.75 (3H, m), 1.99-1.95 (1H, m), 1.80 (1H, br s, O-H), 1.49 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 155.0 (C), 128.7 (CH), 128.2 (CH), 121.8 (C), 121.7 (CH), 117.8 (CH), 80.1 ($CH_2$, *C*H$_2$NO$_2$), 73.1 (CH, O*C*H), 62.3 ($CH_2$, *C*H$_2$OH), 44.6 (CH), 35.4 (CH), 19.9 ($CH_3$); HRMS m/z 238.1084 (M + H), calcd for $C_{12}H_{15}NO_4H$ 238.1079.

**Procedure O: General procedure for amine-catalyzed asymmetric triple domino reaction of acetaldehyde 104 with 2-(2-nitrovinyl)phenol 108a:** (*E*)-2-(2-nitrovinyl)phenol **108a** (49.5 mg, 0.3 mmol) was added to a solution of (*R*)-diphenylprolinol trimethylsilyl ether **4n** (19.5 mg, 0.06 mmol) in $CHCl_3$ (1 mL), taken in an ordinary glass vial equipped with a magnetic stirring bar and it was cooled to –40 °C. Acetaldehyde **104** (49.8 μL, 0.9 mmol, 3 equiv.), dissolved in $CHCl_3$ (1 mL) in another vial, was cooled to –40 °C and this cooled solution was added to the reaction mixture at the same temperature, over 15 minutes time. Then the reaction mixture was warmed to –5 °C and was stirred for 3 h. Then the crude mixture was loaded directly onto the silica gel and eluted with EtOAc/*n*-hexane and concentrated under reduced pressure to afford **109a**.

**(2*S*,3*R*,4*R*)-2-Methyl-4-(nitromethyl)chroman-3-carbaldehyde (109a):** Prepared by following the procedure **O** and purified by column chromatography using EtOAc/hexane and isolated as a yellow 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 = 290 nm), $t_R$ = 8.870 min (minor), $t_R$ = 10.418 min (major). **$[\alpha]_D^{25}$ = –43.0° (*c* = 0.4 g/100 mL, $CHCl_3$, >98% *ee*);** IR (Neat): $\nu_{max}$ 3392, 2981, 2200, 1611, 1578, 1556, 1485, 1458, 1381, 1238 and 762 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 9.86 (1H, s, C*H*O), 7.20 (2H, m), 6.98 (1H, t, *J* = 7.6 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 4.69 (2H, d, *J* = 7.6 Hz, C*H*$_2$NO$_2$), 4.16-4.09 (2H, m), 3.06 (1H, t, *J* = 8.4 Hz), 1.59 (3H, br d, *J* = 6.0 Hz, CHC*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 199.6 (C, *C*HO), 154.6 (C), 128.9 (CH), 127.5 (CH), 122.0 (CH), 119.3 (C), 117.8 (CH), 78.3 ($CH_2$, *C*H$_2$NO$_2$), 71.5 (CH, O*C*H), 55.2 (CH), 33.3 (CH), 19.8 ($CH_3$); HRMS m/z 258.0743 (M + Na ), calcd for $C_{12}H_{13}NO_4Na$ 258.0742



**(-)-109a**

## 8. REFERENCES


1) D. B. Ramachary, P. S. Reddy, M. S. Prasad, *Eur. J. Org. Chem.* **2014**, *15*, 3076–3081.

2) (a) A. Hantzsch, *Chem. Ber.* **1881**, *14*, 1637; (b) E. Knoevenagel, A. Fries, *Chem. Ber.* **1898**, *31*, 761.

3) J. B. Tuttle, S. G. Oulette, D.W. C.MacMillan, *J. Am. Chem. Soc.* **2006**, *128,* 12662.

4) J. W. Yang, B. List, *Org. Lett.* **2006**, *8*, 5653.

5) S. Singh, U. K. Batra, *Ind. J. Chem.* **1989**, *28B*, 1.

6) For selected recent reviews on general domino and multicomponent reactions, see: (a) K. C. Nicolaou, T. Montagnon , S. A. Snyder, *Chem. Commun*. **2003**, 551–564; (b) J.-C. Wasilke, S. J. Obrey, R. T. Baker , G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; (c) D. J. Ramon, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; (d) L. F. Tietze, *Chem. Rev*. **1996**, *96*,115–136; (e) L. F. Tietze, F. Haunert, *Stimulating Concepts in Chemistry*, ed. F. Vogtle, J. F. Stoddart , M. Shibasaki,Wiley-VCH, Weinheim, **2000**, pp. 39–64; (f) L. F. Tietze , Modi, *Med. Res. Rev.* **2000**, *20*, 304–322. For selected recent reviews on organocatalytic sequential one-pot and domino reactions, see: (g) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas III, *ACS Catal.* **2014**, *4*, 743–762; (h) H. Jiang, L. Albrecht, K. A. Jørgensen, *Chem. Sci.* **2013**, *4*, 2287–2300; (i) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865–887; (j) C. Grondal, M. Jeanty, Enders, *Nat. Chem.* **2010**, *2*, 167–178; (k) C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; (l) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; (m) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1–21. For recent papers on organocatalytic cascade or domino reactions see**:** (n) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2003**, *42*, 4233–4237; (o) D. B. Ramachary, C. F. Barbas III, *Chem. Eur. J.* **2004**, *10*, 5323–5331; (p) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037; (q) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053; (r) M. Marigo, S. Bertelsen, A. Landa, K. A. Jorgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475–5479; (s) D. Enders, M. R. M. Huettl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; (t) G.-L. Zhao, W.-W. Liao, A. Cordova, *Tetrahedron Lett.* **2006**, *47*, 4929–4932; (u) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354–10355; (v) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 3683–3686.

7) D. M. Stout, A. I. Meyers, *Chem. Rev*. **1982**, *82*, 223.

8) N. D. Ide, J. A. Ragan, G. Bellavance, S. J. Brenek, E. M. Cordi, G. O. Jensen, K. N. Jones, D. LaFrance, K. R. Leeman, L. J. Letendre, D. Place, C. L. Stanchina, G. W. Sluggett, H. Strohmeyer, *Org. Process Res. Dev.* **2014**, *18*, 45–56.

9) J. Tummatorn, G. B. Dudley, *Org. Lett.* **2011**, *13*, 1572–1575.

10) H. Li, Tatlock, Linton, Gonzalez, Jewell, Patel, Ludlum, Drowns, Rahavendran, Skor, Hunter, Shi, Herlihy, Parge, Hickey, Yu. X, F. Chau, Nonomiya, C. Lewis, *J. Med. Chem*. **2009**, *52*, 1255.

11) G. Toth, S. Molnar, Tamas, Borbely, *Org. Prep. Proced. Int*. **1999**, *31*, 222.

12) H.Chikashita, Miyazaki, K. Ito, *J. Chem. Soc. Perkin Trans*.-1 **1987**, 699.

13) H.Chikashita, K. Itoh, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1747.

14) Kennedy, W. J. Jason, *J. Org. Chem.* **2008**, *73*(13), 5151–5154.

15) For original papers on the development of organocatalytic reductive coupling, see for a review: (a) D. B. Ramachary, S. Jain, *Org. Biomol. Chem.* **2011**, *9*, 1277–1300. For the papers, see: (b) D. B. Ramachary, Y. V. Reddy, *J. Org. Chem.* **2010**, *75*, 74–85; (c) D. B. Ramachary, M. S. Prasad, *Tetrahedron Lett.* **2010**, *51*, 5246–5251; (d) D. B. Ramachary, M. Kishor, *Org. Biomol. Chem.* **2010**, *8*, 2859–2867; (e) D. B. Ramachary, Ch. Venkaiah, Y. V. Reddy, M. Kishor, *Org. Biomol. Chem.* **2009**, *7*, 2053–2062; (f) D. B. Ramachary, M. Kishor, *Org. Biomol. Chem.* **2008**, *6*, 4176–4187; (g) D. B. Ramachary, Y. V. Reddy, M. Kishor, *Org. Biomol. Chem.* **2008**, *6*, 4188–4197; (h) D. B. Ramachary, M. Kishor, Y. V. Reddy, *Eur. J. Org. Chem.* **2008**, 975–993; (i) D. B. Ramachary, M. Kishor, *J. Org. Chem.* **2007**, *72*, 5056–5068; ( j) D. B. Ramachary, G. Babul Reddy, *Org. Biomol. Chem.* **2006**, *4*, 4463–4468; (k) D. B. Ramachary, M. Kishor, G. Babul Reddy, *Org. Biomol. Chem.* **2006**, *4*, 1641–1646; (l) D. B. Ramachary, M. Kishor, K. Ramakumar, *Tetrahedron Lett.* **2006**, *47*, 651–656; (m) D. B. Ramachary, Ch. Venkaiah, Y. V. Reddy, *Org. Biomol. Chem.* **2014**, *12*, 5400–5406; (n) D. B. Ramachary, Madhava chary, *Eur. J. Org. Chem.* **2014**, 7317–7323.

16) For two step synthesis of 2-alkyl cyclohexane 1,3-diones: (*a*) M. Bassetti, G. Cerichelli, B. Floris, *Gazz. Chim. Ital.* **1986**, *116,* 583–585; (*b*) K. Fuchs, L. A. Paquette, *J. Org. Chem.* **1994**, *59*, 528–532; (*c*) L. A. Paquette, D. Backhaus, R. Braun, T. L. Underiner, K. Fuchs, *J. Am. Chem. Soc.* **1997**, *119,* 9662–9671; (*d*) F. S. Pashkovsky, I. P. Lokot, F. A. Lakhvich, *Synlett* **2001**, 1391–1394.

17) For the two-step synthesis of 2-alkyl-cyclopentane-1,3-diones, see: (*a*) K. Takeishi, K. Sugishima,K. Sasaki, K. Tanaka, *Chem. Eur. J.* **2004**, *10*, 5681–5688; (*b*) F. Gao, D. J. Burnell, *J. Org. Chem.* **2006**, *71*, 356–359; (*c*) D. Lertpibulpanya, S. P. Marsden, *Org. Biomol. Chem.* **2006**, *4*, 3498–3504.

18) (*a*) G. Jones, *Org. React.* **1967**, *15,* 204; (*b*) K. Nagarajan, S. J. Shenoy, *Ind. J. Chem. Sect. B* **1992**, *31,* 73–87; (*c*) K. Hobel, P. Margaretha, *Hel*v. *Chim. Acta.* **1989**, *72,* 975–979; (*d*) M. L. Bolte, W. D. Crow, S. Yoshida, *Aust. J. Chem.* **1982**, *35,* 1421–1429.

19) J. R. Dimmock, S. K. Raghavan, G. E. Bigam, *Eur. J. Med. Chem.* **1988**, *23,* 111–117.

20) (*a*) P. Margaretha, O. E. Polansky, *Monatsh. Chem.* **1970**, *101,* 824; (*b*) P. E. Eaton, W. H. Bunnelle, *Tetrahedron Lett.* **1984**, *25,* 23–26; (*c*) P. E. Eaton, W. H. Bunnelle, P. Engel, *Can.*

*J. Chem.* **1984***, 62,* 2612–2626; (*d*) T. Ogawa, T. Murafuji, H. Suzuki, *Chem. Lett.* **1988**, 849–852.

21) (*a*) W. A. Herrmann, *Ger. Offen.* **1991**, 6 pp, CODEN: GWXXBX DE 4101737 A1 19910801, CAN 115:158156 (patent written in German); (*b*) M. L. Bolte,W. D. Crow, S. Yoshida, *Aust. J. Chem.* **1982**, *35*, 1411–1419; (*c*) W. H. Bunnelle, L. A. Meyer, *J. Org. Chem.* **1988**, *53*, 4038–4042.

22) Y. C. Wong, T. T. Kao, J. K. Huang, Y. W. Jhang, M. C. Chou, K. S .Shia, *Adv. Synth.Catal.* **2013***, 356,* 3025–3038.

23) P. A. Peixoto, M. Cormier, J. E. Epane, A. Jean, J. Maddaluno, M. De Paolis, *Org. Chem. Front.* **2014**, *1*, 748–754.

24) Y. C. Wong, T. T. Kao, Y. C. Yeh, B. S. Hsieh, K. S .Shia, *Adv. Synth.Catal.* **2013***, 355,* 1323–1337.

25) T. Tite, M. Sabbah, V. Levacher, F. B. Jean, *Chem. commun*. **2013**, ***49***, 11569–11571.

26) Y.-C. Wong, C.-T. Tseng, T.-T. Kao, Y.-C. Yeh, K.-S. Shia, *Org. Lett*. **2012**, *14*, 6024–6027.

27) K. Hiroya, Y. Ichihashi, A. Furutono, K. Inamoto, T. Sakamoto, T. Doi, *J. Org. Chem*. **2009**, *74*, 6623–6630.

28) B. Bradshaw, J. G. Etxebarria, J. Bonjoch, F. V. Santiago, G. Guillena, C. Najera, *Adv. Synth. Catal.* **2009**, *351*, 2482–2490.

29) E. Elamparuthi, C. Fellay, M. Neuburger, K. Gademann, *Angew. Chem. Int. Ed.* **2012**, *51*, 4071–4073.

30) K. Hiroya, Y. Suwa, Y. Ichihashi, K. Inamoto, T. Doi, *J. Org. Chem.* **2011**, *76*, 4522–4532.

31) L. Miao, H. Shu,A. R. Noble, S. P. Fournet, E. D. Stevens, M. L. Trudell, *ARKIVOC* **2010**, *4*, 6–14.

32) P. K. Amancha, H.-J. Liu, T. W. Ly, K.-S. Shia, *Eur. J. Org. Chem.* **2010**, 3473–3480.

33) C. Ballatore, J. H. Soper, F. Piscitelli, M. James, L. Huang, O. Atasoylu, D. M. Huryn, J. Q. Trojanowski, V. M.-Y. Lee, K. R. Brunden, A. B. Smith III, *J. Med. Chem*. **2011**, *54*, 6969–6983.

34) Jun Che, Yulin Lam, *Adv. Synth. Catal.* **2010**, *352*, 1752–1758.

35) Synthesis of highly functionalized molecules starting from the simple materials in one-pot (*a*) D. B. Ramachary, K. Ramakumar, M. Kishor, *Tetrahedron Lett.* **2005**, *46*, 7037–7042; (b) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem.* **2008**, *6*, 2488–2492; (c) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *J. Org. Chem.* **2007**, *72*, 1458–1463; (d) D. B. Ramachary, G. Babul Reddy, M. Rumpa, *Tetrahedron Lett.* **2007**, *48*, 7618–7623; (e) D. B. Ramachary, Y. V. Reddy, B. V. Prakash, *Org. Biomol. Chem.* **2008**, *6*, 719–726.

36) (a) J. Gavrilyuk, H. Uehara, N. Otsubo, A. Hessell, D. R. Burton, C. F. Barbas-III, *Chem. Bio. Chem.* **2010**, *15,* 2113-2118; (b) S. Belot, S. Sulzer-Mosse, S. Kehrli, A. Alexakis, *Chem. Commun*. **2008**, 4694–4696; (c) N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka, C. F. Barbas-III, *Org. Lett*. **2006**, 8, 2839–2842; (d) R. Thayumanavan, F. Tanaka, C. F. Barbas-III, *Org. Lett.* **2004**, *6*, 3541.

37) (*a*) D. Rajagopal, R. Narayanan, S. Swaminathan, *Proc. Ind. Acad. Sci.* (*Chem. Sci.*) **2001**, *113***,** 197-213; (*b*) K. Inomata, M. Barrague, L. A. Paquette, *J. Org. Chem.* **2005**, ***70***, 533–539; (*c*) H. Shigehisa, T. Mizutani, S. Tosaki, T. Ohshima, M. Shibasaki, *Tetrahedron* **2005**, *61,* 5057–5065; (*d*) T. Nagamine, K. Inomata, Y. Endo, L. A. Paquette, *J. Org. Chem.* **2007**, *72,* 123–131.

38) For applications of 2-alkyl-cyclohexane-1,3-diones, see: (*a*) A. S. Kotnis, *Tetrahedron Lett.* **1991**, *32,* 3441–3444; (*b*) D. M. Jones, S. Kamijo, G. B. Dudley, *Synlett* **2006**, 936–938; (*c*) S. Ina, K. Yamana, K. Noda, T. Akiyama, A. Takahama, *Jpn. Kokai Tokkyo Koho* **1999**, 45 pp, CODEN: JKXXAF JP 11189577 A 19990713, CAN 131:87830 (patent written in Japanese).

39) For applications of 2-alkyl-cyclopentane-1,3-diones, see: (*a*) A. S. R. Anjaneyulu, M. V. R. K. Murthy, P. M. Gowri, M. J. R. V. Venugopal, H. Laatsch, *J. Nat. Prod.* **2000**, *63,* 1425–1426; (*b*) A. Schmidt, W. Bol, *J. Org. Chem.* **2007**, *72*, 1699–1706; for the applications of 2-alkyl-3-methoxycyclopent- 2-enones, see: (*c*) G. A. Tolstikov, S. A. Ismailov, Y. L. Vel'der, M. S. Miftakhov, *Zhurnal Organicheskoi Khimii* **1991**, *27*, 83–90; (*d*) G. L. Nelson, *U. S.* **1982**, 7 pp, CODEN: USXXAM US 4338466 A 19820706, CAN 98:16495 (patent written in English); (*e*) H. Schick, M. Henning, H. P. Welzel, S. Schwarz, *Ger. (East)* **1979**, 8 pp, CODEN: GEXXA8 DD 138767 19791121, CAN 93:71116 (patent written in German); (*f*) P. Aujla, T. J. Norman, J. R. Porter, S. Bailey, S. Brand, *PCT Int. Appl.* **2003**, 97 pp, CODEN: PIXXD2 WO 2003011815 A1 20030213,CAN138:137592 (patent written in English); (*g*) F. A. Lakhvich, F. S. Pashkovskii, L.G. Lis, *SeryyaKhimichnykh Navuk* **1987**, 53–59; (*h*) H. Liang, A. Schule, J.-P. Vors, M. A. Ciufolini, *Org. Lett.* **2007**, *9*, 4119–4122.

40) For applications of Hajos–Parrish ketone analogues, see: (*a*) P. K. Ruprah, J.-P. Cros, J. E. Pease,W. G. Whittingham, J. M. J.Williams, *Eur. J. Org. Chem.* **2002**, 3145–3152; (*b*) L. G. Sevillano, C. P. Melero, M. Boya, J. L. Lopez, F. Tome, E. Caballero, R. Carron, M. J. Montero, M. Medarde, A. San Feliciano, *Bioorg. Med. Chem.* **1999**, *7*, 2991–3001; (*c*) P. A. Grieco, N. Fukamiya, M. Miyashita, *J. Chem. Soc. Chem. Commun.* **1976**, 573–575; (*d*) S. Takano, S. Sato, E. Goto, K. Ogasawara, *J. Chem. Soc. Chem. Commun.* **1986**, 156–158; (*e*) R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott, P. A. Wehrli, *J. Org. Chem.* **1975**, *40*, 675–681.

41) A. Ali, J. M. Balkovec, R. Beresis, S. L. Colletti, D. W. Graham, G. F. Patel, C. J. Smith, *PCT Int. Appl.* **2004**, CODEN: PIXXD2 WO 2004093805 A2 20041104, CAN 141:395547 (in English; 201 pp).

42) (*a*) C. F. Thompson, N. Quraishi, A. Ali, R. T. Mosley, J. R. Tata, M. L. Hammond, J. M. Balkovec, M. Einstein, L. Ge, G. Harris, T. M. Kelly, P. Mazur, S. Pandit, J. Santoro, A. Sitlani, C. Wang, J. Williamson, D. K. Miller, T. D. Yamin, C. M. Thompson, E. A. O'Neill, D. Zaller, M. J. Forrest, E. Carballo-Jane, S. Luell, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3354–3361; (*b*) C. J. Smith, A. Ali, J. M. Balkovec, D. W. Graham, M. L. Hammond, G. F. Patel, G. P. Rouen, S. K. Smith, J. R. Tata, M. Einstein, L. Ge, G. S. Harris, T. M. Kelly, P. Mazur, C. M. Thompson, C. F. Wang, J. M. Williamson, D. K. Miller, S. Pandit, J. C. Santoro, A. Sitlani, T. D. Yamin, E. A. O'Neill, D. M. Zaller, E. Carballo-Jane, M. J. Forrest, S. Luell, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2926–2931.

43) (a) B. S. Weeks, *Med. Sci. Monit.* **2009,** *15,* 256-262; (b) Christmas D, Hood S, Nutt D, *Curr. Pharm. Des.* **2008**, *14*, 3534–3546.; (c) D'Hulst C, Atack JR, Kooy RF, *Drug Discov Today* **2009**, *14,* 866–875; (d).T. Furmark, *Isr J Psychiatry Relat Sci.* **2009**, *46*, 5–12; (d) K. Gajcy, S. Lochynski, T. Librowski, *Current Medicinal Chemistry* **2010**, *17,* 2338–2347

44) J. V. Ragavendran, D. Sriram, S. K. Patel, I. V. Reddy, N. Bharathwajan, J. Stables, P. Yogeeswari, *Eur. J. Med. Chem.* **2007,** *42,* 146-151.

45) B. V.Dean, S. J. Stellpflug, A. M. Burnett, K. M. Engebretsen, *J. Med. Toxicol*. **2013**, *9*, 172–178.

46) Review on Iodine- mediated aromatization: M. J. Mphahlele, *Molecules* **2009**, *14*, 5308–5322.

47) *Stereoselective Synthesis*, ed. R. S. Atkinson, Wiley and Sons, New York, **1995.**

48) V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev*. **2006**, *106*, 2734–2793.

49) a) E. Fogassy, M. Nogradi, D. Kozma, G. Egri, E. Palovics, V. Kiss, *Org. Biomol. Chem*. **2006**, *4*, 3011–3030; b) E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040–4069; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001; c) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Kebeler, R. Strmer, T. Zelinski, *Angew. Chem. 2004*, **116**, 806-843; *Angew. Chem. Int. Ed*. **2004**, *43*, 788–824.

50) Review on Kinetic resolution strategies using non-enzymatic catalysts, D. E. J. E. Robinson, S. D. Bull, *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446.

51) Review on Organocatalyzed Dynamic Kinetic Resolution; H. Pellissier, *Adv. Synth. Catal*. **2011**, *353*, 659–676.

52) For very recent reviews see: (a) B. Bradshaw, J. Bonjoch, *Synlett* **2012**, 337–356; (b) Moyano. A, R. Rios, *Chem. Rev*. **2011**, *111*, 4703–4832; (c) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev*. **2010**, *39*, 1600–1632.

53) (a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621; (b) T. Kanger, K. Kriis, M. Laars, T. Kailas, A. Muurisep, T. Pehk, M. Lopp, *J. Org. Chem.* **2007**, *72*, 5168–5173; (c) Laars, Kriis, Kailas, Müürisep, Pehk, Kanger, Lopp, *Tetrahedron: Asymmetry* **2008**, *19*, 641–645; (d) Fuentes deArriba, D. G.Seisdedos, Simón, Alcázar, Raposo, J. R. Morán, *J. Org.Chem*. **2010**, *75*, 8303–8306.

54) V. D. Elia, H. Zwicknagl, O. Reiser, *J. Org. Chem*. **2008**, *73*, 3262–3265.

55) (a) P. Buchshacher, J. M. Cassal, A. Furst, W. Meier, *Helv. Chim. Acta.* **1977**, *60*, 2747–2755; (b) H. Hagiwara, H. Uda, *J. Org. Chem.* **1988**, *53*, 2308–2311.

56) (a) T. Wakabayashi, K. Watanabe, Y. Kato, *Synth. Commun*. **1977**, *7*, 239–244; (b) S. Davies, A. J. Russell, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Org.Biomol. Chem*. **2007**, *5*, 3190–3200; c) S. G. Davies, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Chem. Commun*. **2005**, 3802–3804.

57) (a) K. Drauz, A. Kleeman, J. Martens, *Angew. Chem. Int. Ed.* **1982**, *21*, 584–608; (b) P. H. Y. Cheong, Houk, Warrier, Hanessian, *Adv. Synth. Catal.* **2004**, *346*, 1111–1115; (c) P. H. Y. Cheong, K. N. Houk, *Synthesis* **2005**,1533–1537; (d) E. Lacoste, E. Vaique, M. Berlande, I. Pianet, J. Vincent, Y. Landais, *Eur. J. Org. Chem*. **2007**, 167–177; (e) Akahane, Inomata, Endo, *Heterocycles* **2009**, *77*, 1065–1078; (f) Y. Akahane, K. Inomata, Y. Endo, *Heterocycles* **2011**, *82*, 1727–1737.

58) (a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1973**, *38*, 3239; (b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1612–1615.

59) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108,* 2353–2357.

60) D. Rajagopal, M. S. Moni, S. Subramanian, S. Swaminathan, *Tetrahedron Asymmetry* **1999**, *10,* 1631–1634.

61) (a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001,** *123,* 9922–9923; (b) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001,** *123,* 11273–11283; (c) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125,* 2475–2479.

62) B. List, L. Hoang, H. Martin, *Proc. Natl. Acad. Sci. U. S. A*. **2004**, *101*, 5839.

63) D. Shabat, C. Rader, B. List, R. A. Lerner, C. F. Barbas, *Proc. Natl. Acad. Sci. USA* **1999**, *96,* 6925.

64) P. Langer, E. Holtz, *Synlett* **2003**, 402.

65) C. F. Allen, G. P. Happ, *Can. J. Chem.* **1964**, *42*, 655.

66) F. R. A. Neto, J. M. Trende, P. Albrecht, *Tetrahedron* **1986**, *42,* 5621.

67) J. X. Wang, T. S. Li, *Collect. Czech. Chem. Commun.* **1999,** *64*, 107.

68) (a) B. M. Trost, *Science* **1991**, *254*, 1471; (b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259.

69) (a) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114,* 4418; (b) B. M. Trost, H. Ito, *J. Am. Chem. Soc*. **2000**, *122*, 12003; (c) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114,* 4418; (d) B. M. Trost, H. Ito, E. R. Siloff, *J. Am. Chem. Soc*. **2001**, *123*, 3367; (e) D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem.Soc*. **2003**, *125*, 8706.

70) For examples, see: (a) C. F. Barbas-III, A. Heine, G. Zhong, T. Hoffmann, S. Gramatikova, R. Bjo rnestedt, B. List, J. Anderson, E. A. Stura, I. A. Wilson, R. Lerner, *Science* **1997**, *278*, 2085; (b) T. Hoffmann, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. Lerner C. F. Barbas-III, *J. Am. Chem. Soc*. **1998**, *120*, 2768; (c) B. List, D. Shabat, C. F. Barbas-III, R. Lerner, *Chem. Eur. J*. **1998**, *4*, 881.

71) For reviews, see: (a) B. List, *Tetrahedron* **2002**, *58*, 5573; (b) B. List, *Synlett* **2001**, 1675; (c) B. Alcaide, P. Almendros, *Angew. Chem. Int. Ed*. **2003**, *42*, 858; (d) B. List, *Acc. Chem. Res*. **2004**, *37*, 548; (e) W. Notz, F. Tanaka, C. F. Barbas-III, *Acc. Chem. Res.* **2004**, *37*, 580; For leading literatures, see: (f) U. Eder, R. Sauer, R. Wiechert, *Angew. Chem. Int. Ed*. **1971**, *10*, 496; (g) B. List, R. A. Lerner, C. F. Barbas-III, *J. Am. Chem. Soc*. **2000**, *122*, 2395; (h) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas-III, *J. Am. Chem. Soc*. **2001**, *123*, 5260; (i) W. Notz, B. List, *J. Am. Chem. Soc*. **2000**, *122*, 7386; (j) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2002**, *124*, 6798; (k) A. Cordova, W. Notz, C. F. Barbas-III, *J. Org. Chem*. **2002**, *67*, 301; (l) A. Bogevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun*. **2002**, 620; (m) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem.Int. Ed*. **2003**, *42*, 2785; (n) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem. Int. Ed*. **2004**, *43*, 2152; (o) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Cordova, *Angew. Chem. Int. Ed*. **2005**, *44*, 1343; (p) S. Samanta, J. Liu, R. Dodda, C. G. Zhao, *Org. Lett*. **2005**, *7*, 5321; (q) J.-R. Chen, H. H. Lu, X. Y. Li, L. Cheng, J. Wan, W. J. Xiao, *Org. Lett.* **2005**, *7*, 4543; (r) C. Cheng, J. Sun, C. Wang, Y. Zhang, S. Wei, F. Jiang, Y. Wu, *Chem. Commun*. **2006**, 215; (s) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas,-III, *J. Am. Chem. Soc*. **2006**, *128*, 734; (t) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed*. **2006**, *45*, 958.

72) (a) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983; (b) H. J. Martin, B. List, *Synlett* **2003**, 1901; (c) T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem. Int. Ed*. **2005**, *44*, 3055; For review, see: (d) S. Saito, H. Yamamoto, *Acc. Chem. Res*. **2004**, *37*, 570.

73) F. Tanaka, C. F. Barbas-III, In *Modern Aldol Reactions*; R. Marhrwald, *Ed.; Wiley- VCH: Weinheim*, **2004**; Vol. *1*, Chapter 6.

74) (a) X-Y. Xu, Y-Z. Wang, L-F. Cun, L-Z. Gong, *Tetrahedron: Asymmetry* **2007**, *18*, 237–242; (b) G. Zhong, J. Fan, C. F. Barbas-III, *Tetrahedron Lett*. **2004**, *45*, 5681–5684; (c) L. He, Z. Tang, L. F. Cun, A. Q. Mi, Y. Z. Jiang, L. Z. Gong, *Tetrahedron* **2006**, *62*, 346–351; (d) V.

Maggiotti, S. Bahmanyar, M. Reiter, M. Resmina, K. N. Houk, V. Gouverneur, *Tetrahedron* **2004**, *60*, 619–632.

75) (a) O. Tokuda, T. Kano, W. G. Gao, T. Ikemoto, K. Moruoka, *Org. Lett*. **2005**, *7*, 5103–5105; (b) G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman, C. Tomasini, *J. Org. Chem*. **2005**, *70*, 7418–7421; (c) S. Samanta, C. Z. Zhao, *Tetrahedron Lett*. **2006**, *47*, 3383–3386; (d) Y. J. Wang, Z. X. Shen, B. Li, Y. W. Zhang, *Chin. J. Chem*. **2006**, *24*, 1196–1199; (e) S. Samanta, C. G. Zhao, *J. Am. Chem. Soc.* **2006**, *128*, 7442–7443; (f) Z. Tang, L. F. Cun, X. Cui, A. Q. Mi, Y. Z. Jiang, L. Z. Gong, *Org. Lett*. **2006**, *8*, 1263–1266; (g) G. Guillena, M. Hita, C. Na`jera, *Tetrahedron: Asymmetry* **2006**, *17*, 1027–1031; (h) X. J. Wang, Y. Zhao, J. T. Liu, Org. *Lett.* **2007**, *9*, 1343–1345; (i) X. Y. Xu, Z. Tang, Y. Z. Wang, S. W. Luo, L. F. Cun, L. Z. Gong, *J. Org. Chem*. **2007**, *72*, 9905–9913.

76) (a) O. O. Shyshkina1, K. S. Popov1, O. O. Gordivska1, T. M. Tkachuk1, N. V. Kovalenko, T. A. Volovnenko1, Y. M. Volovenko, *Chemistry of Heterocyclic Compounds* **2011,** *47*, 923–945; (b) N. S. Simpkins, *Sulfones in organic synthesis*. Oxford: Pergamon Press; **1993**; (c) K. Vandyck, M. D. Cummings, O. Nyanguile, C. W. Boutton, S. Vendeville, D. McGowan, B. Devogelaere, K. Amssoms, S. Last, K. Rombauts, A. Tahri, P. Lory, L. Hu, D. A. Beauchamp, K. Simmen, P. Raboisson, *J. Med. Chem*. **2009**, *52*, 4099; (d) E. L. Hancox, T. A. Hamor, R. T. Walker, *Tetrahedron Lett.* **1994**, *35*, 1291; (e) Ch. Peixoto, P. Laurin, M. Klich, C. Dupuis-Hamelin, P. Mauvais, P. Lassaigne, A. Bonnefoy, B. Musicki, *Tetrahedron Lett.* **2000**, *41*, 1741; (f) Pfizer Incorporation, *US Pat. Appl. 19721259415*; (g) Ch. F. Schwender, J. H. Dodd, *US Pat. Appl. 19884777167*; (h) K. Toshima, K. Ohta, A. Ohtsuka, Sh. Matsumura, M. Nakata, *J. Chem. Soc. Chem. Commun.* **1993**, 1406; (i) R. J. Altenbach, M. E. Brune, S. A. Buckner, M. J. Coghlan, A. V. Daza, A. Fabiyi, M. Gopalakrishnan, R. F. Henry, A. Khilevich, M. E. Kort, I. Milicic, V. E. Scott, J. C. Smith, K. L. Whiteaker, W. A. Carroll, *J. Med. Chem.* **2006**, *49*, 6869.

77) J. H. Dodd, Ch. F. Schwender, Y. Grey-Nunez, *J. Heterocycl. Chem.* **1990**, *27*, 1453.

78) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev*. **2010**, *39*, 1272.

79) (a) J.-L. Chaubard, C. Krishnamurthy, W. Yi, D. F. Smith, L. C. Hsieh-Wilson, *J. Am. Chem. Soc*. **2012**,*134*, 4489; (b) M. Simon, U. Zangemeister-Wittke, A. Plckthun, *Bioconjugate Chem*. **2012**, *23*, 279; (c) S. Arumugam, J. Chin, R. Schirrmacher, V. V. Popik, A. P. Kostikov, *Bioorg. Med. Chem. Lett*. **2011**, *21*, 6987; (d) J. C. Jewett, C. R. Bertozzi, *Org. Lett.* **2011**, *13*, 5937; (e) E. M. Sletten, C. R. Bertozzi, *J. Am. Chem. Soc*. **2011**, *133*, 17570; (f) R. D. Carpenter, S. H. Hausner, J. L. Sutcliffe, *ACS Med. Chem. Lett.* **2011**, *2*, 885; (g) J. Xu, T. M. Filion, F. Prifti, J. Song, *Chem. Asian J*. **2011**, *6*, 2730; (h) T. Zheng, H. Jiang, M. Gros, D. Soriano del Amo, S. Sundaram, G. Lauvau, F. Marlow, Y. Liu, P.Stanley, P. Wu, *Angew. Chem*. **2011**, *123*, 4199; *Angew. Chem. Int. Ed*. **2011**, *50*, 4113.

80) A. Mckillop, J. A. Tarbin, *Tetrahedron Lett*. **1983**, *24*, 1505–1508.

81) J. M. Khurana, A. K. Panda, A. Ray, A. Gogia, *Org. Prep. Proc.* **1996**, *28*, 234–237.

82) J. V. Weber, M. Schneider, B. Salami, D. Paquer, *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 99–102.

83) D. H. R. Barton, W. Li, J. A. Smith, *Tetrahedron Lett*. **1998**, *39*, 7055–7058.

84) (a) R. J. Kennedy, A. M. Stock, *J. Org. Chem*. **1960**, *25*, 1901–1906; (b) B. M. Trost, D. P. Curran, *Tetrahedron Lett*. **1981**, *22*, 1287–1290.

85) D. W. Goheen, C. F. Bennett, *J. Org. Chem*. **1961**, *26*, 1331–1333.

86) T. L. Ho, C. M. Wong, *Synthesis* **1972**, 561–562.

87) (a) N. J. Leonard, C. R. Johnson, *J. Org. Chem*. **1962**, *27*, 282–284; (b) R. S. Varma, R. K. Saini, H. M. Meshram, *Tetrahedron Lett*. **1997**, *38*, 6525–6528.

88) D. Edwards, J. B. Stenlake, *J. Chem. Soc.* **1954**, 3272–3274.

89) G. W. Gokel, H. M. Gerdes, D. M. Dishong, *J. Org. Chem*. **1980**, *45*, 3634–3639.

90) C. Djerassi, R. R. Engle, *J. Am. Chem. Soc.* **1953**, *75*, 3838–3840.

91) C. G. Venier, T. G. Squires, Y. Y. Chen, G. P. Hussmann, J. C. Shei, B. F. Smith, *J. Org. Chem.* **1982**, *47*, 3773–3774.

92) (a) R. W. Murray, R. Jeyaraman, *J. Org. Chem.* **1985**, *50*, 2847–2853; (b) W. Adam, L. Hadjiarapoglou, *Tetrahedron Lett*. **1992**, *33*, 469–470.

93) G. W. Breton, J. D. Fields, P. J. Kropp, *Tetrahedron Lett*. **1995**, *36*, 3825–3828.

94) S. W. Kaldor, M. Hammond, *Tetrahedron Lett*. **1991**, *32*, 5043–5046.

95) L. A. Paquette, R. V. C. Carr, *Org. Synth. Coll.* **1990**, *7*, 453–456.

96) (b) A. L. Fan, S. Cao, Z. J. Zhang, *J. Heterocycl. Chem.* **1997**, *34*, 1657. (c) E. A**.** Fehnel, A. P. Paul, *J. Am. Chem. Soc.* **1955,** *77*, 4241**.**

97) K. Sato, M. Aoki, R. Noyori, *Science* **1998**, *281*, 1646–1647.

98) (a)W. G. Dauben, J. W. McFarland, *J. Am. Chem. Soc.* **1960**, *82* (16), 4245–4248. (b) M. H. Filippini, R. Faure, J. Rodriguez, *J. Org. Chem*. **1995**, *60*, 6872-6882. (c) M. H. Filippini, J. Rodriguez, *J. Org. Chem.* **1997,** *62,* 3034–3035.

99) (a) D. L. Boger, *Tetrahedron* **1983**, *39*, 2869-2939; (b) K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2000**, *39*, 3558; (c) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew.Chem. Int. Ed.* **2002**, *41*, 1668.

100) E. S. Gould, "*Mechanism and Structure in Organic Chemistry*" Holt, Rinehart, Winston, New York, N. Y., **1965**, page number- 379.

101) For the selected organocatalytic double domino reactions, see: a) N. S. Chowdari, D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2003**, *5*, 1685; b) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1272; c) M. Marigo, T. Schulte, J. FranzQn, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710; d) D. Enders, A. A. Narine, T. R.

Benninghaus, G. Raabe, *Synlett* **2007**, 1667; e) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem. Int. Ed.* **2007**, *46*, 4922; f) J. L.Vicario, L. Reboredo, D. Badía, L. Carillo, *Angew. Chem. Int. Ed.* **2007**, *46*, 5168; g) D. Enders, C. Wang, J. W. Bats, *Angew. Chem. Int. Ed.* **2008**, *47*, 7539; h) G. –L. Zhao, R. Rios, J. Vesley, L. Eriksson, A. Córdova, *Angew. Chem. Int. Ed.* **2008**, *47*, 8468; i) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem. Int. Ed.* **2008**, *47*, 10187; j) J. Franzén, A. Fisher, *Angew. Chem. Int. Ed.* **2009**, *48*, 787; k) R. Imashiro, H. Uehara, C. F. Barbas III, *Org. Lett.* **2010**, *12*, 5250; l) B. Tan, N. R. Candeias, C. F. Barbas III, *Nature Chem.* **2011**, *3*, 473; m) K. Albertshofer, B. Tan, C. F. Barbas III, *Org. Lett.* **2012**, *14*, 1834; n) K. Albertshofer, K. E. Anderson, C. F. Barbas III, *Org. Lett.* **2012**, *14*, 5968; o) X. Jiang, B. Tan, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2013**, *52*, 9261; p) B. –C. Hong, W. –K. Liao, N. S. Dange, J. –H. Liao, *Org. Lett.* **2013**, *15*, 468; q) B. –C. Hong, C. –W. Lin, W. –K. Liao, G. –H. Lee, *Org. Lett.* **2013**, *15*, 6258; r) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1909.

102) For the selected organocatalytic triple domino reactions, see: a) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem. Int. Ed.* **2007**, *46*, 467; b) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 1101; c) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267; d) D. Enders, M. Jeanty, J. W. Bats, *Synlett* **2009**, 3175; e) D. Enders, C. Joie, K. Deckers, *Chem. Eur. J.* **2013**, *19*, 10818; f) I. Chatterjee, D. Bastida, P. Melchiorre, *Adv. Synth. Catal.* **2013**, *355*, 3124.

103) For the selected organocatalytic quadruple domino reactions, see: a) P. Kotame, B. –C. Hong, J. –H. Liao, *Tetrahedron Lett.* **2009**, *50*, 704; b) F. –L. Zhang, A. –W. Xu, Y. –F. Gong, M. –H. Wei, X. –L. Yang, *Chem. Eur. J.* **2009**, *15*, 6815; c) D. Enders, C. Wang, M. Mukanova, A. Greb, *Chem. Commun.* **2010**, *46*, 2447; d) K. Jiang, Z. –J. Jia, X. Yin, L. Wu, Y. –C. Chen, *Org. Lett.* **2010**, *12*, 2766; e) M. Rueping, K. –L. Haack, W. Ieawsuwan, H. Sunden, M. Blanco, F. R. Schoepke, *Chem. Commun.* **2011**, *47*, 3828; f) D. Enders, A. Greb, K. Deckers, P. Selig, C. Merkens, *Chem. Eur. J.* **2012**, *18*, 10226.

104) For the total synthesis of natural products and drugs from organocatalytic domino reactions, see: a) J. –F. Austin, S. –G. Kim, C. J. Sinz, W. –J. Hiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482; b) Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185; c) B. –C. Hong, M. –F. Wu, H. –C. Tseng, J. –H. Liao, *Org. Lett.* **2006**, *8*, 2217; d) B. –C. Hong, M. –F. Wu, H. –C. Tseng, G. –F. Huang, C. –F. Su, J. –H. Liao, *J. Org. Chem.* **2007**, *72*, 8459; e) G. –S. Liu, Q. –L. Dong, Y. –S. Yao, Z. –J. Yao, *Org. Lett.* **2008**, *10*, 5393; f) B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2009**, *48*, 4349; g) S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606; h) H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 1304; i)

C. Grondal, M. Jeanty, D. Enders, *Nature Chem.* **2010**, *2*, 167; j) B. –C. Hong, P. Kotame, C. –W. Tsai, J. –H. Liao, *Org. Lett.* **2010**, *12*, 776; k) H. Ishikawa, M. Honma, Y. Hayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 2824; l) D. B. Ramachary, Ch. Venkaiah, P. M. Krishna, *Chem. Commun.* **2012**, *48*, 2252; m) Y. Hayashi, S. Umemiya, *Angew. Chem. Int. Ed.* **2013**, *52*, 3450; n) T. Mukaiyama, H. Ishikawa, H. Koshino, Y. Hayashi, *Chem. Eur. J.* **2013**, *19*, 17789; o) D. B. Ramachary, Y. V. Reddy, A. Banerjee, S. Banerjee, *Org. Biomol. Chem.* **2011**, *9*, 7282.

105) For the selected recent papers based on the domino reactions from *ortho*-substituted β-nitrostyrenes, see: a) H. Mao, A. Lin, Y. Tang, Y. Shi, H. Hu, Y. Cheng, C. Zhu, *Org. Lett.* **2013**, *15*, 4062; b) K. –S. Choi, S. –G. Kim, *Eur. J. Org. Chem.* **2012**, 1119; c) C. Wang, X. Yang, G. Raabe, D. Enders, *Adv. Synth. Catal.* **2012**, *354*, 2629; d) A. Lu, K. Hu, Y. Wang, H. Song, Z. Zhou, J. Fang, C. Tang, *J. Org. Chem.* **2012**, *77*, 6208; e) D. Enders, G. Urbanietz, R. Hahn, G. Raabe, *Synthesis* **2012**, 773; f) M. Rueping, J. Dufour, M. S. Maji, *Chem. Commun.* **2012**, *48*, 3406; g) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runsik, *Chem. Asian. J.* **2011**, *6*, 2255; h) D. Enders, G. Urbanietz, G. Raabe, *Synthesis* **2011**, 1905; i) B. –C. Hong, P. Kotame, G. –H. Lee, *Org. Lett.* **2011**, *13*, 5758; j) D. B. Ramachary, M. S. Prasad, R. Madhavachary, *Org. Biomol. Chem.* **2011**, *9*, 2715; k) B.–C. Hong, P. Kotame, J.–H. Liao, *Org. Biomol. Chem.* **2011**, *9*, 382; l) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem.* **2010**, *8*, 4259; m) D. Enders, C. Wang, X. Yang, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 2869; n) D. Lu, Y. Li, Y. Gong, *J. Org. Chem.* **2010**, *75*, 6900; o) X. Zhang, S. Zhang, W. Wang, *Angew. Chem. Int. Ed*. **2010**, *49*, 1481.

106) For the asymmetric reactions with acetaldehyde through organocatalysis, see: a) H. J. M. Gijsen, C. –H. Wong, *J. Am. Chem. Soc.* **1994**, *116*, 8422; b) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752; c) S. E. Denmark, T. Bui, *J. Org. Chem.* **2005**, *70*, 10190; d) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48; e) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 2762; f) S. M. Dean, W. A. Greenberg, C. –H. Wong, *Adv. Synth. Catal.* **2007**, *349*, 1308; g) P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 4719; *Angew. Chem.* **2008**, *120*, 4797; h) Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem. Int. Ed.* **2008**, *47*, 2082; *Angew. Chem.* **2008**, *120*, 2112; i) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem. Int. Ed.* **2008**, *47*, 4722; *Angew. Chem.* **2008**, *120*, 4800; j) Y. Hayashi, T. Okano, T. Itoh, T. Urushima, H. Ishikawa, T. Uchimaru, *Angew. Chem. Int. Ed.* **2008**, *47*, 9053; *Angew. Chem.* **2008**, *120*, 9193; k) Y. Hayashi, S. Samanta, T. Itoh, H. Ishikawa, *Org. Lett.* **2008**, *10*, 5581; l) J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453; m) C. Chandler, P. Galzerano, A. Michrowska, B. List, *Angew. Chem. Int. Ed.* **2009**, *48*, 1978; *Angew. Chem.*

**2009**, *121*, 2012; n) T. Itoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2009**, *11*, 3854; o) D. Enders, R. Krüll, W. Bettray, *Synthesis* **2010**, 567.

107) For the observation of neighboring *ortho*-hydroxyl group participation in pre-transition state, see: a) D. B. Ramachary, R. Sakthidevi, *Chem. Eur. J.* **2009**, *15*, 4516; b) T. Inokuma, K. Takasu, T. Sakaeda, Y. Takemoto, *Org. Lett.* **2009**, *11*, 2425; c) D. B. Ramachary, R. Madhavachary, M. S. Prasad, *Org. Biomol. Chem*. **2012**, *10*, 5825; d) D. B. Ramachary, R. Sakthidevi, K. S. Shruthi, *Chem. Eur. J.* **2012**, *18*, 8008; e) D. B. Ramachary, M. S. Prasad, S. V. Laxmi, R. Madhavachary, *Org. Biomol. Chem*. **2014**, *12*, 574.

108) For the application of benzopyran structural unit in natural products and also as drug intermediates in pharmaceuticals, see: a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939 and references therein; b) S. A. Buckner, I. Milicic, A. Daza, R. Davis-Taber, V. E. S. Scott, J. P. Sullivan, J. D. Brioni, *Eur. J. Pharmocol*. **2000**, *400*, 287; c) B. Lesch, S. Braese, *Angew. Chem. Int. Ed.* **2004**, *43*, 115; d) J. Posakony, M. Hirao, S. Stevens, J. A. Simon, A. Bedalov, *J. Med. Chem.* **2004**, *47*, 2635; e) S. R. Trenor, A. R. Shultz, B. J. Love, T. E. Long, *Chem. Rev.* **2004**, *104*, 3059; f) M. C. Breschi, V. Calderone, A. Martelli, F. Minutolo, S. Rapposelli, L. Testai, F. Tonelli, A. Balsamo, *J. Med. Chem.* **2006**, *49*, 7600; g) R. C. Neugebauer, U. Uchiechowska, R. Meier, H. Hruby, V. Valkov, E. Verdin, W. Sippl, M. Jung, *J. Med. Chem.* **2008**, *51*, 1203; h) L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith, C. Große, *Chem. Eur. J.* **2008**, *14*, 8956; i) S. Khelili, X. Florence, M. Bouhadja, S. Abdelaziz, N. Mechouch, Y. Mohamed, P. D. Tullio, P. Lebrun, B. Pirotte, *Bioorg. Med. Chem.* **2008**, *16*, 6124; j) A. Coi, A. M. Bianucci, V. Calderone, L. Testai, M. Digiacomo, S. Rapposelli, A. Balsamo, *Bioorg. Med. Chem.* **2009**, *17*, 5565.

109) CCDC-980292 for (−)-**110a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

110) For the excellent work on studying supramolecular complexes through electrospray ionization mass spectrometry, see: a) K. Breuker, F. W. McLafferty, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 18145; b) A. D. Tullio, S. Reale, F. D. Angelis, *J. Mass Spectrom.* **2005**, *40*, 845; c) J. A. Loo, *Int. J. Mass Spectrom.* **2000**, *200*, 175.

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## *LIST OF PUBLICATIONS*

1. "Phthalamidoacetaldehyde in Organocatalytic Reductive Couplings: Synthesis of Highly Useful Synthons for the Natural Products, GABA Drug Anlogues and Wieland-Mischer Ketones", **P. Srinivasa Reddy**, D. B. Ramachary (*to be communicated).*

2. "Dynamic Kinetic Resolution through Proline-catalyzed Robinson Annulation Reactions", **P. Srinivasa Reddy**, D. B. Ramachary (*to be communicated).*

3. "A General Approach to Chiral 8-Hydroxy-2-thiabicyclo[3.3.1]nonane-4,9-diones *via* Direct Amine-catalyzed Reductive Coupling, Michael and Aldol reactions", **P. Srinivasa Reddy**, D. B. Ramachary (*to be communicated).*

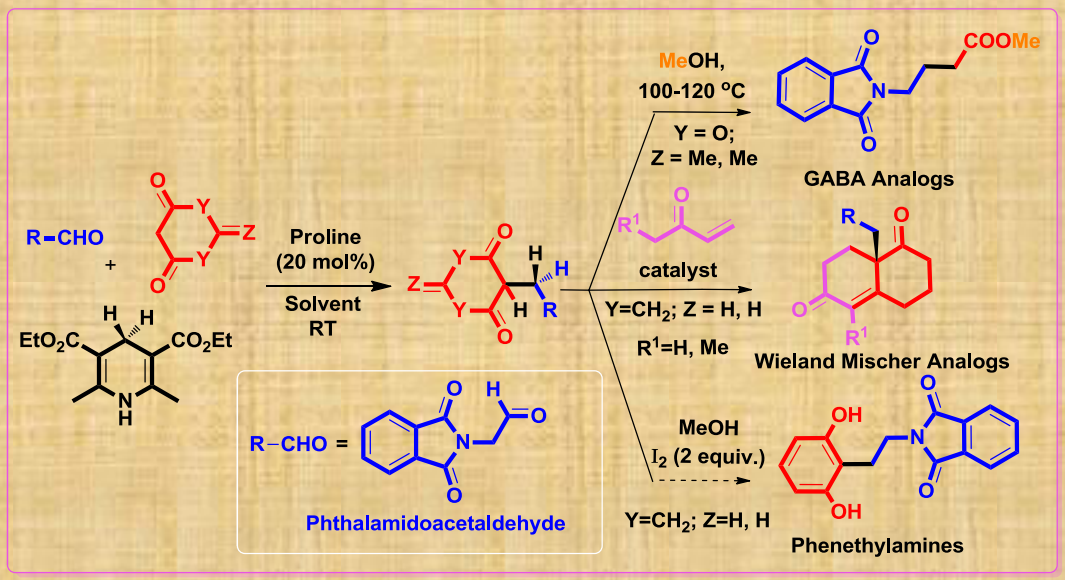
4. "Neighboring *ortho*-Hydroxy Group Directed Catalytic Asymmetric Triple Domino Reactions of Acetaldehyde with (*E*)-2-(2-Nitrovinyl)phenols", D. B. Ramachary, **P. Srinivasa Reddy**, M. Shiva Prasad, *Eur. J. Org. Chem.* **2014**, *15*, 3076–3081.

5. "Direct Organocatalytic Stereoselective Transfer Hydrogenation of Conjugated Olefins of Steroids", D. B. Ramachary, Rajasekar Sakthidevi, **P. Srinivasa Reddy**, *RSC Adv.* **2013**, *3*, 13497–13506.

6. "Formal Asymmetric Total Synthesis of Sesquiterpenoid-Sativene". D. B. Ramachary, **P. Srinivasa Reddy** (*to be communicated*).

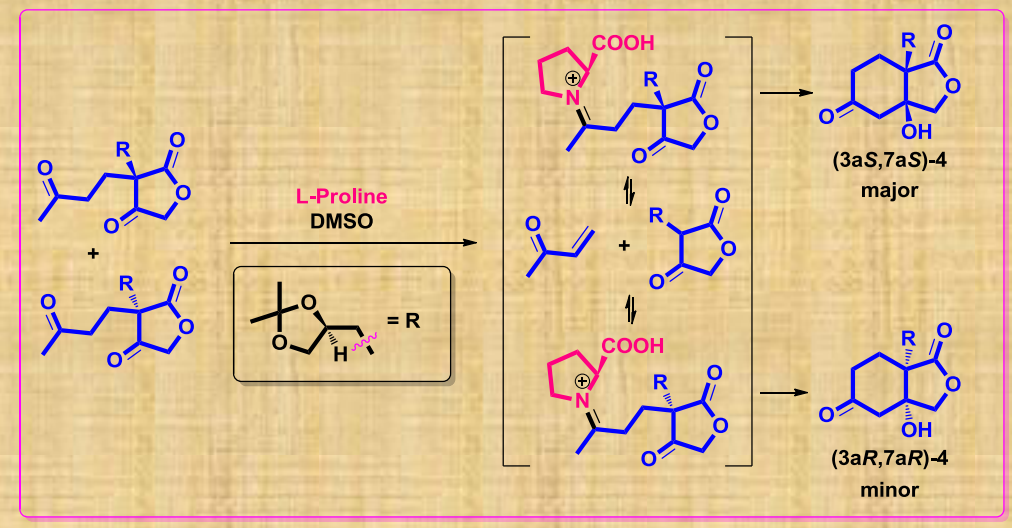
7. "Organocatalytic Reductive Coupling Reaction: Scope and Synthetic Applications", D. B. Ramachary, **P. Srinivasa Reddy**, M. Kishor (*to be communicated*).

## 1. PHTHALAMIDOACETALDEHYDE IN ORGANOCATALYTIC REDUCTIVE COUPLINGS: SYNTHESIS OF HIGHLY USEFUL SYNTHONS FOR THE NATURAL PRODUCTS, GABA DRUG ANLOGUES AND WIELAND-MISCHER KETONES.



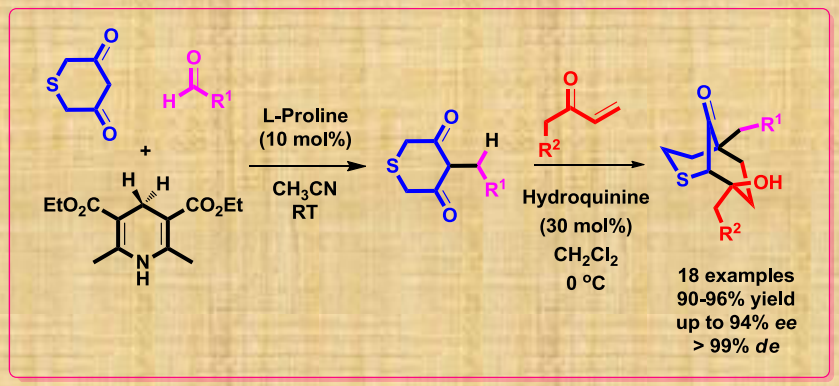

*To be communicated.*

## 2. DYNAMIC KINETIC RESOLUTION THROUGH PROLINE-CATALYZED ROBINSON ANNULATION REACTIONS.



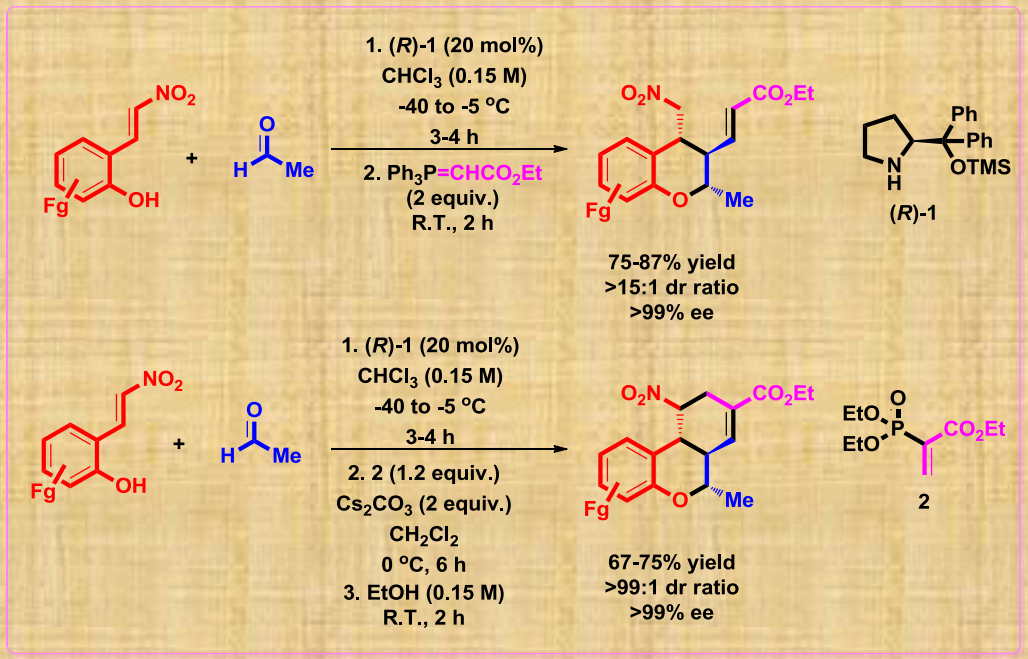

*To be communicated.*

## 3. A General Approach to Chiral 8-Hydroxy-2-thiabicyclo[3.3.1]nonane-4,9-diones *via* Direct Amine-Catalyzed Cascade Reductive Coupling, Michael and Aldol Reactions.




*To be communicated.*

## 4. Neighboring *ortho*-Hydroxy Group Directed Catalytic Asymmetric Triple Domino Reactions of Acetaldehyde with (*E*)-2-(2-Nitrovinyl)phenols.




*Eur. J. Org. Chem.* **2014**, *15*, 3076–3081.