High-yielding Stereoselective Synthesis of Bioactive Molecules through TCRA and Barbas Dienamine Platform

A Thesis
Submitted for the Degree of

Doctor of Philosophy

By

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UNIVERSITY OF HYDERABAD
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DEDICATED TO MY PARENTS

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

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CERTIFICATE

*Certified that the work contained in the thesis entitled "**High-yielding Stereoselective Synthesis of Bioactive Molecules through TCRA and Barbas Dienamine Platform"** has been carried out by **Mr. Vijayendar Reddy Yedulla** under my supervision and the same has not been submitted elsewhere for a degree.*

Dr. Dhevalapally B. Ramachary

(***Thesis Supervisor***)

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CONTENTS

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PREFACE

*Organocatalysis has emerged as a powerful synthetic paradigm that is complementary to metal-catalyzed transformations and has accelerated the development of new methods to make diverse chiral molecules. In recent years, organocatalytic cascade, multi-component and multi-catalysis cascade (MCR/MCC) reactions have been utilized for the synthesis of complex enantiomerically enriched molecules having multiple stereocenters. In comparison to traditional stepwise approaches, the uninterrupted sequence of reactions in one flask reduces the number of manual operations, thereby saving time, effort and production costs. The present thesis entitled "**High-yielding Stereoselective Synthesis of Bioactive Molecules through TCRA and Barbas Dienamine Platform**" describes the synthesis of highly functionalized chiral molecules of Pharmaceutical and biological importance using multi-catalysis cascade (MCC) reactions. In all sections, a brief introduction is provided to keep the present work in proper perspective, the compounds are sequentially numbered (bold), and references are marked sequentially as superscript and listed at the end of the thesis. All the figures included in the thesis were obtained by DIRECT PHOTOCOPY OF THE ORIGINAL SPECTRA, and in some of them uninformative areas have been cut to save the space.*

Highly functionalized heterocycles such as chromenes, chromenones and xanthenones have found wide applications as pharmaceutical drugs, drug intermediates and drug ingredients. To construct such complex molecules a diversity-oriented green synthesis is required. Here we achieved using simple starting materials such as 1,3-diones, salicylic aldehydes, Hantzsch ester and diazomethane through cascade three-component reductive alkylation (TCRA) and three-component reductive alkylation/oxy-Michael/dehydration (TCRA/OM/DH) and three-component reductive alkylation/alkylation/oxy-Michael/dehydration (TCRA/A/OM/DH) reaction sequences in one-pot under stereospecific organo- and organo/Brønsted acid- and self/base-catalysis.

In continuation to the development of TCRA platform, synthesis of highly functionalized chiral building blocks achieved via three component reductive alkylation (TCRA) as an important step. Here, we developed the one-step alkylation of CH-acids with chiral aldehydes and Hantzsch ester through organocatalytic TCRA strategy. In continuation, using combination of L-proline/Brønsted acid-catalyzed cascade three-component reductive alkylation/lactonization/esterification and three-component reductive alkylation/esterification reactions of CH-acids, chiral aldehydes, Hantzsch ester constructed the highly functionalized chiral γ-butyrolactones and protected γ-carboxy-L/D-glutamic acids in good to high yields. This TCRA strategy provided access to HIV-1 protease inhibitors, phospholipase A_2 inhibitors, antibiotic agglomerins, (R)-γ-hexanolide and (+)*-brefeldin-A.*

In the third chapter we carried out the synthesis of highly functionalized molecules through Barbas dienamine platform, Here we developed the facile synthesis of highly functionalized cyclohexanes via proline catalyzed cascade annulations from simple substrates such as aldehydes, enones and CH-acids through olefination/Diels-Alder/epimerization and olefination/Diels-Alder/epimerization/three-component reductive alkylation reaction sequence. In this reaction we observed the novel epimerization at β-position to carbonyl of the trans-isomer to the more stable cis-isomer.

In continuation to the synthesis of bioactive molecules through Barbas dienamine platform, herein we report the amino acid-catalyzed diastereospecific three-component Diels-Alder (DTCDA) reactions that produce highly functionalized chiral spiro[5,5]undecane-1,5,9-triones from commercially available 4-substituted-3-buten-2-ones, protected glyceraldehydes and CH-acids through modern dienamine chemistry. Functionalized chiral spiro[5,5]undecane-1,5,9-triones are biologically active compounds and also attractive intermediates in the total synthesis of natural products.

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
cm	centimeter
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
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplet
ee	enantiomeric excess
ELISA	enzyme-linked immunosorbent assay
eq.	equation
equiv.	equivalent(s)
Et	ethyl
FBS	fetal bovine serum
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

HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
H-P ketone	Hajos-Parrish ketone
^{i}Pr	isopropyl
IR	infrared
lit.	literature
LUMO	lowest unoccupied molecular orbital
m	multiplet
m-CPBA	*m*-chloro perbenzoic acid
M	molarity
Mp.	melting point
Me	methyl
mg	milligram (s)
mL	milliliter
mmol	millimole
MOPAC	molecular orbital package
MVK	methyl vinyl ketone
NEP	neutral endopeptidase
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
PBS	phosphate-buffered saline
PCC	pyridinium chlorochromate
Ph	phenyl
Pg	protecting group
PM3	parameterized model number 3
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
py	pyridine
pr	propyl
q	quartet
RT	room temperature
s	singlet
sec	secondary
t	triplet
td	triplet of doublet
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TsCl	toluenesulphonyl chloride
UV	ultraviolate
W-M ketone	Wieland-Miescher ketone

ABOUT THE AUTHOR

The author, **Mr. Y. Vijayendar Reddy** was born on 27th July 1984 at Mogilidory, Nalgonda district and Andhra Pradesh. After his initial schooling in Chinnakaparthy, he obtained his B.Sc. degree in 2004 from P. G. College of Science, Osmania University, Hyderabad; and M. Sc., degree in 2006 from University of Hyderabad, Hyderabad. He continued as research scholar in the School of Chemistry, University of Hyderabad for the Ph. D. programme from July 2006 onwards.

LIST OF PUBLICATIONS

1. D. B. Ramachary, M. Kishor and **Y. Vijayendar Reddy**, "Development of Pharmaceutical Drugs, Drug Intermediates and Ingredients by Using Direct Organo-Click Reactions", ***Eur. J. Org. Chem.*, 2008,** 975–993.

2. D. B. Ramachary, **Y. Vijayendar Reddy** and B. Veda Prakash, "Double Cascade Reactions Based on the Barbas Dienamine Platform: Highly Stereoselective Synthesis of Functionalized Cyclohexanes for Cardiovascular Agents", ***Org. Biomol. Chem.*, 2008,** *6*, 719-726.

3. D. B. Ramachary, **Y. Vijayendar Reddy** and M. Kishor, "Multi-Catalysis Reactions: Direct Organocatalytic Sequential One-Pot Synthesis of Highly Functionalized Cyclopenta[*b*]chromen-1-ones", ***Org. Biomol. Chem.*, 2008,** *6*, 4188-4197.

4. D. B. Ramachary, C. Venkaiah, **Y. Vijayendar Reddy** and M. Kishor, "Multi-Catalysis Cascade Reactions Based on the Methoxycarbonylketene Platform: Diversity-Oriented Synthesis of Functionalized Non-Symmetrical Malonates for Agrochemicals and Pharmaceuticals", ***Org. Biomol. Chem.*, 2009,** *7*, 2053-2062.

5. D. B. Ramachary and **Y. Vijayendar Reddy**, "A General Approach to Chiral Building Blocks via Direct Amino Acid-Catalyzed Cascade Three-Component Reductive Alkylations: Formal Total Synthesis of HIV-1 Protease Inhibitors, Antibiotic Agglomerins, Brefeldin A, and (R)-γ-Hexanolide", ***J. Org. Chem.,* 2010,** *75*, 74–85.

6. D. B. Ramachary, **Y. Vijayendar Reddy**, A. Banerjee and S. Banerjee, "Design, Synthesis and Biological Evaluation of Optically Pure Functionalized Spiro[5,5]undecane-1,5,9-triones as HIV-1 Inhibitors", ***Org. Biomol. Chem.,* 2011,** *9*, 7282-7286.

7. D. B. Ramachary and **Y. Vijayendar Reddy**, "Dienamine-catalysis: An Emerging Technology in Organic Synthesis", ***Eur. J. Org. Chem.,* 2011,** 000-000 (*Invited Review*).

Posters and Presentations

1. Presented a poster entitled "A General Approach to Chiral Building Blocks via Direct Amino Acid-Catalyzed Cascade Three-Component Reductive Alkylations: Formal Total Synthesis of HIV-1 Protease Inhibitors, Antibiotic Agglomerins, Brefeldin A, and (*R*)-γ-Hexanolide." in 7th in-house symposium *"**Chemfest-2010**"* held at University of Hyderabad, Hyderabad, India on Jan 9-10th, 2010.
2. Given a flash oral presentation entitled "A General Approach to Chiral Building Blocks via *TCRA* Reaction: Formal Total Synthesis of HIV-1 Protease Inhibitors, Antibiotic Agglomerins, Brefeldin A and (*R*)-γ-Hexanolide." in 6th "*J-NOST Conference*" held at University of Hyderabad, Hyderabad, India on Jan 28-31st, 2011.
3. Given a flash oral presentation entitled "Development of Cascade Reactions Based on the Barbas Dienamine and *TCRA* Platform." in 8th in-house symposium *"**Chemfest-2011**"* held at University of Hyderabad, Hyderabad, India on Feb 25-26th, 2011.

High-Yielding Stereoselective Synthesis of Bioactive Molecules through TCRA and Barbas Dienamine Platform

1. ABSTRACT

We developed the new technology called multi-catalysis for the sequential one-pot synthesis of highly functionalized heterocycles. A practical and novel multi-component aniline-, self- and Brønsted acid-catalyzed selective process for the sequential one-pot synthesis of highly substituted 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones, 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones and 3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-ones is reported. Direct combination of aniline- and self-catalyzed cascade three-component reductive alkylation (*TCRA*) and Brønsted acid-catalyzed cascade oxy-Michael/dehydration (OM/DH) of 1,3-diones, salicylic aldehydes and organic-hydride is developed in one-pot to furnish the highly functionalized 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones and 3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-ones with high yields.

Multi-catalysis cascade (MCC) process for the synthesis of highly substituted chiral building blocks (2-alkyl-CH-acids, 2-alkyl-cyclohexane-1,3-diones, 2-alkyl-cyclopentane-1,3-diones and H-P ketone analogs) is presented based on the cascade three-component reductive alkylation's (TCRA) platform. Herein, we developed the high-yielding alkylation

of variety of CH-acids with (*R*)-glyceraldehyde acetonide/(*S*)-Garner aldehyde and Hantzsch ester through amino acid-catalyzed TCRA reaction without racemization at α-position to carbonyl. Direct sequential combination of L-proline-catalyzed TCRA reaction with other reactions like cascade alkylation/ketenization/esterification (A/K/E), alkylation/ketenization/esterification/alkylation (A/K/E/A), Brønsted acid-catalyzed cascade hydrolysis/lactonization/esterification (H/L/E), hydrolysis/esterification (H/E), hydrolysis/oxy-Michael/dehydration (H/OM/DH) and Robinson annulation (RA) of CH-acids, chiral aldehydes, Hantzsch ester, diazomethane, methyl vinyl ketone, various active olefins and acetylenes furnished the highly functionalized chiral building blocks in good to high yields with excellent diastereoselectivities. In this context, many of the pharmaceutically applicable chiral building blocks were prepared via MCC reactions.

Amino acid, proline catalyzed the three- and five-component cascade olefination/Diels-Alder/epimerization and olefination/Diels-Alder/epimerization/three-component reductive alkylation reactions of readily available precursors enones, arylaldehydes, alkyl cyanoacetates and Hantzsch ester to furnish highly substituted prochiral 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters and 1-cyano-4-(cyano-alkoxycarbonyl-methyl)-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters in a highly diastereoselective fashion with excellent yields. Prochiral *cis*-isomers are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products.

Herein, we have designed and prepared the single-step amino acid-catalyzed diastereospecific synthesis of optically pure highly functionalized spiro[5,5]undecane-1,5,9-triones over four stereoisomers in very good yields with >99% ee/de from three components. Preliminary biological *in vivo* screening on these molecules revealed that, (4'*R*,7*S*,11*S*)-7-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-dimethyl-11-phenyl-2,4-dioxaspiro[5.5]undecane-1,5,9-trione and (4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-3,3-dimethyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione become as lead HIV-1 inhibitors than known antiretroviral drug of azidothymidine (AZT).

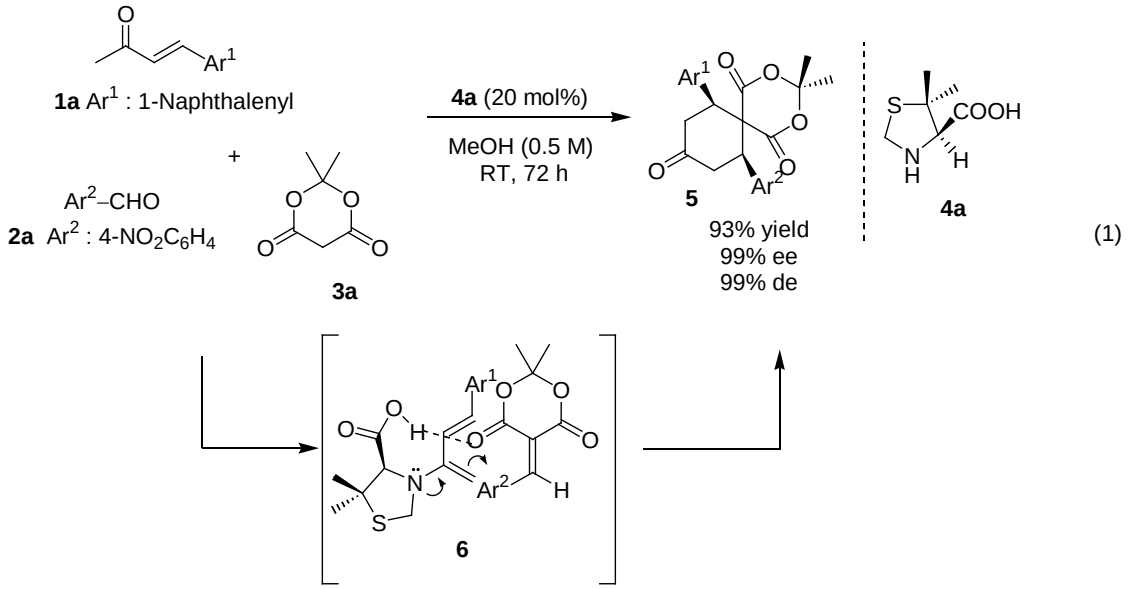
2. INTRODUCTION

Organic synthesis has evolved to a stage, where any desired molecule can be synthesized with enough time, but one of the most important enduring challenges for chemists is the improving synthetic efficiency and selectivity as like cellular reactions.[1] Nature, for one, does not rely on iterative reaction sequences. It sophisticatedly combines select pieces in the midst of a cellular environment containing hundreds of compounds, wasting very little and affording near quantitative yields. The formation of several bonds in one sequence without isolating the intermediates or adding the several reagents sequentially in one-pot for the construction of complex molecules will be better path way.[2] In this regard, sequential one-pot combination of several cascade reactions will be very good technique for the synthesis of complex natural products.[3] In particular, recent developments in organocatalyzed cascade and multi-component reactions give promise that this kind of mild catalysis is suitable for the design of sequential combination of multi-catalysis and multi-component reactions in one-pot to deliver highly functionalized molecules compared to classical reactive metal-mediated reactions.[4]

As the research work described in this thesis deals with development of multi-catalysis cascade reactions through three component reductive alkylation (*TCRA*) reactions and Barbas dienamine platform,[5] a brief overview on the developments of *TCRA* and Barbas dienamine platform are presented below.

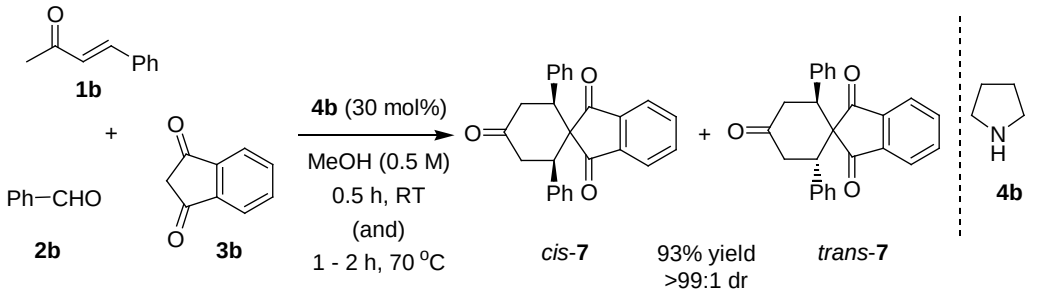
In 2003, Barbas and Ramachary reported the first organocatalytic diastereospecific and enantioselective direct asymmetric domino Knoevenagel/Diels-Alder reaction that produced highly substituted spiro[5,5]undecane-1,5,9-trione **5** via proposed transition state **6** from commercially available 4-substituted-3- buten-2-one **1a**, aldehyde **2a** and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) **3a** as shown in eq. 1.[6] Spirocyclic ketones **5** are attractive intermediates in the synthesis of natural products and in medicinal chemistry, and are the starting materials for the synthesis of

exotic amino acids which are used to modify the physical properties and biological activities of peptides, peptidomimetics and proteins.



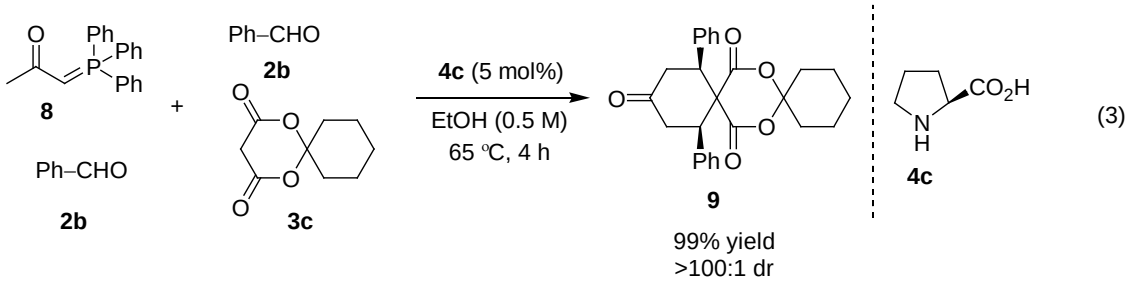
(1)

In 2003, Ramachary and Barbas reported the first highly diastereoselective organocatalytic direct hetero-domino Knoevenagel-Diels-Alder-epimerization (K-DA-E) reactions that provide highly substituted prochiral spiro[cyclohexane-1,2'-indan]-1',3',4-trione **7** from commercially available 4-substituted-3-buten-2-one **1b**, aldehyde **2b** and 1,3-indandione **3b** as shown in eq. 2.[7] Spirocyclic ketones **7** are the excellent starting materials for the synthesis of fenestranes and for the construction of graphite cuttings bearing a saddle-like, three-dimensionally distorted cores.



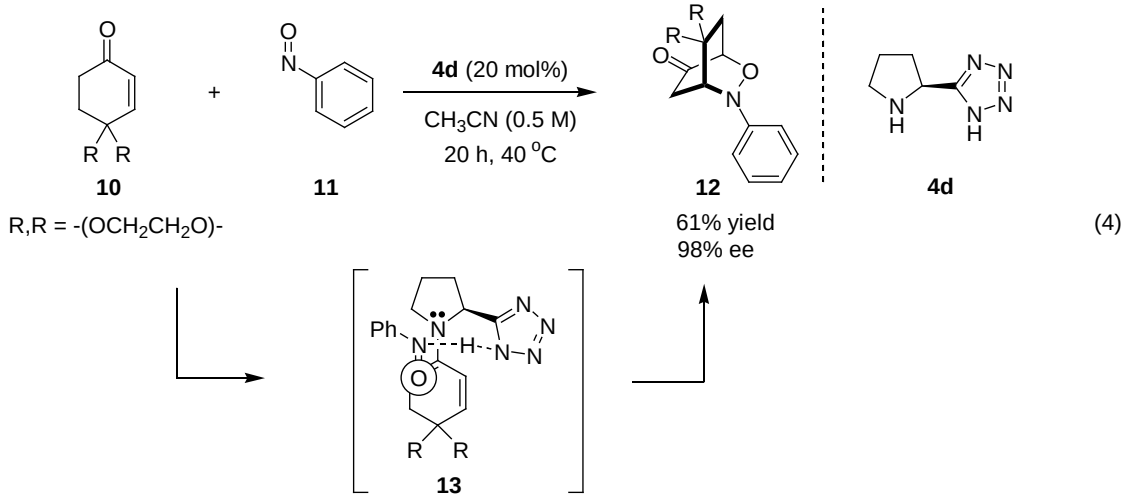
(2)

In 2004, Ramachary and Barbas reported the first organo-click reactions via combination of Wittig/Knoevenagel/Diels-Alder reaction sequence. Simple heating of phosphorane **8**, aldehyde **2b** and spirolactone **3c** with a catalytic amount of L-proline afforded the dispiro[5.2.5.2]hexadecane **9** in quantitative yields with >100:1 diastereoselectivity as shown in eq. 3.[8] This procedure is a manifestation of "organo-click chemistry" transformations.



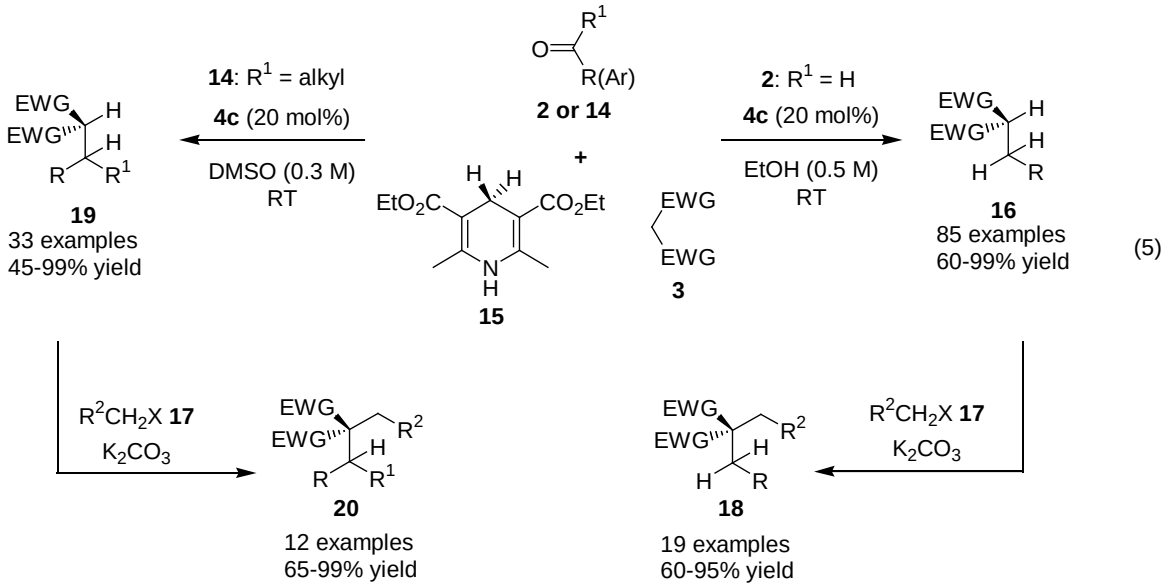
(3)

In 2004, Yamamoto *et al.* documented complete regioselective and efficient enantioselective nitroso Diels-Alder reaction by utilizing *in situ*-generated dienamines. The α,β-unsaturated ketone **10** with catalytic amount of **4d** *in situ*-generates dienamine which employed as a diene precursor with nitrosobenzene **11** to provide the cycloadduct **12** in good yield with very good enantioselectivity as shown in eq. 4.[9]



(4)

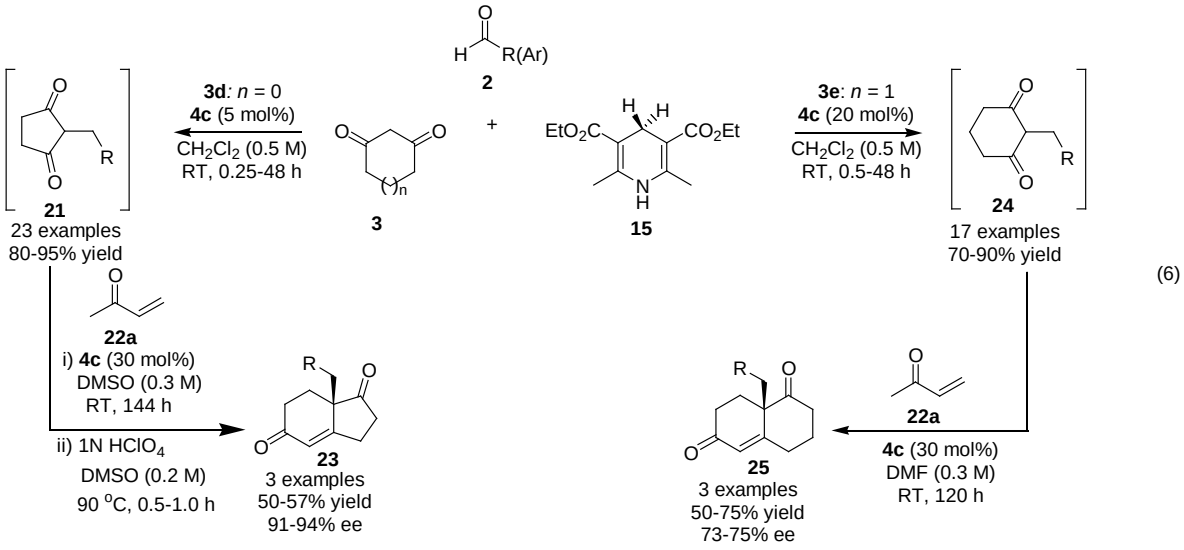
In 2006, Ramachary *et al.* first time reported the reactions of three-component reductive alkylation (*TCRA*) and three-component reductive alkylation/alkylation (*TCRA*/A) reactions of aldehydes **2**/ketones **14**, CH-acids **3**, Hantzsch ester **15** and alkyl halides **17** to afford highly functionalized molecules containing quaternary carbon **18** & **20** in very good yields as shown in eq. 5.[10] These highly functionalized molecules have wide variety of applications in pharmaceutical and medicinal chemistry.



(5)

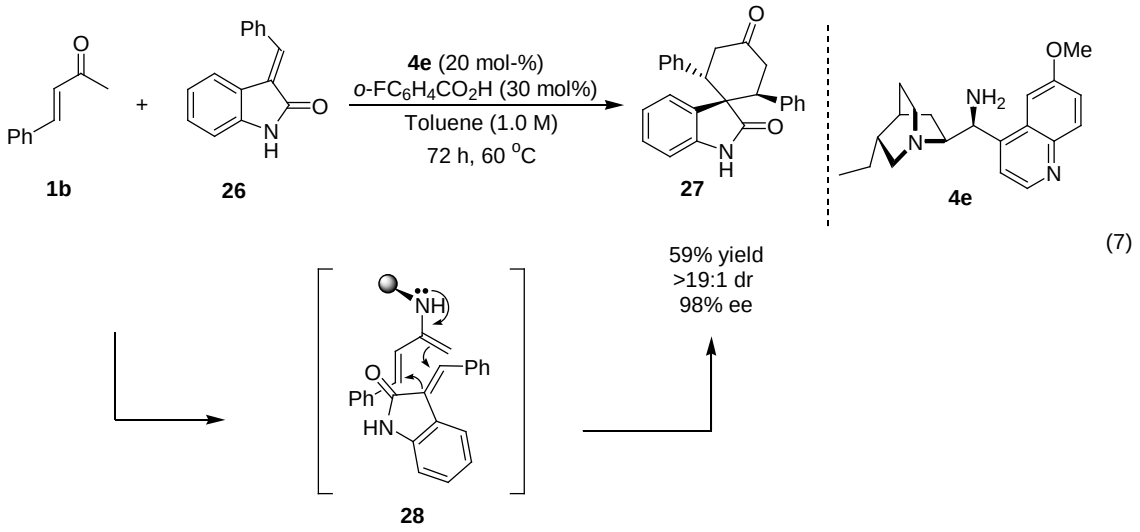
In 2007, Ramachary *et al.* reported a simple natural amino acid L-proline **10a** catalyzed three- and four-component asymmetric cascade three-component reductive alkylation (*TCRA*) and three-component reductive alkylation/Robinson annulation (*TCRA*/RA) reactions of cyclic-1,3-diones **3**, aldehydes **2**, Hantzsch ester **15** and methyl vinyl ketone **22a** to furnish the substituted 2-alkyl-cyclohexane-1,3-diones **24** and Wieland-Miescher (W-M) ketone analogues **25** with good yields and high enantioselectivities as shown in eq. 6.[11] In continuation of the development of organocatalytic cascade reactions, in 2008 the same research group demonstrated a one-pot double cascade reaction, catalyzed by L-proline **4c** to provide the substituted 2-alkyl-cyclopentane-1,3-diones **21** and Hajos-Parrish (H-P) ketone analogues **23** with

good yields and high enantioselectivities from simple starting materials via three-component reductive alkylation (*TCRA*) and three-component reductive alkylation /Robinson annulations (*TCRA*/RA) sequence as shown in eq. 6.[12]



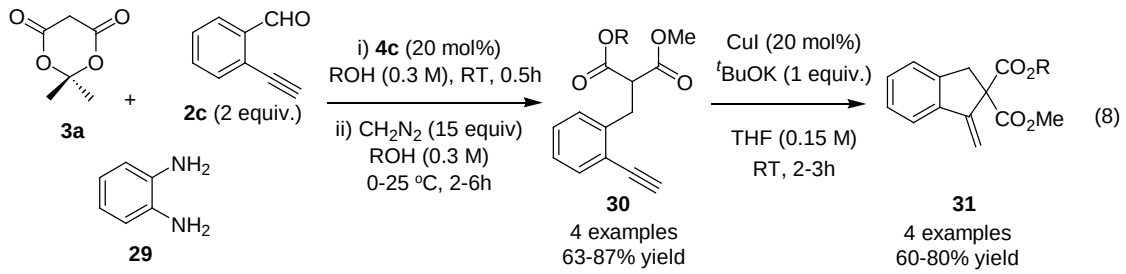
(6)

In 2009, Melchiorre *et al.* reported synthesis of spirocyclic oxindoles having multiple stereocenters through Barbas dienamine Platform. In this report, Barbas dienamine intermediate **28** which is *in situ* generated from α,β-unsaturated ketone **1b** reacts with dienophile **26** to afford the spiro-oxindole derivative **27** with good yield and moderate diastereoselectivity with high enantioselectivity as shown in eq. 7.[13] This spirocyclic oxindole core is found in a number of natural products and as well as medicinally relevant compounds.



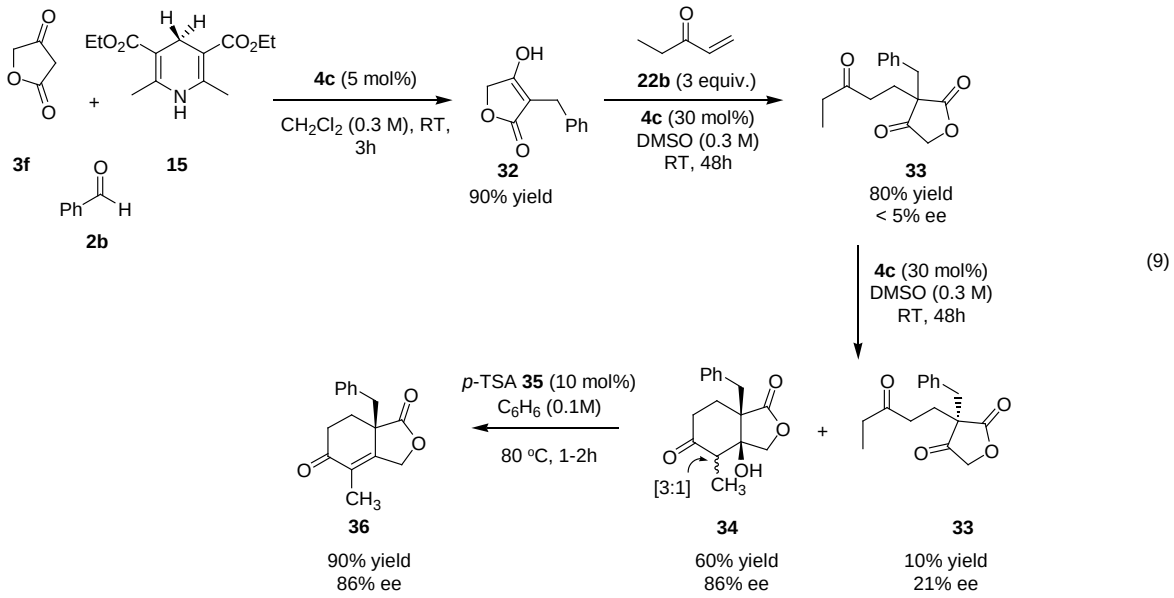
(7)

Ramachary *et al.* demonstrated the Multi-catalysis cascade (MCC) reactions for the synthesis of drug intermediates and ingredients in natural products and pharmaceutical chemistry. The same group in 2010, reported the amino acid/Cu(I) catalyzed sequential three-component reductive alkylation (*TCRA*) and carbocyclization of aldehyde **2c**, Meldrum's acid **3a** and phenylene diamine **29** to furnish highly functionalized indene derivatives **31**. In their report the reaction of aldehyde **2c**, Meldrum's acid **3a** and phenylene diamine **29** under L-proline **4c** catalysis furnishes the *TCRA* product which on *in situ* treatment with ethereal solution of diazomethane in alcoholic solvents affords the unsymmetrical substituted malonates **30** in very good yields. Functionalized unsymmetrical malonates underwent carbocyclization under Cu(I) catalysis to furnish functionalized indene **31** in very good yields as shown in eq. 8.[14]



(8)

In continuation of their quest in organocatalytic three component reductive alkylation (*TCRA*) reactions, in 2010 Ramachary *et al.* reported the synthesis of highly substituted tetrahydro-isobenzofuran-1,5-diones through combination of cascade *TCRA* and Michael-aldol reactions. The reaction of aldehyde **2b**, tetronic acid **3f** and Hantzsch ester **15** under L-proline **4c** catalysis affords the 3-benzyl tetronic acid **32**, which on treatment with ethyl vinyl ketone **22b** under proline **4c** catalysis furnishes the only Michael product **33**. Michael adduct **33** upon L-proline catalysis affords the Michael-aldol product **34** in 60% yield with 86% ee along with some unreacted Michael product **33** as shown in eq. 9.[15] In their communication they also reported that the Michael-aldol reaction proceeds in good yields with high enantioselectivity through kinetic resolution.



(9)

In continuation of synthesis of highly functionalized molecules starting from the simple materials in one-pot,[16] research work has been carried out on the synthesis of highly functionalized chiral molecules through three-component reductive alkylation

(*TCRA*) reactions and Barbas dienamine platform, and the results are presented in this thesis.

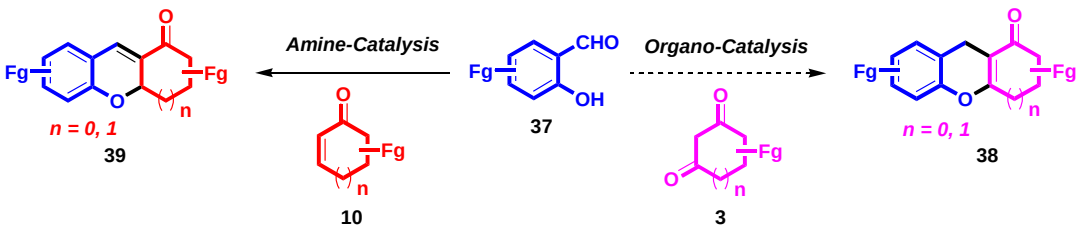
To begin with, using simple starting materials, synthesis of highly functionalized chromenones was developed through Multi-catalysis cascade approach, and the results are presented in the next sections.

3. Multi-catalysis Reactions: Direct Organocatalytic Sequential One-pot Synthesis of Highly Functionalized Cyclopenta[b]chromen-1-ones

3.1 Introduction

Heterocycles such as chromanes, chromenes, coumarins and tetrahydroxanthenones are of considerable importance in a variety of industries. As is well known, these heterocycles are widespread elements in natural products and have attracted much attention from a wide area of science, including physical chemistry, medicinal chemistry, natural product chemistry, synthetic organic chemistry and polymer science.[17] As such, the development of new and more general catalytic methods for their preparation is of significant interest.[18] Recently nucleophilic amine-catalysis is emerging for the reactions of 2-hydroxy-benzaldehyde with substituted enones under the presence of secondary and/or tertiary amines to provide general route to a variety of functionalized 2,3,4,4a-tetrahydro-xanthen-1-ones and 3,3a-dihydro-2H-cyclopenta[b]chromen-1-ones in moderate to good yields (Scheme 1).[18] But interestingly, there is no direct method for the synthesis of functionalized 2,3,4,9-tetrahydro-xanthen-1-ones and 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones from substituted 2-hydroxy-benzaldehydes and enones, which are highly useful starting materials in natural product synthesis (Scheme 1).

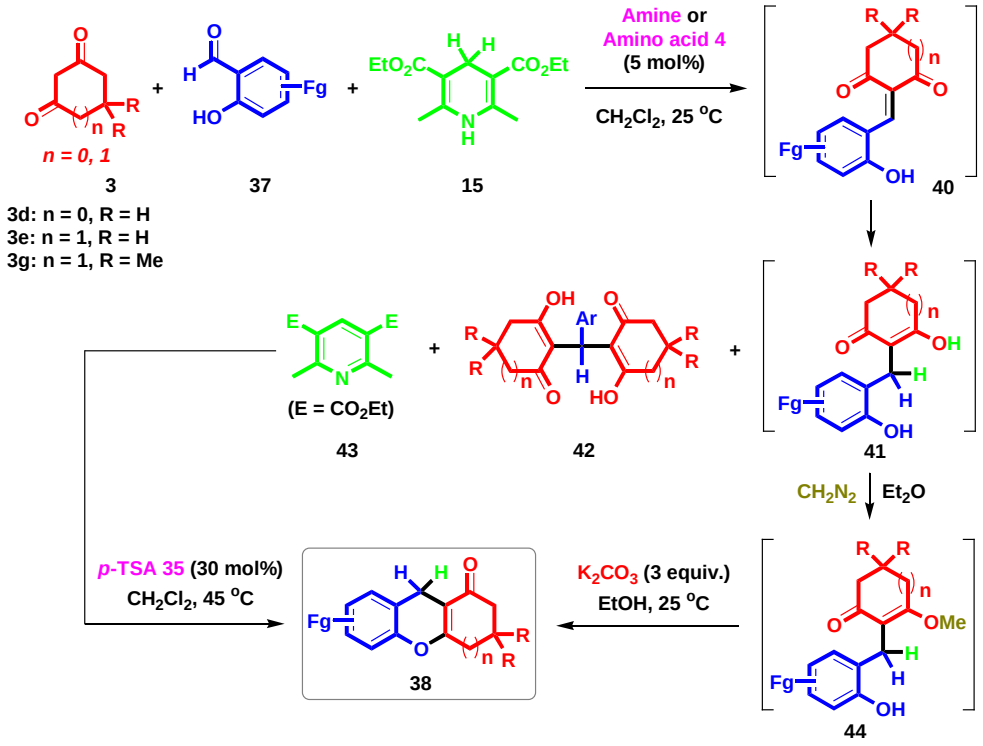
Scheme 1: Synthesis of Highly Substituted 3,9-Dihydro-2*H*-cyclopenta[b]chromen-1-ones.



Herein, we discovered a metal-free, novel and multi-catalysis technology for the synthesis of highly substituted 2,3,4,9-tetrahydro-xanthen-1-ones and 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones by using direct organocatalytic sequential one-pot three-component reductive alkylation/oxy-Michael/dehydration (*TCRA*/OM/DH) and three-component reductive alkylation/alkylation/oxy-Michael/dehydration (*TCRA*/A/OM/DH) reactions from commercially available functionalized 2-hydroxy-benzaldehydes, cyclopentane-1,3-dione or substituted cyclohexane-1,3-dione and Hantzsch ester (organic-hydride) (Scheme 1). Direct combination of amine- or amino acid-catalyzed cascade three-component reductive alkylation (*TCRA*) and Brønsted acid-catalyzed cascade oxy-Michael/dehydration (OM/DH) or combination of amine- or amino acid-catalyzed cascade three-component reductive alkylation (*TCRA*) and self-/base-catalyzed cascade alkylation/oxy-Michael/dehydration (A/OM/DH) of 1,3-diones, salicylic aldehydes, organic-hydride (Hantzsch ester) and diazomethane is developed in one-pot as shown in Scheme 2. 2,3,4,9-Tetrahydro-xanthen-1-ones and 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones are useful starting materials for the synthesis of natural products and their analogues.[17]

In continuation of our recent discovery of bio-mimetic in situ reduction of novel active olefins with Hantzsch ester **15** through self-catalysis by decreasing HOMO-LUMO energy gap between olefins and Hantzsch ester **15** in cascade reactions,[16] we initiated our studies of the cascade TCRA reaction of cyclopentane-1,3-dione **3d** with variety of 2-hydroxy-benzaldehydes **37** and Hantzsch ester **15** under amine- or amino acid-catalysis to furnish the reductive alkylation products **41** and their applications in the synthesis of pharmaceutically useful products with good yields in one-pot (see Scheme 2).

Scheme 2: Combining Multi-Catalysis and Multi-Component Systems for the One-Pot Cascade Reactions.



3.2 *Results and Discussion*

3.2.1 *Reaction Optimization for the Multi-catalysis Reactions in One-pot:*

First we focused on the optimization for high yield synthesis of 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **41da**[*] from **3d**, **37a**, **15** and **4c** through amine- or amino acid-catalysis, which is precursor for our designed cascade TCRA/OM/DH reaction. For that we initiated our studies of the cascade TCRA reaction by screening a number of known and novel organocatalysts for the reductive alkylation of cyclopentane-1,3-dione **3d** with 2-hydroxy-benzaldehyde **37a** and Hantzsch ester **15** as shown in Table 1. Based on our previous experience in the amino acid-promoted reductive alkylation of 1,3-diones with aldehydes and Hantzsch ester via cascade TCRA reactions,[16] we chose CH_2Cl_2 as solvent; and then we decided to investigate the catalyst effect on cascade TCRA reaction of **3d**, **37a** and **15**. It is well established that self-catalyzed reaction of

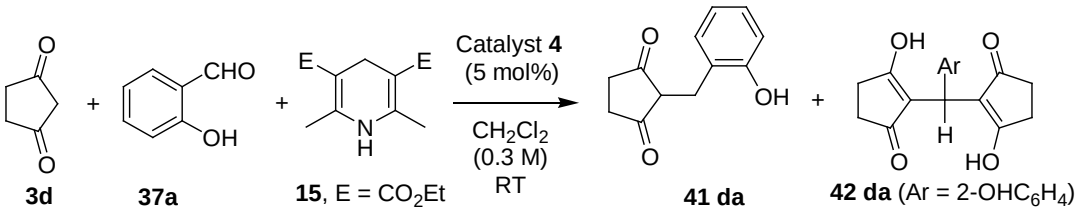
[*] In all compounds denoted **41xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

cyclopentane-1,3-dione **3d** with 3 equiv. of 2-hydroxy-benzaldehyde **37a** furnished only the unexpected bis-adduct **42da**[*] without the expected olefination product 2-(2-hydroxy-benzylidene)-cyclopentane-1,3-dione **40da**[*] (result not shown in Table 1). The same reaction under proline-catalysis also furnished only the bis-adduct **42da** without the product 2-(2-hydroxy-benzylidene)-cyclopentane-1,3-dione **40da**, with reduced reaction time (result not shown in Table 1). Interestingly, proline-catalyzed reaction of cyclopentane-1,3-dione **3d** and 3 equiv. of 2-hydroxy-benzaldehyde **37a** with Hantzsch ester **15** furnished the expected reductive alkylation product **41da** in 80% yield accompanied by the bis-adduct **42da** in 20% yield after 28 h at 25 °C in CH_2Cl_2 as shown in Table 1, entry 1. These preliminary results prompted us to investigate the catalyst effect on in situ trapping of olefination product of cyclopentane-1,3-dione **3d** with 2-hydroxy-benzaldehyde **37a** through bio-mimetic hydrogenation as shown in Table 1. Interestingly, proline-catalyzed cascade TCRA reactions of **3d**, **37a** and **15** are catalyst dependent reactions as shown in Table 1. Simple amino acid glycine **4f** also catalyzed the cascade TCRA of **3d**, **37a** and **15** but result is not superior as compared to proline-catalysis (Table 1, entry 2). The cascade TCRA reaction of **3d**, **37a** and **15** catalyzed by simple amines like benzylamine **4h**, piperidine **4i** and pyrrolidine **4b** in CH_2Cl_2 are also not superior as compared to proline-catalysis with respect to yields as shown in Table 1, entries 4-6. Interestingly, the reaction rate for cascade TCRA under primary amine, benzylamine **4h**-catalysis is 7-fold enhanced compare to other amine catalysts **4b, 4i** or amino acid catalyst **4c, 4f** as shown in Table 1. To increase the dynamics of the cascade TCRA reaction without generating the by-product of bis-adduct **42da**, a suitable amine catalyst is required. Recently, Dawson and coworkers from the Scripps Research Institute found that aniline is a potent nucleophilic catalyst for imine-type reactions.[19] Aniline is a mild nucleophile, which strongly catalyzes aqueous reactions of aldehydes and ketones with amines to form stable imines (RR'C=NR'') such as hydrazones (RR'C=NNHR'') and oximes (RR'C=NOR'').

[*] In all compounds denoted **40xy** and **42xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

In a similar fashion, aniline should catalyze olefination reaction under non-aqueous conditions. Here we show that the dynamics of the cascade TCRA reaction can be significantly accelerated by using aniline as a nucleophilic catalyst.

***Table 1*:** Effect of Catalyst on the Direct Amino Acid or Amine-Catalyzed Reductive Alkylation of **3d** with **37a** and **15**[a]



entry	catalyst **4** (5 mol%)	time (h)	conversion (%)[b]	products yield (%)[c]	
				41 da	**42 da**
1	proline **4c**	28	>99	80	20
2	glycin **4f**	48	75	50	20
3	aniline **4g**	2	>99	80	15
4	benzylamine **4h**	4	>99	80	15
5	piperidine **4i**	24	>95	80	15
6	pyrrolidine **4b**	24	>95	80	15

[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv of **37a** and 1.0 equiv of **15** relative to the **3d** (0.3 mmol) in the presence of 5 mol% of catalyst. [b] Conversion based on TLC analysis. [c] Yield refers to the column purified product.

Surprisingly, the cascade TCRA reaction of **3d**, **37a** and **15** in CH_2Cl_2 under 5 mol% of aniline-catalysis furnished the expected hydrogenated reductive alkylation product **41da** in 80% yield accompanied with 15% yield of bis-adduct **42da** within 2 h at 25 °C (Table 1, entry 3). Interestingly, cascade TCRA reaction rate for aniline-catalysis is 14-fold enhanced compared to proline- or secondary amines-catalysis as shown in Table 1.

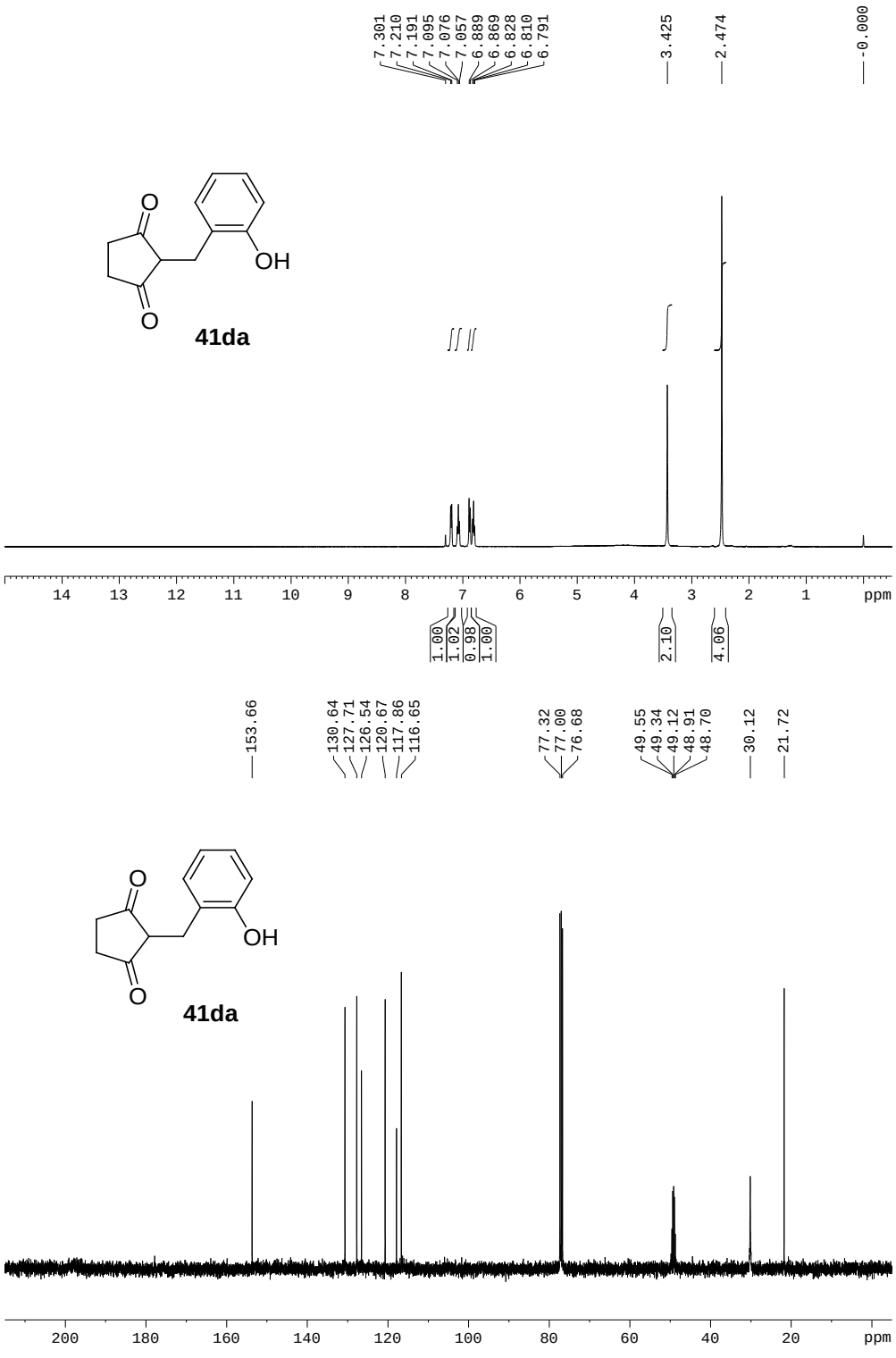


Figure-1: ^{1}H NMR and ^{13}C NMR Spectrum of Product **41da**.

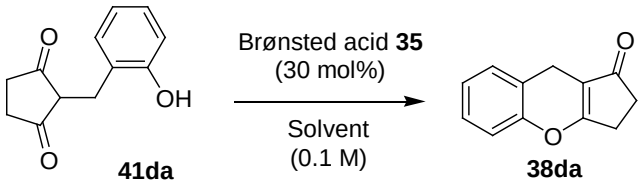
We envisioned the optimized condition to be mixing the 3 equiv. of 2-hydroxy-benzaldehyde **37a** with cyclopentane-1,3-dione **3d** and Hantzsch ester **15** at 25 °C in CH_2Cl_2 under 5 mol% of aniline-catalysis to furnish the hydrogenated product, 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **41da**[*] in 80% yield (Table 1, entry 3). A mechanistic aspect of this selective cascade TCRA reaction is discussed in the next section.

With an efficient aniline-catalyzed cascade reductive alkylation protocol in hand, we continued our investigation of optimization for the synthesis of functionalized 3,9-dihydro-2H-cyclopenta[b]chromen-1-one **38da**[*] from 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **41da** under Brønsted acid-catalysis through cascade oxy-Michael/dehydration (OM/DH) reactions as shown in Table 2. The results in Table 2 demonstrate that *p*-TSA **35a** is the suitable Brønsted acid-catalyst for cascade OM/DH reaction compared to other Brønsted acid catalysts **35a-h** or Lewis acid catalyst **35c**. Treatment of 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **41da** with 30 mol% of $HClO_4$ in CH_2Cl_2 at 25 °C furnished the expected cascade product **38da** in only 20% yield, but interestingly there is no cascade reaction under $BF_3.OEt_2$ catalysis even at hot conditions (Table 2, entries 1-2). Cascade OM/DH reaction of **41da** in CH_2Cl_2 at 25 °C under CH_3SO_3H-catalysis furnished **38da** in only 45% yield, but interestingly there is no cascade reaction under CF_3SO_3H-catalysis (Table 2, entries 3-4). (+)-Camphor sulfonic acid catalyzed the cascade OM/DH reaction of **41da** to furnish the product **38da** with 70% yield in CH_2Cl_2 at 25 °C for 48 h (Table 2, entry 5). Interestingly, same reaction under *p*-TSA catalysis furnished the expected product **38da** in 80% yield (Table 2, entry 7). Phosphoric acid-catalysis for the synthesis of cascade product **38da** is not superior as compare to *p*-TSA catalysis (Table 2, entries 9-10). We envisioned the optimized condition to be mixing the 30 mol% of *p*-TSA **35a** with 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **41da** at 45 °C in CH_2Cl_2 for 10 h to furnish the cascade

* In all compounds denoted **41xy** and **38xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

OM/DH product, 3,9-dihydro-2H-cyclopenta[b]chromen-1-one **38da** in 90% yield (Table 2, entry 8).

Table 2: Reaction Optimization for the Brønsted acid-Catalyzed Cascade OM/DH Reaction of **41da**[a]



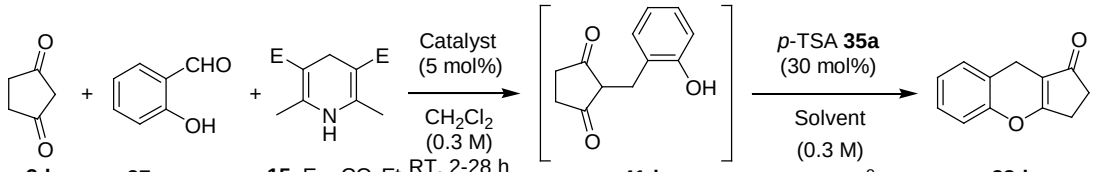
entry	catalyst **35** (30 mol%)	solvent (0.1 M)	time (h)	temperature (^oC)	yield (%)[b] **38da**
1	$HClO_4$ **35b**	CH_2Cl_2	48	25	20
2	$BF_3.OEt_2$ **35 c**	CH_2Cl_2	48	25	–
3	CH_3SO_3H **35 d**	CH_2Cl_2	48	25	45
4	CF_3SO_3H **35 e**	CH_2Cl_2	48	25	–
5	(+)-CSA **35 f**	CH_2Cl_2	48	25	70
6	*p*-TSA **35 a**	$CH_3C_6H_5$	10	95	80
7	*p*-TSA **35 a**	CH_2Cl_2	16	25	80
8	*p*-TSA **35 a**	CH_2Cl_2	10	45	90
9	$(PhO)_2PO_2H$ **35 g**	CH_2Cl_2	40	25	73
10	(*R*)-BNDHP **35 h**[c]	CH_2Cl_2	48	25	50

[a] Reactions were carried out in solvent (0.1 M) with 30 mol% of catalyst **35**. [b] Yield refers to the column purified product. [c] (*R*)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate **35h** and catalyst **35h** was taken as 5 mol%.

After successful optimization of the aniline-catalyzed cascade TCRA and Brønsted acid-catalyzed cascade OM/DH reactions, we decided to investigate the combination of these two cascade reactions in one-pot as shown in Table 3. Cascade TCRA reaction of three equiv. of 2-hydroxy-benzaldehyde **37a** with cyclopentane-1,3-dione **3d** and Hantzsch ester **15** under proline-catalysis in CH_2Cl_2 at 25 °C for

28 h furnished the expected cascade product **41da**, which on evaporation of the solvent CH_2Cl_2 and treatment with 30 mol% of *p*-TSA **35a** at 100 °C in toluene solvent for 10 h furnished the expected sequential one-pot TCRA/OM/DH product **38da** in >99% conversion with 50% yield as shown in Table 3, entry 1. Combination of two cascade TCRA and OM/DH reactions under aniline- and *p*-TSA-catalysis in one-pot was also demonstrated to furnish the sequential one-pot product **38da** in >99% conversion with 50% yield as shown in Table 3, entry 4. Interestingly, combination of two cascade TCRA and OM/DH reactions under proline or aniline- and *p*-TSA-catalysis in CH_2Cl_2 solvent did not furnish the sequential one-pot product **38da** with >99% conversion, but furnished only with ≤50% conversion at 45 °C for 48 h as shown in Table 3, entry 3 may be due to the strong acid-base interactions of *p*-TSA with the pyridine byproduct of 2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester **43**.

***Table 3*:** Reaction Optimization for the Organo-/Brønsted acid-Catalyzed One-Pot Synthesis of **38da**[a]



3d **37a** **15**, E = CO_2Et **41da** **38da**

entry	catalyst (5 mol%)	time (h)	solvent (0.3 M)	temperature (^oC)	time (h)	conversion (%)[b]	yield (%)[c] **38da**
1	proline **4c**	28	$CH_3C_6H_5$	100	10	>99	50
2	proline **4c**	28	$CH_3C_6H_5$	90	10	>99	50
3	proline **4c**	28	CH_2Cl_2	45	48	50	–
4	aniline **4g**	2	$CH_3C_6H_5$	100	10	>99	50

[a] See Experimental Section. [b] Conversion based on TLC analysis. [c] Yield refers to the column purified product.

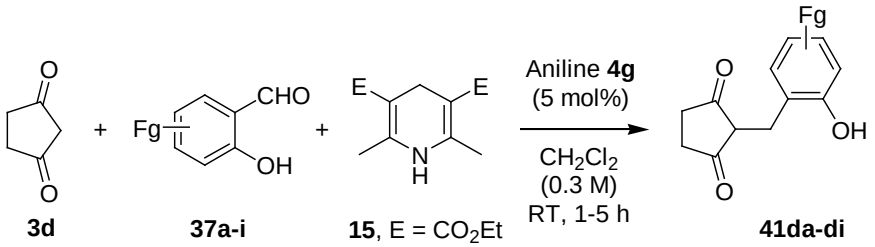
3.2.2 Diversity-Oriented Synthesis of Reductive Alkylation Products 41da-41di: With the three cascade optimized reaction conditions in hand, the scope of the aniline-catalyzed TCRA, *p*-TSA-catalyzed OM/DH and aniline-/*p*-TSA-catalyzed TCRA/OM/DH cascade reactions was investigated with cyclopentane-1,3-dione **3d**, various functionalized 2-hydroxy-benzaldehydes **37a-i** and Hantzsch ester **15** as shown in Tables 4 and 5. A series of functionalized 2-hydroxy-benzaldehydes **37a-i** (3 equiv.) were reacted with cyclopentane-1,3-dione **3d** and Hantzsch ester **15** catalyzed by 5 mol% of aniline at 25 °C in CH_2Cl_2 (Table 4). The substituted 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **41da-41di**[*] were obtained as single isomers (tautomer) with excellent yields. The cascade reaction of cyclopentane-1,3-dione **3d** with 2,3-dihydroxy-benzaldehyde **37b** and **15** furnished the reductive alkylation product **41db** as single isomer (tautomer), in 85% yield after 5 h at 25 °C (Table 4). Synthesis of functionalized 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **41da-41di** from **3d**, **37a-i** and **15** at 25 °C under aniline-catalysis has taken shorter reaction times (1 to 5 h), compared to proline-catalysis as shown in Tables 1 and 4. Interestingly, aniline-catalyzed reductive alkylation reaction of cyclopentane-1,3-dione **3d** with 5-chloro-2-hydroxy-benzaldehyde **37g**/5-bromo-2-hydroxy-benzaldehyde **37h** and Hantzsch ester **15** generated the expected cascade products **41dg**/**41dh** in excellent yields with very good selectivity (Table 4). Structure and regio-chemistry of cascade products **41da-di** were confirmed by NMR analysis [for example see Fig. 1 & 2] and also by X-ray structure analysis on **41dd** as shown in Scheme 3.[20] Interestingly, these 2-alkyl-cyclopentane-1,3-diones **41** existed as an enol in both solid and solution state may be due to the strong intermolecular hydrogen bonding and this same concept is observed in many other 1,3-diketones.[6] The chemical shifts of the C1 and C3 carbon atoms in the isolated, non-hydrogen-bonded enol forms of 2-alkyl-cyclopentane-1,3-diones **41** can hardly be determined in solution, due to the rapid keto-enol and enol-enol tautomerism.[21] Therefore, in 2-alkyl-cyclopentane-1,3-dione compounds **41da-di**, we observed that ^{13}C NMR

shows two of CH_2 carbons α to the carbonyls (*C*=O) including the two carbonyl carbons [2 x CH_2 and 2 x *C*=O] are poor resolution even after 2000 scans on

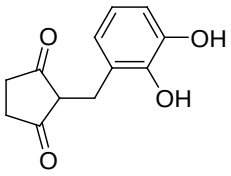
* In all compounds denoted **41xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

standard sampling [see Fig. 1 & Fig. 2]. This same kind of ^{13}C NMR pattern was observed for the other 1,3-diketones in the literature due to the rapid keto-enol and enol-enol tautomerism.[21]

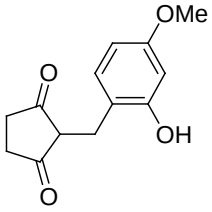
***Table 4*:** Chemically Diverse Libraries of 2-(2-Hydroxy-benzyl)-cyclopentane-1,3-diones **41**[a]



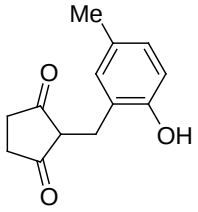
80% (**41da**)



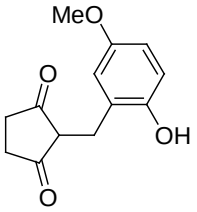
85% (**41db**)



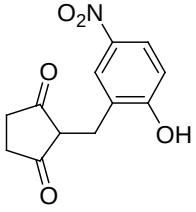
80% (**41dc**)



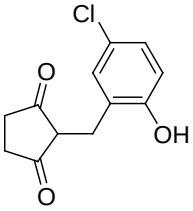
85% (**41dd**)



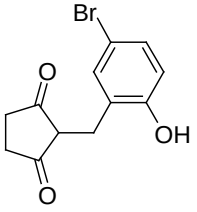
85% (**41de**)



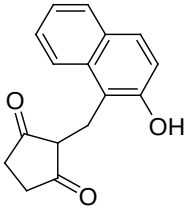
80% (**41df**)



85% (**41dg**)



80% (**41dh**)



80% (**41di**)

[a] Yield refers to the column purified product.

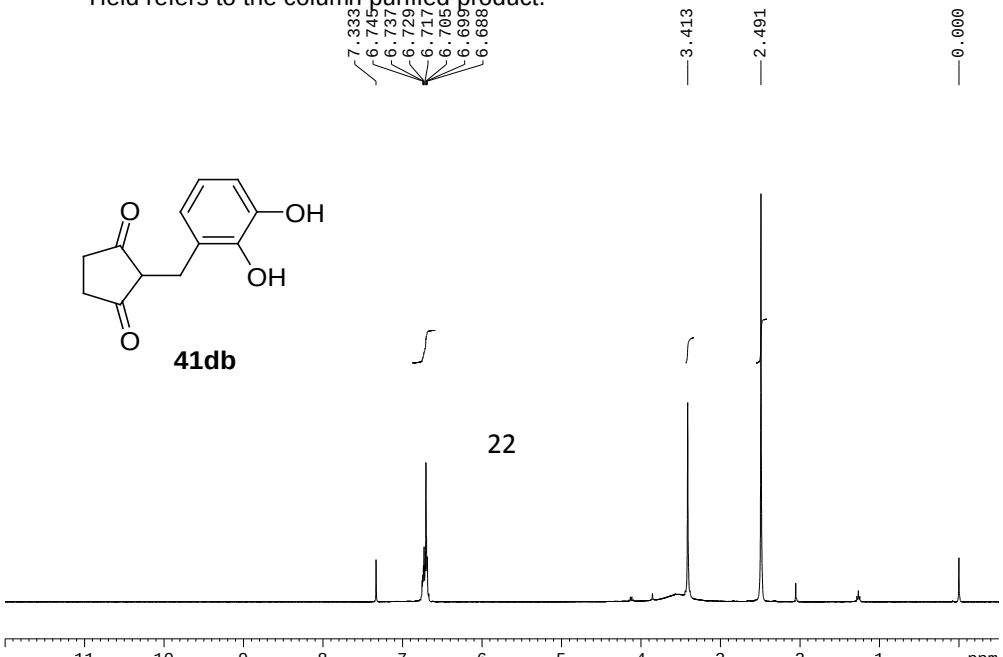
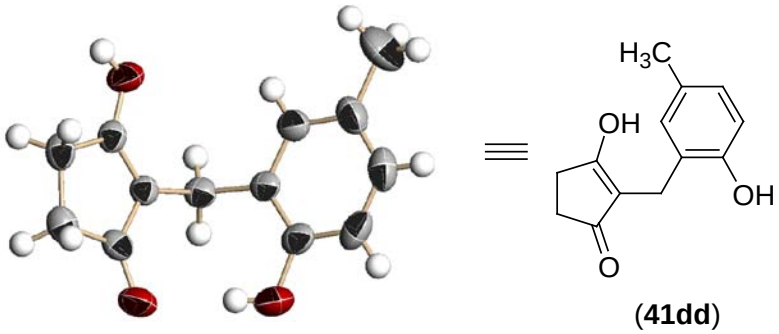


Figure-2: ^{1}H NMR and ^{13}C NMR Spectrum of Product **41db**.

Scheme 3: Crystal Structure of 2-(2-Hydroxy-5-methyl-benzyl)-cyclopentane-1,3-dione (**41dd**).

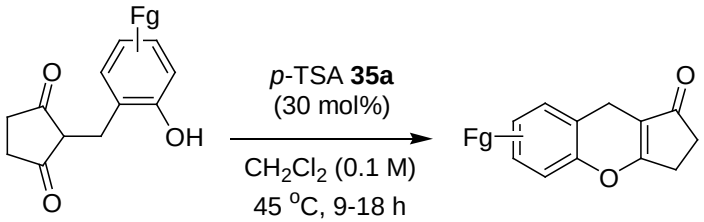


(**41dd**)

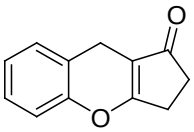
3.2.3 Diversity-Oriented Synthesis of Heterocycles 38da-38di: With the success of cascade synthesis of highly functionalized 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **41**, we continued our investigation for the generation of highly functionalized diversity oriented library of cascade 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones **38** under acid-catalysis. The results in Table 5 demonstrate the broad scope of this novel green methodology covering a structurally diverse group of 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **41da-di**[*]. Cascade OM/DH reaction of 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **41da-di** under acid-catalysis furnished the expected 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones **38da-di**[*] in 75-99% yield with high selectivity (Table 5). Unexpectedly, cascade product **38db** only was obtained with moderate yield from **41db** and **35a**. Interestingly, all the 4- and 5-substituted 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **41dc-di** furnished the expected products **38dc-di** with very good yields as single isomer in acid-catalyzed OM/DH cascade reactions as shown in Table 5. Structure and regio-chemistry of cascade products **38** were confirmed by NMR analysis [for example see Fig. 3] and also by X-ray structure analysis on **38da** as shown in Scheme 4.[20]

[*] In all compounds denoted **41xy** and **38xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

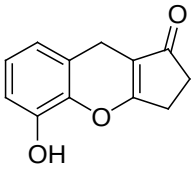
***Table 5*:** Chemically Diverse Libraries of 3,9-Dihydro-2H-cyclopenta[b]chromen-1-ones **38**[a]



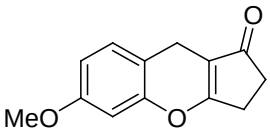
41da-di **38da-di**



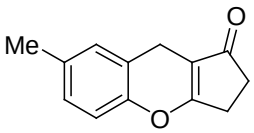
90% (**38da**)



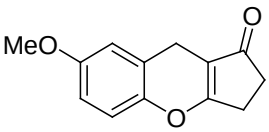
75% (**38db**)*b*



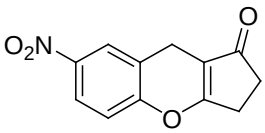
95% (**38dc**)



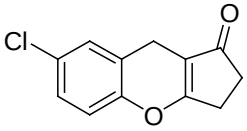
90% (**38dd**)



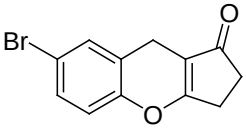
95% (**38de**)



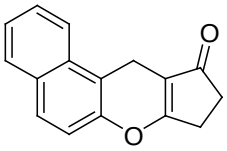
86% (**38df**)



95% (**38dg**)

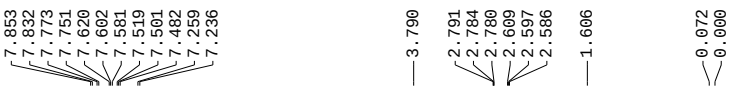


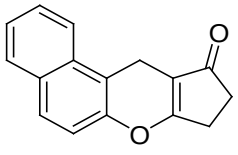
99% (**38dh**)



95% (**38di**)

a Yield refers to the column purified product. *b* Reaction performed at 100 °C for 8 h in the toluene solvent.

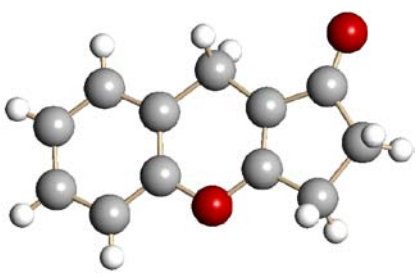


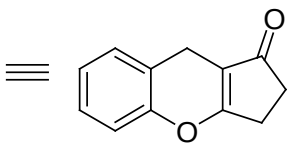


38di

Figure-3: ^{1}H NMR and ^{13}C NMR Spectrum of Product **38di**.

Scheme 4: Crystal Structure of 3,9-Dihydro-2H-cyclopenta[b]chromen-1-one (**38da**).





(**38da**)

3.2.4 Diversity-Oriented Synthesis of 2-Alkyl-3-Methoxy-Cyclopent-2-enones 44da-44di: With synthetic applications in mind, we extended the three-component cascade TCRA reactions into a novel aniline/self-catalyzed four-component TCRA/A reaction of **3d**, **37a-i** and **15** with ethereal solution of diazomethane in one-pot as shown in Table 6. One-pot products **44** were constructed in very good yields with high chemoselectivity as shown in Table 6 and this method will be showing much impact on synthesis of functionalized small molecules. The substituted 2-alkyl-3-methoxy-cyclopent-2-enone unit is a basic building block for a large number of valuable naturally occurring products.[22] Highly substituted 2-alkyl-3-methoxy-cyclopent-2-enones **44** have gained importance in recent years as starting materials and intermediates for the synthesis of prostaglandin analogs, which possess a wide range of physiological and pharmacological properties.[22]

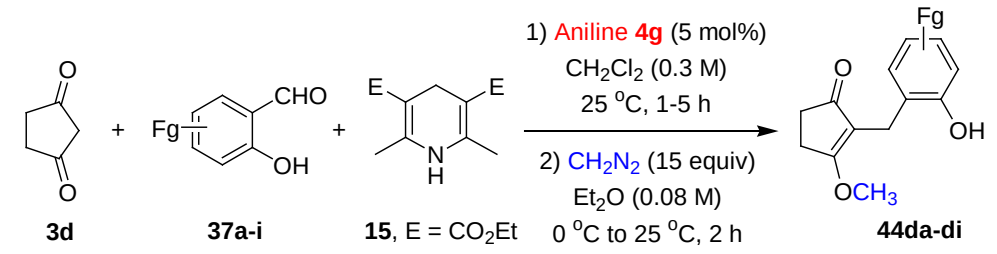
Cascade TCRA reaction of **3d**, **37a** and **15** under 5 mol% of aniline-catalysis furnished the substituted 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **41da** in good yield, which on treatment with ethereal diazomethane at 0 °C to 25 °C for 2 h furnished the chemoselectively one-pot TCRA/A product 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone **44da**[*] in 85% yield as shown in Table 6. Interestingly, phenol group is not methylated under these conditions. Acidic or highly enolizable nature of 2-aryl-cyclopentane-1,3-diones **41** is the main driving force to observe high chemoselective O-alkylation reaction with diazomethane. Generality of the aniline-/self-catalyzed chemo

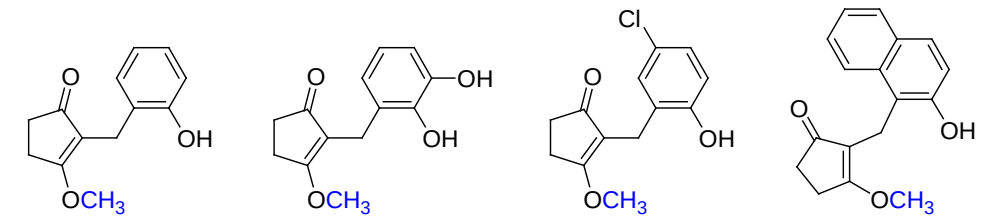
[*] In all compounds denoted **44xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

selective one-pot TCRA/A reaction was further confirmed by three more examples using 2,3-dihydroxy-benzaldehyde **37b**, 5-chloro-2-hydroxy-benzaldehyde **37g** and 2-hydroxy-naphthalene-1-carbaldehyde **37i** to furnish the expected 2-(2,3-dihydroxy-

benzyl)-3-methoxy-cyclopent-2-enone **44db** in 65% yield, 2-(5-chloro-2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone **44dg** in 80% yield and 2-(2-hydroxy-naphthalen-1-ylmethyl)-3-methoxy-cyclopent-2-enone **44di** in 85% yield, respectively as shown in Table 6.For the pharmaceutical applications, diversity-oriented library of enones **44** could be generated by using our aniline-/self-/self-catalyzed, chemoselective one-pot TCRA/A reaction.

Table 6: Chemically Diverse Libraries of 2-(2-Hydroxy-benzyl)-3-methoxy-cyclopent-2-enones **44**[a,b]





85% (**44da**) 96% (**44da**)[c] | 65% (**44db**) | 80% (**44dg**) | 85% (**44di**)

[a] See Experimental Section. [b] Yield refers to the column purified product. [c] Yield represents only etherification reaction.

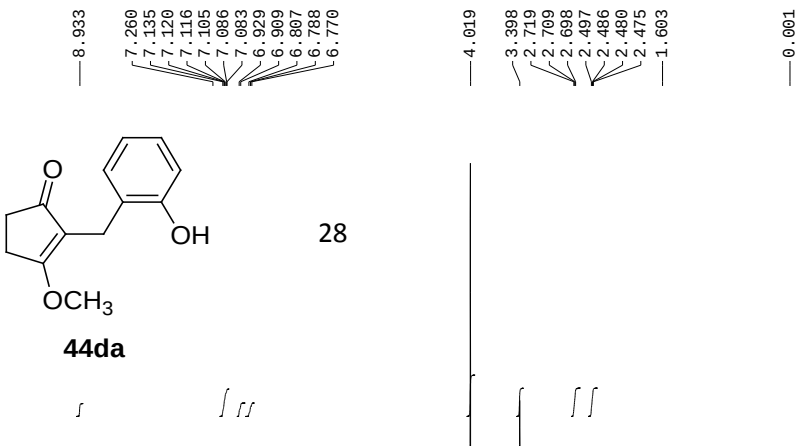
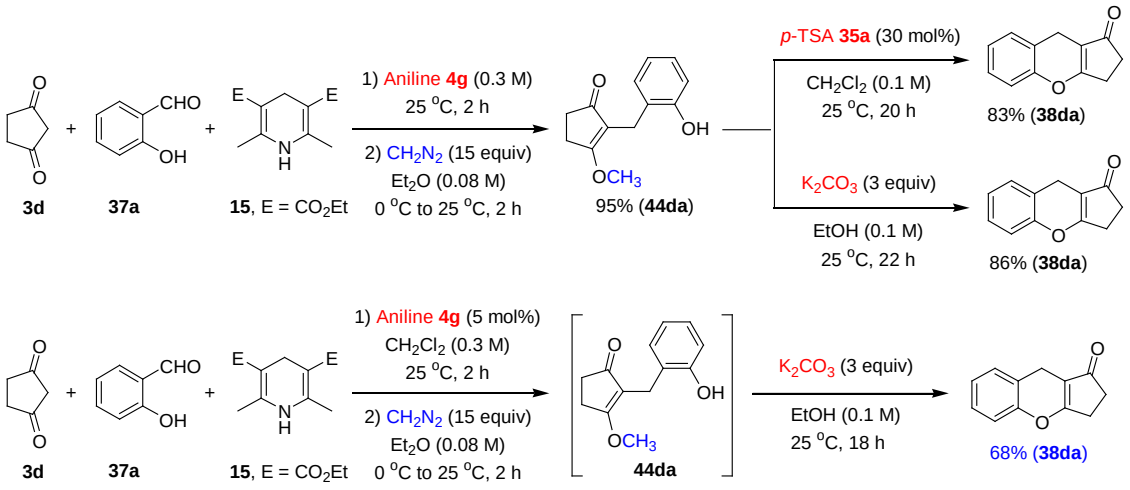


Figure-4: ^{1}H NMR and ^{13}C NMR Spectrum of Product **44da**.

After successful chemoselective synthesis of 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone **44da**[*] in good yield, we decided to test the acid/base effect on this cascade product **44da**. Treatment of **44da** with either acid (*p*-TSA) or base (K_2CO_3) at

room temperature furnished the expected 3,9-dihydro-2H-cyclopenta[b]chromen-1-one **38da*** in good yield as shown in Scheme 5. Interestingly this same reaction when performed in one-pot as four-component, multi-catalysis (aniline-, self-, self- and base-catalysis) of **3d**, **37a**, **15** and CH_2N_2 furnished the one-pot product **38da** in 68% yield as shown in Scheme 5. Even though overall yield of one-pot product **38da** may be less compared to Table 5, this multi-component/multi-catalysis strategy will show much effect on the synthesis of highly functionalized small molecules like **38** and **44**.

Scheme 5: Multi-Catalysis and Multi-Component Approach to the Synthesis of 3,9-Dihydro-2H-cyclopenta[b]chromen-1-one **38da.**



3.2.5 Diversity-Oriented Synthesis of Heterocycles 38ga-38gi: After successful demonstration of the cascade TCRA, TCRA/A, TCRA/OM/DH and TCRA/A/OM/DH reactions on cyclopentane-1,3-dione **3d** with **37**, **15** and **4**, then we

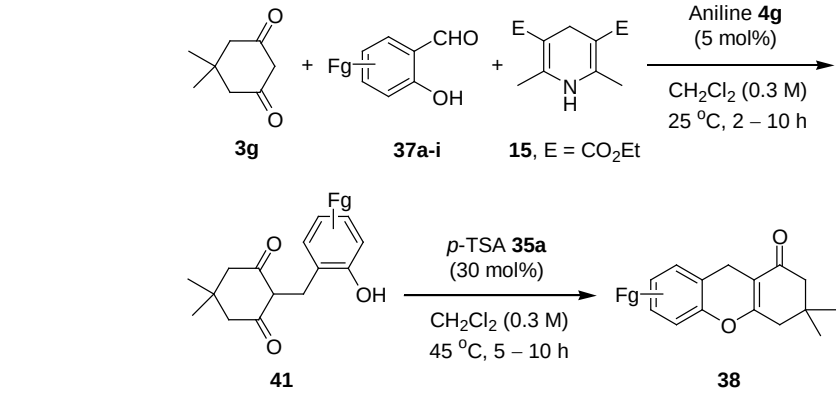
* In all compounds denoted **44xy** and **38xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

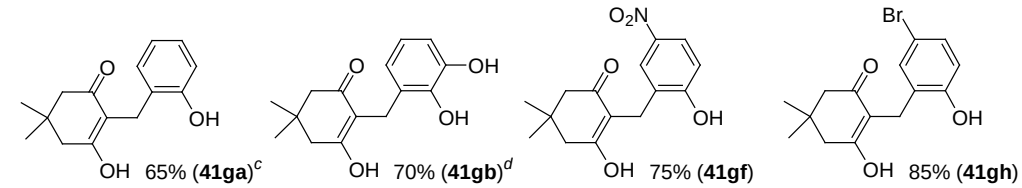
decided to test the same cascade reactions on other 1,3-diones like cyclohexane-1,3-dione **3e** and dimedone **3g**. Interestingly, cascade TCRA reaction of **3e**, **37a** and **15** under proline **4c**- or aniline **4g**-catalysis did not furnish the expected pure product 2-(2-hydroxy-benzyl)-cyclohexane-1,3-dione **41ea*** and the reaction was not clean. But the

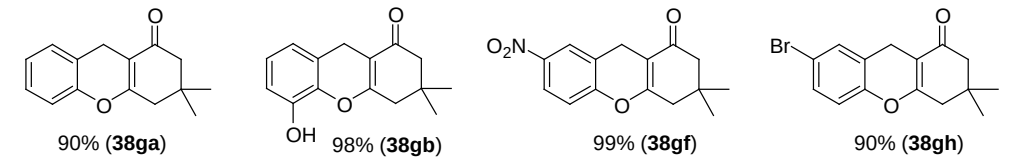
same cascade TCRA reaction with **3g**, **37a** and **15** under proline **4c**- or aniline **4g**-catalysis furnished the expected product 2-(2-hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione **41ga** in only 65% yield, which on acid-catalysis furnished the expected 3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **38ga**[*] in very good yield as shown in Table 7. Interestingly, cascade product **41ga** was accompanied with byproduct 9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **45ga**[*] (**L-152,804**) in 20% yield, which is useful as an orally active and selective neuropeptide Y Y5 receptor antagonist.[23a] But the pure product, **L-152,804** was obtained only after two step TCRA and OM/DH reactions, because separation of **L-152,804** from **41ga** is a tedious job due to the same R_f in TLC plate. In the reaction of **3g**, **37a** and **15** under **4g**-catalysis, the initial byproduct **45ga** (**L-152,804**) was unchanged after heating with *p*-TSA **35a** in CH_2Cl_2. Generality of the aniline- and acid-catalyzed chemoselective cascade TCRA and OM/DH reactions of **3g** with **37** and **15** was further confirmed by three more examples using 2,3-dihydroxy-benzaldehyde **37b**, 5-nitro-2-hydroxy-benzaldehyde **37f** and 5-bromo-2-hydroxy-benzaldehyde **37h** to furnish the expected 2-(2,3-dihydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione **41gb** in 70% yield, 2-(2-hydroxy-5-nitro-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione **41gf** in 75% yield and 2-(5-bromo-2-hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione **41gh** in 85% yield and 5-hydroxy-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **38gb** in 98% yield, 3,3-dimethyl-7-nitro-2,3,4,9-tetrahydro-xanthen-1-one **38gf** in 99% yield and 7-bromo-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **38gh** in 90% yield, respectively as shown in Table 7.

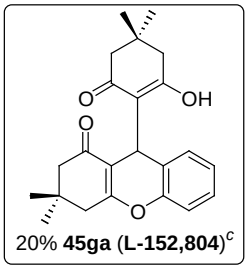
[*] In all compounds denoted **41xy**, **38xy** and **45xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

Table 7: Direct Organocatalytic Synthesis of 2-(2-Hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-diones **41** and 3,3-Dimethyl 2,3,4,9-tetrahydro-xanthen-1-ones **38**[a,b]









[a] See Experimental Section. [b] Yield refers to the column purified product. [c] *20 % of **L-152,804**; an orally active and selective neuropeptide Y Y5 receptor antagonist was accompanied as by-product with **41ga** in aniline-catalyzed reaction of **3g**, **37a** and **15**.* [d] *23% of **38gb** was accompanied as by-product with **41gb** in aniline-catalyzed reaction of **3g**, **37b** and **15**.*

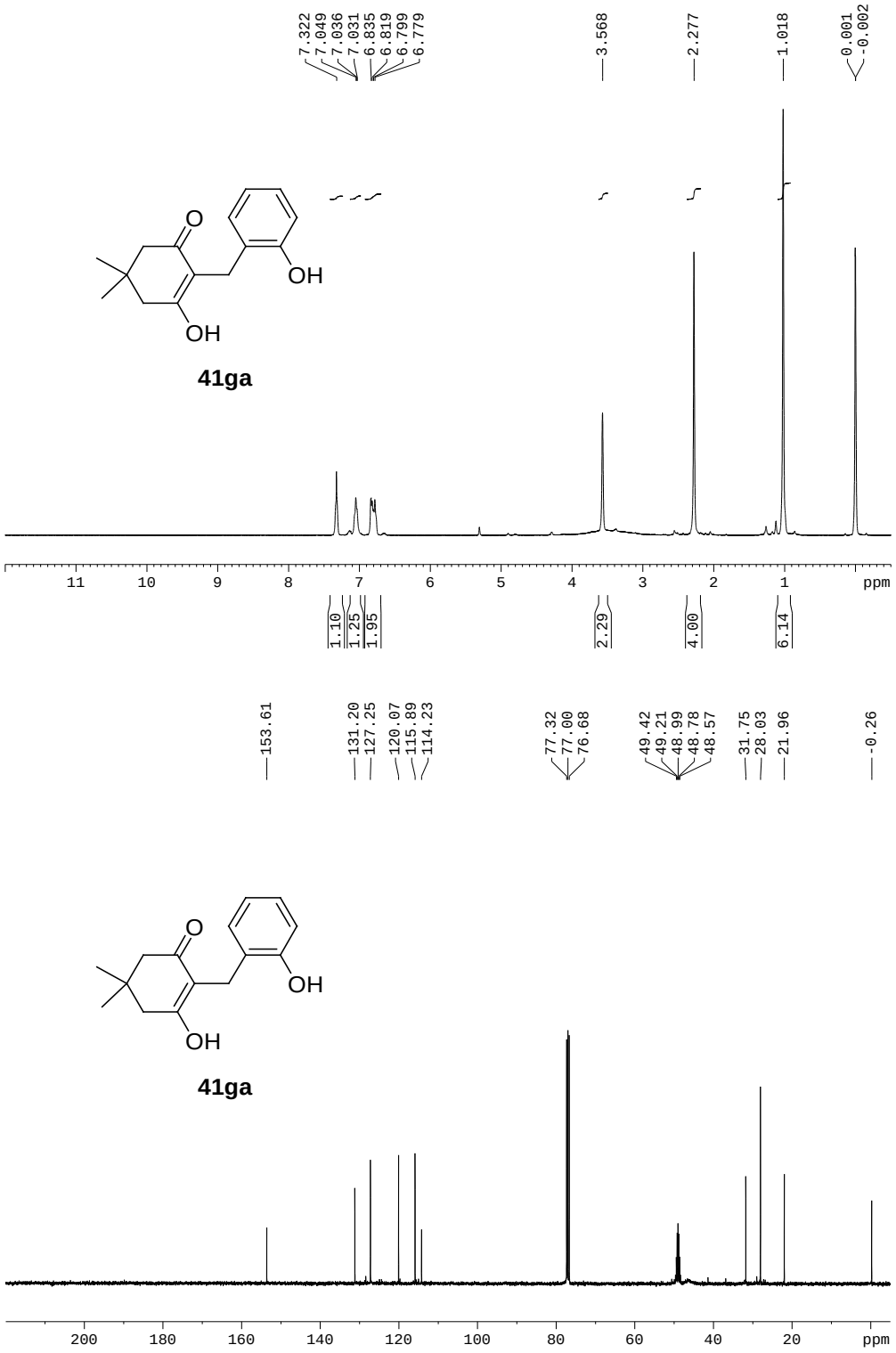


Figure-5: ^{1}H NMR and ^{13}C NMR Spectrum of Product **41ga**.

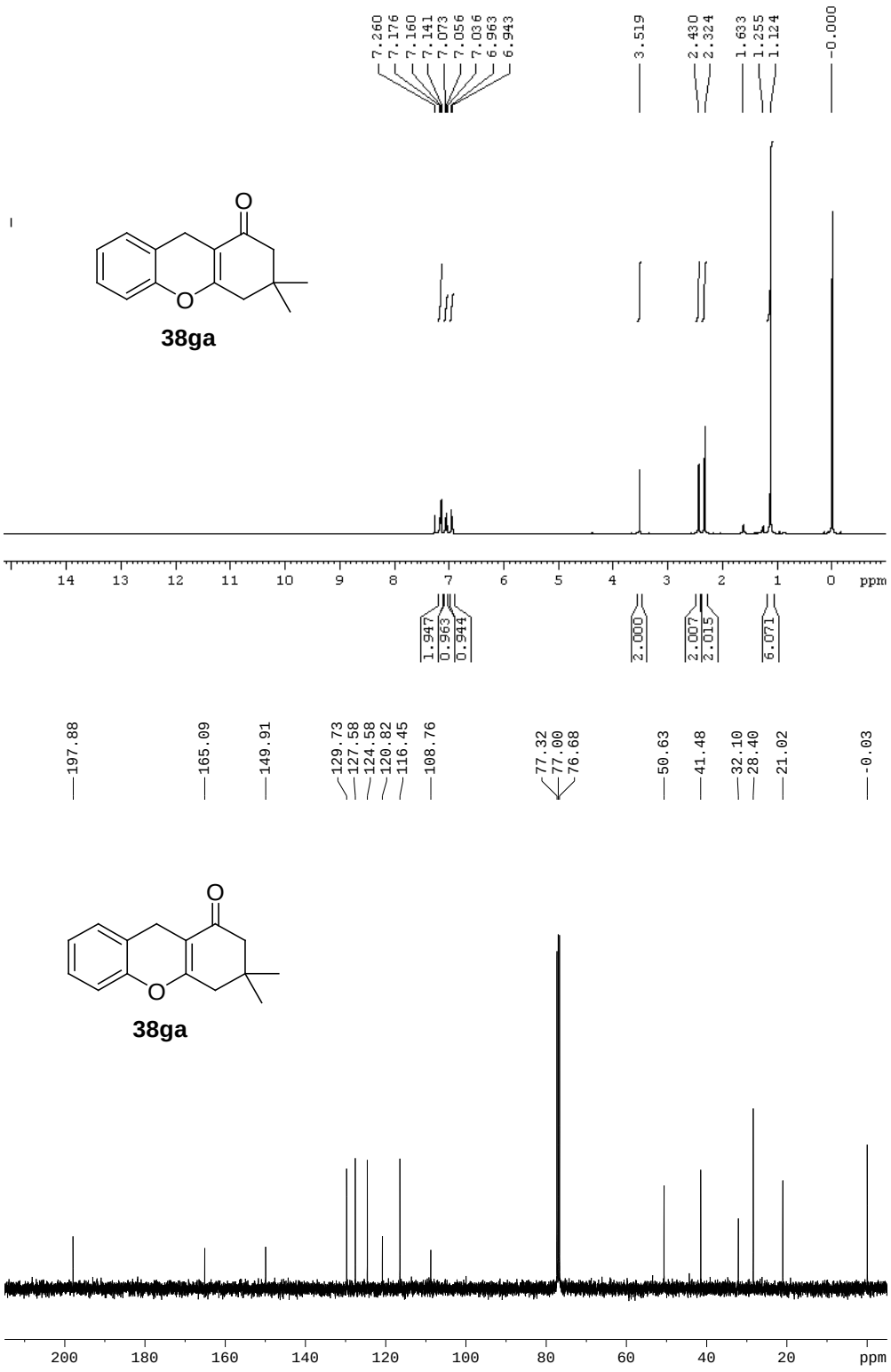


Figure-6: ^{1}H NMR and ^{13}C NMR Spectrum of Product **38ga**.

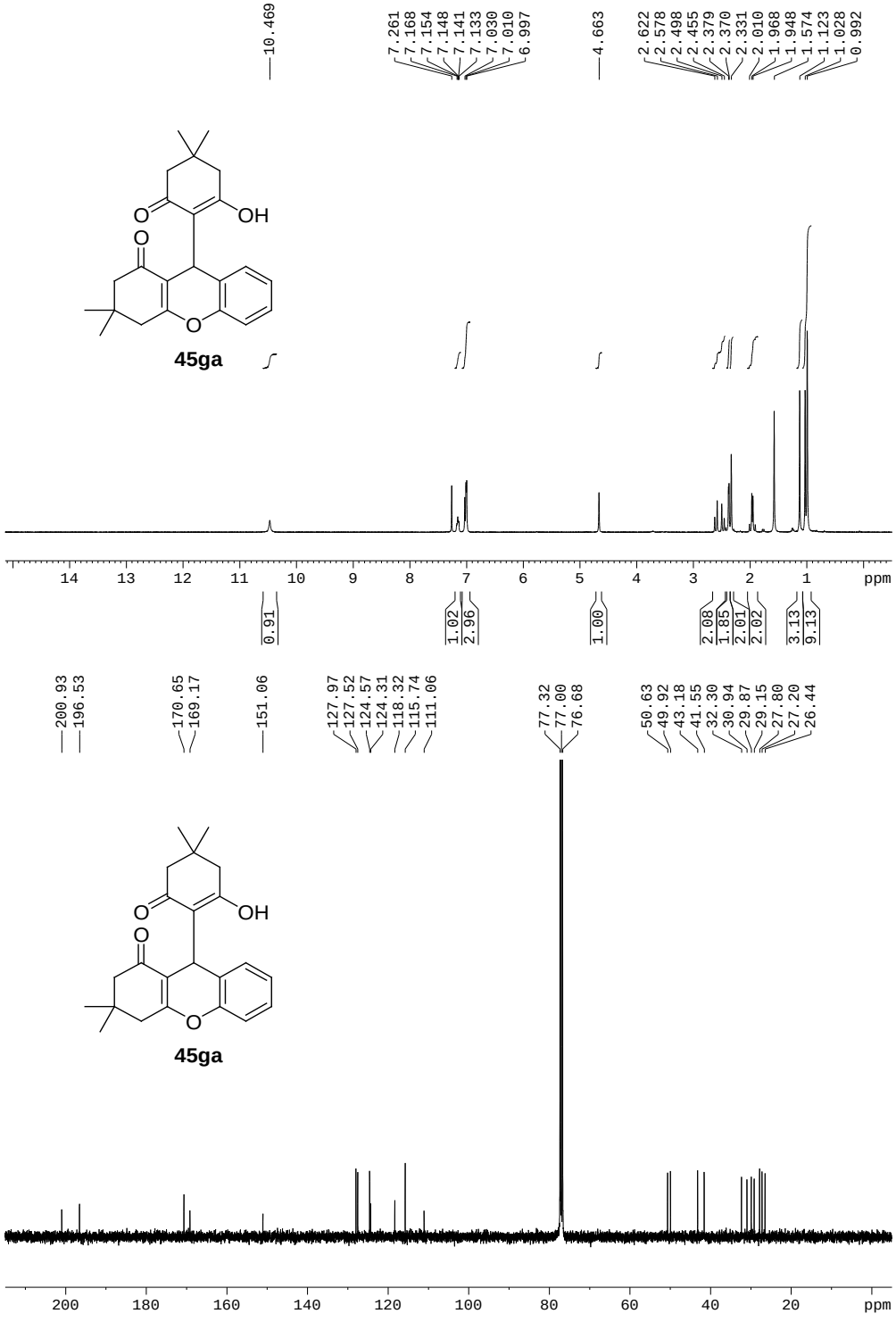
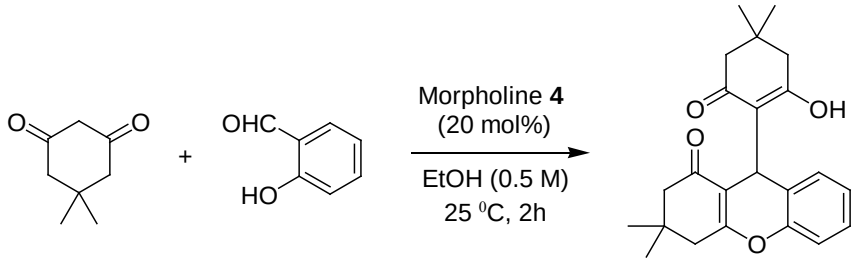


Figure-7: ^{1}H NMR and ^{13}C NMR Spectrum of Product **45ga**.

Interestingly, we could not see the formation of unexpected byproducts like **L-152,804** analogs in the above three reactions. But, the cascade product **41gb**[*] was accompanied with the byproduct 5-hydroxy-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **38gb**[*] in 23% yield. Recently, 5,5-dimethylcyclohexane-1,3-dione derivatives **41ga-gi** were evaluated for their biological activities like anti-ischemic agents, anti-hypertensive and anti-psychotics.[24]



3g **37a** **45ga**
yield: 81%

(10)

9-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **45ga** is an useful compound as an orally active and selective neuropeptide Y Y5 receptor antagonist, accompanied as a byproduct in TCRA reaction of dimedone **3g**, salicylaldehyde **37a** and Hantzsch ester **15**. With the pharmaceutical applications of product **45ga**[*] (**L-152,804**) in mind, we optimized the condition for the synthesis of this useful compound in very good yields under eco-friendly conditions as shown in eq. 10. The reaction of dimedone **3g** and 2-hydroxy benzaldehyde in the presence of morpholine furnished the product **45ga** in 2h with 81% yield as shown in eq. 10.

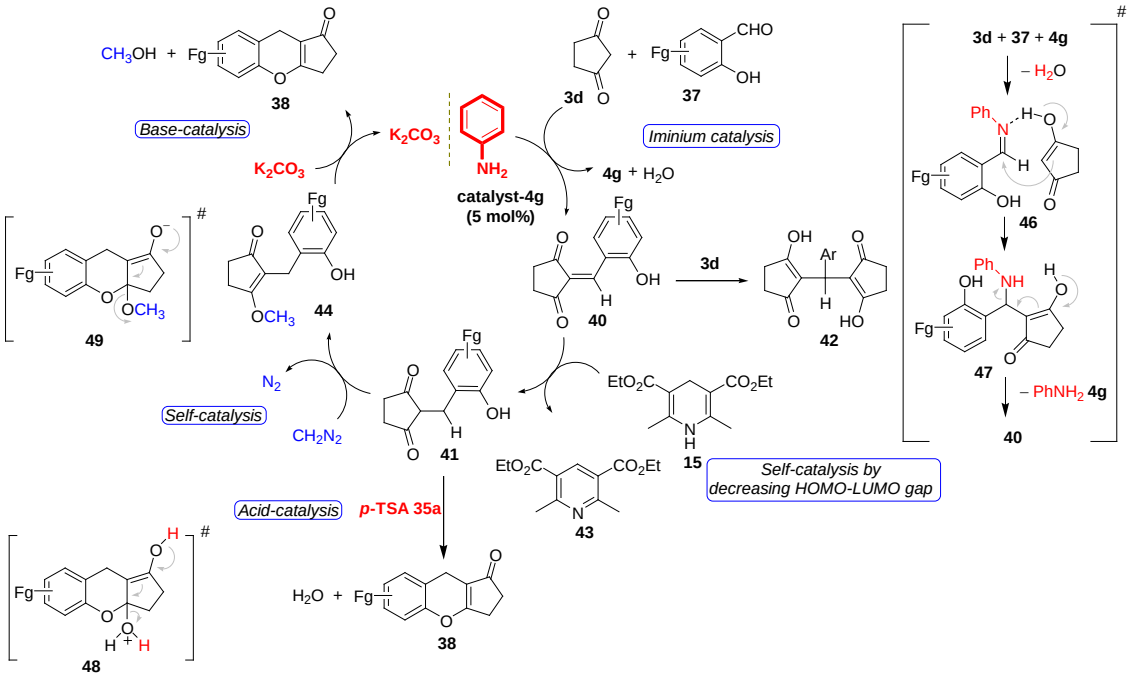
3.3 Mechanistic Insights

The possible reaction mechanism for the aniline-, self-, acid- and base-catalyzed chemoselective synthesis of cascade products **41**, **38** and **44** through reaction of cyclopentane-1,3-dione **3d**, 2-hydroxy-benzaldehydes **37**, Hantzsch ester **15** and diazomethane is illustrated in Scheme 6. This catalytic sequential one-pot,

[*] In all compounds denoted **41xy**, **38xy** and **45xy**, **x** is incorporated from reactant CH-acids **3** and **y** is incorporated from the reactant salicyladehydes **37**.

double cascade is a four component reaction comprising of cyclopentane-1,3-dione **3d**, 2-hydroxy-benzaldehydes **37**, Hantzsch ester **15**, diazomethane and a simple catalyst, aniline **4g**. In the first step (Scheme 6), the catalyst **4g** activates component **37** by most likely imine formation, which then selectively adds to the cyclopentane-

***Scheme 6*:** Proposed Catalytic Cycle for the Multi-Catalysis Reactions.



1,3-dione **3d** *via* a Mannich and amine elimination reaction to generate active olefin **40** (**46** → **47** → **40**). The following second step is bio-mimetic hydrogenation of active olefin **40** by Hantzsch ester **15** to produce **41** through self-catalysis by decreasing HOMO-LUMO energy gap between **15** and **40** respectively. Highly chemoselective synthesis of cascade hydrogenated products **41** over the bis-adduct **42** formations from reactants **3d**, **15** and **40** can be explained by using HOMO/LUMO energy gaps and enthalpy differences of reactants and products.

Recently we published the complete mechanistic information about this type of self-catalyzed chemoselective reductive alkylation of 1,3-dione **3d** with **37** and **15** under **4c**-catalysis through PM3 calculations.[12] For the reductive alkylation of 1,3-diones **3** with **37** and **15** under amine/amino acid **4**-catalysis, 2-hydroxy group is not essential as demonstrated in our previous work.[12]

In the subsequent third step, acid-catalyzed oxy-Michael/dehydration of **41** *via* most likely possible intermediate **48** leads to the formation of one-pot product **38**. In the alternative fourth step, self-catalyzed reaction of **41** with diazomethane leads to the formation of **44**, which on treatment with K_2CO_3 generates the expected one-pot product **38** *via* most likely possible intermediate **49**.

3.4 Conclusion

In summary, for first time we have developed the multi-catalysis technology for the synthesis of highly substituted 2-(2-hydroxy-benzyl)-cyclopentane-1,3-diones **41**, 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones **38** and 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enones **44** from simple starting materials *via* cascade TCRA, OM/DH, TCRA/OM/DH, TCRA/A and TCRA/A/OM/DH reactions under the combinations of aniline-, self-, base- and Brønsted-acid catalysis. The cascade TCRA reaction proceeds in good yields with high selectivity using only 5 mol% of aniline as the catalyst. Furthermore, we have demonstrated the application of bio-mimetic aniline-catalysis for the olefination of aldehydes **37** with CH-acids like cyclopentane-1,3-dione **3d**. Further work is in progress to utilize novel TCRA, OM/DH, TCRA/OM/DH, TCRA/A and TCRA/A/OM/DH reactions and cascade products **41**, **38** and **44** in synthetic chemistry.

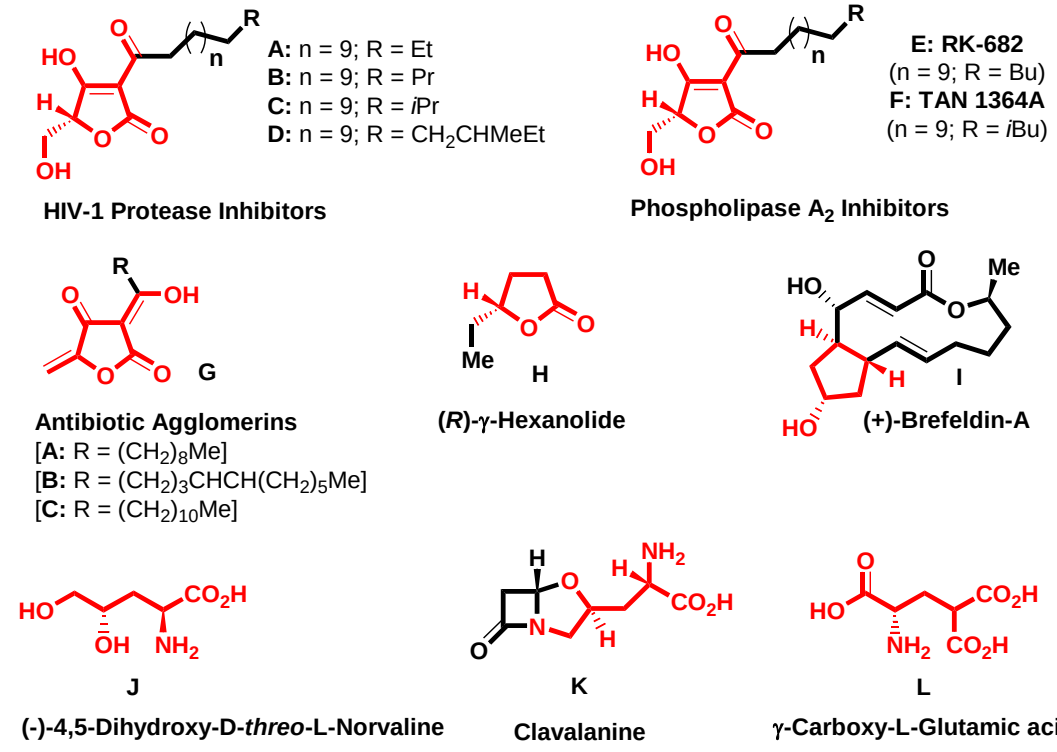
4. Sustainable Approach to the Chiral Building Blocks via Direct Amino Acid-Catalyzed Cascade TCRA Reactions: Formal Total Synthesis of HIV-1 Protease Inhibitors, Antibiotic Agglomerins, Brefeldin A and (R)-γ-Hexanolide

4.1 Introduction

(*R*)-**G**lyceraldehyde acetonide and (*S*)-Garner aldehyde derivatives from three-component reductive alkylation (*TCRA*) are an important class of heterocycles and very good chiral building blocks, which display very large spectrum of biological/chemical activities and are widely used as drug intermediates and ingredients in pharmaceuticals and also in the total synthesis of natural products (see Chart 1).[25] As such, the development of more general catalytic asymmetric methods for their preparation is of significant interest.[26] For example diethyl 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-malonate was utilized as key intermediate in the total synthesis of natural products like HIV-1 protease inhibitors **A-D**, phospholipase A_2 inhibitors **E-F**, antibiotic agglomerins **G**, (*R*)-γ-hexanolide **H** and (+)-brefeldin-A **I**, but which was prepared only in 40% overall yield from four steps starting from (*R*)-glyceraldehyde acetonide (see eq. 11).[25a-i] Interestingly, to the best of our knowledge there is no report on the direct catalytic asymmetric single step method for the synthesis of functionalized dialkyl 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-malonates and dialkyl 2-(3-*tert*-butoxycarbonyl-

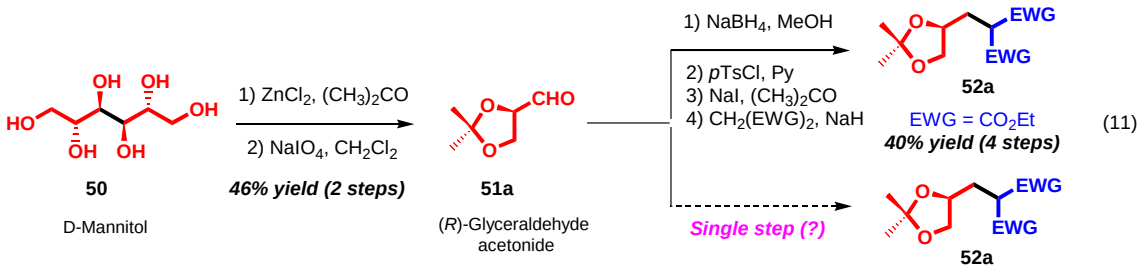
2,2-dimethyl-oxazolidin-4-ylmethyl)-malonates, which are good intermediates for the synthesis of biologically active natural products as shown in Chart 1. Herein, we reported the organocatalytic single step approach to the asymmetric synthesis of functionalized chiral building blocks based on (*R*)-glyceraldehyde acetonide and (*S*)-Garner aldehyde via "three-component reductive alkylation reactions".[11-12]

Chart 1: Natural Products Library Generated from (*R*)-Glyceraldehyde acetonide and (*S*)-Garner aldehyde Derivatives



Recently we discovered the amino acid-catalyzed three-component reductive alkylation reactions of ketones/aldehydes with variety of CH-acids and Hantzsch ester to provide a general route to a variety of alkylation products in good yields with high

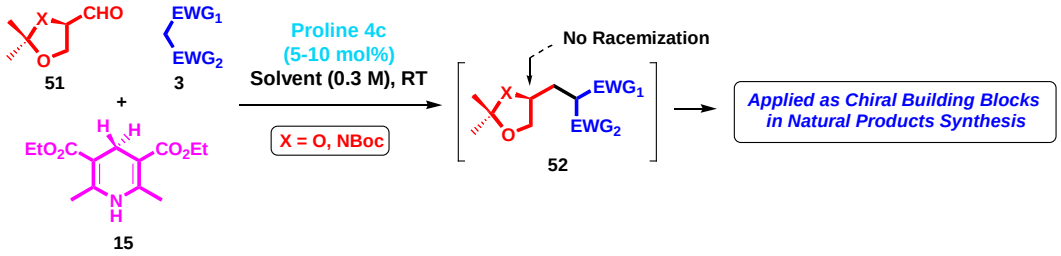
chemoselectivity, which is known as "three-component reductive alkylation (TCRA)" reaction.[11-12] The advent of amino acid-catalyzed TCRA reaction technology triggered a burst of activity in the synthesis of a huge variety of alkylation products through bio-mimetic iminium-catalysis chemistry for the 1 x C-C and 2 x C-H bond formations and also providing high inspiration to develop cellular type cascade reactions based on TCRA platform.[16,27]



(11)

However, the amino acid-catalyzed TCRA reaction of CH-acids **3** and Hantzsch ester **15** with functionalized (*R*)-glyceraldehyde acetonide/(*S*)-Garner aldehyde **51** is not known but the resulting TCRA products **52** have a wide range of applications in pharmaceutical chemistry (see eq 11 and Scheme 7). There is no direct methodology available to prepare **52** by using the classical reaction strategies in a single step. Herein, we have reported a metal-free and green technology for the synthesis of highly substituted (*R*)-glyceraldehyde acetonide and (*S*)-Garner aldehyde derivatives **52** using organocatalytic TCRA reactions from commercially available chiral aldehydes **51**, CH-acids **3**, Hantzsch ester **15** and amines/amino acid **4** (Scheme 7). In this work, we discovered that there is no racemization at the α-position to carbonyl at the normal amino acid-catalyzed TCRA reaction conditions.[7,28]

Scheme 7: Direct Amino acid-Catalyzed Cascade Three-Component Reductive Alkylations.



Over the last five years, we have been interested in an amino acid mediated multi-catalysis cascade (MCC) reactions from multiple components and multiple catalysts for the generation of highly functionalized drug-like molecules through C-C, C-H, C-O and C-N bonds formation in one-pot.[8,16c,g] During our investigation for new reactive species for such MCC processes, we have decided to explore the potential ability of the chiral aldehydes **51** to participate in an amino acid-catalyzed TCRA reaction with CH-acids **3** and Hantzsch ester **15** (see Scheme 7). We imagined that the reaction of (*R*)-glyceraldehyde acetonide **51a** (>98% ee) with Meldrum's acid **3a** and Hantzsch ester **15** under L-proline-catalysis may lead to racemic 5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **52aa**[*]. However, TCRA product **52aa** was not racemized and instead it showed >98% ee (based on HPLC analysis) under the standard reaction conditions. This unexpected result provided a good methodology for the preparation of chiral TCRA products and a new reactivity for amino acid catalysts. Herein, we report our findings regarding these TCRA reactions.

[*] In all compounds denoted **52xy**, **x** is incorporated from reactant chiral aldehydes **51** and **y** is incorporated from the reactant CH-acids **3**.

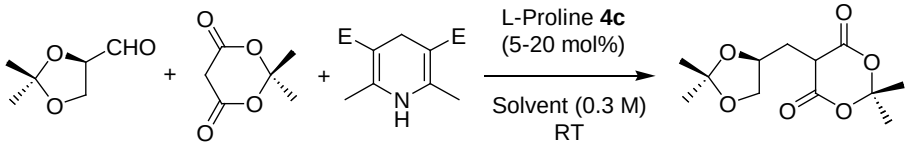
4.2 Results and Discussion

***4.2.1 Three-Component Reductive Alkylation of (R)-Glyceraldehyde acetonide: Reaction Optimization*:** We initiated our preliminary studies of the TCRA reactions by screening a number of protic/aprotic solvents for the three-component reductive alkylation (*TCRA*) of (*R*)-glyceraldehyde acetonide **51a** with Meldrum's acid **3a** and Hantzsch ester **15** under L-proline **4c**-catalysis and some representative results are shown in Table 8. Interestingly, reaction of (*R*)-**51a** (>98% ee) with each 1 equiv. of **3a** and **15** in CH_2Cl_2 under 5 mol% of **4c**-catalysis furnished the TCRA product **52aa**[*] in 91% yield with >98% ee (based on HPLC analysis of (–)-**52aa** derivative) after 2.5 h (Table 8, entry 1). Same reaction in CH_2Cl_2 under 10 mol% of L-proline **4c**-catalysis furnished the TCRA product **52aa** with increased yield (98%) and similar ee ($[\alpha]^{25}_D$ = – 24.4) after 2.5 h (Table 8, entry 2). Interestingly, increasing the catalyst loading from 10 to 20 mol%; yield and ee of the TCRA product **52aa** is affected negatively as shown in Table 8, entry 3. Same TCRA reaction in DCE solvent under 10 mol% of L-proline **4c**-catalysis furnished the TCRA product **52aa** as similar to CH_2Cl_2 (Table 8, entry 4). Interestingly, TCRA reaction of (*R*)-**51a**, **3a** and **15** under 10 mol% of **4c**-catalysis in CH_3CN for 1 h furnished the product **52aa** in 95% yield with sustained ee ($[\alpha]^{25}_D$ = – 24.0) as shown in Table 8, entry 5. But, L-proline **4c**-catalyzed TCRA reaction of **51a**, **3a** and **15** in DMF/DMSO solvents for 2/3 h furnished the product **52aa** in 87/78% yield with decreased ee ($[\alpha]^{25}_D$ = – 22.6) as shown in Table 8, entries 6 and 7 respectively. Surprisingly, L-proline **4c**-catalyzed TCRA reaction of

[*] In all compounds denoted **52xy**, **x** is incorporated from reactant chiral aldehydes **51** and **y** is incorporated from the reactant CH-acids **3**.

51a, **3a** and **15** in EtOH solvent for 1 h furnished the product **52aa** in 91% yield with almost ≤50% ee ($[\alpha]^{25}_{D}$ = – 11.9) as shown in Table 8, entry 8. Which gives strong evidence that enantiomerically pure (*R*)-glyceraldehyde acetonide **51a** is racemizing through iminium-catalysis in protic solvents like ethanol in the process of TCRA reaction.[7, 28] The solvent promoted one-pot TCRA reaction of **51a**, **3a** and **15** in H_2O without catalyst furnished the expected product **52aa** in <5% conversion but the olefination is completed with >95% under green reaction conditions (Table 8, entry 9).

Table 8: Preliminary Studies on Reductive Alkylation of (*R*)-Glyceraldehyde[a]



51a **3a** **15**, E = CO_2Et **52aa**

entry	proline **4c** (mol%)	solvent (0.3 M)	time (h)	conversion (%)[b]	yield (%)[c]	specific rotation ($[\alpha]^{25}_{D}$)[d]
1	5	CH_2Cl_2	2.5	>99	91	– 24.6
2	**10**	**CH_2Cl_2**	**2.5**	**>99**	**98**	**– 24.4**
3	20	CH_2Cl_2	0.75	>99	91	– 23.6
4	10	$(CH_2)_2Cl_2$	2.0	>99	91	– 24.4
5	**10**	**CH_3CN**	**1.0**	**>99**	**95**	**– 24.0**
6	10	DMF	2.0	>99	87	– 22.6
7	10	DMSO	3.0	>99	78	– 22.7
8	**10**	**EtOH**	**1.0**	**>99**	**91**	**– 11.9**
9[e]	–	H_2O	72.0	>95	<5	–
10[f]	**10**	**CH_3CN**	**8 → 9**	**80**	**68**	**– 24.4**

[a] Reactions were carried out in solvent (0.3 M) with each 1.0 equiv of **3a** and **15** relative to the **51a** (0.5 mmol) in the presence of 5-20 mol% of catalyst **4c**. [b] Conversion is based on ^{1}H NMR/TLC analysis. [c] Yield refers to the column purified product. [d] Specific rotation of all entries determined as 1.0 gm/100 mL in $CHCl_3$. [e] Only olefination product 5-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione is formed. [f] Reaction performed in sequential manner.

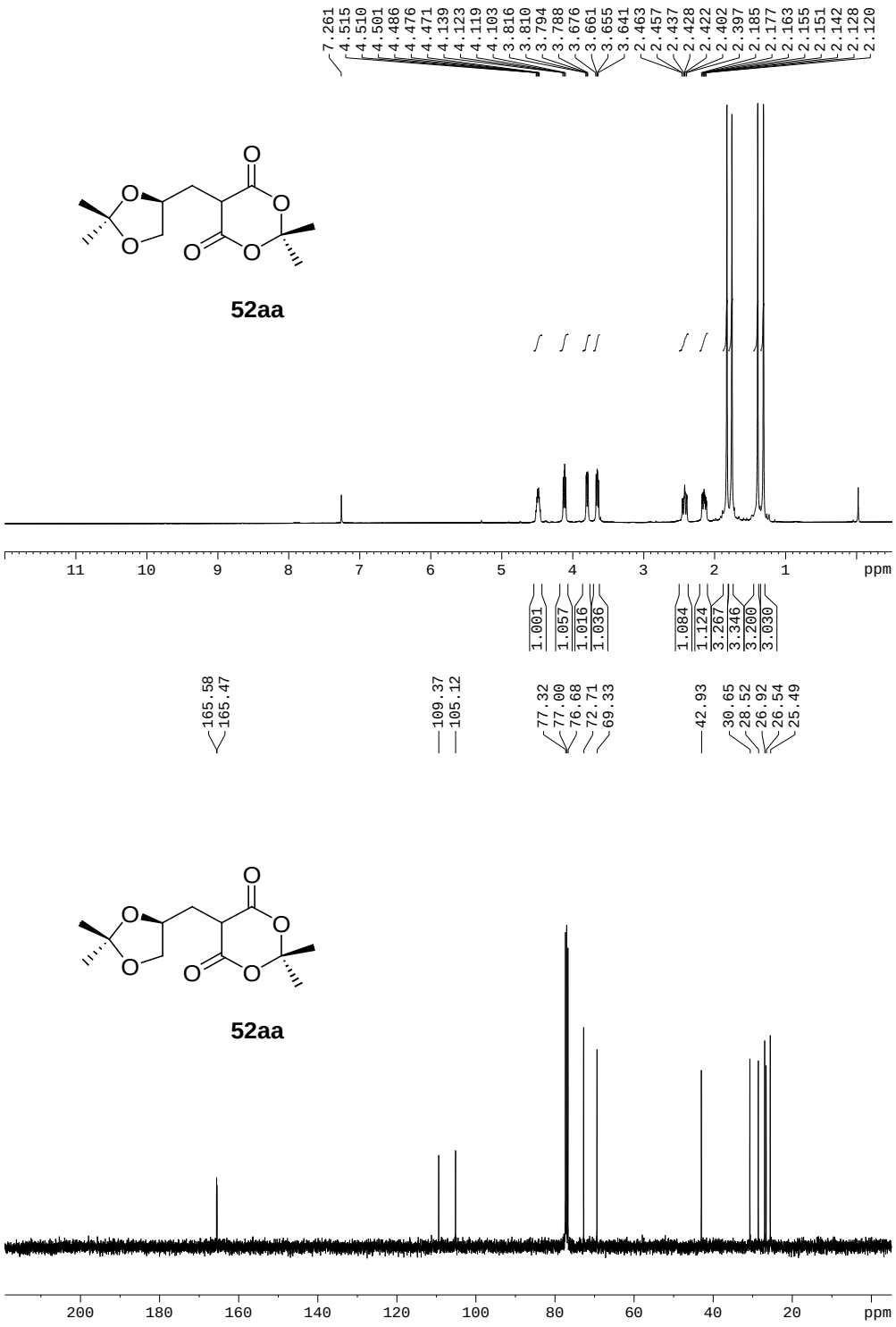


Figure-8: ^{1}H NMR and ^{13}C NMR Spectra of Product **52aa.**

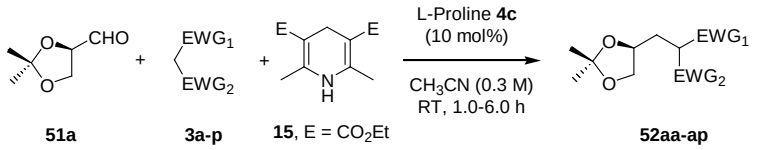
Interestingly, performing the TCRA reaction in sequential one-pot manner took longer reaction times (8 h for olefination and 9 h for hydrogenation) with ≤80% conversion and with sustained ee ($[\alpha]^{25}_{D}$ = – 24.4) as shown in Table 8, entry 10, which may be due to the auto-catalytic nature of the Hantzsch ester **15** in the cascade TCRA reaction.[11-12] The optimized conditions for the TCRA reaction of **51a**, **3a** and **15** in CH_3CN or CH_2Cl_2 at 25 °C to furnish **52aa*** with excellent conversions and without racemization required the presence of a catalytic amount of amino acid **4c** (entries 1-5).

4.2.2 Diversity-Oriented Chiral Synthesis of TCRA Products 52aa-ap: With an efficient amino acid-catalyzed TCRA protocol in hand, the scope of the L-proline-catalyzed TCRA reactions were investigated with various CH-acids **3a-p**. A series of cyclic and acyclic CH-acids **3a-p** were reacted with each 1.0 equiv. of (*R*)-glyceraldehyde acetonide **51a** and Hantzsch ester **15** catalyzed by 10 mol% of L-proline **4c** at 25 °C for 1-6 h in CH_3CN (Table 9). The (*S*)-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **52aa** and (*S*)-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,2-dialkyl-[1,3]dioxane-4,6-diones **52ac** and **52ah** were obtained as enantiomerically pure with excellent yields. The reaction of (*R*)-**51a** and **15** with barbituric acid **3i** and *N,N*-dimethylbarbituric acid **3j** furnished the chiral TCRA products **52ai-aj** as single enantiomers in good yields (Table 9). (*S*)-2-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-cyclohexane-1,3-dione **52ae** and related chiral TCRA products **52ad, 52ag, 52ak** and **52al** were generated as single enantiomers with excellent yields from (*R*)-**51a**, **3d-e, 3g, 3k-l** and **15** at 25 °C under L-proline- catalysis

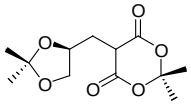
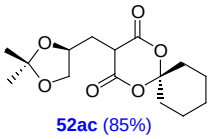
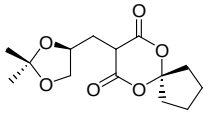
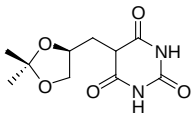
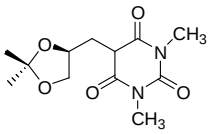
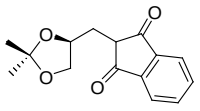
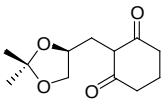
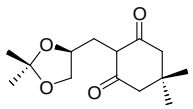
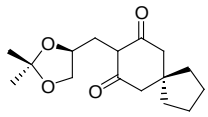
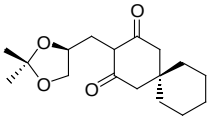
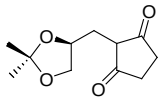
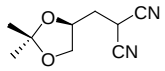
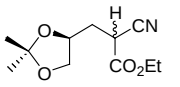
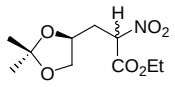
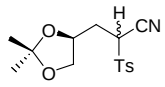
* In all compounds denoted **52xy**, **x** is incorporated from reactant chiral aldehydes **51** and **y** is incorporated from the reactant CH-acids **3.**

and are very good starting materials for the steroid drug analogues synthesis (Table 9 and see eq. 12 for HPLC analysis of **52ab** derivative).[11-12]

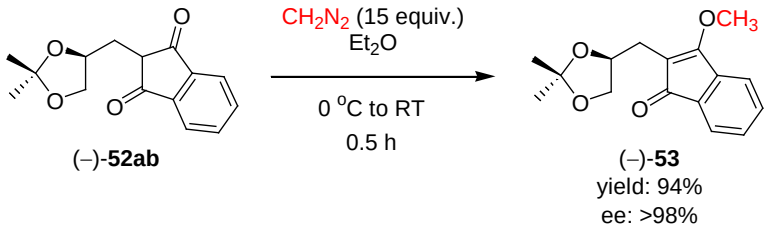
Table 9: Synthesis of Chiral Products **52aa-ap** via Reductive Alkylation Reaction[a]



51a **3a-p** **15**, E = CO_2Et **52aa-ap**

		
52aa (95%)	**52ac** (85%)	**52ah** (91%)
$[\alpha]^{25}_D$ = – 24.4 (*c* 1.0, $CHCl_3$)	$[\alpha]^{25}_D$ = – 26.0 (*c* 1.0, $CHCl_3$)	$[\alpha]^{25}_D$ = – 23.4 (*c* 1.0, $CHCl_3$)
		
52ai (75%)	**52aj** (87%)	**52ab** (98%)
$[\alpha]^{25}_D$ = – 31.4 (*c* 0.45, EtOH)	$[\alpha]^{25}_D$ = – 31.4 (*c* 1.0, $CHCl_3$)	$[\alpha]^{25}_D$ = – 41.5 (*c* 1.2, EtOH)
		
52ae (90%)[b]	**52ag** (85%)	**52ak** (75%)
$[\alpha]^{25}_D$ = – 41.0 (*c* 0.2, EtOH)	$[\alpha]^{25}_D$ = – 4.0 (*c* 1.0, EtOH)	$[\alpha]^{25}_D$ = + 15.0 (*c* 0.4, EtOH)
		
52al (95%)	**52ad** (90%)[b]	**52am** (99%)
$[\alpha]^{25}_D$ = + 14.0 (*c* 0.5, EtOH)	$[\alpha]^{25}_D$ = – 32.1 (*c* 0.3, EtOH)	$[\alpha]^{25}_D$ = – 46.7 (*c* 1.0, $CHCl_3$)
		
52an (70%; dr 1:1)	**52ao** (90%; dr 1:1)	**52ap** (80%; dr 2:1)
$[\alpha]^{25}_D$ = – 17.7 (*c* 1.0, EtOH)	$[\alpha]^{25}_D$ = – 10.5 (*c* 0.4, EtOH)	$[\alpha]^{25}_D$ = – 26.2 (*c* 0.6, $CHCl_3$)

[a] Yield refers to the column purified product. [b] (*R*)-Glyceraldehyde acetonide **51a** was taken as 3 equivalents.



(12)

The reaction of (*R*)-**51a** and **15** with acyclic CH-acids **3m-p** under L-proline-catalysis at 25 °C for 1-6 h in CH_3CN furnished the chiral TCRA products **52am-ap*** as single enantiomers in 2:1 to 1:1 dr ratio with good yields (Table 9). The results in Table 9 demonstrate the broad scope of this TCRA methodology covering a structurally diverse group of CH-acids **3a-p** with many of the yields obtained being very good, or indeed better than previously published four-step alkylation reactions.[26] Structure and regiochemistry of TCRA products **52aa-ap** were confirmed by NMR and mass analysis [for example see Fig. 8, 9 & 10].

Chiral TCRA products **52aa, 52ac** and **52ah** are important intermediates for the asymmetric synthesis of natural products like HIV-1 protease inhibitors **A-D**, phospholipase A_2 inhibitors **E-F**, antibiotic agglomerins **G**, (*R*)-γ-hexanolide **H** and (+)-brefeldin-A **I** as demonstrated in this paper,[25a-i] TCRA products **52ad-ag** and **52ak-al** could be important intermediates for the synthesis of Wieland-Miescher (W-M) ketone and Hajos-Parrish (H-P) ketone analogues which are very good steroids drug intermediates,[11-12] and TCRA product (-)-**52ao** could serve as an useful synthon for the synthesis of (-)-4,5-dihydroxy-*D*-threo-*L*-Norvaline **J** and also for the synthesis of antibiotic clavalanine **K** emphasizing the value of this cascade TCRA approach.

* In all compounds denoted **52xy**, **x** is incorporated from reactant chiral aldehydes **51** and **y** is incorporated from the reactant CH-acids **3**

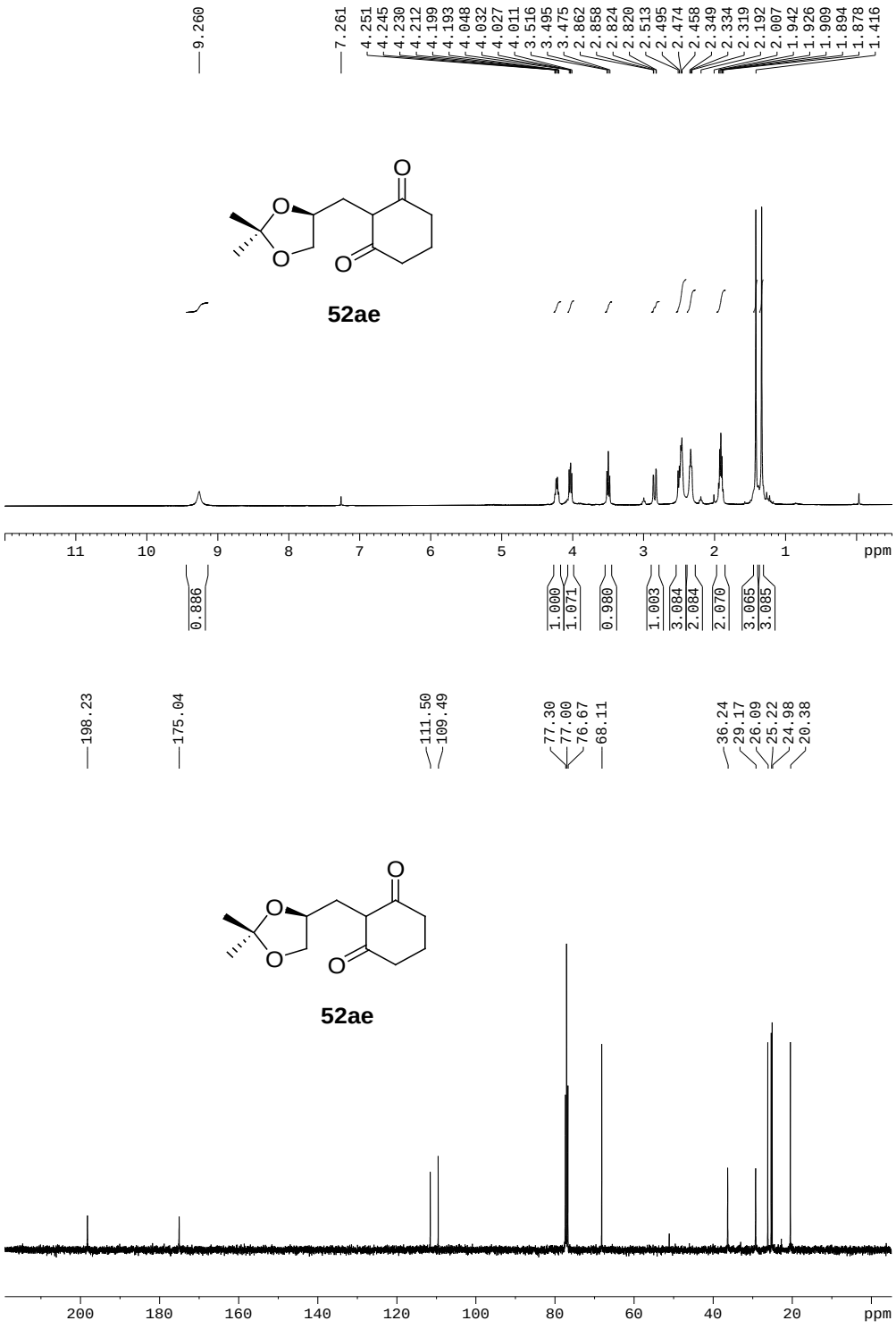


Figure-9: ^{1}H NMR and ^{13}C NMR Spectra of Product **52ae.**

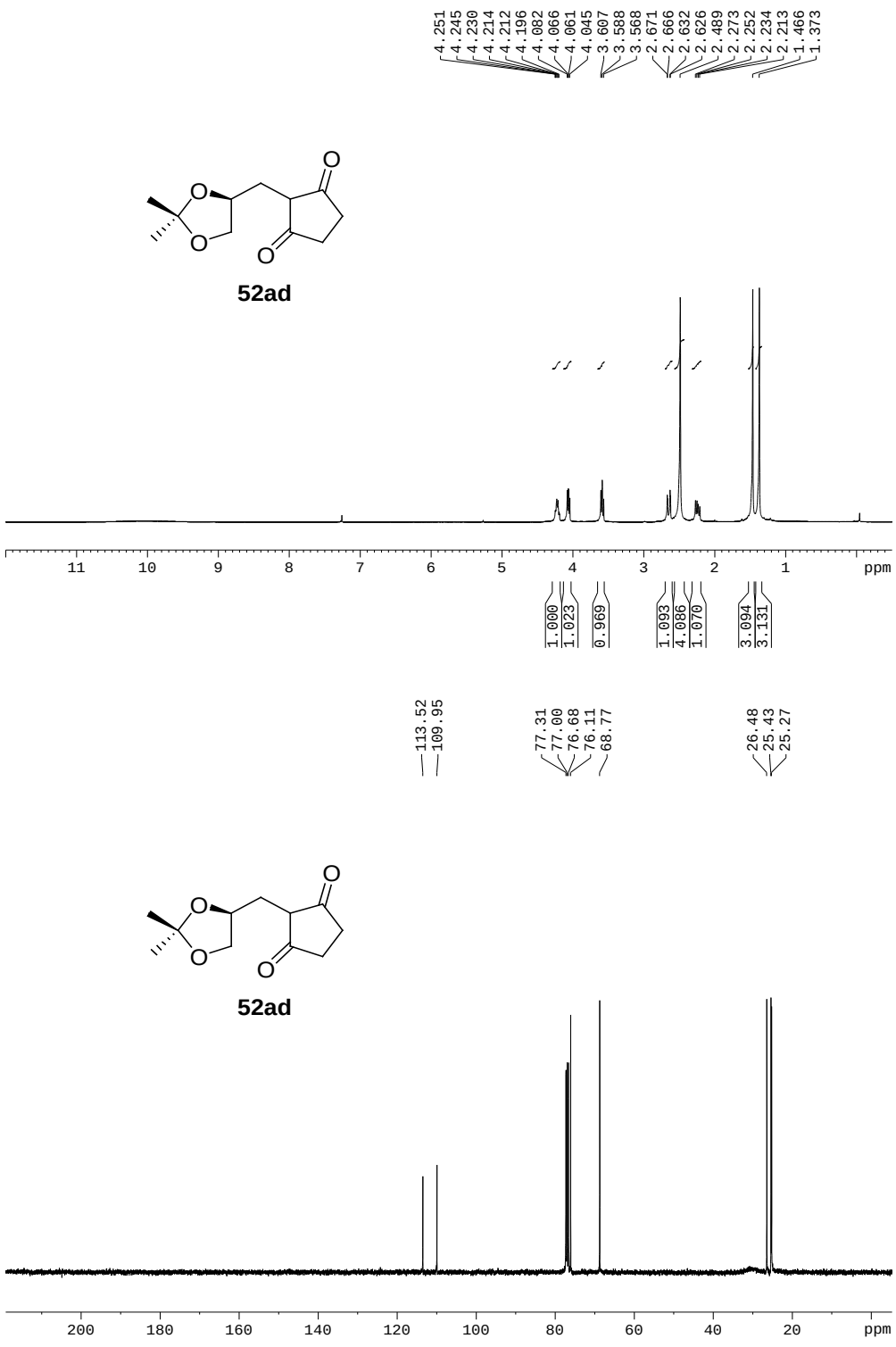
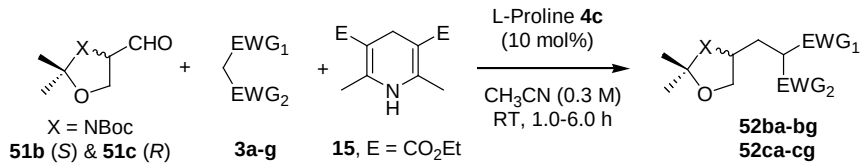
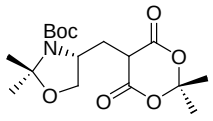


Figure-10: ^{1}H NMR and ^{13}C NMR Spectra of Product **52ad.**

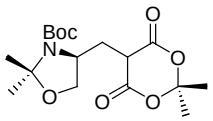
4.2.3 Diversity-Oriented Chiral Synthesis of TCRA Products 52ba-bg: With the optimized TCRA reaction conditions in hand, the scope of the L-proline-catalyzed cascade TCRA reactions were investigated with different chiral α-amino aldehydes **51b-d**, various CH-acids **3a-g** and Hantzsch ester **15** as shown in Table 10. A series of chiral α-amino aldehydes **51b-d** (1 equiv.) were reacted with Meldrum's acid **3a** and Hantzsch ester **15** catalyzed by 10 mol% of L-proline at 25 °C in CH_3CN (Table 10). (*R*)-4-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester **52ba**[*], (*S*)-4-(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester **52ca** and (*R*)-5-(2-dibenzylamino-3-phenyl-propyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **52da** were obtained as enantiomerically pure with excellent to good yields. The reaction of (*S*)-Garner aldehyde **51b** with cyclohexane-1,3-dione **3e** and Hantzsch ester **15** under L-proline-catalysis furnished the TCRA product (*R*)-**52be** as single enantiomer in 90% yield at 25 °C (Table 10). In a similar manner, reaction of (*S*)-Garner aldehyde **51b** with 5,5-dimethyl-cyclohexane-1,3-dione **3g**/cyclopentane-1,3-dione **3d** and Hantzsch ester **15** in CH_3CN at 25 °C for 1-6 h under L-proline-catalysis furnished the TCRA products (*R*)-**52bg** and (*R*)-**52bd** as single enantiomers in 93-95% yields respectively (Table 10). The results in Table 10 demonstrate the broad scope of this reductive methodology covering a structurally diverse group of chiral α-amino aldehydes **51b-d** with many of the yields obtained being very good, or indeed better, than previously published four-step alkylation reactions.[26] Structure and regiochemistry of TCRA products **52ba-bg** were confirmed by NMR and mass analysis [for example see Fig. 11].

Table 10: Synthesis of Chiral Products **52ba-bg** via Reductive Alkylation Reaction[a]

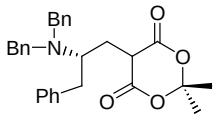




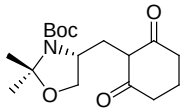
52ba (85%)
$[\alpha]^{25}_{D}$ = – 9.4 (*c* 0.7, EtOH)



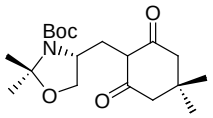
52ca (95%)
$[\alpha]^{25}_{D}$ = + 9.2 (*c* 0.55, EtOH)



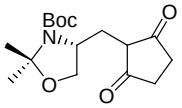
52da (55%)
$[\alpha]^{25}_{D}$ = + 71.3 (*c* 0.35, $CHCl_3$)



52be (90%)[b]
$[\alpha]^{25}_{D}$ = + 24.1 (*c* 0.55, EtOH)



52bg (93%)
$[\alpha]^{25}_{D}$ = + 38.9 (*c* 0.55, EtOH)

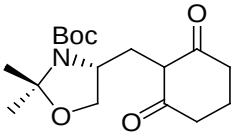


52bd (95%)[b]
$[\alpha]^{25}_{D}$ = + 22.8 (*c* 0.5, EtOH)

[a] Yield refers to the column purified product. [b] Garner aldehyde **51b** was taken as 3 equivalents.

4.3 Applications of Chiral TCRA Products

4.3.1 Development of Product-Specific MCC Reactions based on the TCRA Platform. Chiral 2-alkyl-malonates are an important class of compounds, which are widely used as intermediates in the pharmaceuticals and agrochemicals.[25j-o] Compounds containing chiral 2-alkyl-malonates have found pharmaceutical applications as glucocorticoid receptor modulators, peptide deformylase inhibitors, HIV-1 and HIV-2 protease inhibitors, a potent dual ACE/NEP inhibitors, anti-diabetic agents, ligands for the neuromodulatory receptor and are also starting materials for the synthesis of natural products as shown in Chart 1.[1]



52be

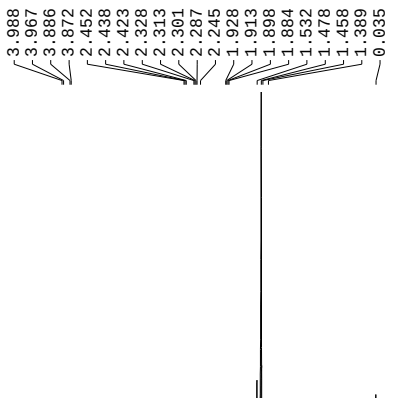
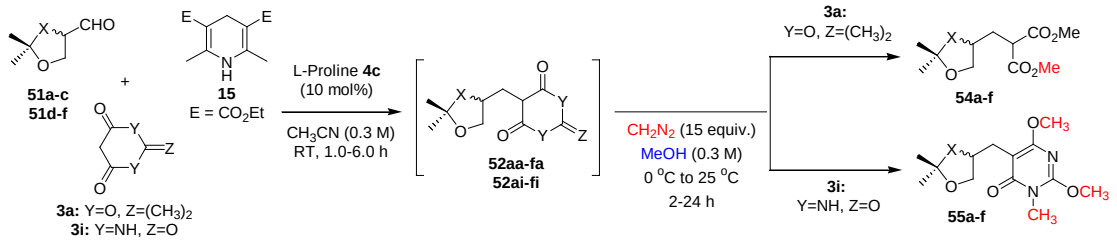
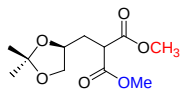


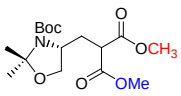
Figure-11: ^{1}H NMR and ^{13}C NMR Spectra of Product **52be.**

Table 11: Synthesis of Chiral Products **54** and **55** *via* MCC Reaction[a]

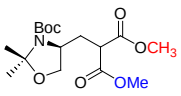




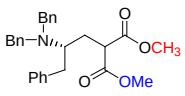
54a (75%)
$[\alpha]^{25}_D$ = – 6.5 (*c* 2.2, MeOH)



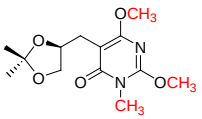
54b (80%)
$[\alpha]^{25}_D$ = – 34.5 (*c* 0.8, $CHCl_3$)



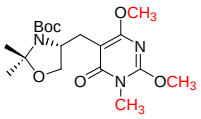
54c (75%)
$[\alpha]^{25}_D$ = + 34.5 (*c* 0.5, $CHCl_3$)



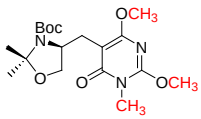
54d (65%)
$[\alpha]^{25}_D$ = + 15.2 (*c* 1.1, $CHCl_3$)



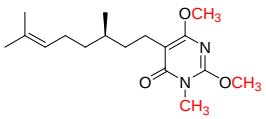
55a (90%)
$[\alpha]^{25}_D$ = – 8.1 (*c* 1.0, EtOH)



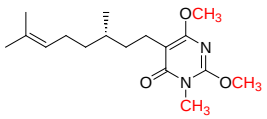
55b (75%)
$[\alpha]^{25}_D$ = + 25.4 (*c* 0.7, EtOH)



55c (80%)
$[\alpha]^{25}_D$ = – 25.3 (*c* 0.7, EtOH)

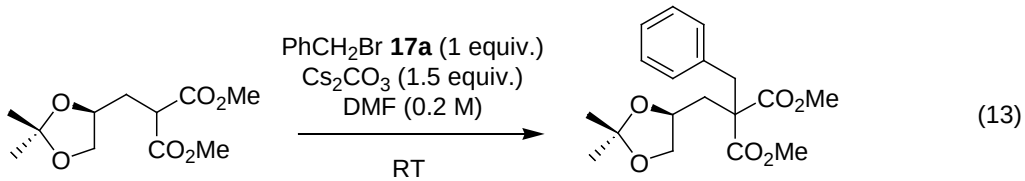


55e (80%)
$[\alpha]^{25}_D$ = – 7.7 (*c* 1.0, $CHCl_3$)



55f (75%)
$[\alpha]^{25}_D$ = + 7.6 (*c* 1.0, $CHCl_3$)

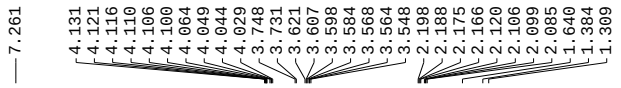
[a] Yield refers to the column purified product.



(–)-**54a**

(+)-**56**
yield: 65%
ee: >98%

(13)



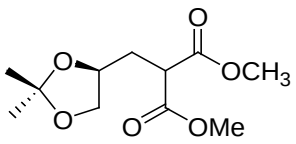


Figure-12: ^{1}H NMR and ^{13}C NMR Spectra of Product **54a.**

The conventional method to synthesize chiral 2-alkyl-malonates is by the alkylation of dialkyl malonates with chiral alkyl halides under dry reaction conditions, (see eq 11).[26] Surprisingly, the amino acid-catalyzed cascade TCRA reaction sequence

did not work with dialkyl-malonates as CH-acid, even the first step of olefination itself not taken place. To overcome this reactivity problem, herein we discovered the synthesis of chiral 2-alkyl-malonates in sequential manner by utilization of reactive species of methoxycarbonylketenes to generate the library of chiral 2-alkyl-malonates *via* in situ *O*-alkylation/ketenization/esterification (A/K/E) of TCRA product **52aa** with CH_2N_2 in one-pot at the ambient conditions, an approach we call "MCC approach to chiral 2-alkyl-malonates" (Table 11).[5d]

L-Proline-catalyzed TCRA reaction of (*R*)-**51a** and Meldrum's acid **3a** with Hantzsch ester **15** in CH_3CN at 25 °C for 1 h furnished the expected TCRA product (*S*)-**52aa** in >99% conversion, which on in situ treatment with ethereal diazomethane in MeOH at 0 °C → 25 °C for 8 h furnished the expected (*S*)-dimethyl 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-malonate **54a** with 75% yield and >98% ee (based on HPLC analysis of **54a** derivative and see eq. 13 for more information) through *O*-alkylation/ketenization/esterification (A/K/E) sequence (Table 11, entry 1). The TCRA/A/K/E reaction of Meldrum's acid analogues **3c** and **3h** with (*R*)-**51a**, **15**, methanol and diazomethane catalyzed by **4c** in methanol at 0 °C → 25 °C for 24 h furnished the expected (*S*)-**54a** with 55-60% yields, >98% ee respectively and these results are not superior as compared to **3a** with respect to yields (results not shown in Table 11). After these interesting results, we decided to investigate the scope and limitations of the MCC reaction with other three chiral α-amino aldehydes **51b-d** with **3a**, **15**, methanol and diazomethane under L-proline-catalysis at the ambient conditions (Table 11, entries 2-4). MCC reaction of chiral α-amino aldehydes (*S*)-**51b**, (*R*)-**51c** and

(*S*)-**51d** with **3a**, **15**, methanol and diazomethane under L-proline-catalysis furnished the expected enantiomerically pure products (–)-**54b**, (+)-**54c** and (+)-**54d** in 80-65% yields respectively as shown in Table 11, entries 2-4. Structure, regiochemistry and ee of MCC products **54** were confirmed by NMR, mass and HPLC analysis [see eq. 13 and Fig. 12 & 14].

After these interesting results, we further decided to investigate the scope and limitations of the MCC reaction with a range of chiral aldehydes **51a-f**, barbituric acid **3i**, **15**, methanol and diazomethane under L-proline-catalysis at the ambient conditions to test the diversity of the MCC reaction (Table 11). As shown in Table 11, MCC reaction of (*R*)-**51a**, barbituric acid **3i**, **15**, methanol and diazomethane furnished the (*S*)-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,6-dimethoxy-3-methyl-3*H*-pyrimidin-4-one **55a** as major single product with 90% yield out of 24 theoretically expected products from the designed reaction as shown in Table 11 and Figure 13. (*S*)-5-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-pyrimidine-2,4,6-trione **52ai**, which is in situ generated from TCRA reaction has many active sites towards methylation with diazomethane but interestingly we are able to obtain **55a** as the single major product, which is confirmed by NMR and UV spectral analysis. Generality of the product-specific MCC reaction was confirmed by four more examples with chiral aldehydes **51b-f**, **3i**, **15**, methanol and diazomethane under L-proline-catalysis and furnished the expected enantiomerically pure single MCC products **55b-f** with 75-80% yields respectively as

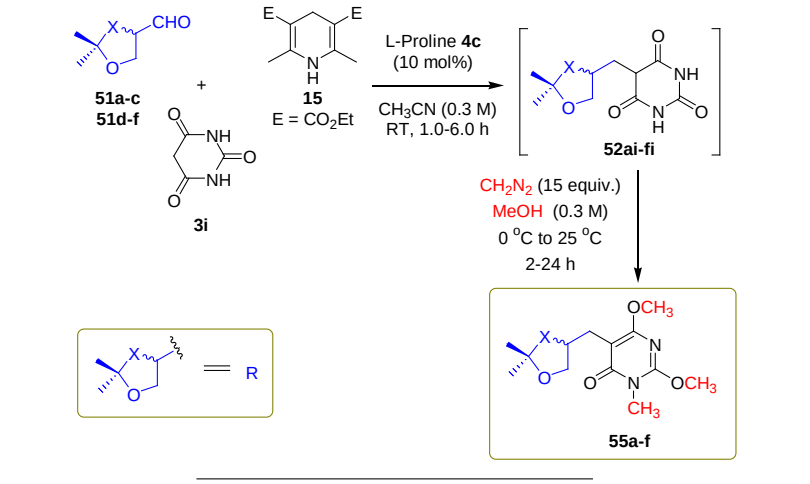


Figure-13: Synthesis of Chiral Products **55a-f** *via* Product-Specific MCC Reaction.

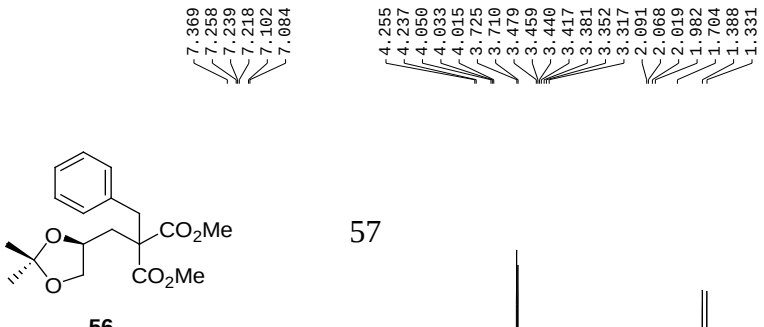


Figure-14: ^{1}H NMR and ^{13}C NMR Spectra of Product **56.**

shown in Table 11. Pyrimidinone derivatives **55a-f** are useful compounds as agrochemical fungicides, potent HIV-1 and HIV-2 inhibitors and have good anti-viral and anti-bacterial activity.[25j-o] This product specific MCC technology may be suitable to

develop large number of diverse-compounds of **52** to screen and identify the suitable bioactive products.

4.3.2 Brønsted Acid-Catalyzed Intramolecular Cyclization of Chiral TCRA Products. Functionalized chiral γ-butyrolactones **57** and protected γ-carboxy-L/D-glutamic acids **58** are very good intermediates for the synthesis of pharmaceutically useful natural and non-natural products as shown in Chart 1.[25] Surprisingly, to the best of our knowledge there is no report for the high-yielding asymmetric synthesis of useful chiral γ-butyrolactones **57** and higher analogues **59** through single step. Herein, we are presenting the asymmetric synthesis of **57**, **58** and **59** with ≥98% ee and 80-99% yields via Brønsted acid-catalyzed cyclization of TCRA products **52** in protic or aprotic solvents as shown in Table 12. With an efficient amino acid-catalyzed reductive alkylation protocol in hand, we continued our investigation for the synthesis of functionalized chiral γ-butyrolactones **57** from (*S*)-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **52aa** under Brønsted acid-catalysis in MeOH/BnOH through cascade hydrolysis/lactonization/esterification (H/L/E) reactions as shown in Table 12, entry 1.

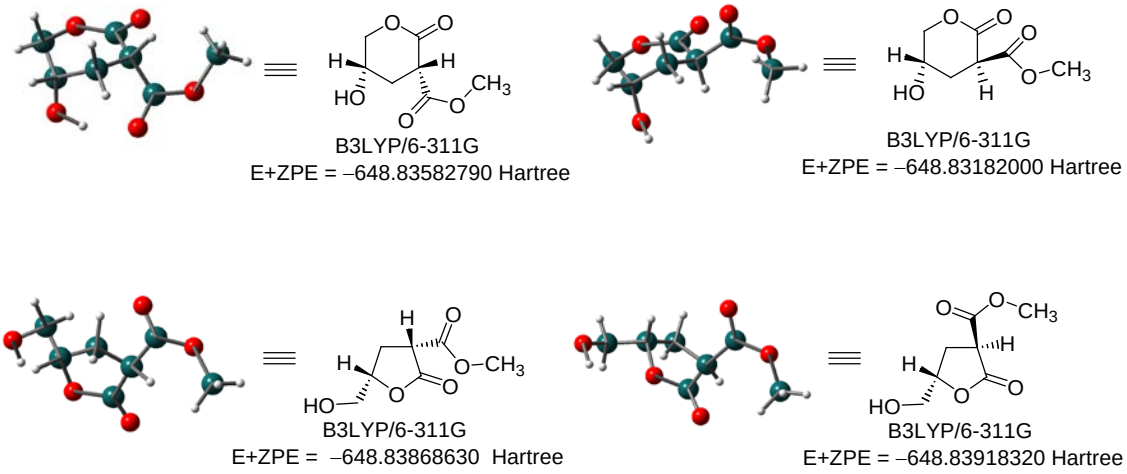
After complete investigation, we came to a conclusion that *p*-TSA is suitable Brønsted acid-catalyst for the H/L/E reactions compared to other Brønsted acid catalysts **(**results not shown in Table 5). Interestingly, reaction of (–)-**52aa** with 30 mol% of *p*-TSA in MeOH at 25 °C for 1-2 h furnished chemoselectively the single compound chiral γ-butyrolactone (+)-**57aaa** with 1:1 dr in 99% yield (Table 12, entry 1). Same H/L/E reaction under *p*-TSA-catalysis in BnOH at 25 °C for 1-2 h furnished

the expected single chiral γ-butyrolactone product (+)-**57aab** with 1:1 dr in 99% yield (Table 12, entry 1). We envisioned that reaction of (–)-**52aa** with *p*-TSA in protic solvents at 25 °C for 1-2 h furnished chemoselectively H/L/E products (+)-**57aaa-aab** as single products in 99% yields instead of 5-hydroxy-2-oxo-tetrahydro-pyran-3-carboxylic acid alkyl esters, which is revealed by NMR analysis [see Fig. 15] and also by DFT calculations (see Scheme 8). The calculated heat of formation (ΔΔE) for the product (+)-**57aaa** is 3.2 kcal/mol more than the six-membered ring formation reaction as shown in Table 12, entry 1. This result strongly suggests that kinetically and thermodynamically γ-butyrolactone product (+)-**57aaa-aab** formation is more favorable than 5-hydroxy-2-oxo-tetrahydro-pyran-3-carboxylic acid alkyl esters formation as revealed by experimental and DFT calculations.

Brønsted acid-catalyzed cascade hydrolysis/esterification (H/E) reaction of (–)-**52ba** at 25 °C for 2 h in MeOH furnished chemoselectively the protected γ-carboxy-L-glutamic acid [L-Gla] (+)-**58ba** with 97% yield as single compound (Table 12, entry 2). In a similar manner, reaction of (+)-**52ca** under *p*-TSA-catalysis at 25 °C for 2.5 h in MeOH furnished the protected D-Gla, (–)-**58ca** with 95% yield as single compound (Table 12, entry 3). Formation of **58ba-ca** as single products/isomers from cascade H/E reaction could be explained on the basis of relatively weak nucleophilic nature of the in situ generated primary OH and NHBoc groups towards the ester. H/E Products of protected L-Gla and D-Gla **58ba-ca** are important components of several vitamin K dependent blood clotting factors, including prothrobin and also potentially useful

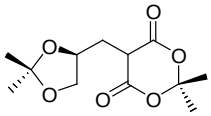
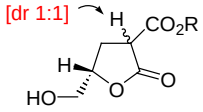
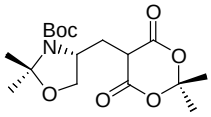
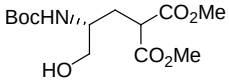
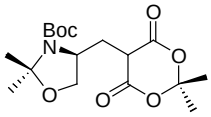
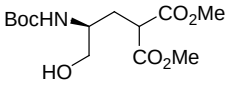
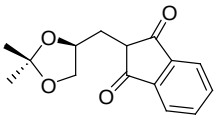
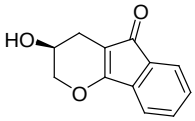
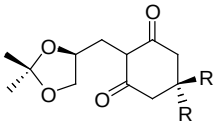
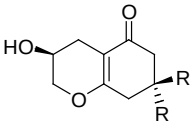
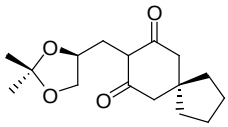
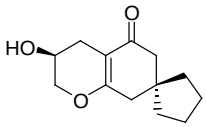
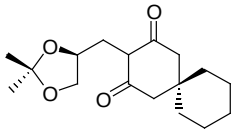
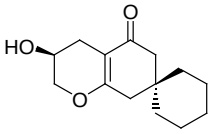
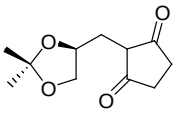
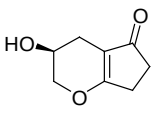
building blocks in the total synthesis of quinocarcin and related bio-active natural products,[25p-q] which emphasizes on the pioneering role of cascade H/E approach.

Scheme 8: Minimized Structures of Hydrolysis/Lactonization/Esterification (H/L/E) Products Based on DFT Calculations.

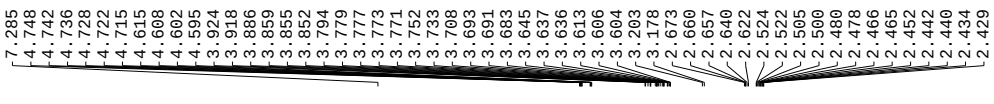


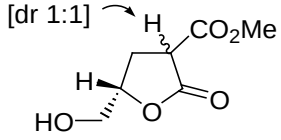
With an efficient Brønsted acid-catalyzed H/L/E and H/E protocol in hand, we continued our investigation for the synthesis of functionalized chiral 3-hydroxy-2,3,4,6,7,8-hexahydro-chromen-5-ones **59ab, 59ad, 59ae, 59ag, 59ak-al** from chiral TCRA products **52ab, 52ad, 52ae, 52ag, 52ak-al** under Brønsted acid-catalysis through cascade hydrolysis/oxy-Michael/dehydration (H/OM/DH) reactions as shown in Table 12, entries 4-8. Interestingly, reaction of (–)-**52ab** with 30 mol% of *p*-TSA in CH_2Cl_2

Table 12: Brønsted Acid-Catalyzed Intramolecular Cyclization of Chiral TCRA Products **52**[a]

entry	substrate	conditions	product
1	 (–)-**52aa**	*p*-TSA (30 mol%) ROH (0.1 M) RT, 1-2 h	 R = Me: (+)-**57aaa** (99%) R = Bn: (+)-**57aab** (99%)
2	 (–)-**52ba**	*p*-TSA (30 mol%) MeOH (0.1 M) RT, 2 h	 (+)-**58ba** (97%)
3	 (+)-**52ca**	*p*-TSA (30 mol%) MeOH (0.1 M) RT, 2.5 h	 (–)-**58ca** (95%)
4	 (–)-**52ab**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 2-3 h	 (–)-**59ab** (88%)
5	 R = H: (–)-**52ae** R = Me: (–)-**52ag**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 3-5 h	 R = H: (–)-**59ae** (93%) R = Me: (–)-**59ag** (91%)
6	 (+)-**52ak**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 4-5 h	 (–)-**59ak** (91%)
7	 (+)-**51al**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 1-2 h	 (–)-**59al** (80%)
8	 (–)-**52ad**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 2-3 h	 (–)-**59ad** (90%)

[a] Yield refers to the column purified product.





57aaa

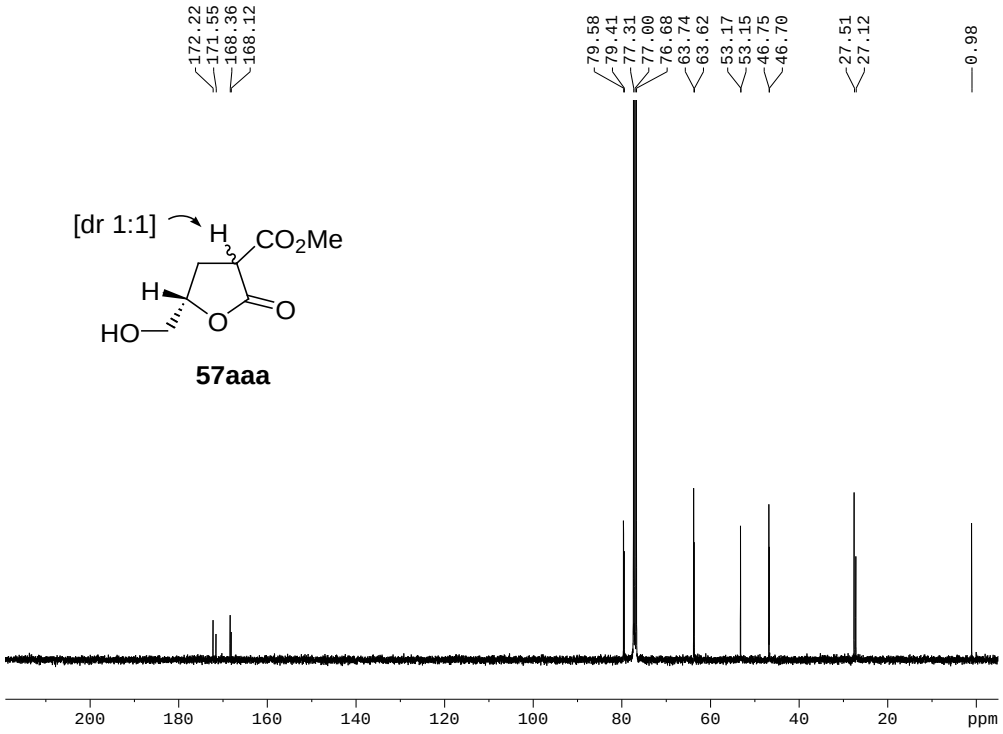
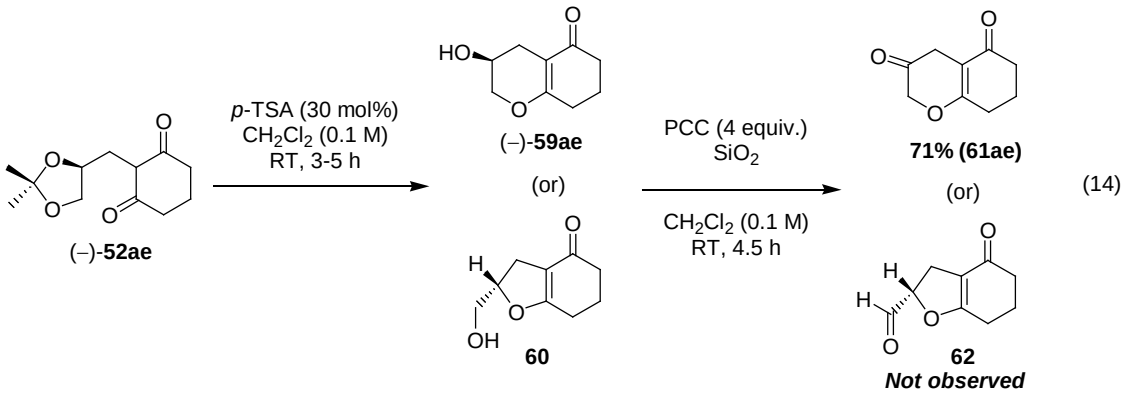


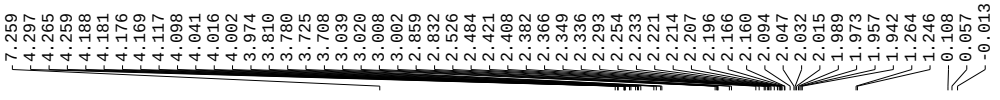
Figure-15: ^{1}H NMR and ^{13}C NMR Spectra of Product **57aaa.**

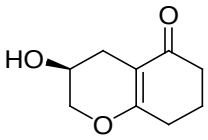
at 25 °C for 2-3 h furnished chemoselectively the single chiral product (–)-**59ab** with 88% yield through H/OM/DH reactions (Table 12, entry 4). In a similar manner, reaction of (–)-**52ae** with 30 mol% of *p*-TSA in CH_2Cl_2 at 25 °C for 3-5 h furnished

chemoselectively the single chiral product (–)-**59ae** with 93% yield through H/OM/DH reactions (Table 12, entry 5). Generality of the product-specific H/OM/DH reaction was confirmed by four more examples with chiral TCRA compounds **52ad, 52ag, 52ak-al** under *p*-TSA-catalysis and furnished the expected enantiomerically pure single H/OM/DH products **59ad, 59ag, 59ak-al** with 80-91% yields respectively as shown in Table 12, entries 5-8. Structure and regiochemistry of products **59** were confirmed by NMR and mass analysis [for example, see Fig. 16 & 17] and also by chemical method as shown in eq. 14. Unexpected chemoselectivity of the H/OM/DH reactions could be explained based on the more nucleophilic nature of in situ generated primary OH group than secondary OH group in the oxy-Michael step.



(14)





59ae

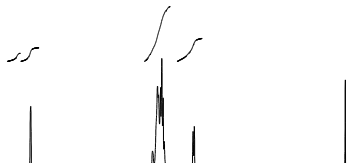
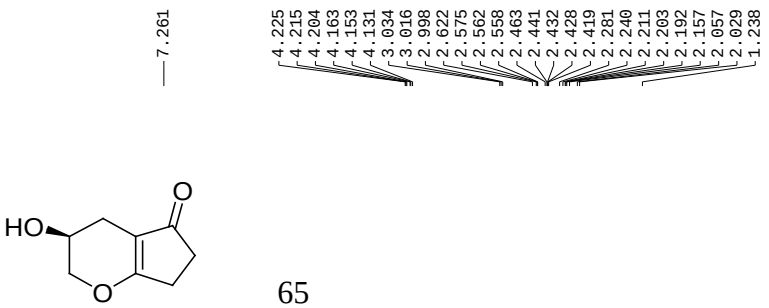


Figure-16: ^{1}H NMR and ^{13}C NMR Spectra of Product **59ae.**



59ad

Figure-17: ^{1}H NMR and ^{13}C NMR Spectra of Product **59ad.**

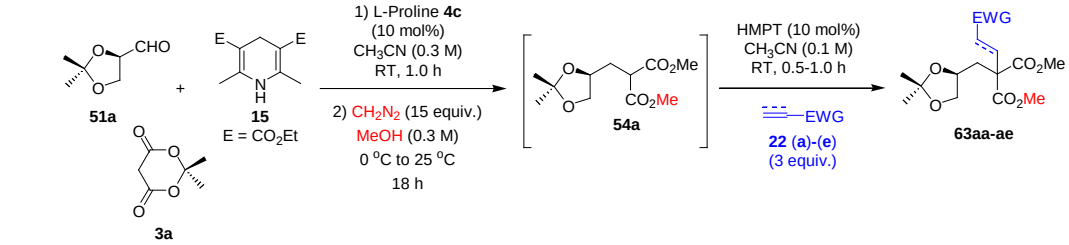
Functionalized chromanes and chromenes are of considerable importance in a variety of industries. These heterocyclic analogues **59ab, 59ad-ae, 59ag, 59ak-al** are widespread elements in natural products and have attracted much attention from a wide area of science, including physical chemistry, medicinal chemistry, natural product

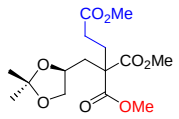
chemistry, synthetic organic chemistry and polymer science.[17] As such, the development of more general catalytic asymmetric methods for their preparation is of significant interest and our presently developed cascade chemistry will be useful to develop library of chiral chromanes and chromenes in very good yields with high selectivity.

4.3.3 Sequential Cascade Synthesis of Asymmetric Compounds with Quaternary Carbons through MCC Reactions based on TCRA Platform.

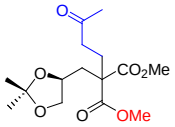
Stereoselective synthesis of highly functionalized chiral compounds with quaternary carbons is an evergreen task in synthetic organic chemistry.[29] As a part of our research program to engineer direct MCC reactions in a sequential manner to deliver the highly functionalized chiral molecules with quaternary carbons and also on the demand of pharmaceutical applications, we extended the five-component TCRA/A/K/E reactions into L-proline-HMPT-catalyzed six-component TCRA/A/K/E/A reaction of (*R*)-glyceraldehyde acetonide **51a**, Meldrum's acid **3a**, Hantzsch ester **15**, diazomethane and methanol with various active olefins and acetylenes (**22a**)-(**22e**) in one-pot (Table 13). MCC products **63** were constructed in very good yields with high selectivity and this method will be showing much impact on the synthesis of functionalized small chiral molecules with quaternary carbon as shown in Table 13. Highly substituted asymmetric 2,2-dialkylated malonates **63** have gained importance in the recent years as starting materials and intermediates for the synthesis of biologically active compounds, for example M_2-selective muscarinic receptor antagonists and isozyme-selective glutathione *S*-transferase inhibitors.[25j-o]

Table 13: Synthesis of Chiral Products **63** with Quaternary Carbons via MCC Reaction[a]

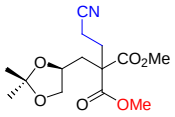




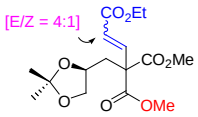
63ac (95%)
$[\alpha]^{25}_{D}$ = – 3.3 (*c* 0.5, EtOH)



63aa (90%)
$[\alpha]^{25}_{D}$ = – 6.2 (*c* 0.5, $CHCl_3$)



63ad (90%)
$[\alpha]^{25}_{D}$ = – 13.0 (*c* 0.5, $CHCl_3$)



63ae (90%)
$[\alpha]^{25}_{D}$ = – 14.2 (*c* 0.6, $CHCl_3$)

[a] Yield refers to the column purified product.

TCRA Reaction of (*R*)-**51a**, **3a** and **15** under 10 mol% of L-proline-catalysis furnished the compound (–)-**52aa** with >99% conversion, which on in situ treatment with ethereal diazomethane at 0 °C to 25 °C for 8 h furnished chemoselectively the TCRA/A/K/E product (–)-**54a** with >99% conversion, which on in situ treatment with methyl acrylate (**22c**) under 10 mol% of hexamethylphosphorous triamide (HMPT)-catalysis in CH_3CN at 25 °C for 0.5-1.0 h furnished the TCRA/A/K/E/A product (–)-**63ac** with 95% yield as shown in Table 13.[30] Generality of the L-proline-HMPT-catalyzed chemoselective sequential one-pot TCRA/A/K/E/A reaction was further confirmed by three more examples using methyl vinyl ketone (**22a**), acrylonitrile (**22d**)

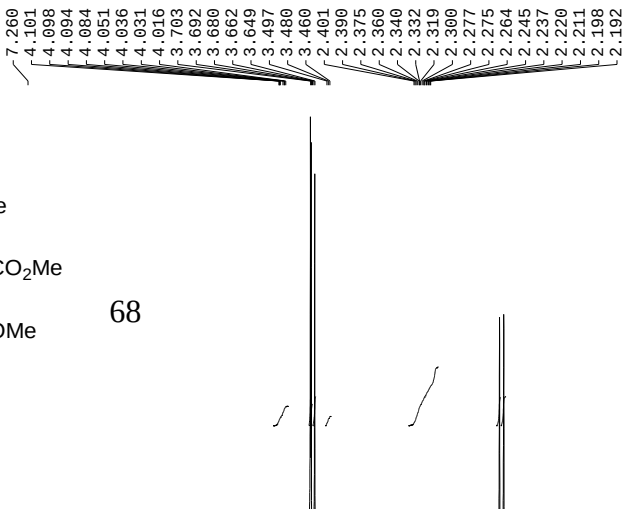


Figure-18: ^{1}H NMR and ^{13}C NMR Spectra of Product **63ac.**

and methyl propiolate (**22e**) to furnish the expected (–)-**63aa** in 90% yield, (–)-**63ad** in 90% yield and (–)-**63ae** in 90% yield with >60% de, respectively as shown in Table 13. For the pharmaceutical applications, diversity-oriented library of chiral malonates **63**

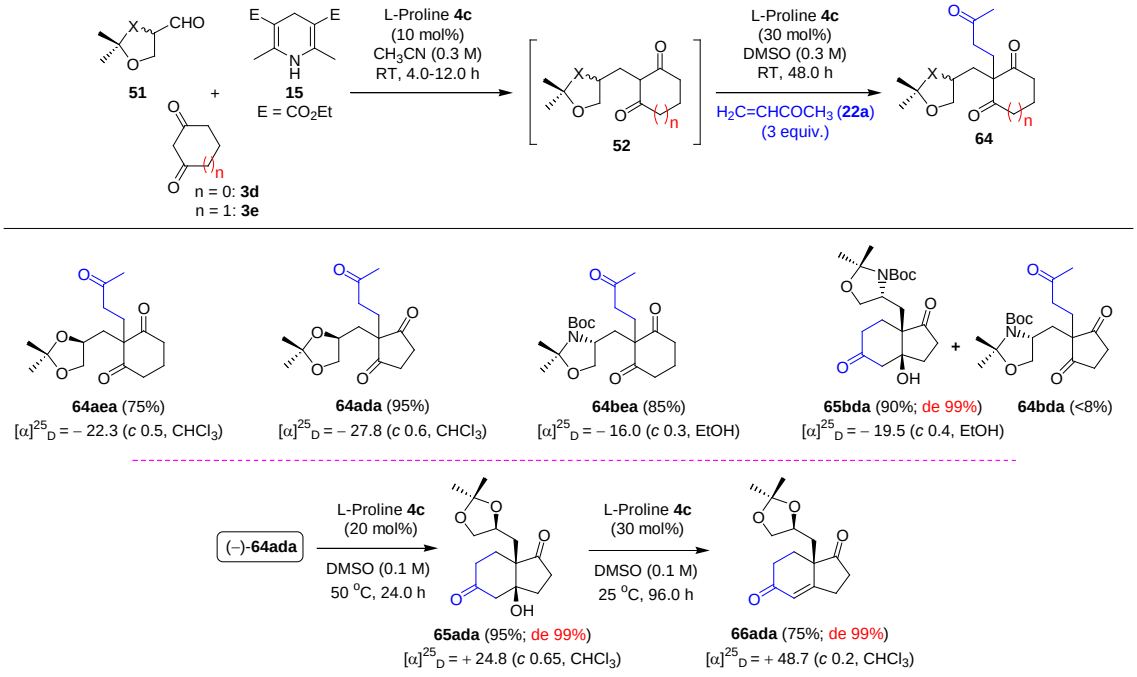
could be generated by using this MCC technology. Structure of the MCC products **63** were confirmed by NMR analysis [for example see Fig. 18].

4.3.4 Sequential Cascade Asymmetric Synthesis of Hajos-Parrish Ketone Analogues through MCC Reactions based on TCRA Platform. Higher alkyl substituted chiral Wieland−Miescher (W-M) and Hajos-Parrish (H-P) ketone analogues **65/66** are good intermediates for the synthesis of natural products like steroids and pharmaceutically acceptable salts or hydrates of hetero-cycles, which are shown as selective glucocorticoid receptor modulators for treating a variety of autoimmune and inflammatory diseases.[31] Interestingly, to the best of our knowledge there is no report for the asymmetric synthesis of useful higher alkyl substituted H-P ketone analogues **65/66**. Here, we are presenting the asymmetric synthesis of H-P ketone analogues **65/66** with very good ee/de and yields through MCC reactions based on TCRA platform as shown in Table 14.

We were surprised to know that L-proline-catalyzed TCRA reaction of three equiv. of (*R*)-glyceraldehyde acetonide **51a** with cyclohexane-1,3-dione **3e** and Hantzsch ester **15** in CH_3CN at 25 °C for 5.0 h furnished the expected TCRA product (–)-**52ae** with good conversion, which on removing the solvent CH_3CN by vacuum pump and adding solvent DMSO, 30 mol% of L-proline **4c** and three equiv. of methyl vinyl ketone (**22a**) to the reaction mixture and stirring at 25 °C for 2 days furnished only the Michael adduct (–)-**64aea*** with 75% yield and >98% ee instead of the expected W-M ketone analogue **65aea*** as shown in Table 14. In a similar manner, L-proline-catalyzed TCRA reaction of three equiv. of (*R*)-**51a** with cyclopentane-1,3-

dione **3d** and Hantzsch ester **15** in CH_3CN at 25 °C for 3.0 h furnished the expected TCRA product (–)-**52ad*** with good conversion, which on removing the solvent CH_3CN by vacuum pump and adding solvent DMSO, 30 mol% of L-proline **4c** and three equiv. of methyl vinyl ketone(**22a**) to the reaction mixture and stirring at 25 °C for 2 days furnished only the

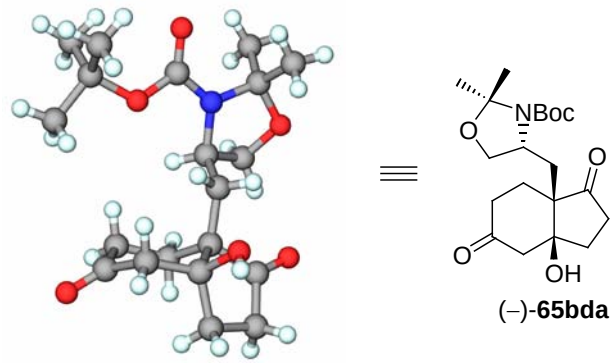
Table 14: Asymmetric Synthesis of H-P Ketone Analogues **65** and **66** via MCC Reactions[a]



[a] Yield refers to the column purified product.

* In all compounds denoted **52xy**, **64xyz** and **65xyz**, **x** is incorporated from reactant chiral aldehydes **51, y** is incorporated from the reactant CH-acids **3** and **z** is incorporated from the reactant methyl vinyl ketone **22.**

Scheme 9: Crystal Structure of 4-(7a-Hydroxy-3,6-dioxo-octahydro-inden-3a-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (**65bda**).



(–)-**65bda**

Michael adduct (–)-**64ada*** with 95% yield and >98% ee instead of the expected H-P ketone analogue **65ada*** as shown in Table 14. Interestingly, treatment of (–)-**64ada** with 20-mol% of L-proline **4c** in DMSO at 50 °C for 24.0 h furnished the expected bicyclic-alcohol (+)-**65ada** in 95% yield with >98% ee and 99% de. Dehydration of the bicyclic-alcohol (+)-**65ada** with L-proline (30 mol%) in DMSO at 25 °C for 96 h furnished the expected bicyclic H-P ketone analogue (+)-**66ada*** in good yield with >98% ee and 99% de as shown in Table 14. Structure of the products **64**, **65** and **66** were confirmed by NMR [for example see Fig. 19] and mass analysis.

* In all compounds denoted **64xyz, 65xyz** and **66xyz**, **x** is incorporated from reactant chiral aldehydes **51, y** is incorporated from the reactant CH-acids **3** and **z** is incorporated from the reactant methyl vinyl ketone **22**.

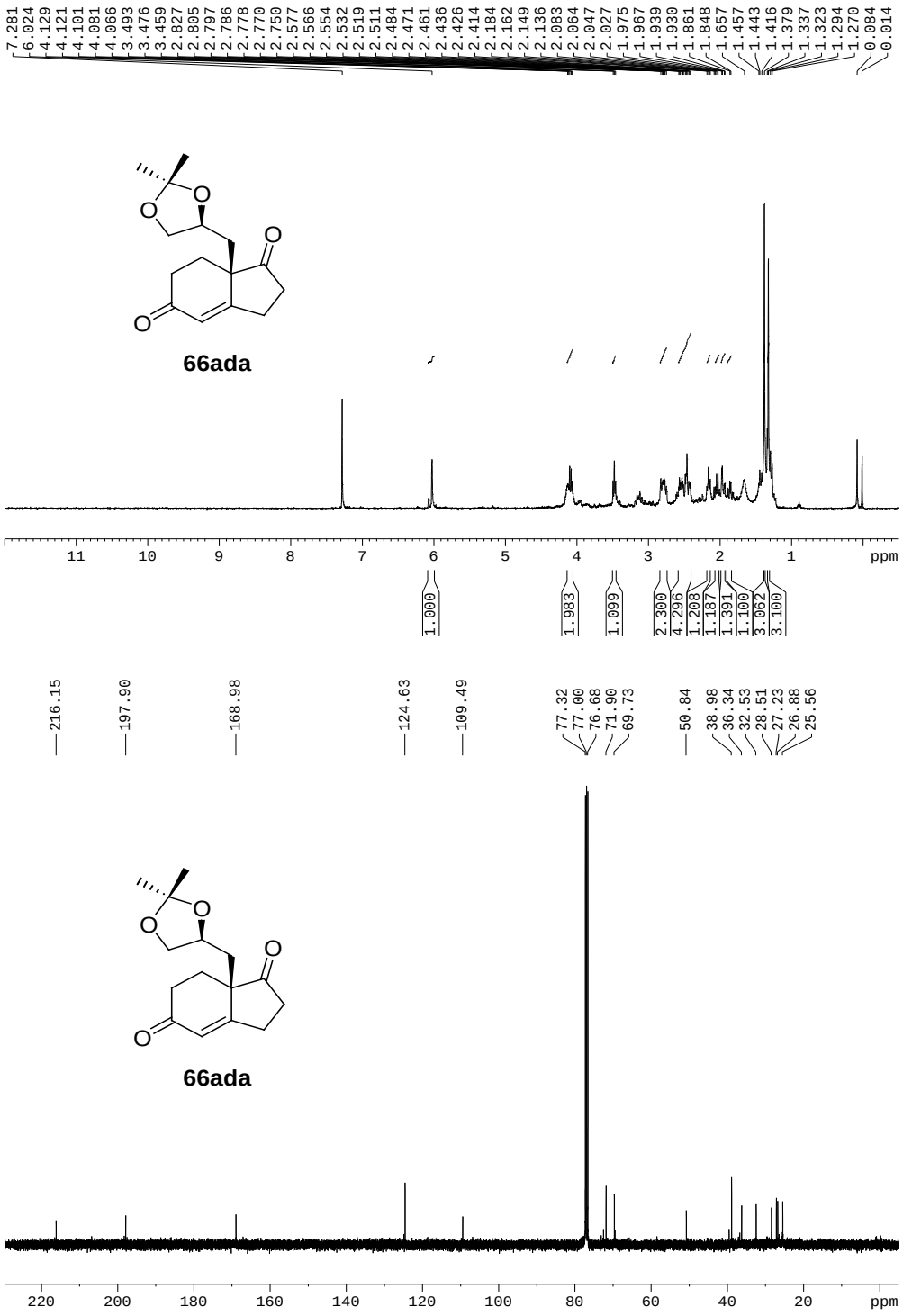


Figure-19: ^{1}H NMR and ^{13}C NMR Spectra of Product **66ada.**

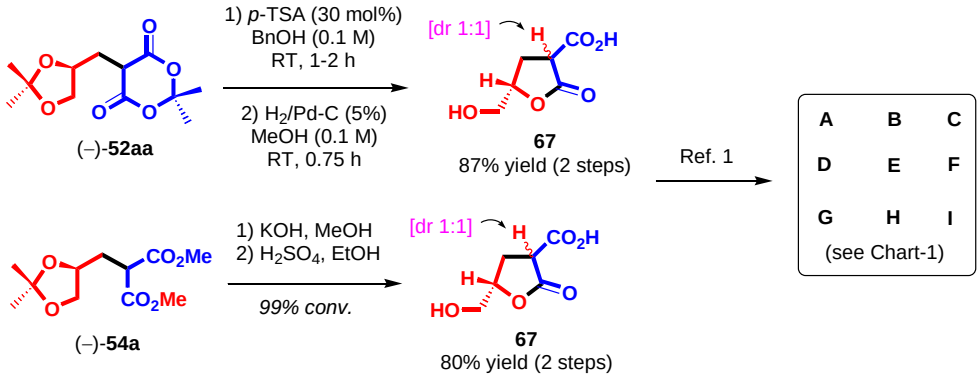
With an efficient organocatalytic asymmetric sequential cascade Robinson annulation (RA) protocol in hand; the scope of the L-proline-L-proline-catalyzed sequential asymmetric RA reactions are investigated with Garner aldehyde (*S*)-**51b**. A series of cyclohexane-1,3-dione **3e**/cyclopentane-1,3-dione **3d** were reacted with 3.0 equiv. of Garner aldehyde (*S*)-**51b** and Hantzsch ester **15** under the 10 mol% of L-proline at 25 °C in CH_3CN for 4-5 h followed by treatment with 3.0 equiv. of methyl vinyl ketone (**22a**) catalyzed by 30 mol% of L-proline at 25 °C in DMSO for 48 h (Table 14). In the case of **3e**, only the expected Michael adduct (–)-**64bea**[*] was obtained in good yields with >98% ee as shown in Table 14. But interestingly, sequential RA reaction with **3d** furnished the bicyclic-alcohol (–)-**65bda**[*] in 90% yield with >98% ee and 99% de along with the Michael adduct **64bda** as a byproduct in <8% yield. The absolute configuration of the product (–)-**65bda** prepared under L-proline-L-proline-catalysis was established by using X-ray crystallography and also by comparison with the L-proline-catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction.[32] The X-ray crystal structure of the product (–)-**65bda** is depicted in Scheme 9.[33]

4.3.5 High-yielding Synthesis of Chiral Building Blocks for Natural Products: Formal Total Synthesis of HIV-1 Protease Inhibitors, Phospholipase A_2 Inhibitors, Antibiotic Agglomerins, Brefeldin A and (R)-γ-Hexanolide: After successful demonstration of the L-proline-catalyzed asymmetric TCRA reactions followed by development of MCC reactions with the combination of

[*] In all compounds denoted **64xyz** and **65xyz**, **x** is incorporated from reactant chiral aldehydes **51, y** is incorporated from the reactant CH-acids **3** and **z** is incorporated from the reactant methyl vinyl ketone **22**.

A/K/E, A/K/E/A, H/L/E, H/E, H/OM/DH and RA reactions, we further decided to synthesize the chiral building blocks for natural products from MCC reactions as shown in Scheme 10. The design and implementation of MCC reactions is a challenging task of organic chemistry, yet one that can impart striking novelty, elegance, and efficiency to synthetic strategies. The application of MCC reactions to natural product synthesis represents a particularly demanding task, but the results can be both stunning and instructive. Herein, we highlight the design and execution of the combination of MCC reactions for the high-yielding synthesis of key intermediates in the total synthesis with minimum synthetic steps as demonstrated with selected natural product examples.[1k]

Scheme 10: High-yielding Synthesis of Chiral Building Block **67**: Formal Synthesis of Natural Products (A-I).



Recently chiral (5*S*)-5-hydroxymethyl-2-oxo-tetrahydro-furan-3-carboxylic acid **67** was used as a key intermediate for the total synthesis of HIV-1 protease inhibitors **A-D**, phospholipase A_2 inhibitors **E-F**, antibiotic agglomerins **G**, (*R*)-γ-hexanolide **H** and (+)-brefeldin-A **I** as shown in Scheme 10.[25a-i] S. Ohta et al and T. Kitahara et al prepared the key intermediate **67** in 6 steps starting from (*R*)-glyceraldehyde acetonide

51a with an overall yield of 40% in their total synthesis of **A-F** and **I** respectively.[25a-i] Herein, by the combination of cascade TCRA and H/L/E reactions, we prepared the key intermediate of chiral acid (5*S*)-**67** by using only 3 synthetic steps [TCRA, H/L/E and hydrogenation] with an overall yield of 83% with >98% ee as shown in Scheme 10. We also developed an alternative method to prepare (5*S*)-**67** with an overall yield of 60% with >98% ee by using again 3 synthetic steps [TCRA/A/K/E, hydrolysis (H) and lactonization (L)], which is similar to the previous approach for cyclization as shown in Scheme 10. Herein, we have demonstrated the successful combination of two cascades TCRA and H/L/E with hydrogenation; or/and TCRA/A/K/E with hydrolysis (H)/lactonization (L) to furnish the (5*S*)-**67** with overall yield of >83% with >98% ee, which is utilized as key chiral building block for the total synthesis of natural products **A-I** as shown in Scheme 10.

4.4 Conclusions

In summary, we have developed the metal-free and MCC process for the asymmetric synthesis of highly substituted chiral building blocks (2-alkyl-CH-acids, 2-alkyl-cyclohexane-1,3-diones, 2-alkyl-cyclopentane-1,3-diones and H-P ketone analogs) based on the three-component reductive alkylation's (*TCRA*) platform. We developed the single-step alkylation of variety of CH-acids with (*R*)-glyceraldehyde acetonide/(*S*)-Garner aldehyde and Hantzsch ester through amino acid-catalyzed TCRA reaction without racemization in very good yields. Direct combination of L-proline-catalyzed TCRA reaction with other reactions like alkylation/ketenization/esterification (A/K/E), alkylation/ketenization/esterification/alkylation (A/K/E/A),

hydrolysis/lactonization/esterification (H/L/E), hydrolysis/esterification (H/E), hydrolysis/oxy-Michael/dehydration (H/OM/DH) and Robinson annulation (RA) of CH-acids, chiral aldehydes, Hantzsch ester, diazomethane and methyl vinyl ketone furnished the highly functionalized chiral building blocks with good to high yields and with excellent diastereoselectivities. Many of the chiral building blocks [**52aa**, **52ba**, **52ca**, **52ae**, **52ad**, **52be**, **52bd**, **52an**, **52ao**, **54a**, **57aab**, **58ba** and **58ca**] prepared via MCC reactions have illustrated the direct application in pharmaceutical chemistry. Further work is in progress to utilize TCRA reactions in synthetic chemistry.

5. Double Cascade Reactions Based on the Barbas Dienamine Platform: Highly Stereoselective Synthesis of Functionalized Cyclohexanes for the Cardiovascular Agents

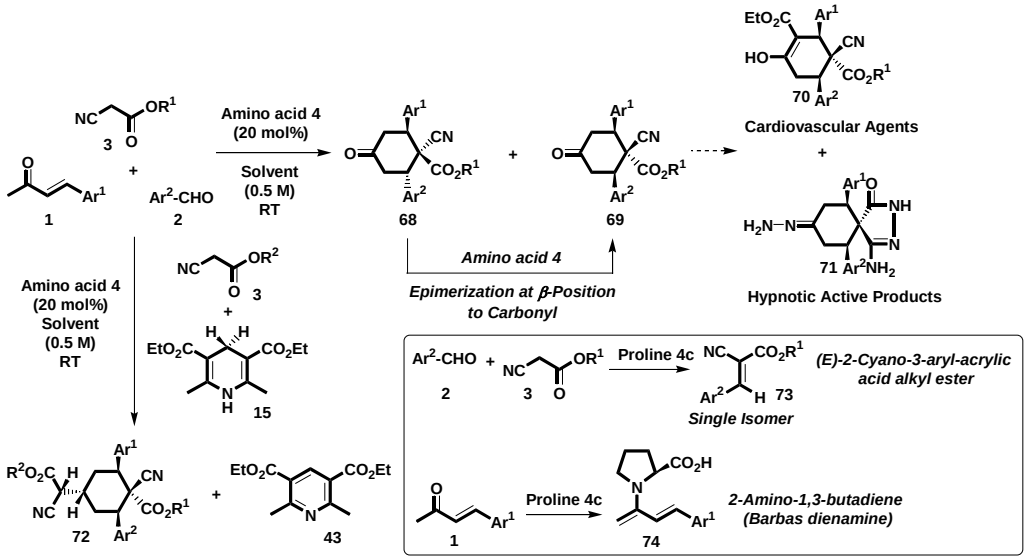
5.1 Introduction

The construction of suitably functionalized cyclohexane frameworks plays a central role in many natural product synthesis.[34] Although the Diels-Alder reaction is among the most powerful tools for generating such carbocycles,[1e] it is often difficult to form systems that are highly congested or possess substituted arrays that are incompatible with the reaction.[35] A number of alternative methods for synthesizing cyclohexanes have arisen from catalytic approaches, such as the base-catalyzed Michael-aldol, Michael-Mannich and Michael-Michael reactions,[36] transition-metal-catalyzed ring-closing metathesis (RCM)[37] followed by hydrogenation, and cycloisomerization reactions.[38] In contradistinction to the widespread use of these intramolecular processes, intermolecular counterparts for catalytic cyclohexane synthesis are less well developed.[39]

Nucleophilic amine catalysis or organocatalysis has emerged recently as an efficient means of generating carbo- and heterocycles.[4] In particular, Barbas three-component [4+2] cycloaddition[6-8] to form functionalized cyclohexanes from 4-substituted-3-buten-2-ones, aldehydes and Meldrum's acid or 1,3-indandione under proline-catalysis has been applied in the syntheses of several *cis*-spirane products.[6-8] Nevertheless, proline-catalysis has not been utilized previously for the formation of functionalized cyclohexanes by utilizing (*E*)-2-cyano-3-aryl-acrylic acid alkyl esters as dienophiles in Diels-Alder chemistry. Building upon our proline-catalyzed regio-selective synthesis of (*E*)-2-cyano-3-aryl-acrylic acid alkyl esters,[11-12,16] we reasoned that it might be possible to use as dienophiles in [4+2] cycloaddition reaction.

Herein, we disclose the facile synthesis of cyclohexanes **68/69** and **72** via proline-catalyzed cascade annulations from simple substrates (Scheme 11).

Scheme 11: Development of Organocatalytic Cascade Reactions Based on Barbas Dienamine Platform.



As a part of our program to engineer novel organocatalytic cascade or multi-component reactions,[11-12,16] herein we reported the highly regio- and diastereoselective direct organocatalytic cascade olefination/Diels-Alder/epimerization, olefination/Diels-Alder/epimerization/three-component reductive alkylation and olefination/Diels-Alder/epimerization/three-component reductive alkylation/*trans*-esterfication reactions that provide highly substituted prochiral 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **68/69** and 1-cyano-4-(cyano-alkoxycarbonyl-methyl)-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **72** from commercially available 4-substituted-3-buten-2-ones **1a-i**, aldehydes **2a-l** and CH-acids, cyano-acetic acid alkyl esters **3n, 3q-t** using *in situ* generated (*E*)-2-cyano-3-aryl-acrylic acid alkyl esters **73** as dienophiles and Barbas dienamines **74** (2-amino-1,3-butadienes)[6-8] as diene source (Scheme 11). The highly

functionalized cyclohexanes **68/69** and **72** are attractive intermediates in the synthesis of natural products, and in materials chemistry and are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products.[40]

In our reaction we envisioned that amino acid, proline **4c** would catalyze the cascade regio-selective olefination reaction of aldehyde **2** with CH-acids (alkyl cyanoacetates) **3** to provide (*E*)-2-cyano-3-aryl-acrylic acid alkyl esters **73** via iminium-catalysis, which would then undergo a concerted [4+2] cycloaddition with a 2-amino-1,3-butadienes **74** (Barbas dienamine) generated *in situ* from enone **1** and proline **4c** to form substituted 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **68** and **69** in a diastereoselective manner. Novel epimerization at α-position to carbonyl of the minor diastereomer *trans*-isomer **68** to the more stable *cis*-isomer **69** could occur under the same reaction conditions as shown in Scheme 11. Further treatment of *cis*-isomer **69** with CH-acids **3** and Hantzsch ester **15** would generate the highly functionalized cyclohexanes **72** in one-pot as shown in Scheme 11. The cascade olefination/Diels-Alder/epimerization, olefination/Diels-Alder/epimerization/three-component reductive alkylation and olefination/Diels-Alder/epimerization/three-component reductive alkylation/*trans*-esterification reaction sequences would then generate a quaternary center with the formation of three new carbon–carbon σ bonds, and four new carbon–carbon σ bonds/two carbon-hydrogen bonds respectively *via* organocatalysis.

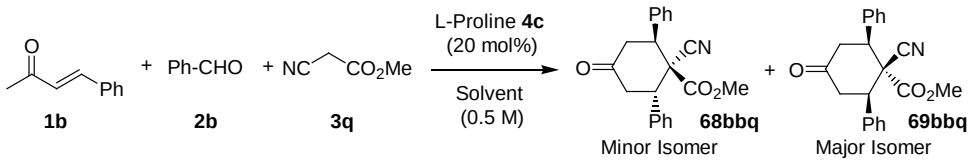
5.2 Results and Discussion

We initiated our investigation by seeking a viable proline **4c** catalyst for the cascade [4+2] annulation of the enone **1b**, benzaldehyde **2b** and methyl cyanoacetate **3q** to provide the cyclohexanone **69bbq**[*] (Table 15). We were pleased to find that the three-component reaction of *trans*-4-phenyl-3-buten-2-one **1b**, benzaldehyde **2b** and methyl cyanoacetate **3q** with a catalytic amount of L-proline **4c** in methanol at

* In all compounds denoted **69xyz**, **x** is incorporated from reactant enones **1**, **y** is incorporated from the reactant aldehydes **2** and **z** is incorporated from the reactant CH-acids **3.**

ambient temperature for 30 h furnished Diels-Alder products **68bbq** and **69bbq** in 76% yield with prochiral *cis*-isomer **69bbq** as the major isomer with only 9% de (Table 15, entry 1).[41]

Table 15: Effect of Solvent on the Direct Amino acid-Catalyzed Cascade O/DA/E Reaction of **1b**, **2b** and **3q**[a]



1b **2b** **3q** **68bbq** Minor Isomer **69bbq** Major Isomer

Entry	Solvent (0.5 M)	Temperature (T° C)	Time (h)	Products	Yield[b] (%)	de[c] (%)
1	MeOH	25° C	30	**68bbq, 69bbq**	76	9
2	MeOH	25° C	96	**68bbq, 69bbq**	78	33
3	EtOH	25° C	96	**68bbq, 69bbq**	75	53
4[d]	EtOH	70° C	72	**69bbq**	80	99
5	DMSO	25° C	6	**68bbq, 69bbq**	80	26
6	DMSO	25° C	72	**69bbq**	85	99
7[d]	DMSO	50° C → 25° C	24 → 48	**69bbq**	80	99
8	DMF	25° C	24	**68bbq, 69bbq**	77	26
9	DMF	25° C	72	**68bbq, 69bbq**	75	26
10	NMP	25° C	24	**68bbq, 69bbq**	76	– 50
11	NMP	25° C	72	**68bbq, 69bbq**	75	– 20
12	THF	25° C	168	**68bbq, 69bbq**	≤ 5%	–
13	CH_3CN	25° C	36	**68bbq, 69bbq**	60	0
14	$CHCl_3$	25° C	72	**68bbq, 69bbq**	73	33
15	$C_6H_5CH_3$	25° C	120	**68bbq, 69bbq**	65	0
16	CH_2Cl_2	25° C	120	**68bbq, 69bbq**	68	20
17	[bmim]Br	25° C	72	**68bbq, 69bbq**	80	44
18	$[bmim]BF_4$	25° C	72	**68bbq, 69bbq**	71	0

[a] Experimental conditions: Amino acid **4c** (0.1 mmol), benzylidene acetone **1b** (1 mmol), benzaldehyde **2b** (0.5 mmol) and CH-acid **3q** (0.5 mmol) in solvent (1 mL) were stirred at ambient temperature for 6 to 120 h.
[b] Yield refers to the purified product obtained by column chromatography.
[c] Diastereomeric excesses determined by using ^1H and ^{13}C NMR analysis on isolated products.
[d] All reactants (**1b**, **2b** and **3q**) were used in same equivalents.

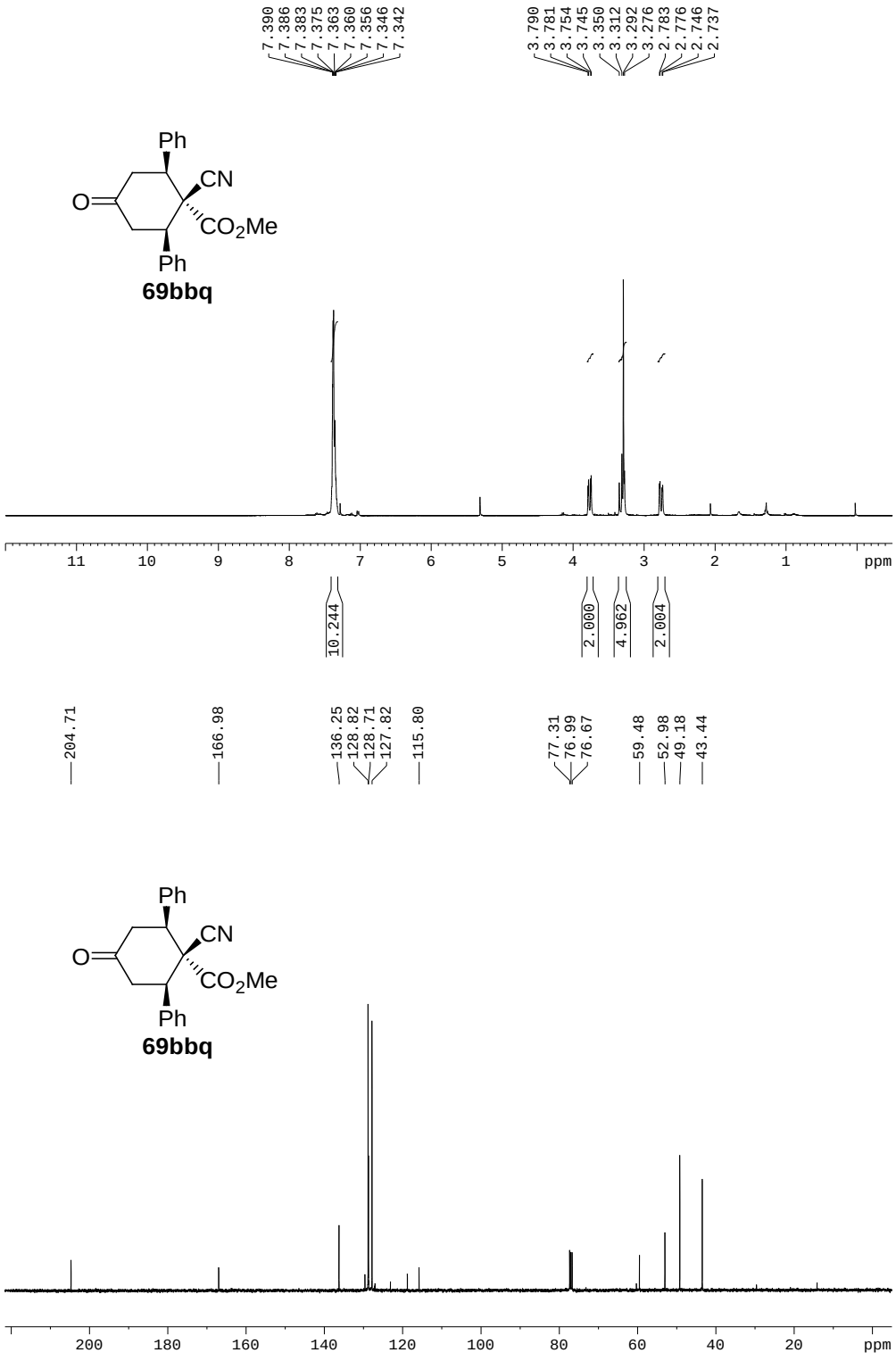


Figure-20: ^{1}H NMR and ^{13}C NMR Spectra of Product **69bbq.**

The same reaction albeit with an extended reaction time furnished *cis*-isomer **69bbq**[*] with 33% de in 78% yield (Table 15, entry 2). The minor diastereomer, *trans*-isomer **68bbq**[*] was effectively epimerized to the thermodynamically stable *cis*-isomer **69bbq** under prolonged reaction times *via* proline catalysis. The stereochemistry of products **68bbq** and **69bbq** was established by NMR analysis [see Fig. 20].

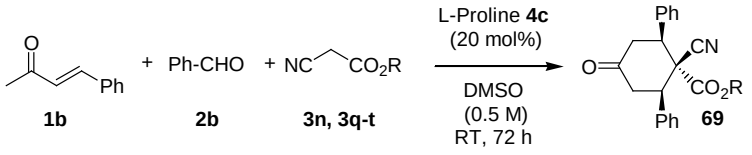
In the three-component cascade olefination/Diels-Alder/epimerization (O/DA/E) reaction of enone **1b**, benzaldehyde **2b** and methyl cyanoacetate **3q** catalyzed directly by L-proline **4c**, we found that the solvent (dielectric constant) and temperature had a significant effect on reaction rates, yields and de's (Table 15). Our studies revealed that the cascade O/DA/E reaction catalyzed by L-proline produces products **68bbq** and **69bbq** in moderate yields and poor selectivity in aprotic non-polar solvents (Table 15, entries 12-16) and with excellent yields and selectivity in protic/polar solvents (Table 15, entries 4-7). But interestingly, cascade O/DA/E reaction in polar solvents like DMF and NMP looks different compared to DMSO as shown in Table 15, entries 8-11. The same cascade reaction in the ionic liquids [bmim]Br and [bmim]BF_4 catalyzed by L-proline provided the cascade product *cis*-isomer **69bbq** with 44% de and 0% de in good yield, respectively (Table 15, entry 17 and 18). Interestingly, under proline catalysis, the cascade O/DA/E reaction worked well in EtOH and DMSO solvents and the optimal conditions involved mixing equimolar amounts of enone **1b**, aldehyde **2b** and CH-acid **3q** in ethanol with heating to 70 °C for 72 h to furnish *cis*-isomer **69bbq** as a single diastereomer in 80% yield (Table 15, entry 4) or mixing equimolar amounts of **1b**, **2b** and **3q** in DMSO with heating to 50 °C for 24 h and 25 °C for 48 h to furnish *cis*-isomer **69bbq** as a single diastereomer in 80% yield (Table 15, entry 7).

After this preliminary understanding, we proceeded to investigate the scope and limitations of the cascade O/DA/E reaction of **1b** and **2b** with a range of active CH-acids **3n** and **3q-t** under proline-catalysis in DMSO (Table 16). As shown in

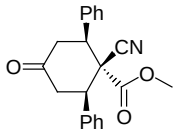
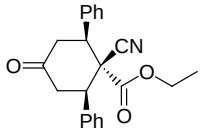
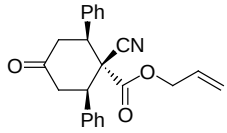
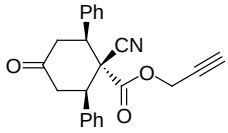
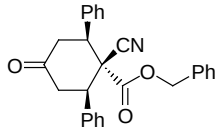
* In all compounds denoted **68xyz** and **69xyz**, **x** is incorporated from reactant enones **1**, **y** is incorporated from the reactant aldehydes **2** and **z** is incorporated from the reactant CH-acids **3.**

Table 16, the acyclic CH-acids **3n** and **3q-t** furnished the expected cascade products **69bbn** and **69bbq-bbt** in good yields with 99% de respectively except for ethyl cyano acetate **3n**, where the cascade product **69bbn** was formed in 92% yield with only 77% de.

Table 16: Effect of CH-acids **3** on the Direct Amino acid-Catalyzed Cascade O/DA/E Reaction of **1b**, **2b** and **3p-t**[a]



1b **2b** **3n, 3q-t** **69**

Entry	Products		Yield[b] (%)	de[c] (%)
1		**69bbq**	85	99
2		**69bbn**	92	77
3		**69bbr**	76	99
4		**69bbs**	80	99
5		**69bbt**	85	99

[a] Amino acid **4c** (0.1 mmol), benzylidene acetone **1b** (1 mmol), benzaldehyde **2b** (0.5 mmol) and CH-acids **3n, 3q-t** (0.5 mmol) in DMSO (1 mL) were stirred at 25^{o} C for 72 h.
[b] Yield refers to the purified product obtained by column chromatography.
[c] Diastereomeric excesses determined by using ^{1}H and ^{13}C NMR analysis on isolated products.

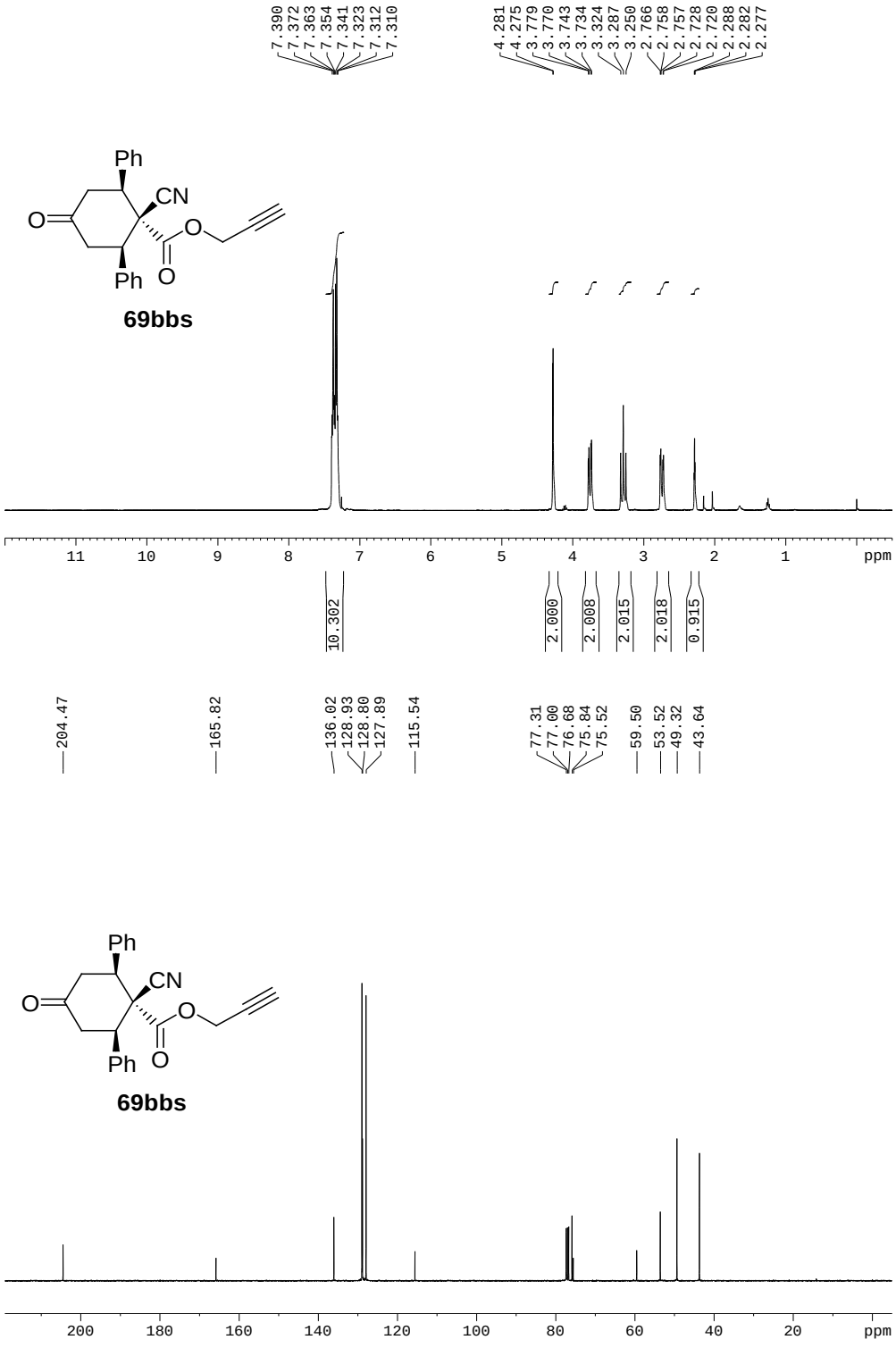
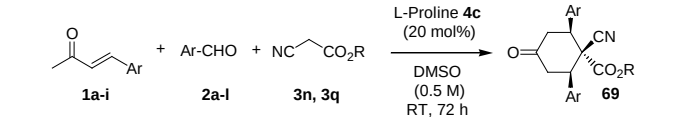
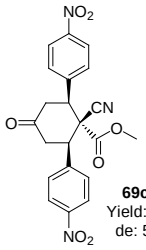


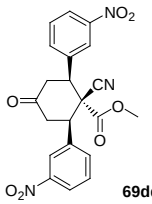
Figure-21: ^{1}H NMR and ^{13}C NMR Spectra of Product **69bbs.**

Table 17: Chemically Diverse Libraries of Cascade O/DA/E Products **68**/**69**[a,b,c]

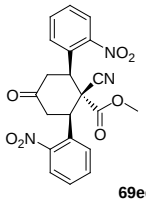




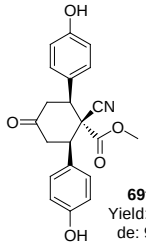
69caq
Yield: 80%
de: 50%



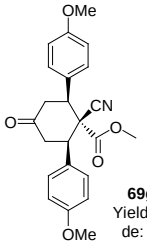
69ddq
Yield: 86%
de: 0%



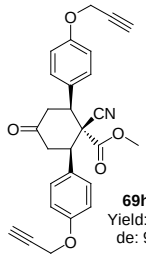
69eeq
Yield: 75%
de: 99%



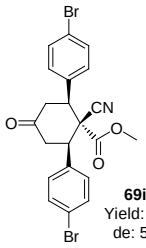
69ffq
Yield: 80%
de: 99%



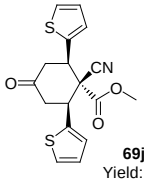
69ggq
Yield: 80%
de: 99%



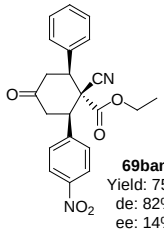
69hhq
Yield: 75%
de: 99%



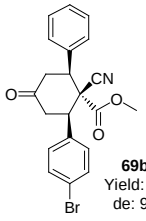
69iiq
Yield: 85%
de: 50%



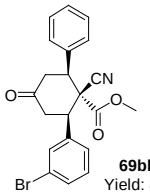
69jjq
Yield: 90%
de: 0%



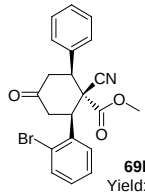
69ban
Yield: 75%
de: 82%
ee: 14%



69biq
Yield: 90%
de: 99%



69bkq
Yield: 80%
de: 99%



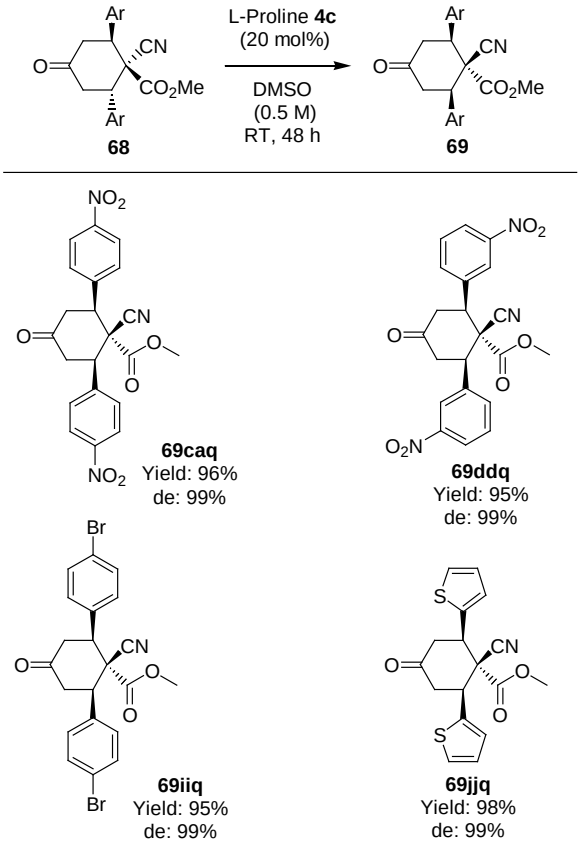
69blq
Yield: 85%
de: 78%

[a] Yield refers to the column purified product. [b] Diastereomeric excesses determined by using ^{1}H and ^{13}C NMR analysis on isolated products. [c] Ee determined by HPLC analysis.

We generated a useful library of cascade O/DA/E products **69** under proline-catalysis. The results in Table 17 demonstrate the broad scope of this green methodology covering a structurally diverse group of less reactive ketones **1a-i**, aldehydes **2a-l** and CH-acids **3n**, **3q-t** with many of the yields and de's obtained being very good, or indeed better, than previously published reactions starting from

the divinyl ketones and CH-acids via double Michael reactions.[42] Each of the targeted prochiral *cis*-isomer **69** was obtained as a single diastereomer in excellent yield. Prochiral *cis*-isomers **69caq-jjq*** were generated in very good yields with aromatics bearing either electron withdrawing or electron donating groups in the *para* position as shown in Table 17. Interestingly, the prochiral hetero aromatic *cis*-isomer **69jjq** was synthesized in 90% yield with only 0% de under the same reaction conditions (Table 17).

Table 18: Direct Proline-Catalyzed Epimerization of trans-isomers of O/DA Products **68**



* In all compounds denoted **69xyz**, **x** is incorporated from reactant enones **1, y** is incorporated from the reactant aldehydes **2** and **z** is incorporated from the reactant CH-acids **3.**

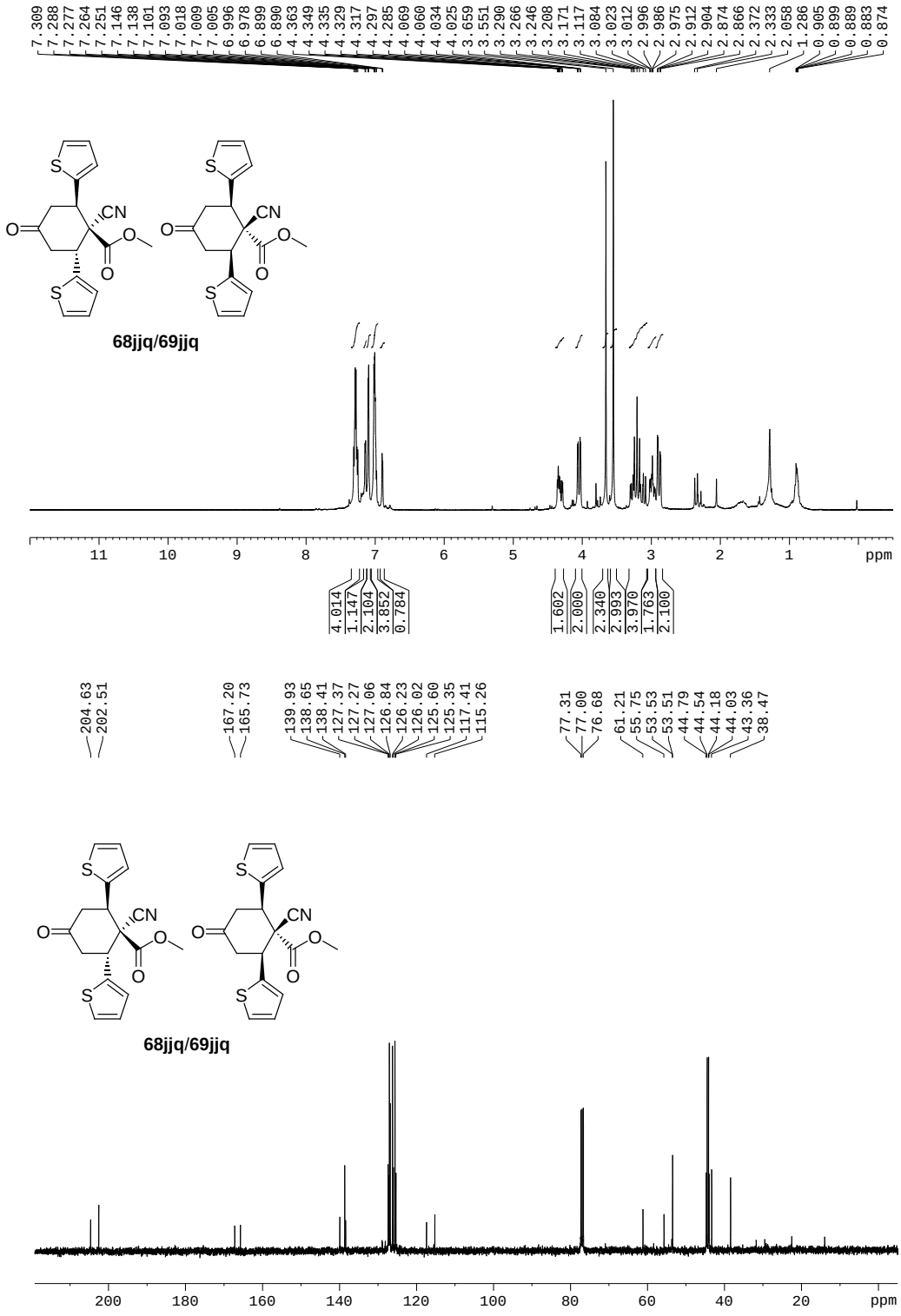


Figure-22: ^{1}H NMR and ^{13}C NMR Spectra of Product **68jjq/69jjq.**

Proline-catalyzed cascade O/DA/E reaction of *trans*-4-(4-nitro-phenyl)-3-buten-2-one **1c**, 4-nitrobenzaldehyde **2a** and methyl cyanoacetate **3q** furnished the cascade esters *cis*-**69caq**[*]/*trans*-**68caq**[*] in 80% yield with 50% de of **69caq** (Table 17, entry 1). Interestingly, cascade reaction of **1d**, **2d** and **3q** furnished the esters **68ddq**/**69ddq** in 86% yield with 0% de. Cascade O/DA/E reactions produced cyclohexanone products **69eeq**, **69ffq**, **69ggq**, **69hhq**, **69biq** and **69bkq** in very good yields with 99% de as shown in Table 17. Proline-catalyzed O/DA/E reaction of **1b**, **2a** and **3n** furnished the non-symmetrical *cis*-isomer **69ban** in 75% yield with 82% de and 14% ee as shown in Table 17. Non-symmetrical *cis*-isomers **69biq**, **69bkq** and **69blq** are also generated using cascade O/DA/E reaction in very good yields with good de's as shown in Table 17. The cascade *trans*-isomers **68caq**, **68ddq**, **68iiq** and **68jjq** were epimerized to *cis*-isomers **69caq**, **69ddq**, **69iiq** and **69jjq** under proline-catalysis in very good yields with complete conversion at 25° C for 48 h (Table 18).

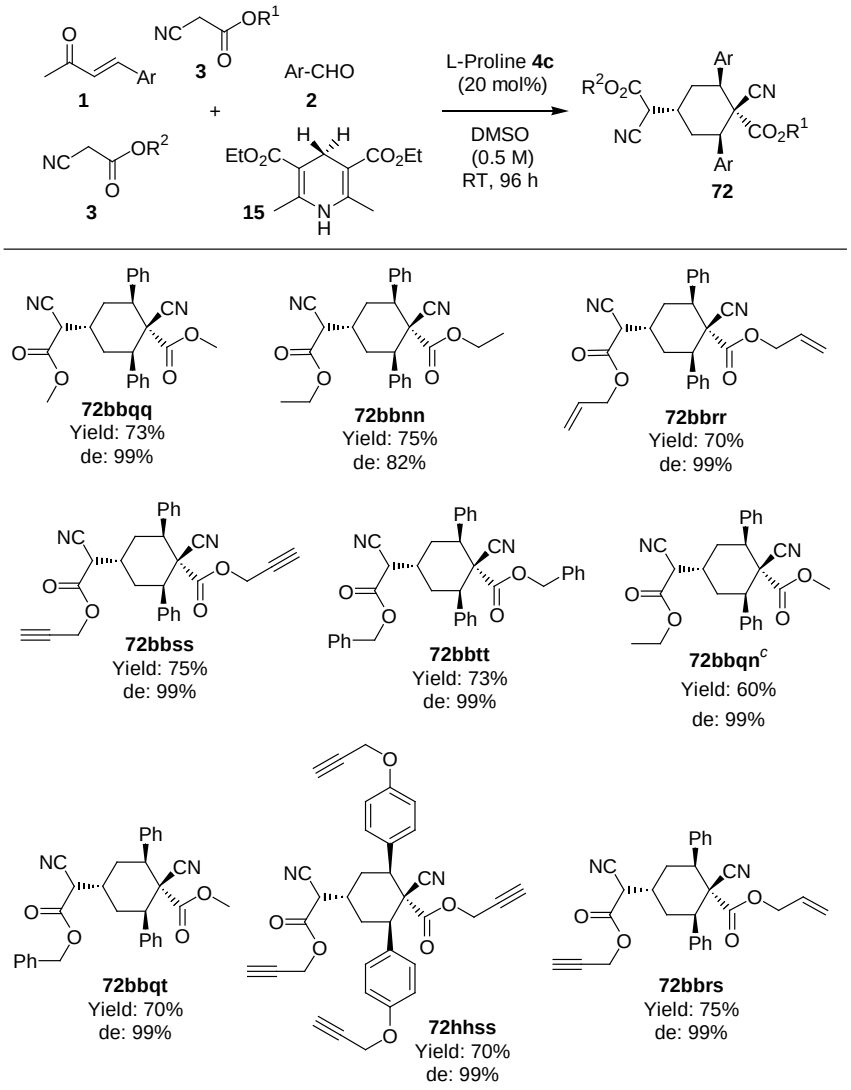
With pharmaceutical and material applications in mind, we extended the three-component cascade O/DA/E reactions into a novel double cascade proline-catalyzed five-component olefination/Diels-Alder/epimerization/three-component reductive alkylation (O/DA/E/*TCRA*) reaction of enones **1**, aldehydes **2**, CH-acids **3**, and Hantzsch ester **15** with various CH-acids **3n** and **3q-t** in one-pot (Table 19). Library of double cascade products **72** as shown in Table 19 are furnished in good yields with 99% de under proline-catalysis at 25° C for 96 h. Interestingly, proline-catalyzed double cascade reaction of **1b**, **2b**, **3q** (2 equiv.) and **15** in EtOH at 70° C for 96 h furnished the product **72bbqn**[Ψ] in 60% yield with 99% de *via* olefination/Diels- Alder/epimerization/three-component reductive alkylation/*trans*-esterfication (O/DA/E/*TCRA*/TE) reaction sequence. Structure and regiochemistry of

[*] In all compounds denoted **68xyz** and **69xyz**, **x** is incorporated from reactant enones **1**, **y** is incorporated from the reactant aldehydes **2** and **z** is incorporated from the reactant CH-acids **3**.

[Ψ] In all compounds denoted **72wxyz**, **w** is incorporated from reactant enones **1**, **x** is incorporated from the reactant aldehydes **2**; **y** and **z** are incorporated from the reactant CH-acids **3.**

the double cascade products **72** were confirmed by NMR analysis [for example see Fig. 23] and also by X-ray structure analysis of **72bbtt** as shown in Scheme 12.[43]

Table 19: Chemically Diverse Libraries of Cascade O/DA/E/TCRA Products **72**[a,b]



[a] Experimental conditions: proline **4c** (0.1 mmol), benzylidene acetone **1b** (0.5 mmol), benzaldehyde **2b** (0.5 mmol), and CH-acid **3** (0.5 mmol) in solvent (1 mL) were stirred at ambient temperature for 72 h, and then CH-acid **3** (0.5 mmol) and Hantzsch ester **15** (0.5 mmol) was added (see the Experimental Section).

[b] Yield refers to the column purified product and diastereomeric excesses determined by using ^{1}H and ^{13}C NMR analysis on isolated products.

[c] Product **72bbqn** were obtained from cascade O/DA/E/O/H/TE reaction of **1b**, **2b**, **3q** (2 equiv), **4c**, and **15** in EtOH (1.0 mL) at 70^{o} C for 96 h.

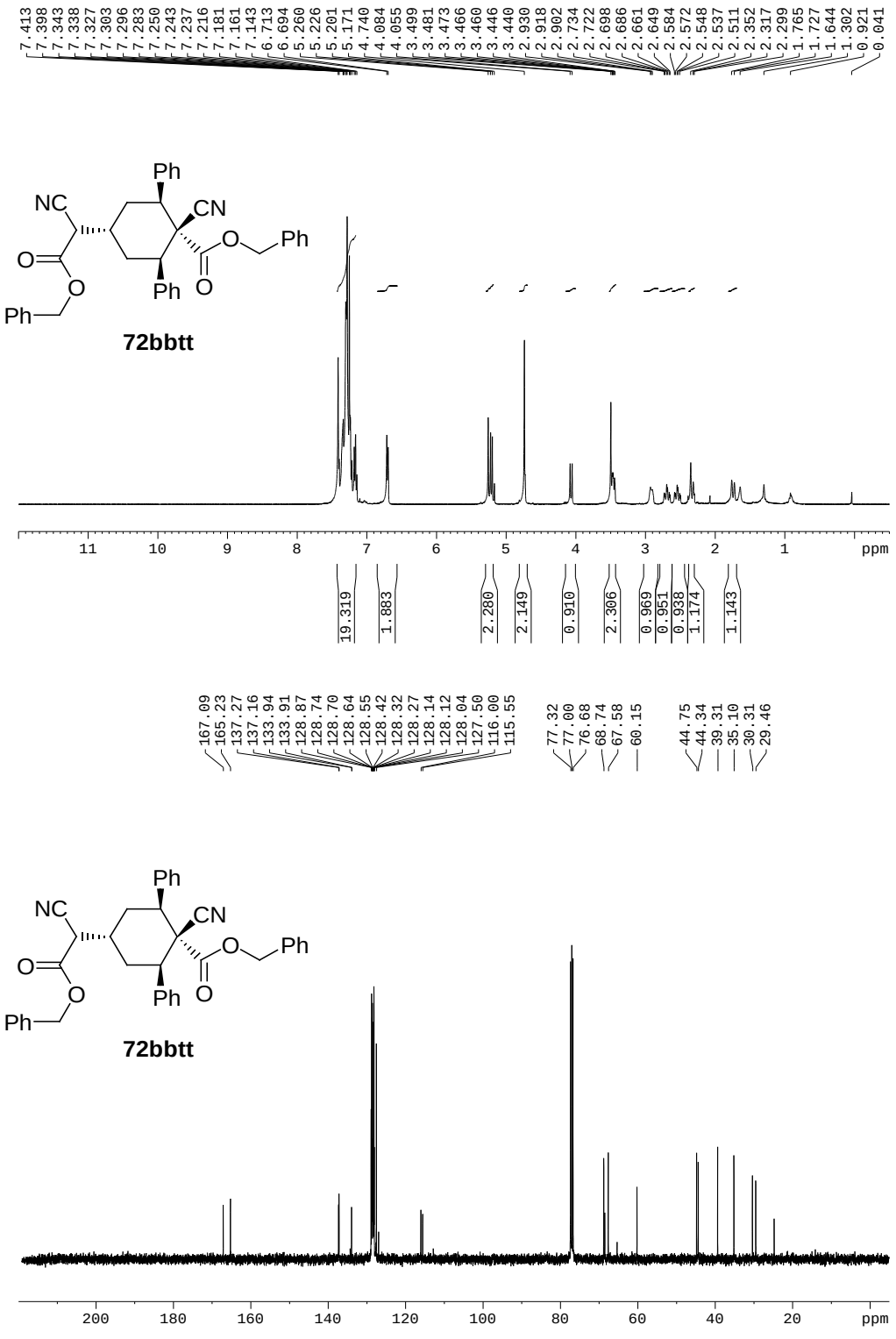
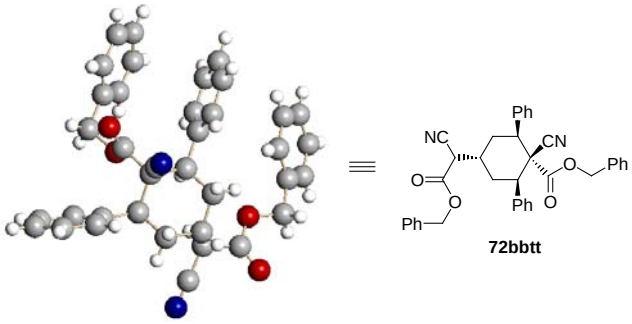


Figure-23: ^{1}H NMR and ^{13}C NMR Spectra of Product **72bbtt.**

Prochiral *cis*-isomers **69** are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products;[40] and the highly functionalized cyclohexanes **72** could serve as suitable synthons for the synthesis of various useful materials with different properties.

Scheme 12: Crystal Structure of 4-(Benzyloxycarbonyl-cyano-methyl)-1-cyano-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (**72bbtt**).

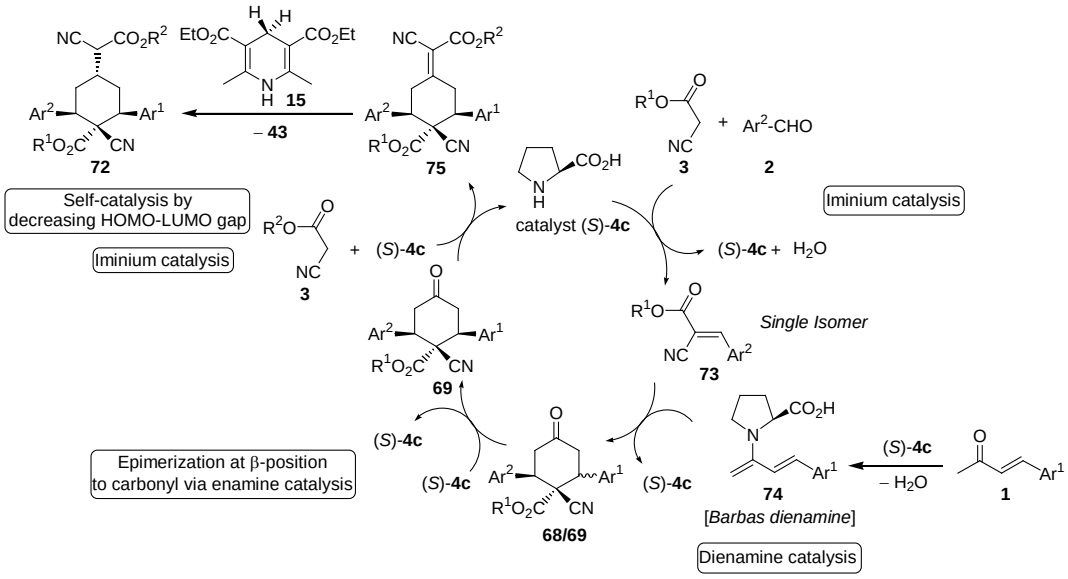


5.3 Mechanistic Insights

The possible reaction mechanism for L-proline-catalyzed regio- and diastereo-selective synthesis of the cascade products **69** and **72** through the reaction of enone **1**, aldehyde **2**, CH-acid **3** and Hantzsch ester **15** is illustrated in Schemes 13 and 14. This catalytic sequential one-pot, double cascade is a five component reaction comprising of enone **1**, aldehyde **2**, CH-acid **3**, Hantzsch ester **15**, CH-acid **3** and a simple chiral amino acid **4c**; which is capable of catalyzing each step of this double cascade reaction. In the first step (Scheme 13), the catalyst (*S*)-**4c** activates component **2** by most likely iminium ion formation, which then selectively adds to the CH-acid **3** via a Mannich and amine elimination reaction to generate regio-selectively active olefin **73** as dienophile. The following second step is proline mediated generation of Barbas dienamine **74** (2-amino-1,3-butadiene)[6-8] as diene source from enone **1** and proline **4c**. In the subsequent third step, Diels-Alder reaction of **73** with in situ generated Barbas dienamine **74** via most likely concerted [4+2]-cycloaddition leads to the formation of cascade O/DA

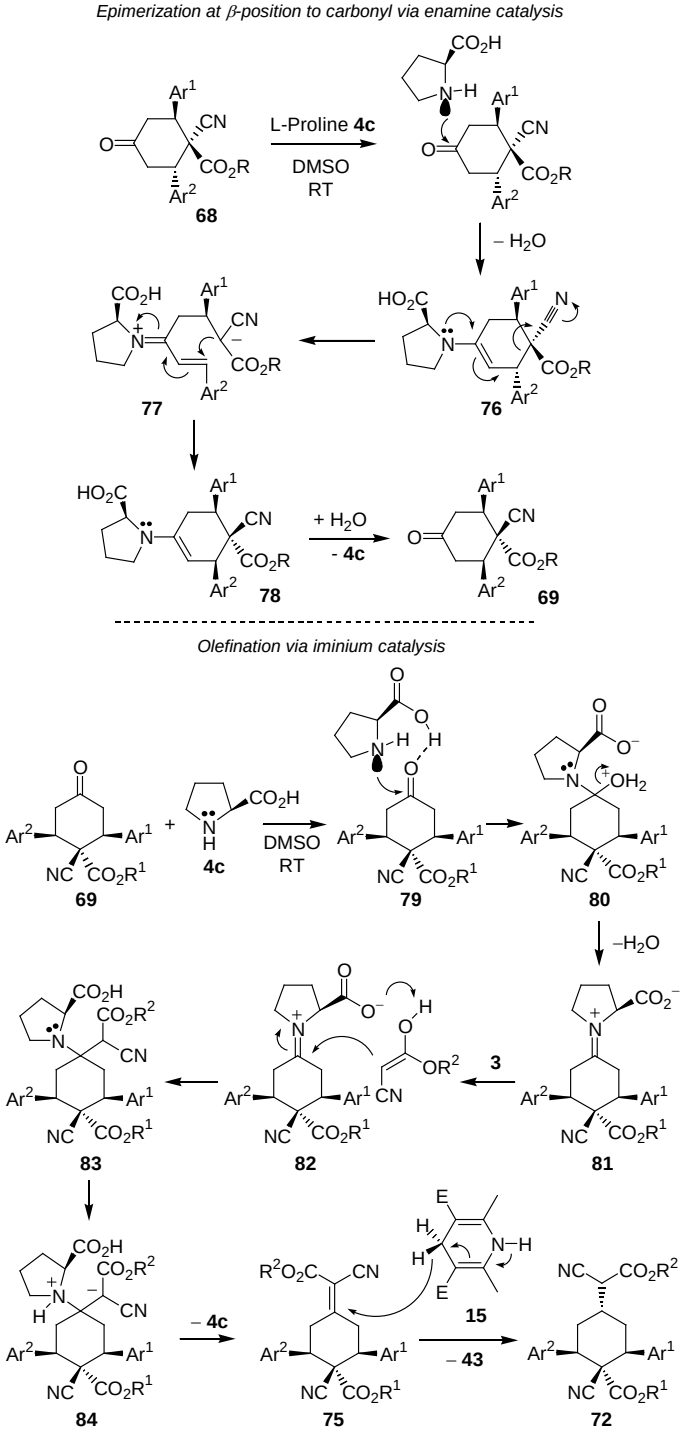
products **68/69** in good yield with prochiral *cis*-isomer **69** as the major isomer with moderate de. In the fourth step, (*S*)-**4c** catalyzed the epimerization at β-position to the carbonyl of *trans*-isomer **68** via enamine catalysis and subsequent hydrolysis returned the catalyst (*S*)-**4c** for further cycles and released the desired major *cis*-isomer **69**. In the fifth step, (*S*)-**4c** catalyzed the olefination of the major isomer **69** with CH-acid **3** to furnish the functionalized olefin **75** via most likely iminium catalysis as like first step. The following sixth step is bio-mimetic hydrogenation of the active olefin **75** by Hantzsch ester **15** to produce **72** through self-catalysis by decreasing HOMO-LUMO energy gap between **75** and **15** respectively.[11-12,16]

Scheme 13: Proposed Catalytic Cycle for the Double Cascade Reactions.



Taking into account the recent applications of amine-catalyzed olefination reactions[6-8,16] and based on the different experiments performed (Tables 15-18), we proposed that the most likely reaction course for the organocatalyzed direct epimerization at β-position to carbonyl of *trans*-isomer **68** and three-component reductive alkylation of *cis*-isomer **69** is the one outlined through amino acid-catalysis as shown in Scheme 14.

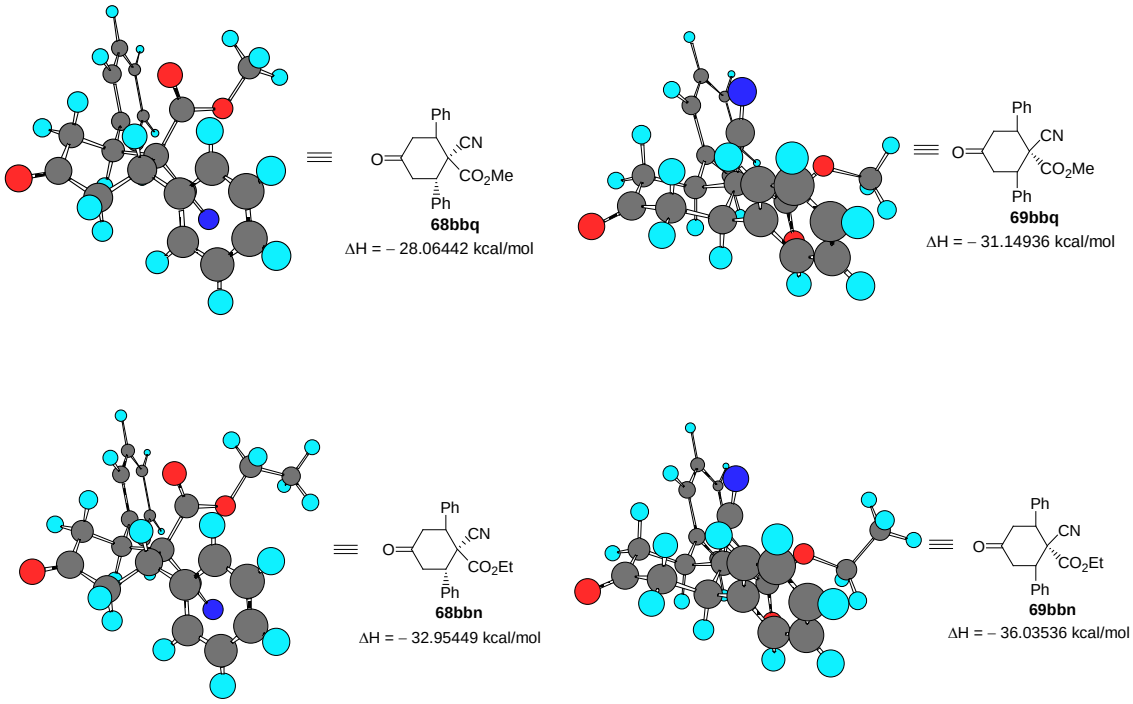
Scheme 14: Proposed Mechanisms for the L-proline **4c** Catalyzed Epimerization and Three-component Reductive Alkylation reactions.



Epimerization of *trans*-isomer **68** or the diastereospecific synthesis of *cis*-isomer **69** in the cascade O/DA/E reaction of enone **1**, aldehyde **2** and CH-acid **3** can be explained as illustrated in Scheme 14. The energy difference (ΔH) between the two isomers **68bbq** and **69bbq** is 3.085 kcal/mol based on PM3 calculations. The energy difference (ΔH) between the two isomers of **68bbn** and **69bbn** is 3.081 kcal/mol based on PM3 calculations. Minimized structures of **68bbq**, **69bbq**, **68bbn**, and **69bbn** are depicted in the Scheme 15. Since the differences in ΔH's between the two isomers of **68bbq**/**69bbq** and **68bbn**/**69bbn** are greater than 3 kcal/mol, the minor kinetic isomers **68bbq** and **68bbn** are epimerized to the thermodynamically more stable *cis*-isomers **69bbq** and **69bbn**, respectively, at room temperature under mild organocatalysis. The minor kinetic isomer *trans*-isomer **68** was epimerized to the thermodynamically stable *cis*-isomer **69** *via* deprotonation/reprotonation or retro-Michael/Michael reactions catalyzed by amino acid. This is in agreement with the previously proposed retro-Michael/Michael reaction mechanism[7a] at the epimerization step (Scheme 14). As shown in Scheme 14, the amino acid reacts with *trans*-isomer **68** to generate the enamine **76**. The retro-Michael reaction to form the ring-opened imine/enolate **77** should be accelerated by hydrogen bonding with protic/polar solvents. Imine/enolate **77** then undergoes Michael reaction to form the enamine of the thermodynamically stable *cis*-isomer **78**, which undergoes hydrolysis *in situ* to furnish the *cis*-isomer **69**.

The possible reaction mechanism for the cascade TCRA reactions of **69**, **3**, **15** and **4c** is illustrated in Scheme 14. First, the reaction of proline **4c** with *cis*-isomer **69** generates the iminium cation **81**, an excellent electrophile that undergoes Mannich type reactions with CH-acid **3** to generate the Mannich product **83**. Base induced elimination reaction of the amine **83** would furnish the active olefin **75**. The next hydrogen transfer reactions are dependent upon the electronic nature of the *in situ* generated conjugated system or, more precisely, the HOMO-LUMO gap of the reactants **15** and **75**.[11-12,16]

Scheme 15: Minimized Structure of **68bbq**/**69bbq** and **68bbn**/**69bbn** Based on MOPAC Calculations



Observed high regio-selectivity in the cascade products **72** can be explained by the approach of the hydride source (Hantzsch ester **15**) to olefins **75** which is the main controlling factor than the thermodynamic stability of the resulting hydrogenated products **72**. Approach of the Hantzsch ester **15** to the olefin **75** through the equatorial position is more favourable than the axial position, may be due to the existence of more steric hindrance in an axial approach. Steric strain control (SSC) is the main controlling factor than the product stability control (PSC) in bio-mimetic cascade reductions, because thermodynamically stable isomer *cis*-**72** is formed as very minor product. This selectivity trend can be easily understood by the approach of bulk hydride source **15** to highly functionalized olefins **75**.

5.4 Conclusions

In summary, we have developed the first amino acid catalyzed direct cascade O/DA/E, O/DA/E/TCRA and O/DA/E/TCRA/TE reactions. This astonishingly simple and atom-economic approach can be used to construct highly functionalized prochiral 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **69** and 1-cyano-4-(cyano-alkoxycarbonyl-methyl)-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **72** in a diastereospecific fashion. Selective multi-step reactions of this type inspire analogies with biosynthetic pathways and compliment traditional multi-component synthetic methodologies. As we have suggested previously, the synthesis of poly-functionalized molecules under amino acid-catalysis provides a unique and under explored perspective on pre-biotic synthesis. A complete understanding of the scope of amino acid-catalysis should not only empower the synthetic chemist but also provide a new perspective on the origin of complex molecular systems.

6. Design, Synthesis and Biological Evaluation of Optically Pure Functionalized Spiro[5,5]undecane-1,5,9-triones as HIV-1 Inhibitors

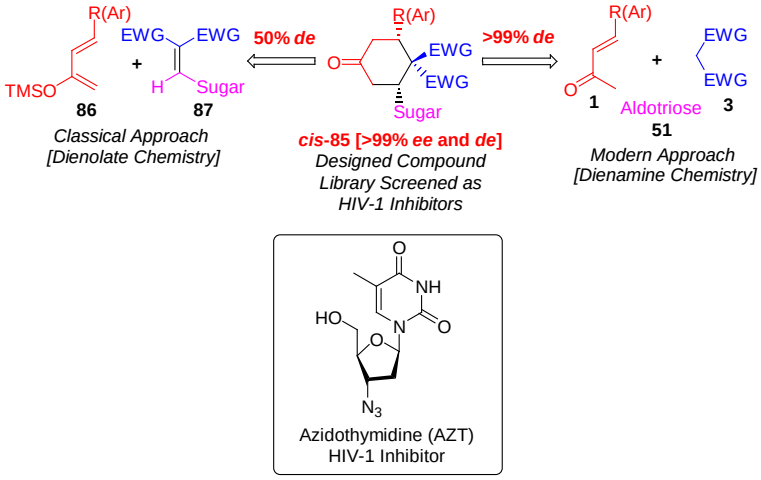
6.1 Introduction

One of the ultimate goals in organic/medicinal chemistry is the high-yielding synthesis of optically pure drugs/natural products through catalytic asymmetric assembly of simple and readily available precursor molecules in one-pot. In this regard, recently developing organocatalytic cascades and sequential one-pot combination of multi-component reactions (MCR's)/multi-catalysis cascade (MCC) reactions will be victorious over this goal.[4] Simultaneously to address the modernization of organic synthesis through high-yielding asymmetric synthesis of optically pure drug-like molecules in one-pot and show them as better molecular therapeutics, herein we are proposing the design, synthesis and biological evaluation of optically pure functionalized spiro[5,5]undecane-1,5,9-triones **85** as HIV-1 inhibitors (see Fig. 24). Recent studies by Yves Pommier et al. on simple achiral spiroundecane derivatives revealed that they can inhibit both 3'-processing and strand transfer reactions catalyzed by HIV-1 integrase.[44] Based on these observations, herein we are proposing to study if optically pure single enantiomer of designed functionalized spiroundecanes **85** will be better inhibitors for HIV-1 compared to previous achiral molecules.

In continuation of our interest in high-yielding asymmetric synthesis of drug-like molecules in one-pot,[16] herein we report the amino acid-catalyzed diastereospecific three-component Diels-Alder (DTCDA) reactions that produce highly functionalized chiral spiro[5,5]undecane-1,5,9-triones **85** from commercially available 4-substituted-3-buten-2-ones **1**, protected glyceraldehydes **51** and CH-acids **3** through modern dienamine chemistry (Fig. 24). Functionalized chiral

spiro[5,5]undecane-1,5,9-triones **85** are biologically active compounds and also attractive intermediates in the total synthesis of natural products.[45]

Figure-24. Design and Synthesis of Chiral Products **85** for HIV-1 Inhibitors.



In our reaction, we designed and proved that diastereospecific synthesis of product *cis*-**85** over four possible stereoisomers is possible through modern Diels-Alder reaction of *in situ* generated 2-amino-1,3-butadiene (Barbas dienamine) with chiral alkylidenes **87** instead of classical Diels-Alder reaction of 1-aryl-3-trimethylsiloxy-butadiene **86** with **87** as shown in Fig. 24.[6-9,13,46]

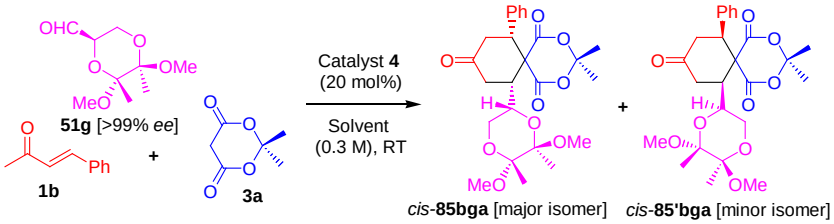
6.2 Results and Discussion

We were pleased to find that the cascade reaction of *trans*-4-phenyl-3-buten-2-one **1b**, butane-2,3-diacetal of (*R*)-glyceraldehyde **51g** (>99% ee) and Meldrum's acid **3a** with a catalytic amount of L-proline **4c** in MeOH at 25 °C for 48 h furnished the Diels-Alder product *cis*-**85bga*** in 60% yield with >99% ee/de out of four stereoisomers (Table 20, entry 1). In the DTCDA reaction of **1b**, (*R*)-**51g** and **3a** catalyzed by L-proline **4c**, we

* In all compounds denoted **85xyz**, **x** is incorporated from reactant enones **1, y** is incorporated from the reactant chiral aldehydes **51** and **z** is incorporated from the reactant CH-acids **3.**

found that the solvent and catalyst had a significant effect on the yields and de's (Table 20). Interestingly, cascade reaction of **1b**, (*R*)-**51g** and **3a** under L-proline **4c**-catalysis in EtOH at 25 °C for 48 h furnished the product *cis*-**85bga** in 67% yield with >99% ee and 85% de (Table 20, entry 2). Surprisingly, same reaction in DMSO furnished the *cis*-**85'bga** in only 40% yield with >99% ee and 15% de (Table 20, entry 3). But the same reaction in THF, CH_3CN and 20% aqueous CH_3CN solvents furnished the expected product *cis*-**85bga** in 55/70/60% yield with >99% ee/de respectively (Table 20, entries 4-6).

***Table 20*:** Preliminary Optimization of DTCDA Reaction[a]



Entry	Catalyst (20 mol%)	Solvent (0.3 M)	Time (h)	Products	Yield[b] (%)	de[c] (%)
1	L-proline **4c**	MeOH	48	*cis*-**85bga**	60	>99
2	L-proline **4c**	EtOH	48	*cis*-**85bga**/*cis*-**85'bga**	67	85
3	L-proline **4c**	DMSO	48	*cis*-**85bga**/*cis*-**85'bga**	40	–15
4	L-proline **4c**	THF	48	*cis*-**85bga**	55	>99
5	**L-proline 4c**	**CH_3CN**	**48**	***cis*-85bga**	**70**	**>99**
6	L-proline **4c**	$CH_3CN + H_2O$	76	*cis*-**85bga**	60	>99
7	**D-proline 4j**	**CH_3CN**	**48**	***cis*-85bga**	**75**	**>99**
8	L-thioproline **4k**	CH_3CN	48	*cis*-**85bga**	51	>99
9	4-hydroxy-L-proline **4l**	CH_3CN	72	–	–	–
10	glycine **4f**	CH_3CN	48	*cis*-**85bga**	50	>99
11[d]	Q-NH_2/PhCO_2H **4m**	CH_3CN	72	*cis*-**85bga**/*cis*-**85'bga**	65	60
12[e]	L-diamine **4n**	CH_3CN	48	*cis*-**85bga**	40	>99

[a] Experimental conditions: Amino acid **4** (0.06 mmol), benzylidene acetone **1b** (0.6 mmol), chiral triose sugar **51g** (0.3 mmol) and Meldrum's acid **3a** (0.3 mmol) in solvent (1 mL) were stirred at ambient temperature for 24 to 76 h.
[b] Yield refers to the purified product obtained by column chromatography.
[c] Diastereomeric excesses determined by using ^1H and ^{13}C NMR analysis on isolated products.
[d] 9-Amino-9-deoxyepiquinine **4m**
[e] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine **4n**.

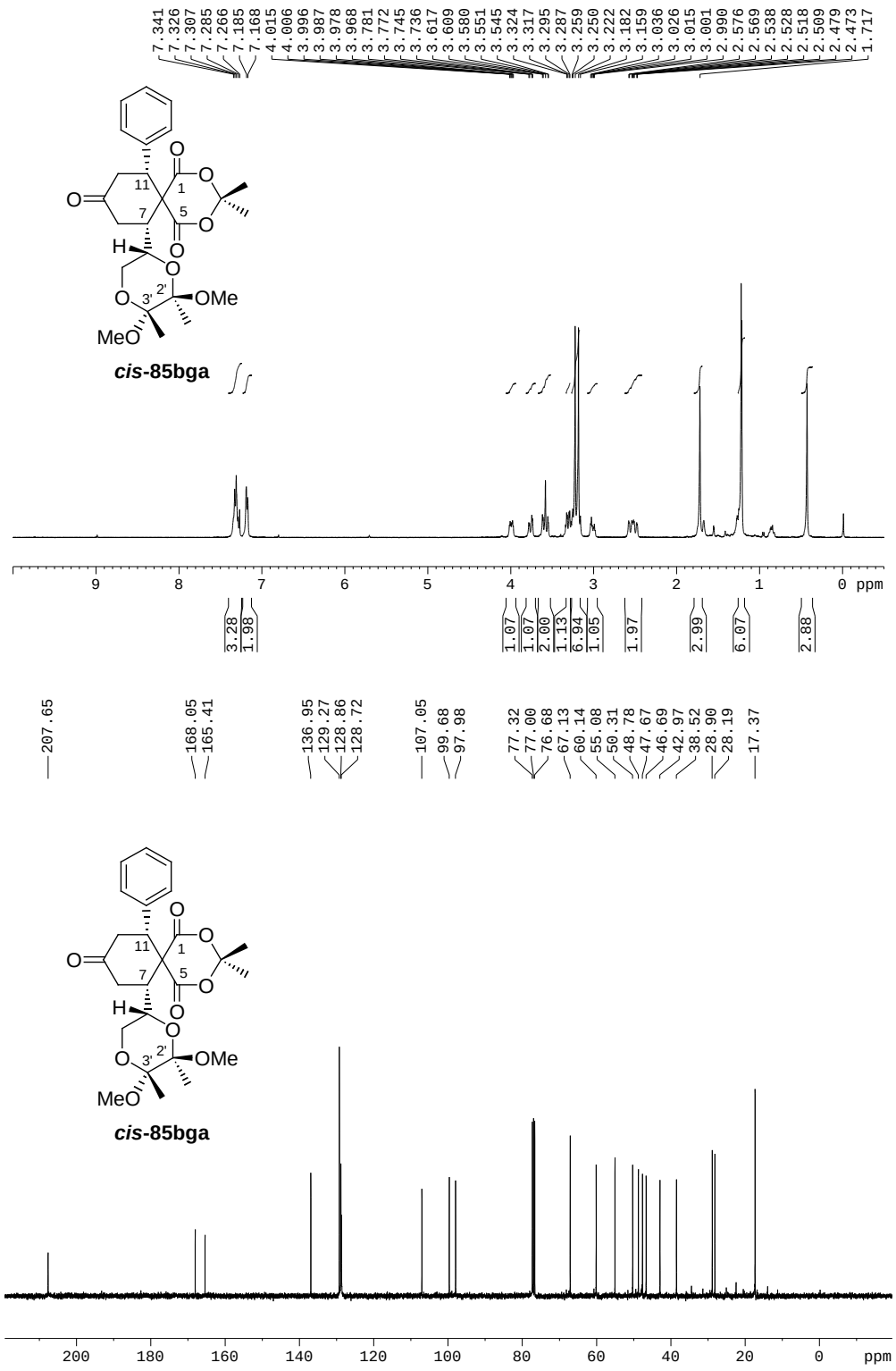


Figure-25: ^{1}H NMR and ^{13}C NMR Spectra of Product *cis*-**85bga.**

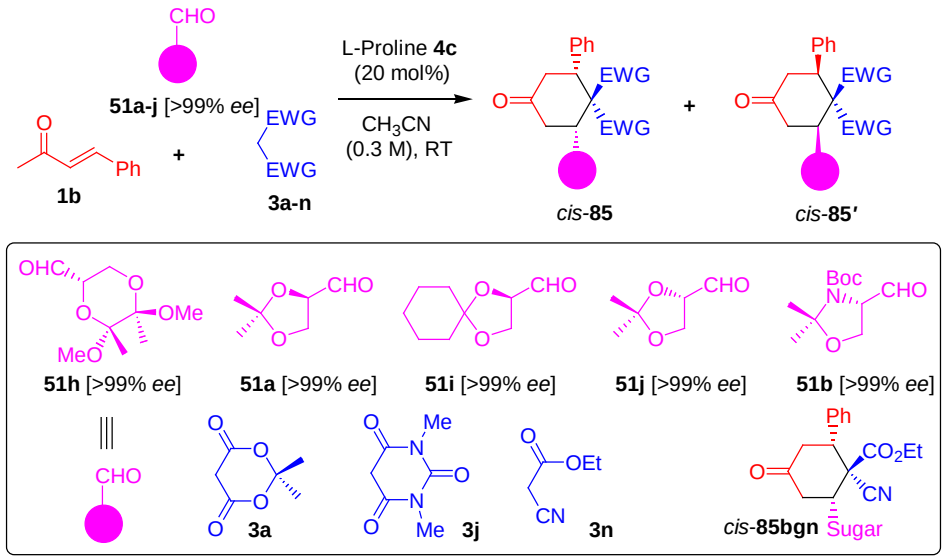
Next we screened structure/reactivity of other amino acids/amines **4j-4n** as catalysts by monitoring reaction yield and de of the DTCDA reaction of enone **1b**, (*R*)-**51g** and **3a** in CH_3CN (Table 20, entries 7-12). Among the catalysts screened, D-proline **4j** proved to be the best catalyst with respect to yield, providing *cis*-**85bga*** in 75% yield with >99% ee/de (Table 20, entry 7). Not much improvement in the yield/de of the reaction beyond L-proline **4c**-catalysis was found in L-thioproline **4k**, *trans*-4-hydroxy-L-proline **4l**, glycine **4f**, Q-NH_2/$PhCO_2H$ **4m**, and L-diamine **4n**-catalyzed DTCDA reactions (Table 20, entries 8-12). Catalyst studies revealed that L/D-proline-catalysis furnished the same isomer (*cis*-**85bga**) as the major compound without consideration of catalyst stereochemistry in the transition state and there is no reaction under **4l**-catalysis. Interestingly, cascade reaction under 9-amino-9-deoxyepiquinine/$PhCO_2H$ **4m**-catalysis furnished the product *cis*-**85bga** in 65% yield with only 60% de as shown in Table 20, entry 11. The stereochemistry of the product **85bga** was established by NMR analysis [see Fig. 25]. *Observation of these results reveals that selective endo-transition state of bimolecular Diels-Alder reaction is affected by protic/polar solvents and catalyst topology by decreasing the strong electrostatic interactions between diene (2-amino-1,3-butadiene) and chiral dienophile*.

We further investigated the proline-catalyzed DTCDA reaction of **1b** with various protected glyceraldehydes **51a-51j**/Garner aldehyde **51b** and CH-acids **3a, 3j** and **3n** to study the effect of electronic factors/electrostatic interactions in the outcome of product formation and selectivity (Table 21). Surprisingly, the reaction of butane-2,3-diacetal of (*S*)-glyceraldehyde **51h** (>99% ee) with Meldrum's acid **3a** and enone **1b** through **4c**-catalysis furnished the chiral spirotrione *cis*-**85'bha*** in 60% yield with only 50% de (Table 21, entry 1). Interestingly, reaction of (*R*)-glyceraldehyde acetonide **51a** and (*R*)-1,4-dioxaspiro[4.5]decane-2-carbaldehyde **51i** with Meldrum's acid **3a** and enone **1b** through **4c**-catalysis furnished the chiral spirotriones *cis*-**85baa** and *cis*-**85bia** in 75% and 50% yields with >99% ee/de respectively (Table 21, entries 2-3).

* In all compounds denoted **85xyz** and **85'xyz**, **x** is incorporated from reactant enones **1, y** is incorporated from the reactant chiral aldehydes **51** and **z** is incorporated from the reactant CH-acids **3**.

Reaction of (*S*)-glyceraldehyde acetonide **51j** with Meldrum's acid **3a** and enone **1b** through **4c**- and **4j**-catalysis furnished the similar chiral spirotrione *cis*-**85'bja** in 55% and 45% yields with >99% ee/de respectively (Table 21, entries 4-5).

***Table 21*:** General Optimization of DTCDA Reaction[a]



Entry	Triose sugar **51**	CH-acid **3**	Time (h)	Products	Yield[b] (%)	de[c] (%)
1	**51h**	**3a**	48	*cis*-**85'bha**	60	50
2	**51a**	**3a**	**72**	***cis*-85baa**	**75**	**>99**
3	**51i**	**3a**	72	*cis*-**85bia**	50	>99
4	**51j**	**3a**	72	*cis*-**85'bja**	55	>99
5[d]	**51j**	**3a**	72	*cis*-**85'bja**	45	>99
6	**51b**	**3j**	48	*cis*-**85'bbj**	76	60
7	**51g**	**3j**	**36**	***cis*-85bgj**	**81**	**>99**
8	**51g**	**3n**	48	*cis*-**85bgn**	52	>99
9	**51a**	**3j**	**48**	***cis*-85baj**	**86**	**>99**

[a] see Experimental section for reaction conditions.
[b] Yield refers to the purified product obtained by column chromatography.
[c] Diastereomeric excesses determined by using ^{1}H and ^{13}C NMR analysis on isolated products.
[d] D-Proline **4j** used as catalyst.

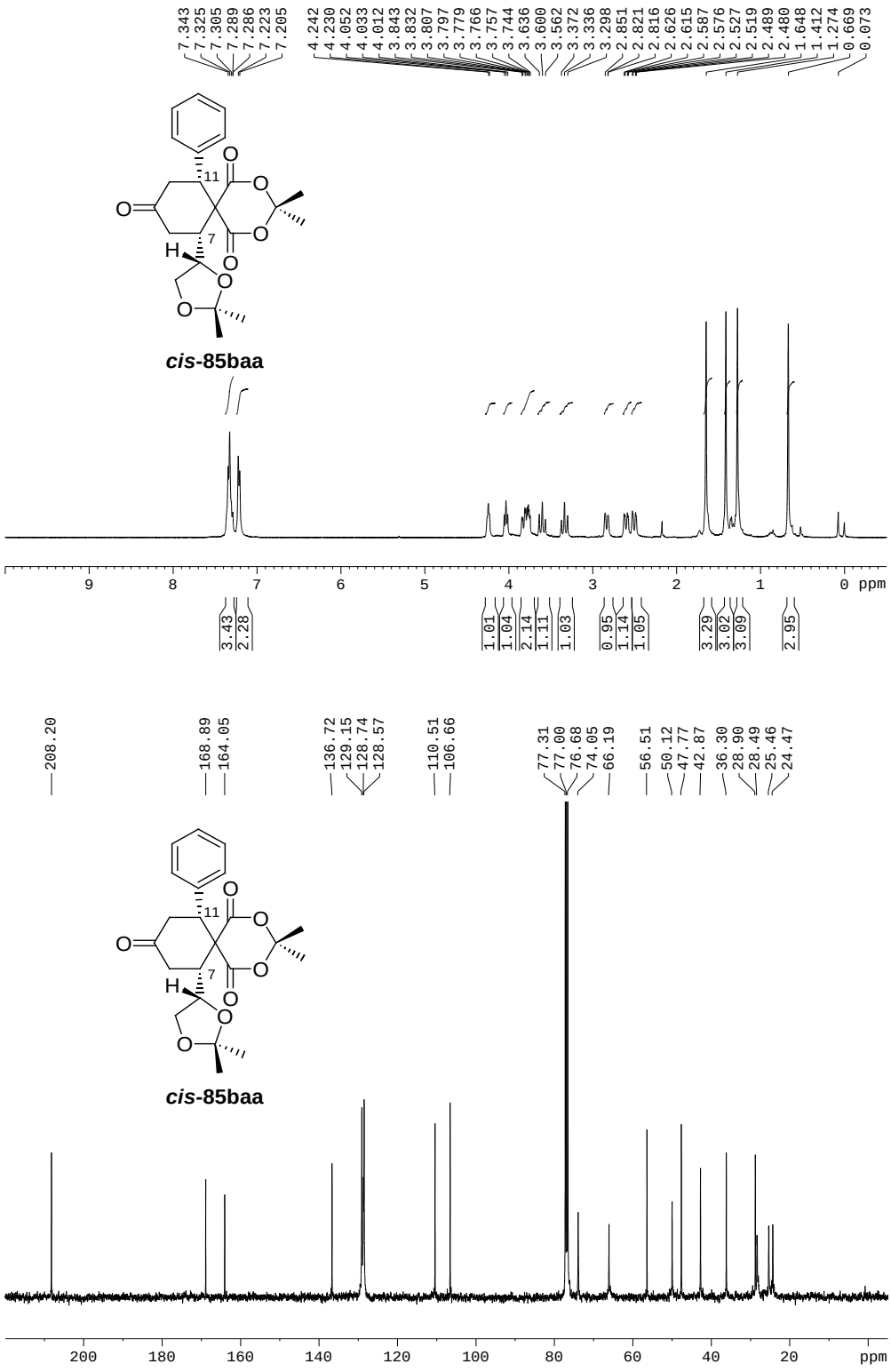


Figure-26: ^{1}H NMR and ^{13}C NMR Spectra of Product *cis*-**85baa.**

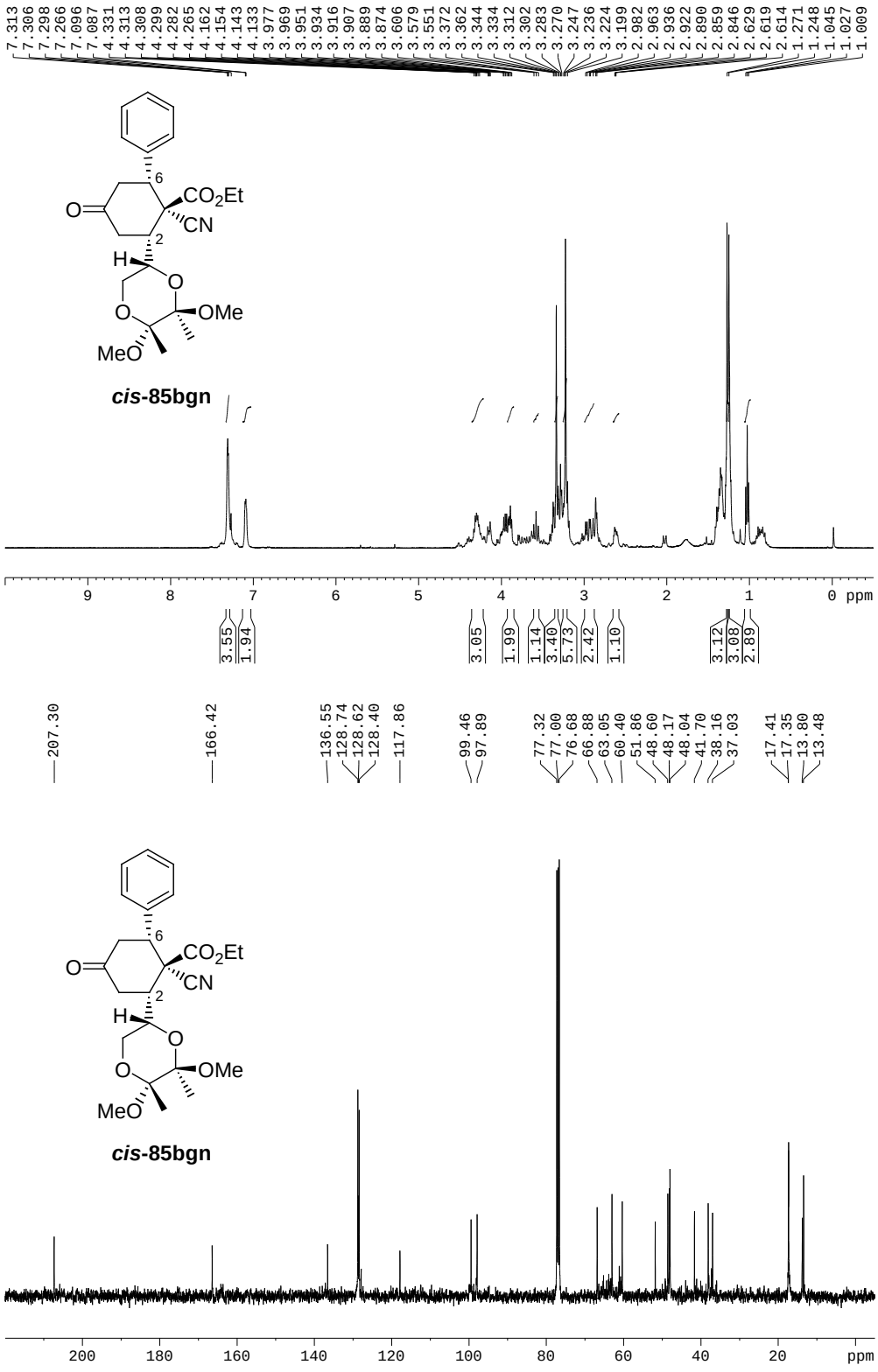


Figure-27: ^{1}H NMR and ^{13}C NMR Spectra of Product *cis*-**85bgn.**

But the reaction of (*S*)-Garner aldehyde **51b** (>99% ee) with 1, 3-dimethylbarbituric acid **3j** and enone **1b** through **4c**-catalysis furnished the chiral spirotrione *cis*-**85'bbj**[*] in 76% yield with only 60% de (Table 21, entry 6). Interestingly, reaction of (*R*)-**51g** with ethyl cyanoacetate **3n** and enone **1b** through **4c**-catalysis furnished the chiral product *cis*-**85bgn**[*] in 52% yields with >99% ee/de out of eight possible stereoisomers (Table 21, entry 8). In a final optimization, cascade reaction of protected glyceraldehydes (*R*)-**51g** and (*R*)-**51a** with **3j** and **1b** through **4c**-catalysis furnished the chiral spirotriones *cis*-**85bgj** and *cis*-**85baj** in 81% and 86% yields with >99% ee/de respectively (Table 21, entries 7/9). The stereochemistry of products **85** were established by NMR analysis [see Fig. 26 & 27]. *Observation of Table 21 results reveals that the outcome of the product selectivity is strongly affected by chiral dienophile structure along with solvents and catalyst topology*.

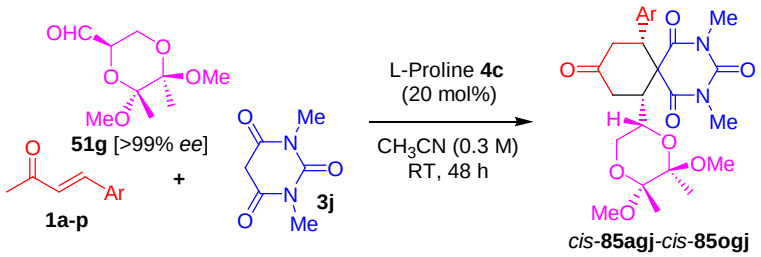
We further explored the scope of the proline-catalyzed DTCDA reaction by developing diversity-oriented synthesis of optically pure products *cis*-**85** through cascade reaction of **3a/3j** with protected (*R*)-glyceraldehydes **51g/51a** and enones **1a-1v** (Tables 22-23). The chiral spirotriones *cis*-**85** were obtained as single diastereomers in good to excellent yields and excellent ee/de's with variety of enones containing neutral, electron-donating, electron-withdrawing, halogen and hetero-atom substituted *trans*-4-aryl-3-buten-2-ones **1a-1p** and also aliphatic *trans*-4-alkyl-3-buten-2-ones **1q-1v** from DTCDA reaction as shown in Table 22 and 23. Structure and absolute stereochemistry of cascade DTCDA products **85** were confirmed by NMR analysis (for example see Fig. 28 & 29) and also finally confirmed by X-ray structure analysis on (–)-**85kgj** and (–)-**85kaj** as shown in Scheme 17-18.[47]

Although further mechanistic studies are needed to firmly elucidate the mechanism of DTCDA reactions through **4c**- or **4j**-catalysis, the reaction proceeds via concerted *endo*-[4+2]-cycloaddition between Barbas dienamine and chiral alkylidenes (Scheme 16).[6-9,13,46] In the case of the treatment of in situ generated

* In all compounds denoted **85xyz** and **85'xyz**, **x** is incorporated from reactant enones **1, y** is incorporated from the reactant chiral aldehydes **51** and **z** is incorporated from the reactant CH-acids **3**.

chiral alkylidene **87aa** with 2-amino-1,3-butadienes generated from **1**, (*R*)-**51a** and **3a** via **4c/4j**-catalysis, we can rationalize the observed high diastereoselectivity through an allowed transition state where the *re*-face of **87aa** approaches the dienamine due to the strong electrostatic interactions as shown in **TS-1**. Lack of formation of other isomer may be explained by model **TS-2**, in which there are very poor electrostatic interactions between the partially positive nitrogen of the dienamine and the lone pair electrons on oxygen of sugar in the transition state (Scheme 16).

Table 22: Diversity-oriented Synthesis of Chiral Products *cis*-**85** from **1a-p**, (*R*)-**51g** and **3j**[a]



Entry	Ar	Products	Yield[b] (%)	de[c] (%)
1	1-Naphthalenyl **1a**	*cis*-**85agj**	75	>99
2	Piperonyl **1m**	*cis*-**85mgj**	65	>99
3	4-OHC_6H_4 **1f**	*cis*-**85fgj**	78	>99
4	4-$OBnC_6H_4$ **1n**	*cis*-**85ngj**	83	>99
5	2-$NO_2C_6H_4$ **1e**	*cis*-**85egj**	60	>99
6	3-BrC_6H_4 **1k**	*cis*-**85kgj**	85	>99
7	2,6-$Cl_2C_6H_3$ **1o**	*cis*-**85ogj**	80	>99
8	2-Thiophenyl **1j**	*cis*-**85jgj**	85	>99
9[d]	2-Furanyl **1p**	*cis*-**85pga**	76	>99

[a] see Experimental section for reaction conditions.
[b] Yield refers to the purified product obtained by column chromatography.
[c] Diastereomeric excesses determined by using ^1H and ^{13}C NMR analysis on isolated products.
[d] Meldrum's acid **3a** used as active methylene.

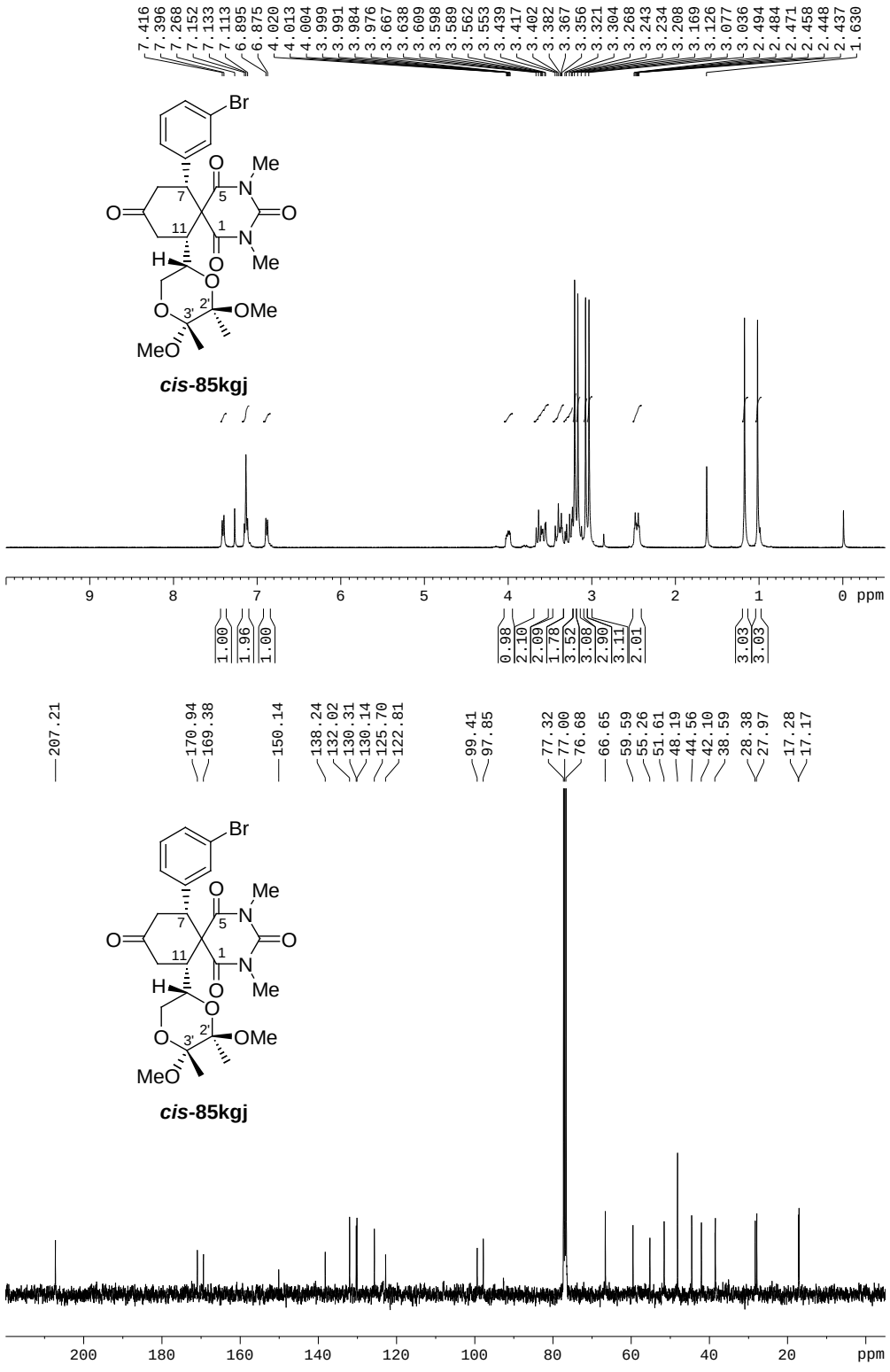
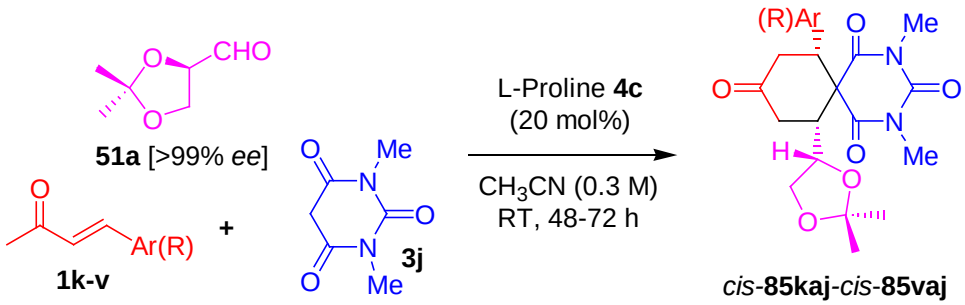


Figure-28: ^{1}H NMR and ^{13}C NMR Spectra of product *cis*-**85kgj.**

***Table 23*:** Diversity-oriented Synthesis of Chiral Products *cis*-**85** from **1k-v**, (*R*)-**51a** and **3j**[a]



Entry	Ar	Products	Yield[b] (%)	de[c] (%)
1	3-BrC_6H_4 **1k**	*cis*-**85kaj**	93	>99
2	2-Furanyl **1p**	*cis*-**85paj**	80	>99
3[d]	**2-Furanyl 1p**	***cis*-85paa**	**78**	**>99**
4	*trans*-PhCH=CH **1q**	*cis*-**85qaj**	80	>99
5	Methyl **1r**	*cis*-**85raj**	72	>99
6	*n*-Propyl **1s**	*cis*-**85saj**	55	>99
7	*n*-Butyl **1t**	*cis*-**85taj**	61	>99
8	*n*-Pentyl **1u**	*cis*-**85uaj**	70	>99
9	*n*-Hexyl **1v**	*cis*-**85vaj**	60	>99

[a] see Experimental section for reaction conditions.

[b] Yield refers to the purified product obtained by column chromatography.

[c] Diastereomeric excesses determined by using ^{1}H and ^{13}C NMR analysis on isolated products.

[d] Meldrum's acid **3a** used as active methylene.

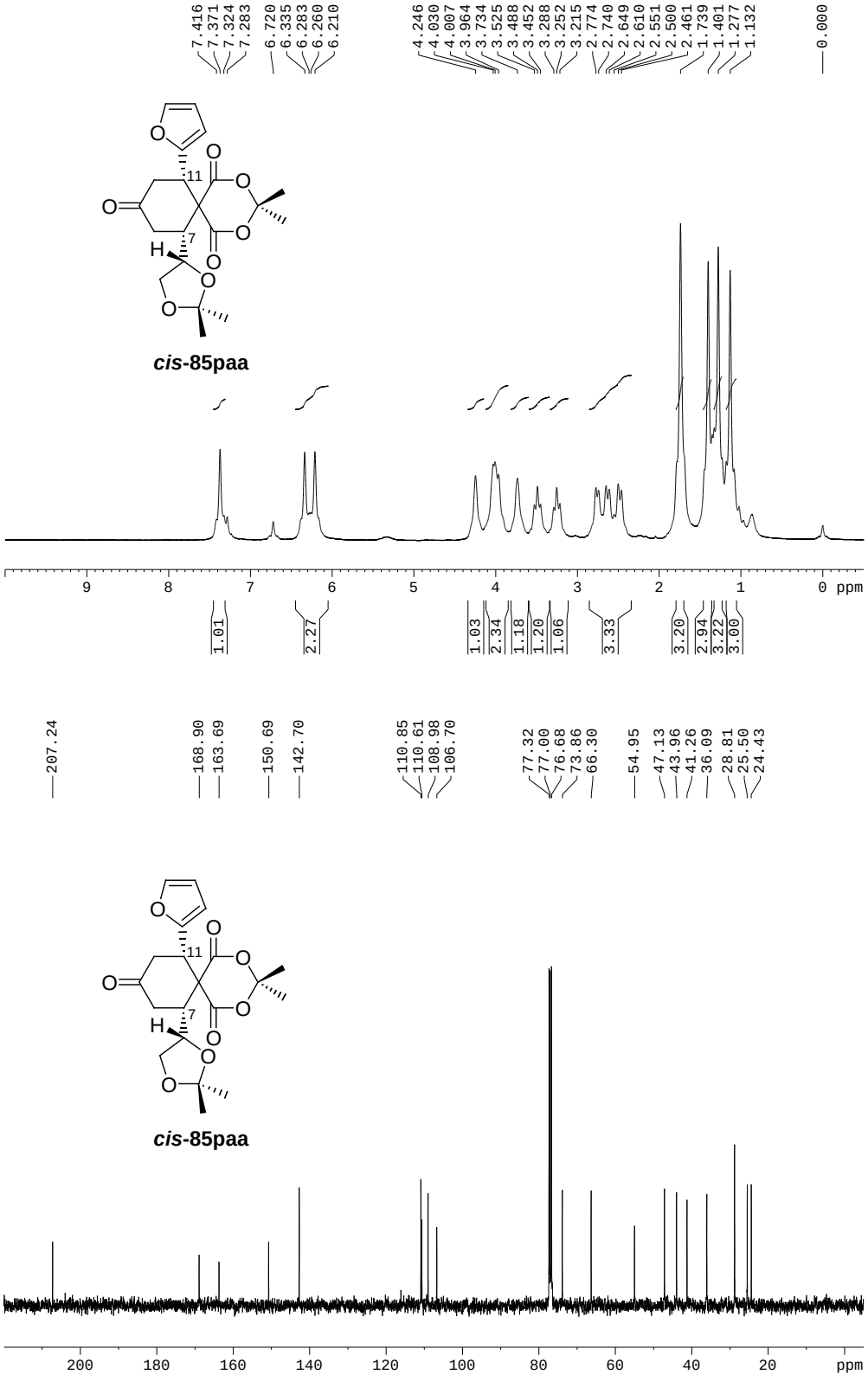
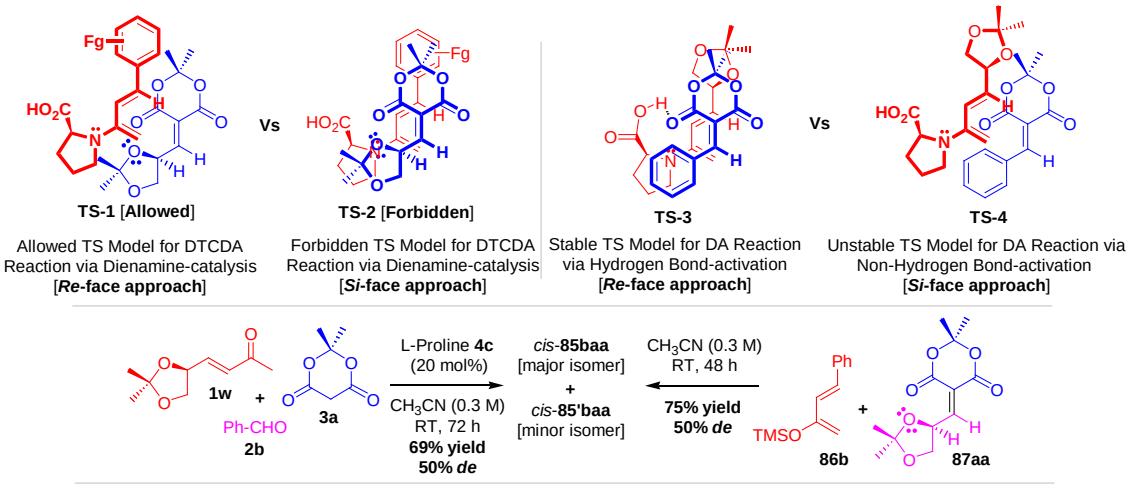


Figure-29: ^{1}H NMR and ^{13}C NMR Spectra of Product *cis*-**85paa.**

***Scheme 16*:** Proposed Transition States for DTCDA Reaction.

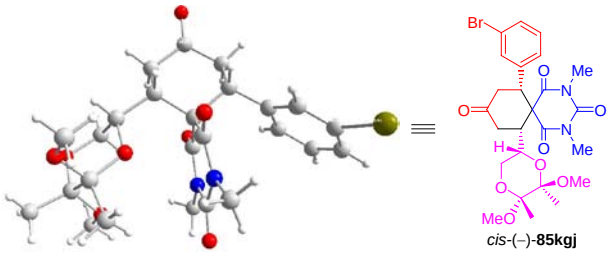


Based on the internal correlation of DTCDA results and X-ray structural analysis, we proposed a transition state where electrostatic interactions are main controlling factor rather than hydrogen bonding interactions in bio-mimetic cascade DTCDA reactions, because L-**4c** or D-**4c** didn't show much impact on the outcome of the product selectivity (see Tables 20 and 21). Importance of electrostatic interactions between partially positive nitrogen of the dienamine and the lone pair electrons on oxygen of sugar can be easily understood through controlled Diels-Alder experiments performed on **1w**, **2b** and **3a** under **4c**-catalysis; and also between **86b** and **87aa** at 25 °C as shown in Scheme 16. Observed poor selectivity in the above reactions can be explained through **TS-3** and **TS-4**, in which only hydrogen-bonding interactions are possible to control the moderate selectivity.

With synthetic and pharmaceutical applications in mind we extended the applications of DTCDA methodology towards the synthesis of chiral cyanohydrins and chiral TCRA products. The reaction of **85paa** with *n*-BuLi, *i*Pr_2NH and cyano ethylformate at –78 °C furnished the chiral cyanohydrin **88paa** in 2 h with 51% yield as shown in Scheme 19. The structure and stereochemistry of the product **88ppa** were confirmed by NMR analysis [see Fig. 30]. Treatment of the spirolactone

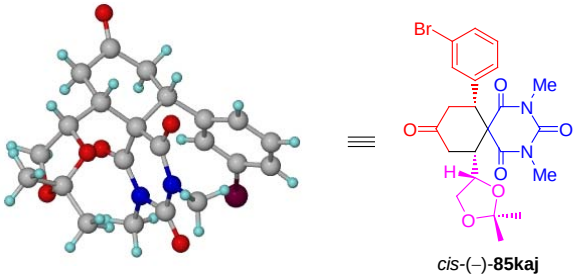
85taj with 1,3-dimethylbarbituric acid **3j** and Hantzsch ester **15** in DMSO at 25 °C furnished the chiral TCRA product **89taj** in 21 h with 91% yield as shown in Scheme 19.

***Scheme 17*:** X-Ray Crystal Structure of Chiral Spiro Compound *c*is-(-)-**85kgj**.



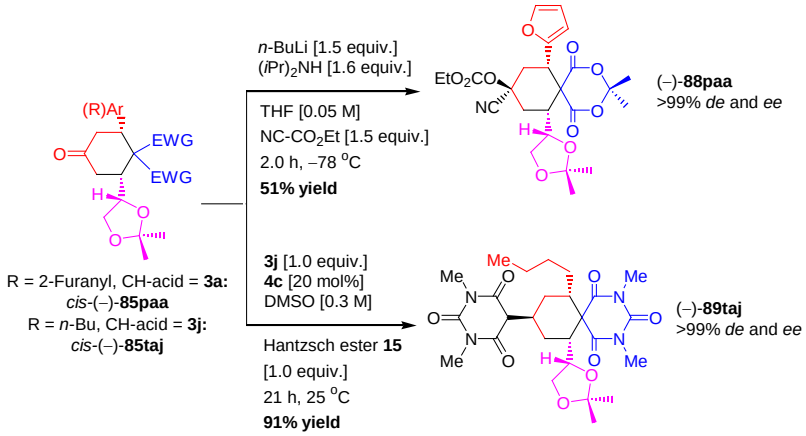
cis-(–)-**85kgj**

Scheme 18: X-Ray Crystal Structure of Chiral Spiro Compound *c*is-(-)-**85kaj**.



cis-(–)-**85kaj**

Scheme 19: Synthetic Application of Chiral DTCDA Products.



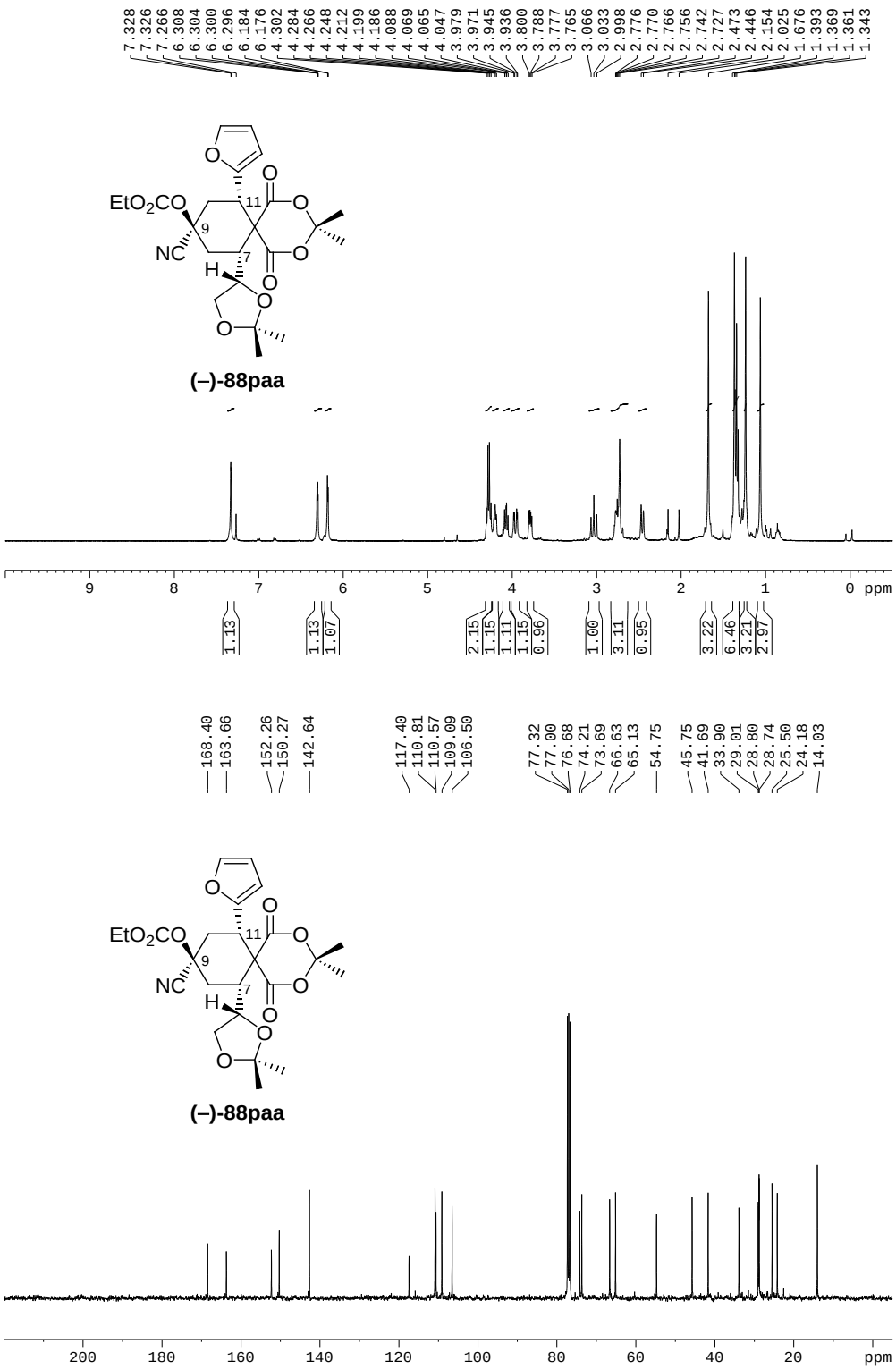


Figure-30: ^{1}H NMR and ^{13}C NMR Spectra of Product *cis*-**88paa.**

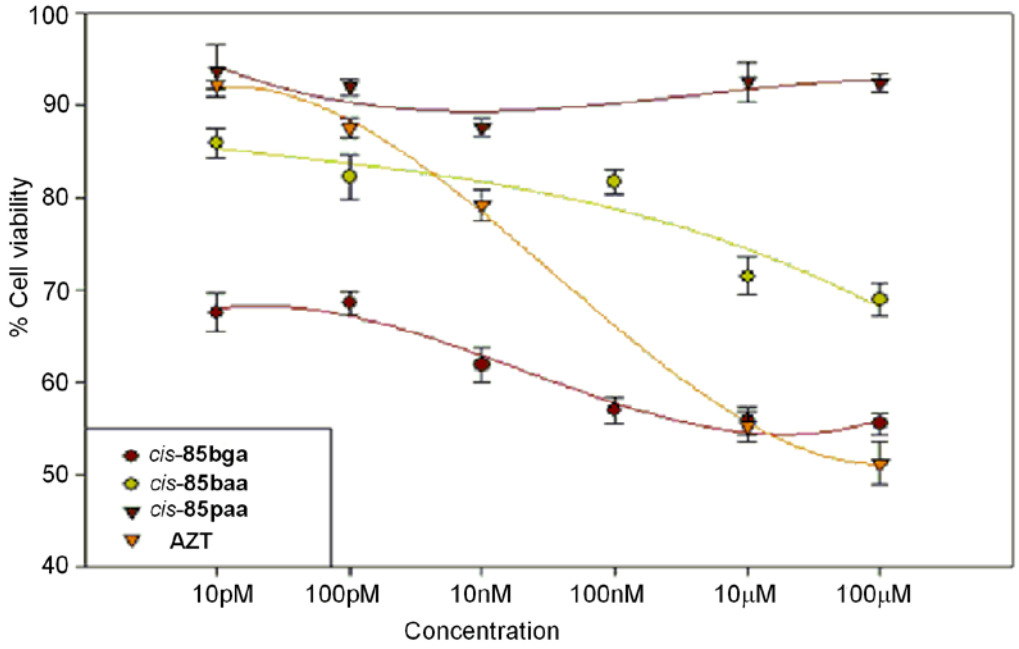


Figure-31: Concentration Dependent Cytotoxicity Expressed as Percentage Cell-viability of the Synthesized Compounds. **AZT** was used as a Reference Compound. Higher Percentage Cell-viability Refers to Less Cytotoxicity.

6.3 Biological Studies on Chiral Products 85 as HIV-1 Inhibitors

After successful high-yielding synthesis of optically pure single enantiomer of functionalized spiroundecanes library **85**, we further showed interest to screen them for anti-retroviral properties. A cell culture based HIV infection model was used for this purpose and differences in HIV turnovers in presence and absence of these compounds were monitored. For all the assays, azidothymidine (AZT), a known anti-HIV compound, was used as a positive control.[48] Before checking for anti-HIV activities, compounds were checked for cytotoxicity in the Sup-T1 cells by MTT assay. The assay is based on the reduction of yellow color tetrazolium salt MTT by a mitochondrial dehydrogenase of viable or live cells, that converts this compound to a purple coloured formazan product that is measured spectrometrically at a wavelength of 570nm. The amount of formazan formed is proportional to the number of living cells. It was interesting to observe that AZT, the molecule that is

used for retroviral treatment was more cytotoxic than *cis*-**85baa**, *cis*-**85paa** and less cytotoxic than *cis*-**85bga** (see Fig. 31). The compound *cis*-**85paa** had the least cytotoxicity in our conditions, with almost 90% alive even after 16 h of treatment. 100 pico molar (pM), 100 nano molar (nM) and 10 micro molar (μM) concentrations were selected for subsequent assays to check the anti-HIV properties of these compounds.

After obtaining the cytotoxic results in hand, the anti-HIV-1 activity of these compounds were tested for 100pM, 100nM and 10μM concentrations (Fig. 32). Cells without any compound treatment, but infected with NL4-3 viruses were taken as background control. As virus infection was expected to increase cell death, the cells were treated with different compounds along with infection for 5 hours only, which was sufficient for viral entry and drug adsorption/absorption. The percentage inhibition (decrease in HIV-1 [here, NL4-3] turnover) as a function of concentration was plotted (Fig. 32). Higher percentage inhibition indicates enhanced decrease in HIV-1 turnover and therefore is indicative of more effective anti-retroviral molecule. We observed that all the three test compounds reduced the NL4-3 turnover on an average by 45%, which was comparable with AZT, the drug in use for HIV-1 treatment. The compound *cis*-**85bga**, even though decreased NL4-3 turnover by 50%, the cells at the end of the experiments was only 69% ± 5% viable. The chiral compound *cis*-**85baa** could reduce NL4-3 turnover rate by as much as 58% at a concentration of 10μM, which was marginally more than the anti-retroviral affect of AZT at that concentration. In both the cases a cell viability of about 77% ± 8% were maintained. The compound *cis*-**85paa** at a concentration of 100nM showed comparatively improved anti-retroviral activity over AZT. The percentage inhibition of *cis*-**85paa** was 56% ± 0.4% with cell viability of 82% ± 5.6%, while that of AZT at 100nM is 51.7% ± 3% with almost equal cell viability. The % inhibition of NL4-3 turnover by *cis*-**85paa** increased to 59% ± 1% at 10μM, which was the highest amongst all the four compounds used. From these experiments, it could be concluded that the newly synthesized chiral compounds, especially *cis*-**85baa** and

cis-**85paa** are bioactive molecules that bear the property of decreasing HIV-1 turnover upon 5 h of treatment, while maintaining more than 75% cell viability.

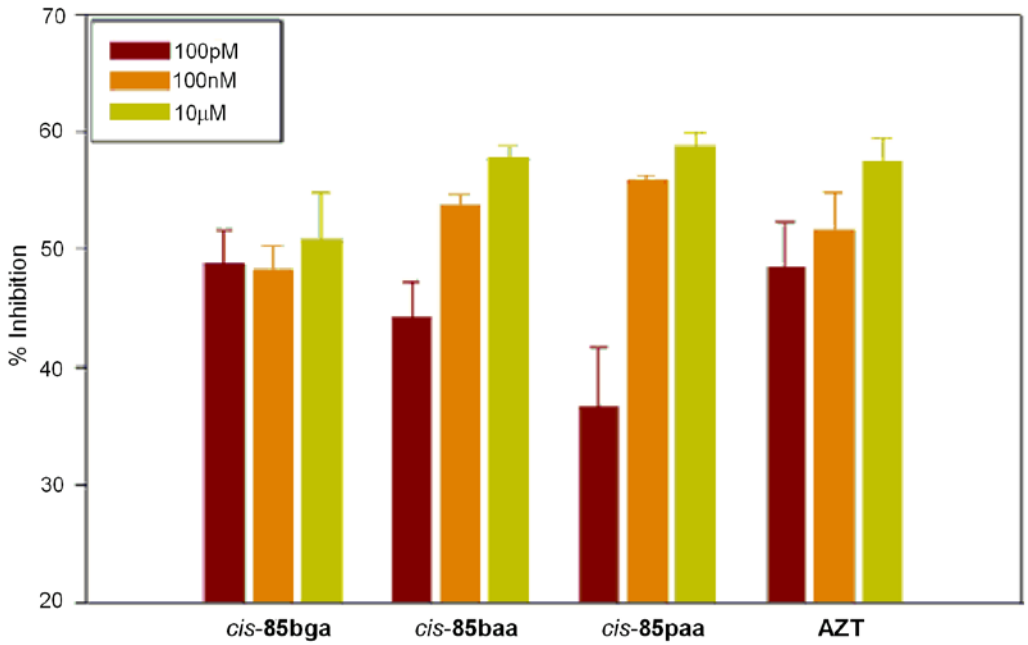


***Figure-32*:** Screening of Products **85** as HIV-1 Inhibitors [Percentage inhibition, measured in terms of decrease in NL4-3 virus, upon treatment with 100pM, 100nM and 10µM of compounds *cis*-**85bga**, *cis*-**85baa** and *cis*-**85paa** for 5 h. AZT was used as a reference compound].

6.4 Conclusions

In summary, we have designed and developed the proline–catalyzed direct DTCDA reaction for diversity-oriented synthesis of optically pure products of spirotriones *cis*-**85**. For the first time we have shown that the electrostatic interactions are the major controlling factor rather than the hydrogen bonding interactions in amino acid-catalyzed Diels-Alder reactions. Biological *in vivo*

screening of chiral *cis*-spirotrione molecules (*cis*-**85baa** and *cis*-**85paa**) shows that these molecules could become as lead HIV-1 inhibitors than the already known antiretroviral drug, azidothymidine (AZT). Further biological/pharmacological studies on these molecules may lead to give better drugs for HIV. Herein for the first time we have shown the experimentally simple and environmentally friendly DTCDA approach as a novel tool for molecular therapeutics.

7. *Experimental Section*

Materials: All solvents and commercially available chemicals were used as received. Acetonide-D-(*R*)-glyceraldehyde **51a** was prepared from D-mannitol with 39% overall yield in two steps according to literature procedure.[50a-b] 1,1-Dimethyl (*S*)- and (*R*)-4-formyl-2,2-dimethyl-3-oxazolidine carboxylates **51b** and **51c** were prepared from L- and D-serine with each 55% yield in three steps according to literature procedure.[50c] *S*-2-(N,N-Dibenzylamino)-3-phenylpropanal **51d** was prepared from L-phenyl alanine with 23% yield in three steps according to literature procedure.[50d] butane-2,3-diacetal of (*R*)- and (*S*)-glyceraldehydes **51g** and **51h** was prepared from D-mannitol according literature procedure.[50e-g] 1,5-Dioxa-spiro[5.5]undecane-2,4-dione **3c** and 6,10-dioxa-spiro[4.5]decane-7,9-dione **3h** were prepared from cyclohexanone and cyclopentanone with each 60% yield in single step according to literature procedure.[50h] Spiro[5.5]undecane-2,4-dione **3l** and spiro[4.5]decane-7,9-dione **3k** were prepared from cyclohexanone and cyclopentanone with each 75% yield in two steps according to literature procedure.[50i-j]

1a: Aniline-Catalyzed Cascade *TCRA* Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **37**, 0.3 mmol of CH-acid **3d**/**3g** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of dichloromethane, and then the catalyst aniline **4g** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1 to 7. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up, and pure cascade products **41** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1b: Acid-Catalyzed Cascade Oxy-Michael/Dehydration Reactions of 2-(2-Hydroxy-benzyl)-Cyclopentane-1,3-Diones 41: A solution of substituted 2-(2-hydroxy-benzyl)-cyclopentane-1,3-diones **41** (0.1 mmol) and *p*-TSA **35a** (0.03 mmol, 30 mol%) in dichloromethane (1.0 ml) was stirred at 45 °C for 9 to 18 h. After cooling, the reaction mixture washed with water and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **38** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

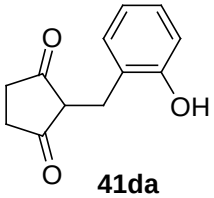
1c: Amino Acid or Aniline-/*p*-TSA-Catalyzed One-Pot Double Cascade Three-component Reductive Alkylation/Oxy-Michael/Dehydration Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **37**, 0.3 mmol of CH-acid **3d** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of dichloromethane, and then the catalyst amino acid **4c** or aniline **4g** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 3. After evaporation of the solvent completely, to the crude reaction mixture added 1.0 mL of toluene solvent and *p*-TSA **35a** (0.09 mmol, 30 mol%) and the reaction mixture was stirred at 90 °C for 10 h. The crude reaction mixture was worked up with aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure one-pot products **38** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1d: General Procedure for the Direct Organocatalytic One-Pot Synthesis of 2-(2-Hydroxy-benzyl)-3-Methoxy-Cyclopent-2-enones 44: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **37**, 0.3 mmol of CH-acid **3d** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of dichloromethane, and then the catalyst aniline **4g** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 6. After evaporation of the solvent completely, to the crude reaction mixture added 15 equivalents of an ethereal solution of diazomethane and the reaction mixture was stirred at room temperature for the 2 h. After evaporation of the solvent and excess diazomethane completely in fume hood, the crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure one-pot products **44** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1e: General Procedure for the Multi-catalysis Synthesis of 3,9-Dihydro-2H-Cyclopenta[b]chromen-1-ones 38: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **37**, 0.3 mmol of CH-acid **3d** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of dichloromethane, and then the catalyst aniline **4g** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 5. After evaporation of the solvent completely, to the crude reaction mixture added 15 equivalents of an ethereal solution of diazomethane and the reaction mixture was stirred at room temperature for the 2 h. After evaporation of the solvent and excess diazomethane completely in

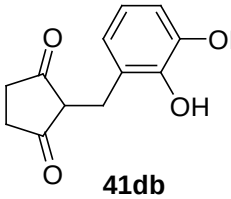
fume hood, to the crude reaction mixture added 3 equivalents of K_2CO_3 and solvent ethanol and the reaction mixture was stirred at room temperature for the 18 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure one-pot products **38** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2-(2-Hydroxy-benzyl)-cyclopentane-1,3-dione (41da): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 156 °C; IR (Neat): ν_{max} 3239, 2924, 1547, 1369, 1262, 1242, 1174, 1101 and 760 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 7.20 (1H, d, *J* = 7.2 Hz), 7.08 (1H, t, *J* = 7.6 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 6.81 (1H, t, *J* = 7.6 Hz) [Ar-H]; 3.43 (2H, s), 2.47 (4H, s, 2 x C*H*$_2$); **^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135]** δ 153.7 (C, C-OH), 130.6 (CH), 127.7 (CH), 126.5 (C), 120.7 (CH), 117.9 (C), 116.6 (CH), 30.1 (2 x CH_2), 21.7 (CH_2); HRMS m/z 205.0842 ($M + H^+$), calcd for $C_{12}H_{12}O_3H$ 205.0864.



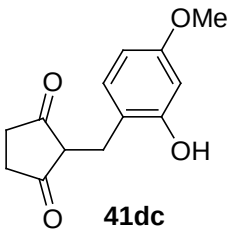
41da

2-(2,3-Dihydroxy-benzyl)-cyclopentane-1,3-dione (41db): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 168 °C; IR (Neat): ν_{max} 3384, 2921, 1540, 1479, 1440, 1373, 1266, 1216, 1175, 1070 and 742 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 6.72 (3H, m) [Ar-H]; 3.41 (2H, s), 2.49 (4H, s, 2 x C*H*$_2$); **^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135]** δ 146.1 (C, C-OH), 141.6 (C, C-OH), 127.3 (C), 121.2 (CH), 120.6 (CH), 118.1 (C), 113.0 (CH), 30.1 (2 x CH_2), 21.8 (CH_2); LRMS m/z 221.00 ($M + H^+$), calcd for $C_{12}H_{12}O_4H$ 221.0736; Anal. calcd for $C_{12}H_{12}O_4$ (220.0736): C, 65.45; H, 5.49. Found: C, 65.426; H, 5.457%.



41db

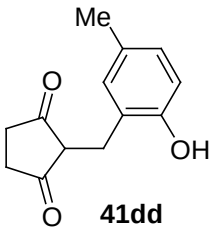
2-(2-Hydroxy-4-methoxy-benzyl)-cyclopentane-1,3-dione (41dc): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 160 °C; IR (Neat): ν_{max} 3297, 2927, 1619, 1583, 1504, 1439, 1354, 1259, 1166, 1099, 1026, 957 and 824 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 7.09 (1H, d, *J* = 8.0 Hz), 6.48 (1H, d, *J* = 2.4 Hz), 6.39 (1H, dd,



41dc

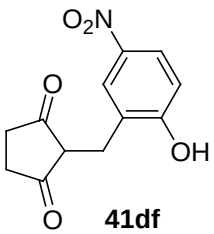
J = 8.4, 2.4 Hz) [Ar-H]; 3.74 (3H, s, OC*H*$_3$), 3.35 (2H, s), 2.47 (4H, s, 2 x C*H*$_2$); **^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135]** δ 159.3 (C), 154.8 (C), 131.0 (CH), 119.0 (C), 118.2 (C), 106.2 (CH), 102.6 (CH), 55.1 (CH_3, O*C*H$_3$), 30.1 (2 x CH_2), 21.0 (CH_2); LRMS m/z 235.00 (M + H$^+$), calcd for $C_{13}H_{14}O_4H$ 235.0892; Anal. calcd for $C_{13}H_{14}O_4$ (234.0892): C, 66.66; H, 6.02. Found: C, 66.613; H, 6.030%.

2-(2-Hydroxy-5-methyl-benzyl)-cyclopentane-1,3-dione (41dd): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 160 °C; IR (Neat): ν_{max} 2931, 2433, 1553, 1373, 1351, 1253, 1171, 843 and 754 cm^{-1}; **^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)]** δ 7.01 (1H, d, *J* = 1.6 Hz), 6.88 (1H, dd, *J* = 8.0, 1.6 Hz), 6.78 (1H, d, *J* = 8.0 Hz) [Ar-H]; 3.39 (2H, s), 2.47 (4H, s, 2 x C*H*$_2$), 2.22 (3H, s, Ar-C*H*$_3$); **^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135]** δ 151.2 (C), 131.1 (CH), 129.9 (C), 128.1 (CH), 126.3 (C), 117.9 (C), 116.4 (CH), 30.0 (2 x CH_2), 21.6 (CH_2), 20.2 (CH_3, Ar-*C*H$_3$); LRMS m/z 219.00 (M + H$^+$), calcd for $C_{13}H_{14}O_3H$ 219.0943; Anal. calcd for $C_{13}H_{14}O_3$ (218.0943): C, 71.54; H, 6.47. Found: C, 71.627; H, 6.461%.



41dd

2-(2-Hydroxy-5-methoxy-benzyl)-cyclopentane-1,3-dione (41de): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 153 °C; IR (Neat): ν_{max} 3307, 2925, 1499, 1361, 1261, 1235, 1172, 1048 and 810 cm^{-1}; **^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)]** δ 6.81 (1H, d, *J* = 8.8 Hz), 6.78 (1H, d, *J* = 1.6 Hz), 6.65 (1H, dd, *J* = 8.8, 2.8 Hz) [Ar-H]; 3.73 (3H, s, OC*H*$_3$), 3.40 (2H, s), 2.48 (4H, s, 2 x C*H*$_2$); **^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135]** δ 153.4 (C), 147.5 (C), 127.7 (C), 117.6 (C), 117.4 (CH), 115.7 (CH), 112.8 (CH), 55.6 (CH_3, OC*H*$_3$), 30.1 (2 x CH_2), 21.9 (CH_2); LRMS m/z 235.00 (M + H$^+$), calcd for $C_{13}H_{14}O_4H$ 235.0892; Anal. calcd for $C_{13}H_{14}O_4$ (234.0892): C, 66.66; H, 6.02. Found: C, 66.683; H, 6.004%.



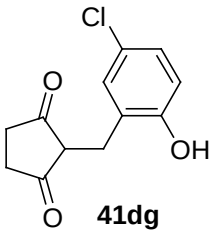
41de

2-(2-Hydroxy-5-nitro-benzyl)-cyclopentane-1,3-dione (41df): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 168 °C; IR (Neat): ν_{max} 3118, 2925, 1588, 1521, 1489, 1338, 1285, 1207, 1084, 832 and 748 cm^{-1}; **^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)]** δ 8.10 (1H, d, *J* = 2.4 Hz), 7.99 (1H, dd, *J* = 8.8, 2.8 Hz), 6.92 (1H, d, *J* = 9.2 Hz) [Ar-H]; 3.46 (2H, s), 2.55 (4H, s, 2 x C*H*$_2$); **^{13}C NMR [CDCl$_3$ + CD$_3$OD (three**

41df

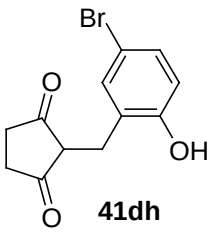
drops), DEPT-135] δ 161.4 (C), 140.5 (C), 127.0 (C), 126.4 (CH), 124.1 (CH), 117.4 (CH), 116.3 (C), 30.2 (2 x CH_2), 22.0 (CH_2); LRMS m/z 250.00 ($M + H^+$), calcd for $C_{12}H_{11}NO_5H$ 250.0637; Anal. calcd for $C_{12}H_{11}NO_5$ (249.0637): C, 57.83; H, 4.45; N, 5.62. Found: C, 57.879; H, 4.461; N, 5.692%.

2-(5-Chloro-2-hydroxy-benzyl)-cyclopentane-1,3-dione (41dg): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 158 °C; IR (Neat): ν_{max} 3282, 2931, 1536, 1482, 1365, 1263, 1235, 1173, 1113, 1023 and 830 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 7.15 (1H, d, *J* = 2.4 Hz), 7.02 (1H, dd, *J* = 8.8, 2.8 Hz), 6.81 (1H, d, *J* = 8.4 Hz) [Ar-H]; 3.37 (2H, s), 2.50 (4H, s, 2 x C*H*$_2$); **^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135]** δ 152.8 (C), 129.9 (CH), 128.3 (C), 127.3 (CH), 124.8 (C), 118.2 (CH), 117.1 (C), 30.1 (2 x CH_2), 21.7 (CH_2); LRMS m/z 239.00 ($M + H^+$), calcd for $C_{12}H_{11}ClO_3H$ 239.0397; Anal. calcd for $C_{12}H_{11}ClO_3$ (238.0397): C, 60.39; H, 4.65. Found: C, 60.324; H, 4.637%.



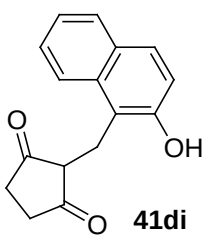
41dg

2-(5-Bromo-2-hydroxy-benzyl)-cyclopentane-1,3-dione (41dh): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 157 °C; IR (Neat): ν_{max} 3283, 2930, 1536, 1482, 1367, 1284, 1235, 1173, 1114, 1023 and 830 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 7.29 (1H, d, *J* = 6.4 Hz), 7.16 (1H, dd, *J* = 8.8, 2.4 Hz), 6.76 (1H, d, *J* = 8.4 Hz) [Ar-H]; 3.37 (2H, s), 2.51 (4H, s, 2 x C*H*$_2$); **^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135]** δ 153.3 (C), 132.8 (CH), 130.3 (CH), 128.8 (C), 118.7 (CH), 117.1 (C), 112.1 (C), 30.0 (2 x CH_2), 21.6 (CH_2); LRMS m/z 283.65 ($M + H^+$), calcd for $C_{12}H_{11}BrO_3$-H 282.9892; Anal. calcd for $C_{12}H_{11}BrO_3$ (281.9892): C, 50.91; H, 3.92. Found: C, 50.887; H, 3.922%.



41dh

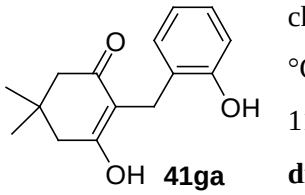
2-(2-Hydroxy-naphthalen-1-ylmethyl)-cyclopentane-1,3-dione (41di): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 228 °C; IR (Neat): ν_{max} 3049, 2988, 2926, 1564, 1512, 1438, 1361, 1311, 1237, 814 and 754 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 8.39 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 7.64 (1H, d, *J* = 8.8 Hz), 7.48 (1H, t, *J* = 7.2 Hz), 7.31 (1H, t, *J* = 7.2 Hz), 7.19 (1H, d, *J* = 8.8 Hz) [Ar-H]; 3.87 (2H, s), 2.48 (4H, s, 2 x C*H*$_2$); **^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135]** δ 151.3 (C),



41di

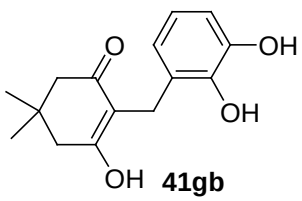
133.1 (C), 129.3 (C), 128.02 (CH), 127.98 (CH), 126.1 (CH), 123.8 (CH), 123.0 (CH), 119.0 (C), 118.9 (CH), 117.7 (C), 17.0 (CH_2); LRMS m/z 255.00 ($M + H^+$), calcd for $C_{16}H_{14}O_3H$ 255.0943; Anal. calcd for $C_{16}H_{14}O_3$ (254.0943): C, 75.57; H, 5.55. Found: C, 75.646; H, 5.550%.

2-(2-Hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (41ga): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 134 °C; IR (Neat): ν_{max} 3071, 2957, 1616, 1570, 1515, 1461, 1376, 1236, 1149, 1102, 1038 and 752 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 7.32 (1H, br d, *J* = 7.2 Hz), 7.03 (1H, m), 6.85-6.75 (2H, m) [Ar-H]; 3.57 (2H, s), 2.28 (4H, s, 2 x C*H*$_2$), 1.02 (6H, s, 2 x CH_3); **^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135]** δ 153.6 (C), 131.2 (CH), 127.26 (CH), 127.22 (C), 120.1 (CH), 116.0 (CH), 114.2 (C), 41.5 (2 x CH_2), 31.7 (C), 28.0 (2 x CH_3), 22.0 (CH_2); LRMS m/z 247.12 ($M + H^+$), calcd for $C_{15}H_{18}O_3H$ 247.1334; Anal. calcd for $C_{15}H_{18}O_3$ (247.1256): C, 73.15; H, 7.37. Found: C, 73.175; H, 7.372%.



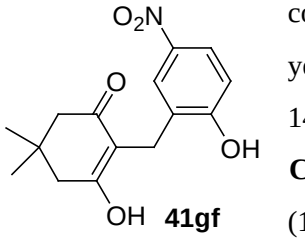
41ga

2-(2,3-Dihydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (41gb): Purified by column chromatography using EtOAc/hexane and isolated as a light yellowish solid. Mp 142 °C; IR (Neat): ν_{max} 3179, 2959, 2873, 1583, 1478, 1386, 1249, 1187, 1071, 753 and 646 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 6.79 (1H, dd, *J* = 9.2, 1.6 Hz), 6.68 (1H, dd, *J* = 9.6, 1.6 Hz), 6.62 (1H, t, *J* = 7.6 Hz) [Ar-*H*]; 3.52 (2H, s, C*H*$_2$Ar), 2.26 (4H, s, 2 x C*H*$_2$C=O), 0.98 (6H, s, 2 x CH_3); **^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135]** δ 145.3 (C), 141.6 (C), 127.8 (C), 122.0 (CH), 120.1 (CH), 114.5 (C), 112.6 (CH), 46.4 (2 x CH_2), 31.9 (C), 28.1 (2 x CH_3), 22.2 (CH_2); LRMS m/z 263.00 ($M + H^+$), calcd for $C_{15}H_{18}O_4H$ 263.1205; Anal. calcd for $C_{15}H_{18}O_3$ (262.1205): C, 68.68; H, 6.92. Found: C, 68.724; H, 6.947%.



41gb

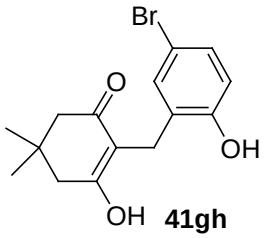
2-(2-Hydroxy-5-nitro-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (41gf): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 142 °C; IR (Neat): ν_{max} 2963, 2613, 1585, 1512, 1458, 1333, 1251, 1196, 1086, 1038 and 613 cm^{-1}; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 8.22 (1H, br s), 7.97 (1H, d, *J* = 8.0 Hz), 6.88 (1H, d, *J* = 8.0 Hz) [Ar-H]; 3.59 (2H, s, ArC*H*$_2$), 2.34 (4H, s, 2 x



41gf

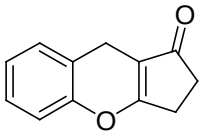
C*H*$_2$C=O), 1.05 (6H, s, 2 x C*H*$_3$); **^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135]** δ 161.5 (C), 140.3 (C), 127.7 (C), 127.4 (CH), 124.0 (CH), 116.9 (CH), 113.1 (C), 32.1 (C), 28.2 (2 x CH_3), 22.8 (CH_2); LRMS m/z 292.00 (M + H^+), calcd for $C_{15}H_{17}NO_5$ 291.1107; Anal. calcd for $C_{15}H_{17}NO_5$ (291.1107): C, 61.85; H, 5.88; N, 4.81. Found: C, 61.832; H, 5.870; N, 4.824%.

2-(5-Bromo-2-hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (41gh): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 146 °C; IR (Neat): ν_{max} 3174, 2960, 2616, 1732, 1584, 1515, 1477, 1380, 1336, 1246, 1173, 1086, 1038 and 817 cm^{-1}; **^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)]** δ 7.42 (1H, d, *J* = 4.0 Hz), 7.14 (1H, dd, *J* = 8.0, 4.0 Hz), 6.72 (1H, d, *J* = 8.0 Hz) [Ar-H]; 3.51 (2H, s, ArC*H*$_2$), 2.29 (4H, s, 2 x C*H*$_2$C=O), 1.03 (6H, s, 2 x C*H*$_3$); **^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135]** δ 153.5 (C), 133.7 (CH), 130.2 (CH), 129.6 (C), 118.2 (CH), 113.9 (C), 111.8 (C), 32.0 (C), 28.2 (2 x CH_3), 22.3 (CH_2); LRMS m/z 325.00 (M + H^+), calcd for $C_{15}H_{17}BrO_3$ 324.0361; Anal. calcd for $C_{15}H_{17}BrO_3$ (324.0361): C, 55.40; H, 5.27. Found: C, 55.452; H, 5.291%.



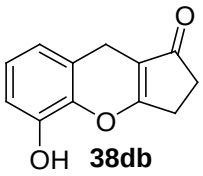
41gh

3,9-Dihydro-2H-cyclopenta[b]chromen-1-one (38da): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 166 °C; IR (neat): ν_{max} 2921, 1656 (C=O), 1489, 1460, 1438, 1395, 1251, 1164, 1115, 761 and 685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21 (1H, t, *J* = 7.6 Hz), 7.18 (1H, d, *J* = 6.8 Hz), 7.11 (1H, t, *J* = 7.2 Hz), 7.05 (1H, d, *J* = 8.0 Hz) [Ar-H]; 3.52 (2H, s, C*H*$_2$Ar), 2.73 (2H, m), 2.54 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.4 (C, *C*=O), 179.2 (C, O-*C*=C), 150.8 (C, *C*-O), 130.4 (CH), 128.0 (CH), 125.1 (CH), 119.6 (C), 117.2 (CH), 114.2 (C), 33.3 (CH_2), 25.8 (CH_2), 20.8 (CH_2); LRMS m/z 187.00 (M + H^+), calcd for $C_{12}H_{10}O_2H$ 187.0681; Anal. calcd for $C_{12}H_{10}O_2$ (186.0681): C, 77.40; H, 5.41. Found: C, 77.372; H, 5.416%.



38da

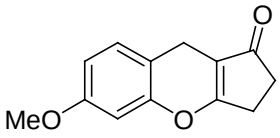
5-Hydroxy-3,9-dihydro-2H-cyclopenta[b]chromen-1-one (38db): Purified by column chromatography using EtOAc/hexane and isolated as a color less solid. Mp 184 °C; IR (neat): ν_{max} 3159, 3115, 2925, 1640 (C=O), 1572, 1477, 1402, 1248, 1232, 1160, 1115, 782 and 714 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 6.97 (1H, t, *J* = 8.0 Hz), 6.82 (1H, d, *J* = 7.6 Hz), 6.69 (1H,



38db

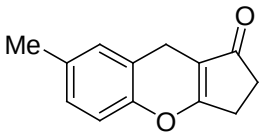
d, *J* = 7.6 Hz) [Ar-H]; 3.78 (1H, br s, O-H), 3.51 (2H, s, CH_2Ar), 2.83 (2H, br s, CH_2), 2.59 (2H, br s, CH_2); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 205.0 (C, *C*=O), 179.9 (C, O-*C*=C), 145.3 (C), 139.1 (C), 125.0 (CH), 120.4 (CH), 120.0 (C), 114.8 (CH), 114.0 (C), 33.0 (CH_2), 25.6 (CH_2), 20.3 (CH_2); LRMS m/z 203.00 (M + H^+), calcd for $C_{12}H_{10}O_3$ 202.0630; Anal. calcd for $C_{12}H_{10}O_3$ (202.0630): C, 71.28; H, 4.98. Found: C, 71.313; H, 5.026%.

6-Methoxy-3,9-dihydro-2H-cyclopenta[b]chromen-1-one (38dc): Purified by column chromatography using EtOAc/hexane and isolated as a color less solid. Mp 168 °C; IR (neat): ν_{max} 2922, 2852, 1656 (C=O), 1495, 1437, 1396, 1240, 1183, 1031, 813 and 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.08 (1H, d, *J* = 8.4 Hz), 6.69 (1H, d, *J* = 8.4 Hz), 6.60 (1H, s) [Ar-H]; 3.80 (3H, s, OCH_3), 3.44 (2H, s, CH_2Ar), 2.71 (2H, m, CH_2), 2.53 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.6 (C, *C*=O), 179.2 (C, O-*C*=C), 159.4 (C), 151.4 (C), 130.8 (CH), 114.7 (C), 111.45 (CH), 111.35 (C), 102.6 (CH), 55.5 (CH_3, O*C*H_3), 33.4 (CH_2), 25.8 (CH_2), 20.1 (CH_2); LRMS m/z 217.00 (M + H^+), calcd for $C_{13}H_{12}O_3H$ 217.0786; Anal. calcd for $C_{13}H_{12}O_3$ (216.0786): C, 72.21; H, 5.59. Found: C, 72.221; H, 5.587%.



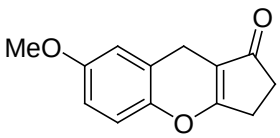
38dc

7-Methyl-3,9-dihydro-2H-cyclopenta[b]chromen-1-one (38dd): Purified by column chromatography using EtOAc/hexane and isolated as a color less solid. Mp 168 °C; IR (neat): ν_{max} 2920, 2852, 1658 (C=O), 1587, 1560, 1494, 1438, 1392, 1258, 1192, 811 and 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.01 – 6.98 (2H, br m), 6.93 (1H, d, *J* = 8.4 Hz) [Ar-H]; 3.47 (2H, s, CH_2Ar), 2.71 (2H, m, CH_2), 2.54 (2H, m, CH_2), 2.30 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.6 (C, *C*=O), 179.5 (C, O-*C*=C), 148.8 (C), 134.8 (C), 130.8 (CH), 128.6 (CH), 119.2 (C), 116.9 (CH), 114.1 (C), 33.3 (CH_2), 25.8 (CH_2), 20.8 (CH_2), 20.6 (CH_3); LRMS m/z 201.00 (M + H^+), calcd for $C_{13}H_{12}O_2$ 200.0837; Anal. calcd for $C_{13}H_{12}O_2$ (200.0837): C, 77.98; H, 6.04. Found: C, 78.013; H, 6.020%.



38dd

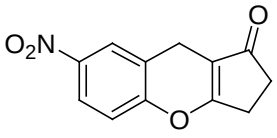
7-Methoxy-3,9-dihydro-2H-cyclopenta[b]chromen-1-one (38de): Purified by column chromatography using EtOAc/hexane and isolated as a yellowish solid. Mp 174 °C; IR (neat): ν_{max} 2923, 2851, 1656 (C=O), 1651, 1494, 1444, 1396, 1239, 1182, 1030, 813 and 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.98 (1H, d, *J* = 8.8 Hz), 6.75 (1H, dd, *J* = 8.8, 2.8 Hz),



38de

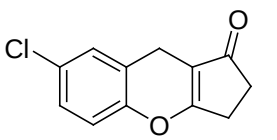
6.67 (1H, d, *J* = 2.4 Hz) [Ar-H]; 3.79 (3H, s, OC*H*$_3$), 3.49 (2H, s, C*H*$_2$Ar), 2.72–2.70 (2H, m, C*H*$_2$), 2.54–2.52 (2H, m, C*H*$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.5 (C, *C*=O), 179.5 (C, O-*C*=C), 156.7 (C), 144.9 (C), 120.5 (C), 118.0 (CH), 114.5 (CH), 113.8 (CH), 113.5 (C), 55.7 (CH_3, O*C*H$_3$), 33.4 (CH_2), 25.8 (CH_2), 21.2 (CH_2); LRMS m/z 217.00 (M + H$^+$), calcd for $C_{13}H_{12}O_3H$ 217.0786; Anal. calcd for $C_{13}H_{12}O_3$ (216.0786): C, 72.21; H, 5.59. Found: C, 72.208; H, 5.566%.

7-Nitro-3,9-dihydro-2H-cyclopenta[b]chromen-1-one (38df): Purified by column chromatography using EtOAc/hexane and isolated as a light yellowish solid. Mp 160 °C; IR (neat): ν_{max} 2924, 2853, 1657 (C=O), 1522, 1437, 1389, 1342, 1236, 1168, 1084, 921, 839, 748 and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.12 (1H, br s), 8.10 (1H, dd, *J* = 8.8, 2.8 Hz), 7.20 (1H, d, *J* = 9.2 Hz) [Ar-H]; 3.62 (2H, s, C*H*$_2$Ar), 2.80–2.77 (2H, m, C*H*$_2$), 2.62–2.58 (2H, m, C*H*$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 202.7 (C, *C*=O), 178.3 (C, O-*C*=C), 155.1 (C), 144.6 (C), 126.3 (CH), 123.99 (CH), 121.2 (C), 118.2 (CH), 114.2 (C), 33.5 (CH_2), 25.6 (CH_2), 21.1 (CH_2); LRMS m/z 232.00 (M + H$^+$), calcd for $C_{12}H_9NO_4$ 231.0532; Anal. calcd for $C_{12}H_9NO_4$ (231.0532): C, 62.34; H, 3.92; N, 6.06. Found: C, 62.346; H, 3.920; N, 6.068%.



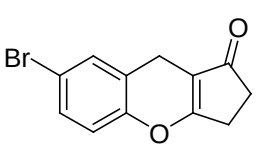
38df

7-Chloro-3,9-dihydro-2H-cyclopenta[b]chromen-1-one (38dg): Purified by column chromatography using EtOAc/hexane and isolated as a color less solid. Mp 162 °C; IR (neat): ν_{max} 2959, 2930, 1661 (C=O), 1480, 1446, 1387, 1247, 1165, 1121, 818, 785 and 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.16 (2H, br s), 6.99 (1H, d, *J* = 9.2 Hz) [Ar-H]; 3.49 (2H, s, C*H*$_2$Ar), 2.72 (2H, br s, C*H*$_2$), 2.55 (2H, br d, *J* = 2.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.1 (C, *C*=O), 179.0 (C, O-*C*=C), 149.4 (C), 130.1 (CH), 130.1 (C), 128.1 (CH), 121.4 (C), 118.5 (CH), 113.8 (C), 33.4 (CH_2), 25.7 (CH_2), 20.9 (CH_2); LRMS m/z 221.00 (M + H$^+$), calcd for $C_{12}H_9ClO_2$ 220.0291; Anal. calcd for $C_{12}H_9ClO_2$ (220.0291): C, 65.32; H, 4.11. Found: C, 65.364; H, 4.132%.



38dg

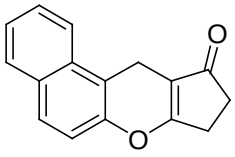
7-Bromo-3,9-dihydro-2H-cyclopenta[b]chromen-1-one (38dh): Purified by column chromatography using EtOAc/hexane and isolated as a color less solid. Mp 172 °C; IR (neat): ν_{max} 2925, 1656 (C=O), 1476, 1439, 1411, 1385, 1252, 1163, 1119, 815 and 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32–7.31 (2H, m), 6.93 (1H, d, *J* = 9.6 Hz) [Ar-H]; 3.50 (2H, s, C*H*$_2$Ar), 2.74–



38dh

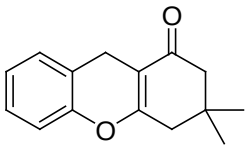
2.71 (2H, m, CH_2), 2.56–2.53 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.1 (C, *C*=O), 178.9 (C, O-*C*=C), 150.0 (C), 133.1 (CH), 131.1 (CH), 121.9 (C), 118.9 (CH), 117.6 (C), 113.9 (C), 33.4 (CH_2), 25.7 (CH_2), 20.8 (CH_2); LRMS m/z 265.00 (M + H^+), calcd for $C_{12}H_9BrO_2H$ 264.9786; Anal. calcd for $C_{12}H_9BrO_2$ (263.9786): C, 54.37; H, 3.42. Found: C, 54.402; H, 3.418%.

8,11-Dihydro-9H-7-oxa-cyclopenta[b]phenanthren-10-one (38di): Purified by column chromatography using EtOAc/hexane and isolated as a color less solid. Mp 244 °C; IR (neat): ν_{max} 2927, 1658 (C=O), 1594, 1440, 1397, 1242, 1209, 1165, 810, 766 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.84 (2H, br d, *J* = 8.4 Hz), 7.76 (1H, d, *J* = 8.8 Hz), 7.60 (1H, t, *J* = 7.2 Hz), 7.50 (1H, t, *J* = 7.2 Hz), 7.25 (1H, d, *J* = 9.2 Hz) [Ar-H]; 3.79 (2H, s, CH_2Ar), 2.79–2.78 (2H, m, CH_2), 2.61–2.59 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.8 (C, *C*=O), 178.9 (C, O-*C*=C), 148.1 (C), 132.3 (C), 131.1 (C), 128.8 (CH), 128.3 (CH), 127.2 (CH), 125.3 (CH), 123.1 (CH), 117.5 (CH), 114.4 (C), 112.8 (C), 32.5 (CH_2), 25.8 (CH_2), 18.8 (CH_2); LRMS m/z 237.00 (M + H^+), calcd for $C_{16}H_{12}O_2H$ 237.0837; Anal. calcd for $C_{16}H_{12}O_2$ (236.0837): C, 81.34; H, 5.12. Found: C, 81.502; H, 5.145%.



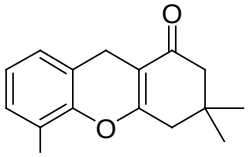
38di

3,3-Dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (38ga): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 80 °C; IR (neat): ν_{max} 2957, 2931, 1632 (C=O), 1578, 1491, 1462, 1389, 1239, 1230, 1180, 1147, 1121, 1016, 765 and 658 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.16 (1H, t, *J* = 8.0 Hz), 7.15 (1H, d, *J* = 8.0 Hz), 7.05 (1H, t, *J* = 6.8 Hz), 6.95 (1H, d, *J* = 8.0 Hz) [Ar-H]; 3.52 (2H, s, CH_2Ar), 2.43 (2H, s, CH_2), 2.32 (2H, s, CH_2), 1.12 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.9 (C, *C*=O), 165.1 (C, O-*C*=C), 149.9 (C), 129.7 (CH), 127.6 (CH), 124.6 (CH), 120.8 (C), 116.4 (CH), 108.8 (C), 50.6 (CH_2), 41.5 (CH_2), 32.1 (C), 28.4 (2 x CH_3), 21.0 (CH_2); LRMS m/z 229.00 (M + H^+), calcd for $C_{15}H_{16}O_2$ 228.1150; Anal. calcd for $C_{15}H_{16}O_2$ (228.1150): C, 78.92; H, 7.06. Found: C, 78.975; H, 7.072%.



38ga

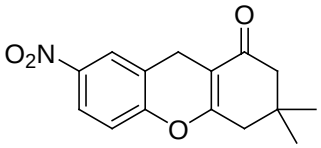
5-Hydroxy-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (38gb): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 194 °C. IR (neat): ν_{max} 3348 (O-H), 3120, 2960, 2892, 1612 (C=O), 1577, 1474, 1398, 1226, 1123, 1059, 764 and 654 cm^{-1}; ^{1}H NMR



38gb

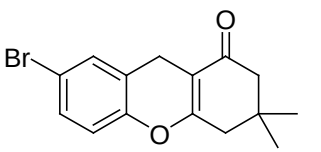
($CDCl_3$) δ 6.95 (1H, t, *J* = 7.6 Hz), 6.81 (1H, br d, *J* = 7.2 Hz), 6.70 (1H, d, *J* = 7.6 Hz) [Ar-H]; 5.42 (1H, s, O-*H*), 3.51 (2H, s, CH_2Ar), 2.48 (2H, s, CH_2), 2.34 (2H, s, CH_2), 1.14 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.8 (C, *C*=O), 163.9 (C, O-*C*=C), 143.9 (C), 137.7 (C), 124.8 (CH), 121.3 (C), 120.7 (CH), 114.0 (CH), 109.4 (C), 50.6 (CH_2), 41.4 (CH_2), 32.2 (C), 28.4 (2 x CH_3), 20.9 (CH_2); LRMS m/z 245.00 (M + H^+), calcd for $C_{15}H_{16}O_3H$ 245.1099; Anal. calcd for $C_{15}H_{16}O_3$ (244.1099): C, 73.75; H, 6.60. Found: C, 73.733; H, 6.602%.

3,3-Dimethyl-7-nitro-2,3,4,9-tetrahydro-xanthen-1-one (38gf): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 116 °C; IR (neat): ν_{max} 2958, 1655, 1649 (C=O), 1583, 1523, 1340, 1234, 1188, 1084, 1023 and 747 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08-8.05 (2H, m), 7.08 (1H, d, *J* = 8.0 Hz) [Ar-H]; 3.60 (2H, s, CH_2Ar), 2.47 (2H, s, CH_2), 2.35 (2H, s, CH_2), 1.15 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.4 (C, *C*=O), 164.2 (C, O-*C*=C), 154.4 (C), 144.2 (C), 125.6 (CH), 123.6 (CH), 122.2 (C), 117.4 (CH), 108.6 (C), 50.5 (CH_2), 41.1 (CH_2), 32.2 (C), 28.4 (2 x CH_3), 21.2 (CH_2); LRMS m/z 274.10 (M + H^+), calcd for $C_{15}H_{15}NO_4$ 273.1001; Anal. calcd for $C_{15}H_{15}NO_4$ (273.1001): C, 65.92; H, 5.53; N, 5.13. Found: C, 65.970; H, 5.525; N, 5.151%.

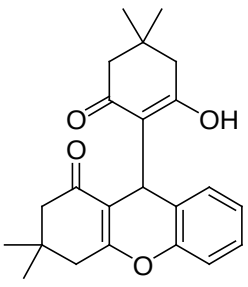


38gf

7-Bromo-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (38gh): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 118 °C; IR (neat): ν_{max} 2956, 1641 (C=O), 1479, 1415, 1385, 1239, 1180 and 814 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28-7.26 (2H, m), 6.84 (1H, d, *J* = 8.4 Hz) [Ar-H]; 3.49 (2H, s, CH_2Ar), 2.42 (2H, s, CH_2), 2.32 (2H, s, CH_2), 1.12 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 164.8 (C, O-*C*=C), 149.0 (C), 132.3 (CH), 130.6 (CH), 123.1 (C), 118.2 (CH), 116.9 (C), 108.4 (C), 50.6 (CH_2), 41.4 (CH_2), 32.1 (C), 28.4 (2 x CH_3), 21.0 (CH_2); LRMS m/z 307.00 (M + H^+), calcd for $C_{15}H_{15}BrO_2$ 306.0255; Anal. calcd for $C_{15}H_{15}BrO_2$ (306.0255): C, 58.65; H, 4.92. Found: C, 58.641; H, 4.964%.



38gh

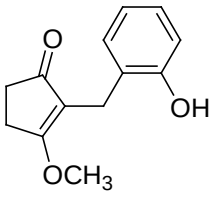


45ga

9-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (45ga): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 206 °C; IR (Neat): ν_{max} 3190 (O-*H*), 2956, 1641 (C=O), 1590, 1376, 1313, 1261, 1231, 1188, 1027 and 756 cm^{-1}; ^{1}H NMR

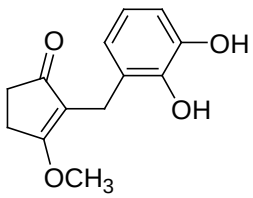
($CDCl_3$) δ 10.47 (1H, s, O-*H*), 7.20-7.13 (1H, m), 7.03-6.99 (3H, m) [Ar-H]; 4.66 (1H, s, C*H*), 2.54 (2H, ABq, *J* = 16.0 Hz), 2.40-2.20 (4H, m), 1.97 (2H, ABq, *J* = 16.0 Hz), 1.12 (3H, s, CH_3), 1.03 (3H, s, CH_3), 0.99 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 200.9 (C, C=O), 196.5 (C, C=O), 170.6 (C, O-C=C), 169.2 (C, O-C=C), 151.1 (C), 128.0 (CH), 127.5 (CH), 124.6 (CH), 124.3 (C), 118.3 (C), 115.7 (CH), 111.1 (C), 50.6 (CH_2), 49.9 (CH_2), 43.2 (CH_2), 41.2 (CH_2), 32.3 (C), 30.9 (C), 29.8 (CH), 29.2 (CH_3), 27.8 (CH_3), 27.2 (CH_3), 26.4 (CH_3); LRMS m/z 367.00 (M + H^+), calcd for $C_{23}H_{26}O_4$ 366.1831; Anal. calcd for $C_{23}H_{26}O_4$ (366.1831): C, 75.38; H, 7.15. Found: C, 75.466; H, 7.143%.

2-(2-Hydroxy-benzyl)-3-methoxy-cyclopent-2-enone (44da): Purified by column chromatography using EtOAc/hexane and isolated as a color less solid. Mp 104 °C; IR (neat): ν_{max} 3071, 2953, 2737, 1584 (C=O), 1459, 1453, 1374, 1269, 1238, 1105, 824 and 749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.93 (1H, s, O-*H*), 7.14–7.08 (2H, m), 6.92 (1H, d, *J* = 8.0 Hz), 6.79 (1H, t, *J* = 7.6 Hz) [Ar-H]; 4.02 (3H, s, OCH_3), 3.40 (2H, s, CH_2Ar), 2.71 (2H, m, CH_2), 2.49 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.6 (C, *C*=O), 186.6 (C, O-*C*=C), 155.3 (C), 130.5 (CH), 128.1 (CH), 126.1 (C), 120.7 (C), 120.0 (CH), 118.1 (CH), 57.0 (CH_3, O*C*H_3), 32.7 (CH_2), 25.2 (CH_2), 22.6 (CH_2); LRMS m/z 219.00 (M + H^+), calcd for $C_{13}H_{14}O_3$ 218.0943; Anal. calcd for $C_{13}H_{14}O_3$ (218.0943): C, 71.54; H, 6.47. Found: C, 71.541; H, 6.465%.



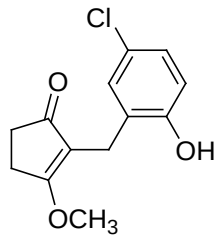
44da

2-(2,3-Dihydroxy-benzyl)-3-methoxy-cyclopent-2-enone (44db): Purified by column chromatography using EtOAc/hexane and isolated as a color less solid. Mp 142 °C; IR (neat): ν_{max} 3381, 2925, 1590 (C=O), 1476, 1369, 1261, 1189, 1087 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.64 (1H, s, O-*H*), 6.77 (1H, br d, *J* = 8.0 Hz), 6.70 (1H, t, *J* = 8.0 Hz), 6.64 (1H, br d, *J* = 8.0 Hz) [Ar-H]; 6.0 (1H, br s, O-*H*), 4.03 (3H, s, OCH_3), 3.39 (2H, s, CH_2Ar), 2.72 (2H, m, CH_2), 2.49 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (C, *C*=O), 187.2 (C, O-*C*=C), 146.8 (C), 142.0 (C), 126.7 (C), 121.1 (CH), 120.9 (C), 120.6 (CH), 112.8 (CH), 57.1 (CH_3, O*C*H_3), 32.6 (CH_2), 25.3 (CH_2), 22.4 (CH_2); LRMS m/z 235.00 (M + H^+), calcd for $C_{13}H_{14}O_4$ 234.0892; Anal. calcd for $C_{13}H_{14}O_4$ (234.0892): C, 66.66; H, 6.02. Found: C, 66.659; H, 6.020%.



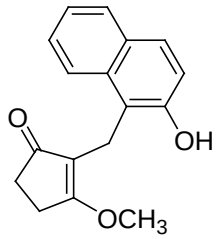
44db

2-(5-Chloro-2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone (44dg): Purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp 98 °C; IR (neat): ν_{max} 2923, 1610 (C=O), 1575, 1483, 1432, 1369, 1264, 1239, 1170, 1114, 817 and 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.10 (1H, s, O-*H*), 7.07 (1H, d, *J* = 2.4 Hz), 7.03 (1H, dd, *J* = 8.4, 2.4 Hz), 6.83 (1H, d, *J* = 8.8 Hz) [Ar-H]; 4.05 (3H, s, O*C*H_3), 3.34 (2H, s, CH_2Ar), 2.74 (2H, m, CH_2), 2.49 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.6 (C, *C*=O), 187.1 (C, O-*C*=C), 154.0 (C), 129.9 (CH), 127.8 (C), 127.7 (CH), 124.4 (C), 119.9 (C), 119.5 (CH), 57.2 (CH_3, O*C*H_3), 32.6 (CH_2), 25.2 (CH_2), 22.4 (CH_2); LRMS m/z 253.00 (M + H^+), calcd for $C_{13}H_{13}ClO_3$ 252.0553; Anal. calcd for $C_{13}H_{13}ClO_3$ (252.0553): C, 61.79; H, 5.19. Found: C, 61.814; H, 5.198%.



44dg

2-(2-Hydroxy-naphthalen-1-ylmethyl)-3-methoxy-cyclopent-2-enone (44di): Purified by column chromatography using EtOAc/hexane and isolated as a light yellowish solid. Mp 154 °C; IR (neat): ν_{max} 2954, 2952, 1602 (C=O), 1588, 1466, 1400, 1368, 1262, 1239, 1091, 829 and 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.85 (1H, s, O-*H*), 8.21 (1H, d, *J* = 8.8 Hz), 7.72 (1H, d, *J* = 8.0 Hz), 7.62 (1H, d, *J* = 8.8 Hz), 7.44 (1H, dt, *J* = 6.8, 0.8 Hz), 7.28 (1H, t, *J* = 8.0 Hz), 7.22 (1H, d, *J* = 8.8 Hz) [Ar-H]; 4.06 (3H, s, O*C*H_3), 3.81 (2H, s, CH_2Ar), 2.66 (2H, m, CH_2), 2.41 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (C, *C*=O), 186.0 (C, O-*C*=C), 153.4 (C), 133.2 (C), 129.3 (C), 128.4 (CH), 128.2 (CH), 125.8 (CH), 123.2 (CH), 122.7 (CH), 121.0 (CH), 120.6 (C), 118.4 (C), 57.0 (CH_3, O*C*H_3), 32.6 (CH_2), 25.1 (CH_2), 17.9 (CH_2); LRMS m/z 269.00 (M + H^+), calcd for $C_{17}H_{16}O_3$ 268.1099; Anal. calcd for $C_{17}H_{16}O_3$ (268.1099): C, 76.10; H, 6.01. Found: C, 76.169; H, 6.057%.



44di

2a: L-Proline-Catalyzed Cascade *TCRA* Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the chiral aldehyde **51**, 0.3 mmol of CH-acid **3a-p** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst amino acid **4** (0.03 mmol, 10 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 8, 9 and 10. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up, and pure cascade TCRA products **52** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2b: L-Proline-Catalyzed Sequential *TCRA*/A/K/E Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the chiral aldehyde **51**, 0.3 mmol of Meldrum's acid **3a** or barbituric acid **3i** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst amino acid **4** (0.03 mmol, 10-mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 11. To the crude reaction mixture added 15 equivalents of an ethereal solution of diazomethane followed by methanol (1.0 mL) and the reaction mixture was stirred at room temperature for the time indicated in Table 11. After evaporation of the solvent and excess diazomethane completely in fume hood, the crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure one-pot MCC products **54** and **55** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

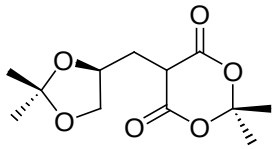
2c: Brønsted Acid-Catalyzed Cascade H/L/E and H/OM/DH Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.1 mmol of the chiral TCRA product **52aa-al** was added 1.0 mL of solvent, and then the catalyst *p*-TSA (0.03 mmol, 30 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 12. The crude reaction mixture washed with water and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure cascade H/L/E and H/OM/DH products **57-59** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2d: L-Proline-HMPT-Catalyzed Sequential *TCRA*/A/K/E/A Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the chiral aldehyde **51**, 0.3 mmol of Meldrum's acid **3a** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of CH_3CN, and then the catalyst amino acid **4** (0.03 mmol, 10-mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 13. To the crude reaction mixture added 15 equivalents of an ethereal solution of diazomethane followed by methanol (1.0 mL) and the reaction mixture was stirred at room temperature for the time indicated in Table 13. After evaporation of the solvent and excess diazomethane completely in fume hood, to the crude reaction mixture was added 3 equivalents of active olefins/acetylenes **22a-22e**, hexamethylphosphorous triamide (HMPT, 10-mol%) and CH_3CN (1.0 mL) and stirred at 25 °C for 0.5 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure

one-pot chiral MCC products **63** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2e: L-Proline-L-Proline-Catalyzed Sequential Double Cascade *TCRA*/Robinson Annulation Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **51**, 0.3 mmol of CH-acids **3d/e** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of CH_3CN, and then the catalyst amino acid **4** (0.03 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 14. After evaporation of the solvent completely, to the crude reaction mixture added 0.9 mmol of methyl vinyl ketone (**22a**), 1.0 mL of DMSO solvent and 0.09 mmol of L-proline **4c** 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 dichloromethane (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure one-pot MCC products **64**, **65** and **66** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

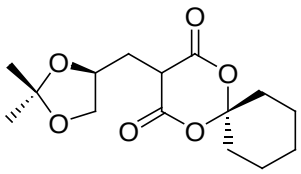
5-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione



52aa

(52aa): Purified by column chromatography using EtOAc/hexane and isolated as white solid. mp.: 112 °C; **$[\alpha]^{25}_D$ = –24.0 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2989, 1789, 1743 (O-C=O), 1366, 1325, 1301, 1059, 935 and 848 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.51-4.47 (1H, m), 4.12 (1H, dd, *J* = 8.0, 6.4 Hz), 3.80 (1H, dd, *J* = 8.8, 2.4 Hz), 3.66 (1H, dd, *J* = 8.4, 6.0 Hz), 2.43 (1H, ddd, *J* = 14.0, 10.4, 2.4 Hz), 2.15 (1H, ddd, *J* = 12.0, 8.8, 3.2 Hz), 1.83 (3H, s, CH_3), 1.76 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.33 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.6 (C, O=C-O), 165.5 (C, O=C-O), 109.4 (C, O-C-O), 105.1 (C, O-C-O), 72.7 (CH, O*C*H), 69.3 (CH_2, O*C*H_2), 42.9 (CH), 30.7 (CH_2), 28.5 (CH_3), 26.9 (CH_3), 26.6 (CH_3), 25.5 (CH_3); LRMS m/z 259.00 ($M+H^+$), calcd $C_{12}H_{18}O_6$ 258.1103; Anal. calcd for $C_{12}H_{18}O_6$ (258.1103): C, 55.81; H, 7.02. Found: C, 55.76; H, 7.06%.

3-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-1,5-dioxaspiro[5.5]undecane-2,4-dione

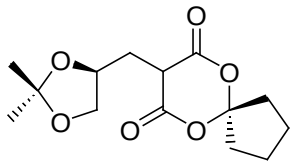


52ac

(52ac): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 102 °C; **$[\alpha]^{25}_D$ = –26.0 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2986, 1783, 1741 (O-C=O), 1360, 1275, 1132, 1047, 991 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.54-4.48 (1H, m), 4.13 (1H,

dd, *J* = 8.0, 6.0 Hz), 3.83 (1H, dd, *J* = 8.8, 2.4 Hz), 3.67 (1H, dd, *J* = 8.0, 5.6 Hz), 2.44 (1H, ddd, *J* = 12.8, 10.4, 2.4 Hz), 2.15 (1H, ddd, *J* = 12.0, 8.8, 3.2 Hz), 2.06 (2H, t, *J* = 5.6 Hz), 1.97 (2H, t, *J* = 5.6 Hz), 1.78 (2H, quintet, *J* = 6.4 Hz), 1.70 (2H, quintet, *J* = 6.0 Hz), 1.55-1.52 (2H, m), 1.42 (3H, s, CH_3), 1.34 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.7 (C, O=C-O), 165.6 (C, O=C-O), 109.4 (C, O-C-O), 106.0 (C, O-C-O), 72.8 (CH, O*C*H), 69.4 (CH_2, O*C*H_2), 43.2 (CH), 37.0 (CH_2), 35.6 (CH_2), 30.9 (CH_2), 27.0 (CH_3), 25.5 (CH_3), 24.1 (CH_2), 22.6 (CH_2), 21.8 (CH_2); LRMS m/z 297.00 (M-H^+), calcd $C_{15}H_{22}O_6$ 298.1416; Anal. calcd for $C_{15}H_{22}O_6$ (298.1416): C, 60.39; H, 7.43. Found: C, 60.45; H, 7.48%.

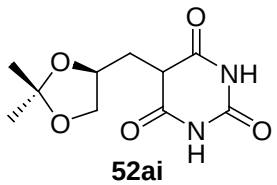
8-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-6,10-dioxaspiro[4.5]decane-7,9-dione



52ah

(52ah): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 108 °C; **$[\alpha]^{25}_D$ = –23.4 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2986, 2879, 1784, 1741 (O-C=O), 1350, 1257, 1063, 994, 844 and 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.51-4.47 (1H, m), 4.13 (1H, dd, *J* = 8.4, 6.0 Hz), 3.86 (1H, dd, *J* = 8.8, 2.4 Hz), 3.66 (1H, dd, *J* = 8.4, 5.6 Hz), 2.37 (1H, ddd, *J* = 12.8, 10.0, 2.4 Hz), 2.30-2.23 (4H, m), 2.14 (1H, ddd, *J* = 12.4, 9.2, 3.2 Hz), 1.93 (2H, quintet, *J* = 7.2 Hz), 1.86 (2H, quintet, *J* = 7.2 Hz), 1.40 (3H, s, CH_3), 1.34 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.97 (C, O=C-O), 165.95 (C, O=C-O), 114.3 (C, O-C-O), 109.3 (C, O-C-O), 72.7 (CH, O*C*H), 69.3 (CH_2, O*C*H_2), 44.2 (CH), 39.2 (CH_2), 38.0 (CH_2), 29.9 (CH_2), 27.1 (CH_3), 25.5 (CH_3), 24.4 (CH_2), 22.5 (CH_2); LRMS m/z 285.00 (M+H^+), calcd $C_{14}H_{20}O_6$ 284.1260; Anal. calcd for $C_{14}H_{20}O_6$ (284.1260): C, 59.14; H, 7.09. Found: C, 59.16; H, 7.10%.

5-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione

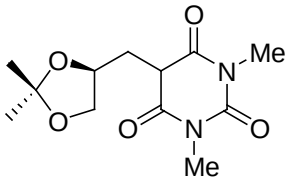


52ai

(52ai): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 88 °C; **$[\alpha]^{25}_D$ = –31.4 (*c* 0.45, EtOH)**; IR (neat): ν_{max} 3229 (N-H), 3008, 1719 (N-C=O), 1692, 1438, 1361, 1275, 1266 and 754 cm^{-1}; ^{1}H NMR (CD_3OD) δ 4.30-4.27 (1H, m), 4.07 (1H, dd, *J* = 8.4, 6.0 Hz), 3.61 (1H, dd, *J* = 8.4, 6.0 Hz), 2.37 (1H, dd, *J* = 14.0, 9.6 Hz), 2.26 (1H, dd, *J* = 14.0, 4.4 Hz), 1.34 (3H, s, CH_3), 1.26 (3H, s, CH_3); ^{13}C NMR (CD_3OD, DEPT-135) δ 171.0 (C), 170.5 (C), 151.1 (C), 109.2 (C, O-C-O), 72.9 (CH, O*C*H), 68.9 (CH_2, O*C*H_2), 47.6 (CH), 32.1 (CH_2), 25.3 (CH_3), 24.3 (CH_3); LRMS m/z 243.75 (M+H^+), calcd $C_{10}H_{14}N_2O_5$ 242.2286;

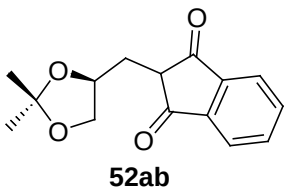
Anal. calcd for $C_{10}H_{14}N_2O_5$ (242.2286): C, 49.58; H, 5.83; N, 11.56. Found: C, 49.51; H, 5.79; N, 11.75%.

5-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (52aj): Purified by column chromatography using EtOAc/hexane and isolated as colorless oil. **$[\alpha]^{25}_D$ = –31.4 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 1686 (N-C=O), 1677, 1666, 1444, 1380, 1288, 1077 and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16-4.13 (1H, m), 4.04 (1H, dd, *J* = 8.4, 6.4 Hz), 3.59-3.55 (2H, m), 3.30 (3H, s, N-C*H*$_3$), 3.27 (3H, s, N-C*H*$_3$), 2.46 (1H, ddd, *J* = 13.2, 10.4, 3.2 Hz), 2.34 (1H, ddd, *J* = 10.8, 7.2, 4.0 Hz), 1.29 (3H, s, CH_3), 1.22 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.7 (C, N-C=O), 168.3 (C, N-C=O), 151.7 (C, N-C=O), 109.5 (C, O-C-O), 72.5 (CH, O*C*H), 69.2 (CH_2, O*C*H_2), 46.0 (CH), 34.4 (CH_2), 28.5 (CH_3, N-*C*H_3), 28.4 (CH_3, N-*C*H_3), 26.4 (CH_3), 25.3 (CH_3); LRMS m/z 269.00 ($M\text{-}H^+$), calcd $C_{12}H_{18}N_2O_5$ 270.1216; Anal. calcd for $C_{12}H_{18}N_2O_5$ (270.1216): C, 53.33; H, 6.71; N, 10.36. Found: C, 53.28; H, 6.77; N, 10.32%.



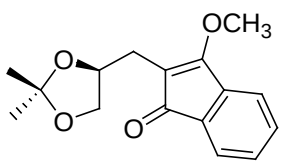
52aj

2-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-1*H*-indene-1,3(2*H*)-dione (52ab): Purified by column chromatography using EtOAc/hexane and isolated as yellow oil. **$[\alpha]^{25}_D$ = –41.5 (*c* 1.0, EtOH);** IR (neat): ν_{max} 2986, 2299, 1710 (C=O), 1598, 1275, 1266, 1063, 754 and 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95-7.92 (2H, m), 7.83-7.79 (2H, m) [Ar-*H*]; 4.41-4.38 (1H, m), 4.02 (1H, dd, *J* = 8.4, 6.0 Hz), 3.59 (1H, dd, *J* = 8.0, 6.0 Hz), 3.17 (1H, dd, *J* = 8.0, 4.0 Hz), 2.26 (1H, ddd, *J* = 14.0, 8.8, 6.4 Hz), 2.04 (1H, ddd, *J* = 12.8, 8.0, 4.8 Hz), 1.28 (3H, s, CH_3), 1.20 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 200.06 (C, C=O), 199.98 (C, C=O), 142.3 (C), 141.9 (C), 135.5 (CH), 135.3 (CH), 123.1 (2 x CH), 109.2 (C), 72.8 (CH, O*C*H), 69.2 (CH_2, O*C*H_2), 50.6 (CH), 30.5 (CH_2), 26.6 (CH_3), 25.4 (CH_3); LRMS m/z 259.00 ($M\text{-}H^+$), calcd $C_{15}H_{16}O_4$ 260.1049; Anal. calcd for $C_{15}H_{16}O_4$ (260.1049): C, 69.22; H, 6.20. Found: C, 69.24; H, 6.19%.



(–)-52ab

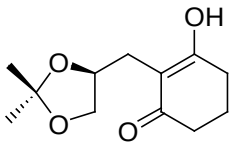
2-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-3-methoxy-1*H*-inden-1-one (53): Purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp: 78 °C; The enantiomeric excess (ee) was



(–)-53

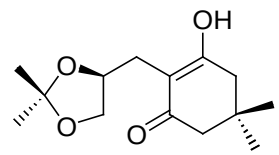
determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 10.98 min (minor), t_R = 12.39 min (major). **$[\alpha]^{25}_D$ = –10.0 (*c* 0.3, $CHCl_3$, >98% ee);** IR (neat): ν_{max} 2982, 1710 (C=O), 1692 (C=O), 1624, 1592, 1372, 1319, 1249, 1160, 1078, 1054, 976 and 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (1H, d, *J* = 7.2 Hz), 7.33 (1H, t, *J* = 7.2 Hz), 7.25 (1H, t, *J* = 8.0 Hz), 7.19 (1H, d, *J* = 7.2 Hz), 4.36 (3H, s, OCH_3), 4.24 (1H, quintet, *J* = 6.4 Hz), 4.06 (1H, dd, *J* = 8.0, 6.4 Hz), 3.61 (1H, t, *J* = 7.6 Hz), 2.75 (2H, dABq, *J* = 14.4, 5.2 Hz), 1.41 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.2 (C, C=O), 173.1 (C, C=*C*-O), 140.9 (C), 132.4 (CH), 131.8 (C), 129.4 (CH), 120.8 (CH), 118.6 (CH), 109.0 (C), 105.7 (C), 75.3 (CH, O*C*H), 68.9 (CH_2, O*C*H_2), 59.3 (CH_3, OCH_3), 26.6 (CH_3), 26.4 (CH_2), 25.4 (CH_3); LRMS m/z 275.15 ($M+H^+$), calcd $C_{16}H_{18}O_4$ 274.1205; Anal. calcd for $C_{16}H_{18}O_4$ (274.1205): C, 70.06; H, 6.61. Found: C, 70.15; H, 6.58%.

2-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}cyclohexane-1,3-dione (52ae): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 82 °C; **$[\alpha]^{25}_D$ = –41.0 (*c* 0.2, EtOH);** IR (neat): ν_{max} 3383 (O-H), 2950, 1723 (C=O), 1605 (C=O), 1398, 1258, 1189, 1130, 1091 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.26 (1H, s, O-*H*), 4.25-4.19 (1H, m), 4.03 (1H, dd, *J* = 8.4, 6.4 Hz), 3.50 (1H, t, *J* = 8.4 Hz), 2.84 (1H, dd, *J* = 15.2, 1.6 Hz), 2.51-2.46 (3H, m), 2.33 (2H, t, *J* = 6.0 Hz), 1.91 (2H, quintet, *J* = 6.4 Hz), 1.42 (3H, s, CH_3), 1.39 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.2 (C, C=O), 175.0 (C, C=*C*-O), 111.5 (C), 109.5 (C, O-*C*-O), 77.0 (CH, O*C*H), 68.1 (CH_2, O*C*H_2), 36.2 (CH_2), 29.2 (CH_2), 26.1 (CH_3), 25.2 (CH_3), 25.0 (CH_2), 20.4 (CH_2); LRMS m/z 227.00 ($M+H^+$), calcd $C_{12}H_{18}O_4$ 226.1205; Anal. calcd for $C_{12}H_{18}O_4$ (226.1205): C, 63.70; H, 8.02. Found: C, 63.65; H, 8.10%.



52ae

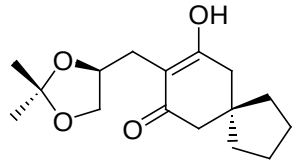
2-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-5,5-dimethylcyclohexane-1,3-dione (52ag): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 72 °C; **$[\alpha]^{25}_D$ = –4.0 (*c* 1.0, EtOH);** IR (neat): ν_{max} 2961, 1721 (C=O), 1605, 1398, 1275, 1266, 1222, 1169 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.21 (1H, s, O-*H*), 4.28-4.25 (1H, m), 4.06 (1H, dd, *J* = 8.4, 6.4 Hz), 3.52 (1H, t, *J* = 8.0 Hz), 2.87 (1H, d, *J* = 15.6 Hz), 2.56 (1H, dd, *J* = 15.6, 6.8 Hz), 2.36 (2H, ABq, *J* = 8.8 Hz), 2.25 (2H, s), 1.45 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ



52ag

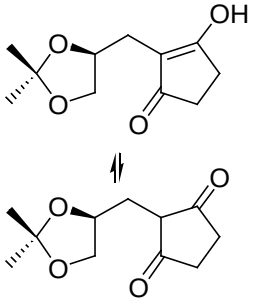
197.9 (C, C=O), 173.3 (C, C=*C*-O), 110.2 (C), 109.6 (C, O-*C*-O), 77.1 (CH, O*C*H), 68.1 (CH_2, O*C*H_2), 50.2 (CH_2), 43.0 (CH_2), 31.6 (C), 28.5 (CH_3), 28.0 (CH_3), 26.2 (CH_3), 25.3 (CH_3), 24.7 (CH_2); LRMS m/z 254.00 (M^+), calcd $C_{14}H_{22}O_4$ 254.1518; Anal. calcd for $C_{14}H_{22}O_4$ (254.1518): C, 66.12; H, 8.72. Found: C, 66.28; H, 8.69%.

8-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}spiro[4.5]decane-7,9-dione (52ak): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_D$ = +15.02 (*c* 0.4, EtOH);** IR (neat): ν_{max} 2954, 1724 (C=O), 1607, 1399, 1275, 1266, 1216 and 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.24 (1H, s, O-*H*), 4.27 (1H, dq, *J* = 8.8, 2.4 Hz), 4.05 (1H, dd, *J* = 8.4, 6.4 Hz), 3.51 (1H, t, *J* = 8.0 Hz), 2.87-2.83 (1H, m), 2.59-2.52 (1H, m), 2.46 (2H, ABq, *J* = 17.2 Hz), 2.35 (2H, s), 1.68-1.65 (4H, m), 1.51-1.50 (4H, m), 1.45 (3H, s, CH_3), 1.37 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.2 (C, C=O), 174.1 (C, C=*C*-O), 110.7 (C), 109.5 (C, O-*C*-O), 77.0 (CH, O*C*H), 68.0 (CH_2, O*C*H_2), 48.6 (CH_2), 42.4 (C), 41.7 (CH_2), 38.2 (CH_2), 37.9 (CH_2), 26.1 (CH_3), 25.3 (CH_3), 24.7 (CH_2), 24.1 (CH_2), 24.0 (CH_2); LRMS m/z 281.00 ($M+H^+$), calcd $C_{16}H_{24}O_4$ 280.1675; Anal. calcd for $C_{16}H_{24}O_4$ (280.1675): C, 68.54; H, 8.63. Found: C, 68.64; H, 8.59%.



52ak

3-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}spiro[5.5]undecane-2,4-dione (52al): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_D$ = +14.0 (*c* 0.5, EtOH);** IR (neat): ν_{max} 2985, 1723 (C=O), 1607, 1275, 1266, 1217, 1100 and 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.23 (1H, s, O-*H*), 4.30-4.24 (1H, m), 4.08-4.05 (1H, m), 3.52 (1H, br t, *J* = 8.0 Hz), 2.85 (1H, br d, *J* = 15.6 Hz), 2.55 (1H, br dd, *J* = 15.2, 6.8 Hz), 2.43 (2H, br s), 2.33 (2H, d, *J* = 3.6 Hz), 1.55-1.40 (10H, m), 1.45 (3H, s, CH_3), 1.38 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.8 (C, C=O), 173.0 (C, C=*C*-O), 110.2 (C), 109.6 (C, O-*C*-O), 77.1 (CH, O*C*H), 68.1 (CH_2, O*C*H_2), 48.1 (CH_2), 40.6 (CH_2), 36.9 (CH_2), 36.2 (CH_2), 34.3 (C), 26.17 (CH_2), 26.15 (CH_3), 25.3 (CH_3), 24.7 (CH_2), 21.6 (2 x CH_2); LRMS m/z 295.00 ($M+H^+$), calcd $C_{17}H_{26}O_4$ 294.1831; Anal. calcd for $C_{17}H_{26}O_4$ (294.1831): C, 69.36; H, 8.90. Found: C, 69.45; H, 8.86%.

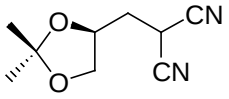


52ad

2-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}cyclopentane-1,3-dione (52ad): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 78 °C; **$[\alpha]^{25}_D$ = –32.0 (*c* 0.3, EtOH);** IR

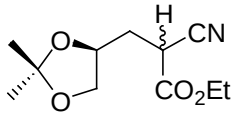
(neat): ν_{max} 2986, 2694, 1574, 1474, 1428, 1369, 1275, 1266, 1075 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25-4.20 (1H, m), 4.06 (1H, dd, *J* = 8.4, 6.4 Hz), 3.59 (1H, t, *J* = 7.6 Hz), 2.65 (1H, dd, *J* = 15.6, 2.0 Hz), 2.49 (4H, br s), 2.24 (1H, dd, *J* = 15.6, 8.4 Hz), 1.47 (3H, s, CH_3), 1.37 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 113.5 (C), 110.0 (C), 76.1 (CH, O*C*H), 68.8 (CH_2, O*C*H_2), 26.5 (CH_3), 25.4 (CH_3), 25.3 (CH_2); LRMS m/z 213.00 ($M+H^+$), calcd $C_{11}H_{16}O_4$ 212.1049; Anal. calcd for $C_{11}H_{16}O_4$ (212.1049): C, 62.25; H, 7.60. Found: C, 62.33; H, 7.58%. *[Due to the keto-enol and enol-enol tautomerism in **52ad**, ^{13}C NMR shows some of carbons (2 x CH_2 and 2 x C=O) are poor resolution even after more than 2000 scans in the solvent system of $CDCl_3$ or $CDCl_3$ + CD_3OD (three drops)]*.

2-([4*S*]-2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-malononitrile (52am): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –46.7 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2989, 2911, 2259 (C≡N), 1378, 1218, 1153, 1071, 884 and 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.29-4.26 (1H, m), 4.14 (1H, dd, *J* = 8.4, 6.4 Hz), 4.01 (1H, dd, *J* = 10.4, 4.4 Hz), 3.67 (1H, dd, *J* = 8.4, 5.2 Hz), 2.24 (1H, dt, *J* = 13.6, 2.8 Hz), 2.13 (1H, dt, *J* = 10.4, 4.8 Hz), 1.41 (3H, s, CH_3), 1.33 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 112.6 (C, *C*N), 112.1 (C, *C*N), 110.2 (C, O-*C*-O), 71.3 (CH, O*C*H), 68.1 (CH_2, O*C*H_2), 35.3 (CH_2), 26.8 (CH), 25.0 (CH_3), 19.6 (CH_3); LRMS m/z 179.00 ($M-H^+$), calcd $C_9H_{12}N_2O_2$ 180.0899; Anal. calcd for $C_9H_{12}N_2O_2$ (180.0899): C, 59.99; H, 6.71; N, 15.55. Found: C, 60.10; H, 6.68; N, 15.61%.



52am

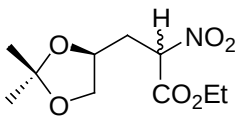
2-Cyano-3-([4*S*]-2,2-dimethyl-[1,3]dioxolan-4-yl)-propionic acid ethyl ester (52an): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –17.7 (*c* 1.0, EtOH);** IR (neat): ν_{max} 2987, 2938, 1747 (O-C=O), 1375, 1263, 1216, 1156, 1069, 754 and 635 cm^{-1}; ^1H NMR ($CDCl_3$, **1:1 mixture of isomers**) δ 4.44-4.26 (6H, m), 4.16 (1H, dd, *J* = 8.4, 6.0 Hz), 4.12 (1H, dd, *J* = 8.4, 6.0 Hz), 3.79 (1H, dd, *J* = 8.8, 4.4 Hz), 3.72 (1H, dd, *J* = 8.0, 5.2 Hz), 3.67 (1H, dd, *J* = 6.0, 3.2 Hz), 3.65 (1H, dd, *J* = 5.6, 2.8 Hz), 2.57-2.05 (4H, m), 1.43 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.35 (6H, t, *J* = 8.0 Hz, 2 x OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **1:1 mixture of isomers**) δ 165.9 (O-C=O), 165.6 (O-C=O), 116.4 (C, CN), 116.1 (C, CN), 109.8 (2 x C, O-*C*-O), 72.5 (CH, OCH), 72.3 (CH, OCH), 68.73 (CH_2, OCH_2), 68.68 (CH_2, OCH_2), 63.0 (CH_2, O*C*H_2CH_3), 62.95 (CH_2, O*C*H_2CH_3), 34.7 (CH), 34.2 (CH_2), 34.0 (CH_2), 33.9 (CH), 27.0 (CH_3), 26.8 (CH_3), 25.32



52an

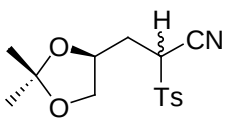
(CH_3), 25.31 (CH_3), 13.93 (CH_3, OCH_2CH_3), 13.90 (CH_3, OCH_2CH_3); LRMS m/z 226.05 ($M-H^+$), calcd $C_{11}H_{17}NO_4$ 227.1158; Anal. calcd for $C_{11}H_{17}NO_4$ (227.1158): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.22; H, 7.51; N, 6.25%.

3-([4*S*]-2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-nitro-propionic acid ethyl ester (52ao): Purified by column chromatography using EtOAc/hexane and isolated as colorless oil. **$[\alpha]^{25}_D$ = –10.5 (*c* 0.4, EtOH);** IR (neat): ν_{max} 2987, 1753 (O-C=O), 1565 (O-N=O), 1374 (O-N=O), 1264, 1214, 1064, 862 and 754 cm^{-1}; ^1H NMR ($CDCl_3$, **1:1 ratio of isomers**) δ 5.40 (1H, dd, *J* = 10.8, 2.0 Hz), 5.29 (1H, t, *J* = 6.8 Hz), 4.45-4.20 (5H, m), 4.13-4.09 (3H, m), 3.67-3.63 (2H, m), 2.56 (1H, dt, *J* = 10.8, 2.0 Hz), 2.50-2.40 (2H, m), 2.27 (1H, ddd, *J* = 12.4, 9.2, 3.2 Hz), 1.42 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.32 (6H, t, *J* = 7.2 Hz, 2 x OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **1:1 ratio of isomers**) δ 164.7 (O-C=O), 164.2 (O-C=O), 109.93 (C, O-C-O), 109.90 (C, O-C-O), 85.11 (CH), 85.05 (CH), 72.1 (CH, OCH), 71.4 (CH, OCH), 68.85 (CH_2, OCH_2), 68.81 (CH_2, OCH_2), 63.21 (CH_2, OCH_2CH_3), 63.17 (CH_2, OCH_2CH_3), 34.71 (CH_2), 34.6 (CH_2), 26.9 (CH_3), 26.7 (CH_3), 25.3 (CH_3), 25.2 (CH_3), 13.8 (2 x CH_3, 2 x OCH_2CH_3); LRMS m/z 248.00 ($M+H^+$), calcld $C_{10}H_{17}NO_6$ 247.1056; Anal. calcd for $C_{10}H_{17}NO_6$ (247.1056): C, 48.58; H, 6.93; N, 5.67. Found: C, 48.61; H, 6.91; N, 5.71%.

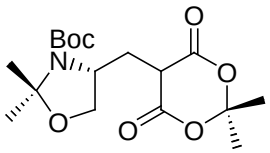


52ao

3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-[(4-methylphenyl)sulfonyl]propanenitrile (52ap): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –26.2 (*c* 0.6, $CHCl_3$);** IR (neat): ν_{max} 2987, 2928, 1596, 1378, 1332, 1214, 1153, 1076, 819 and 668 cm^{-1}; ^1H NMR ($CDCl_3$, **2:1 ratio of isomers, major isomer**) δ 7.91 (2H, d, *J* = 8.4 Hz), 7.45 (2H, d, *J* = 8.0 Hz) [Ar-*H*]; 4.22 (1H, dd, *J* = 12.0, 3.2 Hz), 4.14 (2H, dd, *J* = 8.0, 6.0 Hz), 3.69 (1H, dd, *J* = 8.4, 5.2 Hz), 2.49 (3H, s, Ar-CH_3), 2.35 (1H, dt, *J* = 13.2, 3.2 Hz), 2.06 (1H, dt, *J* = 14.8, 2.8 Hz), 1.42 (3H, s, CH_3), 1.33 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **2:1 ratio of isomers, major isomer**) δ 146.7 (C), 132.4 (C), 130.2 (2 x CH), 129.6 (2 x CH), 113.7 (C, CN), 110.1 (C, O-C-O), 71.7 (CH, OCH), 68.6 (CH_2, OCH_2), 54.8 (CH), 31.5 (CH_2), 26.9 (CH_3), 25.2 (CH_3), 21.7 (CH_3); LRMS m/z 310.20 ($M+H^+$), calcd $C_{15}H_{19}NO_4S$ 309.1035; Anal. calcd for $C_{15}H_{19}NO_4S$ (309.1035): C, 58.23; H, 6.19; N, 4.53. Found: C, 58.16; H, 6.22; N, 4.61%.



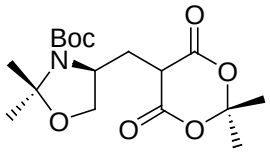
52ap



52ba

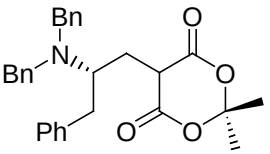
(4*R*)-4-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (52ba): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 148 °C; **$[\alpha]^{25}_{D}$ = –9.4 (*c* 0.7, EtOH);** IR (neat): ν_{max} 2980, 2933, 1746 (O-C=O), 1678, 1396, 1373, 1317, 1204, 1172, 1106, 1055, 959, 844 and 641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.35-4.32 (2H, m), 4.00 (1H, dd, J = 9.2, 6.0 Hz), 3.73 (1H, d, *J* = 8.0 Hz), 2.56-2.53 (1H, m), 2.16-2.13 (1H, m), 1.79 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.42 (9H, s, 3 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.5 (C, O-C=O), 165.4 (C, O-C=O), 153.9 (C, N-C=O), 104.8 (C, O-*C*-O), 94.0 (C, O-*C*-N), 80.5 (C, O*C*$(CH_3)_3$), 68.4 (CH_2, OCH_2), 55.2 (CH, N*C*H), 44.7 (CH), 31.0 (CH_2), 28.5 (CH_3), 28.3 (3 x CH_3), 27.4 (CH_3), 25.9 (CH_3), 24.2 (CH_3); LRMS m/z 359.00 ($M+H^+$), calcd $C_{17}H_{27}NO_7$, 357.1788; Anal. calcd for $C_{17}H_{27}NO_7$ (357.1788): C, 57.13; H, 7.61; N, 3.92. Found: C, 57.26; H, 7.65; N, 3.98%.

(4*S*)-4-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (52ca): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 144 °C; **$[\alpha]^{25}_{D}$ = +9.2 (*c* 0.55, EtOH);** IR (neat): ν_{max} 2979, 1723 (O-C=O), 1694, 1394, 1370, 1252, 1170 and 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.39-4.32 (2H, m), 4.00 (1H, dd, *J* = 9.2, 5.6 Hz), 3.72 (1H, br d, *J* = 8.0 Hz), 2.59-2.54 (1H, m), 2.16-2.13 (1H, m), 1.78 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.42 (9H, s, 3 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.5 (C), 165.4 (C), 153.9 (C), 104.8 (C, O-C-O), 94.0 (C, O-C-N), 80.5 (C, O*C*$(CH_3)_3$), 68.4 (CH_2, OCH_2), 55.2 (CH, N*C*H), 44.7 (CH), 31.0 (CH_2), 28.5 (CH_3), 28.3 (3 x CH_3), 27.4 (CH_3), 25.9 (CH_3), 24.2 (CH_3); LRMS m/z 356.00 ($M-H^+$), calcd for $C_{17}H_{27}NO_7$ 357.1788; Anal. calcd for $C_{17}H_{27}NO_7$ (357.1788): C, 57.13; H, 7.61; N, 3.92. Found: C, 57.18; H, 7.65; N, 3.89%.



52ca

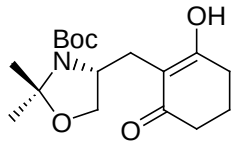
5-[(2*R*)-2-Dibenzylamino-3-phenyl-propyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (52da): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 86 °C; **$[\alpha]^{25}_{D}$ = +71.2 (*c* 0.35, EtOH);** IR (neat): ν_{max} 3489, 2929, 1720 (O-C=O), 1562, 1497, 1454, 1403, 1257, 1205, 1125, 750 and 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32-7.24 (15H, m) [Ar-*H*]; 4.16 (2H, d, *J* = 12.0 Hz), 4.20-4.10 (1H, m), 3.60 (2H, d, *J* = 12.0 Hz), 3.51 (1H, br s), 3.26



52da

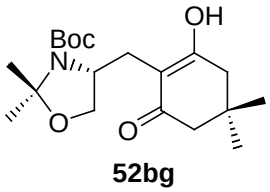
(1H, br d, *J* = 12.0 Hz), 2.73 (1H, br t, *J* = 12.0 Hz), 2.53 (1H, br t, *J* = 12.0 Hz), 2.38 (1H, br d, *J* = 12.0 Hz), 1.56 (3H, s, CH_3), 1.55 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.8 (2 x C, O-C=O), 137.9 (2 x C), 135.5 (C), 129.8 (4 x CH), 129.1 (2 x CH), 128.9 (6 x CH), 128.3 (2 x CH), 126.8 (CH), 103.3 (C, O-*C*-O), 61.1 (CH), 53.6 (2 x CH_2), 35.1 (CH_2), 26.7 (CH_2), 26.6 (2 x CH_3); LRMS m/z 458.40 ($M+H^+$), calcd for $C_{29}H_{31}NO_4$ 457.2253; Anal. calcd for $C_{29}H_{31}NO_4$ (457.2253): C, 76.12; H, 6.83; N, 3.06. Found: C, 76.25; H, 6.75; N, 3.12%.

(4*R*)-4-(2,6-Dioxo-cyclohexylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (52be): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 142 °C; **$[\alpha]^{25}_D$ = + 24.0 (*c* 0.55, EtOH);** IR (neat): ν_{max} 2983, 2876, 1693 (C=O), 1474, 1391, 1274, 1260, 1176, 1105, 854, 754 and 679 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.2 (1H, s, O-*H*), 3.98 (1H, d, *J* = 8.4 Hz), 3.87 (1H, t, *J* = 5.6 Hz), 3.74-3.50 (1H, m), 2.98 (1H, dd, *J* = 14.0, 9.6 Hz), 2.44 (2H, t, *J* = 5.6 Hz), 2.33-2.24 (3H, m), 1.91 (2H, q, *J* = 6.0 Hz), 1.53 (3H, s, CH_3), 1.48 (9H, s, 3 x CH_3), 1.39 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.0 (C, C=O), 174.8 (C, C=*C*-O), 153.9 (C, N-C=O), 112.5 (C), 93.2 (C, O-C-N), 81.8 (C, O*C*(CH_3)$_3$), 68.4 (CH_2, OCH_2), 58.9 (CH, NCH), 36.3 (CH_2), 29.0 (CH_2), 28.3 (3 x CH_3), 27.0 (CH_3), 26.5 (CH_2), 24.0 (CH_3), 20.7 (CH_2); LRMS m/z 326.25 ($M+H^+$), calcd for $C_{17}H_{27}NO_5$ 325.1889; Anal. calcd for $C_{17}H_{27}NO_5$ (325.1889): C, 62.79; H, 8.36; N, 4.30. Found: C, 62.65; H, 8.32; N, 4.35%.



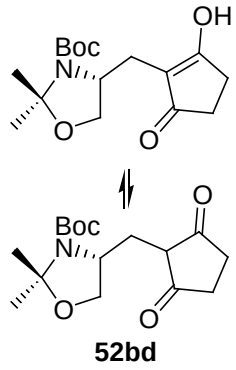
52be

(4*R*)-4-(4,4-Dimethyl-2,6-dioxo-cyclohexylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (52bg): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 128 °C; **$[\alpha]^{25}_D$ = +38.9 (*c* 0.55, EtOH);** IR (neat): ν_{max} 2984, 1704 (C=O), 1556, 1387, 1365, 1303, 1275, 1260, 1175, 1084, 850, 755 and 658 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.15 (1H, s, O-*H*), 3.96 (1H, d, *J* = 8.8 Hz), 3.87 (1H, dd, *J* = 8.4, 6.0 Hz), 3.50 (1H, br t, *J* = 6.0 Hz), 2.98 (1H, dd, *J* = 14.4, 9.6 Hz), 2.35 (2H, s), 2.29 (1H, d, *J* = 16.0 Hz), 2.17 (2H, s), 1.53 (3H, s, CH_3), 1.48 (9H, s, 3 x CH_3), 1.39 (3H, s, CH_3), 1.01 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, C=O), 172.9 (C, C=*C*-O), 153.9 (C, N-C=O), 117.3 (C), 93.3 (C, O-C-N), 81.8 (C, O*C*(CH_3)$_3$), 68.4 (CH_2, OCH_2), 59.0 (CH, NCH), 50.3 (CH_2), 42.8 (CH_2), 31.8 (C), 28.8 (CH_3), 28.4 (3 x CH_3), 27.9 (CH_3), 27.0 (CH_3), 26.4 (CH_2), 24.1 (CH_3); LRMS m/z 354.00 ($M+H^+$), calcd for $C_{19}H_{31}NO_5$ 353.2202;



52bg

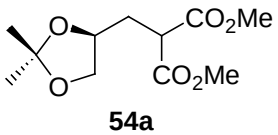
Anal. calcd for $C_{19}H_{31}NO_5$ (353.2202): C, 64.56; H, 8.84; N, 3.96. Found: C, 64.50; H, 8.87; N, 4.01%.



52bd

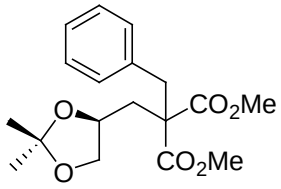
(4*R*)-4-(2,5-Dioxo-cyclopentylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (52bd): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 138-140 °C; **$[\alpha]^{25}_{D}$ = +22.8 (*c* 0.5, EtOH);** IR (neat): ν_{max} 2984, 1704 (C=O), 1386, 1302, 1275, 1261, 1174, 1084, 849, 753 and 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (1H, br t, *J* = 8.0 Hz), 3.82 (1H, d, *J* = 8.0 Hz), 3.68 (1H, br s), 2.71 (1H, br m), 2.48 (4H, s), 2.28 (1H, br d, *J* = 14.4 Hz), 1.53 (3H, s, CH_3), 1.50 (9H, s, 3 x CH_3), 1.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 153.5 (C, N-C=O), 115.1 (C), 93.6 (C, O-C-N), 81.9 (C, O*C*$(CH_3)_3$), 68.9 (CH_2, OCH_2), 57.9 (CH, NCH), 28.3 (3 x CH_3), 26.8 (CH_3), 26.3 (CH_2), 24.2 (CH_3); LRMS m/z 310.00 ($M\text{-}H^+$), calcd for $C_{16}H_{25}NO_5$ 311.1733; Anal. calcd for $C_{16}H_{25}NO_5$ (311.1733): C, 61.72; H, 8.09; N, 4.58. Found: C, 61.65; H, 8.11; N, 4.58%. *[Due to the keto-enol and enol-enol tautomerism in **52bd**, ^{13}C NMR shows some of carbons (2 x CH_2 and 2 x C=O) are poor resolution even after more than 2000 scans in the solvent system of $CDCl_3$ or $CDCl_3$ + CD_3OD (three drops)]*.

Dimethyl {[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}propanedioate (54a): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_{D}$ = –6.5 (*c* 2.2, MeOH);** IR (neat): ν_{max} 2988, 2954, 1737 (O-C=O), 1732 (O-C=O), 1438, 1375, 1244, 1214, 1156, 1064, 864 and 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13-4.10 (1H, m), 4.05 (1H, dd, *J* = 8.0, 6.0 Hz), 3.75 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.60 (1H, dd, *J* = 9.2, 5.6 Hz), 3.57 (1H, dd, *J* = 8.0, 6.4 Hz), 2.20 (1H, ddd, *J* = 12.8, 9.2, 4.0 Hz), 2.08 (1H, ddd, *J* = 14.0, 8.4, 5.6 Hz), 1.38 (3H, s, CH_3), 1.31 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.7 (C, O-C=O), 169.5 (C, O-C=O), 109.3 (C, O-C-O), 73.4 (CH, OCH), 69.0 (CH_2, OCH_2), 52.64 (CH_3, OCH_3), 52.59 (CH_3, OCH_3), 48.4 (CH), 33.0 (CH_2), 26.8 (CH_3), 25.5 (CH_3); LRMS m/z 245.00 ($M\text{-}H^+$), calcd for $C_{11}H_{18}O_6$ 246.1103; Anal. calcd for $C_{11}H_{18}O_6$ (246.1103): C, 53.65; H, 7.37. Found: C, 53.58; H, 7.39%.



54a

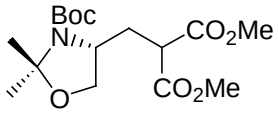
Dimethyl benzyl{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}propanedioate (56): Purified



(+)-**56**

by column chromatography using EtOAc/hexane and isolated as an oil. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 220 nm), t_R = 13.67 min (minor), t_R = 15.13 min (major). **$[\alpha]^{25}_D$ = +1.7 (*c* 0.3, $CHCl_3$, >98% ee);** IR (neat): ν_{max} 2985, 2955, 1736 (O-C=O), 1437, 1374, 1208, 1088, 702 and 632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26-7.22 (3H, m), 7.09 (2H, d, *J* = 7.2 Hz) [Ar-*H*]; 4.26-4.24 (1H, m), 4.03 (1H, t, *J* = 6.8 Hz), 3.72 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.46 (1H, t, *J* = 8.0 Hz), 3.37 (2H, ABq, *J* = 14.4 Hz), 2.10 (1H, dd, *J* = 14.8, 9.2 Hz), 2.00 (1H, d, *J* = 14.8 Hz), 1.39 (3H, s, CH_3), 1.33 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.4 (C, O-C=O), 171.3 (C, O=C-O), 135.8 (C), 129.9 (2 x CH), 128.3 (2 x CH), 127.0 (CH), 109.2 (C, O-*C*-O), 72.3 (CH, OCH), 69.8 (CH_2, OCH_2), 57.3 (C), 52.5 (CH_3, OCH_3), 52.3 (CH_3, OCH_3), 39.0 (CH_2), 36.4 (CH_2), 26.7 (CH_3), 25.7 (CH_3); LRMS m/z 337.10 ($M+H^+$), calcd $C_{18}H_{24}O_6$ 336.1573; Anal. calcd for $C_{18}H_{24}O_6$ (336.1573): C, 64.27; H, 7.19. Found: C, 64.35; H, 7.15%.

2-[(4*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-oxazolidin-4-ylmethyl]-malonic acid dimethyl ester (54b): Purified by column chromatography using EtOAc/hexane and isolated as oil.

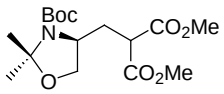


54b

$[\alpha]^{25}_D$ = –34.5 (*c* 0.8, $CHCl_3$); IR (neat): ν_{max} 2979, 2876, 1737 (O-C=O), 1692, 1386, 1251, 1172, 1085, 1023, 852 and 651 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of rotamers at 25 °C) δ 4.04 (1H, m), 3.90 (2H, dd, *J* = 8.8, 5.6 Hz), 3.85 (1H, m), 3.70 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.70-3.60 (2H, m), 3.50-3.38 (2H, br s), 2.25-2.10 (2H, m), 1.56 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.42 (9H, s, 3 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of rotamers at 25 °C) δ 169.7 (C, O-C=O), 169.4 (3 x C, O-C=O), 152.5 (C, N-C=O), 151.6 (C, N-C=O), 94.0 (C, N-*C*-O), 93.5 (C, N-*C*-O), 80.0 (2 x C, 2 x O*C*$(CH_3)_3$), 67.3 (CH_2, OCH_2), 66.8 (CH_2, OCH_2), 55.3 (2 x CH, 2 x NCH), 52.5 (2 x CH_3, OCH_3), 52.48 (2 x CH_3, OCH_3), 48.72 (CH), 48.70 (CH), 33.0 (CH_2), 32.55 (CH_2), 28.3 (6 x CH_3), 27.5 (CH_3), 26.6 (CH_3), 24.2 (CH_3), 22.9 (CH_3); ^1H NMR ($CDCl_3$, single rotamer at 50 °C) δ 3.89 (2H, dd, *J* = 8.4, 4.4 Hz), 3.69 (6H, s, 2 x OCH_3), 3.70-3.69 (1H, m), 3.44 (1H, br s), 2.29-2.10 (2H, m), 1.54 (3H, s, CH_3), 1.44 (6H, s, 2 x CH_3), 1.43 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, single rotamer at 50 °C) δ 169.4 (C, O-C=O), 169.3 (C, O-C=O), 152.2 (C, N-C=O), 93.8 (C, O-C-N), 80.0 (C, O*C*$(CH_3)_3$), 67.2 (CH_2, OCH_2), 55.6 (CH, NCH), 52.30 (CH_3, OCH_3), 52.27 (CH_3, OCH_3), 48.9 (CH), 32.9 (CH_2), 28.3 (3 x CH_3), 26.9 (CH_3), 23.4 (CH_3); LRMS m/z 346.25 ($M+H^+$),

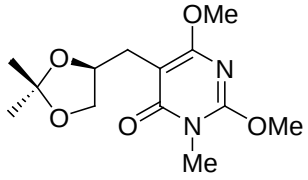
calcd for $C_{16}H_{27}NO_7$ 345.1788; Anal. calcd for $C_{16}H_{27}NO_7$ (345.1788): C, 55.64; H, 7.88; N, 4.06. Found: C, 55.56; H, 7.91; N, 4.11%.

2-[(4*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-oxazolidin-4-ylmethyl]-malonic acid dimethyl ester (54c): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = +34.5 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2979, 2876, 1737 (O-C=O), 1692, 1386, 1251, 1172, 1085, 1023, 852 and 651 cm^{-1}.



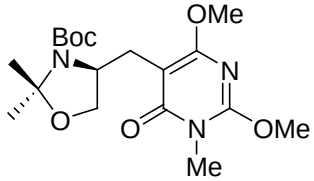
54c

5-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-2,6-dimethoxy-3-methylpyrimidin-4(3*H*)-one (55a): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –8.1(*c* 1.0, EtOH);** IR (neat): ν_{max} 2985, 2927, 1665 (C=O), 1612, 1550, 1378, 1288, 1213, 1144, 1061 and 787 cm^{-1}; UV (*c* 1 x 10^{-3} M, MeOH): λ_{max} 202, 230 and 270 nm; ^{1}H NMR ($CDCl_3$) δ 4.28 (1H, quintet, *J* = 6.4 Hz), 3.97 (3H, s, OCH_3), 3.89 (1H, dd, *J* = 8.0, 6.0 Hz), 3.86 (3H, s, OCH_3), 3.67 (1H, dd, *J* = 8.4, 6.8 Hz), 3.32 (3H, s, N*C*H_3), 2.79 (1H, dd, *J* = 13.2, 6.0 Hz), 2.56 (1H, dd, *J* = 13.2, 7.6 Hz), 1.39 (3H, s, CH_3), 1.28 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.3 (C), 164.1 (C), 155.2 (C), 108.5 (C, O-C-O), 93.2 (C), 74.7 (CH, OCH), 69.2 (CH_2, OCH_2), 55.3 (CH_3, OCH_3), 53.7 (CH_3, OCH_3), 27.8 (CH_3), 27.5 (CH_2), 26.8 (CH_3), 25.7 (CH_3); LRMS m/z 285.00 ($M+H^+$), calcd for $C_{13}H_{20}N_2O_5$ 284.1372; Anal. calcd for $C_{13}H_{20}N_2O_5$ (284.1372): C, 54.92; H, 7.09; N, 9.85. Found: C, 54.88; H, 7.12; N, 9.91%.



55a

(4*R*)-4-(2,4-Dimethoxy-1-methyl-6-oxo-1,6-dihydro-pyrimidin-5-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (55b): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 72-74 °C; **$[\alpha]^{25}_D$ = +25.4 (*c* 0.7, EtOH);** IR (neat): ν_{max} 2979, 1693, 1669, 1550, 1482, 1456, 1388, 1258, 1211, 1177, 1142, 1094 and 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.24-4.09 (1H, m), 3.99 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.78 (2H, br s), 3.35 (3H, s, NCH_3), 2.86-2.76 (1H, m), 2.67 (1H, dd, *J* = 12.8, 8.0 Hz), 1.61 (3H, s, CH_3), 1.43 (12H, s, 4 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.3 (C), 164.3 (C), 155.2 (C), 152.1 (C), 94.4 (C), 93.7 (C), 79.0 (C, O*C*$(CH_3)_3$), 67.0 (CH_2, OCH_2), 56.2 (CH, NCH), 55.3 (CH_3, OCH_3), 53.6 (CH_3, OCH_3), 28.4 (3 x CH_3), 27.9 (CH_3), 26.9 (CH_2), 26.6 (CH_3), 23.3 (CH_3); LRMS m/z 384.05 ($M+H^+$), calcd $C_{18}H_{29}N_3O_6$

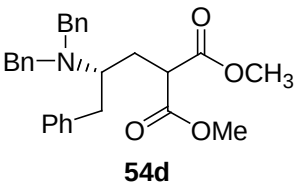


55c

383.2056; Anal. calcd for $C_{18}H_{29}N_3O_6$ (383.2056): C, 56.38; H, 7.62; N, 10.96. Found: C, 56.31; H, 7.65; N, 11.01%.

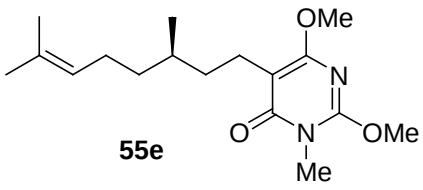
(4*S*)-4-(2,4-Dimethoxy-1-methyl-6-oxo-1,6-dihydro-pyrimidin-5-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (55c): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 72-74 °C; **$[\alpha]^{25}_D$ = –25.3 (*c* 0.7, EtOH);** IR (neat): ν_{max} 2973, 2869, 1693, 1668, 1613, 1550, 1482, 1459, 1388, 1318, 1212, 1178, 1141, 1096, 853 and 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.30-4.19 (1H, m), 4.01 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.80 (2H, br s), 3.36 (3H, s, NCH_3), 2.87-2.63 (2H, m), 1.62 (3H, s, CH_3), 1.45 (12H, s, 4 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.3 (C), 164.3 (C), 155.1 (C), 152.1 (C), 94.3 (C), 93.7 (C), 79.0 (C, O*C*$(CH_3)_3$), 67.0 (CH_2, OCH_2), 56.2 (CH, NCH), 55.3 (CH_3, OCH_3), 53.6 (CH_3, OCH_3), 28.4 (3 x CH_3), 27.8 (CH_3), 26.8 (CH_2), 26.6 (CH_3), 23.3 (CH_3); LRMS m/z 384.00 ($M+H^+$), calcd for $C_{18}H_{29}N_3O_6$ 383.2104.

2-[(2*R*)-2-Dibenzylamino-3-phenyl-propyl]-malonic acid dimethyl ester (54d): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = +15.1 (*c* 1.1, $CHCl_3$);** IR (neat): ν_{max} 3028, 2954, 2928, 1746 (O-C=O), 1735 (O-C=O), 1452, 1274, 1251, 1199, 1157, 1121, 745 and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29-7.19 (13H, m), 7.09 (2H, d, *J* = 7.5 Hz) [Ar-*H*]; 3.84 (2H, d, *J* = 13.5 Hz), 3.83 (1H, m), 3.64 (3H, s, OCH_3), 3.46 (2H, d, *J* = 13.5 Hz), 3.36 (3H, s, OCH_3), 3.20 (1H, dd, *J* = 13.0, 3.0 Hz), 2.88-2.85 (1H, m), 2.44 (1H, dd, *J* = 13.0, 10.0 Hz), 1.99-1.94 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.7 (C, O-C=O), 169.1 (C, O-C=O), 139.7 (C), 139.6 (2 x C), 129.2 (2 x CH), 129.0 (4 x CH), 128.4 (2 x CH), 128.3 (4 x CH), 127.0 (2 x CH), 126.0 (CH), 57.0 (CH), 53.4 (2 x CH_2), 52.5 (CH_3, OCH_3), 52.1 (CH_3, OCH_3), 48.4 (CH), 34.4 (CH_2), 29.7 (CH_2); LRMS m/z 444.60 ($M-H^+$), calcd $C_{28}H_{31}NO_4$ 445.2253; Anal. calcd for $C_{28}H_{31}NO_4$ (445.2253): C, 75.48; H, 7.01; N, 3.14. Found: C, 75.41; H, 7.05; N, 3.18%.



54d

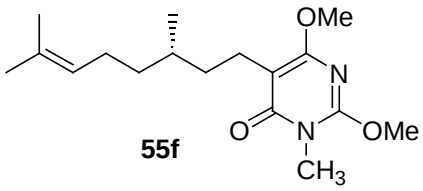
5-[(3*R*)-3,7-Dimethyloct-6-en-1-yl]-2,6-dimethoxy-3-methylpyrimidin-4(3*H*)-one (55e): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –7.7 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2956, 2912, 1668 (O=C-N), 1550, 1453, 1379, 1273, 1212 and 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.09 (1H, br s, C=C*H*), 3.99 (3H, s, OCH_3), 3.88 (3H, s,



55e

OCH_3), 3.36 (3H, s, NCH_3), 2.40-2.35 (2H, m), 2.00-1.93 (2H, m), 1.66 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.42-1.34 (3H, m), 1.27-1.12 (2H, m), 0.92 (3H, d, *J* = 5.2 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.4 (C), 164.2 (C), 154.6 (C), 130.7 (C), 125.3 (CH), 98.5 (C), 55.2 (CH_3, OCH_3), 53.7 (CH_3, OCH_3), 37.0 (CH_2), 35.4 (CH_2), 32.5 (CH), 27.9 (CH_3), 25.7 (CH_3), 25.5 (CH_2), 20.5 (CH_2), 19.4 (CH_3), 17.6 (CH_3); LRMS m/z 309.00 ($M+H^+$), calcd for $C_{17}H_{28}N_2O_3$ 308.2100; Anal. calcd for $C_{17}H_{28}N_2O_3$ (308.2100): C, 66.20; H, 9.15; N, 9.08. Found: C, 66.31; H, 9.11; N, 9.22%.

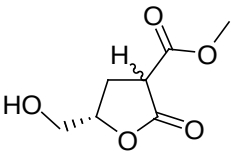
5-[(3*S*)-3,7-Dimethyloct-6-en-1-yl]-2,6-dimethoxy-3-methylpyrimidin-4(3*H*)-one (55f):



55f

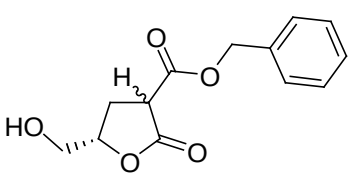
Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = +7.6 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2957, 2912, 2868, 1668 (O=C-N), 1550, 1506, 1482, 1379, 1274, 1212 and 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.09 (1H, t, *J* = 6.8 Hz, C=C*H*), 3.99 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.36 (3H, s, NCH_3), 2.42-2.35 (2H, m), 2.10-1.91 (2H, m), 1.66 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.50-1.35 (3H, m), 1.30-1.10 (2H, m), 0.92 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.3 (C), 164.2 (C), 154.6 (C), 130.7 (C), 125.3 (CH), 98.5 (C), 55.2 (CH_3, OCH_3), 53.7 (CH_3, OCH_3), 37.0 (CH_2), 35.4 (CH_2), 32.5 (CH), 27.8 (CH_3), 25.7 (CH_3), 25.5 (CH_2), 20.5 (CH_2), 19.4 (CH_3), 17.6 (CH_3); LRMS m/z 309.00 ($M+H^+$), calcd $C_{17}H_{28}N_2O_3$ 308.2100; Anal. calcd for $C_{17}H_{28}N_2O_3$ (308.2100): C, 66.20; H, 9.15; N, 9.08. Found: C, 66.15; H, 9.10; N, 9.16%.

Methyl (5*S*)-5-(hydroxymethyl)-2-oxotetrahydrofuran-3-carboxylate (57aaa): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = +18.7 (*c* 0.3, $CHCl_3$);** IR (neat): ν_{max} 3520 (O-H), 2958, 1775 (O-C=O), 1736 (O-C=O), 1441, 1354, 1272, 1164, 1045, 752 and 635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 1:1 mixture of isomers) δ 4.74-4.72 (1H, m), 4.62-4.60 (1H, m), 3.89 (2H, br dt, *J* = 15.2, 2.4 Hz), 3.78 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.79-3.60 (4H, m), 3.20 (1H, s, O-H), 3.18 (1H, s, O-H), 2.67-2.62 (1H, m), 2.52-2.43 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of isomers) δ 172.2 (C, O-C=O), 171.6 (C, O-C=O), 168.4 (C, O-C=O), 168.2 (C, O-C=O), 79.6 (CH, OCH), 79.4 (CH, OCH), 63.8 (CH_2, OCH_2), 63.6 (CH_2, OCH_2), 53.20 (CH_3, OCH_3), 53.18 (CH_3, OCH_3), 46.8 (CH), 46.7 (CH), 27.5 (CH_2), 27.2



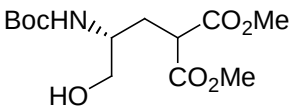
57aaa

(CH_2); LRMS m/z 174.95 ($M+H^+$), calcd for $C_7H_{10}O_5$ 174.0528; Anal. calcd for $C_7H_{10}O_5$ (174.0528): C, 48.28; H, 5.79. Found: C, 48.35; H, 5.75%.


57aab

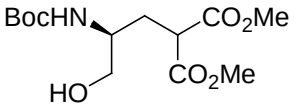
Benzyl (5*S*)-5-(hydroxymethyl)-2-oxotetrahydrofuran-3-carboxylate (57aab): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = +24.0 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 3492 (O-H), 2984, 1774 (O-C=O), 1733 (O-C=O), 1266, 1160, 1093, 799 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of isomers) δ 7.36-7.32 (10 H, m) [Ar-*H*]; 5.22 (2H, s, OC*H*$_2$Ph), 5.21 (2H, s, OC*H*$_2$Ph), 4.72-4.69 (1H, m), 4.59-4.56 (1H, m), 3.87 (2H, t, *J* = 12.8 Hz), 3.80 (2H, dd, *J* = 9.6, 6.8 Hz), 3.71 (1H, t, *J* = 10.0 Hz), 3.62 (1H, dt, *J* = 15.6, 5.2 Hz), 2.82 (2H, br s, 2 x O-H), 2.69-2.54 (1H, m), 2.54-2.44 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of isomers) δ 172.3 (C, O-C=O), 171.7 (C, O-C=O), 167.8 (C, O-C=O), 167.6 (C, O-C=O), 135.0 (2 x C), 128.6 (3 x CH), 128.4 (3 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 79.6 (CH, OCH), 79.5 (CH, OCH), 67.8 (CH_2, OCH_2Ph), 67.7 (CH_2, OCH_2Ph), 63.6 (CH_2, OCH_2), 63.4 (CH_2, OCH_2), 46.9 (CH), 46.8 (CH), 27.5 (CH_2), 27.1 (CH_2); LRMS m/z 251.00 ($M+H^+$), calcd for $C_{13}H_{14}O_5$ 250.0841; Anal. calcd for $C_{13}H_{14}O_5$ (250.0841): C, 62.39; H, 5.64. Found: C, 62.28; H, 5.69%.

2-[(2*R*)-2-tert-Butoxycarbonylamino-3-hydroxy-propyl)]-malonic acid dimethyl ester

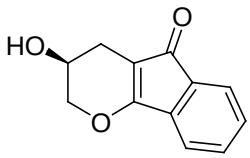

58ba

(58ba): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = +14.1 (*c* 0.22, EtOH);** IR (neat): ν_{max} 3389 (N-H and O-H), 2980, 1738 (O-C=O), 1689 (O-C=O), 1528, 1441, 1169, and 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.82 (1H, d, *J* = 9.2 Hz, N*H*Boc), 3.74 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.90-3.45 (4H, m), 2.60 (1H, O*H*), 2.23-2.15 (1H, m), 2.08-2.00 (1H, m), 1.41 (9H, s, 3 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.1 (C, O-C=O), 169.6 (C, O-C=O), 155.9 (C), 79.7 (C, O*C*(CH_3)$_3$), 65.2 (CH_2, O*C*H_2), 52.7 (2 x CH_3, 2 x O*C*H_3), 50.8 (CH, N*C*H), 48.8 (CH), 30.5 (CH_2), 28.3 (3 x CH_3); LRMS m/z 304.20 ($M-H^+$), calcd for $C_{13}H_{23}NO_7$ 305.1475; Anal. calcd for $C_{13}H_{23}NO_7$ (305.1475): C, 51.14; H, 7.59; N, 4.59. Found: C, 51.15; H, 7.58; N, 4.60%.

2-[(2*S*)-2-tert-Butoxycarbonylamino-3-hydroxy-propyl)]-malonic acid dimethyl ester


58ca

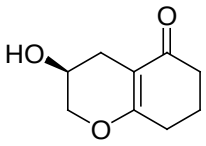
(58ca): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –14.0 (*c* 0.1, EtOH);** IR (neat): ν_{max}


59ab

3386 (N-H and O-H), 2978, 1729 (O-C=O), 1692 (O-C=O), 1521, 1441, 1248, 1169, 1054 and 643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.80 (1H, s, NH), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.90-3.39 (4H, m), 2.50 (1H, br s, O-H), 2.26-2.18 (1H, m), 2.10-1.97 (1H, m), 1.44 (9H, s, 3 x CH_3).

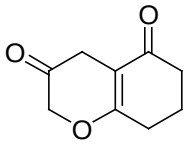
(3*S*)-3-Hydroxy-3,4-dihydroindeno[1,2-*b*]pyran-5(2*H*)-one (59ab): Purified by column chromatography using EtOAc/hexane and isolated as gummy yellow solid. **$[\alpha]^{25}_D$ = –10.7 (*c* 0.2, EtOH);** IR (neat): ν_{max} 3401 (O-H), 2929, 1738, 1704 (C=O), 1628, 1590, 1467, 1336, 1289, 1222, 1151, 1052 and 932 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (1H, br d, *J* = 6.8 Hz), 7.32-7.23 (2H, m), 7.10 (1H, br d, *J* = 6.8 Hz) [Ar-*H*]; 4.37-4.28 (3H, m), 2.64 (1H, dd, *J* = 17.2, 3.2 Hz), 2.40 (1H, dd, *J* = 17.2, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.4 (C, C=O), 173.6 (C, C=*C*-O), 137.5 (C), 133.3 (C), 132.0 (CH), 129.9 (CH), 121.1 (CH), 117.8 (CH), 105.1 (C), 72.3 (CH_2, OCH_2), 62.8 (CH, OCH), 25.5 (CH_2); LRMS m/z 203.05 ($M+H^+$), calcd $C_{12}H_{10}O_3$ 202.0630; Anal. calcd for $C_{12}H_{10}O_3$ (202.0630): C, 71.28; H, 4.98. Found: C, 71.38; H, 4.92%.

(3*S*)-3-Hydroxy-2,3,4,6,7,8-hexahydro-5*H*-chromen-5-one (59ae): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 82 °C; **$[\alpha]^{25}_D$ = –28.0 (*c* 0.5, EtOH);** IR (neat): ν_{max} 3400 (O-H), 1606 (C=O), 1398, 1275, 1266, 1189, 1129, 1093, 1010 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19-4.17 (1H, m), 4.04-4.00 (2H, m), 2.53-2.29 (6H, m), 2.05-1.94 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.5 (C, C=O), 171.1 (C, C=*C*-O), 108.6 (C), 70.2 (CH_2, OCH_2), 62.5 (CH, OCH), 36.5 (CH_2), 28.2 (CH_2), 26.6 (CH_2), 20.7 (CH_2); LRMS m/z 169.00 ($M+H^+$), calcd $C_9H_{12}O_3$ 168.0786; Anal. calcd for $C_9H_{12}O_3$ (168.0786): C, 64.27; H, 7.19. Found: C, 64.32; H, 7.15%.



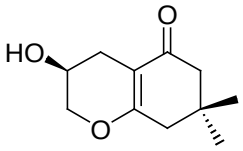
59ae

4,6,7,8-Tetrahydro-chromene-3,5-dione (61ae): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. IR (neat): ν_{max} 2960, 1728 (C=O), 1610 (C=O), 1396, 1270, 1190 and 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.41 (2H, s, OCH_2), 3.13 (2H, s, CH_2), 2.52 (2H, t, *J* = 6.4 Hz), 243 (2H, t, *J* = 6.4 Hz), 2.02 (2H, quintet, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.2 (C, C=O), 197.3 (C, C=O), 170.1 (C, C=*C*-O), 108.3 (C), 72.1 (CH_2, OCH_2), 36.2 (CH_2), 32.4 (CH_2), 28.2 (CH_2), 20.5 (CH_2); LRMS m/z 167.05 ($M+H^+$), calcd $C_9H_{10}O_3$ 166.0630; Anal. calcd for $C_9H_{10}O_3$ (166.0630): C, 65.05; H, 6.07. Found: C, 65.11; H, 6.09%.



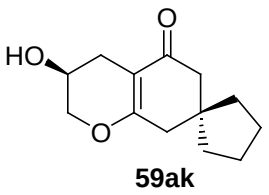
61ae

(3*S*)-3-Hydroxy-7,7-dimethyl-2,3,4,6,7,8-hexahydro-chromen-5-one (59ag): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_{D}$ = –25.7 (*c* 0.75, EtOH);** IR (neat): ν_{max} 3409 (O-H), 1609 (C=O), 1394, 1219, 1124, 1027, 753 and 631 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.15-4.14 (1H, m), 3.99 (2H, dABq, *J* = 13.6, 1.6 Hz), 2.46 (1H, br d, *J* = 3.2 Hz), 2.30-2.25 (3H, m), 2.20 (2H, s), 1.03 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.5 (C, C=O), 169.6 (C, C=*C*-O), 107.3 (C), 70.2 (CH_2, OCH_2), 62.2 (CH, OCH), 50.4 (CH_2), 42.0 (CH_2), 32.0 (C), 28.30 (CH_3), 28.27 (CH_3), 26.4 (CH_2); LRMS m/z 197.00 ($M+H^+$), calcd $C_{11}H_{16}O_3$ 196.1099; Anal. calcd for $C_{11}H_{16}O_3$ (196.1099): C, 67.32; H, 8.19. Found: C, 67.45; H, 8.19%.



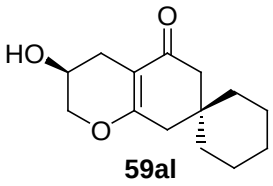
59ag

(3*S*)-3-Hydroxy-2,3,4,8-tetrahydrospiro[chromene-7,1'-cyclopentan]-5(6*H*)-one (59ak): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_{D}$ = –25.3 (*c* 0.7, EtOH);** IR (neat): ν_{max} 3361 (O-H), 2951, 1609 (C=O), 1393, 1215, 1132, 1099, 1071, 664 and 625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.17-4.15 (1H, m), 4.10-3.95 (2H, m), 3.14 (1H, s, O-H), 2.49 (1H, dd, *J* = 16.4, 3.2 Hz), 2.43-2.25 (5H, m), 1.70-1.60 (4H, m), 1.60-1.40 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.7 (C, C=O), 170.4 (C, C=*C*-O), 107.9 (C), 70.2 (CH_2, OCH_2), 62.1 (CH, OCH), 48.8 (CH_2), 42.8 (C), 40.6 (CH_2), 38.11 (CH_2), 38.10 (CH_2), 26.4 (CH_2), 24.00 (CH_2), 23.99 (CH_2); LRMS m/z 223.00 ($M+H^+$), calcd $C_{13}H_{18}O_3$ 222.1256; Anal. calcd for $C_{13}H_{18}O_3$ (222.1256): C, 70.24; H, 8.16. Found: C, 70.16; H, 8.19%.



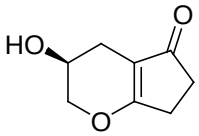
59ak

(3*S*)-3-hydroxy-2,3,4,8-tetrahydrospiro[chromene-7,1'-cyclohexan]-5(6*H*)-one (59al): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_{D}$ = –22.5 (*c* 0.4, EtOH);** IR (neat): ν_{max} 3426 (O-H), 2926, 2858, 1610 (C=O), 1393, 1213, 1075, 1023, 667 and 648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.18 (1H, br s), 4.10-3.96 (2H, m), 2.60-2.45 (2H, m), 2.40-2.22 (4H, m), 1.43-1.31 (10H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.2 (C, C=O), 169.1 (C, C=*C*-O), 107.2 (C), 70.2 (CH_2, OCH_2), 62.4 (CH, OCH), 48.2 (CH_2), 39.8 (CH_2), 36.6 (CH_2), 36.5 (CH_2), 34.8 (C), 26.4 (CH_2), 26.1 (CH_2), 21.6 (2 x CH_2); LRMS m/z 237.05 ($M+H^+$), calcd for $C_{14}H_{20}O_3$ 236.1412; Anal. calcd for $C_{14}H_{20}O_3$ (236.1412): C, 71.16; H, 8.53. Found: C, 71.25; H, 8.49%.



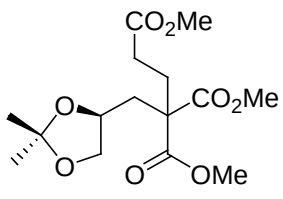
59al

(3*S*)-3-Hydroxy-3,4,6,7-tetrahydro-2H-cyclopenta[b]pyran-5-one (59ad): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_{D}$ = –25.7 (*c* 0.75, EtOH);** IR (neat): ν_{max} 3410 (O-H), 2908, 1682, 1609 (C=O), 1440, 1409, 1369, 1246, 1127, 1063, 953, 813 and 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.25-4.13 (3H, m), 2.62-2.56 (2H, m), 2.46-2.42 (3H, m), 2.26 (1H, br d, *J* = 16.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.6 (C, C=O), 184.2 (C, C=*C*-O), 112.5 (C), 72.2 (CH_2, OCH_2), 61.8 (CH, OCH), 33.6 (CH_2), 26.2 (CH_2), 25.7 (CH_2); LRMS m/z 155.05 ($M+H^+$), calcd $C_8H_{10}O_3$ 154.0630; Anal. calcd for $C_8H_{10}O_3$ (154.0630): C, 62.33; H, 6.54. Found: C, 62.45; H, 6.49%.



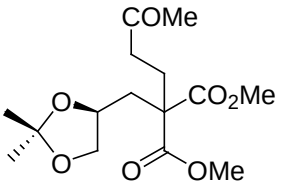
59ad

Trimethyl 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]butane-1,3,3-tricarboxylate (63ac): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_{D}$ = –3.3 (*c* 0.5, EtOH);** IR (neat): ν_{max} 2989, 2954, 1737 (O-C=O), 1731 (O-C=O), 1655, 1438, 1373, 1269, 1208, 1061 and 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.10-4.08 (1H, m), 4.03 (1H, dd, *J* = 8.0, 6.0 Hz), 3.70 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.48 (1H, t, *J* = 6.8 Hz), 2.40-2.17 (6H, m), 1.32 (3H, s, CH_3), 1.27 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 173.0 (C, O-C=O), 171.3 (C, O-C=O), 171.2 (C, O-C=O), 109.3 (C, O-*C*-O), 72.0 (CH, OCH), 69.7 (CH_2, OCH_2), 55.5 (C), 52.6 (CH_3, OCH_3), 52.5 (CH_3, OCH_3), 51.7 (CH_3, OCH_3), 37.3 (CH_2), 29.4 (CH_2), 28.1 (CH_2), 26.6 (CH_3), 25.6 (CH_3); LRMS m/z 333.20 ($M+H^+$), calcd $C_{15}H_{24}O_8$ 332.1471; Anal. calcd for $C_{15}H_{24}O_8$ (332.1471): C, 54.21; H, 7.28. Found: C, 54.25; H, 7.24%.



63ac

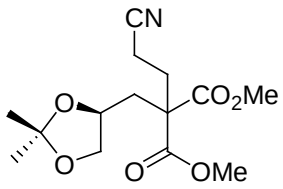
Dimethyl {[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}(3-oxobutyl)propanedioate (63aa): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_{D}$ = –6.2 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2988, 1729 (O-C=O), 1438, 1373, 1208, 1098, 1060 and 626 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.06-3.99 (2H, m), 3.67 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.45 (1H, t, *J* = 7.2 Hz), 2.54-2.48 (1H, m), 2.38-2.00 (5H, m), 2.09 (3H, s, COC*H*$_3$), 1.30 (3H, s, CH_3), 1.24 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.1 (C, C=O), 171.4 (C, O-C=O), 171.3 (C, O-C=O), 109.2 (C, O-*C*-O), 72.0 (CH, OCH), 69.7 (CH_2, OCH_2), 55.4 (C), 52.5 (CH_3, OCH_3), 52.4 (CH_3, OCH_3), 38.7 (CH_2), 37.5 (CH_2), 29.8 (CH_3),



63aa

26.9 (CH_2), 26.6 (CH_3), 25.5 (CH_3); LRMS m/z 315.00 ($M\text{-}H^+$), calcd $C_{15}H_{24}O_7$ 316.1522; Anal. calcd for $C_{15}H_{24}O_7$ (316.1522): C, 56.95; H, 7.65. Found: C, 56.98; H, 7.61%.

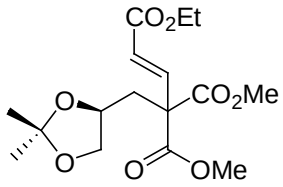
Dimethyl-(2-cyanoethyl){[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}propanedioate



63ad

(63ad): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 54-56 °C; **$[\alpha]^{25}_D$ = –13.0 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2989, 2255 (C≡N), 1736 (O-C=O), 1731 (O-C=O), 1439, 1376, 1258, 1208, 1098, 1055 and 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.07-4.02 (2H, m), 3.72 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.50-3.48 (1H, m), 2.65-2.00 (6H, m), 1.32 (3H, s, CH_3), 1.27 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.44 (C, O-C=O), 170.41 (C, O-C=O), 119.0 (C, *C*N), 109.5 (C, O-*C*-O), 71.9 (CH, OCH), 69.6 (CH_2, OCH_2), 55.5 (C), 52.9 (CH_3, OCH_3), 52.7 (CH_3, OCH_3), 36.8 (CH_2), 28.9 (CH_2), 26.6 (CH_3), 25.5 (CH_3), 12.9 (CH_2); LRMS m/z 300.60 ($M+H^+$), calcd $C_{14}H_{21}NO_6$ 299.1369; Anal. calcd for $C_{14}H_{21}NO_6$ (299.1369): C, 56.18; H, 7.07; N, 4.68. Found: C, 56.12; H, 7.10; N, 4.71%.

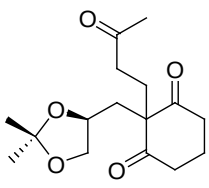
1-Ethyl-3,3-dimethyl (1*E*)-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]but-1-ene-1,3,3-tricarboxylate (63ae):



63ae

Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –6.2 (*c* 0.6, $CHCl_3$);** IR (neat): ν_{max} 2986, 1743 (O-C=O), 1439, 1373, 1268, 1198, 1089, 1043, 753 and 633 cm^{-1}; ^1H NMR ($CDCl_3$, 4:1 mixture of *E/Z* isomers, major *E* isomer)**:** δ 7.42 (1H, d, *J* = 16.4 Hz, C=C*H*), 5.86 (1H, d, *J* = 16.4 Hz, C*H*=C), 4.19 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 4.12-4.06 (1H, m), 4.03-3.99 (1H, m), 3.74 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.50 (1H, dd, *J* = 8.0, 6.8 Hz), 2.40 (1H, dd, *J* = 14.4, 8.8 Hz), 2.27 (1H, dd, *J* = 14.4, 3.6 Hz), 1.31 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.23 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 4:1 mixture of *E/Z* isomers, major *E* isomer)**:** δ 169.44 (C, O-C=O), 169.35 (C, O-C=O), 165.4 (C, O-C=O), 143.3 (CH), 123.2 (CH), 109.3 (C, O-*C*-O), 71.8 (CH, OCH), 69.5 (CH_2, OCH_2), 60.7 (CH_2, O$CH_2$$CH_3$), 57.8 (C), 52.9 (2 x CH_3, OCH_3), 40.2 (CH_2), 26.6 (CH_3), 25.5 (CH_3), 14.1 (CH_3, OCH_2CH_3); LRMS m/z 344.15 (M^+), calcd $C_{16}H_{24}O_8$ 344.1471; Anal. calcd for $C_{16}H_{24}O_8$ (344.1471): C, 55.81; H, 7.02. Found: C, 55.86; H, 7.06%.

2-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-2-(3-oxobutyl)cyclohexane-1,3-dione

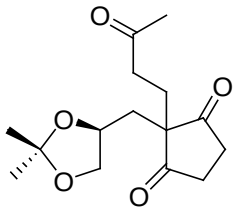


64aea

(**64aea**): Purified by column chromatography using EtOAc/hexane and

isolated as oil. **$[\alpha]^{25}_D$ = –22.2 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2987, 2883, 1718 (C=O), 1691, 1373, 1264, 1213, 1056, 864 and 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.96-3.94 (2H, m), 3.44-3.39 (1H, m), 2.68-2.52 (4H, m), 2.37-2.29 (2H, m), 2.21-2.15 (1H, m), 2.05 (3H, s, C*H*$_3$CO), 2.02-1.87 (5H, m), 1.24 (3H, s, CH_3), 1.19 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 211.0 (C, C=O), 210.1 (C, C=O), 206.9 (C, C=O), 109.2 (C, O-*C*-O), 72.0 (CH, OCH), 69.8 (CH_2, OCH_2), 63.9 (C), 39.1 (CH_2), 38.4 (CH_2), 38.3 (CH_2), 38.0 (CH_2), 30.5 (CH_2), 29.8 (CH_3), 25.9 (CH_3), 25.5 (CH_3), 17.0 (CH_2); LRMS m/z 297.00 ($M+H^+$), calcd $C_{16}H_{24}O_5$ 296.1624; Anal. calcd for $C_{16}H_{24}O_5$ (296.1624): C, 64.84; H, 8.16. Found: C, 64.75; H, 8.13%.

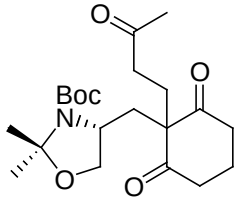
2-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-2-(3-oxobutyl)cyclopentane-1,3-dione



64ada

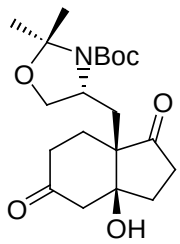
(64ada): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –27.8 (*c* 0.6, $CHCl_3$);** IR (neat): ν_{max} 2927, 1722 (C=O), 1375, 1258, 1215, 1158, 1064 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00-3.93 (2H, m), 3.44-3.42 (1H, m), 2.79-2.66 (4H, m), 2.41 (2H, t, *J* = 7.6 Hz), 2.06 (3H, s, C*H*$_3$CO), 2.02-1.96 (1H, m), 1.83-1.75 (3H, m), 1.24 (3H, s, CH_3), 1.17 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 217.2 (C, C=O), 215.5 (C, C=O), 206.8 (C, C=O), 109.5 (C, O-*C*-O), 71.8 (CH, OCH), 69.4 (CH_2, OCH_2), 56.1 (C), 38.1 (CH_2), 37.1 (CH_2), 35.4 (CH_2), 35.1 (CH_2), 29.8 (CH_3), 28.8 (CH_2), 25.8 (CH_3), 25.3 (CH_3); LRMS m/z 283.10 ($M+H^+$), calcd $C_{15}H_{22}O_5$ 282.1467; Anal. calcd for $C_{15}H_{22}O_5$ (282.1467): C, 63.81; H, 7.85. Found: C, 63.75; H, 7.88%.

(4*S*)-4-[2,6-Dioxo-1-(3-oxo-butyl)-cyclohexylmethyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (64bea): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –16.0 (*c* 0.3, EtOH);** IR (neat): ν_{max} 2976, 2937, 2877, 1717 (C=O), 1687 (C=O), 1395, 1370, 1252, 1172, 1104 and 654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02-4.00 (1H, m), 3.91 (1H, t, *J* = 8.8 Hz), 3.63 (1H, d, *J* = 8.8 Hz), 2.84-2.77 (1H, m), 2.07-2.57 (3H, m), 2.43 (1H, dd, *J* = 14.0, 9.2 Hz), 2.34 (2H, t, *J* = 7.2 Hz), 2.27-2.22 (1H, m), 2.08 (3H, s, C*H*$_3$CO), 2.05-1.98 (3H, m), 1.89-1.82 (1H, m), 1.44 (3H, s, CH_3), 1.41 (9H, s, 3 x CH_3), 1.40 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.8 (C, C=O), 207.8 (C, C=O), 207.1 (C, C=O), 152.6 (C, N-*C*=O), 93.5 (C, O-*C*-N), 79.8 (C, O*C*(CH_3)$_3$), 69.5 (CH_2, OCH_2), 66.2 (C), 53.9 (CH, NCH), 37.6 (CH_2), 37.4 (CH_2), 36.9 (CH_2), 36.0 (CH_2), 31.2 (CH_2), 30.0 (CH_3), 28.5 (3 x CH_3), 27.1 (CH_3), 24.4 (CH_3), 17.2



64bea

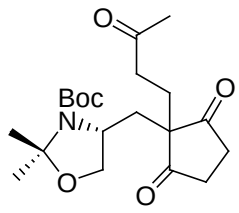
(CH_2); LRMS m/z 418.30 ($M+Na^+$), calcd $C_{21}H_{33}NO_6$, 395.2308; Anal. calcd for $C_{21}H_{33}NO_6$ (395.2308): C, 63.78; H, 8.41; N, 3.54. Found: C, 63.71; H, 8.45; N, 3.62%.



65bda

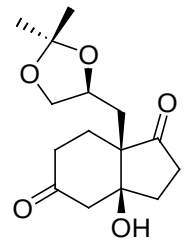
(4*S*)-4-(7a-Hydroxy-3,6-dioxo-octahydro-inden-3a-ylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (65bda): Purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 176-178 °C; **$[\alpha]^{25}_D$ = –19.5 (*c* 0.4, EtOH);** IR (neat): ν_{max} 3484 (O-H), 2978, 1716 (C=O), 1691, 1476, 1390, 1364, 1259, 1178, 1067 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (1H, s, O-H), 4.40 (1H, t, *J* = 6.0 Hz), 4.02 (1H, dd, *J* = 8.4, 5.6 Hz), 3.72 (1H, br d, *J* = 9.2 Hz), 2.73-2.45 (4H, m), 2.37-2.07 (4H, m), 1.98-1.85 (4H, m), 1.55 (3H, s, CH_3), 1.46 (9H, s, 3 x CH_3), 1.43 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 217.4 (C, C=O), 208.4 (C, C=O), 153.1 (C, N-*C*=O), 93.4 (C, O-*C*-N), 82.5 (C, *C*-OH), 81.5 (C, O*C*(CH_3)$_3$), 69.6 (CH_2, OCH_2), 54.3 (C), 53.9 (CH, NCH), 51.1 (CH_2), 37.2 (CH_2), 36.4 (CH_2), 34.1 (CH_2), 33.3 (CH_2), 28.4 (3 x CH_3), 27.4 (CH_3), 27.0 (CH_2), 24.1 (CH_3); LRMS m/z 404.25 ($M+Na^+$), calcd for $C_{20}H_{31}NO_6$ (381.2151); Anal. calcd for $C_{20}H_{31}NO_6$ (381.2151): C, 62.97; H, 8.19; N, 3.67. Found: C, 62.88; H, 8.23; N, 3.75%.

(4*S*)-4-[2,5-Dioxo-1-(3-oxo-butyl)-cyclopentylmethyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (64bda): Purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –6.1 (*c* 0.3, $CHCl_3$);** IR (neat): ν_{max} 2984, 1722 (C=O), 1682, 1399, 1371, 1252, 1173, 1107, 1060 and 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04-3.97 (1H, m), 3.92 (1H, dd, *J* = 8.8, 5.6 Hz), 3.62 (1H, d, *J* = 12.0 Hz), 2.94-2.65 (4H, m), 2.47 (2H, t, *J* = 8.0 Hz), 2.23 (1H, dd, *J* = 12.0, 8.0 Hz), 2.12 (3H, s, C*H*$_3$CO), 1.89-1.81 (1H, m), 1.78-1.70 (2H, m), 1.49 (3H, s, CH_3), 1.43 (9H, s, 3 x CH_3), 1.41 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 214.8 (C, C=O), 212.6 (C, C=O), 206.8 (C, C=O), 153.0 (C, N-C=O), 93.8 (C, O-C-N), 80.1 (C, O*C*(CH_3)$_3$), 69.4 (CH_2, OCH_2), 58.7 (C), 53.6 (CH, NCH), 36.7 (CH_2), 34.5 (CH_2), 34.4 (CH_2), 34.1 (CH_2), 30.1 (CH_3), 29.9 (CH_2), 28.6 (3 x CH_3), 27.5 (CH_3), 24.3 (CH_3); LRMS m/z 382.00 ($M+H^+$), calcd for $C_{20}H_{31}NO_6$ (381.2151); Anal. calcd for $C_{20}H_{31}NO_6$ (381.2151): C, 62.97; H, 8.19; N, 3.67. Found: C, 62.85; H, 8.22; N, 3.71%.



64bda

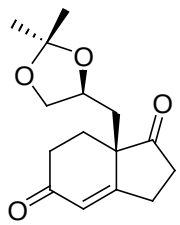
(3a*S*,7a*R*)-7a-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-3a-hydroxyhexahydro-1*H*-indene-1,5(4*H*)-dione (65ada): Purified by column chromatography using



65ada

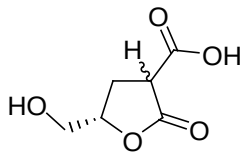
EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = +24.8 (*c* 0.65, $CHCl_3$);** IR (neat): ν_{max} 3424 (O-H), 2934, 1720 (C=O), 1375, 1257, 1157, 1058 871, 749, 660 and 644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.06 (1H, s, O-H), 4.15 (2H, dd, *J* = 6.8, 2.4 Hz), 3.55-3.44 (1H, m), 2.66 (2H, m), 2.57-2.26 (5H, m), 2.09-1.84 (3H, m), 1.72 (1H, dt, *J* = 14.4, 5.2 Hz), 1.55 (1H, ddd, *J* = 9.2, 5.6, 3.2 Hz), 1.42 (3H, s, CH_3), 1.33 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 217.7 (C, C=O), 207.7 (C, C=O), 110.0 (C, O-*C*-O), 80.1 (C, *C*-O), 72.6 (CH, OCH), 70.1 (CH_2, OCH_2), 55.7 (C), 50.4 (CH_2), 35.8 (CH_2), 34.7 (CH_2), 34.0 (CH_2), 32.7 (CH_2), 31.1 (CH_2), 26.7 (CH_3), 25.6 (CH_3); LRMS m/z 283.10 ($M+H^+$), calcd $C_{15}H_{22}O_5$ 282.1467; Anal. calcd for $C_{15}H_{22}O_5$ (282.1467): C, 63.81; H, 7.85. Found: C, 63.75; H, 7.81%.

(7a*R*)-7a-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione (66ada): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_D$ = +48.7 (*c* 0.2, $CHCl_3$);** IR (neat): ν_{max} 2984, 1743 (C=O), 1664, 1374, 1266, 1216, 1152, 1062 753 and 637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.01 (1H, s, C=C*H*), 4.14-4.04 (2H, m), 3.47 (1H, t, *J* = 6.8 Hz), 2.83-2.75 (2H, m), 2.58-2.43 (4H, m), 2.16 (1H, dd, *J* = 13.6, 8.8 Hz), 2.06 (1H, dd, *J* = 14.4, 7.2 Hz), 1.95 (1H, dd, *J* = 14.4, 3.2 Hz), 1.87 (1H, dd, *J* = 14.4, 5.6 Hz), 1.38 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 216.2 (C, C=O), 197.9 (C, C=O), 169.0 (C), 124.6 (CH), 109.5 (C, O-C-O), 71.9 (CH, OCH), 69.7 (CH_2, OCH_2), 50.8 (C), 39.0 (CH_2), 36.3 (CH_2), 32.5 (CH_2), 28.5 (CH_2), 27.2 (CH_2), 26.9 (CH_3), 25.6 (CH_3); LRMS m/z 265.00 ($M+H^+$), calcd $C_{15}H_{20}O_4$ 264.1362; Anal. calcd for $C_{15}H_{20}O_4$ (264.1362): C, 68.22; H, 7.63. Found: C, 68.22; H, 7.59%.



66ada

(5*S*)- 5-Hydroxymethyl-2-oxo-tetrahydro-furan-3-carboxylic acid (67): Purified by column chromatography using EtOAc/hexane and isolated as gummy solid. IR (neat): ν_{max} 3400 (O-H), 2928, 1760 (O-C=O), 1184 and 1061 cm^{-1}; ^1H NMR (**CD_3COCD_3**, **1:1 mixture of isomers**) δ 4.76-4.72 (1H, m), 4.62-4.59 (1H, m), 3.85-3.69 (6H, m), 2.67-2.40 (4H, m); ^{13}C NMR (**CD_3COCD_3**, DEPT-135, **1:1 mixture of isomers**) δ 172.5 (C, O-C=O), 172.2 (C, O-C=O), 169.3 (C, O-C=O), 169.0 (C, O-C=O), 79.6 (2 x CH, 2 x OCH), 63.3 (CH_2, OCH_2), 62.9 (CH_2, OCH_2), 46.9 (CH), 46.75 (CH), 28.0 (CH_2), 27.7 (CH_2); ^1H NMR (DMSO-**D_6**, **1:1 mixture of isomers**) δ 4.58 (1H, br s), 4.44 (1H, br s), 3.59 (2H, m), 3.45 (2H, m), 2.38 (2H, m), 2.21 (2H, br s); ^{13}C NMR (**DMSO-D_6**, DEPT-135, **1:1 mixture of isomers**) δ 174.5



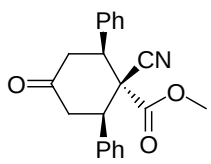
67

(C, O-C=O), 174.1 (C, O-C=O), 170.6 (C, O-C=O), 170.3 (C, O-C=O), 80.25 (CH, OCH), 80.02 (CH, OCH), 63.08 (CH_2, OCH_2), 62.74 (CH_2, OCH_2), 48.31 (CH), 47.97 (CH), 28.61 (CH_2), 28.18 (CH_2).

3a: L-Proline-Catalyzed Cascade O/DA/E Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of the ketone **1**, 0.5 mmol of aldehyde **2** and 0.5 mmol of CH-acid **3** was added 1.0 mL of solvent, and then the catalyst proline **4** (0.1 mmol, 20 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 15, 16 and 17. The crude reaction mixture was directly loaded on silica gel column with or without aqueous work-up and pure cascade products **68/69** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

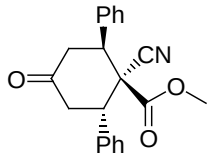
3b: L-Proline-Catalyzed O/DA/E/*TCRA* Reactions in One-Pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the ketone **1**, 0.5 mmol of aldehyde **2** and 0.5 mmol of CH-acid **3** was added 1.0 mL of solvent, and then the catalyst proline **4c** (0.1 mmol, 20 mol%) was added and the reaction mixture was stirred at 25 °C for 72 h then CH-acid **3** (0.5 mmol) and Hantzsch ester **15** (0.5 mmol) was added and stirring continued at the same temperature for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **72** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate). Many of the cascade products **68/69** have been described previously, and their analytical data match literature values; and new compounds were characterized on the basis of IR, ^1H and ^{13}C NMR and analytical data.

1-Cyano-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid methyl ester (69bbq): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 3034, 2953, 1739 (O-C=O), 1714 (C=O), 1498, 1456, 1433, 1234, 1095, 1020, 927, 796, 760 and 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.30 (10H, m) [Ar-H]; 3.74 (2H, dd, *J* = 14.4, 3.6 Hz), 3.29 (2H, t, *J* = 14.4 Hz), 3.26 (3H, s, OCH_3), 2.73 (2H, dd, *J* = 15.2, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.7 (C, *C*=O), 167.0 (C, O-*C*=O), 136.3 (2 x C), 128.8 (4 x CH), 128.7



69bbq

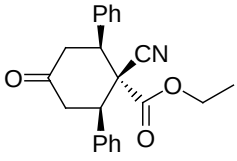
(2 x CH), 127.8 (4 x CH), 115.8 (C, *C*≡N), 59.5 (C), 53.0 (CH_3, O*C*H_3), 49.2 (2 x CH), 43.5 (2 x CH_2); LRMS m/z 334 ($M+H^+$), calcd for $C_{21}H_{19}NO_3$ 333.1365; Anal. calcd for $C_{21}H_{19}NO_3$ (333.14): C, 75.66; H, 5.74; N, 4.20. Found: C, 75.615; H, 5.738; N, 4.328%.



68bbq

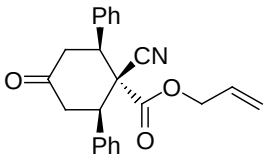
1-Cyano-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid methyl ester (68bbq): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 3034, 2955, 2243 (C≡N), 1741 (O-C=O), 1720 (C=O), 1498, 1456, 1433, 1253, 1097, 1022, 760 and 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–6.99 (10H, m) [Ar-H]; 4.00-3.95 (2H, m), 3.39 (3H, s, OCH_3), 3.21-3.14 (2H, m), 3.04 (1H, dd, *J* = 16.4, 5.6 Hz), 2.82 (1H, dd, *J* = 16.4, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.1 (C, *C*=O), 166.6 (C, O-*C*=O), 137.4 (C), 136.7 (C), 129.7 (CH), 128.8 (2 x CH), 128.78 (2 x CH), 128.73 (CH), 128.47 (2 x CH), 128.43 (2 x CH), 118.9 (C, *C*≡N), 55.7 (C), 53.2 (CH_3, O*C*H_3), 48.2 (CH), 42.9 (CH), 42.4 (CH_2), 41.7 (CH_2).

1-Cyano-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid ethyl ester (69bbn): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 2982, 2924, 2245 (C≡N), 1741 (O-C=O), 1722 (C=O), 1500, 1456, 1412, 1369, 1251, 1099, 1026, 856, 758 and 702 cm^{-1}; ^1H NMR ($CDCl_3$, 7.7:1 ratio, major isomer) δ 7.42–7.28 (10H, m) [Ar-H]; 3.79-3.73 (4H, m), 3.31 (2H, t, *J* = 14.8 Hz), 2.76 (2H, dd, *J* = 14.8, 2.8 Hz), 0.73 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 7.7:1 ratio, major isomer) δ 204.9 (C, *C*=O), 166.5 (C, O-*C*=O), 136.4 (2 x C), 128.9 (4 x CH), 128.7 (2 x CH), 128.1 (4 x CH), 116.1 (C, *C*≡N), 62.6 (CH_2, O*C*H_2CH_3), 59.3 (C), 49.4 (2 x CH), 43.7 (2 x CH_2), 13.4 (CH_3, OCH_2CH_3); LRMS m/z 348 ($M+H^+$), calcd for $C_{22}H_{21}NO_3$ 347.1521; Anal. calcd for $C_{22}H_{21}NO_3$ (347.15): C, 76.06; H, 6.09; N, 4.03. Found: C, 76.197; H, 6.035; N, 4.004%.



69bbn

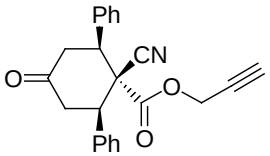
1-Cyano-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid allyl ester (69bbr): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 3036, 2924, 2245 (C≡N), 1743 (O-C=O), 1724 (C=O), 1500, 1454, 1413, 1226, 1101, 1016, 987, 923, 760 and 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–7.12 (10H, m) [Ar-H]; 5.18–5.08 (1H, m, C*H*=CH_2) 4.79 (1H, br d, *J* = 10.48 Hz, CH=CH_2), 4.65 (1H, br d, *J* = 17.16 Hz, CH=CH_2), 4.03 (2H, d, *J* = 5.6 Hz, OCH_2CH=CH_2), 3.60 (2H, dd, *J* = 14.44, 3.56 Hz), 3.16 (2H, t, *J* = 14.8 Hz), 2.61 (2H, dd, *J* = 15.2, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.7 (C, *C*=O),



69bbr

166.2 (C, O-*C*=O), 136.2 (2 x C), 130.0 (CH), 128.8 (4 x CH), 128.7 (2 x CH), 128.0 (4 x CH), 118.7 (CH_2, CH=*C*H_2), 115.9 (C, *C*≡N), 66.7 (CH_2, O*C*H_2CH=CH_2), 59.4 (C), 49.3 (2 x CH), 43.6 (2 x CH_2); LRMS m/z 359.1 (M^+), calcd for $C_{23}H_{21}NO_3$ 359.1521; Anal. calcd for $C_{23}H_{21}NO_3$ (359.15): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.813; H, 5.894; N, 3.798%.

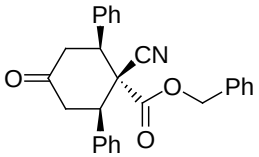
1-Cyano-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid prop-2-ynyl ester (69bbs):



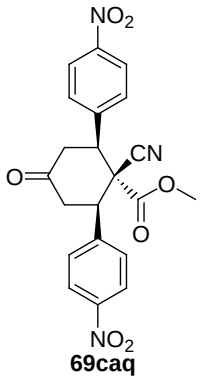
69bbs

Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 3258 (C≡C-H), 3036, 2961, 2123 (C≡C), 1745 (O-C=O), 1714 (C=O), 1602, 1496, 1458, 1410, 1282, 1215, 1093, 758 and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.26 (10H, m) [Ar-H]; 4.28 (2H, d, *J* = 2.0 Hz, OC*H*$_2$C≡CH), 3.76 (2H, dd, *J* = 14.4, 3.6 Hz), 3.29 (2H, t, *J* = 15.2 Hz), 2.74 (2H, dd, *J* = 15.6, 3.6 Hz), 2.28 (1H, t, *J* = 2.4 Hz, $OCH_2C{\equiv}CH$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.5 (C, *C*=O), 165.8 (C, O-*C*=O), 136.0 (2 x C), 128.9 (4 x CH), 128.8 (2 x CH), 127.9 (4 x CH), 115.5 (C, *C*≡N), 75.8 (CH, C≡*C*H), 75.5 (C, *C*≡CH), 59.5 (C), 53.5 (CH_2, O*C*H_2C≡CH), 49.3 (2 x CH), 43.6 (2 x CH_2); LRMS m/z 357.0 (M^+), calcd for $C_{23}H_{19}NO_3$ 357.1365; Anal. calcd for $C_{23}H_{19}NO_3$ (357.14): C, 77.29; H, 5.36; N, 3.92. Found: C, 77.364; H, 5.372; N, 4.177%.

1-Cyano-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (69bbt): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (KBr): ν_{max} 2943, 1747 (O-C=O), 1718 (C=O), 1494, 1456, 1246, 1222, 1101, 1072, 1022, 763, 731 and 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.18 (13H, m), 6.76 (2H, d, *J* = 7.2 Hz) [Ar-H]; 4.75 (2H, s, OC*H*$_2$Ph), 3.79 (2H, br d, *J* = 13.6 Hz), 3.32 (2H, t, *J* = 14.8 Hz), 2.75 (2H, br d, *J* = 14.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 205.2 (C, *C*=O), 166.4 (C, O-*C*=O), 136.1 (2 x C), 133.8 (C), 128.8 (4 x CH), 128.7 (2 x CH), 128.3 (2 x CH), 128.1 (CH), 127.9 (4 x CH), 127.6 (2 x CH), 115.8 (C, *C*≡N), 67.8 (CH_2, O*C*H_2Ph), 59.4 (C), 49.3 (2 x CH), 43.6 (2 x CH_2); LRMS m/z 410 ($M+H^+$), calcd for $C_{27}H_{23}NO_3$ 409.1678; Anal. calcd for $C_{27}H_{23}NO_3$ (409.17): C, 79.20; H, 5.66; N, 3.42. Found: C, 79.172; H, 5.644; N, 3.493%.



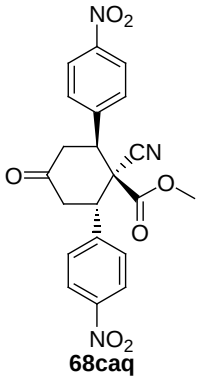
69bbt



69caq

1-Cyano-2,6-bis-(4-nitro-phenyl)-4-oxo-cyclohexanecarboxylic acid methyl ester (69caq): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (KBr): ν_{max} 2955, 2852, 1749 (O-C=O), 1728 (C=O), 1599, 1525 (O-N=O), 1437, 1350 (O-N=O), 1302, 1232, 1109, 1014, 858, 794, 752 and 700 cm^{-1}; ^{1}H NMR (DMSO-D_6) δ 8.24 (4H, d, *J* = 8.8 Hz), 7.64 (4H, d, *J* = 8.8 Hz) [Ar-H]; 4.10 (2H, dd, *J* = 14.2, 3.64 Hz), 3.39 (3H, s, OC*H*$_3$), 3.32 (2H, t, *J* = 15.0 Hz), 2.76 (2H, dd, *J* = 15.32, 3.28 Hz); ^{13}C NMR (DMSO-D_6, DEPT-135) δ 201.4 (C, *C*=O), 165.2 (C, O-*C*=O), 147.0 (2 x C), 142.4 (2 x C), 128.3 (4 x CH), 123.0 (4 x CH), 114.1 (C, *C*≡N), 57.4 (C), 52.7 (CH_3, O*C*H$_3$), 47.0 (2 x CH), 41.8 (2 x CH_2); LRMS m/z 422 (M-H^+), calcd for $C_{21}H_{17}N_3O_7$ 423.1067; Anal. calcd for $C_{21}H_{17}N_3O_7$ (423.11): C, 59.57; H, 4.05; N, 9.93. Found: C, 59.651; H, 4.091; N, 9.996%.

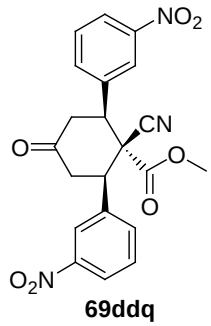
1-Cyano-2,6-bis-(4-nitro-phenyl)-4-oxo-cyclohexanecarboxylic acid methyl ester (68caq):



68caq

Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (Neat): ν_{max} 2924, 1745 (O-C=O), 1723 (C=O), 1529 (O-N=O), 1351 (O-N=O), 1261, 1236, 811 and 693 cm^{-1}; ^{1}H NMR (DMSO-D_6) δ 8.25 (4H, br t, *J* = 8.0 Hz), 7.56 (2H, d, *J* = 8.76 Hz), 7.52 (2H, d, *J* = 8.64 Hz) [Ar-H]; 4.48 (1H, dd, *J* = 10.8, 3.6 Hz), 4.40 (1H, dd, *J* = 10.8, 3.6 Hz), 3.45 (3H, s, OC*H*$_3$), 3.45-3.30 (2H, m), 2.75 (1H, dd, *J* = 16.8, 3.8 Hz), 2.67 (1H, dd, *J* = 16.8, 3.8 Hz); ^{13}C NMR (DMSO-D_6, DEPT-135) δ 206.4 (C, *C*=O), 167.0 (C, O-*C*=O), 147.8 (C), 147.7 (C), 145.6 (C), 144.7 (C), 130.4 (2 x CH), 130.3 (2 x CH), 124.2 (2 x CH), 124.1 (2 x CH), 117.9 (C, *C*≡N), 55.6 (C), 54.2 (CH_3, O*C*H$_3$), 45.4 (CH), 42.4 (CH), 41.1 (CH_2), 40.6 (CH_2).

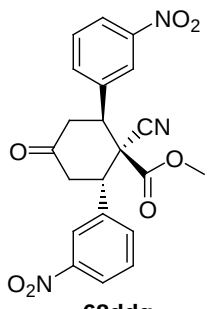
1-Cyano-2,6-bis-(3-nitro-phenyl)-4-oxo-cyclohexanecarboxylic acid methyl ester (69ddq):



69ddq

Purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (KBr): ν_{max} 3090, 2957, 2247 (C≡N), 1743 (O-C=O), 1734 (C=O), 1531 (O-N=O), 1437, 1350 (O-N=O), 1236, 1099, 900, 808, 736 and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25-8.24 (4H, m), 7.79 (2H, d, *J* = 7.76 Hz), 7.63 (2H, t, *J* = 8.52 Hz) [Ar-H]; 3.95 (2H, dd, *J* = 14.36, 3.44 Hz), 3.39 (3H, s, OC*H*$_3$), 3.36 (2H, t, *J* = 14.76 Hz), 2.84 (2H, dd, *J* = 15.04, 3.12 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 202.3 (C, *C*=O), 166.4 (C, O-

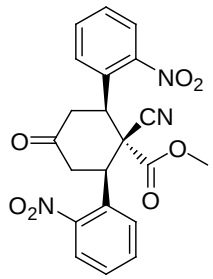
C=O), 148.5 (2 x C), 137.9 (2 x C), 133.8 (2 x CH), 130.3 (2 x CH), 124.1 (2 x CH), 123.2 (2 x CH), 114.8 (C, *C*≡N), 59.0 (C), 53.8 (CH_3, O*C*H_3), 48.5 (2 x CH), 43.0 (2 x CH_2); LRMS m/z 422 (M-H^+), calcd for $C_{21}H_{17}N_3O_7$ 423.1067; Anal. calcd for $C_{21}H_{17}N_3O_7$ (423.11): C, 59.57; H, 4.05; N, 9.93. Found: C, 59.529; H, 4.083; N, 9.975%.



68ddq

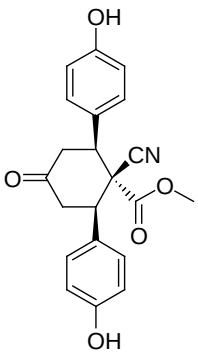
1-Cyano-2,6-bis-(3-nitro-phenyl)-4-oxo-cyclohexanecarboxylic acid methyl ester (68ddq): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (KBr): ν_{max} 3090, 2928, 2253 (C≡N), 1732 (O-C=O), 1531 (O-N=O), 1435, 1352 (O-N=O), 1242, 1101, 1020, 908, 810, 734 and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25 (1H, d, *J* = 8.12 Hz), 8.20-8.19 (2H, m), 8.03 (1H, s), 7.74 (1H, d, *J* = 7.72 Hz), 7.65-7.56 (3H, m) [Ar-H]; 4.17 (1H, t, *J* = 6.2 Hz), 4.05 (1H, dd, *J* = 13.5, 3.8 Hz), 3.56 (3H, s, OC*H*$_3$), 3.31-3.19 (3H, m), 2.91 (1H, dd, *J* = 16.4, 3.72 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.8 (C, *C*=O), 165.9 (C, O-*C*=O), 148.4 (C), 148.3 (C), 138.8 (C), 138.4 (C), 134.4 (CH), 134.3 (CH), 130.3 (CH), 130.0 (CH), 124.0 (2 x CH), 123.7 (CH), 123.5 (CH), 117.1 (C, *C*≡N), 54.9 (C), 53.9 (CH_3, O*C*H_3), 47.5 (CH), 42.4 (CH_2), 42.2 (CH), 41.3 (CH_2).

1-Cyano-2,6-bis-(2-nitro-phenyl)-4-oxo-cyclohexanecarboxylic acid methyl ester (69eeq):



69eeq

Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (KBr): ν_{max} 3090, 2957, 2247 (C≡N), 1745 (O-C=O), 1726 (C=O), 1527 (O-N=O), 1350 (O-N=O), 1236, 1099, 1020, 945, 900, 808, 736 and 690 cm^{-1}; ^{1}H NMR (DMSO-D_6) δ 8.24 (2H, d, *J* = 7.88 Hz), 8.05 (2H, d, *J* = 8.0 Hz), 8.00 (2H, t, *J* = 7.6 Hz), 7.79 (2H, t, *J* = 7.68 Hz) [Ar-H]; 4.68 (2H, dd, *J* = 13.32, 3.2 Hz), 3.50 (2H, t, *J* = 15.76 Hz) 3.39 (3H, s, OC*H*$_3$), 2.91 (2H, dd, *J* = 16.04, 2.92 Hz); ^{13}C NMR (DMSO-D_6, DEPT-135) δ 202.7 (C, *C*=O), 166.4 (C, O-*C*=O), 150.4 (2 x C), 133.8 (2 x CH), 130.4 (2 x CH), 130.3 (2 x C), 129.0 (2 x CH), 125.2 (2 x CH), 119.1 (C, *C*≡N), 57.8 (C), 54.4 (CH_3, O*C*H_3), 43.6 (2 x CH_2), 41.1 (2 x CH); LRMS m/z 422 (M-H^+), calcd for $C_{21}H_{17}N_3O_7$ 423.1067; Anal. calcd for $C_{21}H_{17}N_3O_7$ (423.11): C, 59.57; H, 4.05; N, 9.93. Found: C, 59.646; H, 4.037; N, 10.175%.

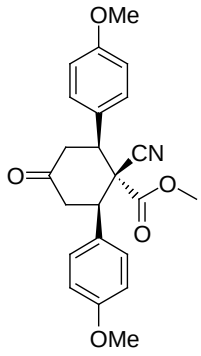


69ffq

1-Cyano-2,6-bis-(4-hydroxy-phenyl)-4-oxo-cyclohexanecarboxylic acid methyl ester (69ffq): Purified by column chromatography using

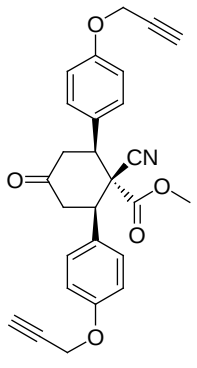
EtOAc/hexane and isolated as a light yellow solid. IR (KBr): ν_{max} 3391 (O-H), 3032, 2955, 2254 (C≡N), 1745 (O-C=O), 1720 (C=O), 1614, 1597, 1516, 1454, 1248, 1176, 1113, 835, 765 and 731 cm^{-1}; ^1H NMR ($CDCl_3$+2 drops of Methanol-D_4) δ 7.17 (4H, d, *J* = 8.4 Hz), 6.78 (4H, d, *J* = 8.8 Hz) [Ar-H]; 3.65 (2H, dd, *J* = 14.4, 3.6 Hz), 3.34 (3H, s, OC*H*$_3$), 3.20 (2H, t, *J* = 14.8 Hz), 2.99 (2H, br s, 2 x OH), 2.67 (2H, dd, *J* = 14.8, 3.2 Hz); ^{13}C NMR ($CDCl_3$+2 drops of Methanol-D_4, DEPT-135) δ 206.0 (C, *C*=O), 167.3 (C, O-*C*=O), 157.0 (2 x C), 128.9 (4 x CH), 127.3 (2 x C), 116.1 (C, *C*≡N), 115.5 (4 x CH), 60.4 (C), 53.0 (CH_3, O*C*H$_3$), 48.3 (2 x CH), 43.6 (2 x CH_2); LRMS m/z 366 ($M+H^+$), calcd for $C_{21}H_{19}NO_5$ 365.1263; Anal. calcd for $C_{21}H_{19}NO_5$ (365.13): C, 69.03; H, 5.24; N, 3.83. Found: C, 69.081; H, 5.246; N, 3.658%.

1-Cyano-2,6-bis-(4-methoxy-phenyl)-4-oxo-cyclohexanecarboxylic acid methyl ester (69ggq): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (KBr): ν_{max} 3003, 2957, 2839, 1741 (O-C=O), 1716 (C=O), 1610, 1514, 1442, 1307, 1253, 1182, 1028, 927, 837, 754 and 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (4H, d, *J* = 8.4 Hz), 6.87 (4H, d, *J* = 8.4 Hz) [Ar-H]; 3.79 (6H, s, 2 x OC*H*$_3$), 3.67 (2H, dd, *J* = 14.4, 3.6 Hz), 3.32 (3H, s, OC*H*$_3$), 3.22 (2H, t, *J* = 14.8 Hz), 2.69 (2H, dd, *J* = 15.2, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 205.0 (C, *C*=O), 167.3 (C, O-*C*=O), 159.7 (2 x C), 129.0 (4 x CH), 128.4 (2 x C), 116.0 (C, *C*≡N), 114.2 (4 x CH), 60.2 (C), 55.1 (CH_3, 2 x O*C*H$_3$), 53.1 (CH_3, O*C*H$_3$), 48.5 (2 x CH), 43.7 (2 x CH_2); LRMS m/z 393.1 (M^+), calcd for $C_{23}H_{23}NO_5$ 393.1576; Anal. calcd for $C_{23}H_{23}NO_5$ (393.16): C, 70.21; H, 5.89; N, 3.56. Found: C, 70.231; H, 5.917; N, 3.523%.



69ggq

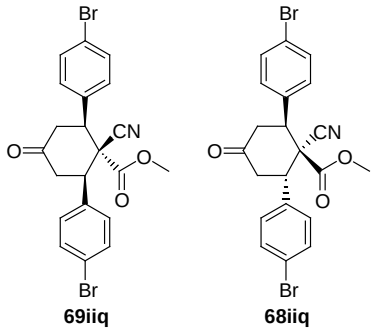
1-Cyano-4-oxo-2,6-bis-(4-prop-2-ynyloxy-phenyl)-cyclohexanecarboxylic acid methyl ester (69hhq): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (KBr): ν_{max} 3283, 3225, 2953, 2121 (C≡C), 1741 (O-C=O), 1716 (C=O), 1608, 1514, 1431, 1373, 1311, 1238, 1184, 1026, 925, 835, 810, 748 and 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (4H, d, *J* = 8.64 Hz), 6.96 (4H, d, *J* = 8.64 Hz) [Ar-H]; 4.68 (4H, d, *J* = 2.2 Hz, 2 x OC*H*$_2$C≡CH), 3.70 (2H, dd, *J* = 14.52, 3.12 Hz), 3.32 (3H, s, OC*H*$_3$), 3.23 (2H, t, *J* = 14.84 Hz), 2.70 (2H, dd, *J* = 14.88, 2.72 Hz), 2.54 (2H, br s, 2 x C≡C*H*); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.8 (C, *C*=O), 167.3 (C, O-



69hhq

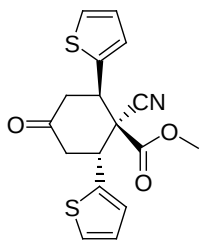
C=O), 157.7 (2 x C), 129.4 (2 x C), 129.1 (4 x CH), 116.0 (C, *C*≡N), 115.2 (4 x CH), 78.3 (2 x C, *C*≡CH), 75.8 (2 x CH, C≡*C*H), 60.1 (C), 55.8 (CH_2, 2 x O*C*H_2C≡CH), 53.2 (CH_3, O*C*H_3), 48.4 (2 x CH), 43.7 (2 x CH_2); LRMS m/z 441.0 (M^+), calcd for $C_{27}H_{23}NO_5$ 441.1576; Anal. calcd for $C_{27}H_{23}NO_5$ (441.16): C, 73.46; H, 5.25; N, 3.17 Found: C, 73.434; H, 5.231; N, 3.216%.

***cis*-2,6-Bis-(4-bromo-phenyl)-1-cyano-4-oxo-cyclohexanecarboxylic acid methyl ester (69iiq) and *trans*-2,6-Bis-(4-bromo-phenyl)-1-cyano-4-oxo-cyclohexanecarboxylic acid methyl ester (68iiq):** Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 2959, 2926, 2854, 2247 (C≡N), 1739 (O-C=O), 1722 (C=O), 1589, 1489, 1236, 1074, 1010, 927, 827, 738 and 715 cm^{-1}; ^1H NMR ($CDCl_3$, 3:1 ratio, major isomer) δ 7.49 (4H, d, *J* = 8.4 Hz), 7.23 (4H, d, *J* = 8.4 Hz) [Ar-H]; 3.69 (2H, dd, *J* = 14.4, 3.2 Hz), 3.34 (3H, s, OC*H*$_3$), 3.21 (2H, t, *J* = 14.8 Hz), 2.71 (2H, dd, *J* = 15.2, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 3:1 ratio, major isomer) δ 203.6 (C, *C*=O), 166.9 (C, O-*C*=O), 135.1 (2 x C), 132.2 (4 x CH), 129.5 (4 x CH), 123.1 (2 x C), 115.5 (C, *C*≡N), 59.1 (C), 53.4 (CH_3, O*C*H_3), 48.7 (2 x CH), 43.3 (2 x CH_2); ^1H NMR ($CDCl_3$, 3:1 ratio, minor isomer) δ 7.50-7.45 (2H, m), 7.26-7.00 (4H, m), 7.02 (2H, d, *J* = 8.4 Hz) [Ar-H]; 3.98-3.80 (2H, m), 3.47 (3H, s, OC*H*$_3$), 3.20-3.00 (3H, m), 2.80 (2H, dd, *J* = 15.2, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 3:1 ratio, minor isomer) δ 206.0 (C, *C*=O), 166.7 (C, O-*C*=O), 136.0 (C), 135.4 (C), 132.07 (2 x CH), 131.99 (2 x CH), 130.13 (2 x CH), 129.97 (2 x CH), 123.10 (C), 122.7 (C), 115.5 (C, *C*≡N), 55.1 (C), 53.4 (CH_3, O*C*H_3), 47.5 (CH), 42.6 (CH), 41.97 (CH_2), 41.4 (CH_2); LRMS m/z 488.9, 490.8, 492.9 (1:2:1), calcd for $C_{21}H_{17}Br_2NO_3$ 488.9575; Anal. calcd for $C_{21}H_{17}Br_2NO_3$ (488.96): C, 51.35; H, 3.49; N, 2.85. Found: C, 51.385; H, 3.493; N, 2.681%.



69iiq **68iiq**

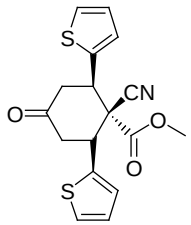
***cis*-1-Cyano-4-oxo-2,6-di-thiophen-2-yl-cyclohexanecarboxylic acid methyl ester (69jjq) and *trans*-1-Cyano-4-oxo-2,6-di-thiophen-2-yl-cyclohexanecarboxylic acid methyl ester (68jjq):** Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (KBr): ν_{max} 2955, 2243 (C≡N), 1722 (C=O and O-C=O), 1433, 1373, 1325, 1267, 1236, 1018, 920, 850, 794 and 706 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 ratio of isomers) δ 7.31-



68jjq

7.25 (4H, m), 7.20-7.09 (3H, m), 7.02-6.98 (4H, m), 6.90 (1H, br d, *J* = 3.3 Hz) [Ar-H]; 4.36-4.28 (2H, m), 4.37 (2H, dd, *J* = 14.2, 3.6 Hz), 3.66 (3H, s, OC*H*$_3$), 3.55 (3H, s, OC*H*$_3$), 3.31-3.08 (2H, m), 3.20 (2H, t, *J* = 15.0 Hz), 3.02-2.95 (2H, m), 2.89 (2H, dd, *J* = 15.16, 3.24 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 ratio of isomers) δ 204.7 (C, *C*=O), 202.6 (C, *C*=O), 167.3 (C, O-*C*=O), 165.8 (C, O-*C*=O), 140.0 (C), 138.8 (2 x C), 138.5 (C), 127.5 (CH), 127.4 (CH), 127.2 (2 x CH), 127.0 (2 x CH), 126.3 (2 x CH), 126.1 (CH), 125.7 (2 x CH), 125.5 (CH), 117.5 (C, *C*≡N), 115.4 (C, *C*≡N), 61.3 (C), 55.9 (C), 53.64 (CH_3, O*C*H$_3$), 53.62 (CH_3, O*C*H$_3$), 44.9 (CH_2), 44.6 (2 x CH_2), 44.3 (2 x CH), 44.1 (CH), 43.5 (CH_2), 38.6 (CH); LRMS m/z 344.90 (M^+), calcd for $C_{17}H_{15}NO_3S_2$ 345.0493; Anal. calcd for $C_{17}H_{15}NO_3S_2$ (345.05): C, 59.11; H, 4.38; N, 4.05; S, 18.57. Found: C, 59.138; H, 4.363; N, 4.107; S, 18.063%.

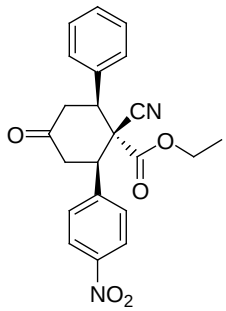
***cis*-1-Cyano-4-oxo-2,6-di-thiophen-2-yl-cyclohexanecarboxylic acid methyl ester (69jjq):**



69jjq

Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (Neat): ν_{max} 2923, 2853, 1723 (C=O and O-C=O), 1433, 1352, 1266, 1235 and 707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (2H, d, *J* = 5.28 Hz), 7.07 (2H, d, *J* = 3.28 Hz), 7.00-6.98 (2H, m) [Ar-H]; 4.02 (2H, d, *J* = 14.24, 3.68), 3.54 (3H, s, OC*H*$_3$), 3.19 (2H, t, *J* = 14.88 Hz), 2.88 (2H, dd, *J* = 15.0, 3.16 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 202.6 (C, *C*=O), 167.3 (C, O-*C*=O), 138.6 (2 x C), 127.1 (2 x CH), 126.3 (2 x CH), 125.7 (2 x CH), 115.3 (C, *C*≡N), 61.3 (C), 53.6 (CH_3, O*C*H$_3$), 44.6 (2 x CH_2), 44.3 (2 x CH).

1-Cyano-2-(4-nitro-phenyl)-4-oxo-6-phenyl-cyclohexanecarboxylic acid ethyl ester (69ban):

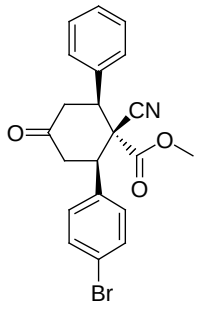


69ban

Purified by column chromatography using EtOAc/hexane and isolated as a solid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak OD-H column (hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 38.410 min (major, major isomer), t_R = 54.330 min (minor, major isomer) (ee = 13.9%), t_R = 61.310 min (major, minor isomer), t_R = 72.147 min (minor, minor isomer) (ee = 3.8%); IR (KBr): ν_{max} 3074, 2982, 1739 (C=O and O-C=O), 1604, 1523 (O-N=O), 1350 (O-N=O), 1230, 1093, 1024, 856, 769, 754 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 10:1 ratio, major isomer) δ 8.22 (2H, d, *J* = 8.76 Hz), 7.60 (2H, d, *J* = 8.76 Hz), 7.36 (5H, br s) [Ar-H]; 3.90 (1H, dd, *J* = 14.44, 3.64 Hz), 3.83-3.70 (3H, m), 3.29 (2H, ABq, *J* = 15.6 Hz), 2.77 (2H, br t, *J* = 16.0 Hz), 0.72 (3H, t, *J* = 7.12 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135,

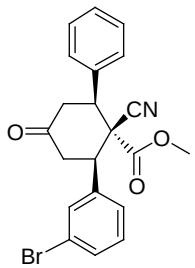
10:1 ratio, major isomer) δ 203.5 (C, *C*=O), 166.1 (C, O-*C*=O), 148.0 (C), 143.4 (C), 135.8 (C), 129.3 (2 x CH), 129.0 (CH), 128.9 (2 x CH), 127.9 (2 x CH), 124.0 (2 x CH), 115.6 (C, *C*≡N), 63.0 (CH_2, O*C*H_2CH$_3$), 58.6 (C), 49.6 (CH), 48.5 (CH), 43.5 (CH_2), 43.1 (CH_2), 13.4 (CH_3, OCH$_2$*C*H$_3$); LRMS m/z 391.0 ($M-H^+$), calcd for $C_{22}H_{20}N_2O_5$ 392.1372; Anal. calcd for $C_{22}H_{20}N_2O_5$ (392.14): C, 67.34; H, 5.14; N, 7.14. Found: C, 67.346; H, 5.144; N, 7.004%.

2-(4-Bromo-phenyl)-1-cyano-4-oxo-6-phenyl-cyclohexanecarboxylic acid methyl ester (69biq): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 3034, 2955, 1743 (O-C=O), 1720 (C=O), 1491, 1456, 1435, 1253, 1074, 1010, 922, 833, 794, 765 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (2H, d, *J* = 8.48 Hz), 7.35 (5H, br s), 7.25 (2H, d, *J* = 8.48 Hz) [Ar-H]; 3.61-3.55 (2H, m), 3.30 (3H, s, OC*H*$_3$), 3.35-3.15 (2H, m), 2.75-2.68 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.2 (C, *C*=O), 166.9 (C, O-*C*=O), 136.0 (C), 135.2 (C), 132.0 (2 x CH), 129.5 (2 x CH), 128.8 (2 x CH), 128.75 (CH), 128.70 (2 x CH), 122.4 (C), 115.5 (C, *C*≡N), 59.2 (C), 53.1 (CH_3, O*C*H_3), 49.2 (CH), 48.4 (CH), 43.3 (CH_2), 43.2 (CH_2); LRMS m/z 411.0 (M^+), calcd for $C_{21}H_{18}BrNO_3$ 411.0470; Anal. calcd for $C_{21}H_{18}BrNO_3$ (411.05): C, 61.18; H, 4.40; N, 3.40. Found: C, 61.184; H, 4.401; N, 3.519%.

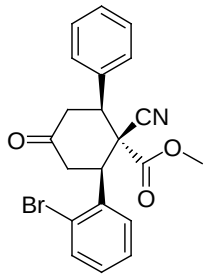


69biq

2-(3-Bromo-phenyl)-1-cyano-4-oxo-6-phenyl-cyclohexanecarboxylic acid methyl ester (69bkq): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 2959, 2243 (C≡N), 1745 (O-C=O), 1716 (C=O), 1591, 1568, 1477, 1435, 1271, 1232, 1195, 1074, 1020, 887, 787, 767 and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48-7.46 (2H, br m), 7.35 (6H, br s), 7.24 (1H, m) [Ar-H]; 3.73 (1H, t, *J* = 3.6 Hz), 3.69 (1H, t, *J* = 3.68 Hz), 3.32 (3H, s, OC*H*$_3$), 3.27-3.19 (2H, m), 2.76-2.70 (2H, br m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.1 (C, *C*=O), 166.9 (C, O-*C*=O), 138.5 (C), 136.1 (C), 132.0 (CH), 131.2 (CH), 130.5 (CH), 129.0 (2 x CH), 128.9 (CH) 127.8 (2 x CH), 126.3 (CH), 122.8 (C), 115.5 (C, *C*≡N), 59.3 (C), 53.2 (CH_3, O*C*H_3), 49.3 (CH), 48.7 (CH), 43.5 (CH_2), 43.2 (CH_2); LRMS m/z 411.0 (M^+), calcd for $C_{21}H_{18}BrNO_3$ 411.0470; Anal. calcd for $C_{21}H_{18}BrNO_3$ (411.05): C, 61.18; H, 4.40; N, 3.40. Found: C, 61.245; H, 4.400; N, 3.655%.



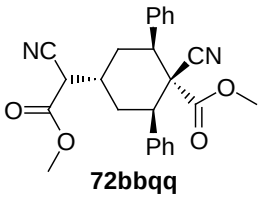
69bkq



69blq

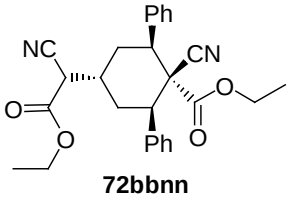
2-(2-Bromo-phenyl)-1-cyano-4-oxo-6-phenyl-cyclohexanecarboxylic acid methyl ester (69blq): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (KBr): ν_{max} 3024, 2957, 2241 (C≡N), 1745 (O-C=O), 1726 (C=O), 1494, 1471, 1427, 1257, 1224, 1101, 1022, 933, 798, 758 and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 8:1 ratio, major isomer) δ 7.96 (1H, d, *J* = 7.96 Hz), 7.61 (1H, d, *J* = 8.04 Hz), 7.41-7.34 (6H, m), 7.19 (1H, t, *J* = 7.8 Hz) [Ar-H]; 4.44 (1H, dd, *J* = 14.24, 3.64 Hz), 3.83 (1H, dd, *J* = 14.28, 3.68 Hz), 3.37 (3H, s, OC*H*$_3$), 3.40-3.29 (1H, m), 3.04 (1H, t, *J* = 15.08 Hz), 2.81 (2H, br d, *J* = 15.56 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 8:1 ratio, major isomer) δ 203.8 (C, *C*=O), 166.2 (C, O-*C*=O), 136.3 (C), 136.0 (C), 133.7 (CH), 129.8 (CH), 128.9 (3 x CH), 128.4 (CH), 128.0 (2 x CH), 127.6 (CH), 124.4 (C), 116.6 (C, *C*≡N), 57.7 (C), 53.2 (CH_3, O*C*H_3), 49.6 (CH), 46.8 (CH), 44.4 (CH_2), 43.7 (CH_2); LRMS m/z 412.0 ($M+H^+$), calcd for $C_{21}H_{18}BrNO_3$ 411.0470; Anal. calcd for $C_{21}H_{18}BrNO_3$ (411.05): C, 61.18; H, 4.40; N, 3.40. Found: C, 61.163; H, 4.402; N, 3.545%.

1-Cyano-4-(cyano-methoxycarbonyl-methyl)-2,6-diphenyl-cyclohexanecarboxylic acid methyl ester (72bbqq): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (KBr): ν_{max} 3034, 2953, 2361 (C≡N), 2247 (C≡N), 1747 (O-C=O), 1602, 1494, 1456, 1255, 1105, 1018, 761 and 721 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33–7.26 (10H, m) [Ar-H]; 4.02 (1H, d, *J* = 11.44 Hz), 3.80 (3H, s, OCH_3), 3.46 (2H, dt, *J* = 14.4, 2.6 Hz), 3.27 (3H, s, OC*H*$_3$), 2.93-2.90 (1H, br m), 2.68 (1H, dt, *J* = 14.8, 4.92 Hz), 2.60 (1H, dt, *J* = 14.56, 4.8 Hz), 2.33 (1H, d, *J* = 14.8 Hz), 1.86 (1H, d, *J* = 14.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 165.8 (C, O-*C*=O), 137.6 (C), 137.4 (C), 128.8 (4 x CH), 128.53 (CH), 128.49 (CH), 128.12 (2 x CH), 128.09 (2 x CH), 116.1 (C, *C*≡N), 115.6 (C, *C*≡N), 60.3 (C), 53.8 (CH_3, O*C*H_3), 52.9 (CH_3, O*C*H_3), 44.7 (CH), 44.4 (CH), 39.3 (CH), 34.8 (CH), 30.3 (CH_2), 29.8 (CH_2); LRMS m/z 415.0 ($M-H^+$), calcd for $C_{25}H_{24}N_2O_4$ 416.1736; Anal. calcd for $C_{25}H_{24}N_2O_4$ (416.17): C, 72.10; H, 5.81; N, 6.73. Found: C, 72.206; H, 5.830; N, 6.629%.



72bbqq

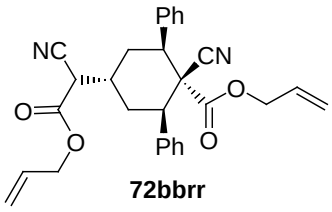
1-Cyano-4-(cyano-ethoxycarbonyl-methyl)-2,6-diphenyl-cyclohexanecarboxylic acid ethyl ester (72bbnn): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (KBr): ν_{max}



72bbnn

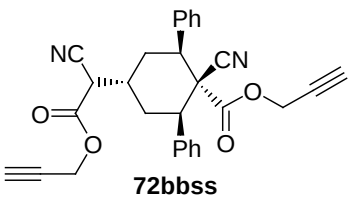
3034, 2984, 2935, 2247 (C≡N), 1743 (O-C=O), 1602, 1494, 1369, 1249, 1180, 1103, 1028, 852, 760 and 702 cm^{-1}; ^1H NMR ($CDCl_3$, 10:1 ratio, major isomer) δ 7.38–7.26 (10H, m) [Ar-H]; 4.24 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 4.01 (1H, d, *J* = 11.6 Hz), 3.74 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.45 (2H, dt, *J* = 14.0, 2.4 Hz), 2.92 (1H, br m), 2.68 (1H, dt, *J* = 14.8, 4.8 Hz), 2.60 (1H, dt, *J* = 14.8, 5.2 Hz), 2.34 (1H, br d, *J* = 15.2 Hz), 1.88 (1H, dd, *J* = 15.2, 2.0 Hz), 1.26 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 0.70 (3H, t, *J* = 7.12 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 10:1 ratio, major isomer) δ 167.1 (C, O-*C*=O), 165.3 (C, O-*C*=O), 137.6 (C), 137.4 (C), 128.6 (4 x CH), 128.33 (CH), 128.29 (CH), 128.2 (2 x CH), 128.1 (2 x CH), 116.2 (C, *C*≡N), 115.7 (C, *C*≡N), 63.1 (CH$_2$, O*C*H$_2$CH$_3$), 62.2 (CH$_2$, O*C*H$_2$CH$_3$), 59.9 (C), 45.1 (CH), 44.7 (CH), 39.4 (CH), 34.8 (CH), 30.4 (CH$_2$), 29.8 (CH$_2$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$), 13.3 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 444.0 (M^+), calcd for $C_{27}H_{28}N_2O_4$ 444.2049; Anal. calcd for $C_{27}H_{28}N_2O_4$ (444.20): C, 72.95; H, 6.35; N, 6.30. Found: C, 72.920; H, 6.381; N, 6.266%.

4-(Allyloxycarbonyl-cyano-methyl)-1-cyano-2,6-diphenyl-cyclohexanecarboxylic acid allyl ester (72bbrr): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (Neat): ν_{max} 2937, 1742 (O-C=O), 1452, 1235, 1172, 990, 937, 763 and 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.26 (10H, m) [Ar-H]; 5.88-5.79 (1H, m, C*H*=CH$_2$), 5.34-5.22 (3H, m, Olefinic-*H*), 4.90 (1H, d, *J* = 10.4 Hz, Olefinic-*H*), 4.74 (1H, d, *J* = 17.2 Hz, Olefinic-*H*), 4.66 (2H, d, *J* = 5.6 Hz, OC*H*$_2$CH=CH$_2$), 4.17 (2H, d, *J* = 5.6 Hz, OC*H*$_2$CH=CH$_2$), 4.03 (1H, d, *J* = 11.6 Hz), 3.45 (2H, dt, *J* = 16.4, 2.8 Hz), 2.91 (1H, br m), 2.69 (1H, dt, *J* = 14.8, 4.8 Hz), 2.60 (1H, dt, *J* = 14.0, 4.8 Hz), 2.32 (1H, d, *J* = 15.2 Hz), 1.87 (1H, d, *J* = 15.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.9 (C, O-*C*=O), 165.0 (C, O-*C*=O), 137.4 (C), 137.3 (C), 130.3 (CH), 130.1 (CH), 128.71 (2 x CH), 128.67 (2 x CH), 128.43 (CH), 128.38 (CH), 128.2 (4 x CH), 120.3 (CH$_2$, CH=*C*H$_2$), 118.5 (CH$_2$, CH=*C*H$_2$), 116.1 (C, *C*≡N), 115.6 (C, *C*≡N), 67.4 (CH$_2$, O*C*H$_2$CH=CH$_2$), 66.5 (CH$_2$, O*C*H$_2$CH=CH$_2$), 60.1 (C), 44.8 (CH), 44.5 (CH), 39.4 (CH), 34.9 (CH), 30.4 (CH$_2$), 29.8 (CH$_2$); LRMS m/z 469.0 ($M+H^+$), calcd for $C_{29}H_{28}N_2O_4$ 468.2049; Anal. calcd for $C_{29}H_{28}N_2O_4$ (468.20): C, 74.34; H, 6.02; N, 5.98. Found: C, 74.390; H, 6.033; N, 6.050%.



72bbrr

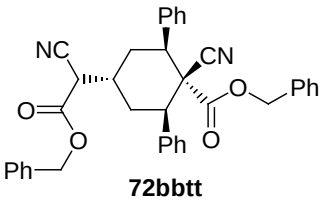
1-Cyano-4-(cyano-prop-2-ynyloxycarbonyl-methyl)-2,6-diphenyl-cyclohexanecarboxylic acid prop-2-ynyl ester (72bbss): Purified by column chromatography using EtOAc/hexane and isolated as a light



72bbss

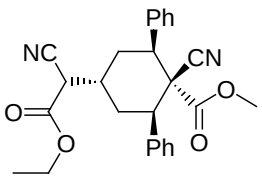
yellow solid. IR (KBr): ν_{max} 3288 (C≡C-*H*), 3035, 2941, 2251 (C≡N), 2131 (C≡C), 1747 (O-C=O), 1602, 1456, 1371, 1230, 1001, 810, 761 and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.32 (10H, m) [Ar-H]; 4.76 (2H, dABq, *J* = 15.6, 2.4 Hz, OC*H*$_2$C≡CH), 4.32 (2H, d, *J* = 2.5 Hz, OC*H*$_2$C≡CH), 4.09 (1H, d, *J* = 11.44 Hz), 3.51 (2H, dt, *J* = 14.0, 2.5 Hz), 2.99-2.96 (1H, br m), 2.64 (1H, dt, *J* = 14.68, 4.8 Hz), 2.64 (1H, dt, *J* = 14.56, 4.72 Hz), 2.39 (1H, t, *J* = 2.8 Hz, C≡C*H*), 2.36 (1H, br d, *J* = 15.0 Hz), 2.30 (1H, t, *J* = 2.8 Hz, C≡C*H*), 1.96 (1H, br d, *J* = 15.28 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.5 (C, O-*C*=O), 164.7 (C, O-*C*=O), 137.2 (C), 137.05 (C), 128.9 (2 x CH), 128.8 (2 x CH), 128.6 (CH), 128.5 (CH), 128.2 (4 x CH), 115.8 (C, *C*≡N), 115.2 (C, *C*≡N), 76.6 (CH, C≡*C*H), 75.83 (CH, C≡*C*H), 75.80 (C, *C*≡CH), 75.7 (C, *C*≡CH), 60.2 (C), 54.2 (CH_2, O*C*H$_2$C≡CH), 53.4 (CH_2, O*C*H$_2$C≡CH), 44.9 (CH), 44.6 (CH), 39.2 (CH), 35.1 (CH), 30.4 (CH_2), 29.8 (CH_2); LRMS m/z 465.0 ($M+H^+$), calcd for $C_{29}H_{24}N_2O_4$ 464.1736; Anal. calcd for $C_{29}H_{24}N_2O_4$ (464.17): C, 74.98; H, 5.21; N, 6.03. Found: C, 74.953; H, 5.202; N, 6.082%.

4-(Benzyloxycarbonyl-cyano-methyl)-1-cyano-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (72bbtt): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 3034, 2937, 2245 (C≡N), 1751 (O-C=O), 1602, 1496, 1454, 1373, 1249, 1159, 1005, 962, 758, 734 and 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–7.14 (18H, m), 6.70 (2H, d, *J* = 7.48 Hz) [Ar-H]; 5.26-5.17 (2H, m, OC*H*$_2$Ph), 4.74 (2H, s, OC*H*$_2$Ph), 4.07 (1H, d, *J* = 11.64 Hz), 3.50-3.44 (2H, m), 2.93-2.90 (1H, br m), 2.69 (1H, dt, *J* = 14.5, 4.88 Hz), 2.54 (1H, dt, *J* = 14.52, 4.76 Hz), 2.39-2.30 (1H, m), 1.75 (1H, d, *J* = 15.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.1 (C, O-*C*=O), 165.3 (C, O-*C*=O), 137.3 (C), 137.2 (C), 134.0 (C), 133.99 (C), 128.9 (CH), 128.81 (2 x CH), 128.78 (2 x CH), 128.71 (2 x CH), 128.6 (2 x CH), 128.5 (CH), 128.4 (CH), 128.3 (2 x CH), 128.22 (2 x CH), 128.20 (2 x CH), 128.11 (CH), 127.58 (2 x CH), 116.1 (C, *C*≡N), 115.6 (C, *C*≡N), 68.8 (CH_2, O*C*H$_2$Ph), 67.6 (CH_2, O*C*H$_2$Ph), 60.2 (C), 44.8 (CH), 44.4 (CH), 39.3 (CH), 35.2 (CH), 30.4 (CH_2), 29.5 (CH_2); LRMS m/z 569.15 ($M+H^+$), calcd for $C_{37}H_{32}N_2O_4$ 568.2362; Anal. calcd for $C_{37}H_{32}N_2O_4$ (568.24): C, 78.15; H, 5.67; N, 4.93. Found: C, 78.155; H, 5.636; N, 4.975%.



72bbtt

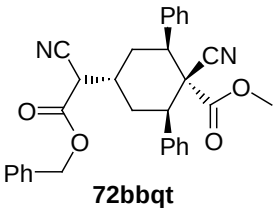
1-Cyano-4-(cyano-ethoxycarbonyl-methyl)-2,6-diphenyl-cyclohexanecarboxylic acid



72bbqn

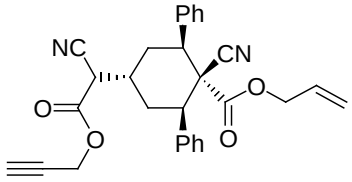
methyl ester (72bbqn): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (Neat): ν_{max} 2931, 2244 (C≡N), 1745 (O-C=O), 1451, 1250, 1179, 1027, 760 and 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.29 (10H, m) [Ar-H]; 4.24 (2H, q, *J* = 7.12 Hz, OC*H*$_2$CH$_3$), 4.00 (1H, d, *J* = 11.56 Hz), 3.46 (2H, dt, *J* = 17.4, 2.52 Hz), 3.28 (3H, s, OC*H*$_3$), 2.93-2.85 (1H, m), 2.68 (1H, dt, *J* = 14.2, 4.6 Hz), 2.60 (1H, dt, *J* = 14.28, 4.84 Hz), 2.32 (1H, d, *J* = 14.72 Hz), 1.86 (1H, d, *J* = 15.04 Hz), 1.26 (3H, t, *J* = 7.12 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.8 (C, O-*C*=O), 165.3 (C, O-*C*=O), 137.5 (C), 137.4 (C), 128.8 (4 x CH), 128.50 (CH), 128.46 (CH), 128.11 (2 x CH), 128.06 (2 x CH), 116.1 (C, *C*≡N), 115.7 (C, *C*≡N), 63.2 (CH$_2$, O*C*H$_2$CH$_3$), 60.3 (C), 52.9 (CH$_3$, O*C*H$_3$), 44.7 (CH), 44.4 (CH), 39.4 (CH), 34.9 (CH), 30.3 (CH$_2$), 29.7 (CH$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 429.0 (M-H$^+$), calcd for $C_{26}H_{26}N_2O_4$ 430.1893; Anal. calcd for $C_{26}H_{26}N_2O_4$ (430.19): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.540; H, 6.102; N, 6.623%.

4-(Benzyloxycarbonyl-cyano-methyl)-1-cyano-2,6-diphenyl-cyclohexanecarboxylic acid methyl ester (72bbqt): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (Neat): ν_{max} 3033, 2952, 1750 (O-C=O), 1735 (O-C=O), 1494, 1452, 1256, 1229, 1166, 1027, 763, 738 and 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–7.20 (15H, m) [Ar-H]; 5.18 (2H, q, *J* = 11.96 Hz, OC*H*$_2$Ph), 4.03 (1H, d, *J* = 11.68 Hz), 3.45-3.39 (2H, m), 3.26 (3H, s, OC*H*$_3$), 2.90-2.87 (1H, br m), 2.64 (1H, dt, *J* = 14.4, 4.76 Hz), 2.50 (1H, dt, *J* = 14.48, 4.48 Hz), 2.30 (1H, d, *J* = 15.04 Hz), 1.71 (1H, d, *J* = 15.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 165.3 (C, O-*C*=O), 137.4 (C), 137.3 (C), 133.9 (C), 128.9 (CH), 128.8 (2 x CH), 128.72 (2 x CH), 128.68 (2 x CH), 128.59 (2 x CH), 128.50 (CH), 128.41 (CH), 128.1 (4 x CH), 116.0 (C, *C*≡N), 115.5 (C, *C*≡N), 68.8 (CH$_2$, OCH$_2$Ph), 60.3 (C), 52.9 (CH$_3$, O*C*H$_3$), 44.7 (CH), 44.2 (CH), 39.3 (CH), 35.1 (CH), 30.2 (CH$_2$), 29.4 (CH$_2$); LRMS m/z 490.85 (M-H$^+$), calcd for $C_{31}H_{28}N_2O_4$ 492.2049; Anal. calcd for $C_{31}H_{28}N_2O_4$ (492.20): C, 75.59; H, 5.73; N, 5.69. Found: C, 75.664; H, 5.783; N, 5.575%.



72bbqt

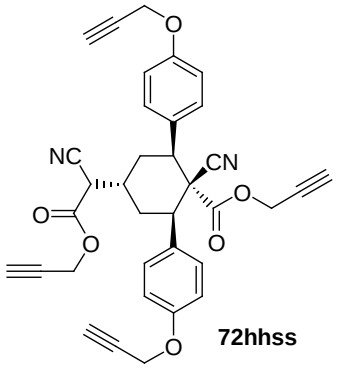
1-Cyano-4-(cyano-prop-2-ynyloxycarbonyl-methyl)-2,6-diphenyl-cyclohexanecarboxylic acid allyl ester (72bbrs): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (KBr): ν_{max} 3283 (C≡C-*H*), 2939, 2247 (C≡N), 2131, 1751 (O-C=O), 1724 (O-C=O), 1494, 1458, 1367, 1311, 1255, 1161,



72bbrs

1005, 943, 760 and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24–7.12 (10H, m) [Ar-H]; 5.14-5.09 (1H, m, C*H*=CH_2), 4.77 (1H, dd, *J* = 10.52, 0.96 Hz, CH=CH_2), 4.67-4.58 (3H, m), 4.04 (2H, d, *J* = 5.56 Hz, OCH_2CH=CH_2), 3.94 (1H, d, *J* = 11.48 Hz), 3.34 (2H, dt, *J* = 14.28, 2.48 Hz), 2.82-2.80 (1H, br m), 2.57 (1H, dt, *J* = 14.72, 4.96 Hz), 2.48 (1H, dt, *J* = 14.88, 4.84 Hz), 2.23 (1H, t, *J* = 2.44 Hz, C≡C*H*), 2.20 (1H, d, *J* = 15.32 Hz), 1.79 (1H, d, *J* = 15.16 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.8 (C, O-*C*=O), 164.6 (C, O-*C*=O), 137.4 (C), 137.2 (C), 130.0 (CH), 128.7 (2 x CH), 128.6 (2 x CH), 128.4 (CH), 128.3 (CH), 128.2 (4 x CH), 118.5 (CH_2, CH=*C*H_2),116.0 (C, *C*≡N), 115.2 (C, *C*≡N), 76.4 (CH, C≡*C*H), 75.7 (C, *C*≡CH), 66.4 (CH_2, O*C*H_2CH=CH_2), 60.0 (C), 54.0 (CH_2, O*C*H_2C≡CH), 44.7 (CH), 44.4 (CH), 39.1 (CH), 35.0 (CH), 30.3 (CH_2), 29.6 (CH_2); LRMS m/z 466.80 ($M+H^+$), calcd for $C_{29}H_{26}N_2O_4$ 466.1893; Anal. calcd for $C_{29}H_{26}N_2O_4$ (466.19): C, 74.66; H, 5.62; N, 6.00. Found: C, 74.671; H, 5.631; N, 6.089%.

1-Cyano-4-(cyano-prop-2-ynyloxycarbonyl-methyl)-2,6-bis-(4-prop-2-ynyloxy-phenyl)-cyclohexanecarboxylic acid prop-2-ynyl ester (72hhss): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (KBr): ν_{max} 3290 (C≡C-*H*), 2930, 2249 (C≡N), 2129 (C≡C), 1747 (O-C=O), 1610, 1512, 1373, 1224, 1026, 831 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (4H, t, *J* = 8.0 Hz), 6.91 (4H, t, *J* = 9.2 Hz) [Ar-H]; 4.80-4.76 (2H, m, OCH_2C≡CH), 4.65 (4H, t, *J* = 2.36, 2 x OCH_2C≡CH), 4.32 (2H, d, *J* = 1.92 Hz, OCH_2C≡CH), 4.03 (1H, d, *J* = 11.44 Hz), 3.42 (2H, dt, *J* = 13.92, 1.92 Hz), 2.93-2.91 (1H, br m), 2.64-2.51 (4H, m), 2.40 (1H, d, *J* = 2.16 Hz), 2.32-2.27 (2H, m), 1.88 (1H, d, *J* = 15.08 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.6 (C, O-*C*=O), 164.6 (C, O-*C*=O), 157.56 (C), 157.48 (C), 130.2 (C), 130.0 (C), 129.2 (4 x CH), 115.8 (C, *C*≡N), 115.3 (C, *C*≡N), 115.1 (2 x CH), 115.0 (2 x CH), 78.3 (CH, C≡*C*H), 76.5 (2 x C, *C*≡CH), 75.8 (CH, C≡*C*H), 75.75 (C, *C*≡CH), 75.72 (C, *C*≡CH), 75.66 (CH, C≡*C*H), 75.62 (CH, C≡*C*H), 60.6 (C), 55.72 (CH_2, O*C*H_2C≡CH), 55.70 (CH_2, O*C*H_2C≡CH), 54.1 (CH_2, O*C*H_2C≡CH), 53.3 (CH_2, O*C*H_2C≡CH), 44.0 (CH), 43.7 (CH), 38.0 (CH), 35.0 (CH), 30.4 (CH_2), 29.8 (CH_2); LRMS m/z 572.80 ($M+H^+$), calcd for $C_{35}H_{28}N_2O_6$ 572.1947; Anal. calcd for $C_{35}H_{28}N_2O_6$ (572.19): C, 73.41; H, 4.93; N, 4.89. Found: C, 73.356; H, 4.921; N, 5.009%.



4: General Experimental Procedures for the Cascade DTCDA Reactions:

4a: L-Proline-Catalyzed Cascade DTCDA Reactions:

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the enone **1**, 0.3 mmol of chiral aldehyde **51** and 0.3 mmol of CH-acid **3** was added 1.0 mL of solvent, and then the catalyst L-proline **4c** (0.06 mmol, 20 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables. The crude reaction mixture was directly loaded on silica gel column with or without aqueous work-up and pure products were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4b: L-Proline-Catalyzed *TCRA* Reaction:

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the spiro ketone *cis*-(–)-**85taj**, 0.3 mmol of CH-acid **3j** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst L-proline **4c** (0.06 mmol, 20 mol%) was added and the reaction mixture was stirred at 25 °C for 24 h. The crude reaction mixture worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot product (–)-**89taj** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4c: Synthesis of Ethyl (4'S,7R,9R,11S)-9-cyano-7-(2,2-dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-3,3-dimethyl-1,5-dioxo-2,4-dioxa-spiro[5.5]undec-9-yl carbonate [(–)-88paa]:

To a stirring solution of 0.5 mmol diisopropylamine in 3 mL of THF, *n*-BuLi (2.0 M, 0.22 mL) was added at 0 °C and stirring continued for 15 min. The reaction mixture was cooled to –78 °C, 0.3 mmol of spiro ketone *cis*-(–)-**85paa** in 3 mL of THF was added, following 15 min additional stirring, 0.45 mmol of ethyl cyanoformate was added and the reaction was allowed to stir at –78 °C for 2 h. The crude reaction mixture was diluted with ether then quenched with aqueous NH_4Cl solution and aqueous layer was extracted with ether. The combined organic layers dried over Na_2SO_4, filtered and concentrated. Pure product **(–)-88paa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4d: Synthesis of 4-Phenyl-2-trimethyl-siloxybuta-1,3-diene 86b:

To the mixture of benzylidene acetone **1b** (1.0 mmol) and chlorotrimethylsilane (1.2 mmol) in dichloromethane (1.0 mL) was added DBU (1.4 mmol) and stirred at 25 °C for 1 h. Then the mixture was diluted with pentane and washed successively with dilute HCl and $NaHCO_3$ solutions and dried over Na_2SO_4, evaporation of the solvent furnished the 4-phenyl-2-trimethyl-siloxybuta-1,3-diene **86b** (80% yield).

4e: Diels-Alder Reaction of 4-Phenyl-2-trimethyl-siloxybuta-1,3-diene 86b with Preformed Olefin 87aa:

Mixture of 4-phenyl-2-trimethyl-siloxybuta-1,3-diene **86b** (0.6 mmol) and (4'*S*)-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **87aa** (0.3 mmol) in dry CH_3CN (1 mL) was stirred at 25 °C for 24 h. The crude reaction mixture worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane. Pure products *cis*-**85baa** and *cis*-**85'baa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Materials and Methods for Biological Studies:

Compounds - AZT- 3'-azido-2', 3'-dideoxythymidine, a known HIV-1 reverse transcriptase inhibitor was taken as a reference compound.[51] MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide was purchased from Himedia. ELISA p24 kit was purchased from Advanced BioSciences Labratories, USA.

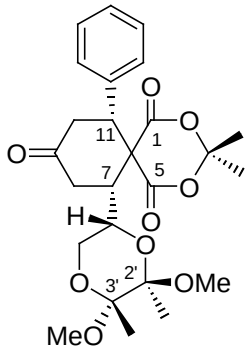
Cells and Viruses - 293T cells were used for production of HIV-1 virus NL4-3. SupT1 cells - a T cell lymphoblastic lymphoma, was used for infection assays. SupT1 cells were subcultured twice a week at a density of 3 X 10^5 cells/ml in RPMI 1640 medium with 10% FBS, 100 U of penicillin per ml, and 100 μg of streptomycin per ml. Pro-viral DNA pNL4-3 and 293T cells were used for virus production as explained in protocol by Kutner R.H et al.[52] The virus batches were quantified for p24 levels by ELISA and stored appropriately in -80ºC until used.

Cytotoxicity Assay - The synthesized compounds were checked for their cytotoxic effect on the cells by MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. In brief SupT1 $0.2x10^6$ (200ul each) were seeded into 96 well plates. Increasing concentration of these synthesized compounds were added and incubated for 18 h at 37 °C, 5% CO_2. Next day, 150μl media was removed and 20μl of MTT was added to each well and incubated for 4 h at 37 °C in dark. Thereafter 100μl of DMSO was used to thoroughly dissolve the purple formazan crystals. The plate was read immediately at 570 nm and background absorbance values at 650 were subtracted from the data obtained. Each experiment was done in triplicate and the data are represented as an average with standard deviations.

Inhibition Assay- Anti HIV activities by the test compounds were assayed as described earlier.[53] In brief SupT1 $0.2x10^6$ (200ul each) were seeded into 96 well plates in RPMI1640

without FBS and antibiotic. Virus NL4-3, at a concentration of 1ng/ml equivalent of p24, without or with increasing concentrations of these compounds [*cis*-**85bga**, *cis*-**85baa**, *cis*-**85paa** and AZT] was added simultaneously to the cells. The cells were then incubated for 5 h at 37 °C in 5% CO_2 incubator. The infected cells were then washed twice with PBS and re-suspended in fresh media with 10% FBS. After 96 hours, cells were collected for MTT assays for cell viability and the supernatant were collected for p24 ELISA to check for virus titers. The experimental set-up with no compound added was taken as zero inhibition and percentage inhibition was calculated for the rest.

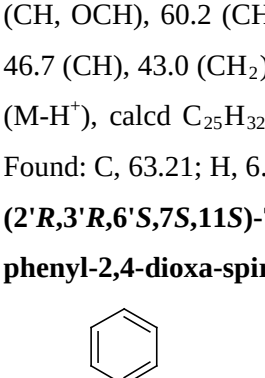
(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-Dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-85bga):



***cis*-85bga**

Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 128 °C; **$[\alpha]^{25}_{D}$ = –98.4 (*c* 1.1, $CHCl_3$)**; IR (neat): ν_{max} 2993, 1761 (O-C=O), 1726 (C=O), 1378, 1282, 1138, 1038, 879, 734 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34-7.27 (3H, m), 7.19-7.17 (2H, m), 3.99 (1H, td, *J* = 11.2, 3.6 Hz), 3.76 (1H, dd, *J* = 14.4, 3.6 Hz), 3.62-3.55 (2H, m), 3.31 (1H, dd, *J* = 11.2, 2.8 Hz), 3.22 (3H, s, OCH_3), 3.18 (3H, s, OCH_3), 3.26-3.16 (1H, m), 3.01 (1H, td, *J* = 14.0, 4.0 Hz), 2.53 (2H, ddd, *J* = 18.8, 14.8, 2.8 Hz), 1.72 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.21 (3H, s, CH_3), 0.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.6 (C, C=O), 168.0 (C, O=C-O), 165.4 (C, O=C-O), 137.0 (C), 129.2 (3 x CH), 128.8 (CH), 128.7 (CH), 107.0 (C, O-C-O), 99.7 (C, O-C-O), 98.0 (C, O-C-O), 67.1 (CH, OCH), 60.2 (CH_2, OCH_2), 55.1 (C), 50.3 (CH_3, OCH_3), 48.8 (CH_3, OCH_3), 47.6 (CH), 46.7 (CH), 43.0 (CH_2), 38.5 (CH_2), 28.9 (CH_3), 28.2 (CH_3), 17.4 (2 x CH_3); LRMS m/z 475.45 ($M\text{-}H^+$), calcd $C_{25}H_{32}O_9$ 476.2046; Anal. calcd for $C_{25}H_{32}O_9$ (476.2046): C, 63.01; H, 6.77. Found: C, 63.21; H, 6.65%.

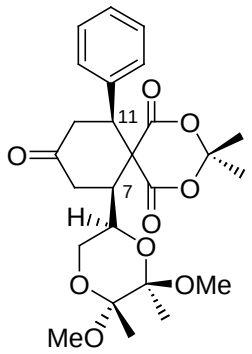
(2'*R*,3'*R*,6'*S*,7*S*,11*S*)-7-(2,3-Dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-85'bga): Prepared following procedure **4a** in DMSO solvent and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. **$[\alpha]^{25}_{D}$ = –77.4 (*c* 0.5, $CHCl_3$)**; IR (neat): ν_{max} 1728 (C=O), 1375, 1282, 1242, 1121, 1039,



***cis*-85'bga**

878, 663 and 621 cm^{-1}; ^1H NMR ($CDCl_3$, isolated as mixture of isomer with *cis*-**1aaa**) δ 7.36-7.30 (3H, m), 7.20-7.18 (2H, m), 4.02-4.00 (1H,m), 3.66 (1H, t, *J* = 11.6 Hz), 3.51-3.39 (2H, m), 3.33-3.26 (2H, m), 3.21 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 3.05-2.96 (1H, m), 2.59-2.48 (2H, m), 1.76 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.22 (3H, s, CH_3), 0.45 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, isolated as mixture of isomer with *cis*-**1aaa**) δ 207.5 (C, C=O), 168.8 (C, O=C-O), 164.7 (C, O=C-O), 136.9 (C), 129.4 (2 x CH), 129.0 (CH), 128.9 (2 x CH), 107.3 (C, O-C-O), 100.4 (C, O-C-O), 98.3 (C, O-C-O), 69.6 (CH, OCH), 60.9 (CH_2, OCH_2), 54.0 (C), 50.9 (CH_3, OCH_3), 48.2 (CH_3, OCH_3), 47.6 (CH), 47.0 (CH), 43.1 (CH_2), 42.0 (CH_2), 28.8 (CH_3), 28.3 (CH_3), 17.6 (CH_3), 17.5 (CH_3).

(2'*R*,3'*R*,6'*R*,7*S*,11*S*)-7-(2,3-Dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-85'bha): Prepared following procedure

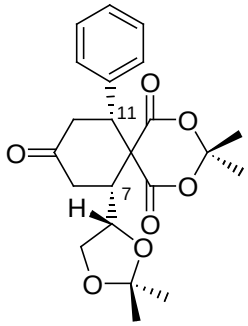


***cis*-85'bha**

4a and purified by column chromatography using EtOAc/hexane and isolated as gummy oil. **$[\alpha]^{25}_D$ = –53.4 (*c* 0.8, $CHCl_3$)**; IR (neat): ν_{max} 1759 (O-C=O), 1726 (C=O), 1375, 1284, 1209, 1064, 704 and 648 cm^{-1}; ^1H NMR ($CDCl_3$, **3:1 ratio of isomers, major**) δ 7.32-7.27 (3H, m), 7.18-6.70 (2H, m), 4.01-3.98 (1H,m), 3.75 (1H, dd, *J* = 14.4, 3.6 Hz), 3.64-3.54 (2H, m), 3.30 (1H, dd, *J* = 11.6, 3.2 Hz), 3.26-3.21 (1H, m), 3.21 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 3.03-2.97 (1H, m), 2.57-2.47 (2H, m), 1.71 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.20 (3H, s, CH_3), 0.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **3:1 ratio of isomers, major**) δ 207.8 (C, C=O), 168.2 (C, O=C-O), 165.6 (C, O=C-O), 137.1 (C), 129.4 (2 x CH), 129.0 (CH), 128.9 (2 x CH), 107.2 (C, O-C-O), 99.8 (C, O-C-O), 98.1 (C, O-C-O), 67.3 (CH, OCH), 60.3 (CH_2, OCH_2), 55.3 (C), 50.5 (CH_3, OCH_3), 48.9 (CH_3, OCH_3), 47.8 (CH), 46.8 (CH), 43.1 (CH_2), 38.7 (CH_2), 29.0 (CH_3), 28.3 (CH_3), 17.5 (2 x CH_3); ^1H NMR ($CDCl_3$, **3:1 ratio of isomers, minor**) δ 7.32-7.27 (3H, m), 7.18-6.70 (2H, m), 3.97-3.92 (1H, m), 3.75 (1H, dd, *J* = 14.4, 3.6 Hz), 3.64-3.54 (2H, m), 3.30 (1H, dd, *J* = 11.6, 3.2 Hz), 3.26-3.21 (1H, m), 3.19 (3H, s, OCH_3), 3.14 (3H, s, OCH_3), 3.03-2.97 (1H, m), 2.57-2.47 (2H, m), 1.74 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.21 (3H, s, CH_3), 0.44 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **3:1 ratio of isomers, minor**) δ 207.5 (C, C=O), 168.8 (C, O=C-O), 164.7 (C, O=C-O), 137.9 (C), 129.4 (2 x CH), 129.0 (2 x CH), 128.9 (CH), 107.2 (C, O-C-O), 100.4 (C, O-C-O), 98.3 (C, O-C-O), 69.6 (CH, OCH), 60.9 (CH_2, OCH_2), 54.0 (C), 50.9 (CH_3, OCH_3), 48.2 (CH_3, OCH_3), 47.6 (CH), 46.9

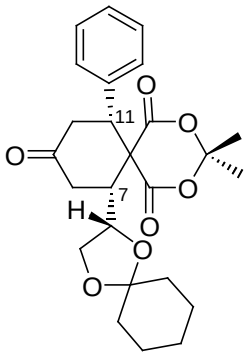
(CH), 43.0 (CH_2), 41.9 (CH_2), 28.8 (CH_3), 28.3 (CH_3), 17.4 (2 x CH_3); LRMS m/z 475.45 ($M-H^+$), calcd $C_{25}H_{32}O_9$ 476.2046; Anal. calcd for $C_{25}H_{32}O_9$ (476.2046): C, 63.01; H, 6.77. Found: C, 63.15; H, 6.71%.

(4'*S*,7*R*,11*R*)-7-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-dimethyl-11-phenyl-2,4-dioxaspiro[5.5]undecane-1,5,9-trione (*cis*-85baa): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 118 °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 0.5 mL/min, λ = 210 nm), t_R = 24.68 min (major); for racemic compound peaks observed at t_R = 19.74 min and t_R = 24.80 min. **$[\alpha]^{25}_D$ = –35.3 (*c* 0.4, $CHCl_3$, >99% ee)**; IR (neat): ν_{max} 2925, 1755 (O-C=O), 1726 (C=O), 1377, 1283, 1247, 1207, 1050, 704 and 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-7.26 (3H, m), 7.20-7.18 (2H, m), 4.22-4.21 (1H, m), 4.01 (1H, t, *J* = 7.6 Hz), 3.80 (1H, dd, *J* = 14.0, 4.0 Hz), 3.74 (1H, dd, *J* = 8.8, 5.2 Hz), 3.58 (1H, t, *J* = 14.4 Hz), 3.32 (1H, t, *J* = 14.4 Hz), 2.81 (1H, dd, *J* = 14.0, 1.6 Hz), 2.58 (1H, dd, *J* = 15.2, 4.0 Hz), 2.48 (1H, dd, *J* = 15.6, 3.2 Hz), 1.63 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.25 (3H, s, CH_3), 0.65 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.2 (C, C=O), 168.9 (C, O=C-O), 164.0 (C, O=C-O), 136.7 (C), 129.2 (2 x CH), 128.7 (CH), 128.6 (2 x CH), 110.5 (C, O-C-O), 106.7 (C, O-C-O), 74.0 (CH, OCH), 66.2 (CH_2, OCH_2), 56.5 (C), 50.1 (CH), 47.8 (CH), 42.9 (CH_2), 36.3 (CH_2), 28.9 (CH_3), 28.5 (CH_3), 25.5 (CH_3), 24.5 (CH_3); LRMS m/z 403.40 ($M+H^+$), calcd $C_{22}H_{26}O_7$ 402.1679; Anal. calcd for $C_{22}H_{26}O_7$ (402.1679): C, 65.66; H, 6.51. Found: C, 65.51; H, 6.68%.



***cis*-85baa**

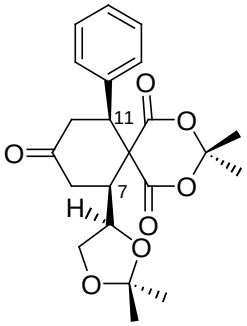
(2'*S*,7*R*,11*R*)-7-(1,4-Dioxa-spiro[4.5]dec-2-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-85bia): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 110 °C; **$[\alpha]^{25}_D$ = –38.2 (*c* 0.8, $CHCl_3$)**; IR (neat): ν_{max} 2938, 1727 (C=O), 1678, 1376, 1280, 1111, 1069, 1038, 810 and 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35-7.29 (3H, m), 7.20 (2H, d, *J* = 4.0 Hz), 4.22 (1H, t, *J* = 4.8 Hz), 4.03



***cis*-85bia**

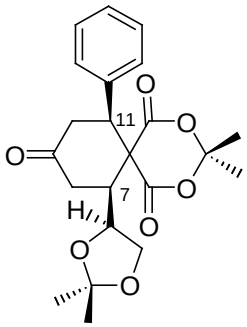
(1H, dd, *J* = 8.8, 6.8 Hz), 3.78 (2H, ddd, *J* = 18.4, 14.0 4.4 Hz), 3.60 (1H, t, *J* = 14.8 Hz), 3.33 (1H, t, *J* = 14.4 Hz), 2.85-2.80 (1H, m), 2.58 (1H, dd, *J* = 15.6, 4.0 Hz), 2.49 (1H, dd, *J* = 15.6, 3.6 Hz), 1.68 (3H, s, CH_3), 1.66-1.46 (10H, m), 0.64 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (C, C=O), 169.0 (C, O=C-O), 164.1 (C, O=C-O), 136.8 (C), 129.2 (2 x CH), 128.8 (CH), 128.6 (2 x CH), 111.4 (C, O-C-O), 106.7 (C, O-C-O), 73.9 (CH, OCH), 65.9 (CH_2, OCH_2), 56.6 (C), 50.1 (CH), 48.0 (CH), 42.9 (CH_2), 36.6 (CH_2), 35.2 (CH_2), 34.3 (CH_2), 29.1 (CH_3), 28.4 (CH_3), 25.0 (CH_2), 23.7 (2 x CH_2); LRMS m/z 443.25 ($M+H^+$), calcd $C_{25}H_{30}O_7$ 442.1992; Anal. calcd for $C_{25}H_{30}O_7$ (442.1992): C, 67.86; H, 6.83. Found: C, 67.91; H, 6.78%.

(4'*R*,7*S*,11*S*)-7-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-dimethyl-11-phenyl-2,4-dioxaspiro[5.5]undecane-1,5,9-trione (*cis*-85'bja): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 119 °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 0.5 mL/min, λ = 210 nm), t_R = 19.17 min (major); for racemic compound peaks observed at t_R = 19.74 min and t_R = 24.80 min. **$[\alpha]^{25}_D$ = +34.1 (*c* 0.3, $CHCl_3$, >99% ee)**; IR (neat): ν_{max} 1759 (O-C=O), 1725 (C=O), 1375, 1285, 1121, 1063, 647 and 616 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36-7.27 (3H, m), 7.22-7.20 (2H, m), 4.24 (1H, br t, *J* = 4.8 Hz), 4.03 (1H, t, *J* = 8.8 Hz), 3.82 (1H, dd, *J* = 14.0, 4.4 Hz), 3.76 (1H, dd, *J* = 9.2, 5.2 Hz), 3.60 (1H, t, *J* = 14.8 Hz), 3.33 (1H, t, *J* = 14.8 Hz), 2.82 (1H, br dd, *J* = 14.0, 2.0 Hz), 2.60 (1H, dd, *J* = 15.6, 4.4 Hz), 2.50 (1H, dd, *J* = 15.6, 4.0 Hz), 1.64 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.27 (3H, s, CH_3), 0.66 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (C, C=O), 169.0 (C, O=C-O), 164.1 (C, O=C-O), 136.8 (C), 129.2 (2 x CH), 128.8 (CH), 128.6 (2 x CH), 110.6 (C, O-C-O), 106.7 (C, O-C-O), 74.1 (CH, OCH), 66.2 (CH_2, OCH_2), 56.6 (C), 50.2 (CH), 47.8 (CH), 42.9 (CH_2), 36.4 (CH_2), 29.0 (CH_3), 28.5 (CH_3), 25.5 (CH_3), 24.5 (CH_3); LRMS m/z 401.20 ($M-H^+$), calcd $C_{22}H_{26}O_7$ 402.1679; Anal. calcd for $C_{22}H_{26}O_7$ (402.1679): C, 65.66; H, 6.51. Found: C, 65.58; H, 6.56%.



***cis*-85'bja**

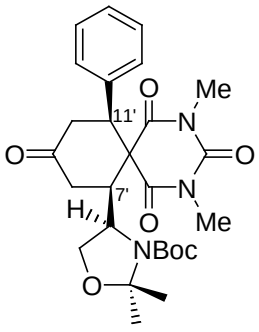
(4'*R*,7*S*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-85'baa): Prepared following procedure **4e** and purified by column chromatography using EtOAc/hexane and isolated as gummy solid. IR



***cis*-85'baa**

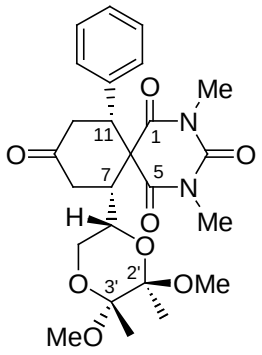
(neat): ν_{max} 1746 (O-C=O, C=O), 1375, 1285, 1217, 1155, 1068, 841 and 611 cm^{-1}; ^{1}H NMR ($CDCl_3$, **3:1 ratio of isomers, minor isomer**) δ 7.33-7.26 (3H, m), 7.19-7.16 (2H, m), 4.11 (1H, dd, *J* = 8.4, 6.4 Hz), 3.94-3.91 (1H, m), 3.81-3.72 (1H, m), 3.67 (1H, dd, *J* = 8.4, 6.0 Hz), 3.46 (1H, t, *J* = 14.8 Hz), 3.13-3.06 (1H, m), 2.89 (1H, t, *J* = 14.4 Hz), 2.47 (1H, dd, *J* = 15.6, 2.8 Hz), 2.22 (1H, dd, *J* = 14.4, 3.6 Hz), 1.64 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.27 (3H, s, CH_3), 0.49 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **3:1 ratio of isomers, minor isomer**) δ 206.3 (C, C=O), 168.0 (C, O=C-O), 165.1 (C, O=C-O), 136.5 (C), 129.1 (2 x CH), 128.8 (CH), 128.7 (2 x CH), 110.8 (C, O-C-O), 107.4 (C, O-C-O), 76.1 (CH, OCH), 68.3 (CH_2, OCH_2), 54.9 (C), 50.5 (CH), 48.7 (CH), 42.5 (CH_2), 40.0 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 25.4 (CH_3), 25.0 (CH_3); LRMS m/z 403.25 ($M+H^+$), calcd $C_{22}H_{26}O_7$ 402.1679; Anal. calcd for $C_{22}H_{26}O_7$ (402.1679): C, 65.66; H, 6.51. Found: C, 65.71; H, 6.48%.

(4*R*,7'*S*,11'*S*)-4-(2,4-Dimethyl-1,3,5,9-tetraoxo-11-phenyl-2,4-diaza-spiro[5.5]undec-7-yl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (*cis*-85'bbj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 160 °C; **$[\alpha]^{25}_{D}$ = +6.6 (*c* 0.8, $CHCl_3$)**; IR (neat): ν_{max} 2360, 2336, 1711 (C=O), 1676 (N-C=O), 1450, 1422, 1382, 1374, 1263, 1103, 1065, 809 and 658 cm^{-1}; ^{1}H NMR ($CDCl_3$, **4:1 ratio of isomers, major**) δ 7.27-7.25 (3H, m), 6.90-6.88 (2H, m), 4.12 (1H, d, *J* = 6.4 Hz), 3.99 (1H, dd, *J* = 9.2, 7.2 Hz), 3.78 (1H, d, *J* = 9.6 Hz), 3.63-3.50 (2H, m), 3.27-3.13 (2H, m), 3.02 (6H, s, 2 x *N*CH_3), 2.66 (1H, dd, *J* = 15.6, 3.6 Hz), 2.50 (1H, dd, *J* = 15.2, 2.8 Hz), 1.52 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.38 (9H, s, 3 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **4:1 ratio of isomers, major**) δ 208.8 (C, C=O), 170.8 (C, O=C-N), 168.4 (C, O=C-N), 154.3 (C), 150.4 (C), 136.0 (C), 129.0 (CH), 128.3 (2 x CH), 127.2 (2 x CH), 95.0 (C, Me_3C-O), 80.8 (C, N-C-O), 67.7 (CH_2, OCH_2), 57.8 (C), 57.5 (CH, NCH), 54.0 (CH), 47.9 (CH), 42.0 (CH_2), 39.0 (CH_2), 28.3 (3 x CH_3), 28.2 (CH_3), 27.9 (CH_3), 26.2 (CH_3), 23.8 (CH_3); LRMS m/z 514.00 ($M+H^+$), calcd $C_{27}H_{35}N_3O_7$ 513.2475; Anal. calcd for $C_{27}H_{35}N_3O_7$ (513.2475): C, 63.14; H, 6.87; N, 8.18. Found: C, 63.25; H, 6.79; N, 8.22%.



***cis*-85'bbj**

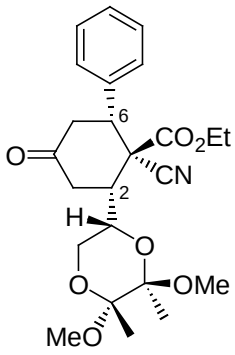
(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-Dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-11-phenyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85bgj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as



***cis*-85bgj**

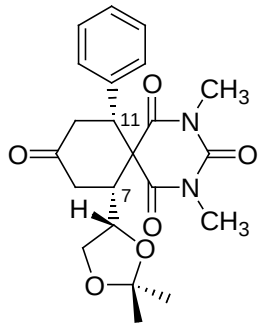
colorless solid. mp.: 114 °C; **$[\alpha]^{25}_{D}$ = –50.1 (*c* 0.6, $CHCl_3$)**; IR (neat): ν_{max} 2954, 1716 (C=O), 1667 (N-C=O), 1422, 1379, 1124, 1038, 879 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27-7.24 (3H, m), 6.94-6.93 (2H, m), 4.01-3.96 (1H, m), 3.64 (1H, t, *J* = 11.2 Hz), 3.59 (1H, dd, *J* = 14.4, 3.6 Hz), 3.43 (1H, t, *J* = 14.8 Hz), 3.31-3.19 (3H, m), 3.16 (6H, s, 2 x OCH_3), 3.06 (3H, s, NCH_3), 2.97 (3H, s, NCH_3), 2.48-2.44 (2H, m), 1.16 (3H, s, CH_3), 1.01 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.9 (C, C=O), 171.1 (C, O=C-N), 169.5 (C, O=C-N), 150.2 (C), 135.9 (C), 128.9 (CH), 128.6 (2 x CH), 127.0 (2 x CH), 99.3 (C, O-C-O), 97.8 (C, O-C-O), 66.7 (CH, OCH), 59.7 (CH_2, OCH_2), 55.5 (C), 52.1 (CH), 48.1 (2 x CH_3, OCH_3), 44.5 (CH), 42.3 (CH_2), 38.6 (CH_2), 28.3 (CH_3, NCH_3), 27.9 (CH_3, NCH_3), 17.3 (CH_3), 17.2 (CH_3); LRMS m/z 489.00 ($M+H^+$), calcd $C_{25}H_{32}N_2O_8$ 488.2159; Anal. calcd for $C_{25}H_{32}N_2O_8$ (488.2159): C, 61.46; H, 6.60; N, 5.73. Found: C, 61.32; H, 6.68; N, 5.65%.

Ethyl (1*R*,2*R*,2'*R*,3'*R*,6'*S*,6*R*)-1-cyano-2-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-4-oxo-6-phenyl-cyclohexanecarboxylate (*cis*-85bgn): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_{D}$ = –71.5 (*c* 2.0, $CHCl_3$)**; IR (neat): ν_{max} 2965, 1746 (O-C=O), 1729 (C=O), 1374, 1262, 1232, 1141, 1036, 878 and 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31-7.27 (3H, m), 7.10-7.09 (2H, m), 4.31-4.26 (3H, m), 3.97-3.87 (2H, m), 3.58 (1H, t, *J* = 10.8 Hz), 3.34 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 3.30-3.18 (2H, m), 2.98-2.85 (2H, m), 2.64-2.59 (1H, m), 1.27 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.03 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.3 (C, C=O), 166.4 (C, O=C-O), 136.6 (C), 128.7 (2 x CH), 128.6 (CH), 128.4 (2 x CH), 117.9 (C, CN), 99.5 (C, O-C-O), 97.9 (C, O-C-O), 66.9 (CH, OCH), 63.0 (CH_2, OCH_2CH_3), 60.4 (CH_2, OCH_2), 51.9 (C), 48.6 (CH_3, OCH_3), 48.2 (CH_3, OCH_3), 48.0 (CH), 41.7 (CH_2), 38.2 (CH), 37.0 (CH_2), 17.4 (CH_3), 17.3 (CH_3), 13.5 (CH_3, OCH_2CH_3); LRMS m/z 445.05 (M^+), calcd $C_{24}H_{31}NO_7$ 445.2101; Anal. calcd for $C_{24}H_{31}NO_7$ (445.2101): C, 64.70; H, 7.01; N, 3.14. Found: C, 64.71; H, 7.11; N, 3.22%.



***cis*-85bgn**

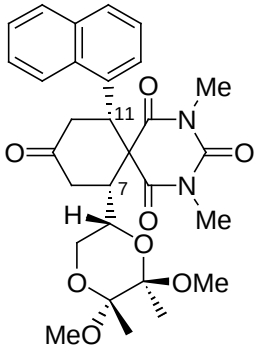
(4'*S*,7*R*,11*R*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-11-phenyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85baj): Prepared following procedure **4a** and



***cis*-85baj**

purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 132 °C; **$[\alpha]^{25}_{D}$ = –19.1 (*c* 0.5, $CHCl_3$)**; IR (neat): ν_{max} 2926, 2855, 1718 (C=O), 1674 (N-C=O), 1446, 1422, 1378, 1254, 1210, 1125, 1060, 704 and 643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (3H, br s, Ph-*H*), 6.99 (2H, br s, Ph-*H*), 3.99-3.98 (1H, m), 3.86 (1H, t, *J* = 8.4 Hz), 3.75-3.66 (2H, m), 3.54 (1H, t, *J* = 14.8 Hz), 3.27 (1H, t, *J* = 14.4 Hz), 3.13-3.05 (1H, m), 3.13 (3H, s, NCH_3), 3.05 (3H, s, NCH_3), 2.56-2.47 (2H, m), 1.26 (3H, s, CH_3), 1.14 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.2 (C, C=O), 171.2 (C, O=C-N), 168.5 (C, O=C-N), 150.2 (C), 136.3 (C), 128.7 (3 x CH), 127.3 (2 x CH), 109.7 (C, O-C-O), 74.7 (CH, OCH), 66.0 (CH_2, OCH_2), 56.8 (C), 51.3 (CH), 46.4 (CH), 42.7 (CH_2), 37.4 (CH_2), 28.4 (CH_3, N*C*H_3), 28.1 (CH_3, N*C*H_3), 25.6 (CH_3), 24.7 (CH_3); LRMS m/z 415.20 ($M+H^+$), calcd $C_{22}H_{26}N_2O_6$ 414.1791; Anal. calcd for $C_{22}H_{26}N_2O_6$ (414.1791): C, 63.76; H, 6.32; N, 6.76. Found: C, 65.85; H, 6.28; N, 6.63%.

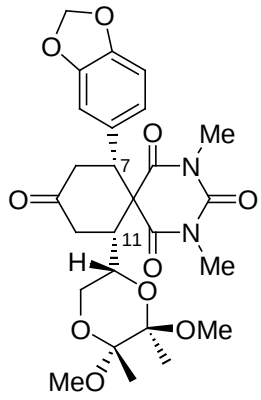
(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-11-naphthalen-1-yl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85agj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_{D}$ = –260.7 (*c* 1.5, $CHCl_3$);** IR (neat): ν_{max} 3011, 1718 (C=O), 1672 (N-C=O), 1448, 1423, 1377, 1272, 1128, 1036, 879, 802 and 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93 (1H, d, *J* = 8.4 Hz), 7.82 (1H, d, *J* = 6.8 Hz), 7.78 (1H, d, *J* = 8.0 Hz), 7.53-7.48 (2H, m), 7.38 (1H, t, *J* = 7.6 Hz), 7.18 (1H, d, *J* = 7.2 Hz), 4.56 (1H, dd, *J* = 14.0, 3.6 Hz), 4.05 (1H, ddd, *J* = 11.6, 6.8, 3.2 Hz), 3.74 (1H, t, *J* = 11.6 Hz), 3.68-3.61 (1H, m), 3.57 (1H, t, *J* = 14.4 Hz), 3.42 (1H, t, *J* = 14.4 Hz), 3.25 (1H, dd, *J* = 11.6, 3.2 Hz), 3.20 (3H, s, OCH_3), 3.18 (3H, s, OCH_3), 3.05 (3H, s, NCH_3), 2.55 (2H, d, *J* = 14.8 Hz), 2.27 (3H, s, NCH_3), 1.17 (3H, s, CH_3), 0.96 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.2 (C, C=O), 170.6 (C, O=C-N), 169.9 (C, O=C-N), 150.0 (C), 133.7 (C), 132.4 (C), 130.5 (C), 129.4 (CH), 128.8 (CH), 126.5 (CH), 126.1 (CH), 124.4 (CH), 123.8 (CH), 122.7 (CH), 99.4 (C, O-C-O), 97.8 (C, O-C-O), 66.4 (CH, OCH), 59.9 (CH_2, OCH_2), 55.1 (C), 48.1 (2 x CH_3, OCH_3), 44.5 (CH), 44.1 (CH), 43.6 (CH_2), 38.8 (CH_2), 27.9 (CH_3, NCH_3), 27.8 (CH_3, NCH_3), 17.3 (CH_3),



***cis*-85agj**

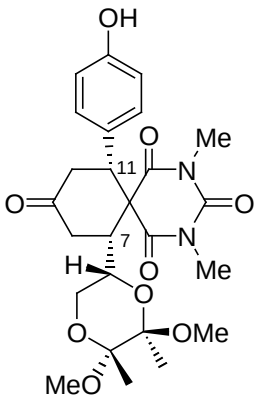
17.0 (CH_3); LRMS m/z 537.35 ($M\text{-}H^+$), calcd $C_{29}H_{34}N_2O_8$ 538.2315; Anal. calcd for $C_{29}H_{34}N_2O_8$ (538.2315): C, 64.67; H, 6.36; N, 5.20. Found: C, 64.55; H, 6.28; N, 5.16%.

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-Benzo[1,3]dioxol-5-yl-11-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85mgj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 138 °C; **$[\alpha]^{25}_D$ = –67.4 (*c* 0.4, $CHCl_3$);** IR (neat): ν_{max} 2926, 2854, 1721 (C=O), 1673 (N-C=O), 1445, 1376, 1284, 1257, 1120, 1037, 880, 817 and 653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.66 (1H, d, *J* = 7.6 Hz), 6.44-6.41 (2H, m), 5.93 (2H, br s, OCH_2O), 4.00-3.97 (1H, m), 3.63 (1H, t, *J* = 11.2 Hz), 3.54 (1H, dd, *J* = 14.4, 3.2 Hz), 3.40-3.31 (2H, m), 3.29-3.25 (2H, m), 3.22 (3H, s, OCH_3), 3.18 (3H, s, OCH_3), 3.08 (3H, s, NCH_3), 3.06 (3H, s, NCH_3), 2.44 (2H, d, *J* = 12.8 Hz), 1.18 (3H, s, CH_3), 1.04 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.8 (C, C=O), 172.2 (C, O=C-N), 169.6 (C, O=C-N), 150.4 (C), 148.0 (C), 147.7 (C), 129.7 (C), 120.8 (CH), 108.2 (CH), 106.9 (CH), 101.4 (CH_2, OCH_2O), 99.4 (C, O-*C*-O), 97.8 (C, O-*C*-O), 66.7 (CH, OCH), 59.6 (CH_2, OCH_2), 55.5 (C), 51.8 (CH), 48.2 (2 x CH_3, OCH_3), 44.5 (CH), 42.8 (CH_2), 38.6 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 17.3 (CH_3), 17.2 (CH_3); LRMS m/z 533.00 ($M+H^+$), calcd $C_{26}H_{32}N_2O_{10}$ 532.2057; Anal. calcd for $C_{26}H_{32}N_2O_{10}$ (532.2057): C, 58.64; H, 6.06; N, 5.26. Found: C, 58.72; H, 6.13; N, 5.19%.



***cis*-85mgj**

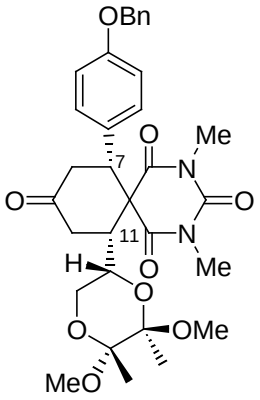
(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-11-(4-hydroxyphenyl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85fgj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 108 °C; **$[\alpha]^{25}_D$ = –70.4 (*c* 0.6, $CHCl_3$);** IR (neat): ν_{max} 1711 (C=O), 1672 (N-C=O), 1425, 1379, 1274, 1137, 1034, 879, 756 and 661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (2H, d, *J* = 8.4 Hz), 6.67 (2H, d, *J* = 8.4 Hz), 3.95-3.93 (1H, m), 3.59 (1H, t, *J* = 11.6 Hz), 3.50 (1H, dd, *J* = 14.0, 3.2 Hz), 3.38-3.29 (2H, m), 3.26-3.19 (2H, m), 3.14 (3H, s, OCH_3), 3.12 (3H, s, OCH_3), 3.03 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 2.43-2.40 (2H, m), 1.13 (3H, s, CH_3), 0.99 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-



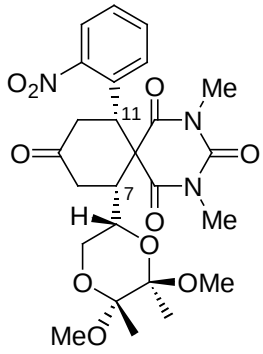
***cis*-85fgj**

135) δ 208.9 (C, C=O), 171.3 (C, O=C-N), 169.6 (C, O=C-N), 156.6 (C), 150.4 (C), 128.2 (2 x CH), 127.1 (C), 115.4 (2 x CH), 99.3 (C, O-C-O), 97.8 (C, O-C-O), 66.6 (CH, OCH), 59.6 (CH_2, OCH_2), 55.6 (C), 51.4 (CH), 48.0 (2 x CH_3, OCH_3), 44.2 (CH), 42.6 (CH_2), 38.5 (CH_2), 28.3 (CH_3, NCH_3), 27.9 (CH_3, NCH_3), 17.2 (CH_3), 17.1 (CH_3); LRMS m/z 505.00 ($M+H^+$), calcd $C_{25}H_{32}N_2O_9$ 504.2108; Anal. calcd for $C_{25}H_{32}N_2O_9$ (504.2108): C, 59.51; H, 6.39; N, 5.55. Found: C, 59.42; H, 6.45; N, 5.48%.

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(4-Benzyloxy-phenyl)-11-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85ngj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_D$ = –74.3 (*c* 1.2, $CHCl_3$);** IR (neat): ν_{max} 2960, 1717 (C=O), 1673 (N-C=O), 1469, 1446, 1424, 1378, 1261, 1131, 1036, 876, 812 and 629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38-7.31 (5H, m), 6.86-6.80 (4H, m), 5.00 (2H, s, OC*H*$_2$Ph), 3.98-3.95 (1H, m), 3.62 (1H, t, *J* = 11.6 Hz), 3.56 (1H, dd, *J* = 14.4, 4.0 Hz), 3.42-3.22 (4H, m), 3.160 (3H, s, OCH_3), 3.157 (3H, s, OCH_3), 3.06 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 2.45-2.42 (2H, m), 1.17 (3H, s, CH_3), 1.02 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.7 (C, C=O), 171.0 (C, O=C-N), 169.4 (C, O=C-N), 158.6 (C), 150.0 (C), 136.3 (C), 128.4 (2 x CH), 128.0 (2 x CH), 127.8 (CH), 127.2 (2 x CH), 127.2 (C), 114.7 (2 x CH), 99.1 (C, O-C-O), 97.6 (C, O-C-O), 69.6 (CH_2, O*C*H$_2$Ph), 66.5 (CH, OCH), 59.4 (CH_2, OCH_2), 55.4 (C), 51.2 (CH), 47.9 (2 x CH_3, OCH_3), 44.2 (CH), 42.4 (CH_2), 38.4 (CH_2), 28.1 (CH_3), 27.7 (CH_3), 17.1 (CH_3), 17.0 (CH_3); LRMS m/z 593.00 ($M-H^+$), calcd $C_{32}H_{38}N_2O_9$ 594.2577; Anal. calcd for $C_{32}H_{38}N_2O_9$ (594.2577): C, 64.63; H, 6.44; N, 4.71. Found: C, 64.45; H, 6.58; N, 4.78%.



***cis*-85ngj**

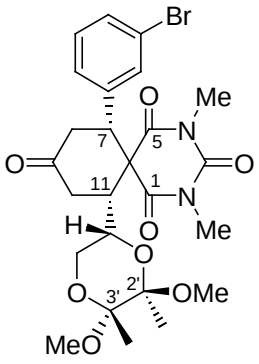


***cis*-85egj**

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-11-(2-nitro-phenyl)-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85egj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. mp.: 72 °C; **$[\alpha]^{25}_D$ = –269.2 (*c* 1.0, $CHCl_3$)**; IR (neat): ν_{max} 1719 (C=O), 1675 (N-C=O), 1533, 1446, 1377, 1189, 1126, 1038, 878, 736, 702 and 683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (1H,

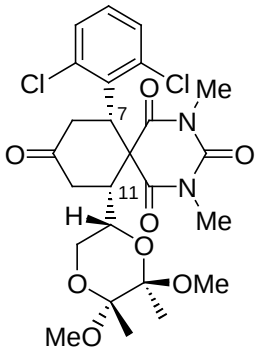
dd, *J* = 7.6, 1.2 Hz), 7.49 (1H, dt, *J* = 7.2, 1.2 Hz), 7.43 (1H, dt, *J* = 7.6, 1.6 Hz), 7.20 (1H, dd, *J* = 7.6, 0.8 Hz), 4.49 (1H, dd, *J* = 14.0, 4.0 Hz), 4.00-3.95 (1H, m), 3.57 (1H, t, *J* = 11.2 Hz), 3.40-3.33 (3H, m), 3.25 (3H, s, OCH_3), 3.26-3.24 (1H, m), 3.16 (3H, s, OCH_3), 3.03 (3H, s, NCH_3), 2.97 (3H, s, NCH_3), 2.67 (1H, dd, *J* = 15.2, 4.0 Hz), 2.48 (1H, dd, *J* = 15.2, 4.4 Hz), 1.16 (3H, s, CH_3), 0.98 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.0 (C, C=O), 170.3 (C, O=C-N), 169.8 (C, O=C-N), 150.3 (C), 150.1 (C), 132.3 (CH), 130.2 (C), 129.5 (CH), 127.4 (CH), 124.9 (CH), 99.4 (C, O-C-O), 97.9 (C, O-C-O), 66.6 (CH, OCH), 59.3 (CH_2, OCH_2), 54.5 (C), 48.2 (2 x CH_3, OCH_3), 45.1 (CH), 44.4 (CH), 42.0 (CH_2), 38.2 (CH_2), 28.7 (CH_3), 28.2 (CH_3), 17.2 (CH_3), 17.1 (CH_3); LRMS m/z 533.40 (M^+), calcd $C_{25}H_{31}N_3O_{10}$ 533.2009; Anal. calcd for $C_{25}H_{31}N_3O_{10}$ (533.2009): C, 56.28; H, 5.86; N, 7.88. Found: C, 56.41; H, 5.80; N, 7.81%.

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(3-Bromophenyl)-11-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85kgj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 128 °C; **$[\alpha]^{25}_D$ = –74.3 (*c* 1.0, $CHCl_3$)**; IR (neat): ν_{max} 1721 (C=O), 1672 (N-C=O), 1426, 1381, 1133, 1084, 1039, 881, 798, 665 and 625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.41 (1H, d, *J* = 8.0 Hz), 7.13 (1H, s), 7.13 (1H, t, *J* = 7.6 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 4.02-3.98 (1H,m), 3.64 (1H, t, *J* = 11.6 Hz), 3.58 (1H, dd, *J* = 14.4, 3.6 Hz), 3.44-3.36 (2H, m), 3.32-3.23 (2H, m), 3.21 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 3.08 (3H, s, NCH_3), 3.04 (3H, s, NCH_3), 2.46 (2H, td, *J* = 14.4, 4.0 Hz), 1.18 (3H, s, CH_3), 1.02 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.2 (C, C=O), 170.9 (C, O=C-N), 169.4 (C, O=C-N), 150.1 (C), 138.2 (C), 132.0 (CH), 130.3 (CH), 130.1 (CH), 125.7 (CH), 122.8 (C), 99.4 (C, O-C-O), 97.8 (C, O-C-O), 66.6 (CH, OCH), 59.6 (CH_2, OCH_2), 55.3 (C), 51.6 (CH), 48.2 (2 x CH_3, OCH_3), 44.6 (CH), 42.1 (CH_2), 38.6 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 17.3 (CH_3), 17.2 (CH_3); LRMS m/z 565.35 ($M\text{-}H^+$), calcd $C_{25}H_{31}BrN_2O_8$ 566.1264; Anal. calcd for $C_{25}H_{31}BrN_2O_8$ (566.1264): C, 52.92; H, 5.51; N, 4.94. Found: C, 52.85; H, 5.59; N, 5.07%.



***cis*-85kgj**

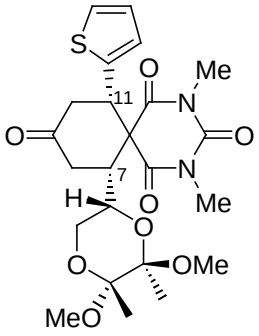
(2'*R*,3'*R*,6'*S*,7*S*,11*R*)-7-(2,6-Dichlorophenyl)-11-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85ogj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and



***cis*-85ogj**

isolated as colorless solid. mp.: 192 °C; **$[\alpha]^{25}_{D}$ = –78.3 (*c* 0.7, $CHCl_3$)**; IR (neat): ν_{max} 1719 (C=O), 1676 (N-C=O), 1442, 1425, 1375, 1265, 1129, 1108, 1038, 875 and 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (1H, d, *J* = 8.0 Hz), 7.19 (1H, d, *J* = 8.0 Hz), 7.08 (1H, t, *J* = 8.0 Hz), 4.62 (1H, dd, *J* = 14.8, 3.2 Hz), 4.04-3.96 (2H, m), 3.72 (1H, t, *J* = 11.6 Hz), 3.59-3.52 (1H, m), 3.33-3.24 (1H, m), 3.28 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 3.20-3.14 (1H, m), 3.04 (3H, s, NCH_3), 2.85 (3H, s, NCH_3), 2.53 (1H, dd, *J* = 15.6, 5.2 Hz), 2.41 (1H, dd, *J* = 15.6, 2.4 Hz), 1.14 (3H, s, CH_3), 0.96 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.6 (C, C=O), 169.5 (C, O=C-N), 169.2 (C, O=C-N), 150.7 (C), 137.2 (C), 135.2 (C), 131.6 (C), 130.8 (CH), 130.0 (CH), 129.5 (CH), 99.5 (C, O-C-O), 97.8 (C, O-C-O), 66.2 (CH, OCH), 59.9 (CH_2, OCH_2), 53.8 (C), 48.3 (CH_3, OCH_3), 48.1 (CH_3, OCH_3), 47.5 (CH), 44.8 (CH), 40.1 (CH_2), 38.8 (CH_2), 28.9 (CH_3), 28.4 (CH_3), 17.3 (CH_3), 17.0 (CH_3); LRMS m/z 557.00 ($M+H^+$), calcd $C_{25}H_{30}Cl_2N_2O_8$ 556.1379; Anal. calcd for $C_{25}H_{30}Cl_2N_2O_8$ (556.1379): C, 53.87; H, 5.42; N, 5.03. Found: C, 53.65; H, 5.48; N, 5.12%.

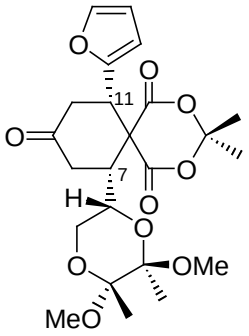
(2'*R*,3'*R*,6'*S*,7*R*,11*S*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-11-thiophen-2-yl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85jgj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow oil. **$[\alpha]^{25}_{D}$ = –84.7 (*c* 1.3, $CHCl_3$)**; IR (neat): ν_{max} 2954, 1674 (N-C=O), 1595, 1386, 1253, 1122, 1037, 1002, 879, 732 and 648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17 (1H, d, *J* = 5.2 Hz), 6.88 (1H, t, *J* = 4.0 Hz), 6.72 (1H, d, *J* = 3.2 Hz), 3.99 (2H, dd, *J* = 14.0, 4.0 Hz), 3.60 (1H, t, *J* = 11.2 Hz), 3.38 (1H, t, *J* = 14.8 Hz), 3.26-3.21 (3H, m), 3.21 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 3.12 (3H, s, NCH_3), 3.09 (3H, s, NCH_3), 2.63 (1H, dd, *J* = 15.2, 4.4 Hz), 2.45 (1H, d, *J* = 10.8 Hz), 1.19 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.8 (C, C=O), 171.3 (C, O=C-N), 169.4 (C, O=C-N), 150.5 (C), 139.0 (C), 126.9 (CH), 125.8 (CH), 125.6 (CH), 99.4 (C, O-C-O), 97.9 (C, O-C-O), 66.9 (CH, OCH), 59.6 (CH_2, OCH_2), 55.9 (C), 48.2 (2 x CH_3, OCH_3), 47.6 (CH), 44.6 (CH), 44.2 (CH_2), 38.4 (CH_2), 28.6 (CH_3, NCH_3), 28.3 (CH_3, NCH_3), 17.3 (2 x CH_3); LRMS m/z 463.50 ($M-OMe^+$),



***cis*-85jgj**

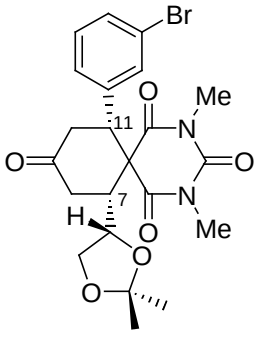
calcd $C_{23}H_{30}N_2O_8S$ 494.1723; Anal. calcd for $C_{23}H_{30}N_2O_8S$ (494.1723): C, 55.86; H, 6.11; N, 5.66. Found: C, 55.92; H, 6.03; N, 5.58%.

(2'*R*,3'*R*,6'*S*,7*R*,11*S*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-11-furan-2-yl-3,3-dimethyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-85pga): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 88 °C; **$[\alpha]^{25}_D$ = –71.5 (*c* 1.4, $CHCl_3$)**; IR (neat): ν_{max} 2986, 1766 (O-C=O), 1730 (C=O), 1377, 1281, 1207, 1129, 1037, 879, 657 and 611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (1H, s), 6.28 (1H, s), 6.17 (1H, d, *J* = 2.8 Hz), 3.97-3.95 (1H, m), 3.88 (1H, dd, *J* = 14.4, 4.0 Hz), 3.54 (1H, t, *J* = 11.6 Hz), 3.49 (1H, t, *J* = 9.6 Hz), 3.27 (1H, dd, *J* = 9.6, 2.8 Hz), 3.20 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 3.08 (1H, t, *J* = 14.4 Hz), 2.87-2.83 (1H, m), 2.51 (2H, dt, *J* = 16.0, 2.8 Hz), 1.76 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.19 (3H, s, CH_3), 0.84 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.8 (C, C=O), 168.2 (C, O=C-O), 165.2 (C, O=C-O), 150.5 (C), 142.7 (CH), 111.0 (CH), 109.6 (CH), 106.8 (C), 99.6 (C, O-C-O), 98.0 (C, O-C-O), 66.7 (CH, OCH), 60.2 (CH_2, OCH_2), 53.9 (C), 48.9 (CH_3, OCH_3), 47.8 (CH_3, OCH_3), 46.5 (CH), 44.0 (CH), 41.4 (CH_2), 38.2 (CH_2), 28.7 (CH_3), 28.6 (CH_3), 17.4 (2 x CH_3); LRMS m/z 465.45 ($M\text{-}H^+$), calcd $C_{23}H_{30}O_{10}$ 466.1839; Anal. calcd for $C_{23}H_{30}O_{10}$ (464.1839): C, 59.22; H, 6.48. Found: C, 59.35; H, 6.41%.



***cis*-85pga**

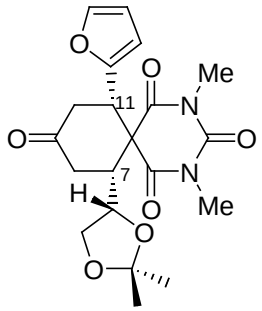
(4'*S*,7*R*,11*R*)-7-(3-Bromo-phenyl)-11-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85kaj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 122°C; **$[\alpha]^{25}_D$ = –21.2 (*c* 1.1, $CHCl_3$)**; IR (neat): ν_{max} 1722 (C=O), 1672 (N-C=O), 1424, 1379, 1265, 1205, 1047, 858, 800 and 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (1H, s), 7.13-7.08 (2H, m), 6.89 (1H, d, *J* = 5.6 Hz), 3.94 (1H, br s), 3.85-3.81 (1H, m), 3.68-3.64 (2H, m), 3.48-3.40 (1H, m), 3.24-3.17 (1H, m), 3.20-3.06 (1H, m), 3.12 (3H, s, NCH_3), 3.06 (3H, s, NCH_3), 2.45 (2H, t, *J* = 20.0 Hz), 1.22 (3H, s, CH_3), 1.14 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.4 (C, C=O), 170.9 (C, O=C-N), 168.2 (C, O=C-N), 149.9 (C), 138.6 (C), 131.7 (CH), 130.4 (CH), 130.1 (CH), 125.8 (CH), 122.7 (C), 109.6 (C, O-C-O), 74.4 (CH,



***cis*-85kaj**

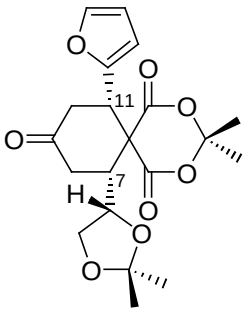
OCH), 65.8 (CH_2, OCH_2), 56.4 (C), 50.5 (CH), 46.5 (CH), 42.3 (CH_2), 37.1 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 25.4 (CH_3), 24.6 (CH_3); LRMS m/z 493.00 ($M+H^+$), calcd $C_{22}H_{25}BrN_2O_6$ 492.0896; Anal. calcd for $C_{22}H_{25}BrN_2O_6$ (492.0896): C, 53.56; H, 5.11; N, 5.68. Found: C, 53.45; H, 5.18; N, 5.61%.

(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85paj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 98 °C; **$[\alpha]^{25}_D$ = –21.2 (*c* 1.3, $CHCl_3$)**; IR (neat): ν_{max} 2926, 2361, 2335, 1714 (C=O), 1677 (N-C=O), 1451, 1422, 1378, 1282, 1150, 1061, 754 and 638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (1H, s), 6.22 (1H, d, *J* = 1.6 Hz), 5.99 (1H, d, *J* = 2.8 Hz), 3.95-3.83 (3H, m), 3.63 (1H, dd, *J* = 8.4, 6.0 Hz), 3.39 (1H, t, *J* = 14.0 Hz), 3.25 (3H, s, NCH_3), 3.18-3.13 (1H, m), 3.13 (3H, s, NCH_3) 2.94-2.90 (1H, m), 2.60 (1H, dd, *J* = 15.2, 4.4 Hz), 2.44-2.39 (1H, m), 1.25 (3H, s, CH_3), 1.16 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.4 (C, C=O), 171.3 (C, N- C=O), 168.0 (C, N=C-O), 151.1 (C), 150.5 (C), 142.5 (CH), 110.5 (CH), 109.8 (C), 107.4 (CH), 74.3 (CH, OCH), 65.9 (CH_2, OCH_2), 55.3 (C), 46.3 (CH), 44.3 (CH), 41.0 (CH_2), 36.7 (CH_2), 28.7 (CH_3, N*C*H_3), 28.2 (CH_3, N*C*H_3), 25.5 (CH_3), 24.6 (CH_3); LRMS m/z 405.00 ($M+H^+$), calcd $C_{20}H_{24}N_2O_7$ 404.1584; Anal. calcd for $C_{20}H_{24}N_2O_7$ (404.1584): C, 59.40; H, 5.98; N, 6.93. Found: C, 59.51; H, 5.92; N, 6.85%.



***cis*-85paj**

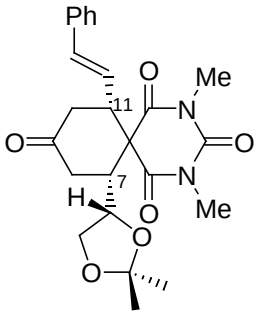
(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-3,3-dimethyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-85paa): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 106 °C; **$[\alpha]^{25}_D$ = –41.6 (*c* 1.0, $CHCl_3$)**; IR (neat): ν_{max} 2928, 1726 (O-C=O), 1687, 1376, 1287, 1210, 1060 and 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (1H, br s), 6.34 (1H, s), 6.21 (1H, s), 4.25 (1H, br s), 4.03-3.96 (2H, m), 3.73 (1H, br s), 3.49 (1H, t, *J* = 14.8 Hz), 3.25 (1H, t, *J* = 14.42 Hz), 2.76 (1H, d, *J* = 13.6 Hz), 2.63 (1H, d, *J* = 15.6 Hz), 2.48 (1H, d, *J* = 15.6 Hz), 1.74 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.13 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.2 (C, C=O), 168.9 (C, O=C-O), 163.7 (C, O=C-O), 150.7 (C), 142.7 (CH), 110.8



***cis*-85paa**

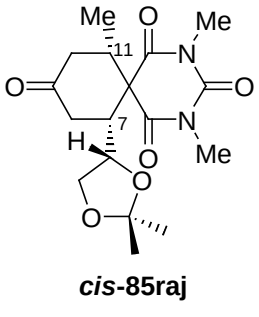
(CH), 110.6 (C, O-C-O), 109.0 (CH), 106.7 (C, O-C-O), 73.9 (CH, OCH), 66.3 (CH_2, OCH_2), 54.9 (C), 47.1 (CH), 44.0 (CH), 41.3 (CH_2), 36.1 (CH_2), 28.8 (2 x CH_3), 25.5 (CH_3), 24.4 (CH_3); LRMS m/z 393.00 ($M+H^+$), calcd $C_{20}H_{24}O_8$ 392.1471; Anal. calcd for $C_{20}H_{24}O_8$ (392.1471): C, 61.22; H, 6.16. Found: C, 61.33; H, 6.21%.

(4'*S*,7*R*,11*R*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-11-styryl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85qaj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. mp.: 176 °C; **$[\alpha]^{25}_D$ = +12.6 (*c* 1.2, $CHCl_3$)**; IR (neat): ν_{max} 2928, 1681 (N-C=O),1444, 1421, 1375, 1268, 1212, 1118, 1057, 850 and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29-7.22 (5H, m, Ph-*H*), 6.44 (1H, d, *J* = 15.6 Hz), 5.73 (1H, dd, *J* = 15.6, 8.8 Hz), 3.98 (1H, br s), 3.90 (1H, t, *J* = 8.4 Hz), 3.67 (1H, t, *J* = 6.4 Hz), 3.44-3.43 (1H, m), 3.30 (3H, s, NCH_3), 3.29 (3H, s, NCH_3), 3.21 (1H, t, *J* = 14.8 Hz), 3.10 (1H, t, *J* = 14.8 Hz), 2.86 (1H, d, *J* = 13.6 Hz), 2.49 (1H, dd, *J* = 15.6 4.8 Hz), 2.41 (1H, dd, *J* = 15.6 4.8 Hz), 1.31 (3H, s, CH_3), 1.21 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.1 (C, C=O), 171.4 (C, O=C-N), 168.6 (C, O=C-N), 150.8 (C), 135.7 (C), 134.6 (CH), 128.7 (2 x CH), 128.3 (CH), 126.4 (2 x CH), 124.5 (CH), 109.9 (C, O-C-O), 74.4 (CH, OCH), 66.0 (CH_2, OCH_2), 56.1 (C), 48.8 (CH), 47.0 (CH), 42.9 (CH_2), 36.5 (CH_2), 28.8 (CH_3, NCH_3), 28.5 (CH_3, NCH_3), 25.6 (CH_3), 24.7 (CH_3); LRMS m/z 441.55 ($M+H^+$), calcd $C_{24}H_{28}N_2O_6$ 440.1947; Anal. calcd for $C_{24}H_{28}N_2O_6$ (440.1947): C, 65.44; H, 6.41; N, 6.36. Found: C, 65.29; H, 6.49; N, 6.28%.



***cis*-85qaj**

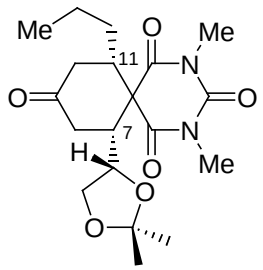
(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4,11-trimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85raj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 138 °C; **$[\alpha]^{25}_D$ = –20.0 (*c* 0.2, $CHCl_3$);** IR (neat): ν_{max} 2928, 1713 (C=O), 1674 (N-C=O), 1446, 1422, 1376, 1275, 1058, 755 and 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (1H, dt, *J* = 6.0, 2.8 Hz), 3.87 (1H, dd, *J* = 8.8, 6.4 Hz), 3.62 (1H, dd, *J* = 8.8, 6.0 Hz), 3.39 (3H, s, NCH_3), 3.30 (3H, s, NCH_3), 3.02-2.88 (2H, m), 2.78-2.74 (2H, m), 2.37 (2H, m), 1.29 (3H, s, CH_3), 1.20 (3H, s, CH_3), 0.86 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.8 (C, C=O), 172.0 (C, O=C-N), 168.6



***cis*-85raj**

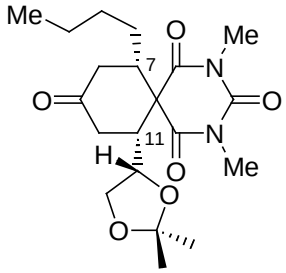
(C, O=C-N), 151.0 (C), 109.9 (C, O-C-O), 74.4 (CH, OCH), 66.0 (CH_2, OCH_2), 56.1 (C), 47.4 (CH), 44.8 (CH_2), 40.3 (CH), 36.4 (CH_2), 28.9 (CH_3), 28.5 (CH_3), 25.6 (CH_3), 24.7 (CH_3), 16.8 (CH_3); LRMS m/z 352.85 ($M+H^+$), calcd $C_{17}H_{24}N_2O_6$ 352.1634; Anal. calcd for $C_{17}H_{24}N_2O_6$ (352.1634): C, 57.94; H, 6.86; N, 7.95. Found: C, 57.98; H, 6.79; N, 7.88%.

(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-11-propyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85saj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 92 °C; **$[\alpha]^{25}_D$ = –13.0 (*c* 0.7, $CHCl_3$);** IR (neat): ν_{max} 2985, 2361, 1679 (C=O), 1449, 1420, 1376, 1269, 1058 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93-3.89 (1H, m), 3.86 (1H, t, *J* = 8.4 Hz), 3.60 (1H, dd, *J* = 8.0, 5.2 Hz), 3.37 (3H, s, NCH_3), 3.27 (3H, s, NCH_3), 2.99 (1H, t, *J* = 15.2 Hz), 2.79 (1H, dd, *J* = 14.8, 11.2 Hz), 2.72-2.61 (2H, m), 2.53 (1H, dd, *J* = 15.2, 4.8 Hz), 2.33 (1H, dd, *J* = 15.6, 3.6 Hz), 1.36-1.30 (1H, m), 1.27 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.14-1.04 (3H, m), 0.81 (3H, t, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.0 (C, C=O), 172.1 (C, O=C-N), 168.8 (C, O=C-N), 151.0 (C), 109.8 (C, O-C-O), 74.3 (CH, OCH), 66.0 (CH_2, OCH_2), 56.1 (C), 47.7 (CH), 44.5 (CH), 42.0 (CH_2), 36.4 (CH_2), 33.8 (CH_2), 28.9 (CH_3), 28.4 (CH_3), 25.6 (CH_3), 24.6 (CH_3), 19.6 (CH_2), 13.7 (CH_3); LRMS m/z 381.35 ($M+H^+$), calcd $C_{19}H_{28}N_2O_6$ 380.1947; Anal. calcd for $C_{19}H_{28}N_2O_6$ (380.1947): C, 59.98; H, 7.42; N, 7.36. Found: C, 59.88; H, 7.37; N, 7.45%.



***cis*-85saj**

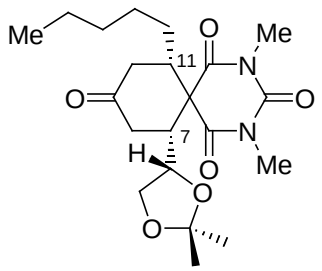
(4'*S*,7*S*,11*R*)-7-Butyl-11-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85taj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 90 °C; **$[\alpha]^{25}_D$ = –13.6 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2986, 2361, 1678 (C=O), 1450, 1377, 1275, 1266, 1060 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90-3.86 (1H, m), 3.84 (1H, t, *J* = 8.0 Hz), 3.59 (1H, dd, *J* = 8.4, 5.6 Hz), 3.35 (3H, s, NCH_3), 3.26 (3H, s, NCH_3), 2.98 (1H, t, *J* = 14.4 Hz), 2.78 (1H, t, *J* = 12.8 Hz), 2.71-2.67 (1H, m), 2.62-2.48 (2H, m), 2.31 (1H, dd, *J* = 15.6, 4.0 Hz), 1.26 (3H, s, CH_3), 1.22-1.20 (2H, m), 1.16 (3H, s, CH_3), 1.16-1.10 (4H, m), 0.79 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.9 (C, C=O), 172.0 (C, O=C-N), 168.8 (C, O=C-N), 151.0



***cis*-85taj**

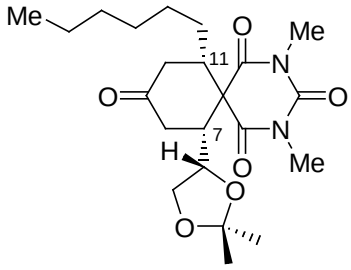
(C), 109.8 (C, O-C-O), 74.3 (CH, OCH), 65.9 (CH_2, OCH_2), 56.1 (C), 47.6 (CH), 44.6 (CH), 42.0 (CH_2), 36.4 (CH_2), 31.4 (CH_2), 28.8 (CH_3), 28.5 (CH_2), 28.4 (CH_3), 25.6 (CH_3), 24.6 (CH_3), 22.2 (CH_2), 13.7 (CH_3); LRMS m/z 395.40 ($M+H^+$), calcd $C_{20}H_{30}N_2O_6$ 394.2104; Anal. calcd for $C_{20}H_{30}N_2O_6$ (394.2104): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.75; H, 7.61; N, 7.22%.

(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-11-pentyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85uaj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 88 °C; **$[\alpha]^{25}_D$ = –13.0 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2924, 1677 (C=O), 1421, 1376, 1132, 1056, 880 and 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91-3.84 (2H, m), 3.60 (1H, dd, *J* = 8.4, 5.6 Hz), 3.37 (3H, s, NCH_3), 3.27 (3H, s, NCH_3), 3.00 (1H, t, *J* = 14.4 Hz), 2.82-2.68 (2H, m), 2.63-2.52 (2H, m), 2.33 (1H, dd, *J* = 15.6, 3.6 Hz), 1.27 (3H, s, CH_3), 1.28-1.10 (8H, m), 1.17 (3H, s, CH_3), 0.82 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.0 (C, C=O), 172.1 (C, O=C-N), 168.8 (C, O=C-N), 151.0 (C), 109.8 (C, O-C-O), 74.3 (CH, OCH), 66.0 (CH_2, OCH_2), 56.1 (C), 47.7 (CH), 44.7 (CH), 42.0 (CH_2), 36.4 (CH_2), 31.7 (CH_2), 31.3 (CH_2), 28.8 (CH_3), 28.4 (CH_3), 26.1 (CH_2), 25.6 (CH_3), 24.6 (CH_3), 22.3 (CH_2), 13.8 (CH_3); LRMS m/z 409.00 ($M+H^+$), calcd $C_{21}H_{32}N_2O_6$ 408.2260; Anal. calcd for $C_{21}H_{32}N_2O_6$ (408.2260): C, 61.75; H, 7.90; N, 6.86. Found: C, 61.82; H, 7.82; N, 6.75%.



***cis*-85uaj**

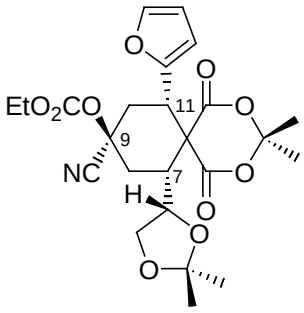
(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-11-hexyl-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-85vaj): Prepared following procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 88 °C; **$[\alpha]^{25}_D$ = –13.8 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2988, 2361, 1675 (C=O), 1451, 1421, 1378, 1274, 1209,, 1056, 878, 755 and 653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89-3.88 (1H, m), 3.84 (1H, t, *J* = 8.4 Hz), 3.59 (1H, dd, *J* = 8.4, 5.6 Hz), 3.36 (3H, s, NCH_3), 3.26 (3H, s, NCH_3), 2.98 (1H, t, *J* = 14.8 Hz), 2.77 (1H, t, *J* = 14.4 Hz), 2.68 (1H, br dd, *J* = 14.0, 2.0 Hz), 2.61-2.56 (1H, m), 2.51 (1H, dd, *J* = 15.2, 4.8 Hz), 2.31 (1H, dd, *J* = 15.6, 3.6 Hz), 1.26 (3H, s, CH_3), 1.22-1.08 (10H, m), 1.16 (3H, s, CH_3), 0.82 (3H, t, *J* =



***cis*-85vaj**

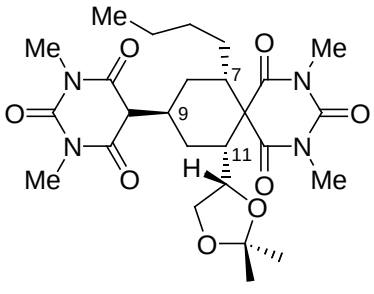
6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.9 (C, C=O), 172.0 (C, O=C-N), 168.8 (C, O=C-N), 151.0 (C), 109.8 (C, O-C-O), 74.3 (CH, OCH), 65.9 (CH_2, OCH_2), 56.1 (C), 47.6 (CH), 44.7 (CH), 42.0 (CH_2), 36.4 (CH_2), 31.7 (CH_2), 31.4 (CH_2), 28.85 (CH_2), 28.83 (CH_3), 28.4 (CH_3), 26.4 (CH_2), 25.6 (CH_3), 24.6 (CH_3), 22.4 (CH_2), 13.9 (CH_3); LRMS m/z 423.00 ($M+H^+$), calcd $C_{22}H_{34}N_2O_6$ 422.2417; Anal. calcd for $C_{22}H_{34}N_2O_6$ (422.2417): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.48; H, 8.23; N, 6.55%.

Ethyl (4'*S*,7*R*,9*R*,11*S*)-9-cyano-7-(2,2-dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-3,3-dimethyl-1,5-dioxo-2,4-dioxa-spiro[5.5]undec-9-yl carbonate [(–)-88paa]: Prepared following procedure **4c** and purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_D$ = –33.5 (*c* 0.5, $CHCl_3$)**; IR (neat): ν_{max} 2990, 1757 (O-C=O), 1736 (C=O), 1374, 1257, 1067, 1014, 735 and 627 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (1H, d, *J* = 0.8 Hz), 6.30 (1H, dd, *J* = 3.2, 1.6 Hz), 6.18 (1H, d, *J* = 3.2 Hz), 4.28 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.21-4.19 (1H, m), 4.07 (1H, dd, *J* = 9.2, 7.6 Hz), 3.96 (1H, dd, *J* = 13.6, 3.2 Hz), 3.78 (1H, dd, *J* = 9.2, 4.8 Hz), 3.03 (1H, t, *J* = 13.2 Hz), 2.78-2.73 (3H, m), 2.46 (1H, d, *J* = 10.8 Hz), 1.68 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.34 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.24 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.5 (C,O-C=O), 163.7 (C, O=C-O), 152.3 (C, O-(O=*C*)-O), 150.4 (C), 142.7 (CH), 117.5 (C, CN), 110.9 (CH), 110.6 (C, O-C-O), 109.2 (CH), 106.6 (C, O-C-O), 74.3 (C), 73.8 (CH, OCH), 66.7 (CH_2, OCH_2), 65.2 (CH_2, O*C*H$_2$CH$_3$), 54.8 (C), 45.8 (CH), 41.8 (CH), 34.0 (CH_2), 29.1 (CH_2), 28.9 (CH_3), 28.8 (CH_3), 25.6 (CH_3), 24.2 (CH_3), 14.1 (CH_3, OCH_2CH_3); LRMS m/z 490.25 ($M-H^+$), calcd $C_{24}H_{29}NO_{10}$ 491.1791; Anal. calcd for $C_{24}H_{29}NO_{10}$ (491.1791): C, 58.65; H, 5.95; N, 2.85. Found: C, 58.47; H, 5.89; N, 2.90%.



(–)-88paa

(4'*S*,7*S*,9*S*,11*R*)-7-Butyl-11-(2,2-dimethyl-[1,3]dioxolan-4-yl)-9-(1,3-dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5-trione [(–)-89taj]: Prepared following procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 96 °C; **$[\alpha]^{25}_D$ = –31.6 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2958, 2926, 2360, 1675 (N-C=O), 1445, 1373, 1261, 1131, 1062, 758 and 641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ



(–)-89taj

3.88-3.78 (3H, m), 3.37 (3H, s, NC*H*$_3$), 3.28 (6H, s, 2 x NC*H*$_3$), 3.24 (3H, s, NC*H*$_3$), 2.69 (1H, d, *J* = 12.4 Hz), 2.53-2.48 (1H, m), 2.31-2.17 (3H, m), 1.85 (1H, d, *J* = 13.2 Hz), 1.52 (1H, d, *J* = 13.6 Hz), 1.26 (3H, s, CH_3), 1.26-1.18 (5H, m), 1.18 (3H, s, CH_3), 0.95-0.84 (5H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 173.0 (C, O=C-N), 169.3 (C, O=C-N), 168.8 (C, O=C-N), 168.6 (C, O=C-N), 151.9 (C), 151.4 (C), 109.4 (C, O-C-O), 75.0 (CH, OCH), 66.0 (CH_2, OCH_2), 57.0 (C), 51.5 (CH), 42.9 (CH), 39.7 (CH), 37.2 (CH), 31.3 (CH_2), 28.77 (CH_3), 28.75 (CH_3), 28.72 (CH_3) 28.4 (CH_3), 27.2 (2 x CH_2), 25.7 (CH_3), 24.5 (CH_3), 22.5 (CH_2), 22.2 (CH_2), 13.8 (CH_3); LRMS m/z 535.25 ($M+H^+$), calcd $C_{26}H_{38}N_4O_8$ 534.2690; Anal. calcd for $C_{26}H_{38}N_4O_8$ (534.2690): C, 58.41; H, 7.16; N, 10.48. Found: C, 58.29; H, 7.22; N, 10.55%.

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682180 contains the supplementary crystallographic data for this crystal structure; X-ray crystal data of **38da**: $C_{12}H_{10}O_2$; MW = 186.20, Triclinic, space group p-1, with a = 6.589(3) Å, b = 7.550(3) Å, c = 9.691(4) Å, α = 97.609º, β = 103.781º, γ = 106.000º. CCDC-681487 contains the supplementary crystallographic data for this crystal structure.

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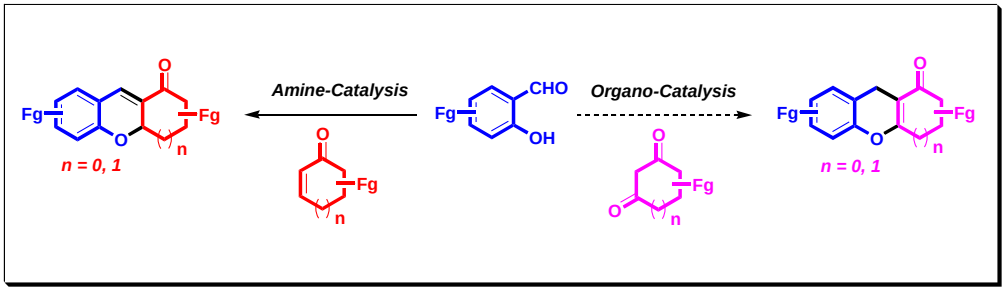
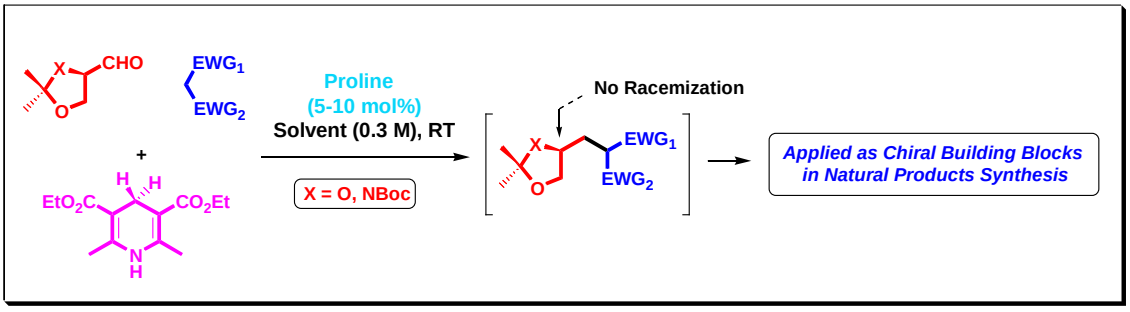
1. Multi-catalysis Reactions: Direct Organocatalytic Sequential One-pot Synthesis of Highly Functionalized Cyclopenta[b]chromen-1-ones.



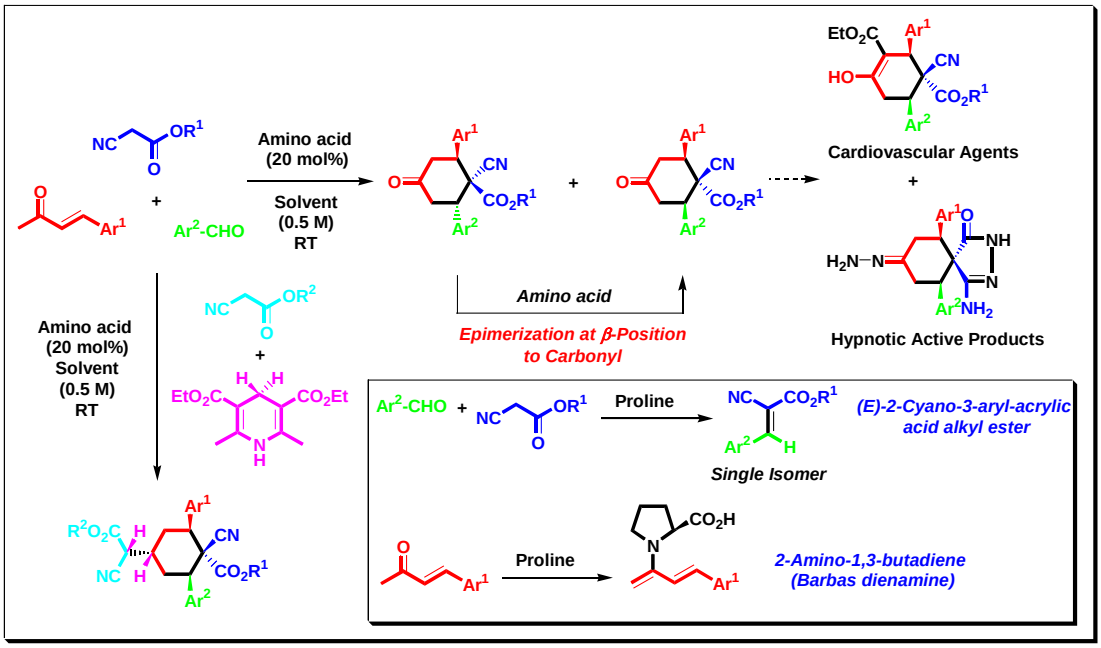
***Org. Biomol. Chem.*, 2008**, *6*, 4188–4197.

2. Sustainable Approach to the Chiral Building Blocks *via* Direct Amino Acid-Catalyzed Cascade *TCRA* Reactions: Formal Total Synthesis of HIV-1 Protease Inhibitors, Antibiotic Agglomerins, Brefeldin A and (*R*)-γ-Hexanolide.



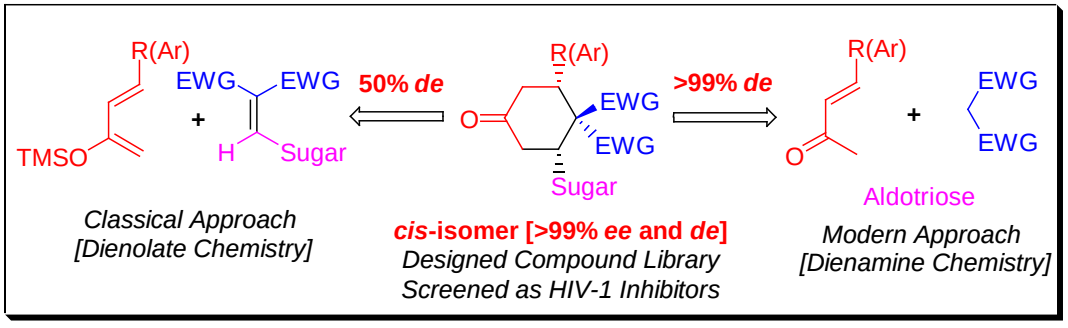
***J. Org. Chem.*, 2010**, *75*, 74-85.

3. Double Cascade Reactions Based on the Barbas Dienamine Platform: Highly Stereoselective Synthesis of Functionalized Cyclohexanes for the Cardiovascular Agents.



***Org. Biomol. Chem.*, 2008**, *6*, 719–726.

4. Design, Synthesis and Biological Evaluation of Optically Pure Functionalized Spiro[5,5]undecane-1,5,9-triones as HIV-1 Inhibitors.



***Org. Biomol. Chem.*, 2011**, *9*, 7282-7286.