Development of Organocatalytic Biomimetic Reductions:
Scope and Synthetic Applications

A Thesis
Submitted for the Degree of

Doctor of Philosophy

By

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DEDICATED TO

MY AMMA AND NANNA

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

KISHOR MAMILLAPALLI
(Candidate)

CERTIFICATE

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

Dr. D. B. RAMACHARY
(THESIS SUPERVISOR)

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PREFACE

*Catalysis is the very important tool in organic synthesis to access highly functionalized molecules with stereo- and regioselectivities. In this field, mainly, metal catalysis exploited to synthesize complex functionalities with good selectivity. Recently, using substoichiometric organic compounds namely organocatalysts to perform reactions is dominating as in explosive growth and introduced a new area of catalysis with best characteristics compared to metal catalysis. The present thesis entitled "***Development of Organocatalytic Biomimetic Reductions: Scope and Synthetic Applications***" describes the first applications of Hantzsch ester in cascade reactions and its pharmaceutical applications. 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 diverse compounds such as biologically active products, 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 aldehydes, ketones, CH-acids, Hantzsch ester and alkyl halides through cascade olefination-hydrogenation-alkylation (O/H/A) and hydrogenation-olefination-hydrogenation (H/O/H) reaction sequences in one-pot under stereospecific organo- and organo/metal-carbonate-catalysis. Along with we demonstrated highly substituted 1,2,3-traizole from simple substrates by means two step combination of olefination-hydrogenation-alkylation and Huisgen cycloaddition reaction sequences under stereospecific organo-copper-catalysis. The products formation has given strong support to our hypothesis that, "by decreasing the HOMO-LUMO energy gap between olefins and Hantzsch ester will drive the bio-mimetic hydrogenation reaction by self-catalysis".

In a similar manner, a practical and novel organocatalytic chemo- and enantioselective process for the cascade synthesis of highly substituted 2-alkyl-cyclohexane-1,3-diones and W-M ketone analogs is presented first time via three component reductive alkylation (TCRA) as an important step. Here, we developed the one-step alkylation of dimedone and 1,3-cyclohexanedione with aldehydes and Hantzsch ester through organocatalytic TCRA strategy. In continuation, using combination of L-proline-catalyzed cascade olefination/hydrogenation and cascade Robinson annulation of 1,3-cyclohexanedione, aldehydes, Hantzsch ester and methyl vinyl ketone constructed the highly functionalized W-M ketone analogs in good to high yields and with excellent enantioselectivities. This TCRA strategy provided access to synthesize natural product skeletons and intermediates for the pharmaceutical chemistry.

In continuation to TCRA strategy, first time we applied this technique for the cascade synthesis of 2-alkyl-cyclopentane-1,3-diones, 2-alkyl-3-methoxy-cyclopent-2-enones and Hajos-Parrish (H-P) ketone analogs from cyclopentane-1,3-dione with aldehydes/ketones and Hantzsch ester in organocatalytic strategy. Direct combination of amino acid-catalyzed cascade olefination/hydrogenation and cascade Robinson annulation's of cyclopentane-1,3-dione, aldehydes/ketones, Hantzsch ester and methyl vinyl ketone furnished the highly functionalized H-P ketone analogues in good to high yields and with excellent enantioselectivities and also shown direct application in pharmaceutical chemistry.

Further extension of TCRA strategy, first time we succeeded in the synthesis of highly substituted tetrahydro-isobenzofuran-1,5-diones in practical and sustainable manner through asymmetric cascade Michael-aldol reaction of 4-hydroxy-3-alkyl-5H-furan-2-ones with alkyl vinyl ketones in the presence of a catalytic amount of L-proline or 9-amino-9-deoxyepiquinine/TCA. In this chapter, first time we achieved the asymmetric synthesis of privileged bicyclic lactones through kinetic resolution and shown as synthetic application to the pharmaceuticals and natural products synthesis.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Anal.	analysis
aq.	Aqueous
Ar	aryl
Bn	benzyl
Bp	boiling point
br	broad
Bu	butyl
t-Bu or ^{t}Bu	*tertiar*y-butyl
Bz	benzoyl
Calcd.	calculated
cat.	catalytic
cm	centimeter
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
ddt	doublet of doublet of triplet
dt	doublet of triplet
ddd	doublet of doublet of doublet
DEPT	distortionless enhancement by polarization transfer
DMAP	dimethylaminopyridine
DME	dimethoxy ethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
eq.	equation
equv.	equivalent(s)
Et	ethyl
EVK	ethyl vinyl ketone
EWG	electron withdrawing group
Fig.	figure
gm	gram (s)
h	hour (s)
Hz	hertz
Hex	hexyl
^{i}Pr	isopropyl
IR	infrared
LAH	lithium aluminum hydride
lit.	literature
m	multiplet
Mp.	melting point
Me	methyl
mg	milligram (s)
mL	milliliter
mmol	millimole

MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
py	pyridine
pr	propyl
q	quartet
rt	room temperature
s	singlet
sec	secondary
t	triplet
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
W-M ketone	Wieland-Miescher ketone
H-P ketone	Hajos-Parrish ketone
TCA	trichloro aceticacid

ABOUT THE AUTHOR

The author, **Mr. Kishor Mamillapalli** was born on 5th December 1978 at Appalarajugudem, West Godavari, Andhra Pradesh. After his initial schooling in Kamavarapukota, he obtained his B.Sc. degree in 1999 from Sir. C. R. R. College, Eluru; and M. Sc., degree in 2002 from D. L. R. P. G. Courses, G. Mamida, East Godavari. He joined the School of Chemistry, University of Hyderabad in the Ph. D. degree programme in March 2005.

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2. D. B. Ramachary, **M. Kishor** and K. Ramakumar, A novel and green protocol for two-carbon homologation: a direct amino acid/K_2CO_3-catalyzed four-component reaction of aldehydes, active methylenes, Hantzsch esters and alkyl halides, ***Tetrahedron Lett.,*** **2006**, *47*, 651–656.
3. D. B. Ramachary, **M. Kishor** and G. Babul Reddy, Development of drug intermediates by using direct organocatalytic multi-component reactions, ***Org. Biomol. Chem.,*** **2006**, *4*, 1641–1646.
4. D. B. Ramachary and **M. Kishor**, Organocatalytic sequential one-pot double cascade asymmetric synthesis of Wieland-Miescher ketone analogues from a Knoevenagel/hydrogenation/Robinson annulation sequence: scope and applications of organocatalytic biomimetic reductions, ***J. Org. Chem.,*** **2007**, *72*, 5056–5068.

5. D. B. Ramachary, **M. Kishor** and Y. V. Reddy, Development of pharmaceutical drugs, drug intermediates and ingredients by using direct organo-click reactions, ***Eur. J. Org. Chem.*,** **2008**, 975–998.
6. D. B. Ramachary and **M. Kishor**, Direct amino acid-catalyzed cascade biomimetic reductive alkylations: application to the asymmetric synthesis of Hajos–Parrish ketone analogues, ***Org. Biomol. Chem.*,** **2008**, *6*, 4176–4187.
7. D. B. Ramachary, Y. V. 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.
8. D. B. Ramachary, C. Venkaiah, Y. V. 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.
9. D. B. Ramachary and **M. Kishor**, Direct catalytic asymmetric synthesis of highly functionalized tetronic acids/tetrahydro-isobenzofuran-1,5-diones *via* combination of cascade three-component reductive alkylations and Michael-aldol reactions, ***Org. Biomol. Chem.*,** **2010**, *8*, 2859–2867.

Development of Organocatalytic Biomimetic Reductions: Scope and Synthetic Applications

1. ABSTRACT

A diversity-oriented green synthesis of highly useful compounds were assembled from simple substrates like aldehydes, ketones, CH-acids, Hantzsch ester and alkyl halides through cascade olefination-hydrogenation (O/H), olefination-hydrogenation-alkylation (O/H/A) and hydrogenation-olefination-hydrogenation (H/O/H) reaction sequences in one-pot under stereospecific organo- and organo/metal-carbonate-catalysis. Highly functionalized diverse compounds such as biologically active products, have found wide applications as pharmaceutical drugs, drug intermediates and drug ingredients. Additionally we have developed green synthesis of highly substituted 1,2,3-traizole from simple substrates by means two step combination of olefination-hydrogenation-alkylation and Huisgen cycloaddition reaction sequences under stereospecific organo-copper-catalysis. The products formation has given strong support to our hypothesis that, “by decreasing the HOMO-LUMO energy gap between olefins and Hantzsch ester will drive the bio-mimetic hydrogenation reaction by self-catalysis”. This self-catalysis was further confirmed with many varieties of examples.

A practical and novel organocatalytic chemo- and enantioselective process for the cascade synthesis of highly substituted 2-alkyl-cyclohexane-1,3-diones and W-M ketone analogs is presented via reductive alkylation as a key step. First time, we developed the one-step alkylation of dimedone and 1,3-cyclohexanedione with aldehydes and Hantzsch ester through organocatalytic reductive alkylation strategy. Direct combination of L-proline-catalyzed cascade olefination/hydrogenation and

cascade Robinson annulation of CH-acids (dimedone and 1,3-cyclohexanedione), aldehydes, Hantzsch ester and methyl vinyl ketone furnished the highly functionalized W-M ketone analogs in good to high yields and with excellent enantioselectivities. Many of reductive alkylation products are showed direct application in pharmaceutical chemistry.

Direct amino acid-catalyzed chemo- and enantioselective process for the double cascade synthesis of highly substituted 2-alkyl-cyclopentane-1,3-diones, 2-alkyl-3-methoxy-cyclopent-2-enones and Hajos-Parrish (H-P) ketone analogs is presented via reductive alkylation chemistry. First time, we developed the single-step alkylation of cyclopentane-1,3-dione with aldehydes/ketones and Hantzsch ester through an organocatalytic reductive alkylation strategy. Direct combination of amino acid-catalyzed cascade olefination/hydrogenation and cascade Robinson annulation’s of cyclopentane-1,3-dione, aldehydes/ketones, Hantzsch ester and methyl vinyl ketone furnished the highly functionalized H-P ketone analogues in good to high yields and with excellent enantioselectivities. Many of the reductive alkylation products are showed direct application in pharmaceutical chemistry.

A practical and sustainable chemical process for the synthesis of highly substituted tetrahydro-isobenzofuran-1,5-diones was achieved for the first time through asymmetric cascade Michael-aldol reaction of 4-hydroxy-3-alkyl-5*H*-furan-2-ones with alkyl vinyl ketones in the presence of a catalytic amount of L-proline or 9-amino-9-deoxyepiquinine/TCA. In this chapter, first time we discovered the asymmetric synthesis of privileged bicyclic lactones through kinetic resolution and shown as synthetic application to the pharmaceuticals and natural products synthesis.

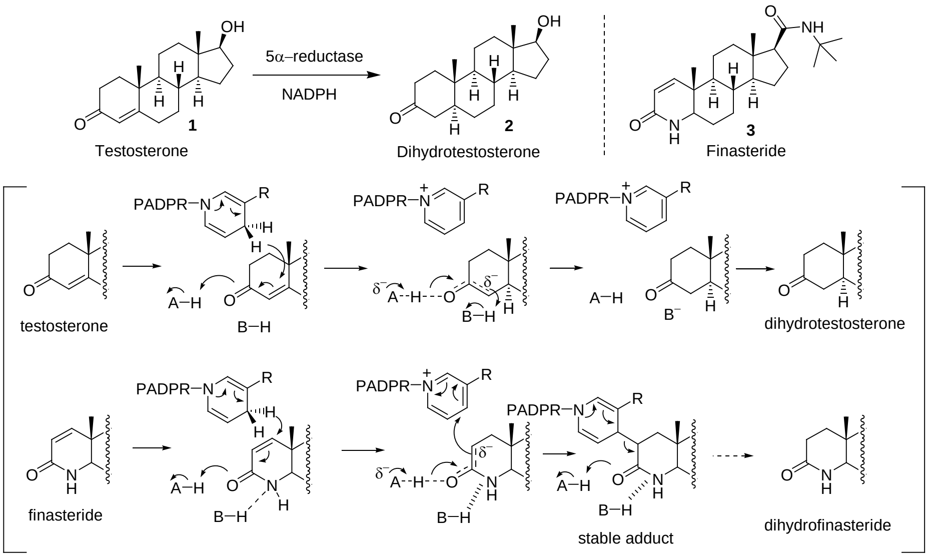
2. INTRODUCTION

All biological systems contain DNA, RNA, enzymes, proteins and peptides, which are the basic functionalities for existing cellular systems. In that, enzymes play a vital role in the cellular reactions, which are the constituent parts of the proteins. Catalytic efficiency of enzymes will be controlled by number of functional groups from amino acids and the chemical potential of side chains found in amino acids is limited because of no efficient electron acceptors. Therefore, enzyme catalysis incorporates specific metal ions, such as Mg^{2+}, Mn^{2+}, Cu^{+}, Zn^{2+}, Fe^{2+}, Co^{2+}, and Cu^{2+} for the coordination of the transition metal ions in enzyme structures. In addition to the bulk metals (K, Na, Ca, Mg, Fe) and the trace metals (Cu, Co, Mn, Zn, Mo) known to be essential in animal and plant cellular systems, certain other metals such as Ba, V, Ni, As, Al and Rb are present in trace amounts in various animal and plant tissues, although it is not known whether or not they are nutritionally essential. Besides metal ions, cofactors or coenzymes (NADP, FAD, TPP, FAD and CoA) serve to activate groups and participate in the catalytic process.

Coenzymes, cofactors or prosthetic groups may act by nucleophilic or electrophilic attack on the substrate (s) to initiate a reaction. Cofactors are tightly (covalently) bound to the protein and may undergo cyclic reactions during the catalytic process but will return to the ground state at the end. Coenzymes are bound in an association and dissociation equilibrium to enzymes and have to be present in sufficient concentration to obtain maximal enzymatic activity. Some are regenerated in the catalytic cycle while bound to the enzyme.

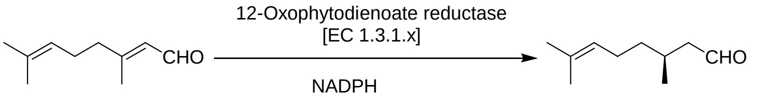
As the research work described in this thesis deals with the amino acid-catalyzed biomimetic hydrogenations[1], a brief overview on the enzyme and non-enzyme-catalyzed hydrogenations using NADPH and analogues as hydrogen source are presented below.

The enzyme steroid 5α-reductase [NADPH-Δ^4-3-oxosteroid-5α-oxidoreductase (EC 1.3.99.5)] is an NADPH-dependent enzyme that catalyses the *in vivo* reduction of testosterone **1** to the more potent androgen dihydrotestosterone (DHT) **2** as shown in eq. 1.[2] Finasteride **3** [17*β*-(*N*-*tert*-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one (MK-906)] is a potent inhibitor of the human prostate 5α-reductase enzyme and, under the trademark Proscar, is employed in treatment of benign prostatic hyperplasia (BPH), a condition afflicting to some degree the majority of men over age 55. Finasteroid selectively binds to the 5α-reductase and inhibits the formation of DHT as shown in eq. 1 and these kind of *in vivo* reactions are more interesting to mimic in vial.



(1)

In addition to the *in vivo* enzymatic reductions of olefins, *in vitro* enzymes are employed for double bond reductions using NADP, $FADH_2$ etc as cofactor. Especially for asymmetric reduction of alkenes bearing electron withdrawing groups is well exploited in recent years with enoate reductases (EC 1.3.1.x) from the family of old yellow enzymes. Addition of hydrogen molecule is dictated by enzymatic mechanism in *trans*-fashion. Faber and coworkers reported that the asymmetric reduction of citral **4** in a chemo-, regio-, and stereoselective fashion to give (*S*)-**5** in greater than 95% ee using 12-oxophytodienoate reductase (OPR) as enzyme and NADPH as cofactor as shown in eq. 2.[3]



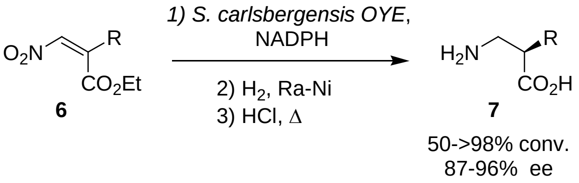
(2)

4

(*S*)-**5**
99% conv.
>95% ee

Stewart *et al.* reported the asymmetric reduction of *β*-nitroacrylates **6** by *Saccharomyces carlsbergensis* old yellow enzyme as the key catalyst in a concise route to optically active *β*-amino acids (*R*)-**7**. The enzymatic reductions occur with

87-96% ee, with larger substrates providing greater stereoselectivities as shown in eq. 3.[4]

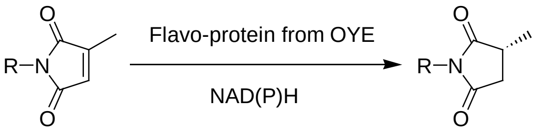


6 **7**

50->98% conv.
87-96% ee

(3)

Recently, Faber reported that four flavoproteins from the old yellow enzyme (OYE) family, pentaerythritol tetranitrate (PETNR) reductase, *N*-ethylmaleimide reductase (NEMR), morphinone reductase (MorR) and estrogen-binding protein (EBP1), exhibited a broad substrate tolerance by accepting conjugated enals, enones, imides, dicarboxylic acids and esters, as well as a nitroalkene and therefore can be employed for the asymmetric bioreduction of carbon-carbon double (C=C) bonds as shown in eq. 4.[5] In particular, morphinone reductase and estrogen-binding protein often showed a complementary stereochemical preference in comparison to that of previously investigated OYEs.

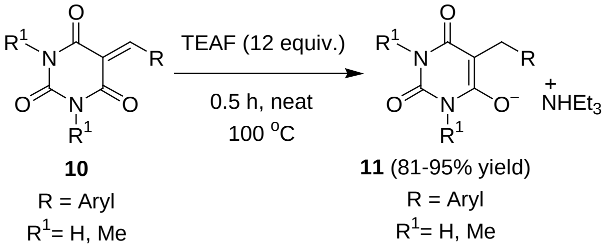


(4)

8a: R = H
8b: R = Ph

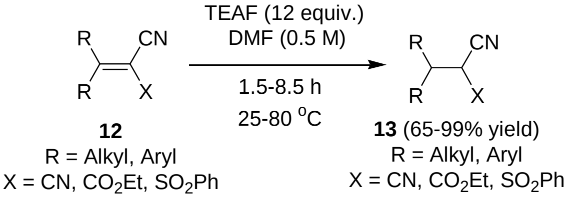
(*R*)-**9a:** R = H
(*R*)-**9b:** R = Ph
100% conv.
97-99% ee

In recent years chemists have been inspired by the outstanding efficiency of biological metal-free enzyme systems to develop in a vial by developing metal free chiral amines or amino acids (organocatalysts) as catalysts and small molecule Hantzsch ester as NADPH mimetic hydride source in a many number of reactions with excellent chemo-, regio- and stereoselectivities. Along with Hantzsch ester, formic acid/triethylamine combination reported as hydride source. In 1969, Sekiya and Yanaihara disclosed the reduction of 5-arylmethylenebarbituric acid and some of analogous derivatives by using TEAF [$5HCO_2H.2NEt_3$] as a hydride source. In these reactions, they employed 12 equiv. of TEAF at 100 °C for 0.5 h and yields are isolated in the range of 81-95% (eq. 5).[6]



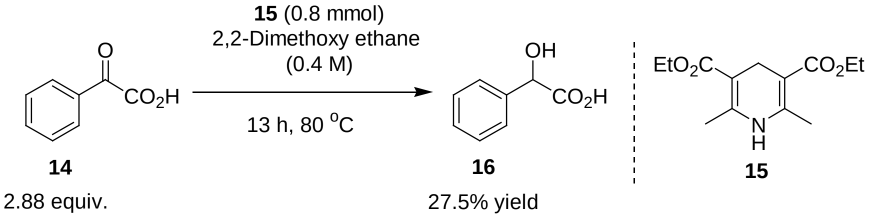
(5)

In 1977, Sekiya *et al.* extended the TEAF mediated reductions to conjugate nitrile systems. They obtained the reduced products by treatment of olefins with 12 equiv. of TEAF in DMF solvent at 25-80 °C for 1.5-8.5 h and expected products isolated in the range of 65-99% yields (eq. 6).[7]



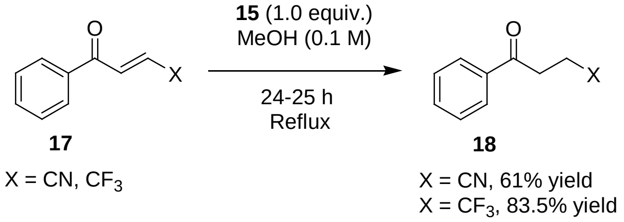
(6)

In 1958, Westheimer and Abeles, various attempts have been made to construct a new strategy alternative to the metal and enzymatic reductions. They reported the reduction of benzoyl formic acid with NADPH model compound namely Hantzsch ester in 2,2-dimethoxy ethane solvent at 80 °C for 13 h to isolate mandelic acid with 27.5% yield (eq. 7).[8] This is the first report of Hantzsch ester using as a bio-mimetic reducing agent. Nevertheless, less yields and higher temperatures of this chemistry stimulates the progress of mimicking nature's process continuously.



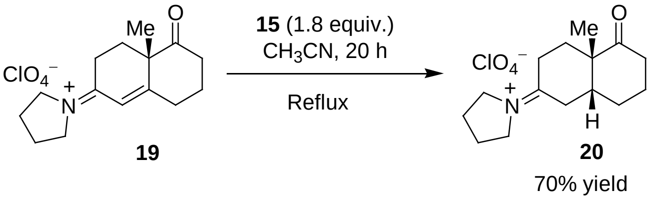
(7)

In 1962, Westheimer *et al.*, successfully demonstrated the Hantzsch ester as bio-mimetic reducing agent by the reduction of active olefins such as 1-phenyl-4,4,4-trifluorobutan-1-one and β-benzoylacrylic acid in a non-enzymatic model by direct transfer hydrogen with good yields (eq. 8).[9]



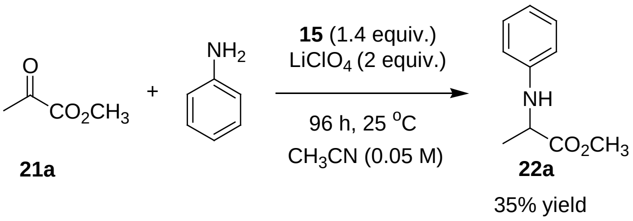
(8)

After a decade in 1974, Pandit *et al.*, first time reduced the preformed iminium salts by 1, 4-dihydropyridine derivatives. In this report, they prepared initially pyrrolidene salt of bicyclic ketone **19** and subjected to Hantzsch ester **15** in acetonitrile solvent for 20 h at the refluxing temperature to furnish the reduced product of imine **20** with 70% yield (eq. 9).[10]



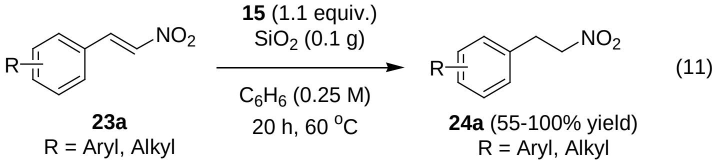
(9)

In 1977, Ohno *et al.*, described one-step synthesis of aminoester **22a** derived from the corresponding α-keto acids by consecutive imine formation and reduction with the aid of Hantzsch ester as a bio-mimetic reducing agent (eq. 10).[11] This reaction is similar to glutamate dehydrogenase, which catalyse an inter-conversion between alpha ketoglutarate and L-glutamate by the support of NADPH.

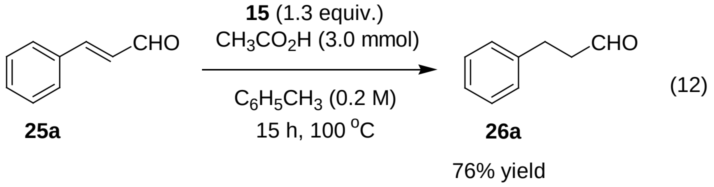


(10)

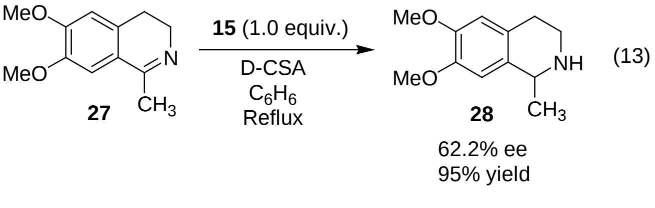
In 1985, Ohno *et al.* successfully reduced the carbon-carbon double bonds in α,β-unsaturated nitro compounds into the corresponding nitro alkanes by Hantzsch ester in benzene solvent in the presence of silica gel (eq. 11)[12]. Other functional groups are inert under this reaction conditions and yields also good.



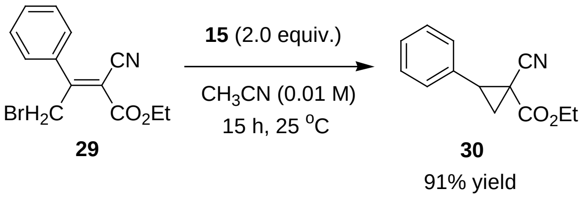
In 1988, Yoshio Inoue *et al.* first time developed the reduction of α,β-unsaturated carbonyl compounds with the aid of Hantzsch ester. In their general procedure, *trans*-cinnamaldehyde was added to a mixture of AcOH and Hantzsch ester (2.3:1 ratio) in toluene at 100 °C for 15 h to furnish the expected 3-phenyl propanaldeyde in 76% yield (eq. 12).[13]



In 1989, Singh and Batra first time utilized Hantzsch ester **15** as reducing agent in the asymmetric reduction of dihydroisoquinoline moieties under the chiral acid-catalysis as shown in eq. 13. Under the chiral D-CSA-catalysis, imine **27** reduced with **15** to furnish the amine **28** with good yield and ee (eq. 13).[14]

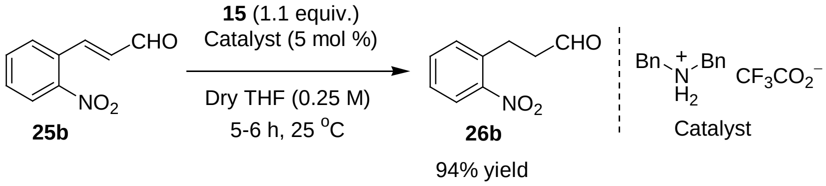


In 2001 Liu *et al.* reported a novel, new and high-yielding route to synthesize various 3-, 5-, or 7-membered rings with the assistance of Hantzsch ester as mild reducing agent. To the α-cyano-β-bromomethyl cinnamate **29** was added Hantzsch ester **15** in CH_3CN and stirred for 7-20 h to furnish the cyclopropane derivative with 91% yield (eq. 14).[15] This reaction is good example to demonstrate the application of NADPH mimic reactions in organic synthesis, so as to attract more attention to the application of bio-mimetic reactions in organic synthesis.



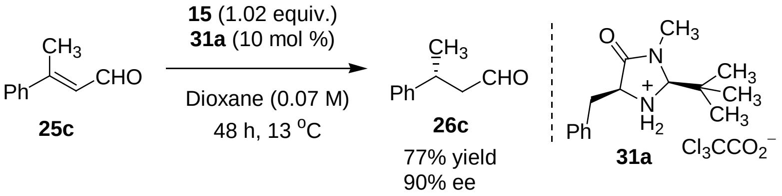
(14)

In 2004, List *et al.* reported a highly efficient and remarkably chemoselective metal-free catalytic transfer hydrogenation of α,β-unsaturated aldehydes using iminium-catalysis. This novel hydrogenation requires low catalyst loadings and tolerates various functional groups that are sensitive to the conditions of standard hydrogenations and alternative conjugate reductions. For example, to a solution of o-nitrocinnamalehyde in dry THF was added Hantzsch ester **15** and 5 mol% of dibenzylammonium trifluoroacetate, after 5 h at room temperature, furnished the corresponding saturated analogue with 94% yield (eq. 15).[16]



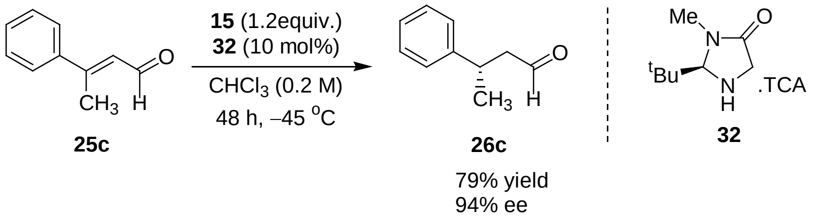
(15)

In subsequent communication, List *et al.* described the first metal-free catalytic asymmetric transfer hydrogenation using MacMillan imidazolidinone catalysts. The transfer hydrogenation of α,β-unsaturated aldehydes has attractive features such as high yield, chemo-, enantioselective, simplicity and practicability (eq. 16). One of major advantage is either of *E*/*Z* isomers gave same configuration of the hydrogenation product from these reaction conditions, which means that initially the double bond is isomerizing and subsequent hydride addition occurred.[17]



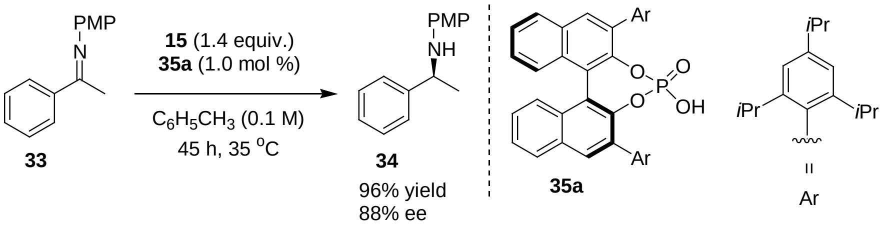
(16)

In 2005, MacMillan *et al.* reported enantioselective transfer hydrogenation from Hantzsch ester to enal olefin using their simple imidazolidinone catalyst. This methodology is bio-inspired protocol as well as metal free hydrogenation. Exposure of 3-methyl-(*E*)-cinnamaldehyde to Hantzsch ester **15** in chloroform under **32**-catalysis furnished the hydrogenated product **26c** with highest levels of enantiocontrol at lower temperatures with excellent yields (eq. 17).[18]



(17)

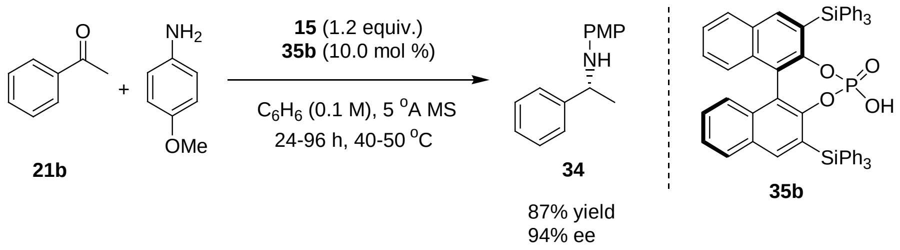
Recently List *et al.* developed an efficient organocatalytic ketimine reduction using Hantzsch ester as a bio-mimetic reducing agent. Akiyama and Terada introduced relatively strong chiral phosphoric acids as Brønsted acid catalysts for asymmetric addition reactions. Inspired by those studies, List group employed these Brønsted acid catalysts for the reduction of ketimine with superior levels of enantioselectivity and excellent yields (eq. 18). They envisioned that a catalytic cycle which is initiated by protonation of ketimine from a chiral Brønsted acid catalyst and the resulting iminium ion pair, which may be stabilized by hydrogen-bonding is chiral and its reaction with the Hantzsch dihydropyridine could give an enantiomerically enriched amines.[19]



(18)

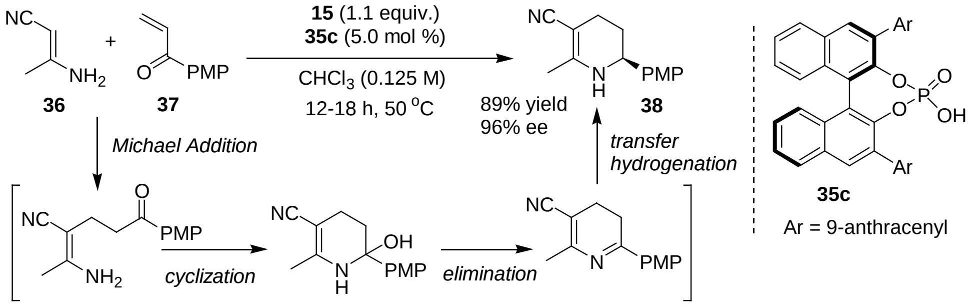
In a similar time, MacMillan and co-workers reported the first organocatalytic reductive amination under the modified Brønsted acid catalysis employing Hantzsch ester as a bio-mimetic reducing agent. In this paper they discovered that *ortho*-triphenylsilyl variant of the Terada-Akiyama catalyst facilitates the desired coupling in high conversion and with excellent levels of enantiocontrol at 40-50 °C (eq. 19).[20]

This catalytic reaction conditions are good to develop variety of chiral amines via treatment of variety of ketones with amines without isolating the unstable imines.



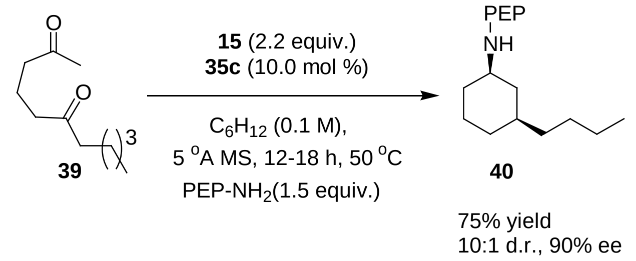
(19)

In 2008, Rueping *et al.* reported a new asymmetric organocatalytic cascade reaction in which multiple steps are catalyzed by a chiral Brønsted acid catalyst and which allows rapid, direct and valuable efficient access to the tetrahydropyridines and azadecalinones with high enantioselectivities (eq. 20). They envisioned that cascade sequence comprising a Michael addition, cyclization, elimination, isomerization and transfer hydrogenation in which each single step is catalyzed by a chiral Brønsted acid (eq. 20).[21]



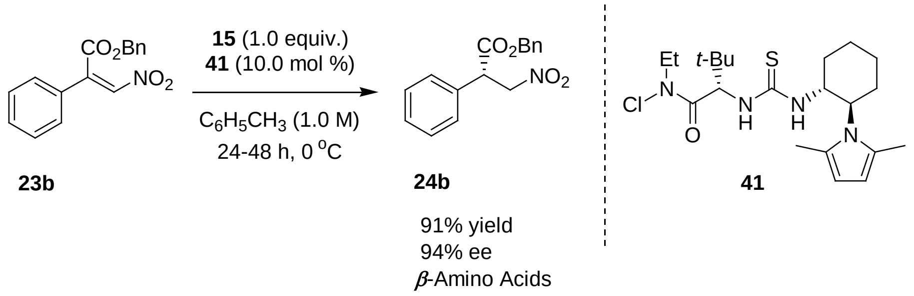
(20)

In 2007, List and Zhou reported a novel methodology by combining enamine catalysis and iminium catalysis with Brønsted acid catalysts to constitutes a powerful strategy for organic cascade reactions which selectively provided *cis*-3-substituted (hetero)-cyclohexylamines from 2,6-diones (eq. 21).[22] They observed in their work that catalyst **35c** is gave selectively *cis*-conformation. This novel activation provided the path to access a wide variety of natural products.



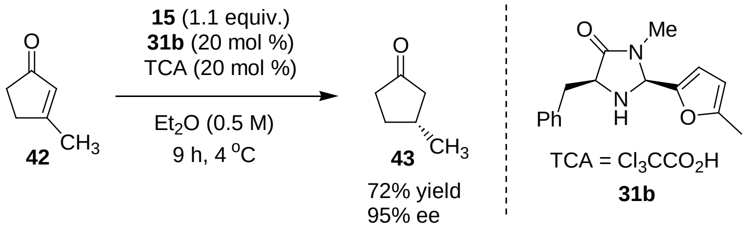
(21)

In 2008, List *et al.* first time reported a catalytic asymmetric conjugate reduction of readily available nitroacrylates to the corresponding nitroesters with Hantzsch ester using chiral Jacobson type thiourea catalyst **41**, which are easily converted into *β*-amino acids via hydrogenation (eq. 22). This strategy provided a route map to beta amino acids which are useful to a new class of peptidomimetics and also useful for the potentially widespread biological and medicinal applications.[23]



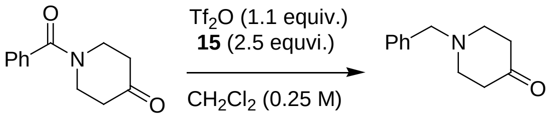
(22)

In 2006, MacMillan *et al.* described the first asymmetric organocatalytic transfer hydrogenation of α,β-unsaturated cyclic ketones which is an operationally simple protocol that allows rapid access to enantioenriched cycloalaknones using an aerobically stable catalyst, wet solvents and an inexpensive hydride source. They employed a modified 2,5-furylbenzyl disubstituted amine as catalyst, which generates high enantioselectivity with excellent yields (eq. 23).[24]



(**23**)

In 2008, Charette and Barbe reported a novel metal-free reduction of tertiary amides using Hantzsch ester as a bio-mimetic reducing agent. They evaluated the chemoselectivity of reduction process by grafting different functionalities at the 4-position of the piperidine moiety (eq. 24).[25] Treating an amide with Tf_2O would generate a highly electrophilic iminium derivative that could subsequently be reduced to the corresponding amine using a mild reducing agent.



44 **45**

86% yield

(24)

With this literature background, and in continuation of synthesis of highly functionalized molecules starting from the simple materials in one-pot,[26] research work has been carried out on the synthesis of drugs and drug-like molecules in a single step, and the results are presented in this thesis.

To begin with, starting from simple starting materials, a simple and convenient cascade three-component reductive alkylation (TCRA) methodology was developed[1] for the synthesis of drug molecules, and the results are presented in the next section.

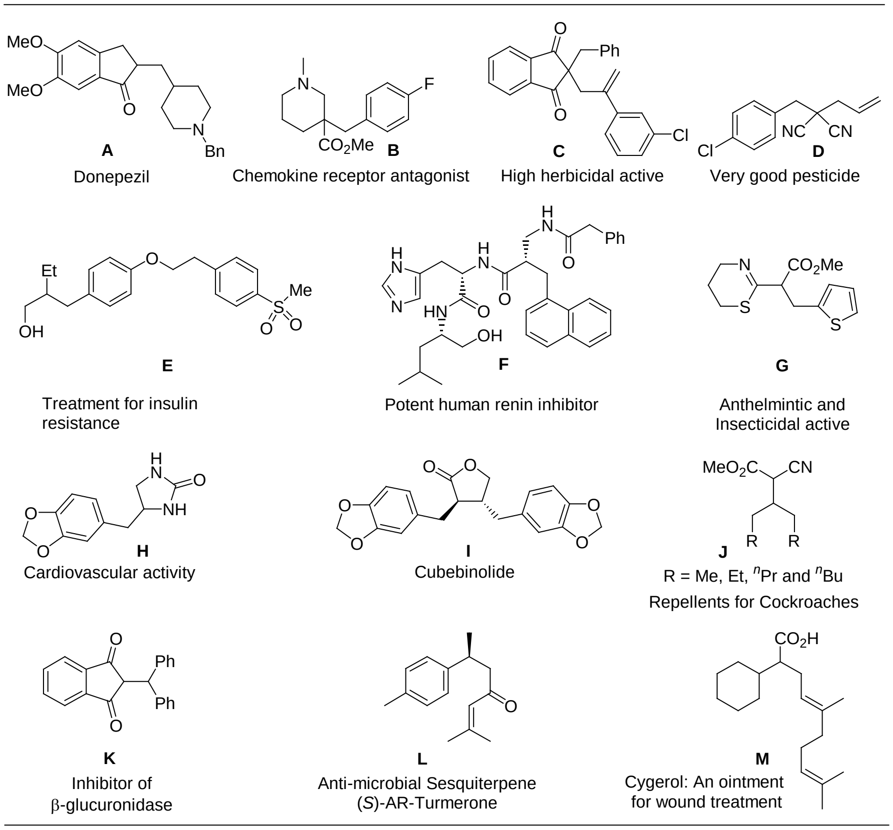
3. Development of Pharmaceutical Drugs, Drug Intermediates and Ingredients by Using direct organo-click Reactions

3.1 Introduction

Development of drug-like small molecules from simple substrates through cascade reactions is one of the emerging areas in modern synthetic chemistry, even though there are already many common organic reactions and reaction strategies for the construction of C-C, C-N, C-O, C-S and C-X (X = halogen) bonds in structurally diverse natural and non-natural products by conventional methods. More typically, these reactions and reaction strategies are not ideal in comparision with biochemical reactions in terms of selectivity (chemo-, regio-, diastereo- and enantio-) or in the ecology and economy of chemical reactions. From the organic chemist's point of view, ideal reaction strategies for the preparation of structurally diverse substances would involve sequences in which stereo-controlled formation of multiple carbon-carbon and carbon-hetero atom bonds occur in a single step from simple, readily available materials. As a result, great attention has been paid to the development of cascade or domino reactions, because of their high degrees of atom economy and their applications in combinatorial chemistry as well as diversity-oriented synthesis.[27] Despite intense interest, there are few reports of organo-catalyzed cascade reactions for the synthesis of stereochemically complex compounds.[27,26] A key to many interesting cascade reactions is the incorporation of biomimetic olefination, hydrogenation and alkylation reaction sequences to enable construction of structurally diverse compounds in a completely stereoselective manner.[1,26]

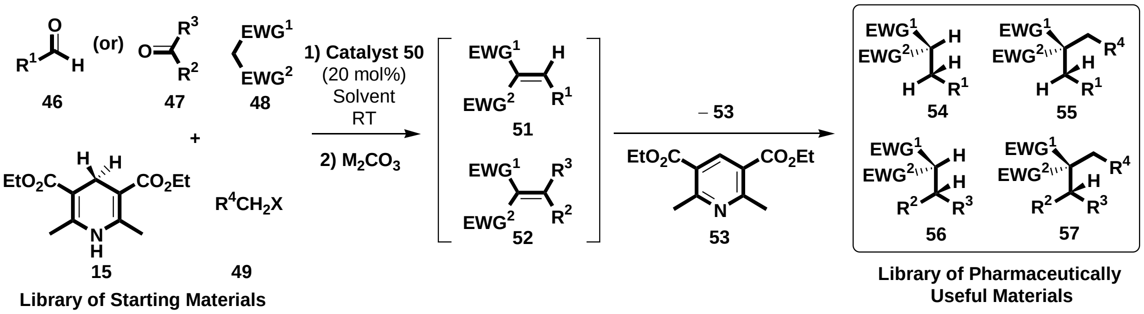
Taking our cue from nature, here we address the development of a set of powerful, reliable and selective cascade reactions for the rapid synthesis of combinatorial libraries for use as pharmaceutical drugs, drug intermediates and ingredients through organo/metal carbonate- and organo/Cu^{I}-catalysed cascade olefination/hydrogenation, olefination/hydrogenation/alkylation, hydrogenation/olefination/hydrogenation, olefination/hydrogenation/hydrolysis and olefination/hydrogenation/alkylation/Huisgen cycloaddition reaction sequences, an approach we call “organo-click reactions”. K. B. Sharpless and co-workers recently provided guidelines for click chemistry,[28] while Ramachary and Barbas later combined organocatalytic reactions with click chemistry (organo-click chemistry).[27,26] Ideally, organocatalytic cascade reactions can also fulfill all aspects of click reaction conditions, among these the reactions must be modular, wide in scope and high yielding, generate only inoffensive by-products, and must also be stereospecific (Scheme 1).

Chart 1: Natural and unnatural products library generated from cascade olefination/hydrogenation and olefination/hydrogenation/alkylation products.



As part of our research program to engineer direct organocatalytic cascade or domino reactions, here we report onepot organo- and organo-metal carbonate catalyzed chemo-selective direct cascade olefination-hydrogenation, olefination-hydrogenation-alkylation, hydrogenation-olefination-hydrogenation and olefination-hydrogenation-hydrolysis reaction sequences that produce very useful pharmaceutical drugs, drug intermediates and ingredients of types **54**, **55**, **56**, **57** and **58** from commercially available aldehydes **46**, ketones **47**, CH-acids **48**, Hantzsch ester **15**, alkyl halides **49**, amino acid or amines **50**, K_2CO_3 and Cs_2CO_3 as shown in Scheme 1. Structurally diverse compounds **54**-**57** are attractive intermediates in the synthesis of natural products and in medicinal chemistry, while compounds **54** and **55** have a broad utility in pharmaceutical chemistry and are excellent starting materials in the natural product synthesis as shown in Chart 1.[29] Hence, their preparation has continued to attract considerable synthetic interest in the form of development of new methods for their syntheses.

Scheme 1: Direct organo-metal carbonate catalyzed cascade reactions.



3.2 Results and Discussion

3.2.1 Cascade Olefination-Hydrogenation Reactions of Aldehydes 46 with CH-Acid 48 and Organic-hydride 15 – Reaction Optimization: We were pleased to find that the one-pot reaction of benzaldehyde **46a**, *N*,*N*-dimethylbarbituric acid **48a** and Hantzsch ester **15** in the presence of a catalytic amount of L-proline **50a** in EtOH at

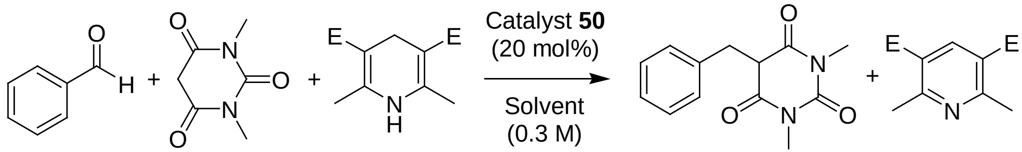
25 °C for 2 to 14 h furnished the hydrogenated product 5-benzyl-1,3-dimethyl-pyrimidine-2,4,6-trione **54aa**† as a single isomer, with 99% conversion (Table 1, entry 1) [**†** In all compounds denoted **51xy**, **52xy**, **54xy**, **55xyz**, **56xy**, **57xyz** and **58xy**, **x** is incorporated from reactant aldehydes **46** or ketones **47**; **y** is incorporated from the reactant CH-acids **48** and **z** is incorporated from the reactant alkyl halides **49**]. The same reaction, catalyzed by L-proline **50a** in EtOH at 25 °C under cascade conditions furnished the product **54aa** with 98% conversion in a shorter reaction time (Table 1, entry 7), perhaps due to the catalytic nature of the Hantzsch ester **15** in the cascade olefination/hydrogenation (O/H) reaction.

Interestingly, there is little solvent effect on the proline catalyzed cascade O/H reaction of **46a**, **48a** and **15** in three different type of solvents (protic polar, aprotic polar and aprotic non-polar) as shown in Table 1, entries 1-13. The simple amino acid, glycine **50b** also catalyzed the cascade O/H reaction to furnish hydrogenated product **54aa** with 99% conversion as a 1:1 ratio of keto/enol forms (Table 1, entry 14). The simple amines pyrrolidine **50c**, piperidine **50d**, morpholine **50e** and benzylamine **50f** also catalyzed the cascade O/H reaction to furnish hydrogenated product **54aa** with 98-99% conversion as shown in Table 1, entries 15-18. Interestingly, the cascade O/H reaction of **46a**, **48a** and **15** without catalyst at 25 °C for 5 h also furnished the expected product **54aa** with 99% conversion (Table 1, entry 19), which is the best demonstration for the catalytic nature of the reagent in cascade reactions.

The solvent promoted one-pot O/H reaction of **46a**, **48a** and **15** in H_2O without catalyst furnished the expected hydrogenated product **54aa** with very good conversion, and these are the optimal reaction conditions for the construction of C-C and C-H bonds under green reaction conditions (Table 1, entry 21).

The optimized conditions for the cascade O/H reaction of **46a**, **48a** and **15** in CH_3CN, EtOH or H_2O at 25 °C to furnish **54aa** with excellent conversions required the presence of the catalytic amounts of amino acid **50a** or piperidine **50d** (entries 7-8 and 16), but not in the cases of entries 19 and 21.

Table 1: Optimization of the direct organocatalytic cascade olefination/hydrogenation reactions of **46a**, **48a** and **15**[a]



46a **48a** **15**, E = CO_2Et **54aa** **53**

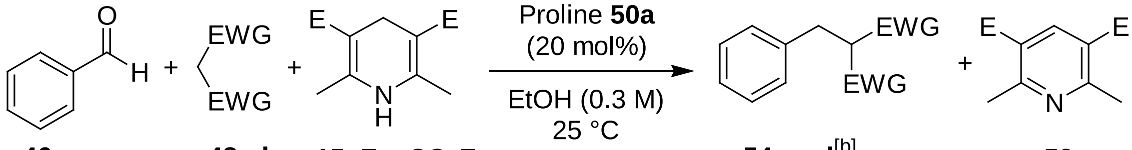
Entry	Catalyst	Solvent	Ester **15** [equiv]	Time [h]	Conversion [%][b]
1	proline **50a**	EtOH	1.06	2 → 14	99
2	proline **50a**	MeOH	1.06	4 → 6	82
3	proline **50a**	DMF	1.06	3 → 6	99
4	proline **50a**	DMSO	1.06	4 → 6	90
5	proline **50a**	$CHCl_3$	1.06	3 → 6	98
6	proline **50a**	CH_3CN	1.06	2 → 14	99
7	**proline 50a**	**EtOH**	**1.00**	**2**	**98**
8[c]	**proline 50a**	**EtOH**	**1.00**	**8**	**98**
9	proline **50a**	CH_3CN	1.00	2	97
10	proline **50a**	$[bmim]BF_4$	1.00	2	98
11	proline **50a**	CH_2Cl_2	1.00	8	98
12	proline **50a**	THF	1.00	2	98
13	proline **50a**	Et_2O	1.00	8	98
14[d]	glycine **50b**	EtOH	1.00	3	99
15	pyrrolidine **50c**	EtOH	1.00	6	98
16	piperidine **50d**	EtOH	1.00	2	98
17	morpholine **50e**	EtOH	1.00	6	98
18	benzylamine **50f**	EtOH	1.00	6	98
19	–	**CH_3CN**	**1.00**	**5**	**99**
20[e]	–	CH_3CN	–	48	–
21	–	**H_2O**	**1.00**	**0.25 → 2**	**99**

[a] see experimental section. [b] Determined by ^1H NMR spectroscopy. [c] Proline **50a** were taken as 5 mol-%. [d] Product **54aa** were isolated as a 1:1 mixture of keto and enol forms. [e] olefination product **51aa** did not form.

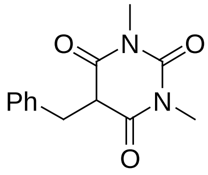
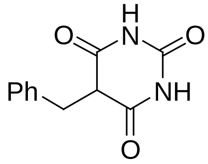
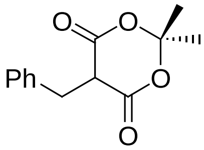
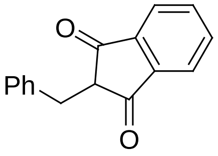
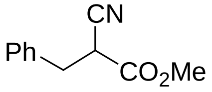
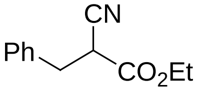
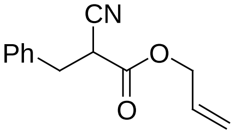
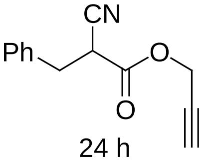
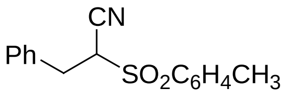
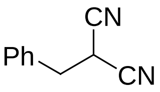
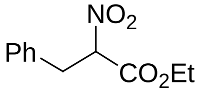
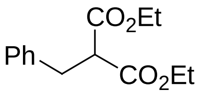
Following these promising results, we proceeded to investigate the scope and limitations of the cascade O/H reaction with a range of CH-acids **48a-l** and Hantzsch ester **15** with and without catalyst (Tables 2 and 3). L-Proline **50a**-catalyzed cascade O/H reactions of benzaldehyde **46a** and Hantzsch ester **15** with a variety of CH-acids **48a-k** in EtOH at 25 °C for 2-27 h furnished the expected cascade three-component reductive alkylation (TCRA) products, 2-benzyl-CH-acids **54aa-ak,** in very good yields as shown in Table 2, entries 1-11. Interestingly, diethyl malonate **48l** did not furnish the expected reductive alkylation product **54al** in the proline-catalyzed cascade O/H reaction with **46a** and **15** in EtOH, we also found that **48l** did not undergo olefination reaction either (Table 2, entry 12). The same reaction in DMSO under proline-catalysis furnished the only the olefination product **51al** without the expected hydrogenated product **54al** (result not shown in Table 2).

After successful demonstration of the one of the optimized reaction conditions (Table 1, entry 7) for the cascade O/H reaction with a variety of CH-acids **48a-l**, we decided to investigate the same with other two optimized conditions (cascade reactions promoted by H_2O and Hantzsch ester **15**). The selective solvent promoted one-pot O/H reaction of benzaldehyde **46a** and Hantzsch ester **15** with a variety of CH-acids **48a-l** was screened in H_2O at 25 °C without catalysis, which furnished the expected hydrogenated products **54aa-ak** in yields ranging from very good to poor as shown in Table 3. Hantzsch ester **15** promoted cascade O/H reactions with various CH-acids **48** and aldehydes **46** promoted by hantzsch ester **15** furnished the expected cascade products **54** with poor to moderate yields (results discussion is there on next section). After testing the autocatalytic nature of the reactions promoted by Hantzsch ester **15** and H_2O promoted reactions in one-pot O/H reactions with different CH-acids **48** and aldehydes **46** as shown in Table 3, we decided to generate a pharmaceutically useful library of cascade products **54** under proline- or piperidine-catalysis conditions.

Table 2: Direct organocatalytic cascade olefination/hydrogenation reactions of **46a** and **15** with a variety of CH-acids **48a-l**[a]

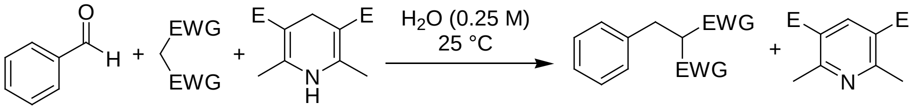


46a **48a-l** **15**, E = CO_2Et **54aa-al**[b] **53**

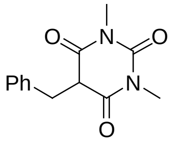
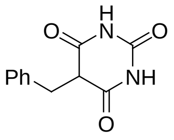
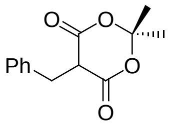
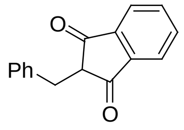
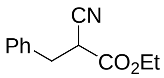
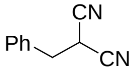
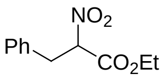
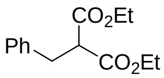
 2 h 98% (**54aa**)	 5 h 95% (**54ab**)	 4 h 90% (**54ac**)	 26 h 88% (**54ad**)
 5 h 95% (**54ae**)	 16 h 85% (**54af**)	 12 h 91% (**54ag**)	 24 h 85% (**54ah**)
 24 h 85% (**54ai**)	 7 h 95% (**54aj**)	 27 h 65% (**54ak**)	 24 h 5% (**54al**)

[a] See Experimental Section. [b] Yield refers to the column purified product.

Table 3: Direct water promoted cascade olefination/hydrogenation reactions of **46a** and **15** with a variety of CH-acids **48a-l**[a]



46a **48a-l** **15**, E = CO_2Et **54aa-al**[b] **53**

 2 h 99% (**54aa**)	 4 h 99% (**54ab**)	 16 h 85% (**54ac**)	 25 h 40% (**54ad**)
 54 h 40% (**54af**)[c]	 25 h 60% (**54aj**)	 48 h <25% (**54ak**)[c]	 40 h 0% (**54al**)[c]

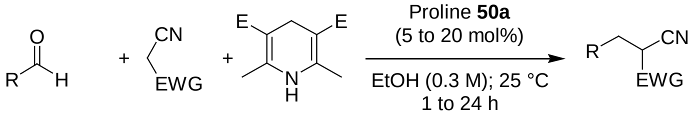
[a] A mixture of **46a** (0.5 mmol) and **48** (0.5 mmol) were stirred at room temperature for 0.25 to 5 h then **15** was added and stirring continued at the same temperature. [b] Determined by ^1H NMR analysis and conversion given. [c] Olefin formation was very poor.

3.2.2 Diversity-Oriented Green Synthesis of Reductive Alkylation Products 54af-54m'f: With an efficient organocatalytic cascade TCRA protocol to hand, the scope of the proline-catalyzed cascade O/H reactions was investigated with various aldehydes **46a-z**, **46a'-m'** and CH-acids **48e-j** through the generation of highly useful diversity-oriented library. A series of substituted aromatic, heteroaromatic and aliphatic aldehydes **46a-m'** were treated with 1.0 equiv. of methyl cyanoacetate **48e**, ethyl cyanoacetate **48f** or malononitrile **48j** and Hantzsch ester **15** (1.0 equiv.) catalyzed by 5 to 20 mol% of proline **50a** at 25 °C in EtOH (Table 4). The ethyl 2-aryl-2-cyanoacetates **54af-d'f**, ethyl 2-alkyl-2-cyanoacetates **54e'f-m'f** and 2-alkylmalononitriles **54ij-m'j** were obtained as single isomers with excellent yields. Catalyst loading for the cascade O/H reactions can be taken from 5 to 20 mol% without effecting reaction yields but reaction times vary from 1 to 24 h. Interestingly, both proline- and piperidine-catalyzed cascade O/H reaction of ethyl cyanoacetate **48f** with naphthalene-1-carbaldehyde **46b** at

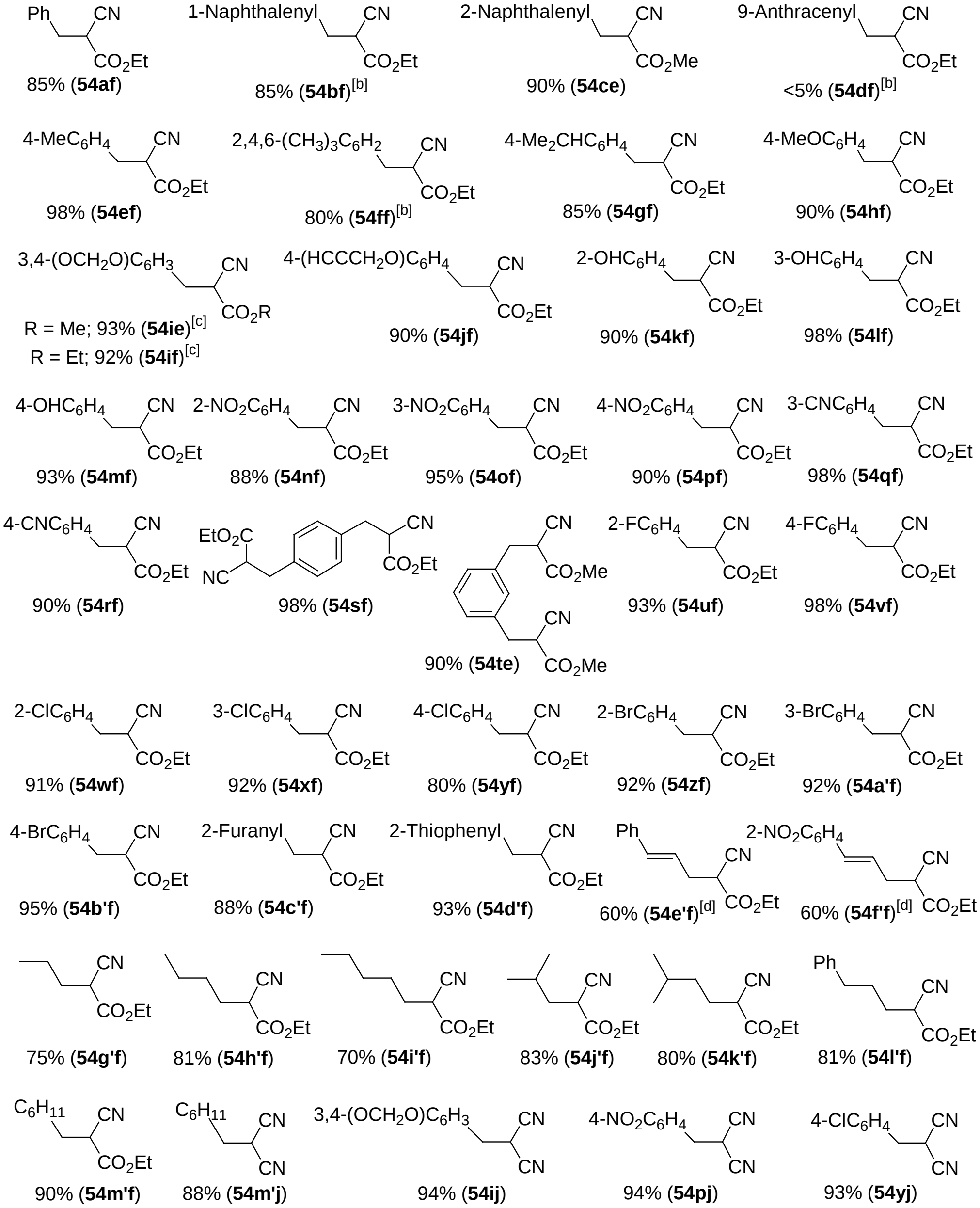
25 °C in EtOH furnished the reductive alkylation product **54bf** with poor to moderate yields (not shown in Table 4), but the same reaction under 10 mol% of DMAP-catalysis in EtOH at 80 °C furnished the reductive alkylation product **54bf** with very good yield (Table 4). A similar type of reaction trend was observed for the synthesis of cyano-(2,4,6-trimethyl-benzyl)-acetic acid ethyl ester **54ff** from cascade O/H reaction as shown in Table 4. This may be due to the generation of more steric hindrance in the transition state of olefin's formation from aldehydes **46b** or **46f** with CH-acid **48f** through enamine/iminium catalysis. The structures of all the products were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 1-5] and mass analysis.

The results in Table 4[29a-29p] demonstrate the broad scope of this reductive methodology, covering a structurally diverse group of activated aldehydes **46a-m'** and CH-acids **48e-f** and **48j** with many of the yields obtained being very good, or indeed better than those of previously published alkylation reactions starting from the corresponding olefins **51** or aldehydes **46**. Cascade O/H reaction of *E*-cinnamaldehyde **25a** and 3-(2-nitrophenyl)-propenal **25b** with **48f** and Hantzsch ester **15** furnished the chemoselectively hydrogenated esters **54e'f** and **54f'f** respectively, in good yields (Table 4). Hydrogenated esters ethyl 2-cyano-3-(1-naphthyl) propionate **54bf** and ethyl 2-cyano-3-(2-naphthyl)propionate **54ce** are important intermediates for the synthesis of potent human renin inhibitors **F**,[29j] while cascade esters ethyl 2-cyano-3-(2-fluorophenyl)propionate **54uf** and ethyl 2-cyano-3-(4-fluorophenyl)propionate **54vf** are important intermediates for the synthesis of chemokine receptor antagonists **B**,[29h] ethyl and methyl 3-(benzo-1,3-dioxol-5- yl)-2-cyanopropionates **54ie** and **54if** are useful synthons for the synthesis of cardiovascular active products **H**[29m] and for the synthesis of cubebinolide **I.**[29n] In addition, ethyl 2- cyano-3-(thiophen-2-yl)propionate **54d'f** are important intermediates for the synthesis of anthelmintic and insecticidal active products **G**,[29k] while ethyl 2-cyano-3-(4-hydroxyphenyl)propionate **54mf** is useful material for the synthesis of insulin resistance products **E**[29i] emphasizing the value of this cascade approach.

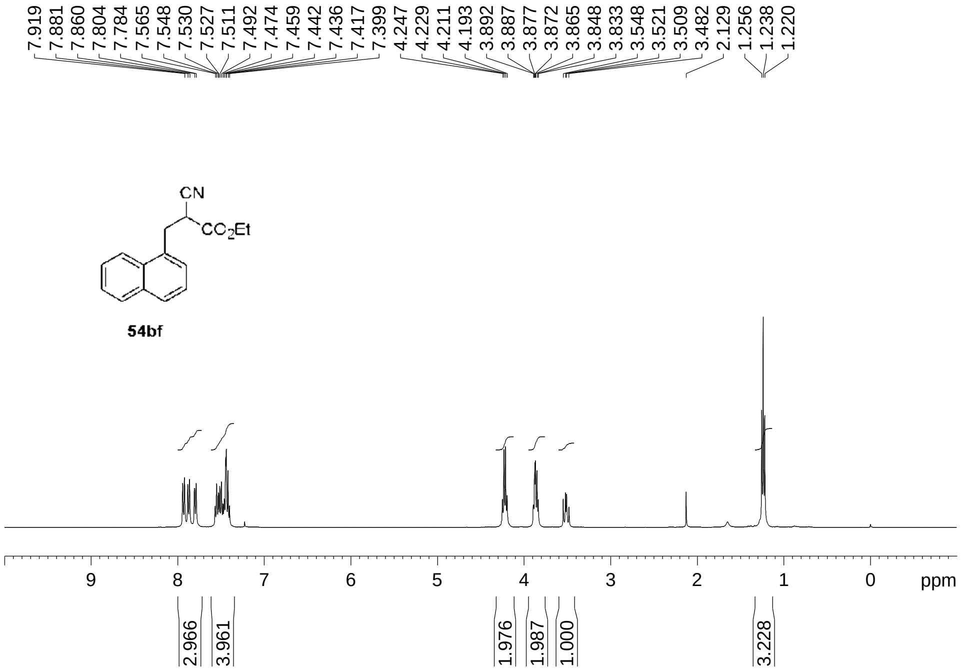
Table 4: Synthesis of chemically diverse libraries of alkyl 2-alkyl-2-cyanoacetates **54** *via* organocatalyzed cascade olefination/hydrogenation reactions[a]



46 **48** **15** **54**



[a] Yield refers to the column purified product. [b] Reaction stirred at 80 °C for 5-24 h under DMAP-catalysis in EtOH. [c] Reaction stirred at 50 °C for 12 h. [d] Nearly 10-15% of completely reduced products were isolated.



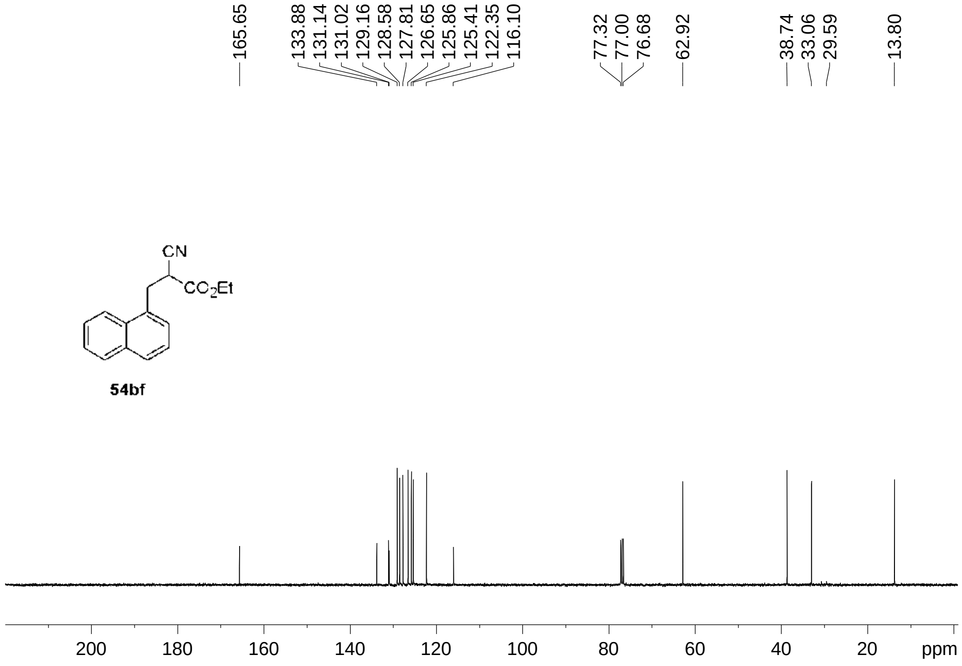


Figure-1: ^{1}H NMR and ^{13}C NMR Spectrum of product **54bf**.

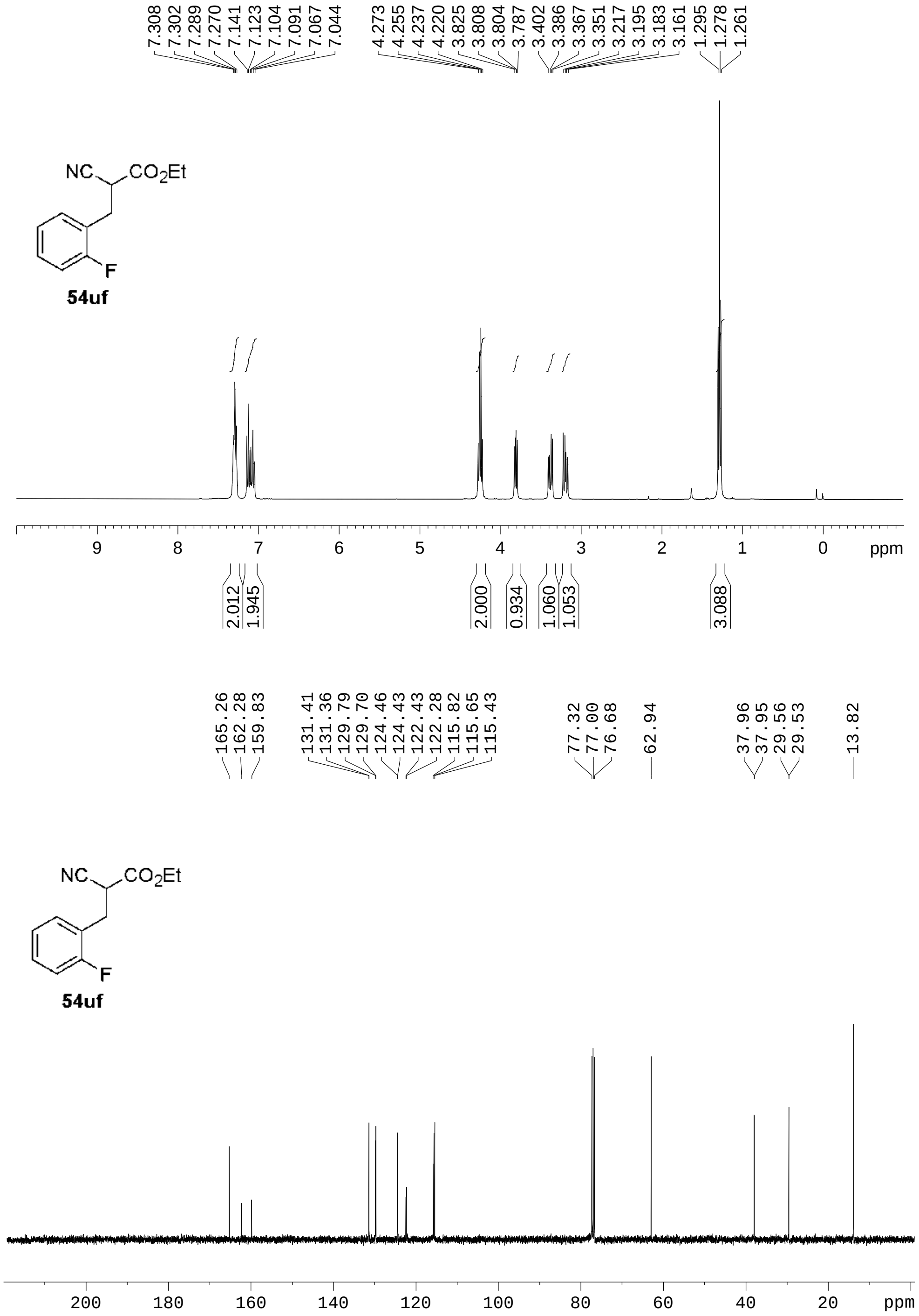


Figure-2: ^{1}H NMR and ^{13}C NMR Spectrum of product **54uf**.

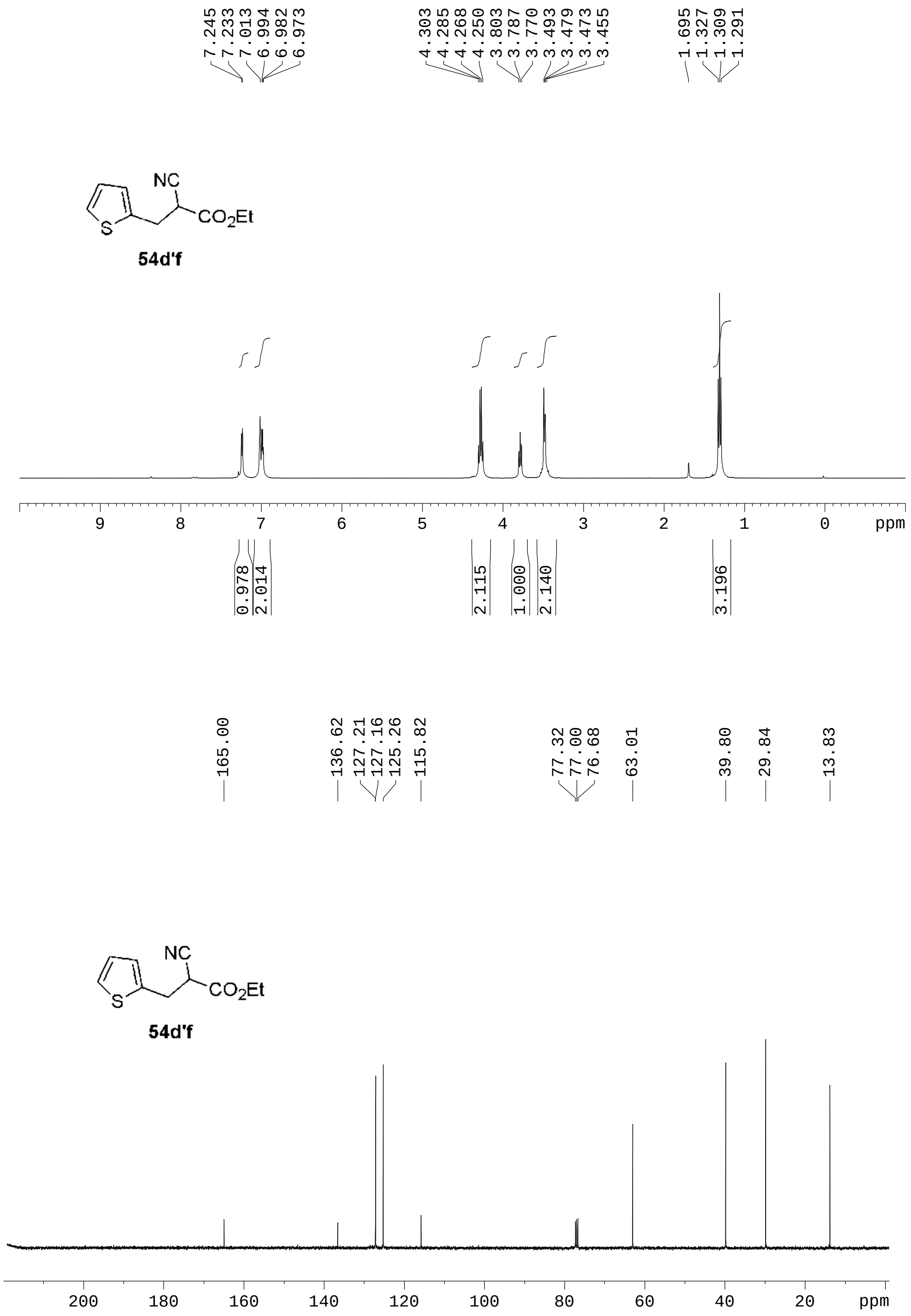
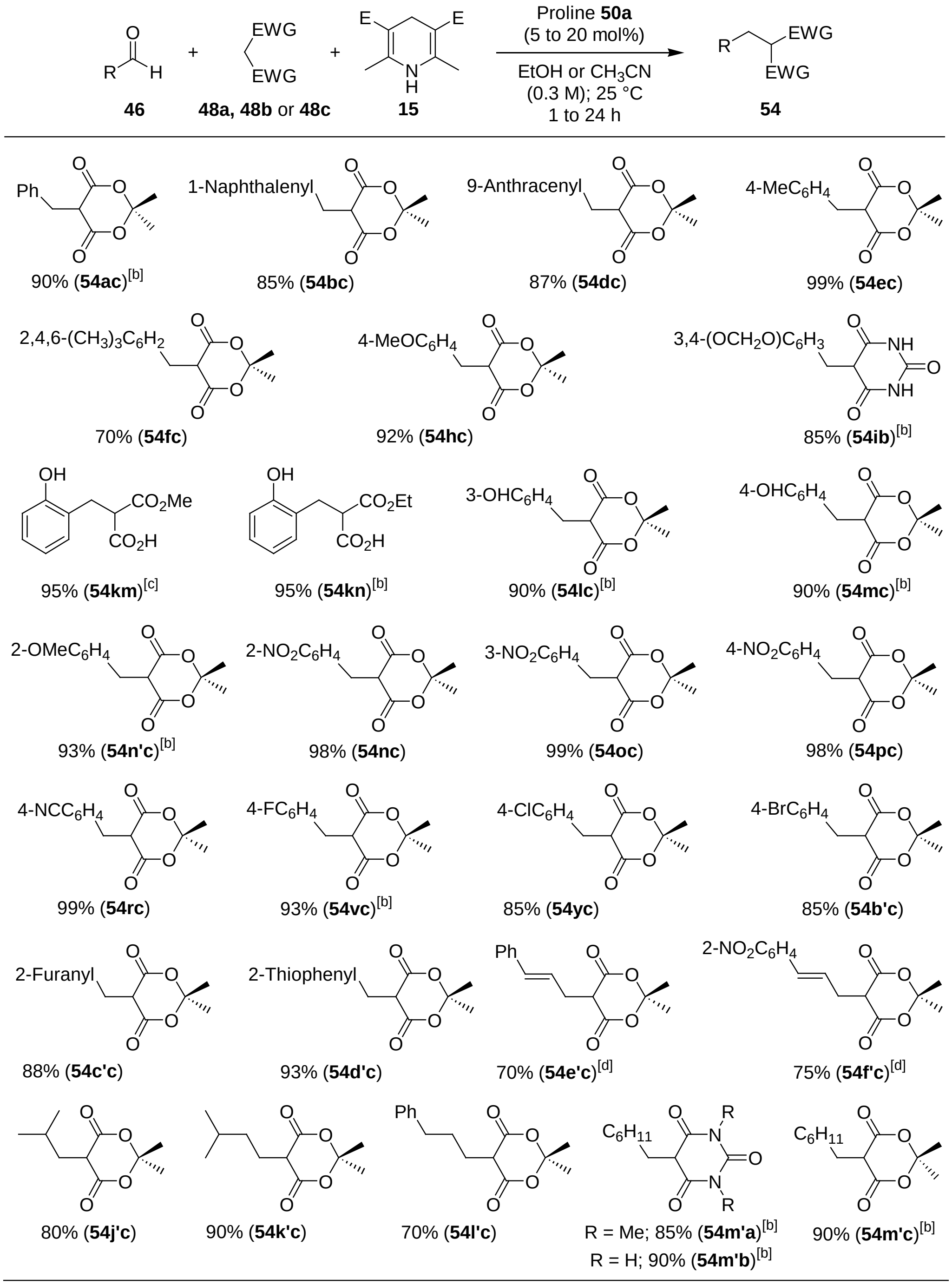


Figure-3: ^{1}H NMR and ^{13}C NMR Spectrum of product **54d'f**.

Table 5: Synthesis of chemically diverse libraries of 5-alkyl-2,2-dimethyl-1,3-dioxane-4,6-diones **54** *via* organocatalyzed cascade olefination/hydrogenation reactions[a]



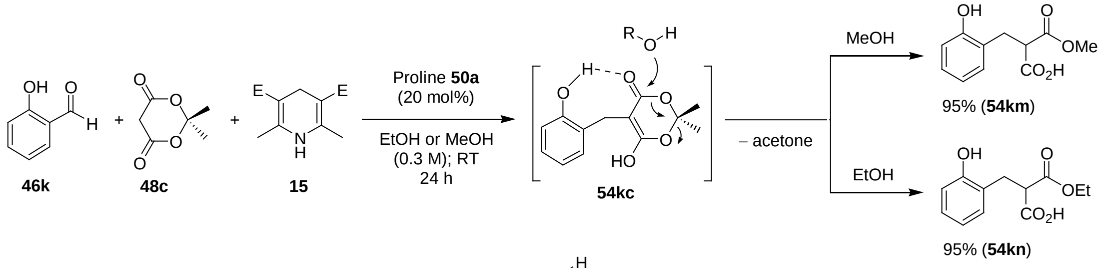
90% (**54ac**)[b]
85% (**54bc**)
87% (**54dc**)
99% (**54ec**)
70% (**54fc**)
92% (**54hc**)
85% (**54ib**)[b]
95% (**54km**)[c]
95% (**54kn**)[b]
90% (**54lc**)[b]
90% (**54mc**)[b]
93% (**54n'c**)[b]
98% (**54nc**)
99% (**54oc**)
98% (**54pc**)
99% (**54rc**)
93% (**54vc**)[b]
85% (**54yc**)
85% (**54b'c**)
88% (**54c'c**)
93% (**54d'c**)
70% (**54e'c**)[d]
75% (**54f'c**)[d]
80% (**54j'c**)
90% (**54k'c**)
70% (**54l'c**)
R = Me; 85% (**54m'a**)[b]
R = H; 90% (**54m'b**)[b]
90% (**54m'c**)[b]

[a] Yield refers to the column purified product. [b] EtOH used as solvent. [c] MeOH used as solvent. [d] Reaction performed in CH_2Cl_2 and nearly 15% of completely reduced products were isolated.

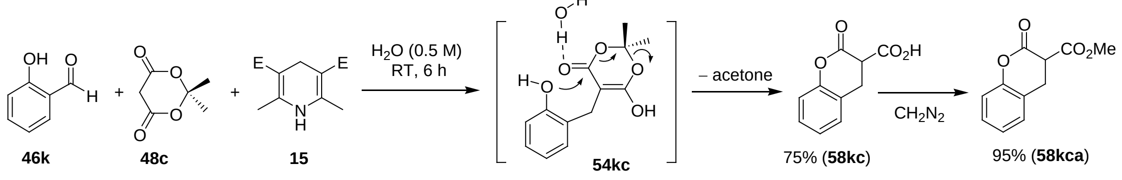
3.2.3 Diversity-Oriented Green Synthesis of Reductive Alkylation Products 54ac-54n'c: After successful demonstration of the cascade O/H reaction for the library generation of ethyl 2-aryl-2-cyanoacetates **54af-d'f** and ethyl 2-alkyl-2-cyanoacetates **54e'f-m'f**, we then decided to apply the same synthetic strategy to the green synthesis of 5-aryl-2,2-dimethyl-1,3-dioxane-4,6-diones **54ac-d'c** and 5-alkyl-2,2-dimethyl-1,3-dioxane-4,6-diones **54e'c-n'c**, which are highly useful materials in chemistry. One of the major application of 5-aryl-2,2-dimethyl-1,3-dioxane-4,6-diones **54ac-d'c** and 5-alkyl-2,2-dimethyl-1,3-dioxane-4,6-diones **54e'c-n'c** is two-carbon homologation of corresponding aldehydes **46a-n'**. Two-carbon homologation is a very important transformation in synthetic organic chemistry, and numerous methods are available, although most involve redox functional group transformations rather than carbon–carbon bond formation.[30] In this regard, the development of two-carbon homologation through carbon-carbon bond formation using organocatalytic cascade reductive methodology might provide an expedient access to homologated products **54ac-n'c** from simple starting materials. Homologated esters **54ac-n'c** are attractive intermediates in medicinal chemistry, and analogues have broad utility in pharmaceutical chemistry[29a-29p] (herbicidal, anti-diabetic, analgesic, anti-inflammatory and anti-thrombotics) and in organic synthesis. Hence, new methods for their syntheses have continued to attract considerable interest.

The results in Table 5 demonstrate the broad scope of this reductive green homologation, covering a structurally diverse group of aldehydes **46a-n'** and CH-acids **48a-c** with many of the yields obtained being very good, or indeed better than those of previously published homologation reactions starting from the corresponding aldehydes **46a-n'** or olefins **51**.[30] A series of substituted aromatic, hetero-aromatic and aliphatic aldehydes **46a-n'** were treated with 1.0 equiv. of Meldrum’s acid **48c**, *N,N*-dimethylbarbituric acid **48a** or barbituric acid **48b** and Hantzsch ester **15** (1.0 equiv.) catalyzed by 5 to 20 mol-% of proline **50a** at 25 °C in EtOH or CH_3CN (Table 5). The 5-aryl-2,2-dimethyl-1,3-dioxane-4,6-diones **54ac-d'c**, 5-alkyl-2,2-dimethyl-1,3-

dioxane-4,6-diones **54e'c-n'c** and 5-alkylpyrimidine-2,4,6-trione **54m'b** were obtained as single isomers with excellent yields. Interestingly, the proline-catalyzed cascade O/H reaction of Meldrum's acid **48c** with 2-hydroxybenzaldehyde **46k** and Hantzsch ester **15** at 25 °C in EtOH furnished the unexpected cascade olefination/hydrogenation/hydrolysis (O/H/H) product monoethyl 2-(2-hydroxybenzyl)malonate **54kn** with very good yield [Table 5 and eq. 25]. The same reaction in MeOH also furnished the unexpected cascade O/H/H product monomethyl 2-(2-hydroxybenzyl)malonate **54km** with very good yield as shown in Table 5 and eq. 25, through the same proline-catalyzed cascade O/H reaction of Meldrum's acid **48c** with 3-hydroxybenzaldehyde **46l** or 4-hydroxybenzaldehyde **46m** and Hantzsch ester **15** at 25 °C in EtOH furnished the expected cascade O/H products **54lc** and **54mc,** respectively, in very good yields as shown in Table 5.



(25)



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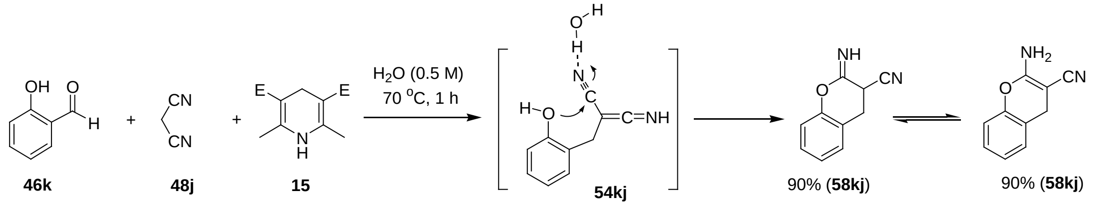


(27)

Interestingly, water-promoted cascade O/H reaction of Meldrum's acid **48c** with 2-hydroxy-benzaldehyde **46k** and Hantzsch ester **15** at 25 °C in water furnished unexpected cascade O/H/H product 2-oxochroman-3-carboxylic acid **58kc** with good yield (eq. 26). In addition, water-promoted cascade O/H reaction of malononitrile **48j** with 2-hydroxybenzaldehyde **46k** and Hantzsch ester **15** at 70 °C in water furnished unexpected cascade O/H/H product 2-amino-4*H*-chromene-3-carbonitrile **58kj** with very good yield (eq. 27). Formation of unexpected cascade O/H/H products **54km**, **54kn**, **58kc** and **58kj** from **46k**, **48c**, **48j** and **15** under with and without proline-catalysis in MeOH, EtOH and H_2O respectively can be explained as shown in eq. 25-27. Inter and intra-molecular hydrolysis of in situ generated cascade O/H products **54kc** and **54kj** with solvents like MeOH/EtOH or H_2O gives the cascade O/H/H products **54km**, **54kn**, **58kc** and **58kj** respectively. These two different types of hydrolysis might be possible due to the nucleophilic nature of the alcoholic solvents and the possibility of additional weak interactions in water (see eq. 25–27).

Homologated ester 5-(4-cyanobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **54rc** is an important intermediate for herbicidal and antithrombotic[29c] chemicals and the cascade ester 5-[(anthracen- 9-yl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione **54dc** is a very useful intermediate to prepare dienophile scavengers,[29d] while 5-(cyclohexylmethyl)pyrimidine-2,4,6-trione **54m'b** is shows narcotizing properties[29p] emphasizing the value of this reductive homologation approach. Interestingly, the cascade O/H products 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione **54ac** was converted into two-carbon homologated ester ethyl 3-phenyl-propionate **59ac** by a cascade O/H/H sequence in good yield with HCO_2H/NEt_3 in one-pot as shown in Scheme 2.

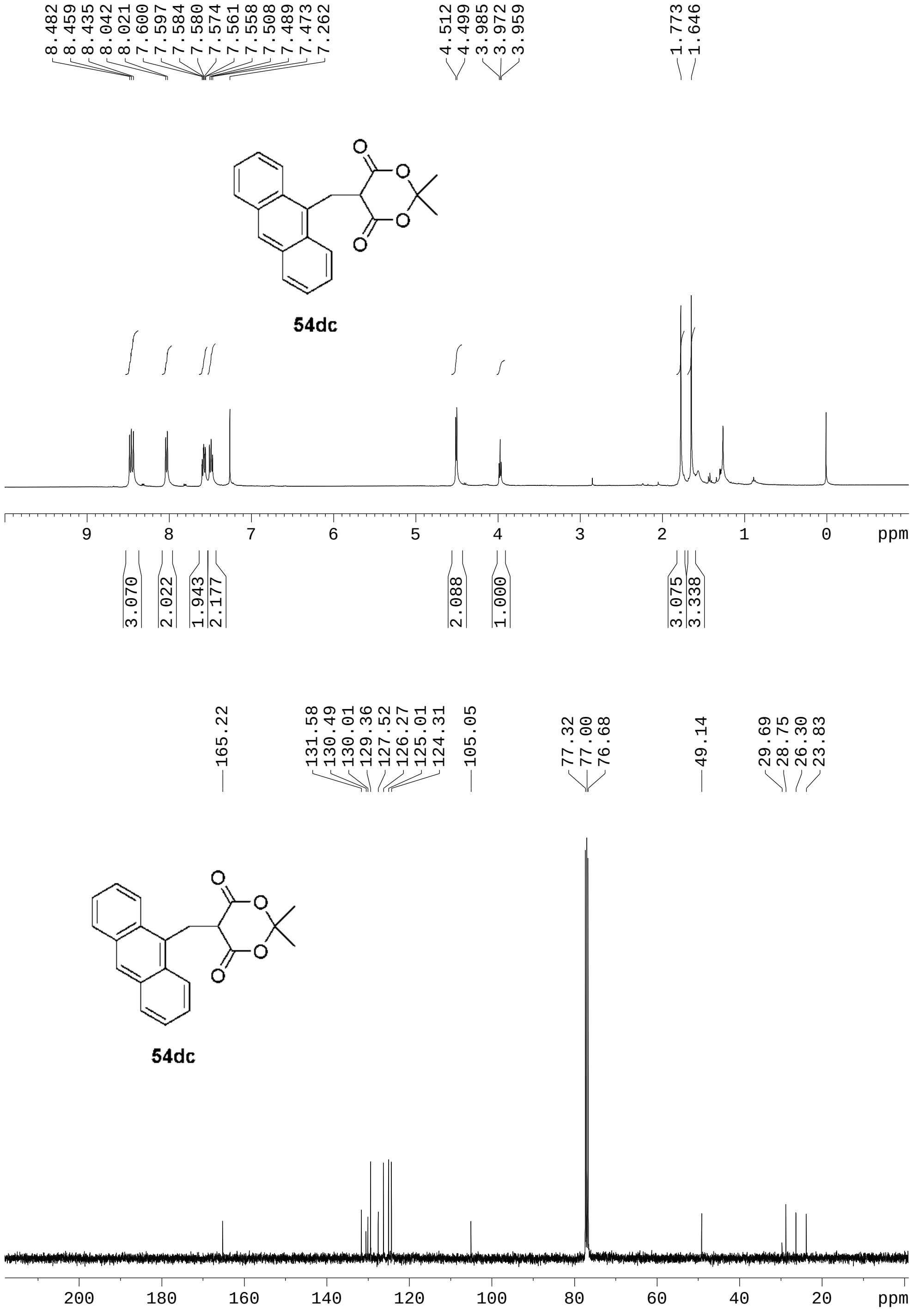


Figure-4: ^{1}H NMR and ^{13}C NMR Spectrum of product **54dc**.

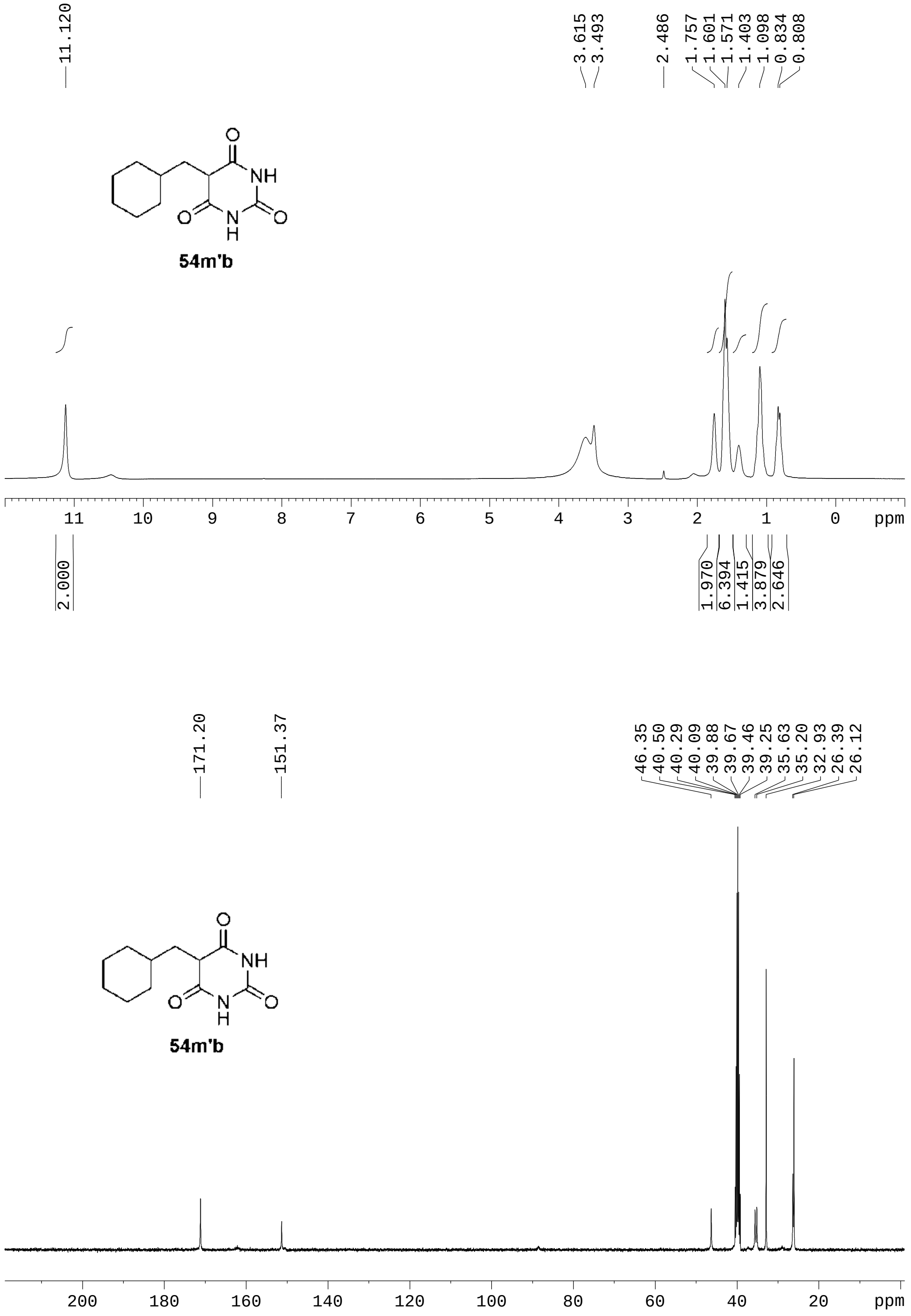
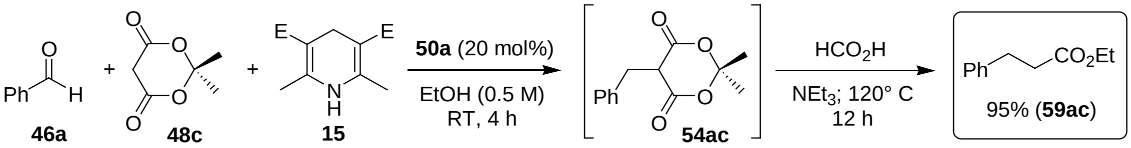


Figure-5: ^{1}H NMR and ^{13}C NMR Spectrum of product **54m’b**.

Scheme 2: Direct organocatalytic two-carbon homologation *via* cascade olefination/hydrogenation/hydrolysis reactions in one pot.

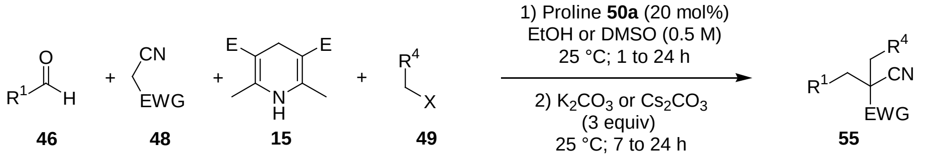


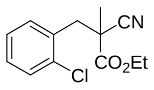
3.2.4 Diversity-Oriented Green Synthesis of Reductive Alkylation Products 55:

In view of the results of the proline-catalyzed three- and four-component O/H and O/H/H reactions with various aldehydes **46a-n'** and CH-acids **48a-l**, we also engineered a novel proline/K_2CO_3-catalyzed four-component O/H/A reaction of aldehydes **46**, ethyl cyanoacetate **48f**, or malononitrile **48j**, Hantzsch ester **15** and alkyl halides **49a-e** in one-pot (Table 6). Highly substituted cyanoesters **55** containing a quaternary carbon were constructed in good yields with various substitutions as shown in Table 6 and this process is the first example of the utility of the proline/K_2CO_3 combination in green catalysis.

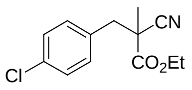
We have demonstrated, direct organo-/K_2CO_3-catalytic double-alkylation's approach to the synthesis of highly substituted cyano-esters **55kfc-mfc** with good yields in a single step (Table 6, entries 7-9). We have also demonstrated the double cascade O/H/A reaction on benzene-1,3-dicarbaldehyde **46t** with **48f**, **15** and **49e** under proline/K_2CO_3 catalysis as shown in Table 6, entry 15. One-pot products, cyano-esters **55** have direct applications in pharmaceutical and agricultural chemistry.[29a-29p] For example cascade O/H/A generated products, ethyl 2-(4-chlorobenzyl)-2-cyanopropionate **55yfa** is anti-inflammatory active,[29b] ethyl 2-(2-chlorobenzyl)-2-cyanobutyrate **55wfb** is analgesic active,[29b] and 2-allyl-2-(4-chlorobenzyl)malononitrile **55yjc** (**D**) is very good pesticide, which showed 100% control against Musca domestica, German cockroach.[29o]

Table 6: Synthesis of chemically diverse libraries of analgesic and anti-inflammatory cyano-esters **55** via organo-/metal carbonate-catalyzed cascade olefination/hydrogenation/alkylation reactions[a]

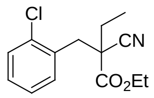




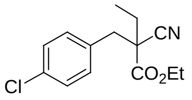
65% (**55wfa**)



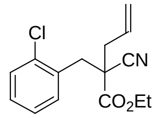
75% (**55yfa**)



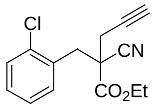
65% (**55wfb**)



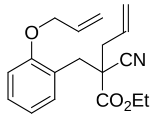
60% (**55yfb**)



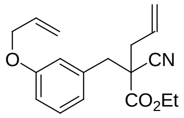
80% (**55wfc**)



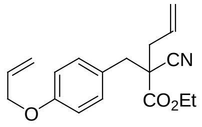
80% (**55wfd**)



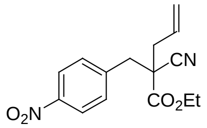
80% (**55kfc**)[b]



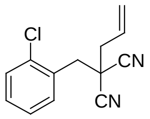
85% (**55lfc**)[b]



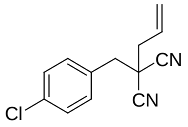
83% (**5**5mfc)[b]



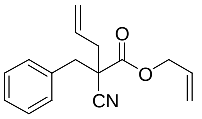
75% (**55pfc**)



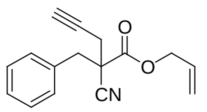
95% (**55wjc**)



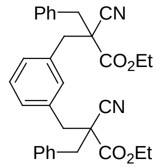
93% (**55yjc**)[c]



90% (**55agc**)[d]



80% (**55agd**)[d]



60% (**55tfe**)

[a] See Experimental Section, yield refers to the column purified product and EtOH/K_2CO_3, R^4CH_2X used [b] Product obtained from olefination/hydrogenation/*C*-alkylation/*O*-alkylation sequence.[c] DMF/Cs_2CO_3 used. [d] DMSO/K_2CO_3 used.

As shown in Table 6, entries 13 and 14, cascade O/H/A reaction of **46a**, **48g**, **59** and **49c/49d** in DMSO solvent under proline/K_2CO_3 catalysis furnished the expected one-pot products **55agc** and **55agd** with good yields. Interestingly, the same procedure in EtOH as solvent furnished the one-pot *trans*-esterfication products **55afc** and **55afd** in good yields as shown in Scheme 3. This is the best demonstration for the biomimetic *trans*-esterfication[31] of highly functionalized allyl esters **55agc** and **55agd** under mild basic conditions and also this is first observation in organocatalysis. The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 6-9] and mass analysis.

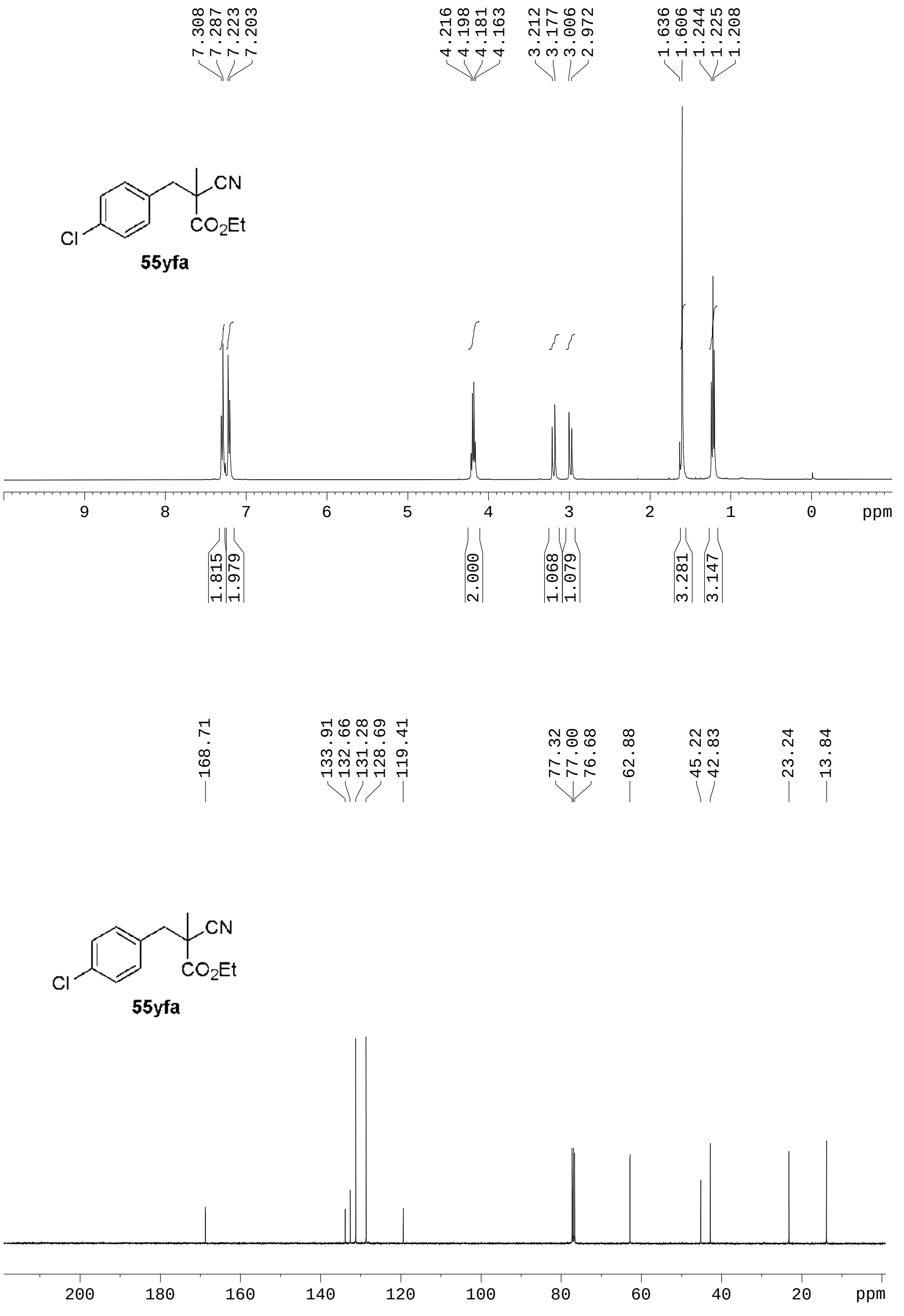


Figure-6: ^{1}H NMR and ^{13}C NMR Spectrum of product **55yfa**.

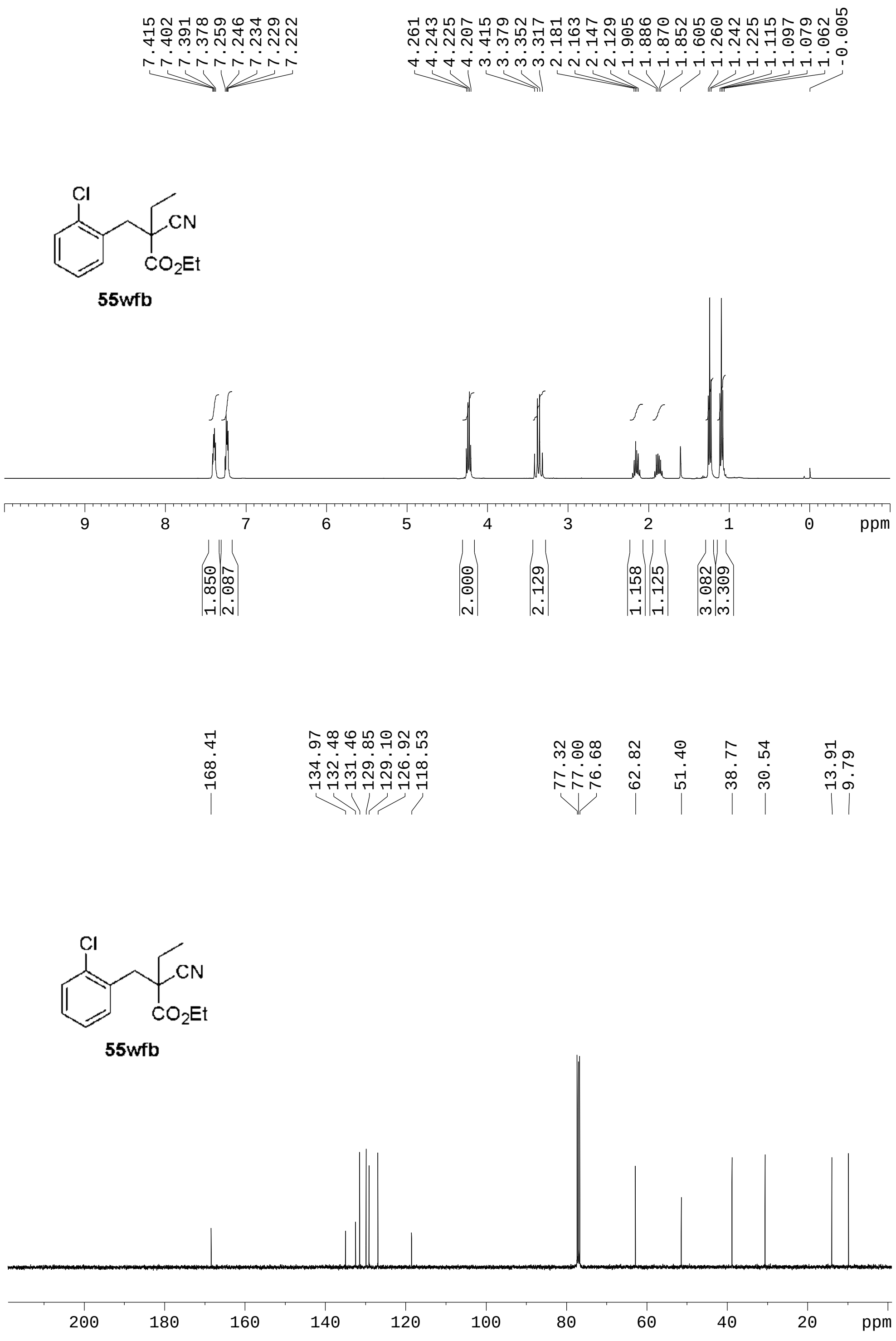


Figure-7: ^{1}H NMR and ^{13}C NMR Spectrum of product **55wfb**.

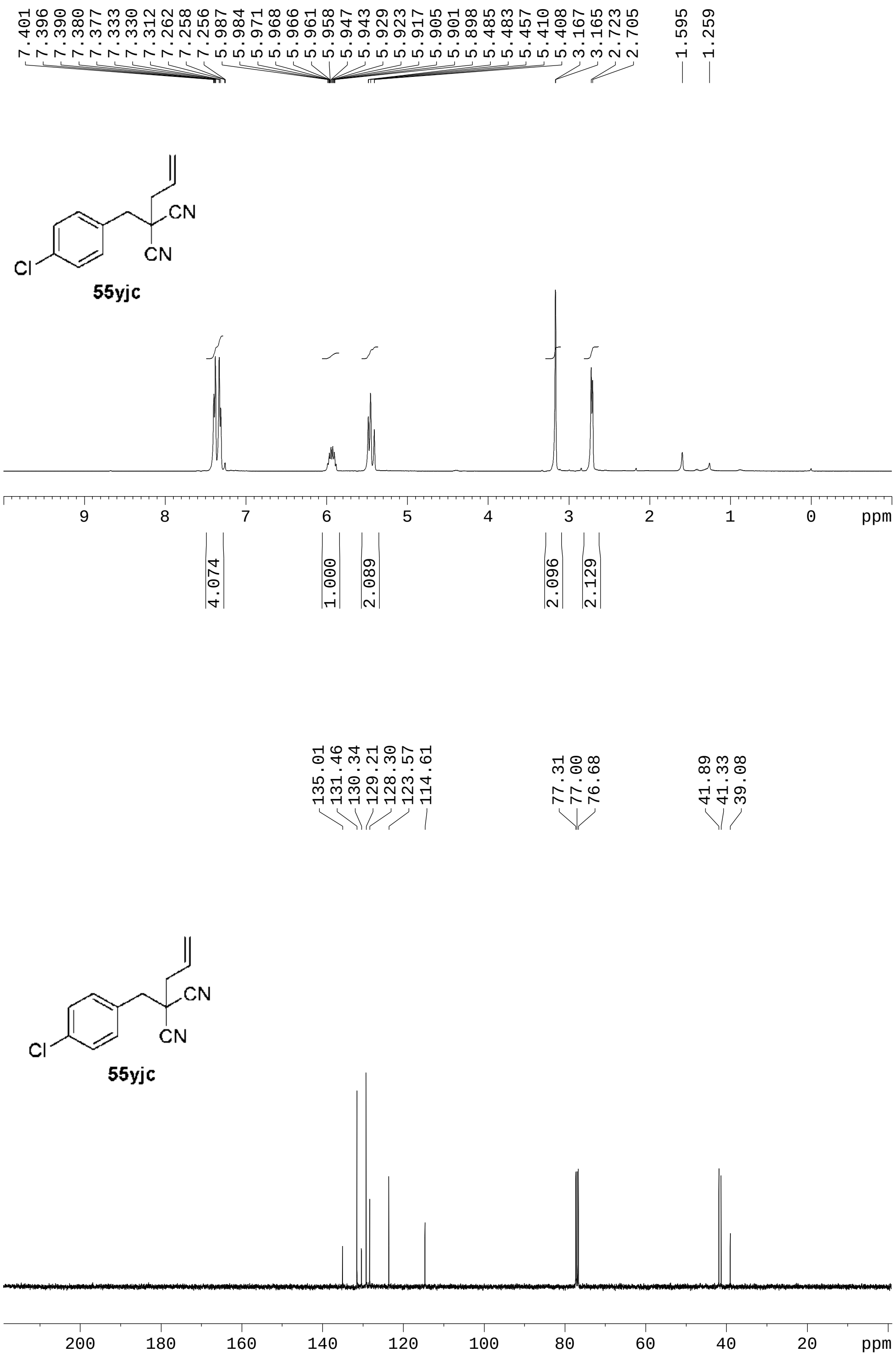
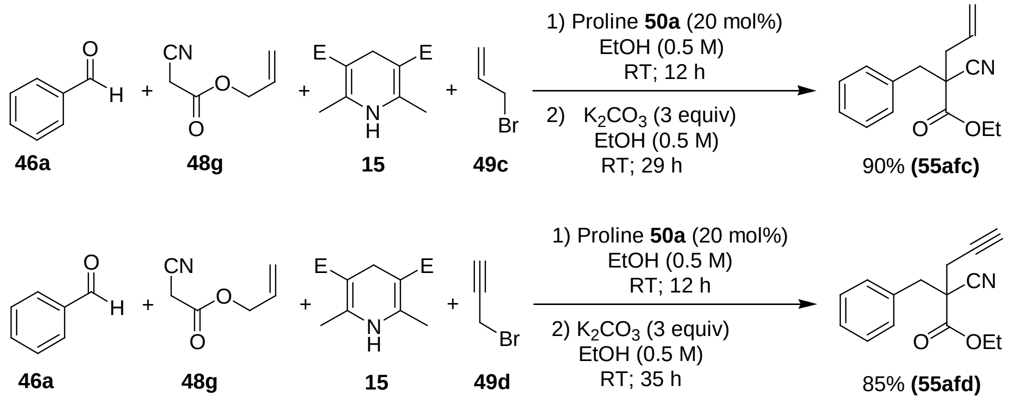
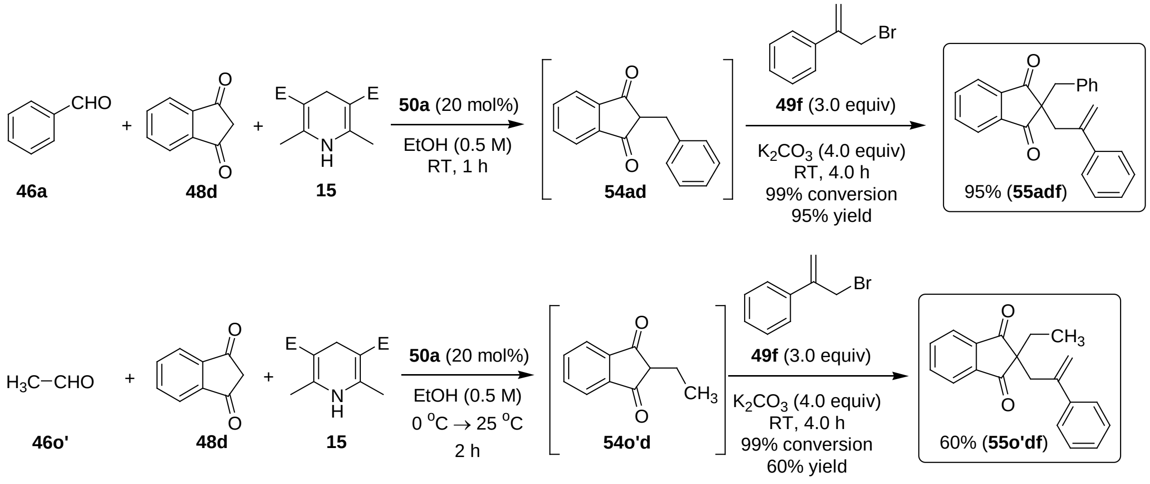


Figure-8: ^{1}H NMR and ^{13}C NMR Spectrum of product **55yjc**.

Scheme 3: Observation of *trans*-esterfication in sequential cascade O/H/A reactions



Scheme 4: Synthesis of Highly Active Herbicidal Products from Direct Cascade O/H/A Reactions in One-Pot**.**



To show the more direct applications of cascade O/H/A reactions to pharmaceutical chemistry, here we present the direct one-step synthesis of highly active herbicidal products **55adf** and **55o'df** with very good yields from simple starting materials (**46a** or **46o'**, **48d**, **15** and **49f**) under proline/K_2CO_3-catalysis at room temperature as shown in Scheme 4.

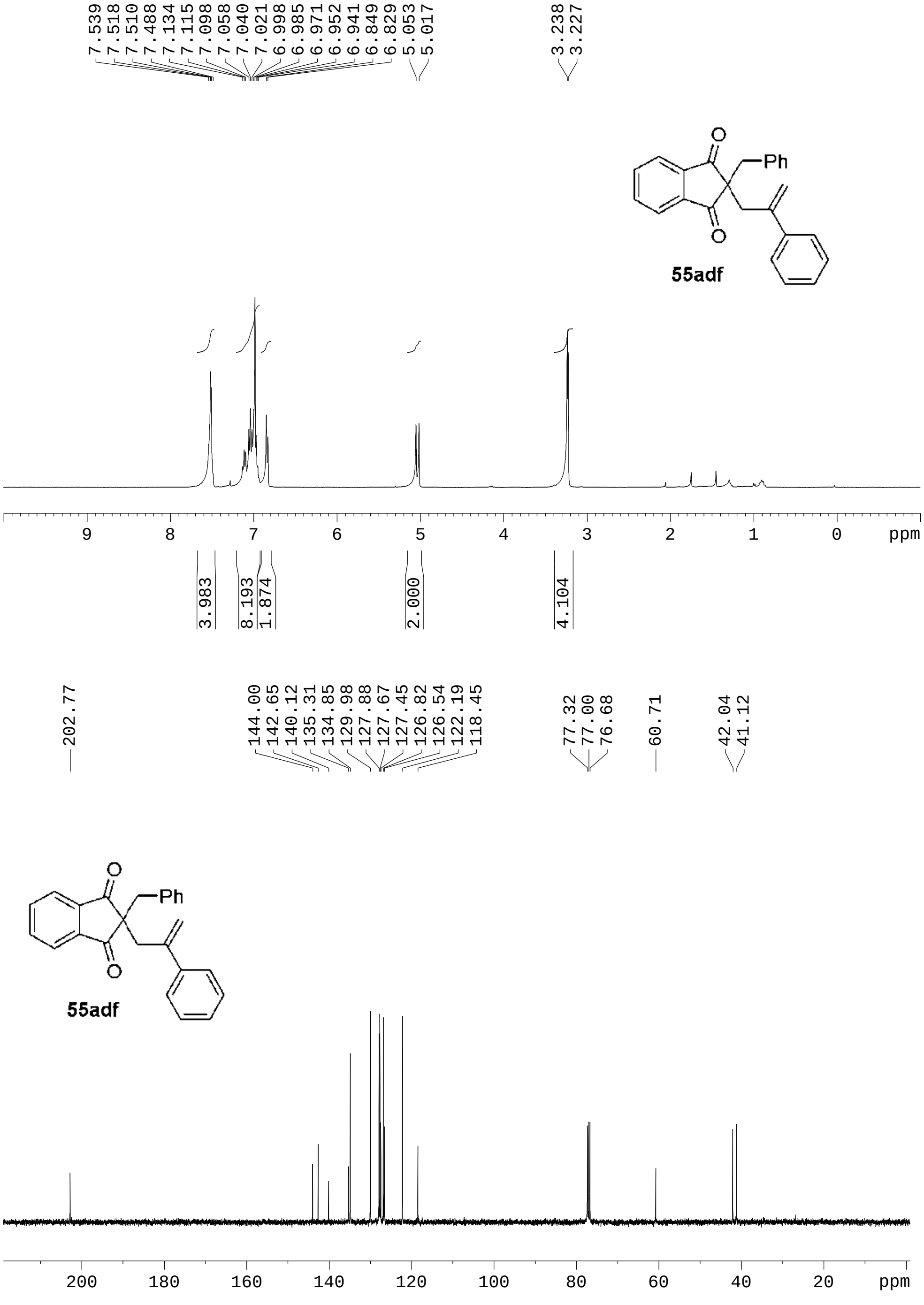
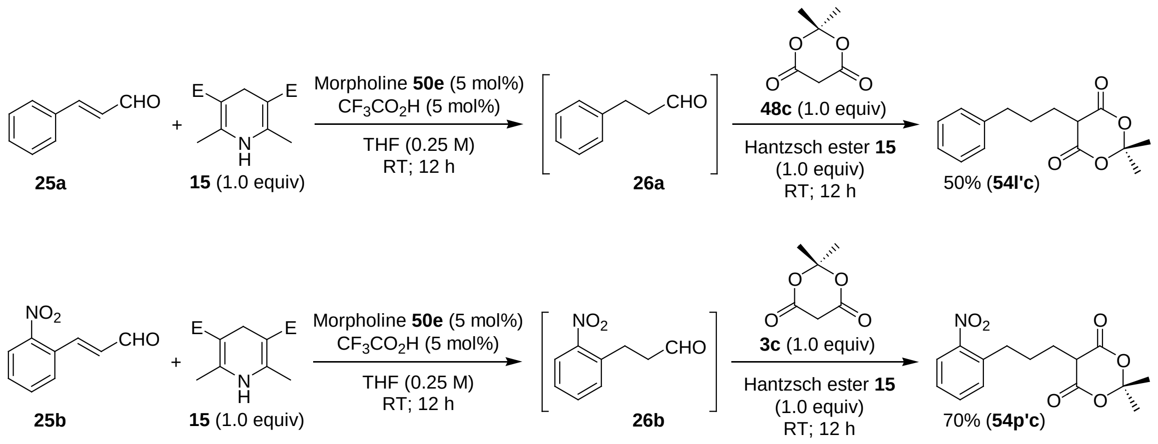


Figure-9: ^{1}H NMR and ^{13}C NMR Spectrum of product **55adf**.

The developed cascade O/H/A methodology can be utilized to develop the diversity-oriented library of analogues of herbicidal products **55adf** with very good yields in comparision with the two-step synthesis demonstrated by Mitsubishi Kasei Corporation, Japan in their patent.[29a,29f]

Scheme 5: Organocatalytic Cascade Hydrogenation-Olefination-Hydrogenation Reactions.



List *et al.* recently demonstrated the amine/acid-catalyzed hydrogenation of α, β-unsaturated aldehydes **25a** and **25b** with Hantzsch ester **15** to furnish the saturated aldehydes **26a** and **26b**, respectively with good yields.[32] Here we utilized the List technique to obtain the saturated aldehydes **26a** and **26b** in situ from α, β-unsaturated aldehydes **25a** and **25b,** and further allowed them to react with CH-acid **48** and Hantzsch ester **15** to generate the highly functionalized CH-acids **54** with good yields in one-pot fashion. Morpholine/CF_3CO_2H-catalyzed hydrogenation of *trans*-cinnamaldehyde **25a** in the presence of 1.0 equiv. of Hantzsch ester **15** in THF at 25 °C furnished the 3-phenylpropionaldehyde **26a**, which on treatment with each 1.0 equiv. of Meldrum's acid **48c** and Hantzsch ester **15** at 25 °C in the same solvent furnished the cascade H/O/H product **54l'c** in 50% yield as shown in Scheme 5. The same reaction sequence with *trans*-2-nitrocinnamaldehyde **25b** also furnished the cascade H/O/H product **54p'c** with 70% yield as shown in Scheme 5. Combination of amine/acid- and self-catalyzed cascade hydrogenation reactions will surely show much impact on synthetic sequences utilized in total synthesis of natural products.

3.2.5 Cascade Olefination-Hydrogenation Reactions of Ketones 47 with 48 and 15: Reaction Optimization: After successful demonstration of the amino acid and metal carbonate-promoted cascade O/H, O/H/A, O/H/A/TE, H/O/H and O/H/H reactions for the library generation of highly useful products **54** and **55** from aldehydes **46**, CH-acids **48**, Hantzsch ester **15** and alkyl halides **49**; then we decided to apply the same cascade strategy for the generation of cascade products **56** and **57** from less reactive ketones **47**, CH-acids **48**, Hantzsch ester **15** and alkyl halides **49**, which are highly useful materials in medicinal chemistry.

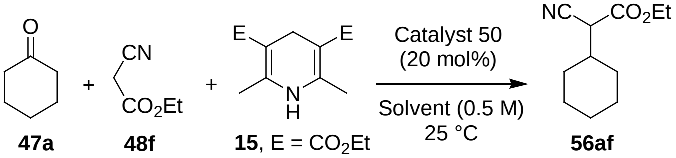
Cascade products **56** and **57** are attractive intermediates in the medicinal chemistry, and their analogues have broad utility in pharmaceutical chemistry[29q-29z] (insect repellent, dental adhesives, CRF antagonists, antispasmodics, antiulcer agents, drugs for skin diseases, against tuberculosis and leprosy bacteria and wound healing etc.) and in organic synthesis.

We found that amino acid, proline **50a** readily catalyses the olefination of cyclohexanone **47a** with CH-acid, ethyl cyanoacetate **48f** to furnish the active olefin **52af**, which on treatment with Hantzsch ester **15** produced the hydrogenated product **56af** with very good yield in MeOH at 25 °C for 24 h (Table 7, entry 1). The same reaction catalyzed by L-proline **50a** at 25 °C under cascade conditions furnished the product **56af** with 90 to 95% yield in protic solvents (Table 7, entries 1-3). The use of polar aprotic solvents (DMF and DMSO) gave similar yields to the reactions in MeOH and EtOH (Table 7, entries 4-7). Interestingly, proline-catalyzed cascade O/H reactions on ketones **47** are solvent dependent reactions (Table 7) as compared to same reactions with aldehydes **46** (Tables 1-6), may be due to the less reactive nature of ketones **47**. Simple amino acid, glycine **50b** also catalyzed the cascade O/H reaction to furnish cascade product **56af** in 72% yield (Table 7, entry 10). The simple amines, pyrrolidine **50c**, piperidine **50d**, morpholine **50e** and benzylamine **50f** also catalyzed the cascade O/H reaction to furnish hydrogenated product **56af** with 90% yield at 25 °C for 48 h as shown in Table 7, entries 11-14. Interestingly, cascade O/H reaction of **47a**, **48f** and **15** in the absence of catalyst at 25 °C for 48 h furnished the expected product **56af** in 80% and 75% yields in EtOH and DMSO solvents respectively (Table 7, entries 15 and 16). This is best demonstration of the self-catalytic nature of reagent in cascade reactions, and also for mimicking the hydrogenation-dehydrogenation of pyridine nucleotide-linked dehydrogenases.[33] The optimum conditions (entries 3-5 and 11-14) involved the use of catalyst, amino acid **50a** or amines **50c-f** in cascade O/H reaction of **47a**, **48f** and **15** in EtOH, DMF or DMSO at 25 °C to furnish **56af** in very good yields.

After preliminary understanding, we proceeded to investigate the scope and limitations of the cascade O/H reaction of cyclohexanone **47a** with a range of active CH-acids **48a-o** and Hantzsch ester **15** under proline-catalysis in DMSO (Table 8). Even though cascade O/H reactions gave good yields in EtOH (Table 7), but here we used DMSO or DMF as solvent because of the poorer solubilities of reactants in EtOH. As shown in Table 8, acyclic CH-acids **48e-j** are furnished cascade products **56ae-aj** in less yields than cyclic CH-acids **48a-d** and **48o** in cascade O/H reactions, possibly due to the difference in acid strength and HOMO-LUMO energy gap between Hantzsch ester **15** and in situ generated olefins **52** respectively. Cyclic CH-acids **48a-d** and **48o** have a higher acid strength than acyclic CH-acids **48e-j**, and the same acidic property also continues in olefins **52**. Cascade products **56aa-ao** have many applications in pharmaceutical chemistry.[29q-29z]

3.2.6 Diversity-Oriented Green Synthesis of Reductive Alkylation Products 56af-56tf: With an ideal cascade reductive alkylation protocol in hand, the scope of the proline-catalyzed cascade O/H reactions was investigated with various ketones **47a-t** and CH-acids **48e-j** by generating highly useful diversity-oriented library **56**. The results in Table 9 demonstrate the broad scope of this reductive green methodology covering a structurally diverse group of less reactive ketones **47a-t** and CH-acids **48e-j** with many of the yields obtained being very good, or indeed better, than previously published reactions starting from the corresponding olefins **52** or ketones **48**. Cascade O/H reaction of (*R*)-3-methylcyclohexanone **47c**, malononitrile **48j** and Hantzsch ester **15** furnished the regioselective chiral hydrogenated product (1*R*,3*R*)-2-(3-methylcyclohexyl)malononitrile **56cj** in 3.0:1 ratio with 86% yield.

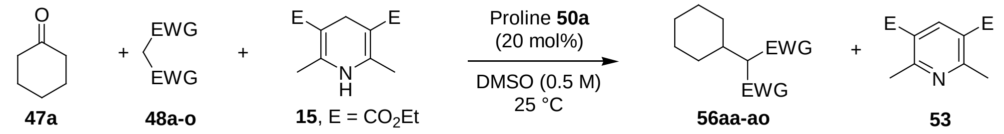
Table 7: Optimization of the direct organocatalytic cascade olefination/hydrogenation reactions of **47a**, **48f** and **15**.[a]

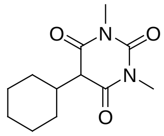


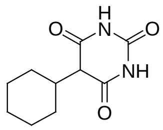
Entry	Catalyst	Solvent	Time [h]	Yield [%][b]
1	proline **50a**	MeOH	24	90
2	proline **50a**	EtOH	24	93
3	proline **50a**	EtOH	36	95
4	proline **50a**	DMF	24	86
5	proline **50a**	DMSO	24	86
6	proline **50a**	$CHCl_3$	24	48
7	proline **50a**	CH_3CN	24	68
8	proline **50a**	[bmim]BF_4	48	50
9	proline **50a**	THF	48	–
10	glycine **50b**	EtOH	48	72
11	pyrrolidine **50c**	EtOH	48	90
12	piperidine **50d**	EtOH	48	90
13	morpholine **50e**	EtOH	48	90
14	benzylamine **50f**	EtOH	48	90
15	–	EtOH	48	80
16	–	DMSO	48	75
17	–	H_2O	48	15

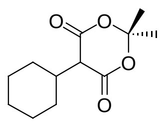
[a] Experimental conditions: All reactants (**47a**, **48f**, **15**) and catalyst **50** were mixed at the same time in solvent and stirred at room temperature. [b] Yield refers to the column purified product.

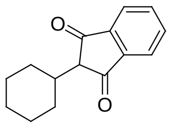
Table 8: Direct organocatalytic cascade olefination/hydrogenation reactions of **47a** and **15** with a variety of CH-acids **48a-m**.[a]

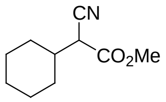



24 h
99% (**56aa**)

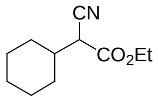

12 h
90% (**56ab**)


24 h
99% (**56ac**)

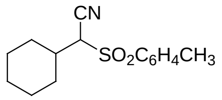

48 h
95% (**56ad**)



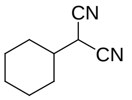
24 h
99% (**56ae**)



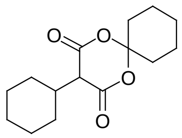
24 h
86% (**56af**)



60 h
60% (**56ai**)



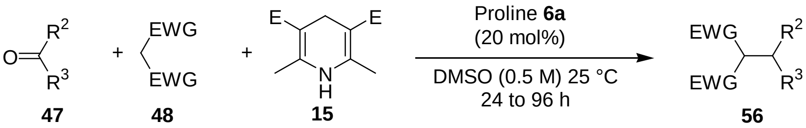
19 h
90% (**56aj**)

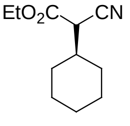

24 h
93% (**56ao**)

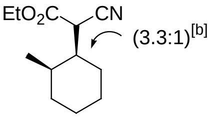
[a] See Experimental Section. [b] Yield refers to the column purified product.

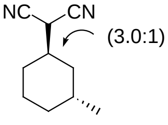
Cascade O/H reaction of 4-methylcyclohexanone **47d**, ethyl cyanoacetate **48f** and Hantzsch ester **15** furnished the regioselective hydrogenated ester *cis*-**56df** in 3.4:1 ratio with 90% yield (Table 9, entry 4). Cascade O/H reaction of cyclohexane-1,4-dione **47g** with CH-acids **48e,f** and Hantzsch ester **15** under proline-catalysis furnished the double cascade products **56ge** and **56gf** in good yields with high selectivity as shown in Table 9. Cascade O/H reaction of highly substituted cyclohexanones **47h,i** with CH-acids **48f,j** and Hantzsch ester **15** under proline-catalysis furnished the cascade products **56hf**, **56if** and **56ij** in good yields with high selectivity as shown in Table 9. Structure and regio-chemistry of cascade O/H products **56bf-ij** was confirmed by NMR analysis and also by X-ray structure analysis on **56if** as shown in Scheme 6.[34]

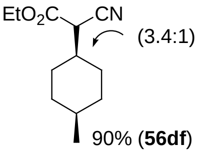
Table 9: Synthesis of chemically diverse libraries of **56** via organocatalyzed cascade olefination/hydrogenation reactions of **47**, **48** and **15**.[a]

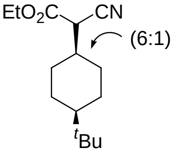


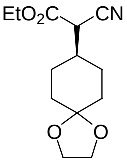

95% (**56af**)

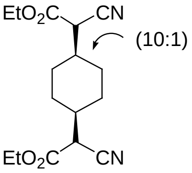

45% (**56bf**)

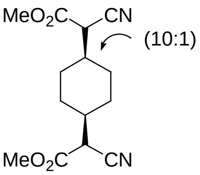

86% (**56cj**)

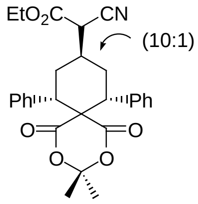

90% (**56df**)

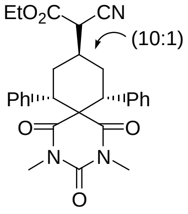

95% (**56ef**)

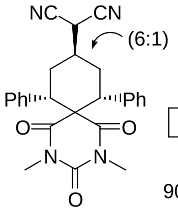

75% (**56ff**)

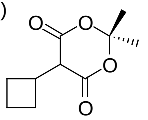

70% (**56gf**)[c]

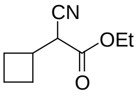

70% (**56ge**)[c]

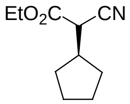

99% (**56hf**)

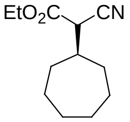

95% (**56if**)

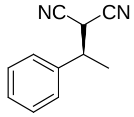

95% (**56ij**)

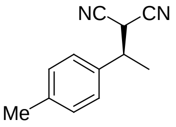

90% (**56jc**)

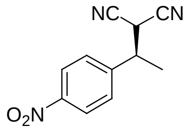

75% (**56jf**)

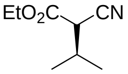

90% (**56kf**)

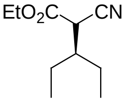

90% (**56lf**)

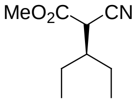

99% (**56mj**)

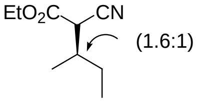

85% (**56nj**)

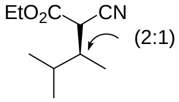

95% (**56oj**)

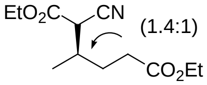

93% (**56pf**)


60% (**56qf**)


92% (**56qe**)

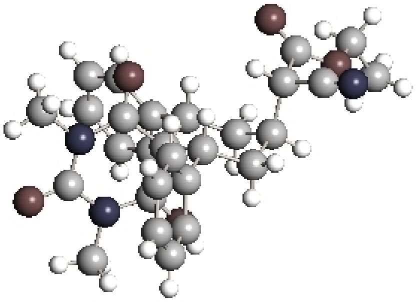

92% (**56rf**)


61% (**56sf**)


85% (**56tf**)

[a] Yield refers to the column purified product. [b] Ratio determined by ^{1}H and ^{13}C NMR analysis. [c] Cyclohexane-1,4-dione **47g** is starting material for these products.

Scheme 6: Crystal structure of cyano-(2,4-dimethyl-1,3,5-trioxo-7,11-diphenyl-2,4-diaza-spiro[5.5]undec-9-yl)-acetic acid ethyl ester (**56if**).



56if

Observed high regio-selectivity in cascade **56bf-ij** products can be explained as shown in Scheme **7**. Here approach of the hydride source (Hantzsch ester **15**) to olefin **52bf-ij** is main controlling factor than thermodynamic stability of the resulting hydrogenated products **56bf-ij**. Approach of the Hantzsch ester **15** to olefin **52if** through equatorial position is more favourable than axial position, may be due to the existence of more steric hindrance in an axial approach. As shown in Scheme **7**, steric strain control (SSC) is main controlling factor than product stability control (PSC) in bio-mimetic cascade reductions, because thermodynamically stable isomer *cis*-**56if** is formed as minor product. This selectivity trend can be easily understood by the approach of bulk hydride source **15** to olefins **52**.

Simple cyclic ketones cyclobutanone **47j**, cyclopentanone **47k** and cycloheptanone **47l** reacted with **48** and **15** under amino acid-catalysis to furnish the expected cascade O/H products **56jc**, **56jf**, **56kf** and **56lf** with very good yields as shown in Table 9. Acyclic ketones **47m-t** also involved in the three-component cascade O/H reaction with **48** and **15** to furnish the cascade products **56mj-56tf** in very good yields as shown in Table 9. Cascade O/H reactions produced hydrogenated products **56bf**, **56cj**, **56df**, **56ef** and **56sf** with good regio-selectivity's compared to $NaBH_4$ reduction of corresponding olefins,[35] as shown in Table **9**. The products structures were confirmed by ^1H NMR, ^{13}C NMR [for example see Fig. 10-13] and mass analysis.

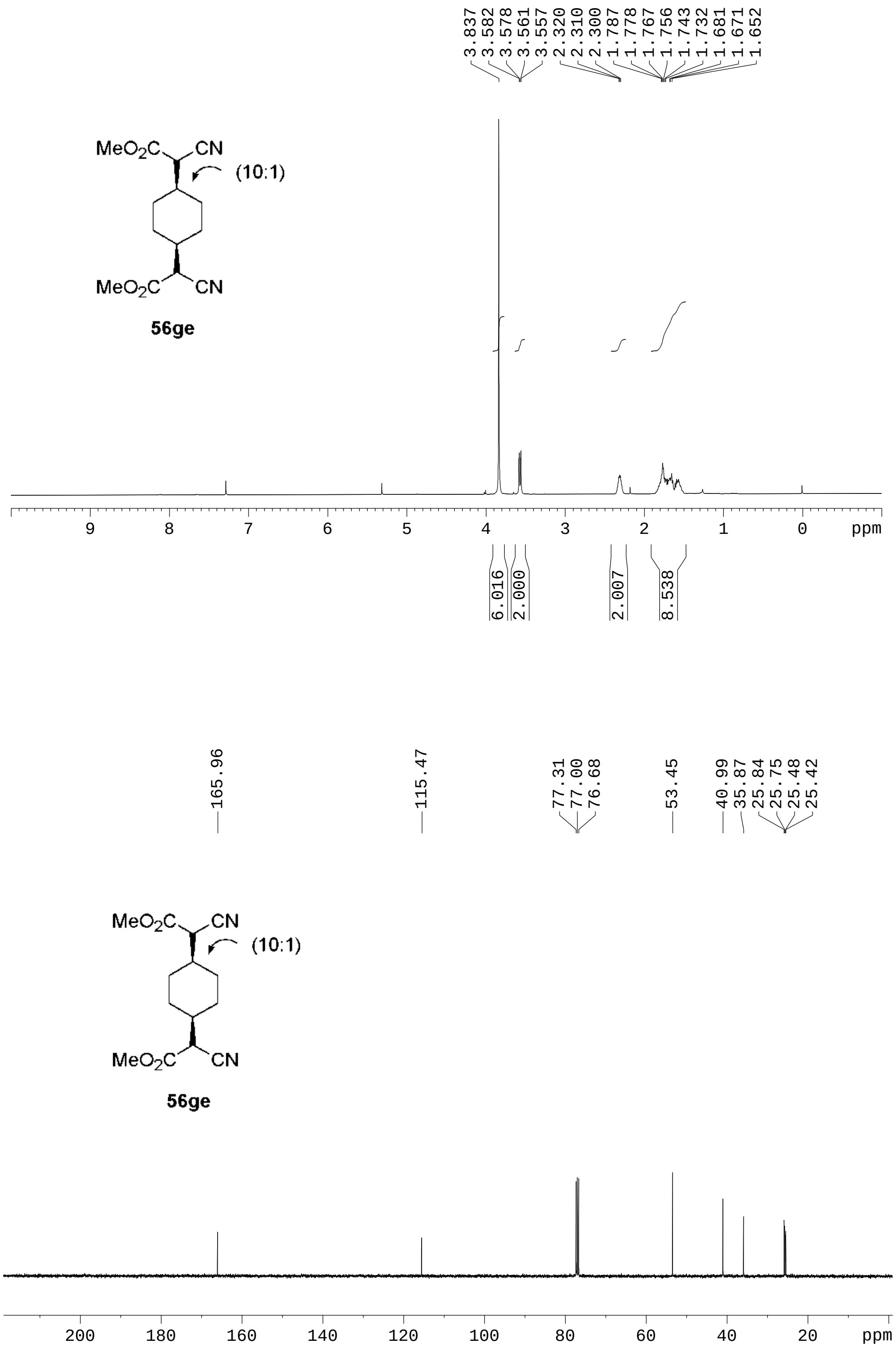


Figure-10: ^{1}H NMR and ^{13}C NMR Spectrum of product **56ge**.

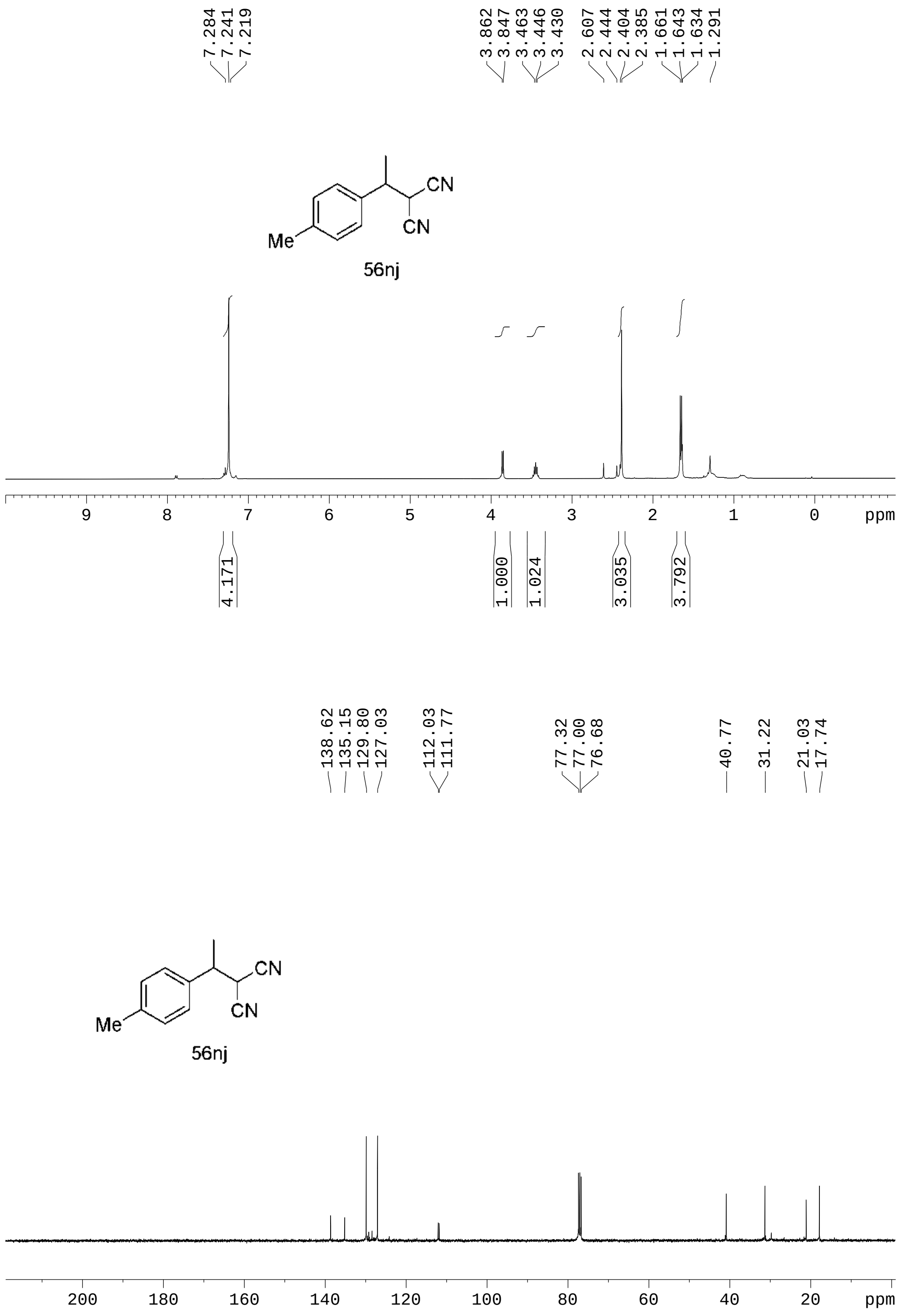


Figure-11: ^{1}H NMR and ^{13}C NMR Spectrum of product **56nj**.

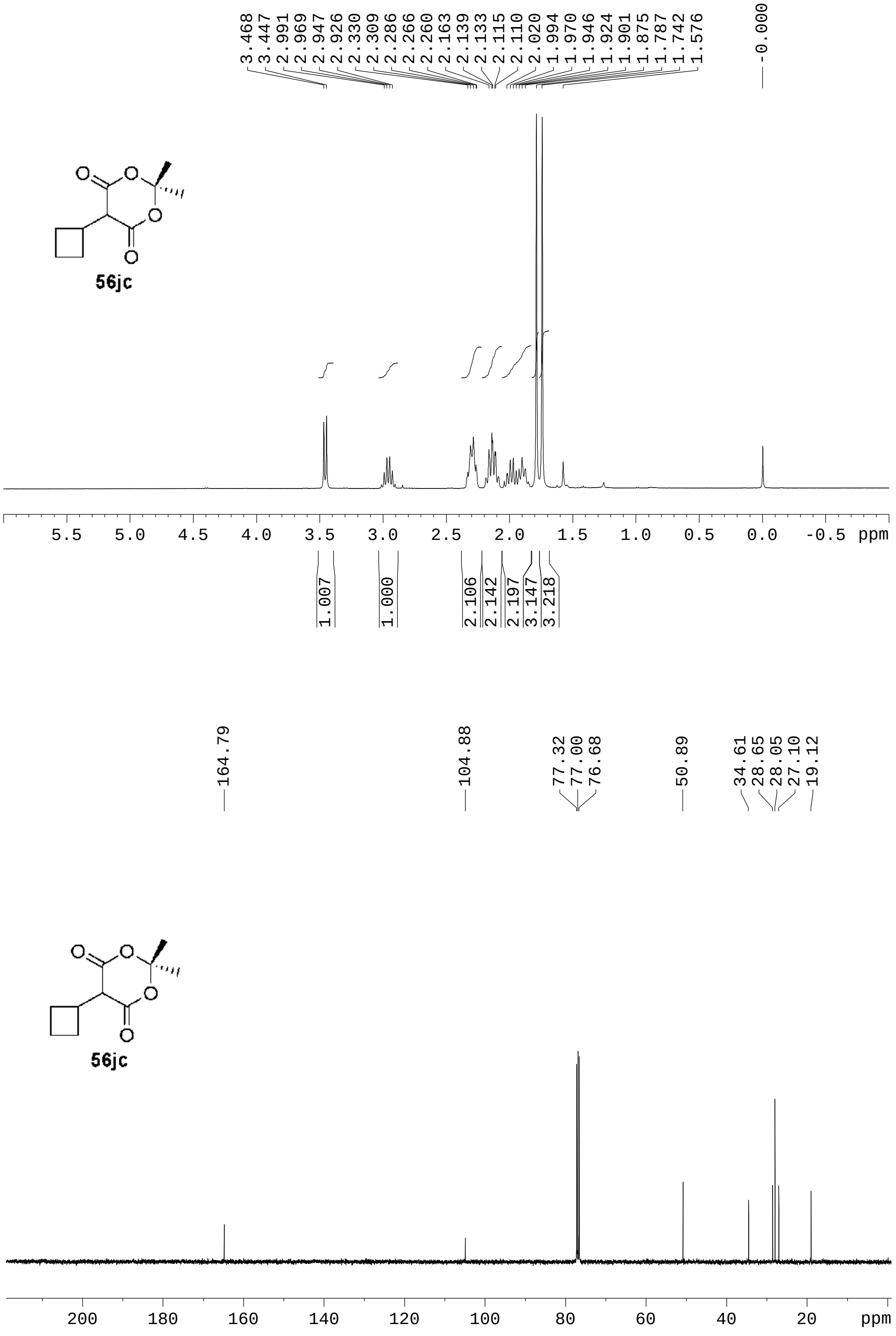
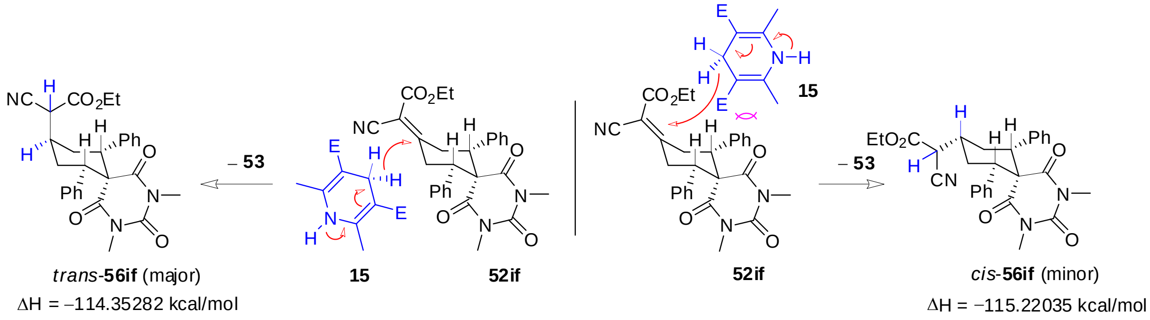


Figure-12: ^{1}H NMR and ^{13}C NMR Spectrum of product **56jc**.

Scheme 7: Observation of steric strain control (SSC) as dominating factor than product stability control (PSC) in bio-mimetic cascade reductions.



The Hydrogenated ester **56af** and its analogues are important intermediates for the synthesis of cygerol (wound treatment ointment),[29u] perfumes, anti-ulcer agents and drugs for skin diseases; cascade esters **56ge** and **56gf** are useful materials for the synthesis of alignment films for liquid crystal displays,[29y] cascade esters **56jc** and **56jf** are useful intermediates for the synthesis of prostaglandin analogues,[29z] cascade products **56mj-oj** are useful intermediates for the synthesis of anti-microbial sesquiterpene (*S*)-ar-turmerone **L** and analogues,[29w] cascade ester **56tf** used as intermediate in the synthesis of ophiobolins natural product,[29v] cascade products **56kf**, **56sf** and analogues used for the preparation of active antispasmodics,[29t] and cascade hydrogenated product **56qe** using as repellents for cockroaches,[29q] in USA emphasizing the value of this cascade approach.

3.2.7 Diversity-Oriented Green Synthesis of Reductive Alkylation Products 57:

With pharmaceutical applications in mind, we extended the three-component cascade O/H reactions to a novel proline/Cs_2CO_3- and proline/K_2CO_3-catalyzed four-component O/H/A reaction of ketones **47**, CH-acids **48**, Hantzsch ester **15** with various alkyl halides **49a-g** (Table 10). 2, 2-Disubstituted ethyl cyanoacetates and malononitriles **57** were constructed in good yields with various substituents as shown in Table 10. Here we have demonstrated a direct organocatalytic approach to the synthesis

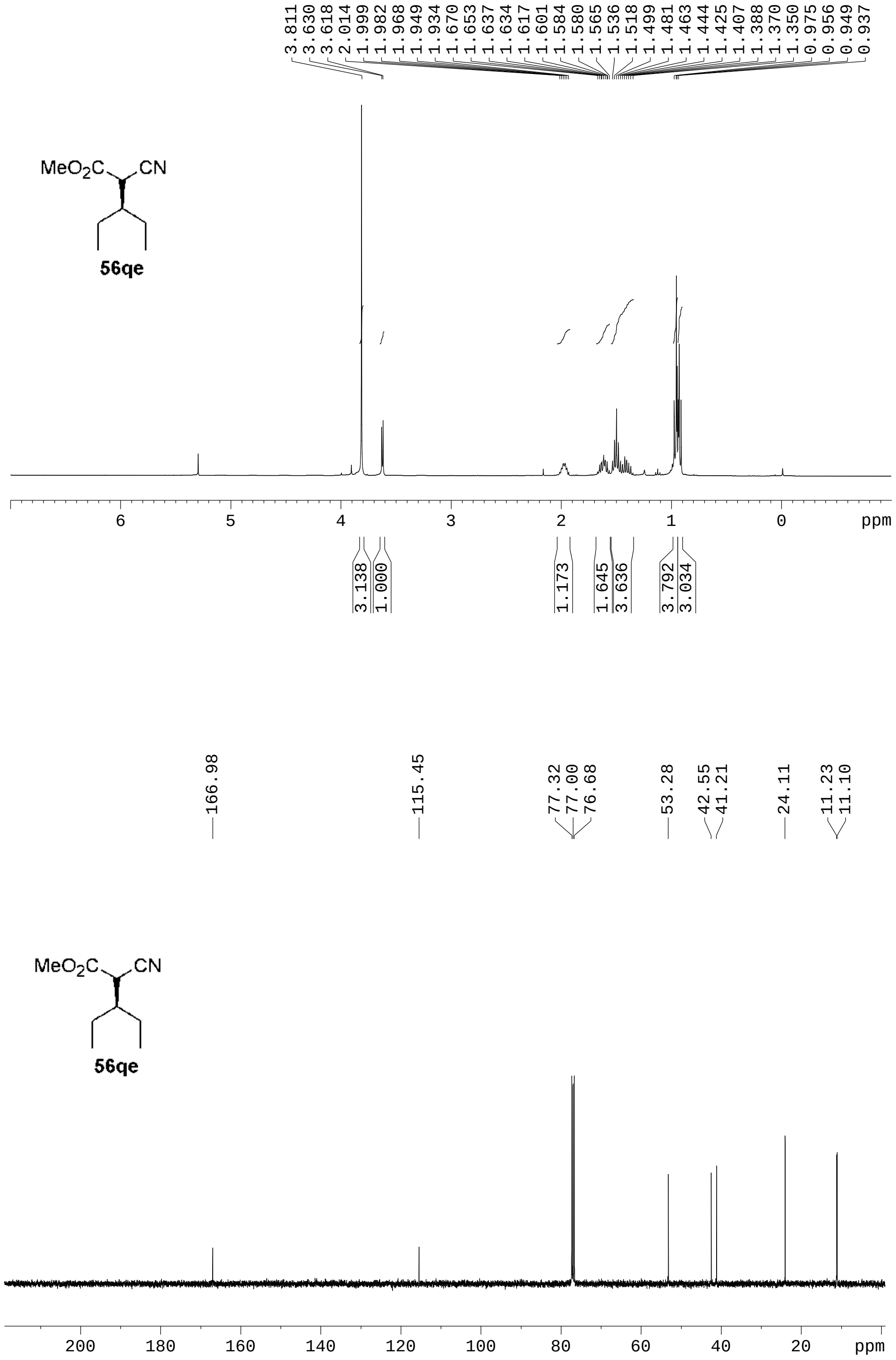


Figure-13: ^{1}H NMR and ^{13}C NMR Spectrum of product **56qe**.

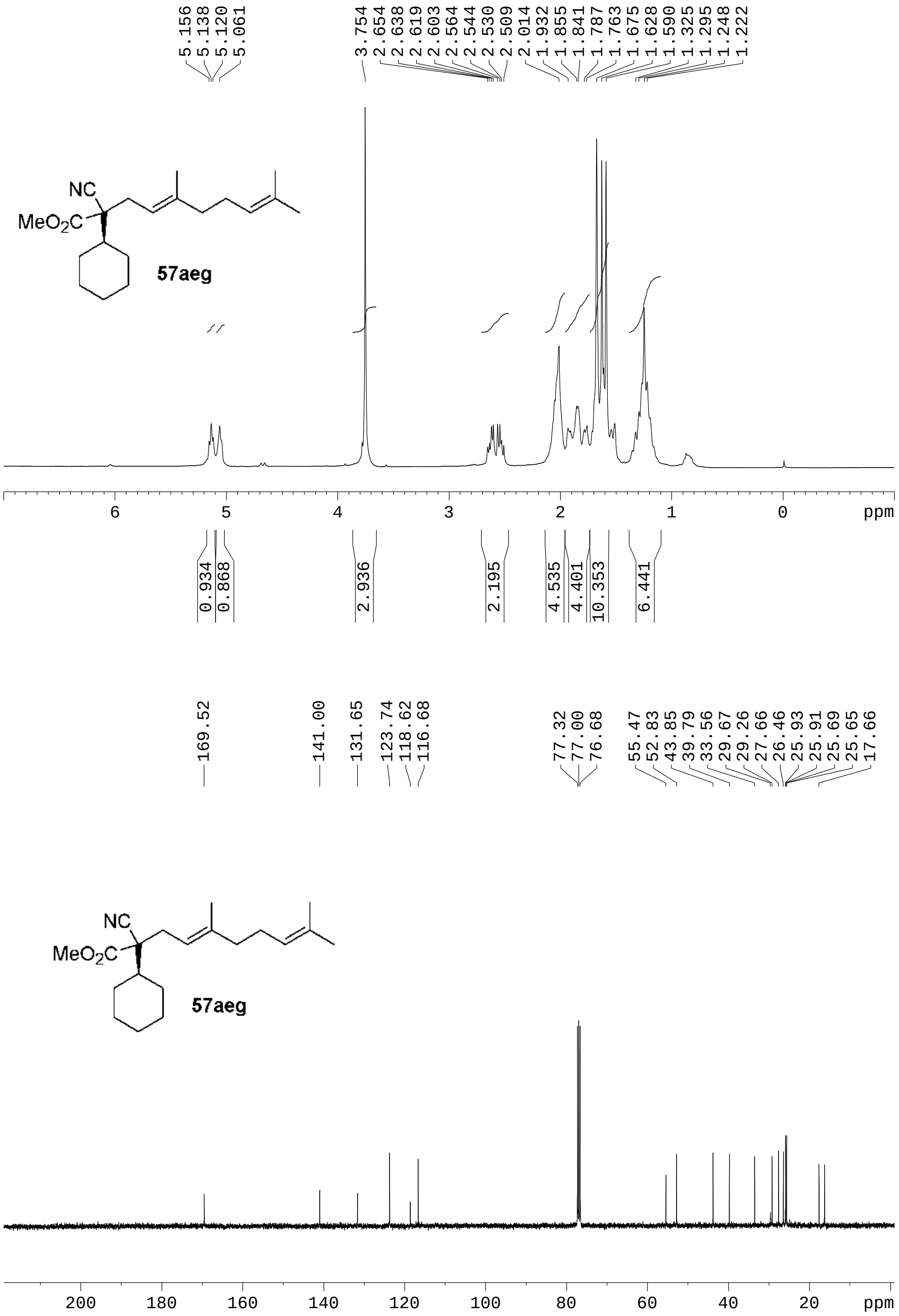
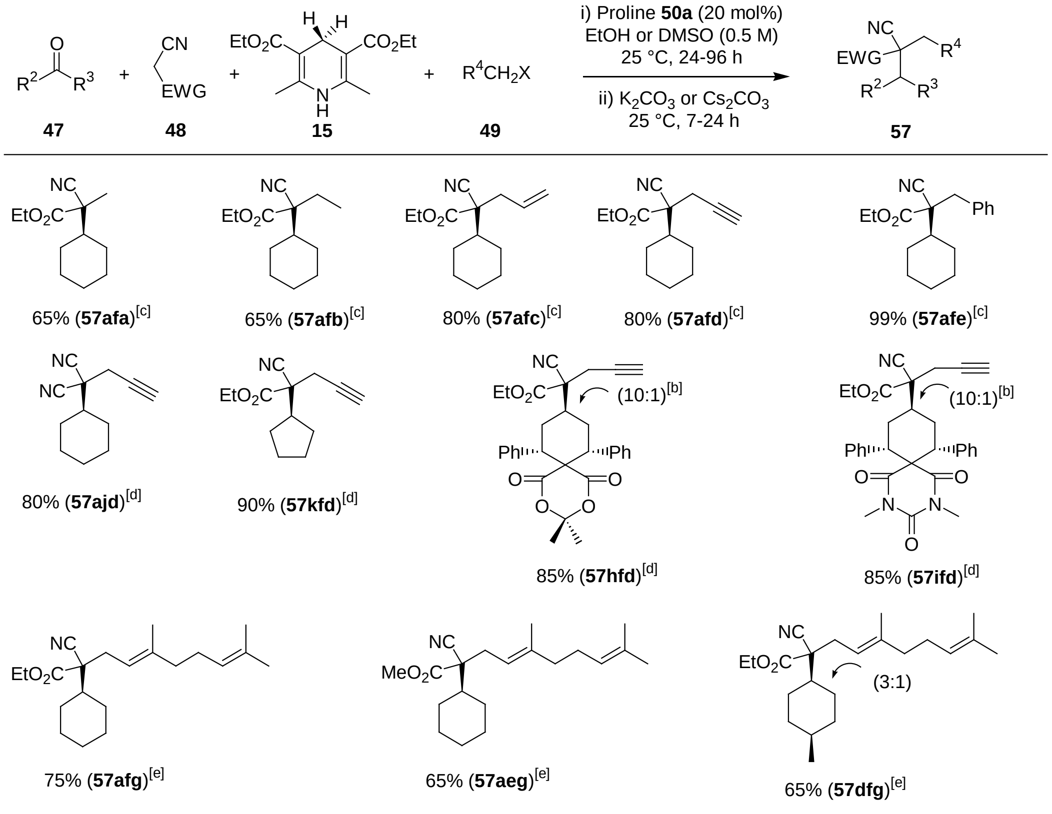


Figure-14: ^{1}H NMR and ^{13}C NMR Spectrum of product **57aeg**.

of key intermediates of pharmaceutical drug cygerol **M** (see Chart 1) in a single step (Table 10, entries 10-12). Decyanation followed by hydrolysis of **57aeg** or **57afg** furnish the cyclohexylgeranylacetic acid **M**, useful for wound healing as demonstrated by Joseph and George in their patent.[29u] The products structures were confirmed by ^{1}H and ^{13}C NMR [for example see Fig. 14] and mass analysis.

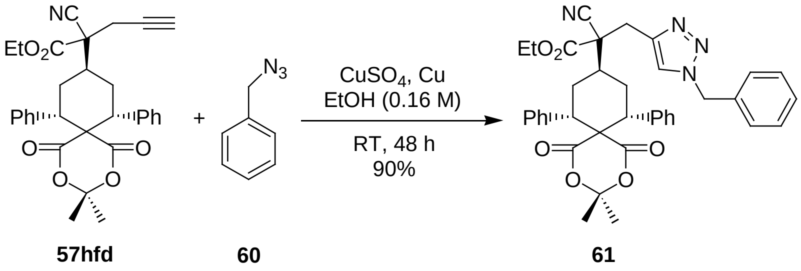
Table 10: Synthesis of chemically diverse libraries of **57** via organocatalyzed cascade olefination/hydrogenation/alkylation reactions of **47**, **48**, **15** and **49**.[a]



65% (**57afa**)[c]
65% (**57afb**)[c]
80% (**57afc**)[c]
80% (**57afd**)[c]
99% (**57afe**)[c]
80% (**57ajd**)[d]
90% (**57kfd**)[d]
85% (**57hfd**)[d]
85% (**57ifd**)[d]
75% (**57afg**)[e]
65% (**57aeg**)[e]
65% (**57dfg**)[e]

[a] Yield refers to the column purified product. [b] Ratio determined by ^{1}H and ^{13}C NMR analysis. [c] Alkylation performed under K_2CO_3/EtOH conditions. [d] Alkylation performed under K_2CO_3/DMSO conditions. [e] Alkylation performed under Cs_2CO_3/DMF conditions.

Scheme 8: Huisgen Cycloaddition Reactions on Cascade O/H/A Products.



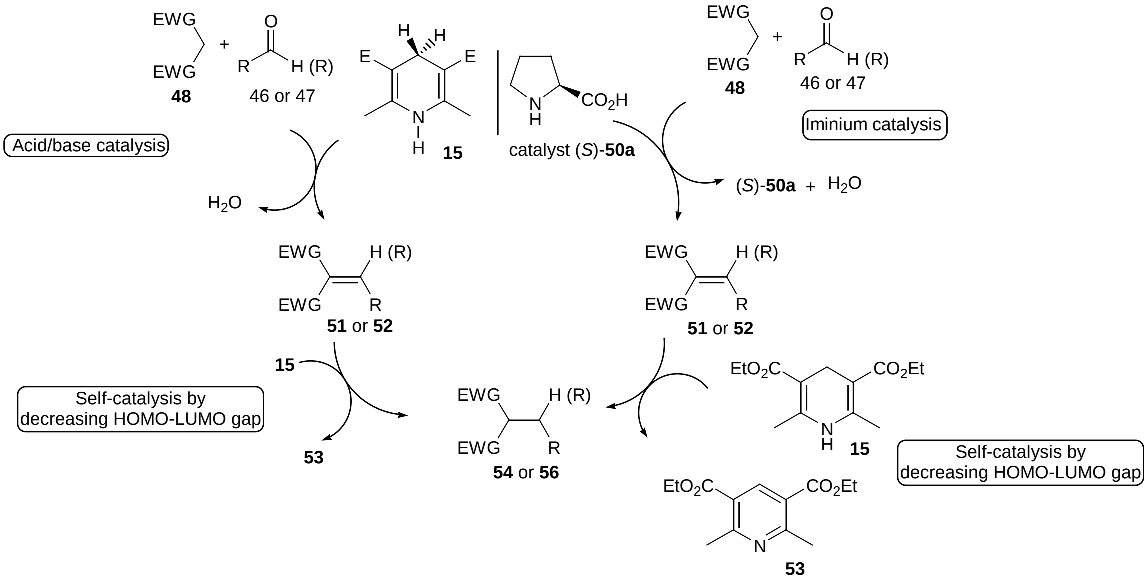
Huisgen 1,3-dipolar cycloadditions[36a] are important ring-fusion processes, the most useful members of this class arguably being the cycloaddition of azides and alkynes to give triazoles. The Huisgen cycloaddition of propargyl substituted cascade product **57hfd** with benzyl azide **60** under $CuSO_4$/Cu catalysis furnished the regiospecifically 1,4-disubstituted [1,2,3]-triazole **61** in very good yield as shown in Scheme 8. 1,2,3-Triazoles have found wide applications in biology, chemistry, and materials science,[36b] so it is important to develop new and more efficient cascade approaches to develop a diverse array of starting materials **57** and **60** for the library generation of [1,2,3]-triazoles **61**, which can be tested for the pharmaceutical applications. In this respect our cascade O/H/A reactions can deliver a diversity-oriented library of click-chemistry precursors.

3.2.8 Mechanistic Insights:

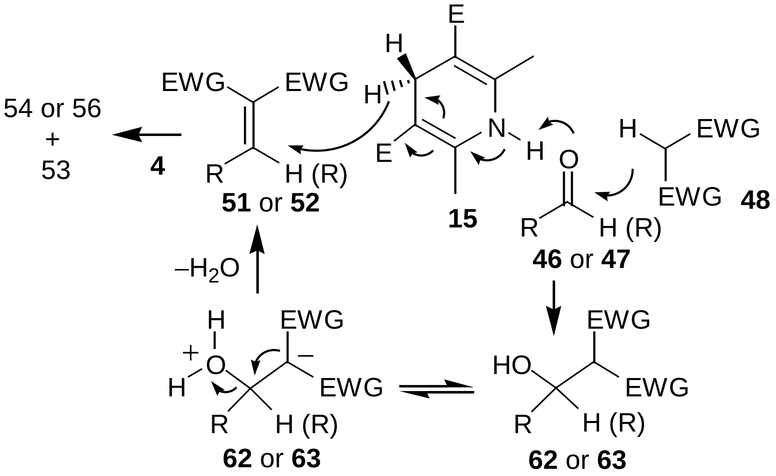
The possible reaction mechanism for proline-, self- and auto-catalyzed regio- and chemo-selective synthesis of cascade products **54** and **56** through reaction of aldehyde **46** or ketone **47**, CH-acid **48**, and Hantzsch ester **15** is illustrated in Scheme 9 and Scheme 10. This double catalytic cascade reaction is a three component reaction involving aldehyde **46** or ketone **47**, CH-acid **48**, Hantzsch ester **15** and a simple catalyst amine or amino acid **50a,** which is capable of catalyzing each step of this double catalytic cascade reaction. In the first step (Scheme 9), the catalyst **50a** activates component **46**/**47,** most probably by iminium ion formation, and this then selectively adds to the CH-acid **48** through a Mannich- and retro-Mannich-type reaction to generate active olefin **51/52**.[1] The following second step is biomimetic hydrogenation of active olefin **51/52** by Hantzsch ester **15** to produce **54/56** through self-catalysis by decreasing the HOMO-LUMO energy gap between **15** and **51/52**.[1c]

Interestingly, one of the reagents in cascade reaction is also catalyses the cascade sequence to furnish the products **54/56** in good yields. In the first step (Scheme 10), the Hantzsch ester **15** activates components **46**/**47** most probably by acid/base catalysis, and these then selectively adds to the CH-acid **48** in a aldol-type reaction to generate active olefins **51/52.**[1a-c, 26b] The following second step is biomimetic hydrogenation of active olefins **51/52** by Hantzsch ester **15** to produce **54/56** through self-catalysis. As shown in Scheme 10, Hantzsch ester **15** simultaneously catalyses the activation of carbonyls **46/47** to form olefins **51/52** and the reduction of active olefins **51/52** to generate cascade products **54/56** in a single step.

Scheme 9: Proposed catalytic cycle for the organocatalytic olefination/hydrogenation reactions of **46**, **47**, **48** and **15**.

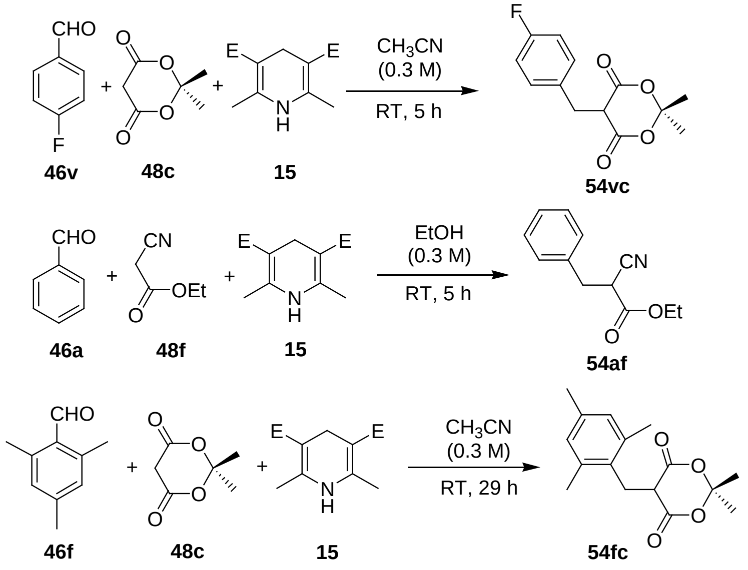


Scheme 10: Observation of auto-catalysis in cascade TCRA reactions



The dual role of Hantzsch ester **15** as a catalyst and reagent in the cascade O/H reactions was further confirmed by conducting controlled experiments on various substrates as shown in Scheme 11 and Table 11.

Scheme 11: Dual role of Hantzsch ester **15** as a catalyst and reagent in the cascade olefination/hydrogenation reactions



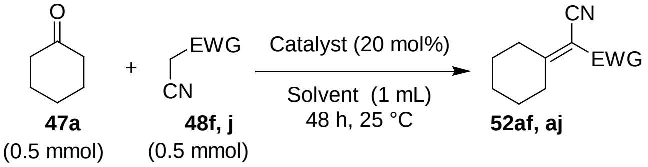
75% conversion [99% conversion at RT for 3 h under proline catalysis]

75% conversion [99% conversion at RT for 2 h under proline catalysis]

<15% conversion [80% conversion at RT for 29 h under proline catalysis]

Cascade O/H reactions of 4-fluorobenzaldehyde **46v**, Meldrum's acid **48c** and Hantzsch ester **15** in CH_3CN at 25 °C for 5 h; and benzaldehyde **46a**, ethyl cyanoacetate **48f** and Hantzsch ester **15** in EtOH at 25 °C for 5 h furnished the cascade products 5-(4-fluorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **54vc** and ethyl 2-cyano-2-phenylpropionate **54af** respectively, with 75% conversions.

Table 11: Olefination of cyclohexanone **47a** with **48f** and **48j** under organo- and self-catalysis



Entry	EWG	Catalyst	Solvent	Conversion [%][a]
1[b]	CO_2Et	**50a**	EtOH	**52af** (66)
2	CO_2Et	**53**	EtOH	**52af** (<3)
3	CO_2Et	**53**	DMSO	**52af** (<3)
4	CO_2Et	–	EtOH	**52af** (<3)
5	CO_2Et	–	DMSO	**52af** (<3)
6	CO_2Et	–	H_2O	**52af** (<4)
7	CN	–	EtOH	**52aj** (70)
8	CN	–	DMSO	**52aj** (70)
9	CN	–	H_2O	**52aj** (75)

[a] Determined by ^1H NMR analysis. [b] Reaction time was 24 h.

However, the same reactions under proline catalysis conditions furnished the expected products **54vc** and **54af** with 99% conversions and in shorter times (Scheme 11). To understand more about the self-catalysis of **15** in cascade O/H reactions, we performed olefination reaction of **47a** with **48f** and **48j** in the presence of **53** and in the absence of catalyst **50a** and **15** in EtOH, DMSO and H_2O solvents as shown in Table 11. Olefin product **52af** was furnished in very poor conversions after 48 h at 25 °C, with and without pyridine **53** catalysis in EtOH, DMSO and H_2O solvents starting from **47a** and **48f** (Table 11, entries 2-6). Interestingly, olefin product **52aj** was furnished from **47a** and **48j** in moderate yields under catalyst free conditions as shown in Table 11, entries 7-9; this may be due to the highly acidic nature of malononitrile **48j** in relation to ethyl cyanoacetate **48f**. From these results we have strong support for the self-catalysis of **15** in cascade O/H reactions.

Taking the recent applications of amine-catalyzed olefination reactions[27g] into account, and in view of the different experiments performed (Scheme 11 and Table 11), we propose that this cascade reaction is double catalytic cascade reaction: catalysis by a combination of amine **15** and amino acid as shown in Scheme 9 and 10.

3.3 Conclusion

In this chapter, we have demonstrated the organo-, organo/metal carbonate- and organo/Cu^I-catalyzed enzyme-like assembly of cascade products **54**, **55**, **56, 57**, **58**, **59** and **61** from readily available precursors via O/H, O/H/A, O/H/A/TE, H/O/H, O/H/H and O/H/A/HC reaction sequences. Combination of proline/M_2CO_3 and proline/Cu^I-ions proved to be optimal organo/metal catalysts for the cascade reactions in one-pot. This simple one-pot procedure provides direct access to functionalized diversity-oriented products **54** to **61**, shown to be pharmaceutical drugs, drug intermediate and ingredients in medicinal chemistry. First time in organo-catalysis, we reported the O/H/A/TE reaction to furnish the high yields of *trans*-esterfication products **55** by simply mixing the reactants under proline/K_2CO_3-catalysis. Additionally, a novel organocatalytic H/O/H reaction sequence was developed for the synthesis of alkyl substituted aromatics.

Furthermore, first time we developed the organo-catalyzed cascade O/H/H reactions to furnish the highly useful materials like 2-oxo-chroman-3-carboxylic acid **58kc** and 2-amino-4*H*-chromene-3-carbonitrile **58kj** with good yields. We also demonstrated the two-carbon homologation of aldehydes via organo-catalyzed O/H/H reactions in one-pot with high yields. Simple amines **50c-f** and amino acids **50a-b** were used as organo-catalyst for the catalyzing olefin formation in cascade reactions. Cascade reactions catalyzed by combinations of primitive bio-molecules and metal ions will open the new doors for bio-mimetic strategies in organic synthesis; and also will give possible reaction mechanisms in the pre-biotic evolution of molecular world.[27,37] These reactions can be performed on a multi-gram scale under operationally simple and environmentally safe conditions.

4. Organocatalytic Sequential One-Pot Double Cascade Asymmetric Synthesis of Wieland-Miescher Ketone Analogues via Olefination/Hydrogenation/Robinson Annulation Sequence

4.1 Introduction

Critical objectives in modern organic chemistry include the improvement of reaction efficiency, the avoidance of toxic reagents, the reduction of waste, and the responsible utilization of our resources. Organocatalytic cascade reactions, which consist of several bond-forming reactions, address many of these objectives.[27] Organocatalytic cascade reactions involve two or more bond-forming transformations that take place under the same reaction conditions from simple starting materials catalyzed by small molecular units of antibodies or enzymes.[27] One of the ultimate goals in organic synthesis is the catalytic asymmetric assembly of simple and readily available precursor molecules into bioactive products, a process that ultimately mimics biological synthesis. Cascade reactions have gained wide acceptance because they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used.[27b] Thus, these reactions can facilitate ecologically and economically favorable syntheses such as in vitro biological reactions.[27b]

We are in the "golden age of organocatalysis", and organocatalytic reactions have in the past few years emerged as a powerful synthetic tool for the construction of highly functionalized and optically active compounds.[38] Especially, organocatalytic cascade or tandem reactions have emerged as ideal synthetic strategies for the synthesis of highly functionalized compounds and drug-like small molecules in one-pot syntheses, mimicking biological reactions.[1a-c,26a-b,27,37a-c] The use of natural and unnatural amino acids and chiral secondary amines as catalysts for the α-functionalization of aldehydes and ketones via iminium and enamine formation represents an important breakthrough in modern asymmetric synthesis, and a large variety of functionalizations, such as C-C,[39] C-N,[40] C-O,[41] C-S,[42] and C-X (X =

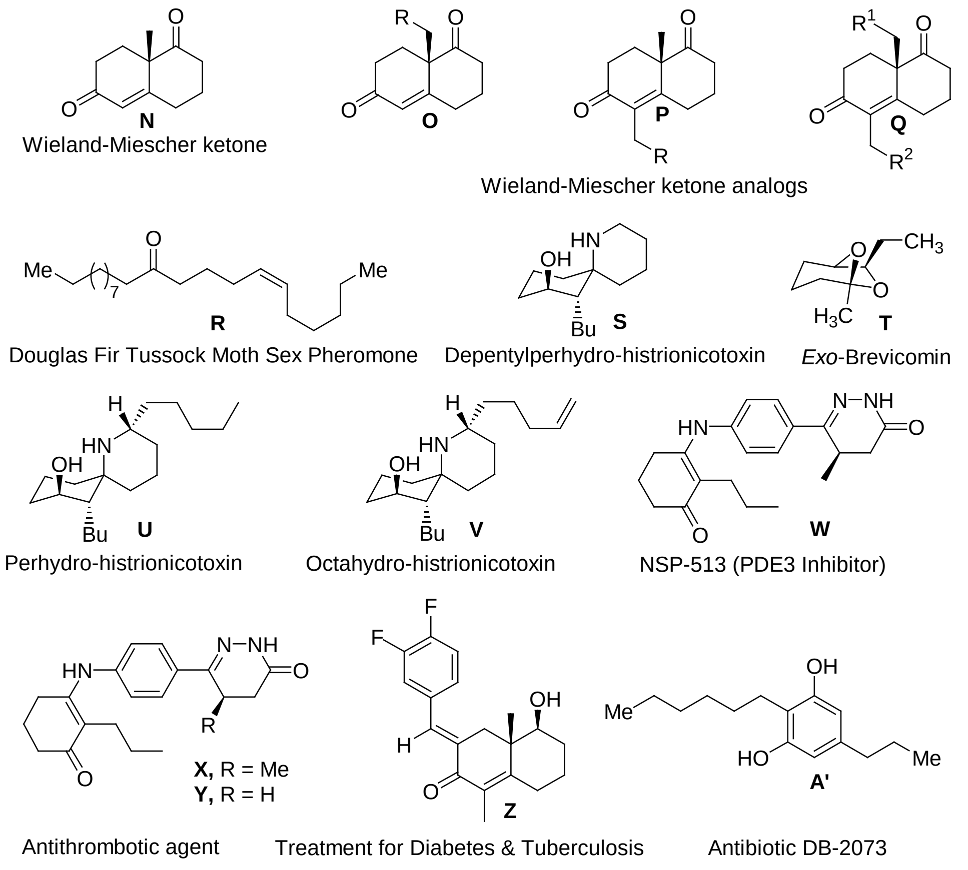
halogen)[43] bond forming reactions among others, has been developed. The combination of two or more organocatalytic reactions with a proper synthetic plan utilizing one or more organocatalysts in a one-pot synthesis delivers complex products, which is presently being developed as a new strategy in cascade reactions.

A natural amino acid, proline, is certainly part of this noble catalyst club, and in the recent past, it has been defined as a universal catalyst and a simple enzyme because of its high utility especially in enantioselective aldol,[44] Mannich,[45,37,27] amination,[40] and α-aminoxylation reactions.[41]

As part of our program to engineer direct organocatalytic cascade or multicomponent reactions,[1] herein we report the first organocatalytic asymmetric chemoselective direct cascade olefination/hydrogenation (O/H) and olefination/hydrogenation/Robinson annulation (O/H/RA) reactions that produce very useful drug synthons, 2-alkyl-cyclohexane-1,3-diones **67** and Wieland-Miescher (W-M) ketone analogues **69** from commercially available cyclohexane-1,3-diones **64**, aldehydes **46**, Hantzsch ester **15**, methyl vinyl ketone **68a**, and amino acid **50** as shown in Scheme 12.

2-Alkyl-cyclohexane-1,3-diones **67** and W-M ketone analogues **69** are attractive intermediates in the synthesis of natural products and in medicinal chemistry,[46,27] while 2-alkyl-cyclohexane-1,3-diones **67** have a broad utility in pharmaceutical chemistry[47] and are excellent starting materials in the natural product synthesis as shown in Chart 2. Hence, their preparation has continued to attract considerable synthetic interest in developing new methods for their syntheses.[48]

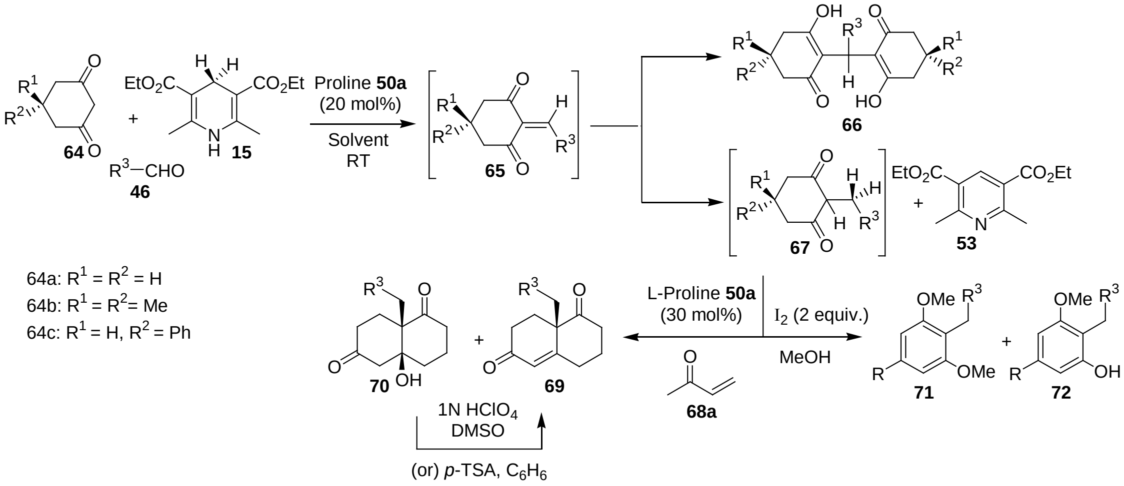
Chart 2: Natural and Non-natural Products Library Generated from 2-Alkyl-Cyclohexane-1,3-Diones



Surprisingly, there is no direct method for the synthesis of useful 2-alkyl-cyclohexane-1,3-diones **67**, and only two-step methods are known to prepare them.[48] Recently, Paquette *et al.* developed the two-step synthesis of 2-alkyl-cyclohexane-1,3-diones **67** in moderate to good yields via an in situ protection and deprotection sequence on 2-alkylidene-1,3-diones **65** with thiophenol and Raney nickel, respectively.[48a,b] As shown in Scheme 12, the well-recognized fact is the inability to arrest olefination reactions involving CH acids **64** (dimedone and 1,3-cyclohexanedione) and aliphatic or aromatic aldehydes **46** at the monoaddition stage.[49] Very few adducts such as **65** have been isolated.[50] This is because these olefination products **65** are highly reactive

Michael acceptors capable of engaging the unreacted CH acid reagent in kinetically rapid 1,4-addition to give bis-adducts such as **66**. Also, there is no report on the asymmetric synthesis of higher alkyl substituted W-M ketone analogues **69**. This has prompted us to investigate the cascade synthesis of very useful 2-alkyl-cyclohexane-1,3-diones **67** and W-M ketone analogs **69** in a single step through mild amino acid-catalysis.

Scheme 12: Direct Organocatalytic Asymmetric Cascade O/H and O/H/RA Reactions



We therefore set out to develop an amino acid-catalyzed asymmetric cascade synthesis of W-M ketones **69** from simple starting materials, which have not been prepared in the past. In this chapter, we present the development and application of the proline-catalyzed reductive alkylation of CH acids through the cascade O/H reaction of reactive CH acids **64** (dimedone and 1,3-cyclohexanedione), aldehydes **46**, and Hantzsch ester **15**. Furthermore, we will present mechanistic insight into the reaction course, applying a new concept of self-catalysis leading to an understanding of the cascade O/H reaction. We envisioned that an amino acid would catalyze the cascade olefination condensation of CH acid **64** with an aldehyde **46** to form substituted 2-alkylidene-cyclohexane-1,3-diones **65**, which are very reactive intermediates and further undergo chemoselective reactions with both CH acids **64** and Hantzsch ester **15** to produce bis-adducts **66** and hydrogenated 2-alkylcyclohexane-1,3-diones **67**, respectively, based on reaction conditions. Proline-catalyzed Robinson annulation of products **67** with methyl vinyl ketone **68** furnishes the W-M ketones **69** and alcohols **70** in good yield with interesting enantioselectivity, and alcohol **70** could be converted into ketone **69** without losing enantioselectivity as shown in Scheme 12.

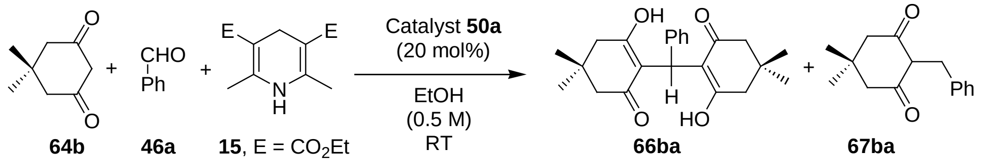
4.2 Results and Discussion

4.2.1 Preliminary Studies on Reductive in Situ Trapping of 2-Alkylidene-cyclohexane-1,3-diones. On the basis of our recent discovery of bio-mimetic reduction of novel active olefins with Hantzsch ester **15** through self-catalysis by decreasing the HOMO-LUMO energy gap between olefins and Hantzsch ester **15**,[1a-b,26b] we initiated our preliminary studies of the reductive in situ trapping of 2-benzylidene-5,5-dimethyl-cyclohexane-1,3-dione **65ba** as shown in Table 12 (In all compounds denoted **65xy**, **66xy**, **67xy**, **69xy**, **70xy**, **71xy**, **72xy**, and **73xy**, **x** is incorporated from reactant CH acids **64**, and **y** is incorporated from the reactant aldehydes **46**).

The self-catalyzed reaction of dimedone **64b** with 5 equiv. of benzaldehyde **46a** furnished the only unexpected bis-adduct **66ba** without the expected olefination product **65ba** (Table 12, entry 1). The same reaction under proline catalysis also furnished the only bis-adduct **66ba** without product **65ba** with reduced reaction time (Table 12, entry 2). Interestingly, the self-catalyzed reaction of dimedone **64b** and 2 equiv. of benzaldehyde **46a** with Hantzsch ester **15** furnished the bis-adduct **66ba** and the expected reductive alkylation product **67ba** in a 1:1 ratio with 99% yield after 24 h at 25 °C (Table 12, entry 3). The self-catalyzed reductive alkylation reaction with 3 equiv. of benzaldehyde **46a** furnished the product **67ba** in 83% yield (Table 12, entry 4). Interestingly, the same reaction under proline catalysis furnished the expected reductive alkylation product **67ba** with 90% yield after 12 h at 25 °C in EtOH as shown in Table 12, entry 5. The same reaction under proline catalysis in CH_2Cl_2 furnished the expected product **67ba** in 90% yield with a reduced reaction time (Table 12, entry 6).

The reductive alkylation reaction under base catalysis in CH_2Cl_2 furnished the bis-adduct **66ba** as a major product (Table 12, entries 7 and 8). The same reaction under acid catalysis in CH_2Cl_2 furnished the bis-adduct **66ba** and reductive alkylation product **67ba** in a 1:2 ratio with 99% yield after 20 h at 25 °C (Table 12, entry 9). There is not much effect of the byproduct pyridine **53** on the reductive alkylation reaction as shown Table 12, entries 10 and 11. These preliminary results prompted us to investigate the solvent effect on in situ trapping of the olefination product of dimedone **64b** with benzaldehyde **46a** through biomimetic hydrogenation as shown in Table 13.

Table 12: Preliminary Studies on Reductive In Situ Trapping of 2-Alkylidene-Cyclohexane-1,3-Diones.[a]

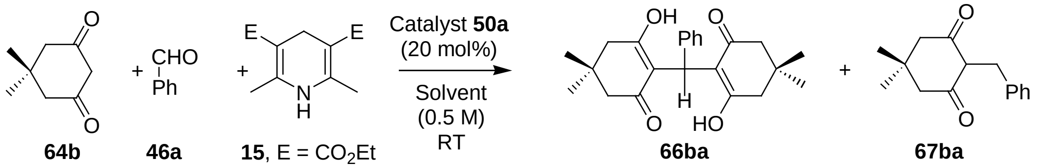


entry	catalyst **50a** [20 mol%]	aldehyde **46a** [equiv.]	H. ester **15** [equiv.]	time [h]	products yield [%][b] **66ba**	**67ba**
1		5.0	–	2	>95	–
2	proline	5.0	–	1	>95	–
3		2.0	1.0	24	50	50
4		3.0	1.0	24	17	83
5	proline	3.0	1.0	12	10	90
6[c]	proline	3.0	1.0	3	10	90
7[c]	triethyl amine **50h**	3.0	1.0	3	95	5
8[c]	quinine **50i**	3.0	1.0	3	95	5
9[c]	acetic acid **50j**	3.0	1.0	20	33	67
10[c]	pyridine **53**	3.0	1.0	24	20	80
11[c]		3.0	1.0	24	20	80

[a] Reactions were carried out in EtOH (0.5 M) with 2.0 to 5.0 equiv. of **46a** and 1.0 equiv. of **15** relative to the **64b** (0.5 mmol) in the presence of 20 mol% of catalyst **50**. [b] Yield refers to the column purified product. [c] CH_2Cl_2 (0.5 M) used as solvent

4.2.2 Direct Organocatalyzed Cascade TCRA Reaction of Dimedone: Reaction Optimization. We were pleased to find that proline-catalyzed cascade three component reductive alkylation (TCRA) or the cascade O/H reaction of dimedone **64b** and benzaldehyde **46a** (5 equiv.) with Hantzsch ester **15** furnished the expected product **67ba** in 95% yield after 12 h at 25 °C (Table 13, entry 1). Interestingly, there is little solvent effect on the direct proline-catalyzed TCRA or cascade O/H reaction of **64b**, **46a**, and **15** as shown in Table 13. The proline-catalyzed cascade O/H reaction can be performed in three types of solvents (protic polar, aprotic polar, and aprotic nonpolar) with good yields as shown in Table 13.

Table 13: Effect of Solvent on the Direct Amino Acid Catalyzed TCRA Reaction of Dimedone **64b** with **46a** and **15**[a]



entry	solvent [0.5 M]	aldehyde **46a** [equiv.]	time [h]	products yield [%][b] **66ba**	**67ba**
1	EtOH	5.0	12	5	95
2	EtOH	3.0	12	10	90
3	MeOH	3.0	24	10	90
4	H_2O	3.0	24	13	87
5	DMSO	3.0	24	20	80
6	DMF	3.0	24	15	85
7	CH_3CN	3.0	24	10	90
8	CH_2Cl_2	3.0	12	3	97
9	**CH_2Cl_2**	**1.0**	**12**	**5**	**95**

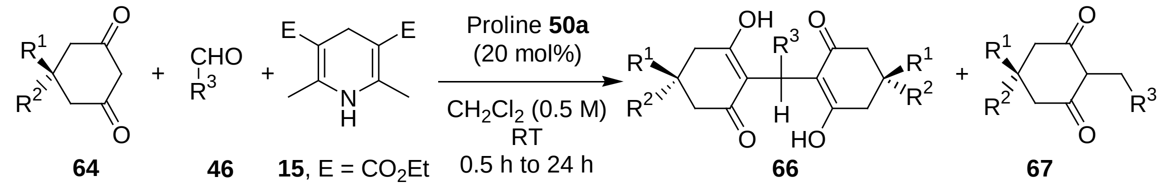
[a] Reactions were carried out in solvent (0.5 M) with 1.0 to 5.0 equiv. of **46a** and 1.0 equiv. of **15** relative to the **64b** (0.5 mmol) in the presence of 20 mol% of proline **50a**. [b] Yield refers to the column purified product.

Surprisingly, the cascade O/H reaction of **64b**, **46a**, and **15** in H_2O also furnished the expected hydrogenated product **67ba** in 87% yield after 24 h at 25 °C (Table 13, entry 4). We envisioned the optimized condition to be mixing the equivalent molar ratios of starting materials at 25 °C in CH_2Cl_2 under 20 mol% of proline catalysis to furnish hydrogenated product **67ba** in 95% yield (Table 13, entry 9).

4.2.3 Diversity-Oriented Synthesis of TCRA Products 67ba-67ca. With an efficient organocatalytic cascade reductive alkylation protocol in hand, the scope of the proline catalyzed cascade O/H reactions was investigated with various aldehydes **46a-h'** and CH acids **64b**,**c**. A series of aromatic and aliphatic aldehydes **46a-h'** was reacted with 1.0 equiv. of dimedone **64b** or 5-phenyl-cyclohexane-1,3-dione **64c** catalyzed by 20 mol% of proline at 25 °C in CH_2Cl_2 (Table 14). The 2-alkyl-5,5-dimethyl-cyclohexane-1,3-diones **67ba-67bh'** and 2-alkyl-5-phenyl-cyclohexane-1,3-diones **67ca** were obtained as single isomers with excellent yields. The reaction of dimedone **64b** with naphthalene-1-carbaldehyde **46b** furnished the reductive alkylation product **67bb** as a single isomer, in good yield (Table 14). The synthesis of 2-arylmethyl-5,5-dimethyl-cyclohexane- 1,3-diones **67ba-67bb'** from **64b**, **46a-b'**, and **15** at 25 °C under proline catalysis has a longer reaction time (24 h), as compared to aliphatic aldehydes **46h'-o'** (Table 14). Both aliphatic aldehydes **46h'-o'** generated expected 2-alkyl-5,5-dimethyl-cyclohexane-1,3- diones **67bf'-67bh'** with dimedone **64b** in excellent yields (Table 14).

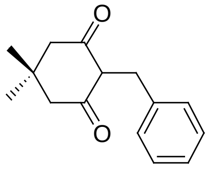
The results in Table 14 demonstrate the broad scope of this reductive cascade methodology covering a structurally diverse group of aldehydes **46a-h'** and CH acids **64b**,**c** with many of the yields obtained being very good, or indeed better, than previously published two-step alkylation reactions.[48] Structure and regiochemistry of 2-alkyl-5,5-dimethyl-cyclohexane-1,3-diones **67ba-67bh'** were confirmed by ^{1}H NMR and ^{13}C NMR analysis [see for example Fig. 15-18] and also confirmed by mass analysis and X-ray structure analysis of **67bb** and **67bx** as shown in Scheme 13 and 14.[51,52]

Table 14: Synthesis of TCRA Library via Cascade O/H Reactions from Dimedone **64a** and Aldehydes **46**[a]

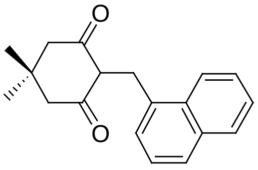


64b: $R^1 = R^2 = Me$

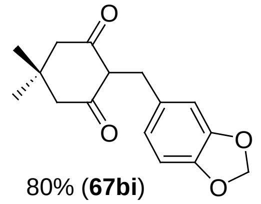
64c: $R^1 = H$, $R^2 = Ph$



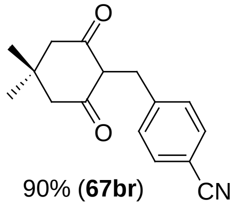
95% (**67ba**)



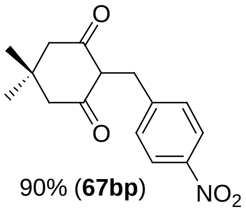
80% (**67bb**)



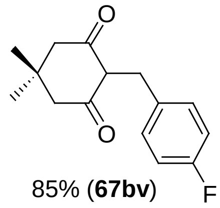
80% (**67bi**)



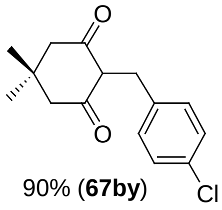
90% (**67br**)



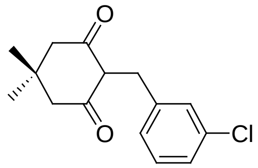
90% (**67bp**)



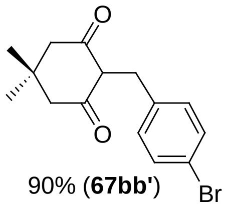
85% (**67bv**)



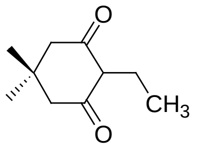
90% (**67by**)



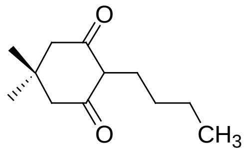
85% (**67bx**)



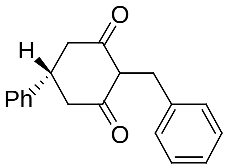
90% (**67bb'**)



90% (**67bo'**)[b]



90% (**67bh'**)[c]



70% (**67ca**)

85% (**67ca**)[d]

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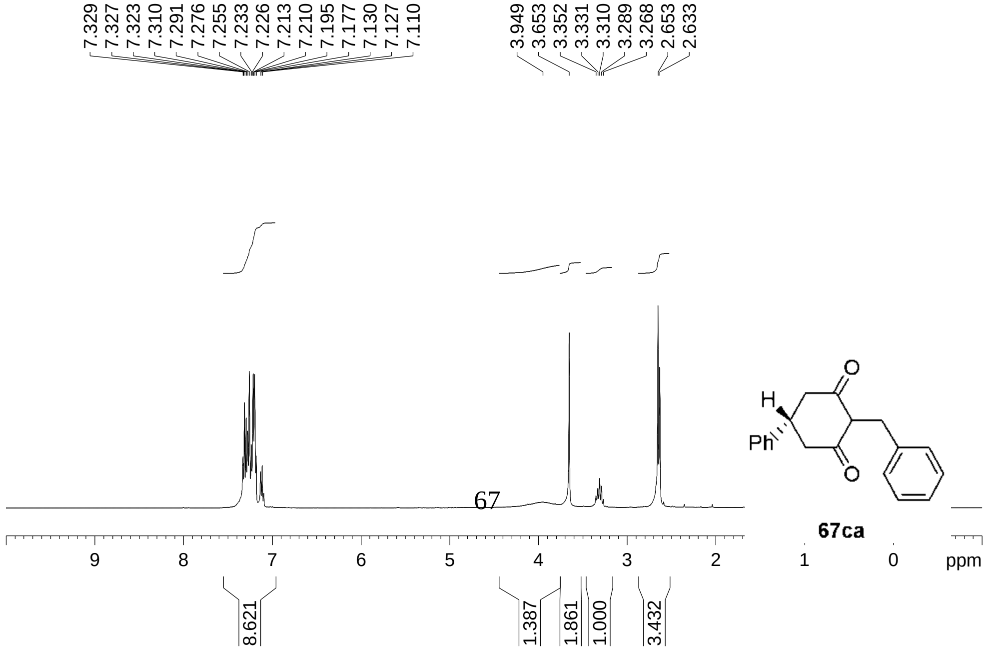
[a] Yield refers to the column purified product and 5 to 20% of bis-adducts **66** were isolated in all reactions. [b] Acetaldehyde **46o'** was taken as 5 equiv. and reaction time is 1 h. [c] Butyraldehyde **46g'** was taken as 2 equiv. and reaction time is 0.5 h. [d] Benzaldehyde **46a** was taken as 3 equiv.



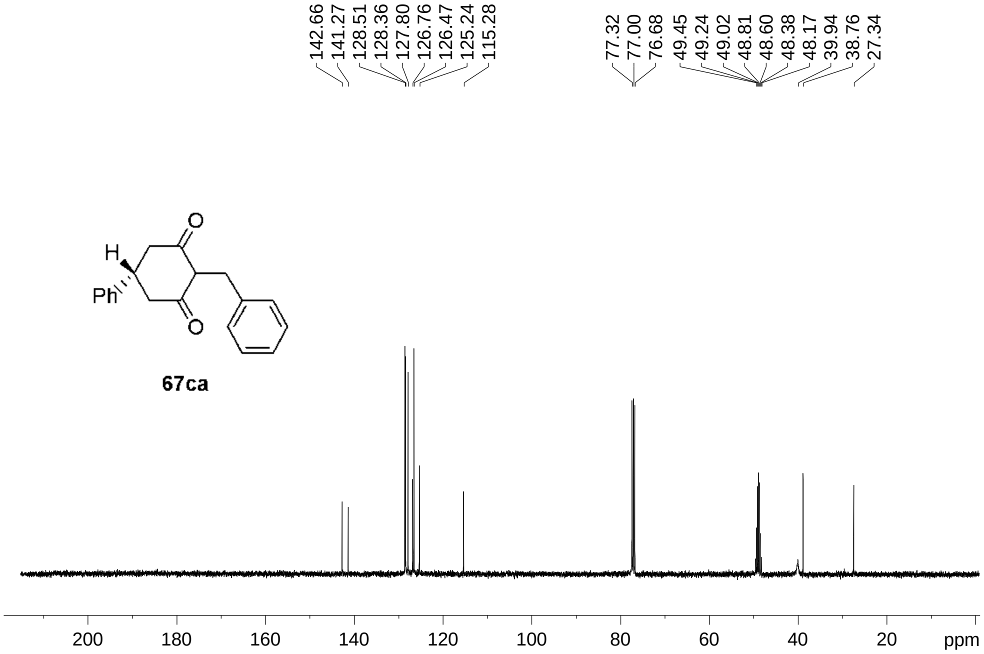
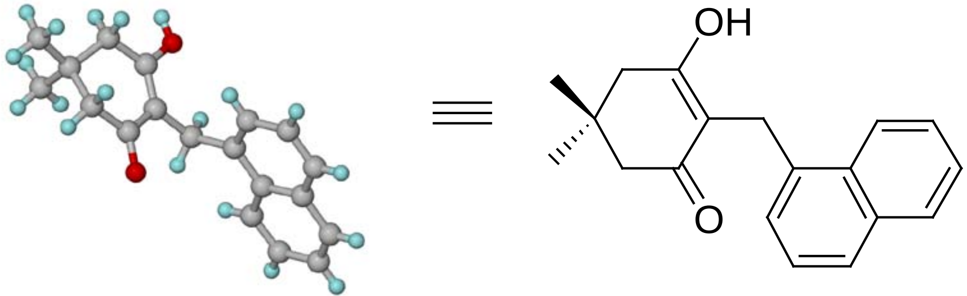


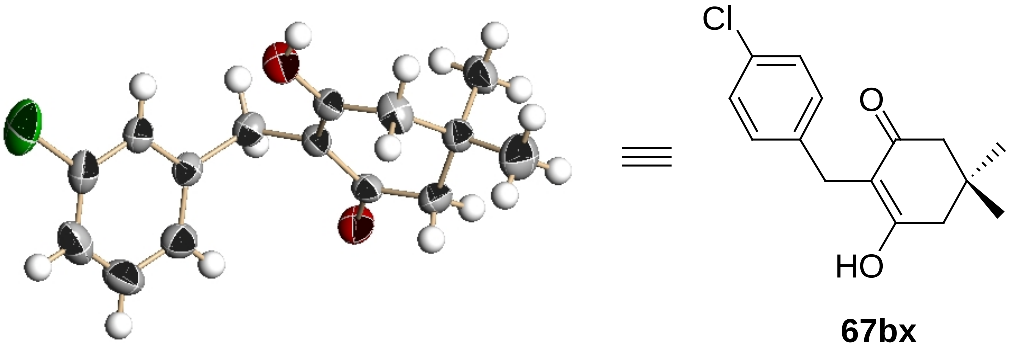
Figure-15: ^{1}H NMR and ^{13}C NMR Spectrum of product **67ca**.

Scheme 13: Crystal structure of 3-hydroxy-5,5-dimethyl-2-naphthalen-1-ylmethyl-cyclohex-2-enone (**67bb**).



67bb

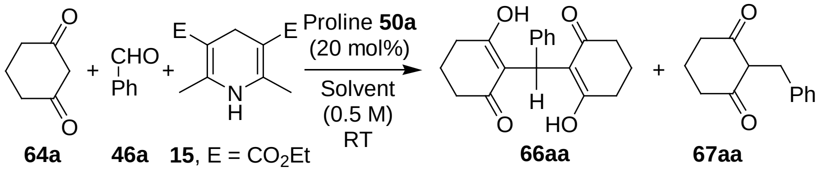
Scheme 14: Crystal structure of 2-(3-chloro-benzyl)-3-hydroxy-5,5-dimethyl-cyclohex-2-enone (**67bx**).



67bx

4.2.4 Direct Organocatalyzed Cascade Reductive Alkylation of Cyclohexane-1,3-Dione: Reaction Optimization. Because of the more pharmaceutical applications of 2-alkyl-cyclohexane-1,3-diones **67**, we further extended the application of the organocatalyzed cascade reductive alkylation methodology to cyclohexane-1,3-dione **64a** and various aldehydes 46**a-m'** as shown in Tables 15 and 16. Surprisingly, the reactivity pattern of cyclohexane-1,3-dione **64a** looks different as compared to dimedone **64b** in the proline-catalyzed cascade reductive alkylation reaction with benzaldehyde **46a** and Hantzsch ester **15** as shown in Table 15. Unexpectedly, the proline-catalyzed reductive alkylation of cyclohexane-1,3-dione **64a**, benzaldehyde **46a** (3 equiv.), and Hantzsch ester **15** furnished the expected product **67aa** in only 60% yield, accompanied by 40% yield of the bis-adduct **66aa** at 25 °C for 20 h (Table 15, entry 1). Interestingly, there is a large solvent effect on the direct proline-catalyzed reductive alkylation or cascade O/H reaction of **64a**, **46a**, and **15** as shown in Table 15 as compared to dimedone **64b** (see Tables 12 and 13).

Table 15: Effect of Solvent on the Direct Amino Acid Catalyzed TCRA Reaction of Cyclohexane-1,3-Dione **64a** with **46a** and **15**[a]



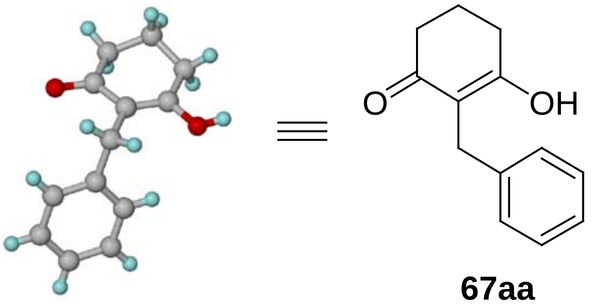
64a **46a** **15**, E = CO_2Et **66aa** **67aa**

entry	solvent [0.5 M]	aldehyde **46a** [equiv.]	time [h]	products yield [%][b]	
				66aa	**67aa**
1	EtOH	3.0	20	40	60
2	THF	3.0	24	65	35
3	CH_3CN	3.0	20	40	60
4	CH_2Cl_2	1.0	24	30	70
5	CH_2Cl_2	2.0	24	25	75
6	**CH_2Cl_2**	**3.0**	**24**	**10**	**90**

[a] Reactions were carried out in solvent (0.5 M) with 1.0 to 3.0 equiv. of **46a** and 1.0 equiv. of **15** relative to the **64a** (0.5 mmol) in the presence of 20 mol% of proline **50a**. [b] Yield refers to the column purified product.

Proline-catalyzed cascade O/H reactions are performed in three types of solvents (protic polar, aprotic polar, and aprotic nonpolar) and furnished the expected product **67aa** in good to moderate yields as shown in Table 15 (some of the solvents are not shown). Surprisingly, the cascade O/H reaction of **64a**, **46a**, and **15** in THF furnished the expected hydrogenated product **67aa** in 35% yield accompanied by 65% yield of the bis-adduct **66aa** at 25 °C for 24 h (Table 15, entry 2). We envisioned the optimized condition to be mixing the 3 equiv. of benzaldehyde **46a** with cyclohexane-1,3-dione **64a** and Hantzsch ester **15** at 25 °C in CH_2Cl_2 under 20 mol% of proline catalysis to furnish the hydrogenated product **67aa** in 90% yield (Table 15, entry 6). The structure and regiochemistry of 2-benzyl-cyclohexane-1,3-dione **67aa** were confirmed by X-ray structure analysis as shown in Scheme 15.[53] Interestingly, the cascade product **67aa** was obtained in a completely enolic form in crystals as compared to in solution. The products structures were confirmed by ^{1}H and ^{13}C NMR [for example see Fig. 16-18] and mass analysis.

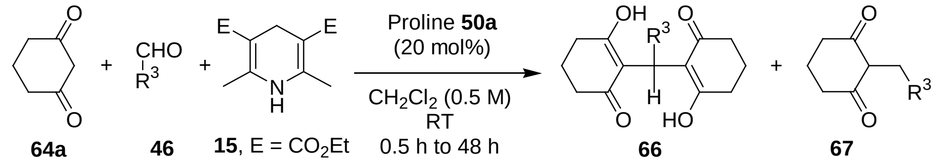
Scheme 15: Crystal structure of 2-benzyl-3-hydroxy-cyclohex-2-enone (**67aa**).

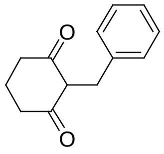


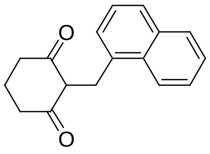
67aa

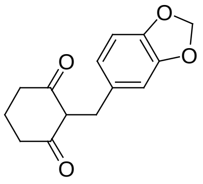
4.2.5 Diversity-Oriented Synthesis of TCRA Products 67aa-67am′. With the optimized reaction conditions in hand, the scope of the proline-catalyzed O/H cascade reactions was investigated with cyclohexane-1,3-dione **64a**, various aldehydes **46a-m'**, and Hantzsch ester **15** as shown in Table 16. A series of aromatic and aliphatic aldehydes **46a-m'** (3 equiv) was reacted with cyclohexane-1,3-dione **64a** and Hantzsch ester **15** catalyzed by 20 mol % of proline at 25 °C in CH_2Cl_2 (Table 16). The 2-arylmethyl-cyclohexane-1,3-diones **67aa-67ab′** and 2-alkylcyclohexane- 1,3-diones **67ae′-67am′** were obtained as single isomers with excellent yields. The reaction of cyclohexane-1,3- dione **64a** with piperonal **46i** and Hantzsch ester **15** under proline-catalysis furnished the reductive alkylation product **67ai** in 70% yield at 70 °C, and there was no reaction at 25 °C (Table 16). The synthesis of 2-arylmethyl-cyclohexane-1,3-diones **67aa-67ab′** from **64a**, **46a-b'**, and **15** at 25 °C under proline catalysis took a longer reaction time (24-48 h), as compared to aliphatic aldehydes **46e'-m'** as shown in Table 16.

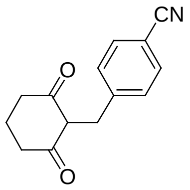
Table 16: Synthesis of Reductive Alkylation Library via Cascade K/H Reactions from Cyclohexane-1,3-Dione **64a** and Aldehydes **46**[a]

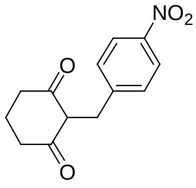


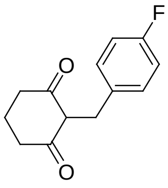

24 h, 90% (**67aa**)

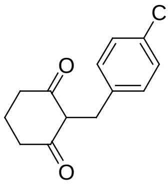

48 h, 70% (**67ab**)

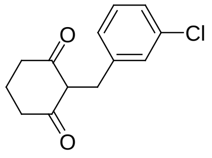

10 h, 70% (**67ai**)[b]

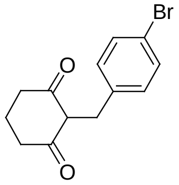

24 h, 80% (**67ar**)

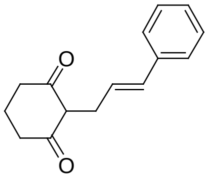

24 h, 80% (**67ap**)

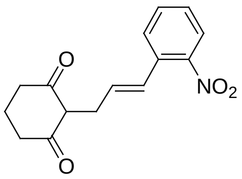

48 h, 80% (**67av**)

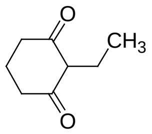

48 h, 85% (**67ay**)

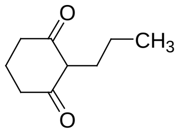

48 h, 80% (**67ax**)

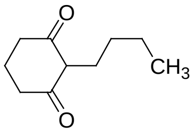

48 h, 85% (**67ab'**)

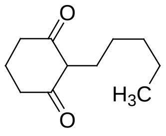

2 h, 80% (**67ae'**)

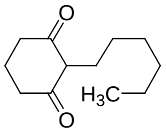

2 h, 80% (**67af'**)[c]

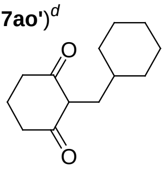

0.5 h, 80% (**67ao'**)[d]


0.5 h, 75% (**67ag'**)


0.5 h, 80% (**67ah'**)


1 h, 90% (**67ai'**)


96 h, 70% (**67ap'**)


72 h, 75% (**67am'**)

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[a] Yield refers to the column purified product and 10 to 30% of bis-adducts **66** were isolated in all reactions. [b] Reaction performed at 70 °C. [c] 3-(2-Nitrophenyl)-propenal **46f'** was taken as 1 equiv. [d] Acetaldehyde **46o'** was taken as 5 equiv.

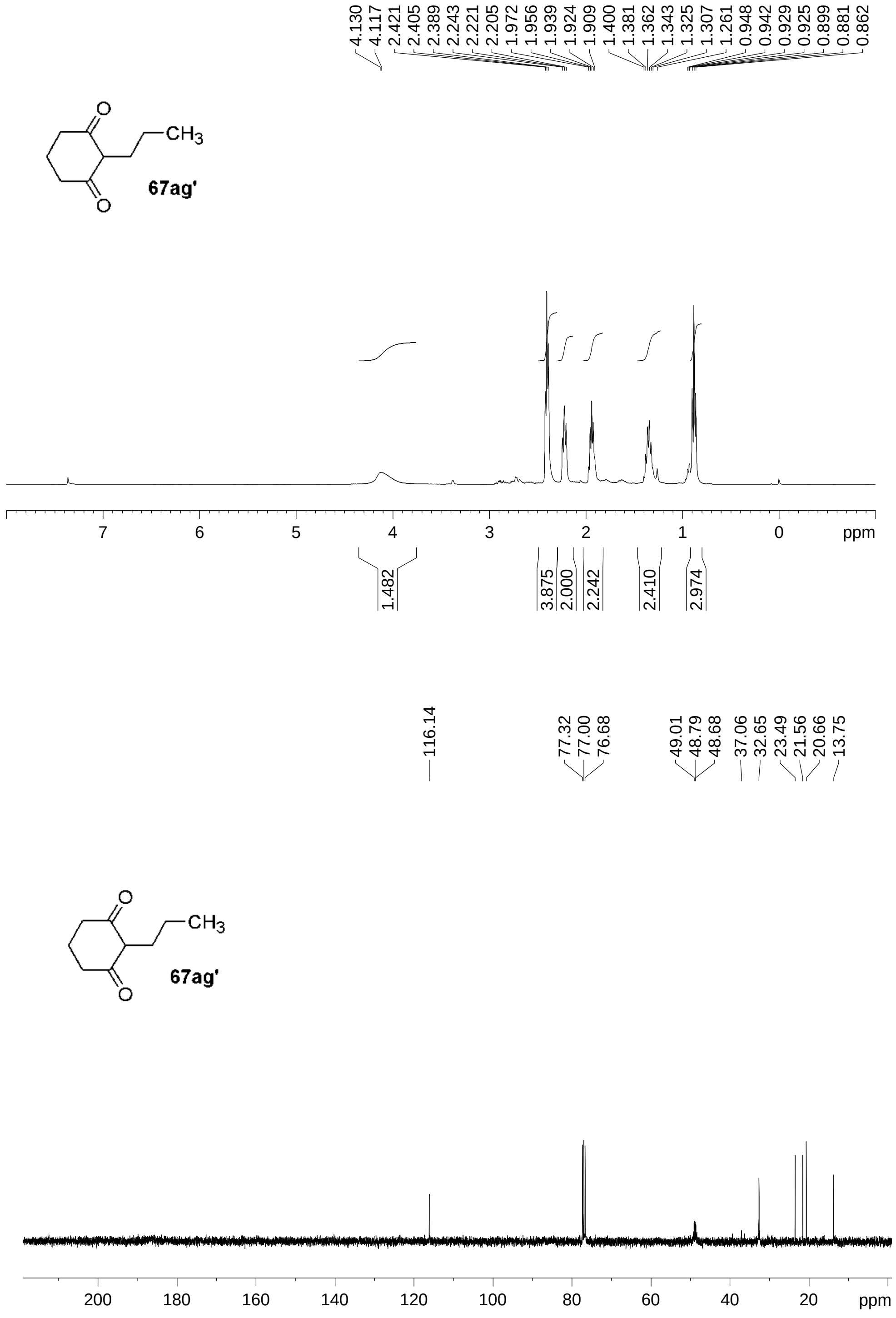


Figure-16: ^{1}H NMR and ^{13}C NMR Spectrum of product **67ag'**.

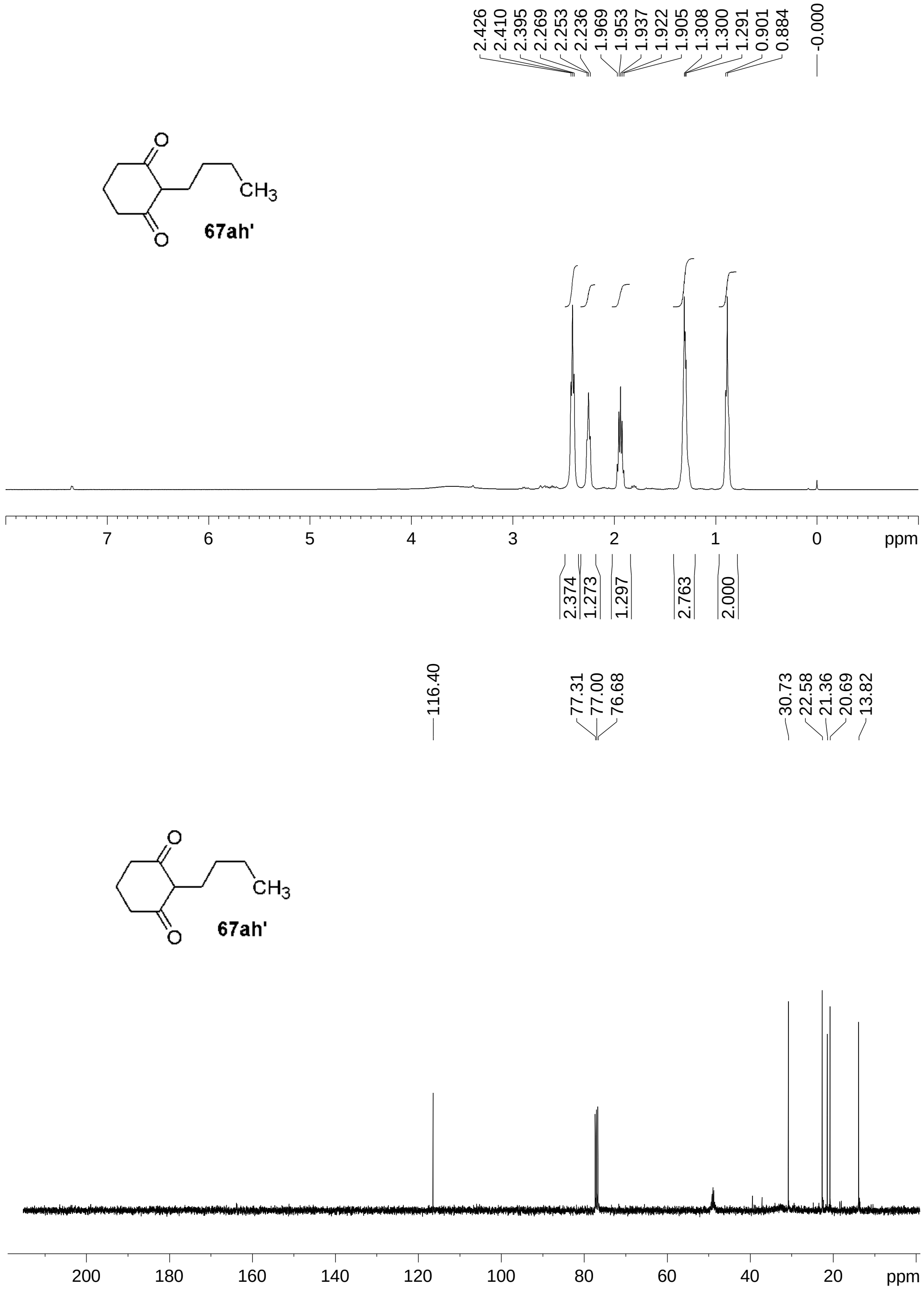
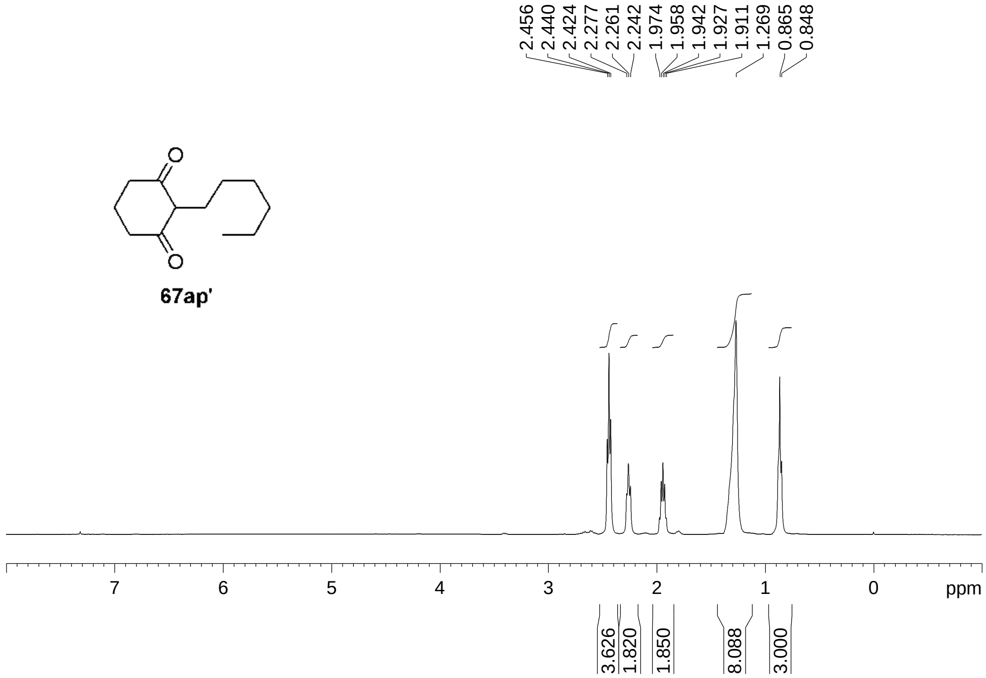


Figure-17: ^{1}H NMR and ^{13}C NMR Spectrum of product **67ah'**.



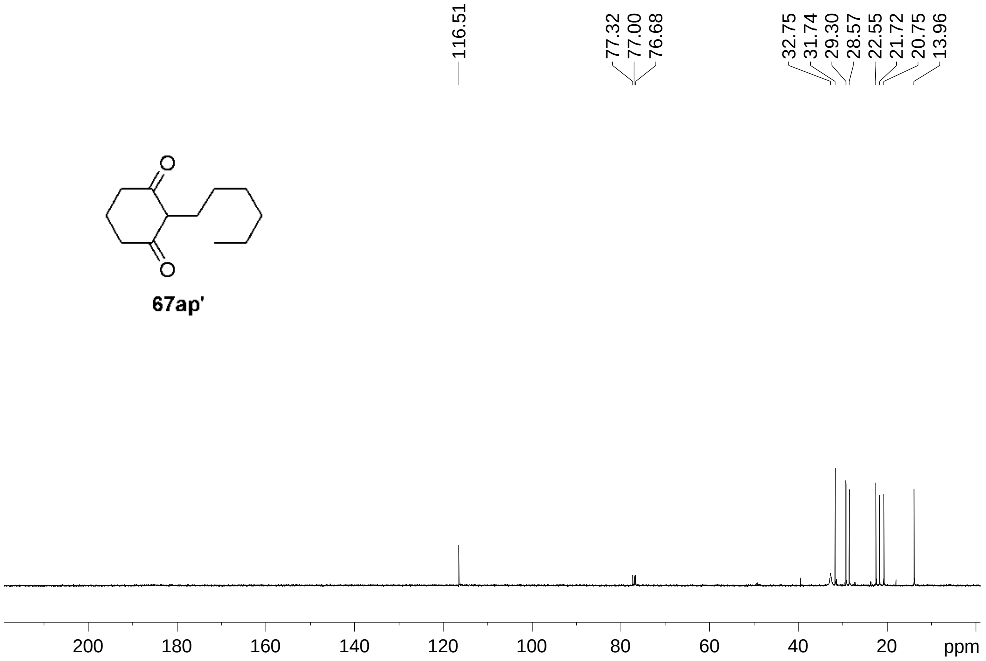
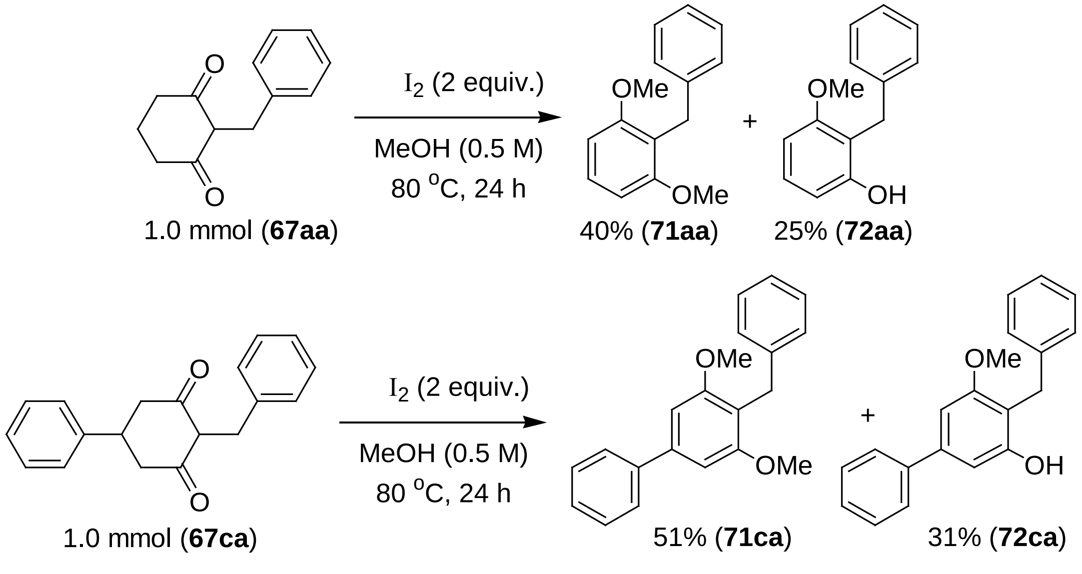


Figure-18: ^{1}H NMR and ^{13}C NMR Spectrum of product **67ap′**.

Interestingly, the proline catalyzed reductive alkylation reaction of cyclohexane-1,3-dione **64a**, *α,β*-unsaturated aldehydes **46e′,f′**, and Hantzsch ester **15** generated the expected 2-alkyl-cyclohexane-1,3-diones **67ae'- 67af'** in excellent yields with high regioselectivity (Table 16).The results in Table 16 demonstrate the broad scope of this reductive cascade methodology covering a structurally diverse group of aldehydes **46a-m'** with many of the yields obtained being very good, or indeed better, than the previously published two-step alkylation reactions.[48] The structure and regiochemistry of 2-alkyl-cyclohexane-1,3-diones **67aa-67am′** were confirmed by X-ray structure analysis on **67aa** as shown in Scheme 15.[53]

4.2.6 Applications of TCRA Products 67.

4.2.6.1 Aromatization of 2-Alkyl-cyclohexane-1,3-diones. 2-Alkylcyclohexane-1,3-diones **67** were readily transformed into substituted monomethyl and dimethyl resorcinols with iodine and methanol as shown in Scheme 16.[47]



Scheme 16: Synthesis of 2,5-Dialkylresorcinols from Reductive Alkylation Products **67**.

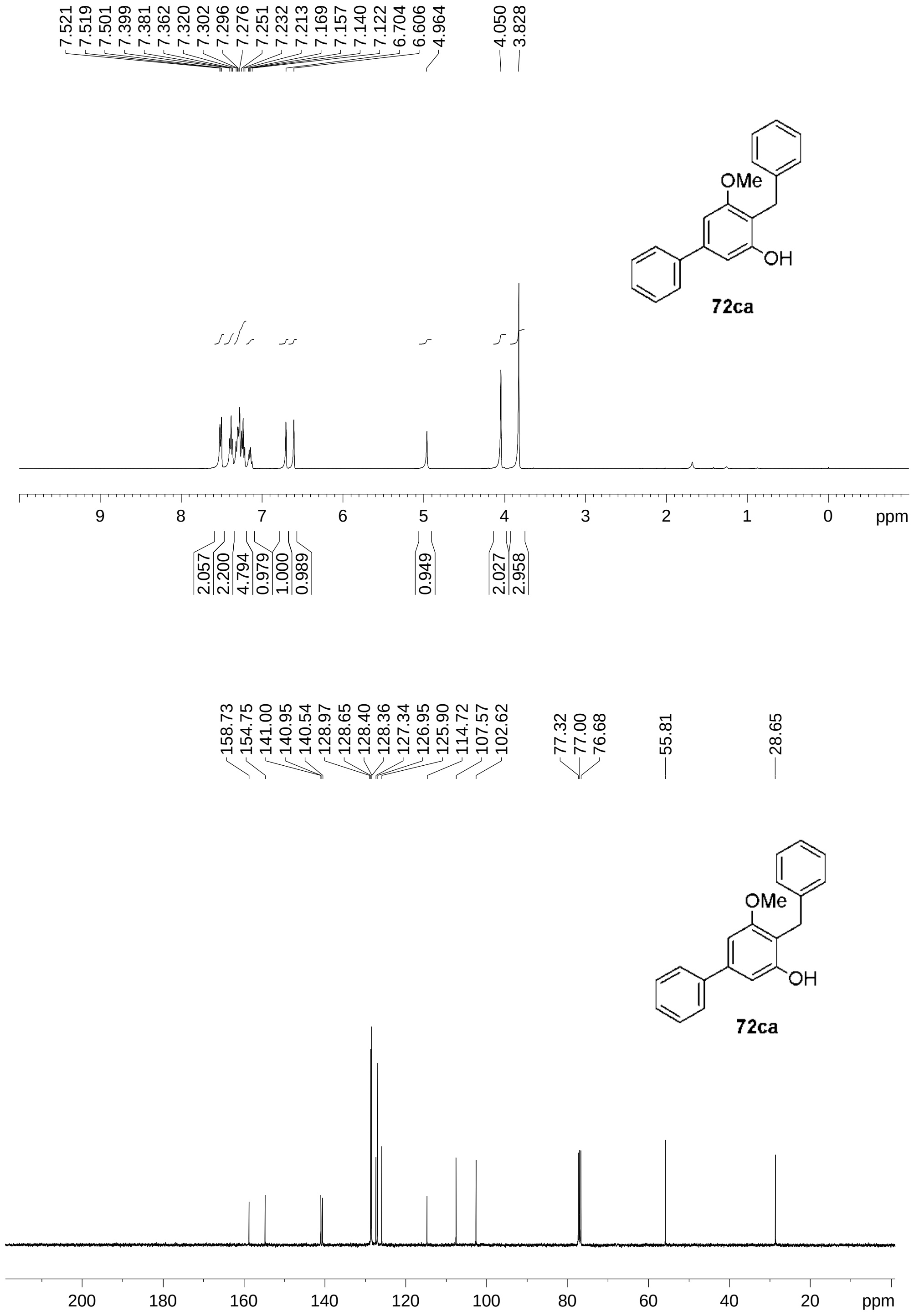
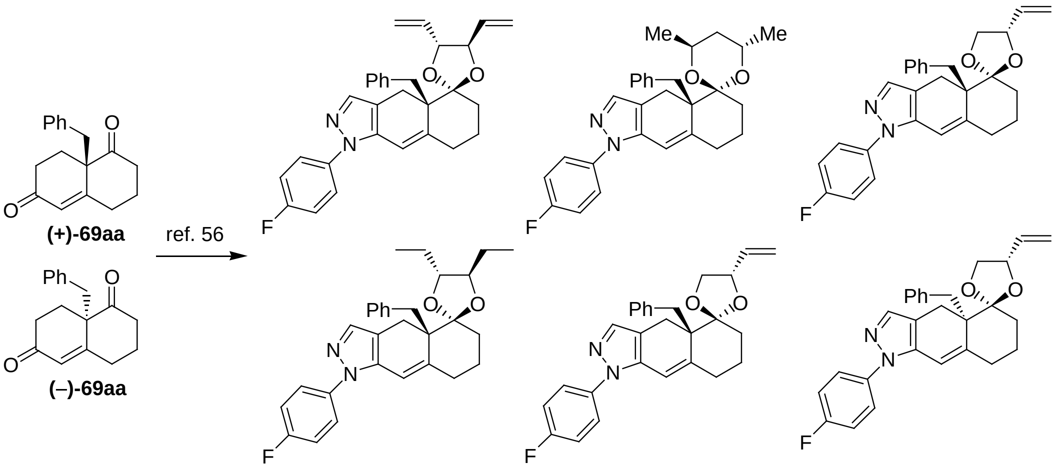


Figure-19: ^{1}H NMR and ^{13}C NMR Spectrum of product **72ca**.

The substituted resorcinol unit is a basic building block of a large number of valuable naturally occurring polyketide metabolites.[55a] Highly substituted resorcinols have gained importance in recent years as starting materials and intermediates for the synthesis of cannabinoids and benzochroman derivatives, which possess a wide range of physiological and pharmacological properties.[55b] Long chain 5-alkyl resorcinols have been successfully utilized as ideal models for sequence-selective DNA strand scissions and as leukotriene antagonists for the treatment or prevention of Alzheimer's disease.[55c] I_2/MeOH mediated aromatization of highly substituted cyclohexane-1,3-diones **67** gave good yields of medicinally important dimethyl and monomethyl resorcinols **71** and **72** as shown in Scheme 16.[47] For the pharmaceutical applications, the diversity-oriented library of resorcinols **71** and **72** could be generated by using our amino acid-catalyzed diversity-oriented library of highly substituted cyclohexane-1,3-diones **67** through a simple I_2/MeOH reaction. The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 19] and mass analysis.

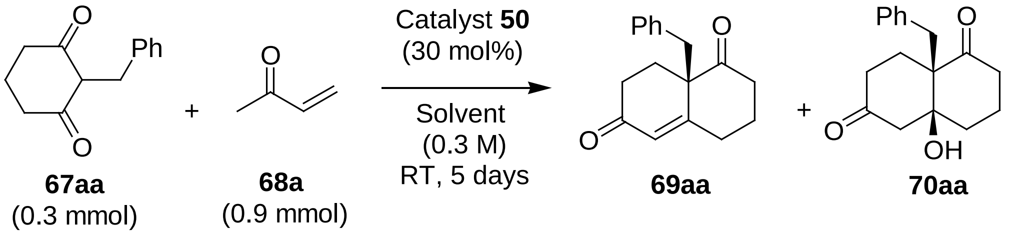


(28)

Glucocorticoid Receptor Modulators

4.2.6.2 ***Amino Acid-Catalyzed Asymmetric Robinson Annulations.*** W-M ketone analogues **69** are very good intermediates for the synthesis of steroids,[46] and also recently, Ali et al. reported in their patent[56] that W-M ketone analogue **69aa** is a very good intermediate for the synthesis of pharmaceutically acceptable salts or hydrates of spiro-heterocycles, which are disclosed as selective glucocorticoid receptor modulators for treating a variety of autoimmune and inflammatory diseases or conditions (eq. 28). Surprisingly, to the best of our knowledge, there is no report on the asymmetric synthesis of useful W-M ketone analogues **69**. In this chapter, we are presenting the asymmetric synthesis of W-M ketone analogues **69** with interesting ee and yields via amino acid-catalyzed asymmetric RA of 2-alkyl-cyclohexane-1,3-diones **67** with methyl vinyl ketone **68a** as shown in Tables 17 and 18 and Scheme 17.

Table 17: Direct Amino Acid Catalyzed Robinson Annulation of **67aa** with **68a**[a]

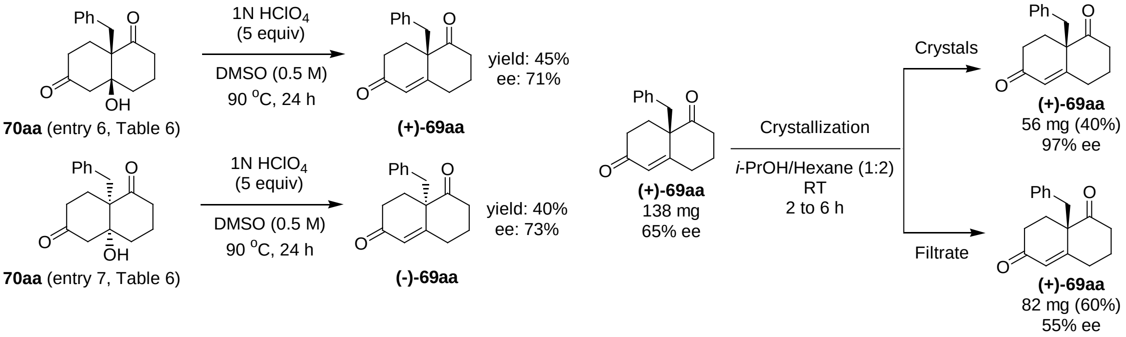


entry	solvent [0.3 M]	catalyst **50** [30 mol%]	yield [%][b] **69aa**	ee [%][c] **69aa**
1[d]	THF	**50a**	70	33
2[d]	CH_3CN	**50a**	85	51
3[d]	DMSO	**50a**	50	64
4[d]	DMF	**50a**	65	65
5[d]	DMF	**50g**	65	–50
6[e]	DMF	**50a**	50	72
7[e]	DMF	**50g**	50	–74

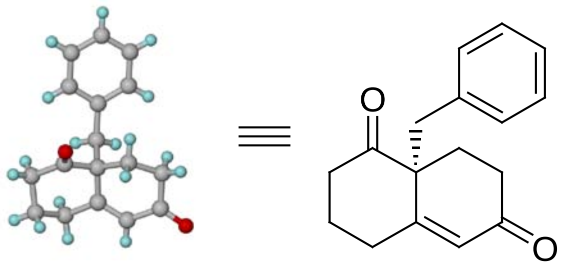
[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **68** in the presence of 30 mol% of proline **50**a. [b] Yield refers to the column purified product. [c] ee determined by HPLC analysis. [d] Product **70aa** were isolated in 10 to 15% yield. [e] Freshly distilled methyl vinyl ketone **68** was used and Product **70aa** were isolated in 30 to 45% yield.

We were pleased to find that the L-proline-catalyzed RA reaction of 2-benzyl-cyclohexane-1,3-dione **67aa** with 3 equiv of methyl vinyl ketone **68a** in THF furnished the expected product **69aa** in 70% yield with 33% ee and alcohol **70aa** in 10-15% yield at 25 °C for 5 days (Table 17, entry 1). Solvent screening on the direct L-proline-catalyzed RA reaction of **67aa** with **68a** revealed that DMF and DMSO solvents were suitable to achieve high ee values as shown in Table 17. Interestingly, the freshly distilled methyl vinyl ketone **68a** showed a large effect on the proline-catalyzed RA reaction of **67aa** and **68a** with respect to yield and ee values as shown in Table 17. We envisioned the optimized condition to be mixing the CH acid **67aa** and 3 equiv of freshly distilled methyl vinyl ketone **68a** at 25 °C in DMF under 30 mol % of L-proline catalysis to furnish W-M ketone analogue **69aa** in 50% yield with 72% ee and alcohol **70aa** in 30-45% yield (Table 17, entry 6). The D-proline-catalyzed RA reaction of **67aa** with **70** furnished the opposite enantiomer of the W-M ketone analogue **69aa** in 50% yield with 74% ee and alcohol **70aa** in 30-45% yield (Table 17, entry 7). The hydrolysis of bicyclic alcohols (+)/(–)-**70aa** obtained from L/D-proline catalysis with 1 N $HClO_4$ in DMSO at 90 °C for 24 h furnished the expected bicyclic ketones (+)/(–)-**69aa** in good yields with 71-73% ee as shown in Scheme 17. The crystallization of the 65% ee W-M ketone analogue (+)-**69aa** in a 2:1 mixture of hexane and isopropyl alcohol at 25 °C for 2-6 h furnished the brown block-shaped crystals in 40% yield with an enriched ee value of 97% (Scheme 17). The absolute configuration of product (+)-**69aa** prepared under L-proline catalysis was established by using X-ray crystallography and also by comparison with the proline-catalyzed Hajos-Parrish- Eder-Sauer-Wiechert reaction.[57] The crystal structure of product (+)-**69aa** is depicted in Scheme 18.[54] The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 20] and mass analysis.

Scheme 17: Hydrolysis of alcohol **70aa** and enantioenrichment of Wieland-Miescher ketone analog **69aa** by crystallization.

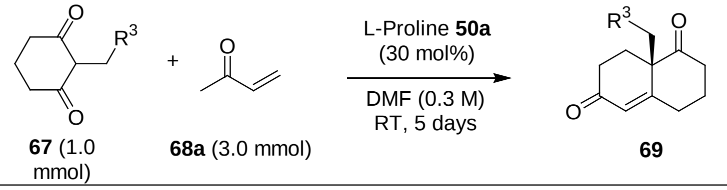


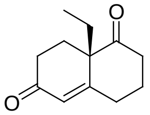
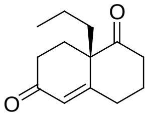
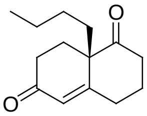
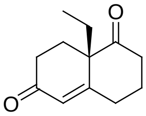
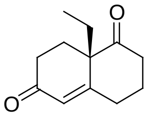
Scheme 18: Crystal structure of (+)-(*R*)-8a-benzyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione (**69aa**).



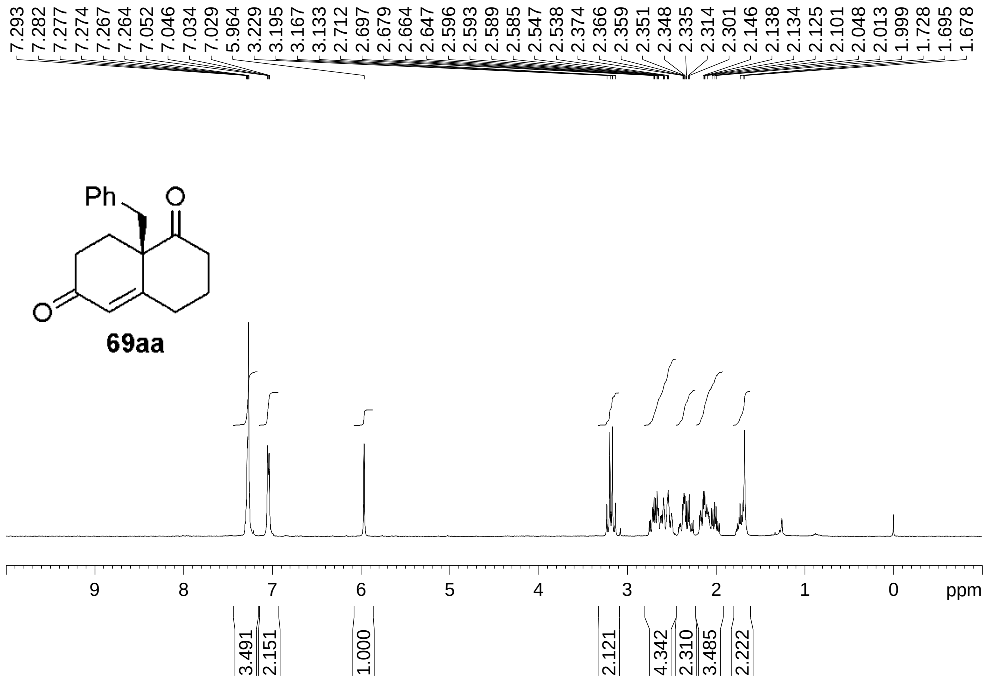
69aa

Table 18: Organocatalytic asymmetric synthesis of Wieland-Miescher ketone analogs **69**[a,b]



 **69ao'** 75% yield 75% ee	 **69ag'** 50% yield 73% ee	 **69ah'** 60% yield 75% ee	 **69ao'**[c] 40% yield 45% ee	 **69ao'**[d] 50% yield 9% ee

[a] See Experimental Section. [b] Yield refers to the column purified product and ee determined by HPLC analysis. [c] Reaction were carried out without solvent. [d] Reaction were carried out without solvent with 1.0 equiv. of **50a** and 2.0 equiv. of **68a** relative to the **67ao'**.



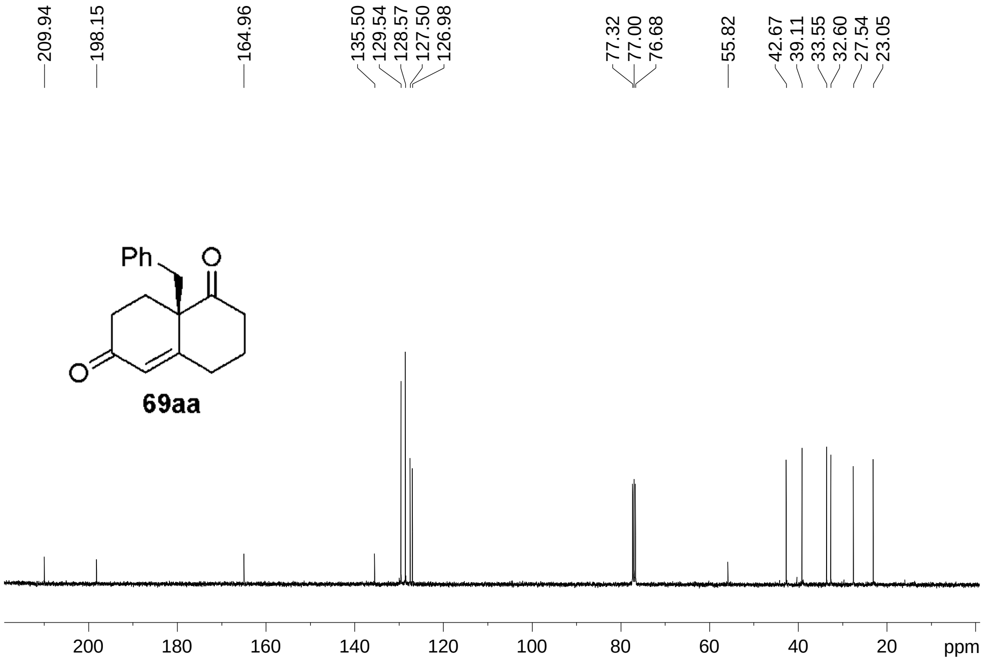


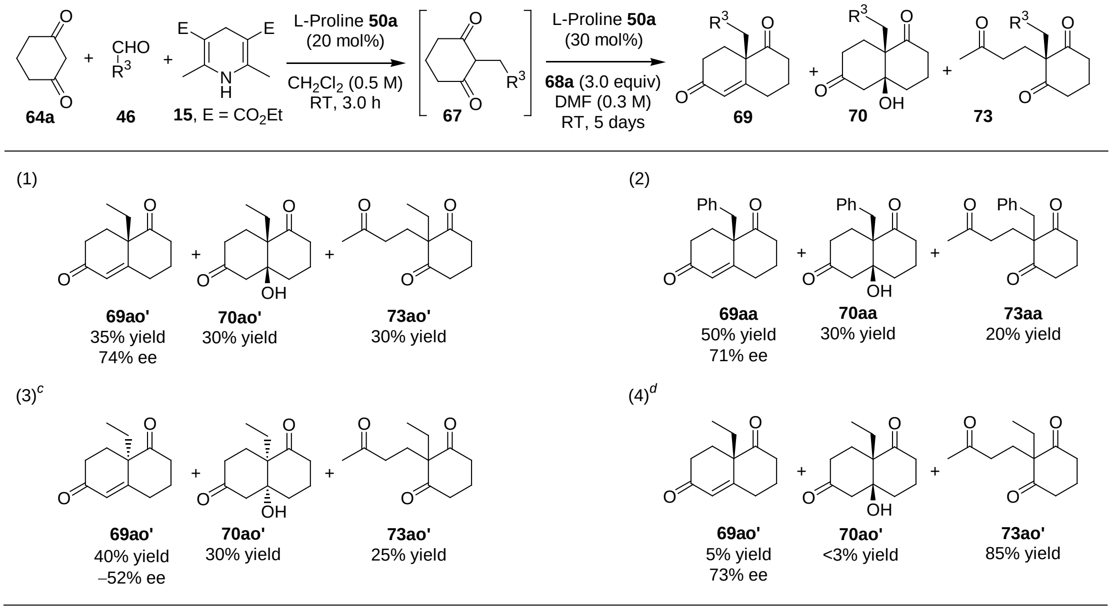
Figure-20: ^{1}H NMR and ^{13}C NMR Spectrum of product **69aa**.

With an efficient organocatalytic asymmetric cascade RA protocol in hand, the scope of the proline-catalyzed cascade asymmetric RA reactions was investigated with various 2-alkylcyclohexane-1,3-diones **67** and methyl vinyl ketone **68a**. A series of 2-alkyl-cyclohexane-1,3-diones **67ao'-67ah'** was reacted with 3.0 equiv of methyl vinyl ketone **68a** catalyzed by 30 mol % of L-proline at 25 °C in DMF for 5 days (Table 18). All expected W-M ketone analogues **69ao'-69ah'** were obtained in good yields with 73-75% ee as shown in Table 18. Interestingly, in these reactions, only trace amount of bicyclic alcohols **70ao'-70ah'.** were isolated. L-Proline-catalyzed asymmetric RA reactions of **67ao'** with **68a** were effected by solvent and catalyst loading on ee as shown in Table 18. Interestingly, ee values of product **69ao'** were drastically smaller when the reaction was performed under neat and L-proline **50a** as compared to 1.0 equiv of **67ao'**. The same results were observed by Swaminathan *et al.* in their attempt to synthesize the asymmetric W-M ketone analogue **69ao'**.[46a]

4.2.6.3 Amino Acid-Catalyzed Asymmetric Double Cascade One-Pot Robinson Annulations. After successful demonstration of the L-proline-catalyzed cascade asymmetric O/H and RA reactions, we decided to investigate the combination of these two cascade reactions in one pot. The reaction of 5 equiv of acetaldehyde **46o′** with CH acid **64a** and Hantzsch ester **15** under L-proline catalysis in CH_2Cl_2 at 25 °C for 3.0 h furnished the expected 2-ethyl-cyclohexane-1,3-dione **67ao'** in good yield. Removing the solvent CH_2Cl_2 by vacuum pump and adding solvent DMF and 30 mol % of L-proline **50a** and methyl vinyl ketone **68a** to the reaction mixture of cascade asymmetric O/H/ RA furnished the expected W-M ketone analogue **69ao'** in 35% yield with 74% ee accompanied by bicyclic alcohol **11al** in 30% yield and the Michael adduct **73ao'** in 30% yield as shown in Table 19. In L-proline-catalyzed sequential one-pot double cascade asymmetric O/H/RA reactions, the ee values were not effected by the reaction byproduct 2,6-dimethyl-pyridine-3,5- dicarboxylic acid diethyl ester **53**, but the rate of the RA reaction was affected, and the requirement came to add another 30 mol % of catalyst to the one-pot reaction as shown in Table 19, entries 3- and 4.

The successful combination of two cascade O/H and RA reactions under L-proline catalysis was demonstrated by two more examples as shown in Table 19, and this one-pot synthetic strategy shows a large impact on the asymmetric synthesis of functionalized small molecules.

Table 19: Direct Organocatalytic One-Pot Double Cascade Asymmetric Synthesis of Wieland-Miescher Ketone Analogs **69**[a,b]

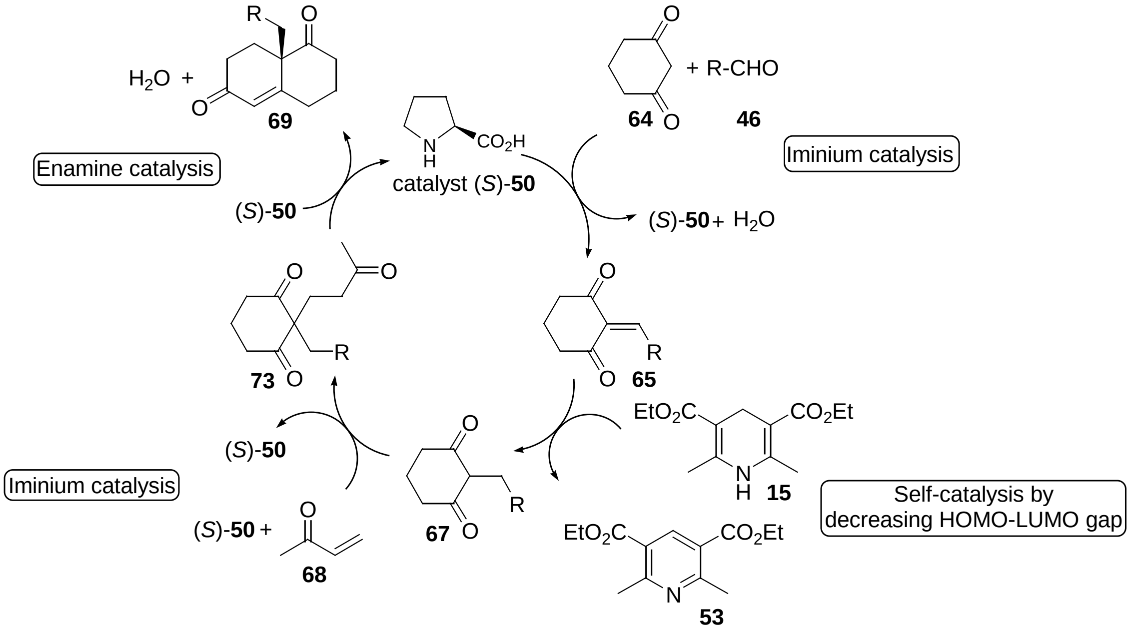


[a] See Experimental Section. [b] Yield refers to the column purified product and ee determined by HPLC analysis. [c] D-Proline **50g** (20 mol%) were used for Robinson annulation step. [d] One-pot reaction were carried out without addition of second catalyst **50**.

4.2.7 Mechanistic Insights. The possible reaction mechanism for L-proline-catalyzed regio- and chemoselective and enantioselective synthesis of cascade products **67** and **69** through reaction of CH acid **64**, aldehyde **46**, and Hantzsch ester **15** is illustrated in Scheme 19. This catalytic sequential one-pot double cascade is a four component reaction comprised of CH acid **64**, aldehyde **46**, Hantzsch ester **15**, methyl vinyl ketone **68a**, and a simple chiral amino acid **50**, which is capable of catalyzing each step of this double cascade reaction. In the first step (Scheme 19), the catalyst (*S*)-**50** activated component **46** by most likely iminium ion formation, which then selectively added to the CH acid **64** via a Mannich and retro-Mannich-type reaction to generate active olefin **65**.[1] The following second step was biomimetic hydrogenation[1a-b,]

[26b] of active olefin **65** by Hantzsch ester **15** to produce **67** through self-catalysis by decreasing HOMO-LUMO energy gap between **15** and **65**, respectively.[58,30a]

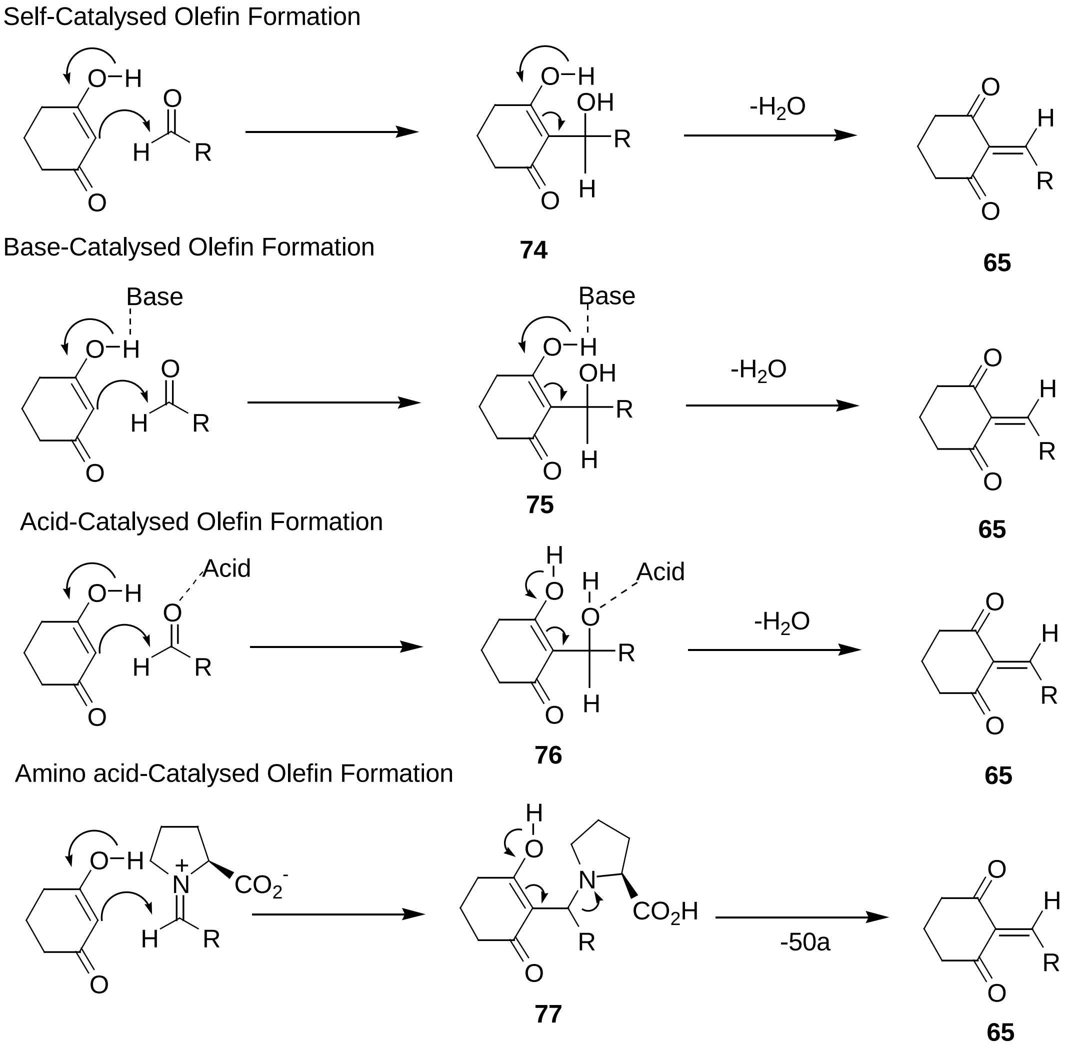
Scheme 19: Proposed Catalytic Cycle for the Double Cascade Reactions.



In the subsequent third step, the Michael addition of **67** to methyl vinyl ketone **68a** via most likely iminium ion activation led to the formation of Michael adduct **73**.[55] In the fourth step, (*S*)-**50** catalyzed the asymmetric intramolecular aldol condensation of **73** via enamine catalysis,[55] and subsequent hydrolysis returned the catalyst (*S*)-**50** for further cycles and released the desired W-M ketone analogue **69**.

Taking into account the recent applications of amine-catalyzed olefination reactions[27,59] and based on the different experiments performed (Table 12), we proposed that the most likely reaction course for the organocatalyzed direct addition of CH acids **64** to aldehydes **46** is the one outlined through amino acid catalysis in Scheme 20. Self- and acid-catalyzed olefin formation is slow reaction, but base and amino acid-catalyzed olefin formation is a very fast reaction and may be due to their high activation effect. The formation of active olefins **65** through proline catalysis by means of Mannich and retro-Mannich reactions support our hypothesis that aldol products **74** did not form in these reactions. This hypothesis is also supported by the recent discovery of organo-click reactions[27g] and the mechanistic investigation of pyrrolidine-catalyzed enal formation through aldehyde self-condensation reported by Saito *et al.*[59b]

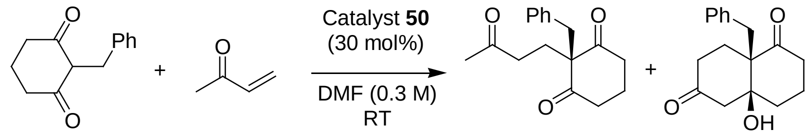
Scheme 20: Proposed mechanism for olefin formation



Our proposal of the Michael addition of **67** to methyl vinyl ketone **68a** via iminium ion activation or base catalysis is supported by results presented in Table 20. The values for the simultaneous proline-catalyzed Michael reaction followed by aldol reaction of **67aa** with **68a** is shown in Table 20, entry 1. Triethyl amine **50h** and quinine **50i** catalyzed the only Michael addition of **67aa** to **68a** (Table 20, entries 2 and 3), but there is not much product formation on acidic and uncatalyzed conditions as shown in

Table 20. On the basis of the previous results, we proposed that the most likely activation for the proline-catalyzed Michael reaction is iminium ion activation.[39]

Table 20: Effect of catalyst on Robinson annulation of **67aa** with **68**[a]



67aa (0.3 mmol) **68a** (0.9 mmol) **73aa** **70aa**

entry	catalyst **50** [30 mol%]	time (h)	conversion (%)^b	yield [%]^c **73aa**	yield [%]^c **70aa**
1	**50a**	11	99	50	24
2	**50h**	8	99	90	
3	**50i**	11	99	90	
4	**50j**	24	<10	5	
5		24	<10	5	

[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **68a** in the presence of 30 mol% of **50**. [b] Conversio based on TLC analysis. [c] Yield refers to the column purified product.

4.3 Conclusion

In summary, we have developed a metal-free one-pot cascade synthesis of highly substituted 2-alkyl-cyclohexane-1,3-diones **67** and chiral W-M ketone analogues **69** from simple starting materials via cascade O/H, RA, and O/H/RA reactions under amino acid catalysis. First time, we have reported the reductive alkylation of highly reactive CH acids (cyclohexane-1,3-dione and dimedone) with aldehydes and Hantzsch ester under amino acid catalysis. The TCRA strategy or cascade O/H reaction proceeds in good yield with high chemo- and regioselectivity using amino acids as the catalysts. In this article, we demonstrated the concept of self-catalysis by decreasing the HOMO-LUMO energy gap between in situ generated olefins **65** and Hantzsch ester **15**. Furthermore, we have demonstrated the synthetic application of reductive alkylation products **67**.

5. Direct Amino Acid-catalyzed Cascade Three Component Reductive Alkylations: Application to the Asymmetric Synthesis of Hajos–Parrish Ketone Analogues

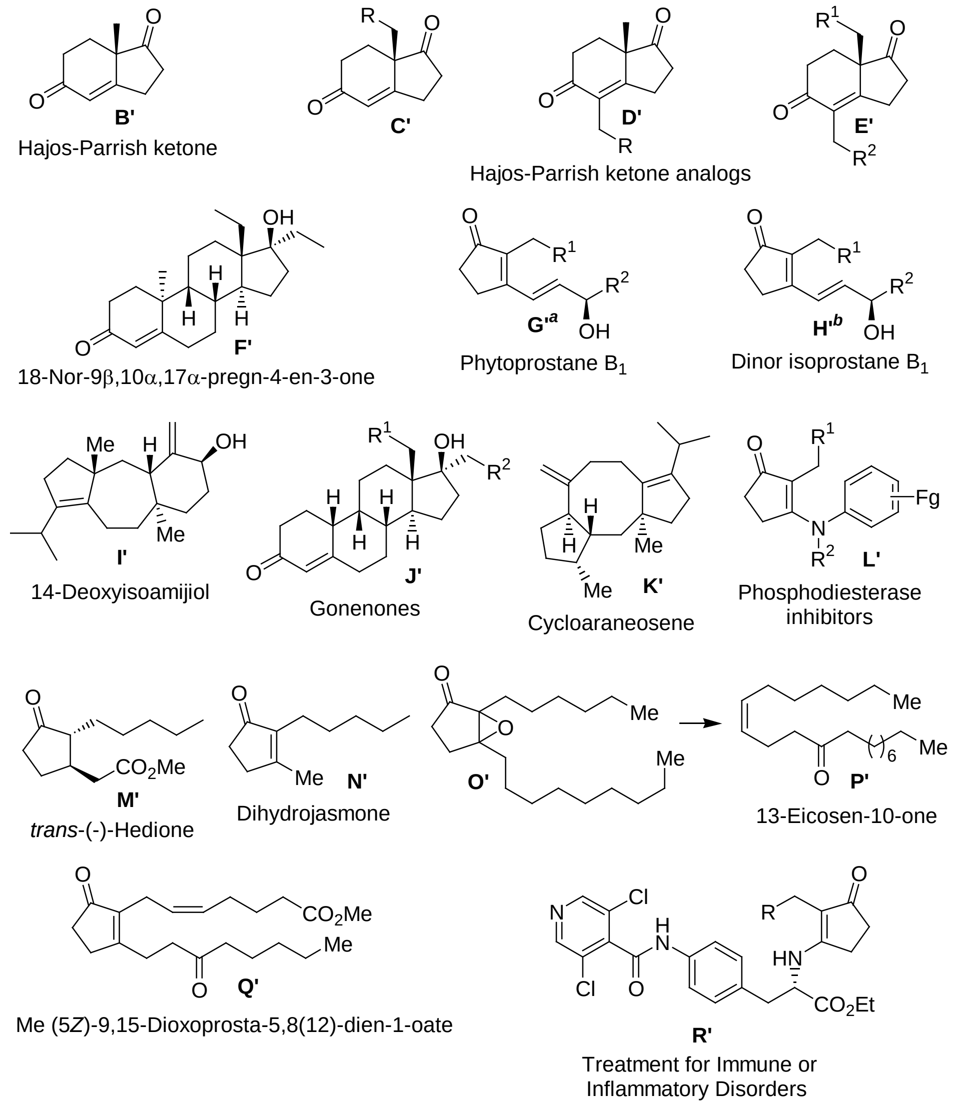
5.1 Introduction

Cascade and multi-component reactions are processes in which three or more easily accessible components are combined together in a single reaction vessel to produce a functionalized product displaying features of all inputs; thus, the processes offer greater possibilities for molecular diversity per step with a minimum of synthesis time, solvents and effort.[27] As cascade reactions are onepot reactions, they are easier to carry out than classical multistep syntheses. Combined with high-throughput library screening, this cascade strategy was an important development for drug discovery in the context of rapid identification and optimization of biologically active lead compounds. Libraries of small-molecule organic compounds are perhaps the most desired class of potential drug candidates. With a small set of starting materials, very large libraries can be built up within a short time,which can then be used for research on medicinal substances. In spite of the significant useful attributes of cascade and multi-component reactions for modern organic chemistry and their suitability for building up large compound libraries, these reactions have received limited interest over the past fifty years. However, in the last decade, with the introduction of high-throughput biological screening, the importance of cascade and multi-component reactions for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focused especially on the design and development of multi-component procedures for the generation of libraries of highly functionalized compounds.[27] In continuation of the development of novel biomimetic cascade reactions, recently, amino acid- or amine-catalyzed cascade and multi-component reactions have attracted a considerable amount of attention from chemists and biologists. Amino acid- or amine-catalyzed cascade and multi-component reactions involve two or more bond-forming transformations that take place under the same reaction conditions from simple starting materials catalyzed by small molecular units of metal-free proteins.[27] Amino acid/amine-catalyzed reactions have in the past few years emerged as a powerful synthetic tool for the construction of highly functionalized, complex and optically active compounds,[38] in particular, amino acid-catalyzed cascade and multi-component reactions emerging as ideal synthetic strategies for the synthesis of highly functionalized compounds and drug like small molecules in one pot, mimicking biological reactions.[27,37c]

As part of our research program to engineer direct amino acid/amine-catalyzed cascade, multi-component or organo-click reactions,[1a-d, 26a-e] herein we report the first organocatalytic asymmetric chemo-selective direct cascade olefination–hydrogenation (O–H), olefination–hydrogenation–Robinson annulation (O–H–RA) and olefination–hydrogenation–etherfication (O–H–E) reactions that produce very useful drug synthons, 2-alkyl-cyclopentane-1,3- diones **82** and **83**, Hajos–Parrish (H–P) ketone analogs **84** and 2-alkyl-3-methoxy-cyclopent-2-enones **86** from commercially available cyclopentane-1,3-dione **78**, aldehydes or ketones **46 or 47**, Hantzsch ester **15**, methyl vinyl ketone **68a** and amino acid **50** as shown in Scheme 21. 2-Alkyl-cyclopentane-1,3-diones **82** and **83**, H–P ketone analogues **84** and 2-alkyl-3-methoxy-cyclopent-2-enones **87** are attractive intermediates in the synthesis of natural products and in medicinal chemistry,[60] whilst 2-alkyl-cyclopentane-1,3-diones **82** and **83** and 2-alkyl-3-methoxy-cyclopent-2-enones **87** have broad utility in pharmaceutical chemistry[47l,61] and are excellent starting materials in natural product synthesis as shown in Chart 3.

Hence, their preparation has continued to attract considerable synthetic interest in developing new methods for their syntheses.[48a-d,62] Interestingly, there is no direct methodology for the synthesis of useful 2-alkyl-cyclopentane-1,3-diones **82** and **83** and only two-step methods are known to prepare them. [48a-d,62] Recently, Paquette *et al.* developed the two-step synthesis of 2-alkyl-cyclopentane-1,3- diones **82** and **83** in moderate to good yields *via* an *in situ* protection and deprotection sequence on 2-alkylidene-1,3-diones **79** with thiophenol and Raney nickel, respectively.[48b]

Chart 3: Natural and Non-natural Products Library Generated from 2-Alkyl-Cyclopentane-1,3-Diones



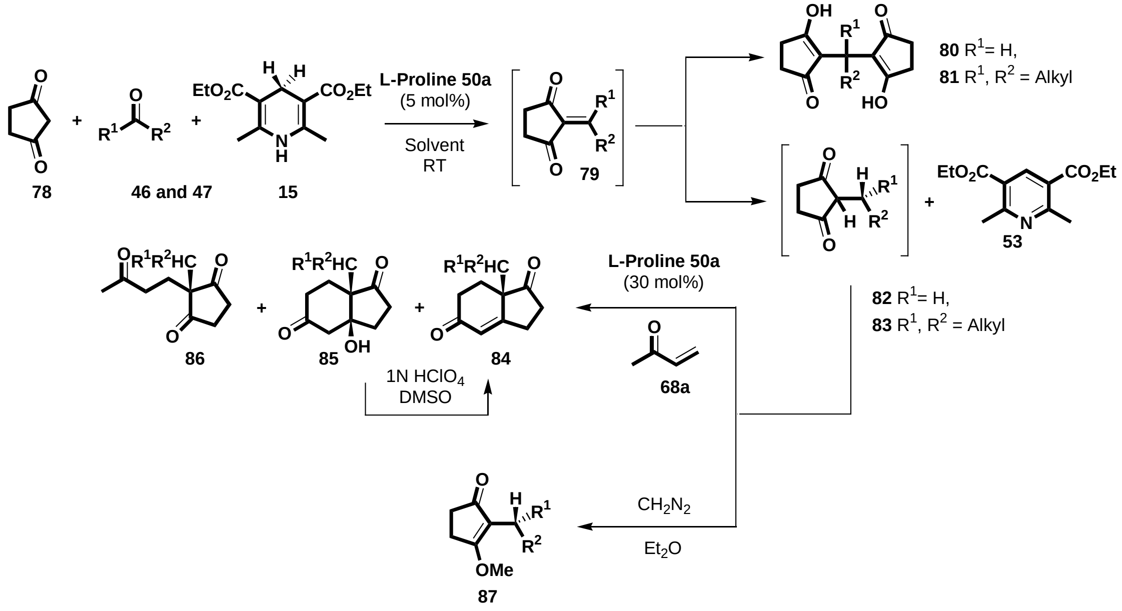
[a] **PPB_1 type I:** $R^1 = (CH_2)_6CO_2H$, $R^2 = CH_2CH_3$; **PPB_1 type II:** $R^1 = CH_3$, $R^2 = (CH_2)_7CO_2H$

[b] **$DIPB_1$ type III:** $R^1 = (CH_2)_3CO_2H$, $R^2 = (CH_2)_4CH_3$; **$DIPB_1$ type IV:** $R^1 = (CH_2)_3CH_3$, $R^2 = (CH_2)_4CO_2H$

As shown in Scheme 21, the well-recognized fact is the inability to arrest olefination reactions involving cyclopentane-1,3-dione **78** and aliphatic or aromatic aldehydes **46** at the mono-addition stage.[63] Very few adducts such as **79** have been isolated.[64a-c,50b-c,49d] This is because these olefination products **79** are highly reactive

Michael acceptors capable of engaging the unreacted cyclopentane-1,3-dione **78** reagent in kinetically rapid l,4-addition to give bis-adducts such as **80** and **81**. Also, there is no report on the asymmetric synthesis of higher alkyl substituted H–P ketone analogues **84**. This has prompted us to investigate the cascade synthesis of very useful 2-alkyl-cyclopentane-1,3-diones **82** and **83**, H–P ketone analogues **84** and 2-alkyl-3-methoxy-cyclopent-2- enones **87** in a single step through mild amino acid-catalysis.

Scheme 21: Direct Organocatalytic Asymmetric Cascade O/H, O/H/RA and O/H/E Reactions



We consequently set out to develop an amino acid-catalyzed asymmetric cascade synthesis of higher alkyl analogues of H–P ketones **84** from simple starting materials, which have not been prepared in the past. In this chapter, we present the development and application of the amino acid-catalyzed reductive alkylation of cyclopentane-1,3-dione **78** through cascade O–H reaction of reactive 1,3-dione **78**, aldehydes or ketones **46 or 47** and Hantzsch ester **15**. Furthermore, we will present mechanistic insight into the reaction course, applying a new concept of self-catalysis leading to an understanding of the cascade O–H reaction with utilization of calculations.

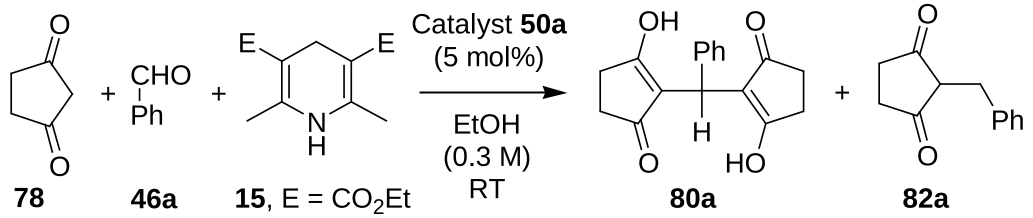
We imagine that an amino acid or amine would catalyze the cascade olefination reaction of 1,3-dione **78** with an aldehyde or ketone **46 or 47** to form substituted 2-alkylidene-cyclopentane-1,3-diones **79**, which are very reactive intermediates and further undergo chemoselective reactions with both 1,3-dione **78** and Hantzsch ester **15** to produce bis-adducts **80** and **81** and hydrogenated 2-alkylcyclopentane-1,3-diones **82** and **83**, respectively, based on reaction conditions. Amino acid-catalyzed Robinson annulation of products **82** and **83** with methyl vinyl ketone **68a** furnishes the H–P ketones **84** and alcohols **85** in good yield with very good enantioselectivity, and alcohol **85** would be converted into ketone **84** without losing enantioselectivity as shown Scheme 21.

5.2 Results and discussion

5.2.1 Direct amino acid-catalyzed cascade reductive alkylation of cyclopentane-1,3-dione: reaction optimization: We initiated our preliminary investigation by the *in situ* reduction of 2-benzylidene-cyclopentane-1,3-dione **79a**‡ (In all compounds denoted **79x**, **80x and 81x**, **82x and 83x**, **84x**, **85x**, **86x** and **87x**, **x** is incorporated from reactant aldehydes **46** or ketones **47)** with Hantzsch ester **15** as shown in Table 21. The self-catalyzed reaction of cyclopentane-1,3-dione **78** with 3 equiv. of benzaldehyde **46a** furnished the only unexpected bis-adduct **80a** without the expected olefination product **79a** (Table 21, entry 1). The same reaction under proline catalysis also furnished the only bis-adduct **80a** without product **79a** with reduced reaction time (Table 21, entry 2). Interestingly, self-catalyzed reaction of cyclopentane-1,3-dione **78** and 2 equiv. of benzaldehyde **46a** with Hantzsch ester **15** furnished the bis-adduct **80a** and expected reductive alkylation product **82a** with 80% overall yield in 1:4.3 ratio respectively after 24 h at 25 °C (Table 21, entry 3). The self-catalyzed reductive alkylation reaction with 3 equiv. of benzaldehyde **46a** furnished the product **82a** in 90% yield after 24 h at 25 °C (Table 21, entry 4). Interestingly, the same reaction under proline-catalysis furnished the expected reductive alkylation product **82a** with

90% yield after 12 h at 25 °C in EtOH as shown in Table 21, entry 5. These preliminary results prompted us to investigate the solvent and catalyst effect on *in situ* trapping of olefination product of cyclopentane-1,3-dione **78** with benzaldehyde **46a** through biomimetic hydrogenation as shown in Table 22.

Table 21: Preliminary Studies on Reductive *In Situ* Trapping of 2-Alkylidene-Cyclopentane-1,3-Diones[a]



entry	catalyst **50a** (5 mol%)	aldehyde **46a** (equiv.)	H. ester **15** (equiv.)	time (h)	products yield (%)[b]	
					80a	**82a**
1	–	3.0	–	24	75	–
2	proline	3.0	–	12	75	–
3	–	2.0	1.0	24	15	65
4	–	3.0	1.0	24	10	90
5	**proline**	**3.0**	**1.0**	**12**	**10**	**90**

[a] Reactions were carried out in ethanol (0.3 M) with 2.0 to 3.0 equiv. of **46a** and 1.0 equiv. of **15** relative to the **78** (0.3 mmol) in the presence of 5 mol% of catalyst **50a**. [b] Yield refers to the column purified product.

After preliminary demonstration of the amino acid-promoted cascade O–H reactions for the generation of cascade product **82a** from **78**, **46a** and **15**, we decided to investigate the solvent and catalyst effect on cascade O–H reactions. Interestingly, proline catalyzed cascade O–H reactions of **78**, **46a** and **15** are solvent and catalyst dependent reactions as shown in Table 22. The cascade O–H reaction of **78**, **46a** and **15** catalyzed by simple amines like benzylamine **50f**, pyrrolidine **50c**, piperidine **50d** and

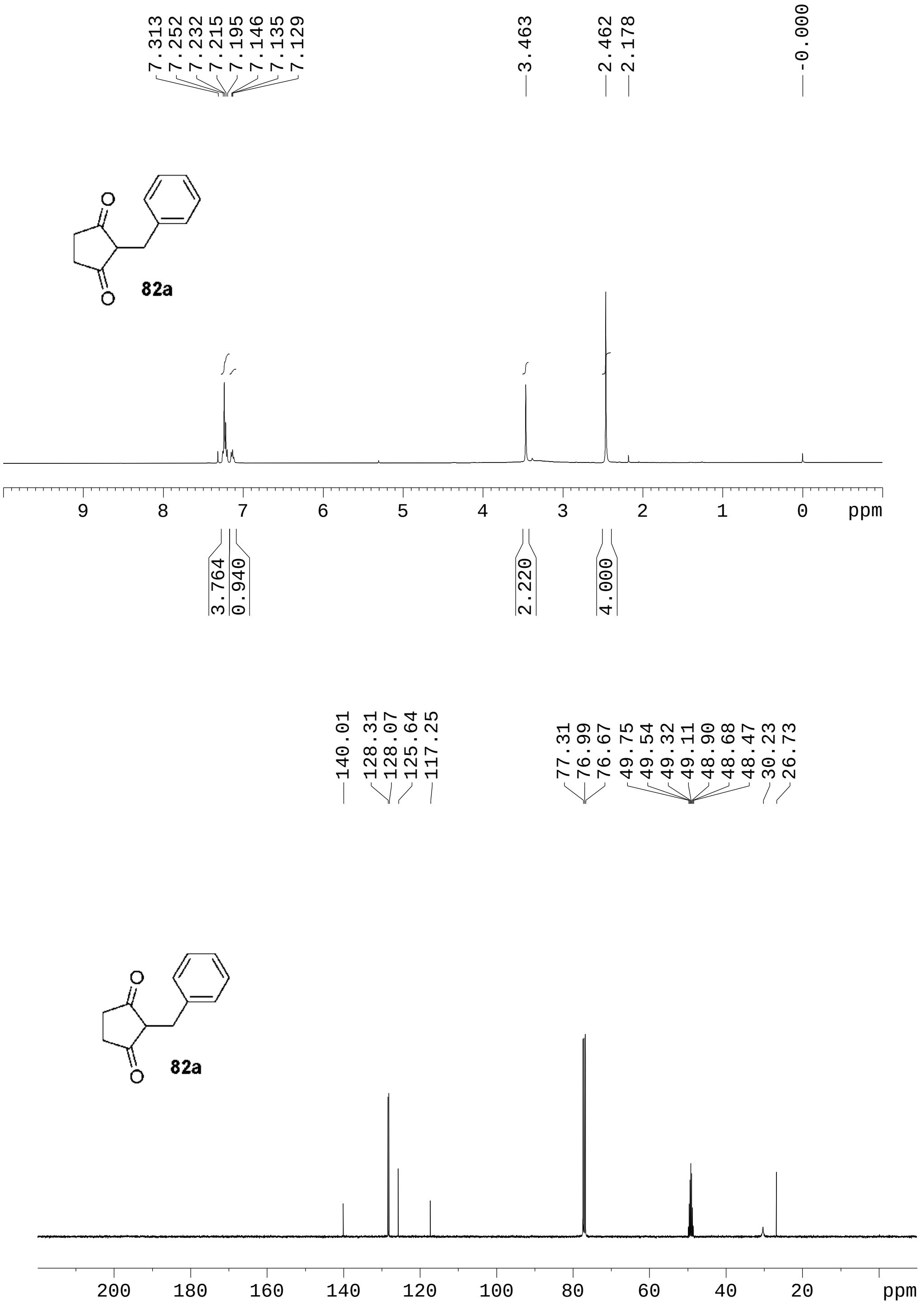


Figure-21: ^{1}H NMR and ^{13}C NMR Spectrum of product **82a**.

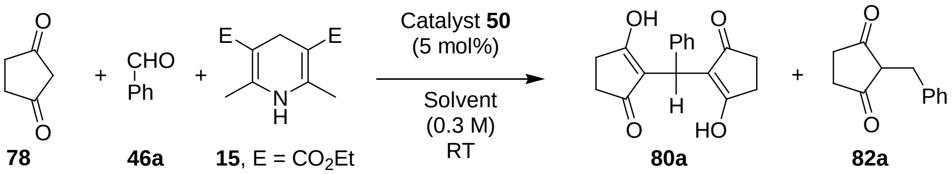
morpholine **50e** in ethanol are not superior compared to self- and proline-catalysis as shown in Table 22, entries 1–4. There is a large amount of solvent effect on the direct proline-catalyzed reductive alkylation or cascade O–H reaction of **78**, **46a** and **15** as shown in Table 22. Proline-catalyzed cascade O–H reactions can be performed in three types of solvents (protic polar, aprotic polar and aprotic non-polar) with moderate to good yields as shown in Table 22. Surprisingly, the cascade O–H reaction of **78**, **46a** and **15** in H_2O furnished the expected hydrogenated product **82a** in 26% yield accompanied by a 71% yield of bis-adduct **80a** after 3 h at 25 °C (Table 22, entry 6). The same cascade reaction under proline-catalysis in CH_2Cl_2 furnished the expected product **82a** in 93% yield after 2 h at 25 °C (Table 22, entry 10). We envisioned the optimized conditions to be mixing the 3 equiv. of benzaldehyde **46a** with cyclopentane-1,3-dione **78** and Hantzsch ester **15** at 25 °C in CH_2Cl_2 under 5 mol% of proline-catalysis to furnish the hydrogenated product **82a** in 93% yield (Table 22, entry 10). The products structures were confirmed by ^{1}H and ^{13}C NMR [for example see Fig. 21] and mass analysis.

5.2.2 Diversity-oriented synthesis of reductive alkylation products **82** and **83:**

With the optimized reaction conditions in hand, the scope of the proline-catalyzed O–H cascade reactions was investigated with cyclopentane-1,3-dione **78**, various aldehydes **46a–s′** or ketones **47a–p** and Hantzsch ester **15** as shown in Table 23. A series of aromatic and aliphatic aldehydes **46a–s′** (3 equiv.) were reacted with cyclopentane-1,3-dione **78** and Hantzsch ester **15** catalyzed by 5 mol% of proline at 25 °C in CH_2Cl_2 (Table 23).

The 2-arylmethyl-cyclopentane-1,3-diones **82a–n** and 2-alkyl-cyclopentane-1,3-diones **82e′–s′** and **83a-p** were obtained as single isomers (tautomer) with excellent yields. The cascade reaction of cyclopentane-1,3-dione **78** with naphthalene-1-carbaldehyde **46b** and **15** furnished the reductive alkylation product **82b** as a single tautomer, in 80% yield after 5 h at 25 °C (Table 23). But the same cascade reaction with naphthalene-2-carbaldehyde **46c** and **15** furnished the reductive alkylation product **82c** as a single tautomer, with 93% yield after 1 h at 25 °C (Table 23). Synthesis of 2-arylmethyl-cyclopentane-1,3-diones **82a–n** from **78**, **46a–n** and **15** at 25 ◦C under proline-catalysis has taken longer reaction times (1–28 h), compared to aliphatic aldehydes **46e′-s′** as shown in Table 23. Interestingly, proline-catalyzed reductive alkylation reaction of cyclopentane-1,3-dione **78**, α,β-unsaturated aldehydes **46e′–f′** and Hantzsch ester **15** generated the expected 2-alkyl-cyclopentane-1,3-diones **82e′–f′** in excellent yields with moderate chemoselectivity (Table 23). Completely hydrogenated products **82e″/82f″** and 1,4-reduction products **82e′/82f′** are furnished in a 1:2.0 ratio respectively as shown in Table 23.

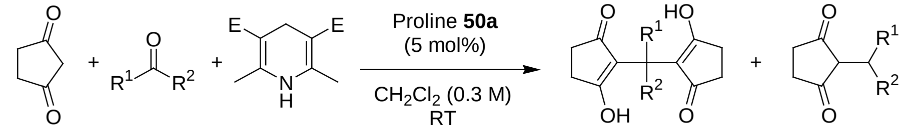
Table 22: Effect of Solvent and Catalyst on the Direct Amino Acid Catalyzed Reductive Alkylation of **78** with **46a** and **15**



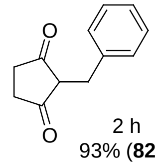
entry	solvent (0.3 M)	catalyst **50** (5 mol%)	time (h)	products **80a**	yield (%)^b **82a**
1	EtOH	benzylamine **50f**	24	40	60
2	EtOH	pyrrolidine **50c**	24	50	50
3	EtOH	piperidine **50d**	24	50	50
4	EtOH	morpholine **50e**	24	50	50
5	MeOH	proline **50a**	3	8	88
6	H_2O	proline **50a**	3	71	26
7	DMSO	proline **50a**	6	40	60
8	DMF	proline **50a**	6	40	60
9	CH_3CN	proline **50a**	6	10	88
10	**CH_2Cl_2**	proline **50a**	**2**	**7**	**93**
11^c	CH_2Cl_2	proline **50a**	6	20	80
12^d	CH_2Cl_2	proline **50a**	6	40	60

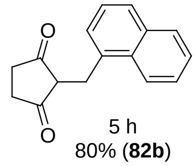
^{a} Reactions were carried out in solvent (0.3 M) with 1.0 to 3.0 equiv. of **46a** and 1.0 equiv. of **15** relative to the **78** (0.3 mmol) in the presence of 5 mol% of catalyst **50**. ^{b} Yield refers to the column purified product. ^{c} 2.0 Equiv of **46a** was used. ^{d} 1.0 equiv. of **46a** was used.

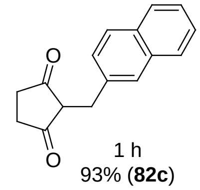
Table 23: Synthesis of Reductive Alkylation Library via Cascade O/H Reactions from Cyclopentane-1,3-Dione **78** and Aldehydes **46**/Ketones **47**

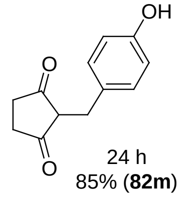


78 **46** or **47** **15**, E = CO_2Et 0.25 h to 48 h **80** or **81** **82** and **83**

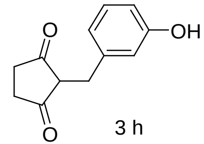

2 h
93% (**82a**)
7% (**80a**)


5 h
80% (**82b**)
20% (**80b**)

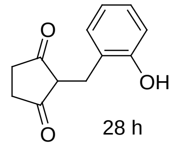

1 h
93% (**82c**)
7% (**80c**)



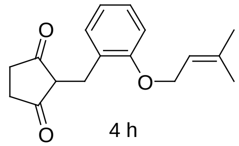
24 h
85% (**82m**)
15% (**80m**)

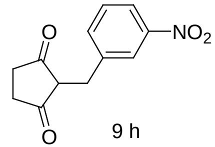


3 h
95% (**82l**)
5% (**80l**)

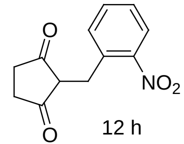


28 h
80% (**82k**)
20% (**80k**)

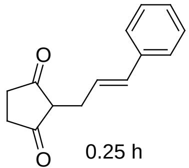

4 h
95% (**82t'**)
5% (**80t'**)

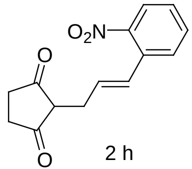


9 h
90% (**82o**)
10% (**80o**)

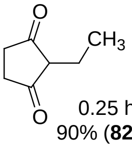


12 h
90% (**82n**)
10% (**80n**)

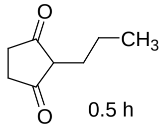

0.25 h
85% (**82e'**)[b]
15% (**80e'**)



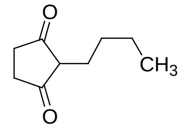
2 h
85% (**82f'**)[b]
15% (**80f'**)



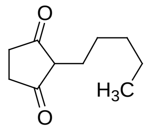
0.25 h
90% (**82o'**)
10% (**80o'**)



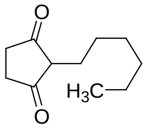
0.5 h
90% (**82g'**)
10% (**80g'**)



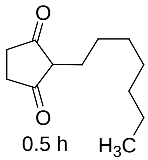
0.5 h
90% (**82h'**)
10% (**80h'**)



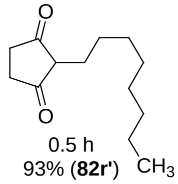
0.5 h
90% (**82i'**)
10% (**80i'**)



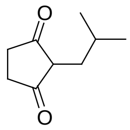
0.5 h
90% (**82p'**)
10% (**80p'**)

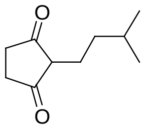


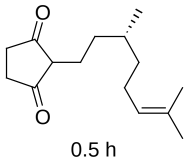
0.5 h
93% (**82q'**)
7% (**80q'**)

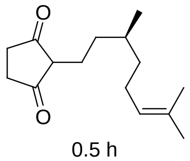


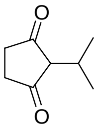
0.5 h
93% (**82r'**)
7% (**80r'**)

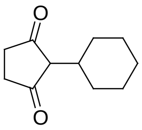

24 h
90% (**82j'**)
10% (**80j'**)


0.5 h
90% (**82k'**)
10% (**80k'**)


0.5 h
90% (***R*)-82s'**
10% (***R*)-80s'**


0.5 h
90% (***S*)-82s'**
10% (***S*)-80s'**


24 h
90% (**83p**)[c]
<5% (**83p**)


48 h
90% (**83a**)[c]
10% (**81a**)

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[a] Yield refers to the column purified product. [b] A 1:2.0 ratio of completely reduced and 1,2-reduction **82e'/f'** products were formed (see Supporting information). [c] Solvent CH_2Cl_2 and ketones **83p/83a** were taken in 1:1 ratio.

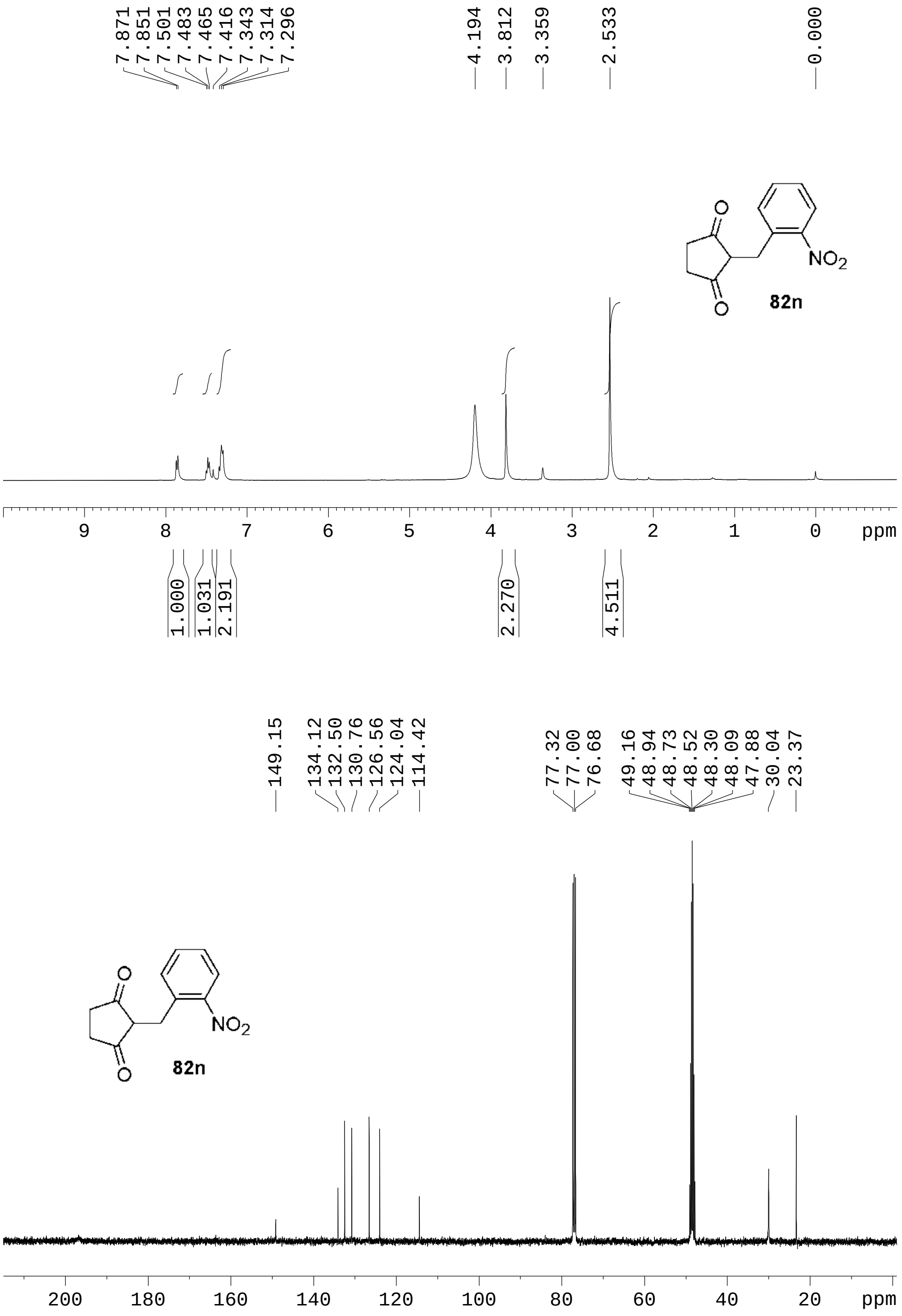


Figure-22: ^{1}H NMR and ^{13}C NMR Spectrum of product **82n**.

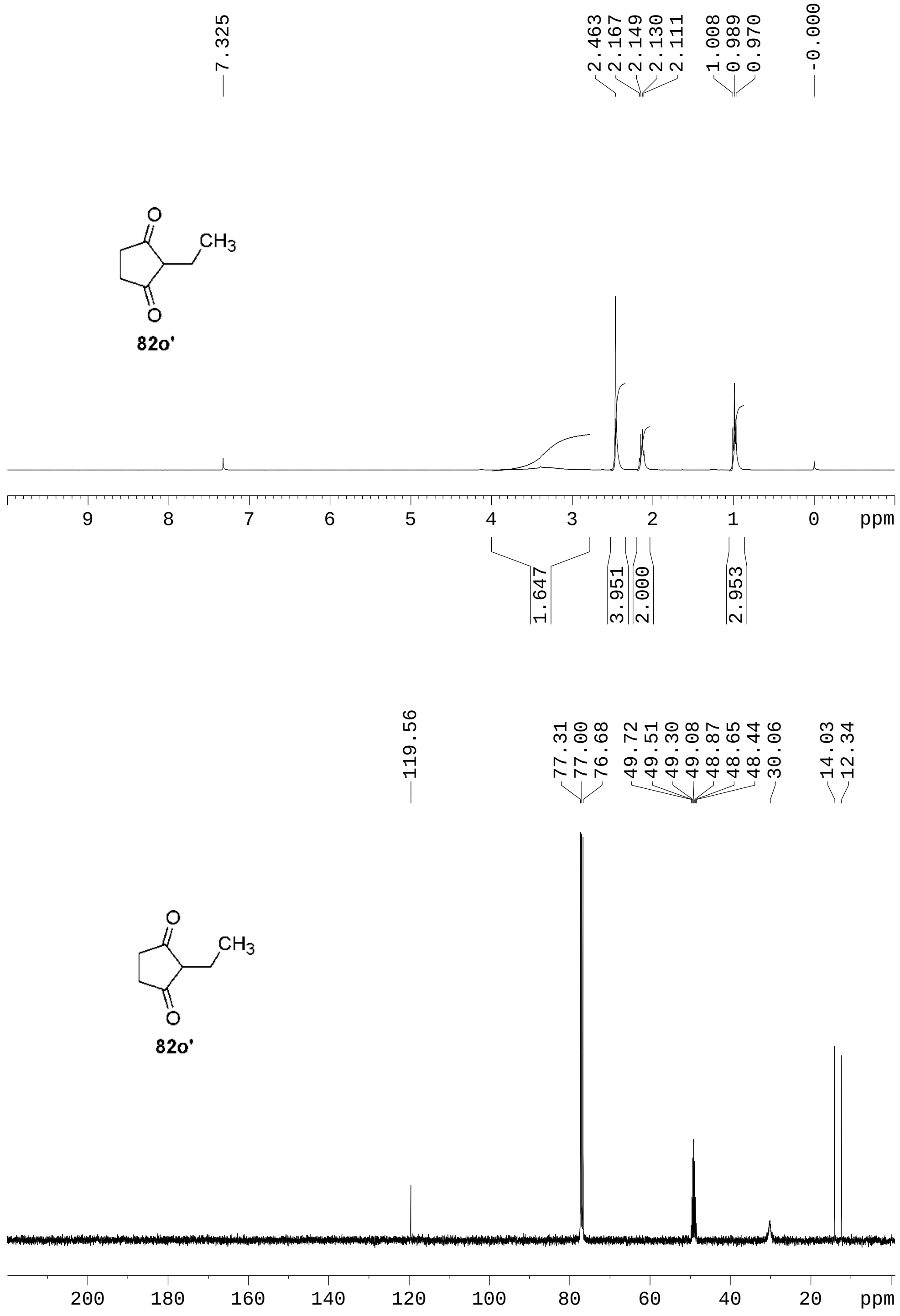


Figure-23: ^{1}H NMR and ^{13}C NMR Spectrum of product **82o'**.

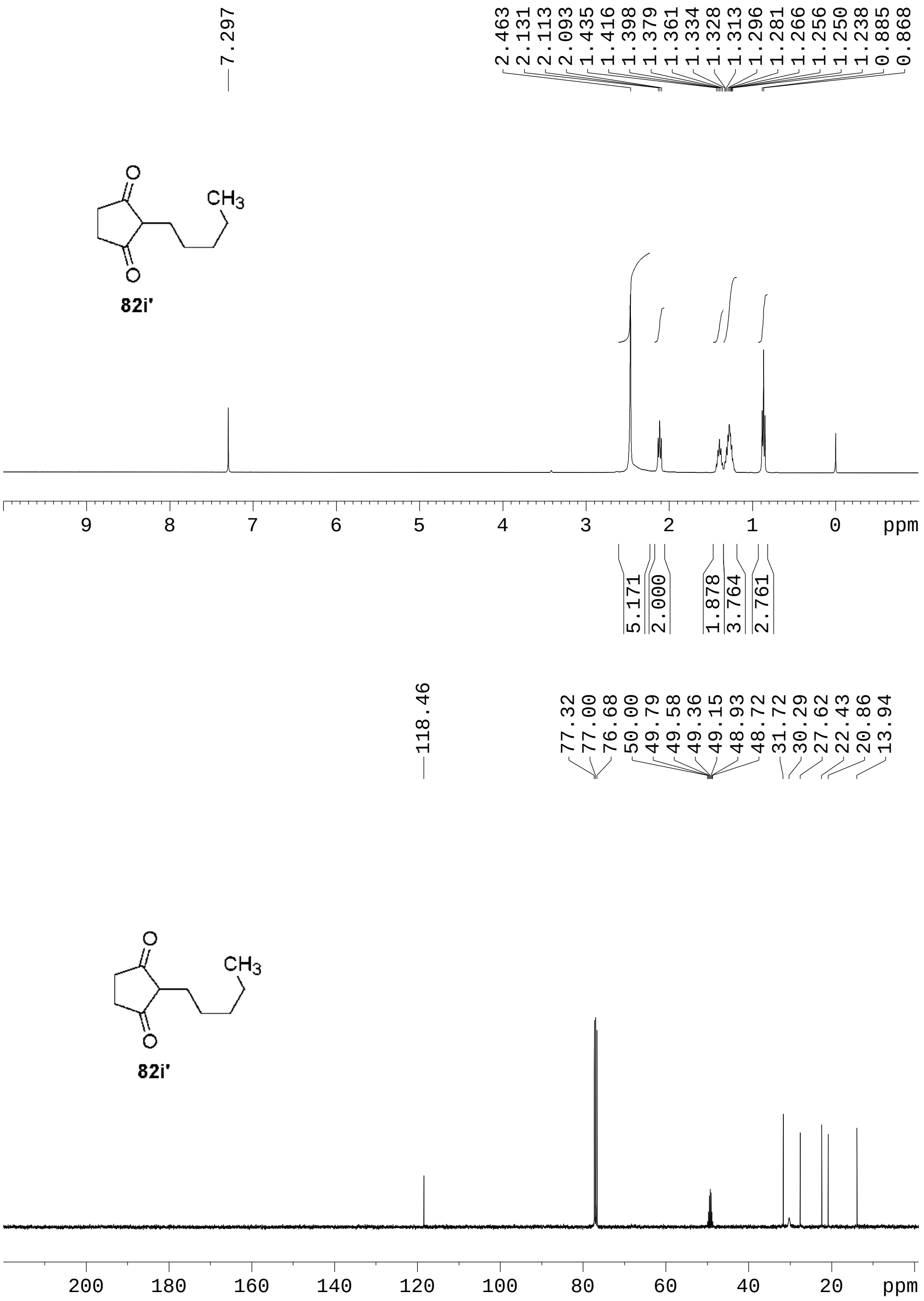
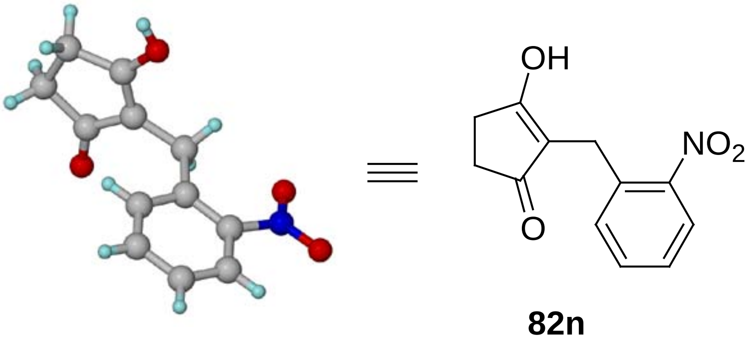


Figure-24: ^{1}H NMR and ^{13}C NMR Spectrum of product **82i'**.

Interestingly, proline-catalyzed cascade reductive alkylation reaction of cyclopentane-1,3-dione **78** with chiral aldehydes ***R*-46s′** and ***S*-46s′** and Hantzsch ester **15** furnished the expected single enantiomer of 2-alkylcyclopentane-1,3-diones ***R*-82s′** and ***S*-82s′** in excellent yields with high stereoselectivity (Table 23).Cascade products (*R*)-(-)-2-(3,7-dimethyl-oct-6-enyl)-cyclopentane-1,3-dione ***R*-82s′** and (*S*)-(+)-2-(3,7-dimethyloct-6-enyl)-cyclopentane-1,3-dione ***S*-82s′** are generated in 90% yields *via* cascade O–H reaction. Proline-catalyzed cascade reductive alkylation of cyclopentane-1,3-dione **78** was further extended with ketones also as shown in Table 23. Cascade reductive alkylation reaction of cyclopentane-1,3-dione **78** with acetone **47p** or cyclohexanone **47a** and Hantzsch ester **15** under 5 mol% of proline-catalysis furnished the expected single isomers of 2-alkyl-cyclopentane-1,3-diones **83a–p** in excellent yields (Table 23). The results in Table 23 demonstrate the broad scope of this reductive cascade methodology covering a structurally diverse group of aldehydes **46a–s′** and ketones **47a–p** with many of the yields obtained being very good, or indeed better, than previously published two-step alkylation reactions.[48a-d,62] The structure and regiochemistry of 2-alkylcyclopentane-1,3-diones **82a–s′** and **83a-p** were confirmed by ^{1}H NMR,^{13}C NMR [Fig 22–25] and mass analysis and also X-ray structure analysis on **82n** as shown in Scheme 22.[65]

Interestingly, many of the 2-alkyl-cyclopentane-1,3-diones **82a–s′** and **83a-p** exist in the enol form in both the solid state and solution state, which may be due to the strong intermolecular hydrogen bonding. Also, this characteristic is observed in many other 1,3-diketones.[48a-d,62] 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 **82a–s′** and **83a-p** can hardly be determined in solution, due to the rapid keto–enol and enol–enol tautomerism.[62c] Therefore, in 2-alkyl-cyclopentane-1,3-dione compounds **82a–s′** and **83a-p**, 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 standard sampling. 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.[48a-d,62]

Scheme 22: Crystal structure of 2-(2-nitro-benzyl)-cyclopentane-1,3- dione (**82n**).

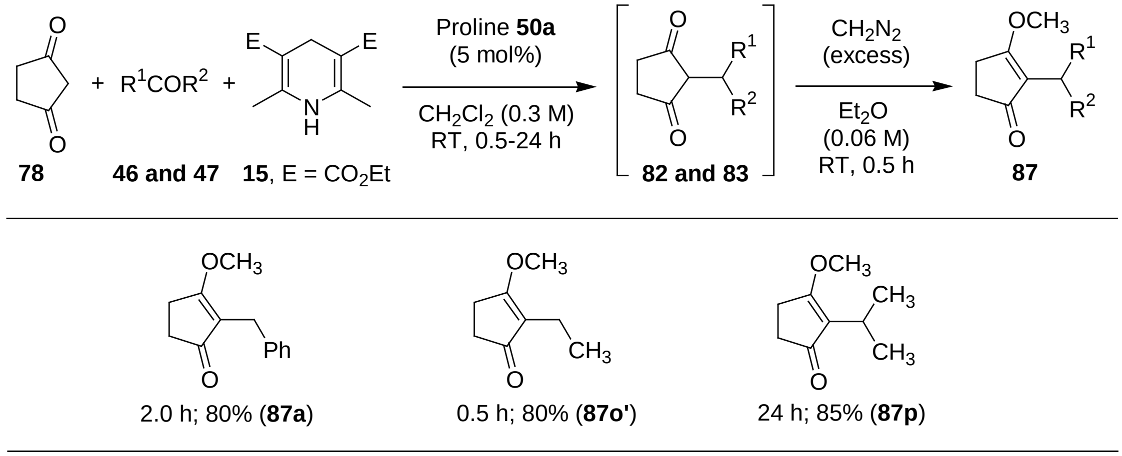


82n

5.2.3 Applications of reductive alkylation products

5.2.3.1 Chemoselective O-alkylation of 2-alkyl-cyclopentane-1,3-diones: Cascade products 2-alkyl-cyclopentane-1,3-diones **82** and **83** are readily transformed into substituted 2-alkyl-3-methoxy-cyclopent-2-enones **87** by treatment with an ethereal solution of diazomethane in one pot as shown in Scheme 23. The highly functionalized 2- alkyl-3-methoxy-cyclopent-2-enone unit is a basic building block for a large number of valuable naturally occurring products.[61c-h] Highly functionalized 2-alkyl-3-methoxy-cyclopent-2-enones **87** have gained importance in recent years as starting materials and intermediates for the synthesis of prostaglandin analogues, which possess a wide range of physiological and pharmacological properties.[61c-h] Long chain 2-alkyl-3-methoxy-cyclopent-2-enones **87** have been successfully utilized as ideal synthons for the synthesis of prostaglandin analogues, which are used for the treatment or prevention of cancer.[61c-h] Cascade O–H reaction of **78**, **46a** and **15** under 5 mol% of proline-catalysis furnished the substituted 2-benzyl-cyclopentane-1,3-dione **82a** in good yield, which on treatment with ethereal diazomethane at 25 °C for 0.5 h furnished the chemoselectively one-pot O–H–E product 2-benzyl-3-methoxy-cyclopent-2-enone **87a** in 80% yield through self-catalysis as shown in Scheme 23.

Scheme 23: Direct Organocatalytic One-Pot Synthesis of 2-Alkyl-3-methoxy-cyclopent-2-enones **87**[a]



[a] Yield refers to the column purified product.

The acidic or highly enolizable nature of 2-alkyl-cyclopentane-1,3-diones **82** and **83** is the main driving force in leading us to observe a highly chemoselective O-alkylation reaction with diazomethane. The generality of the proline/self-catalyzed chemoselective one-pot O–H–E reaction was further confirmed by two more examples using aliphatic acetaldehyde **46o′** and acetone **47p** to furnish the expected 2-ethyl-3-methoxy-cyclopent-2-enone **87o′** in 80% yield and 2-isopropyl-3-methoxy-cyclopent-2-enone **87p** in 85% yield, respectively as shown in Scheme 23. For pharmaceutical applications, a diversity-oriented library of enones **87** could be generated by using our amino acid/self-catalyzed, chemoselective one-pot O–H–E reaction. The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 26] and mass analysis.

5.2.3.2 Amino acid-catalyzed asymmetric Robinson annulations

Higher alkyl substituted H–P ketone analogues **84** are very good intermediates for the synthesis of natural products like steroids.[60] Recently, Ali Amjad *et al.* reported in their

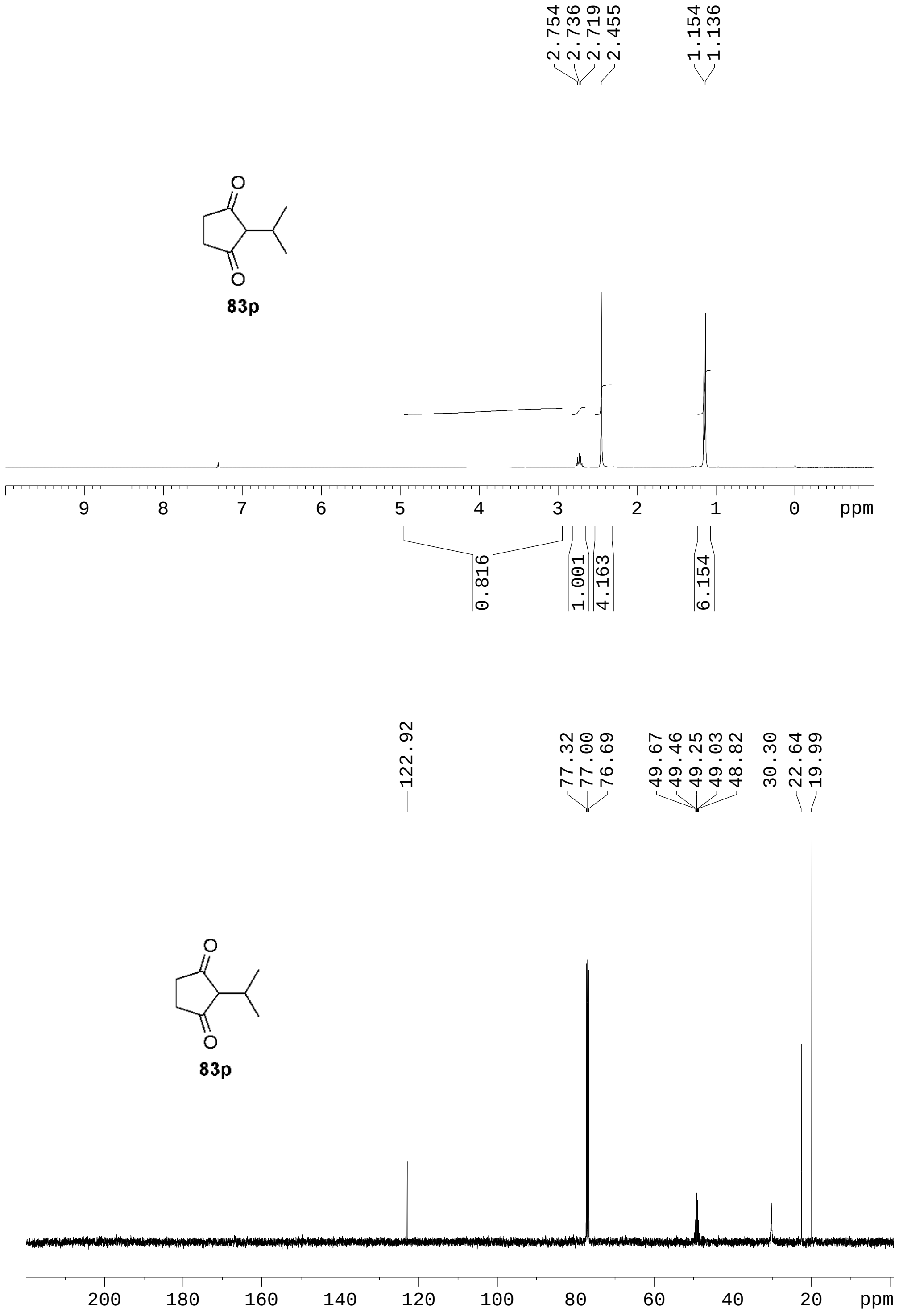


Figure-25: ^{1}H NMR and ^{13}C NMR Spectrum of product **83p**.

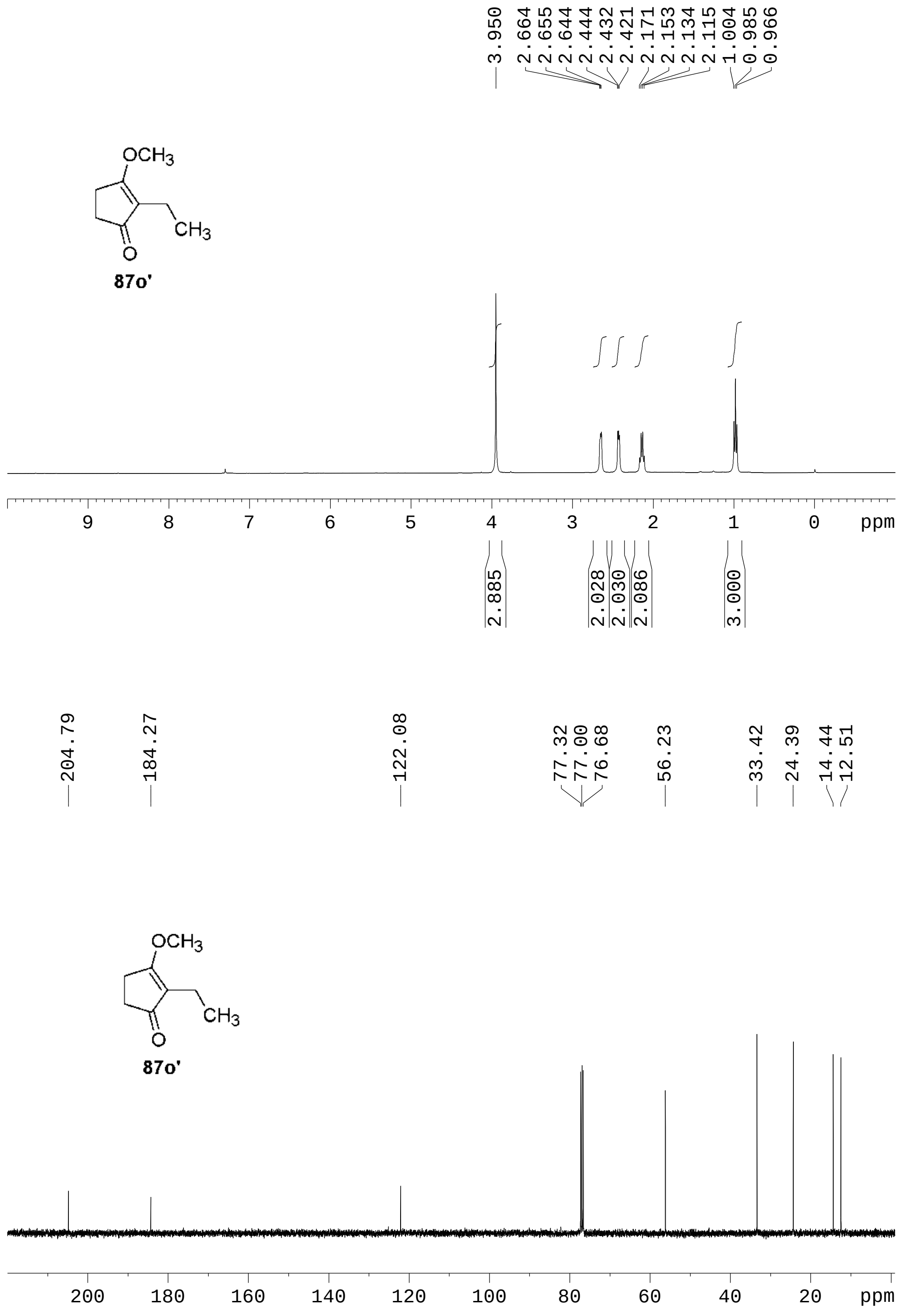
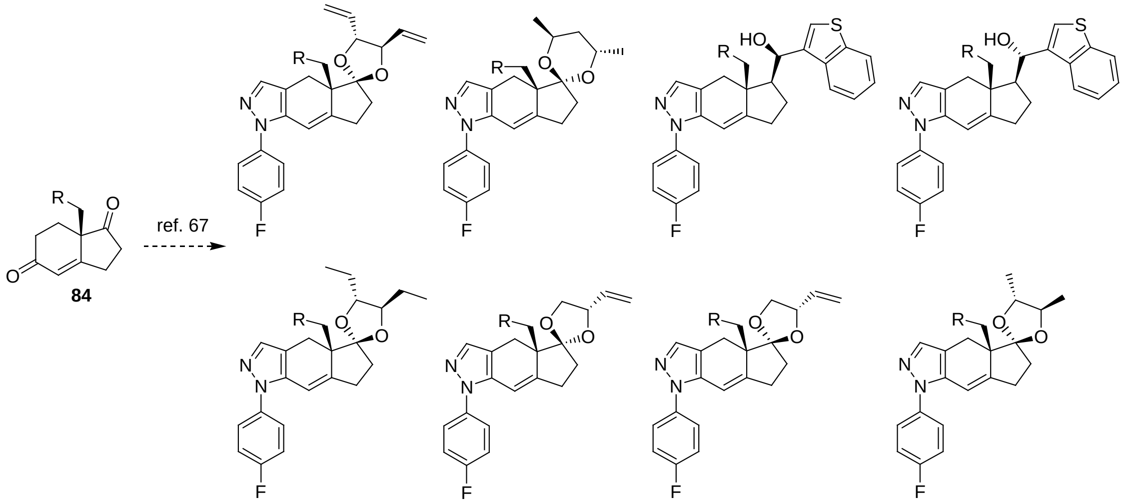


Figure-26: ^{1}H NMR and ^{13}C NMR Spectrum of product **87o'**.

papers[67] that higher alkyl H–P ketone analogues **84** are very good intermediates for the synthesis of pharmaceutically acceptable salts or hydrates of heterocycles, which are shown as selective glucocorticoid receptor modulators for treating a variety of autoimmune and inflammatory diseases or conditions (see Chart 4).

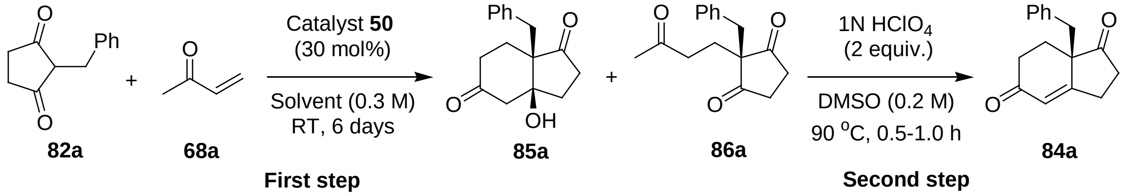
Chart 4: Selective Ligands Analogs for the Human Glucocorticoid Receptor



Interestingly, to the best of our knowledge, there is no report for the asymmetric synthesis of useful higher alkyl substituted H–P ketone analogues **84**. In this chapter, we are presenting the asymmetric synthesis of H–P ketone analogs **84** with very good ee and yields *via* amino acid-catalyzed asymmetric RA of 2-alkyl-cyclopentane-1,3-diones **82** with methyl vinyl ketone **68a** as shown in Tables 24–25.

Interestingly, L-proline-catalyzed RA reaction of 2-benzylcyclopentane-1,3-dione **82a** with 3 equiv. of freshly distilled methyl vinyl ketone **68a** in CH_3CN furnished the expected alcohol product **85a** in 60% yield accompanied by Michael adduct **86a** in 26% yield at 25 °C for 6 days (Table 24, entry 1). Hydrolysis of bicyclic-alcohol **85a** obtained from L-proline **50a** catalysis with 1 N $HClO_4$ in DMSO at 90 °C for 1 h furnished the expected bicyclic-ketone (+)-**84a** in 80% yield with 85% ee as shown in Table 24, entry 1. Solvent screening on the direct L-proline-catalyzed RA reaction of **82a** with **68a** revealed that DMSO solvent is suitable to achieve high yields and ee's as shown in Table 24. We envisioned the optimized conditions to be mixing the 2-benzyl-cyclopentane-1,3-dione **82a** and 3 equiv. of freshly distilled methyl vinyl ketone **68a** at 25 °C in DMSO under 30 mol% of L-proline to furnish the alcohol of H–P ketone analogue **85a** in 67% yield accompanied by Michael adduct **86a** in 33% yield, which on hydrolysis with 1 N $HClO_4$ in DMSO at 90 °C for 1 h furnished the expected bicyclic-ketone (+)-**84a** in 85% yield with 91% ee as shown in Table 24, entry 2. D-Proline-catalyzed RA reaction of **82a** with **68a** followed by hydrolysis furnished the opposite enantiomer of H–P ketone analogue (–)-**84a** in 96% yield with 90% ee (Table 24, entry 4). The absolute configuration of product (+)-**84a** prepared under L-proline-catalysis was established by using X-ray crystallography and also by comparison with the proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction.[57] The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 27] and mass analysis. The crystal structure of product (+)-**84a** is depicted in Scheme 24.[66]

Table 24: Direct amino acid-catalyzed Robinson annulation of **82a** with **68a**[a]



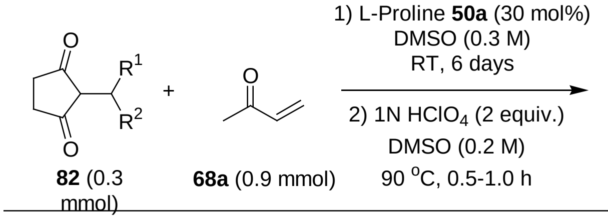
entry	solvent [0.3 M]	catalyst **50** [30 mol%]	yield [%][b] **85a**	yield [%][b] **86a**	yield [%][b,c] **84a**	ee [%][d] **84a**
1	CH_3CN	**50a**	60	26	80	85
2	DMSO	**50a**	67	33	85	91
3	DMF	**50a**	58	22	80	91
4	DMSO	**50g**	66	34	96	–90

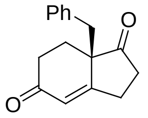
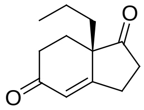
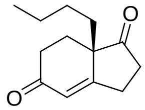
[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of freshly distilled methyl vinyl ketone **68a** in the presence of 30 mol% of Catalyst. [b] Yield refers to the column purified product. [c] Yield of **84a** is based on **85a**. [d] ee determined by HPLC analysis.

With an efficient amino acid-catalyzed asymmetric cascade RA protocol in hand, the scope of the proline-catalyzed cascade asymmetric RA reactions was investigated with various 2-alkylcyclopentane-1,3-diones **82** and methyl vinyl ketone **68a**. A series of 2-alkyl-cyclopentane-1,3-diones **82a–h′** were reacted with 3.0 equivalents of methyl vinyl ketone **68a** catalyzed by 30 mol% of L-proline at 25 °C in

DMSO for 6 days (Table 25). All expected bicyclic-alcohols of H–P ketone analogs **85a–h′** were obtained in good yields, which on hydrolysis with 1 N $HClO_4$ in DMSO at 90 °C for 0.5–1 h furnished the expected bicyclic-ketones **84a–h'** in good yields with 91–94% ee as shown in Table 25.

Table 25: Organocatalytic Asymmetric Synthesis of H-P Ketone Analogs **84**[a,b]



 **84a**[c] 57% yield 91% ee	 **84g'**[d] 50% yield 94% ee	 **84h'**[d] 50% yield 94% ee

[a] See Experimental Section. [b] Yield refers to the column purified product and ee determined by HPLC analysis. [c] Michael adduct **86a** were isolated in 33% yield. [d] Michael adducts **86g'** and **86h'** were isolated in 40-50% yields respectively.

5.2.3.3 Amino acid-catalyzed asymmetric double cascade one-pot Robinson annulations: After successful demonstration of the amino acid-catalyzed cascade asymmetric O–H and RA reactions, we decided to investigate the combination of these two cascade reactions in one pot. Reaction of three equivalents of benzaldehyde **46a** with cyclopentane-1,3-dione **78** and Hantzsch ester **15** under 5 mol% of L-proline in CH_2Cl_2 at 25 °C for 2.0 h furnished the expected 2-benzyl-cyclopentane-1,3-dione **82a** in good yield. Removing the solvent CH_2Cl_2 by vacuum pump and adding DMSO solvent, 30 mol% of L-proline **50a** and freshly distilled methyl vinyl ketone **68a** to the reaction mixture of cascade asymmetric O–H–RA furnished the expected bicyclic-alcohol of the H–P ketone analogue **85a** in 65% yield accompanied by Michael adduct **86a** in 35% yield as shown in Scheme 25.

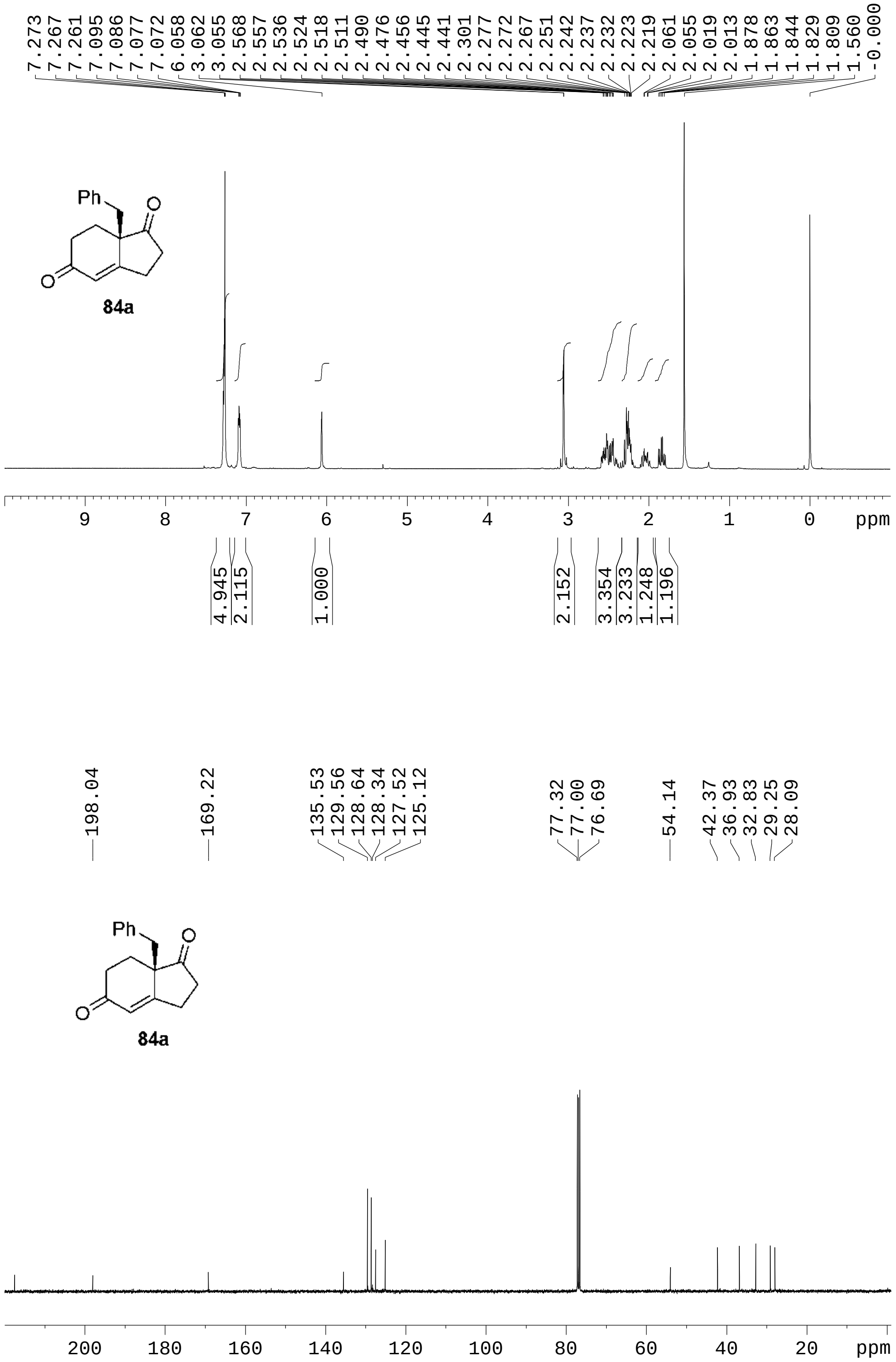
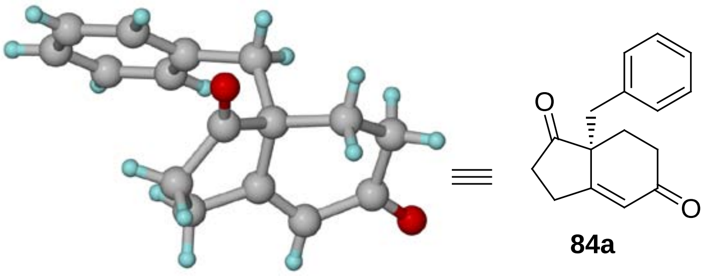


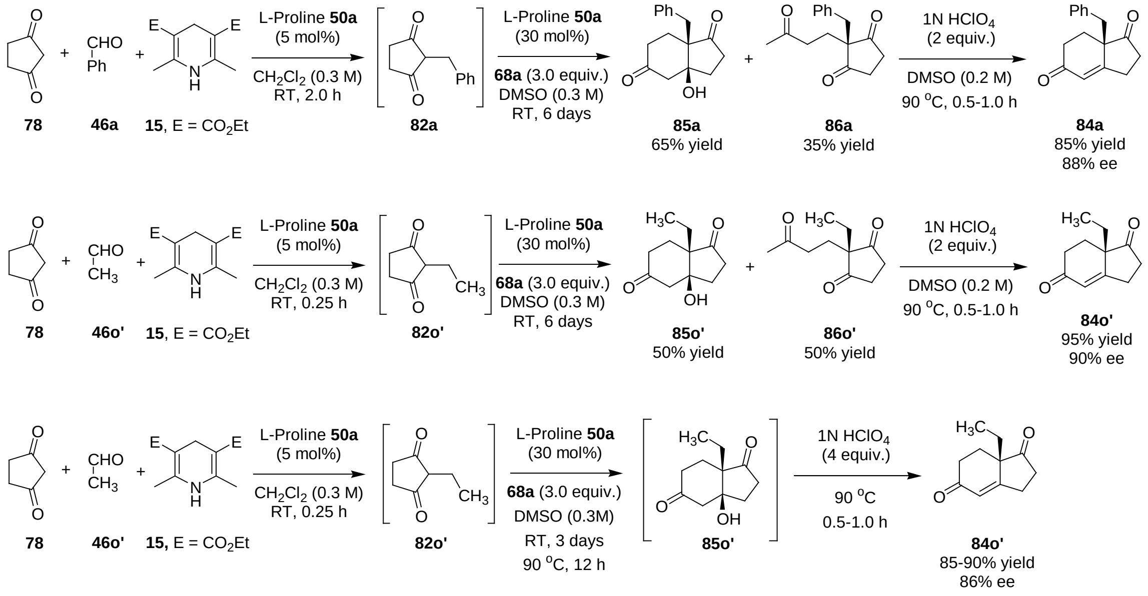
Figure-27: ^{1}H NMR and ^{13}C NMR Spectrum of product **84a**.



Scheme 24: Crystal structure of (+)-(*R*)-7*a*-benzyl-2,3,7,7*a*-tetrahydro-6*H*-indene-1,5-dione (**84a**).

Hydrolysis of one-pot bicyclic-alcohol **85a** with 1 N $HClO_4$ in DMSO at 90 °C for 1 h furnished the expected bicyclic-ketone (+)-**84a** in 85% yield with 88% ee as shown in Scheme 25. Interestingly, in L-proline-catalyzed sequential one pot double cascade asymmetric O–H–RA reactions, ee's were not effected by reaction by-product 2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester **53**. Successful combination of two cascade O–H and RA reactions under L-proline-catalysis was demonstrated by one more example as shown in Scheme 25.

Scheme 25: Direct Organocatalytic One-Pot Double Cascade Asymmetric Synthesis of H-P Ketone Analogs **84.**

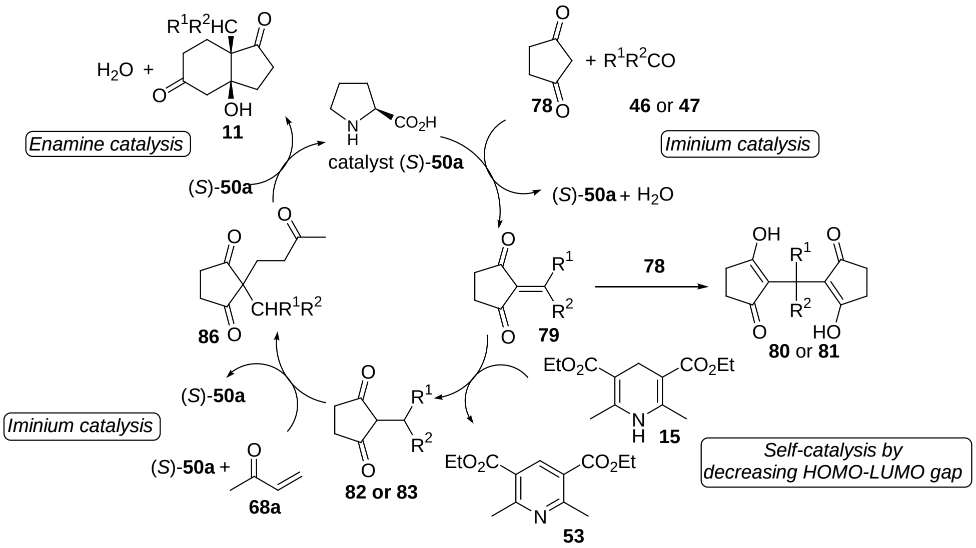


Even after 6 days at 25 °C, the double cascade asymmetric O–H–RA reaction of **78**, **46o′**, **15** and **68a** under **50a**-catalysis furnished the unreacted Michael adduct **86o′** in 50% yield (see Scheme 25). For the complete conversion of Michael adduct **46o′** into chiral bicyclic-alcohol **85o′** in the double cascade reaction process, we performed the second step at 25 ◦C for 72 h and at 90 °C for 12 h followed by hydrolysis with 1 N $HClO_4$, furnishing the only expected H–P ketone analogue **84o′** in 85–90% overall yield with 86% ee as shown in Scheme 25. Interestingly, there was only a 4% decrease in ee compared to the room temperature reaction and this one-pot double cascade synthetic strategy will have much impact on the asymmetric synthesis of functionalized small molecules.

5.2.4 Mechanistic insights

The most possible reaction mechanism for L-proline-catalyzed regio-, chemo- and enantio-selective synthesis of cascade products **82** and **84** through reaction of cyclopentane-1,3-dione **78**, aldehydes **46** and Hantzsch ester **15** is illustrated in Scheme 26. This catalytic sequential one-pot, double cascade is a four component reaction comprising a cyclopentane-1,3-dione **78**, aldehyde **46**, Hantzsch ester **15**, methyl vinyl ketone **68a** and a simple chiral amino acid **50a**, which is capable of catalyzing each step of this double cascade reaction.

Scheme 26: Proposed Catalytic Cycle for the Double Cascade Reactions

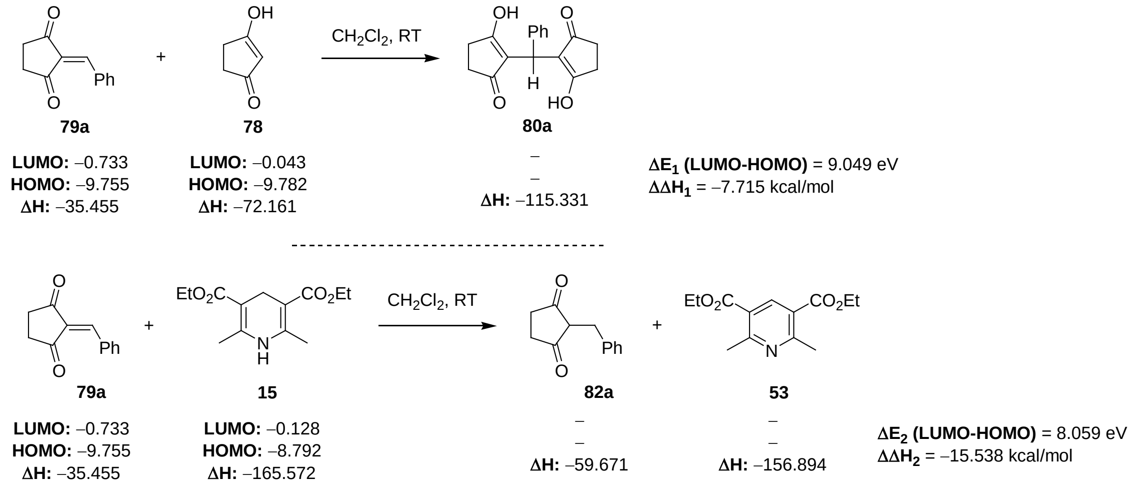


In the first step (Scheme 26), the catalyst (*S*)-**50a** activates component **46** by, most likely, iminium ion formation, which then selectively adds to the cyclopentane-1,3-dione **78** *via* a Mannich and retro-Mannich type reaction to generate active olefin **79**.[1c] The following second step is biomimetic hydrogenation of active olefin **79** by Hantzsch ester **15** to produce **82** through selfcatalysis by decreasing the HOMO–LUMO energy gap between **15** and **79** respectively.[1c-d,26d-e] In the subsequent third step, Michael addition of **82** to methyl vinyl ketone **68a** *via*, most likely, iminium ion activation leads to the formation of Michael adduct **86**.[57] In the fourth step, (*S*)-**50a** catalyzed the asymmetric intra-molecular aldol condensation of **86** *via* enamine catalysis[57] and returns the catalyst (*S*)-**50a** for further cycles and releases the desired bicyclic-alcohol of H–P ketone analogue **85**.

Considering the recent applications of amino acid or amine catalyzed olefination reactions[1a-d,26a-e] and based on our recent discovery of reductive alkylation of CH-acids,[1a-d,26a-e] we proposed that the most likely reaction course for the amino acid-catalyzed direct addition of cyclopentane-1,3-dione **78** to aldehydes **46** is the one outlined through iminium-catalysis as shown in Scheme 25. Formation of active olefins **79** through proline-catalysis by means of Mannich and retro-Mannich reactions supports our hypothesis that aldol products did not form in these reactions. This hypothesis is also supported by our recent discovery of organo-click reactions[1d] and the mechanistic investigation of pyrrolidine-catalyzed enal formation through aldehyde self-condensation reported by Saito *et al.*[59] Highly chemoselective formation of cascade hydrogenated products **82** over bis-adduct **80** formation from reactants **78**, **15** and **79** can be explained by using HOMO–LUMO energy gaps and enthalpy differences as shown in Scheme 26. We have chosen **78**, **15** and **5a** for the model theoretical studies.**[68]** Self-catalyzed Michael reaction of cyclopentane-1,3-dione **78** with *in situ* generated active olefin **79a** furnishes the bis-adduct **80a**. For the same length of time, self-catalysis furnishes the hydrogenated product **82a** and pyridine **53** from hydride transfer reaction of Hantzsch ester **15** with *in situ* generated active olefin **79a**. Electronically and thermodynamically, the self-catalyzed hydride transfer reaction is more favorable than bis-adduct formation as revealed in Scheme 27.

In a first step to probe the competition between two self-catalyzed reactions between **78**, **15** and **79a**, we analyzed the energies of the HOMO and the LUMO for each compound involved in the reactions (Scheme 27). The calculated energy gaps between the LUMO of the active olefin **79a** and the HOMO of **78** are greater than the energy gaps between the LUMO of **79a** and the HOMO of the Hantzsch ester **15**. This result suggests that a self-catalyzed hydride transfer reaction proceeds faster than a Michael reaction of cyclopentane-1,3-dione **78** with active olefin **79a**, in agreement with the experimental results. Moreover, the energy gaps between the LUMO of **79a** and the HOMO of **78**/**15** agree with the experimental reactivity order, indicating that the hydride transfer is the rate-determining step and is a dynamically fast reaction compared to the Michael reaction.

Scheme 27: HOMO/LUMO Energy Gaps and Enthalpy Differences for Self-Catalyzed Hydrogenation and Bis-Adduct Formation Reactions



In a second step to probe the competition between two self-catalyzed reactions between **78**, **15** and **79a**, we analyzed the net heat of formations (Δ*ΔH*) of the two reactions (Scheme 27). The calculated heat of formation for the hydride transfer reaction is 7.823 kcal/mol more than the bis-adduct formation reaction as revealed in

Scheme 27. This result also strongly suggests that a self-catalyzed hydride transfer reaction is thermodynamically a more favorable reaction than bis-adduct formation.

5.3 Conclusions

In summary, we have developed the metal-free double cascade synthesis of highly functionalized 2-alkyl-cyclopentane-1,3-diones **82** and **83**, chiral H–P ketone analogues **84** and 2-alkyl-3-methoxy-cyclopent-2-enones **87** from simple starting materials *via* cascade O–H, RA, O–H–RA and O–H–E reactions under amino acid-catalysis in one pot. For the first time, we have reported the reductive alkylation of highly reactive cyclopentane-1,3-dione **78** with aldehydes **46**/ketones **47** and Hantzsch ester **15** under amino acid-catalysis. The reductive alkylation strategy, or cascade O–H reaction, proceeds in good yields with high chemo- and regio-selectivity using only 5 mol% of amino acid as the catalyst. In this article, we have demonstrated the concept of self-catalysis by decreasing the HOMO–LUMO energy gap between *in situ* generated olefins **79** and Hantzsch ester **15**. Furthermore, we have demonstrated the synthetic application of reductive alkylation products **82** and **83**.

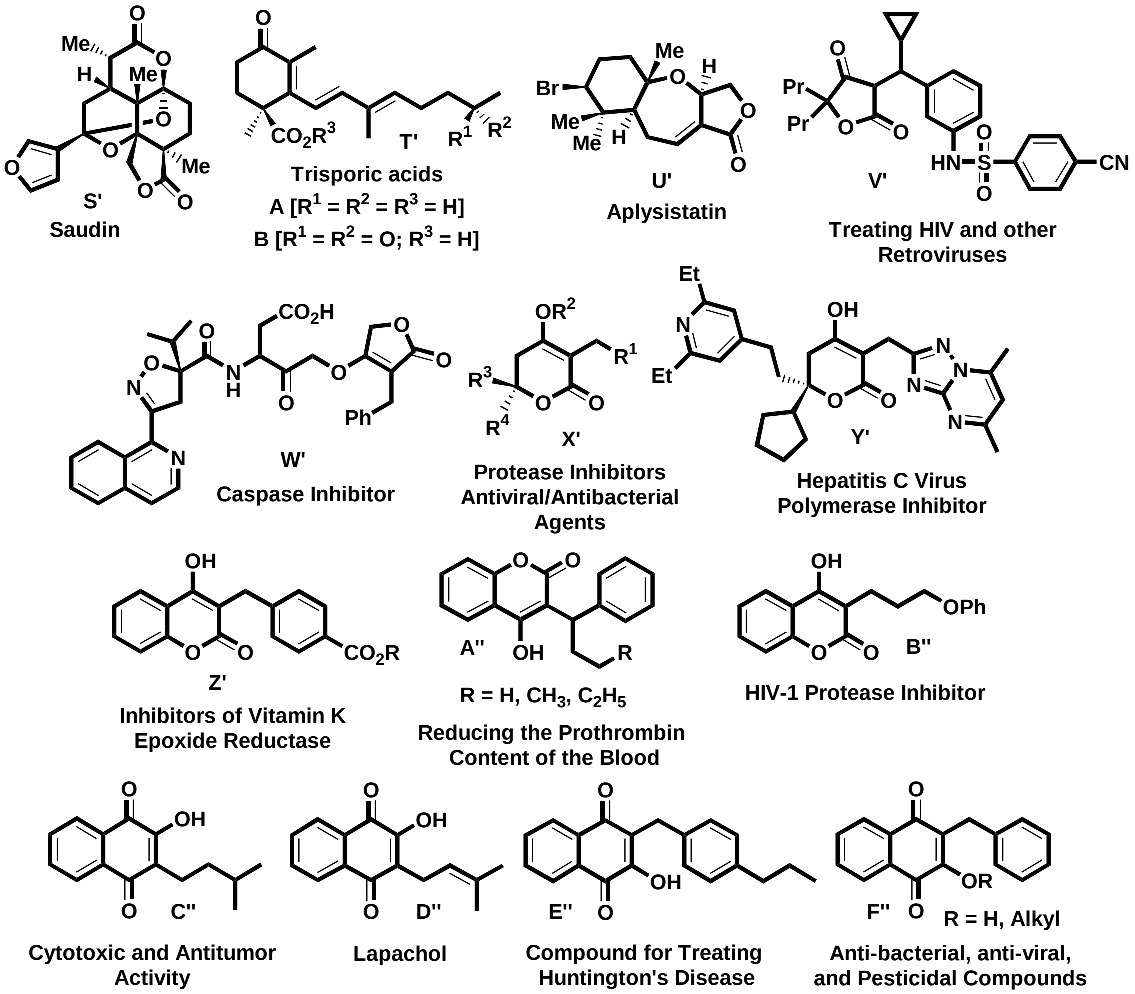
6. Direct Catalytic Asymmetric Synthesis of Highly Functionalized Tetronic acids/Tetrahydro-isobenzofuran-1,5-diones *via* Combination of Cascade Three-component Reductive Alkylations and Michael-aldol reactions

6.1 Introduction

Functionalized tetronic acids, 5,6-dihydro-pyran-2-ones, 4-hydroxy-chromen-2-ones and tetrahydro-isobenzofuran-1,5-diones are an important class of heterocycles, which display very large spectrum of biological activities and are widely used as synthetic intermediates, drug intermediates/ingredients in natural product synthesis and also in pharmaceuticals (see Chart 5).[69] As such, the development of new and more general catalytic asymmetric methods for their preparation is of significant interest.[70] Interestingly, to the best of our knowledge there is no report on the direct catalytic asymmetric method for the synthesis of functionalized tetrahydro-isobenzofuran-1,5-diones, which can serve as good intermediates for the total synthesis of natural and non-natural products as demonstrated in this work. Herein, first time we reported the organocatalytic cascade approach to the asymmetric synthesis of functionalized tetrahydro-isobenzofuran-1,5-diones via "sequential combination of cascade three-component reductive alkylation (TCRA) and Michael-aldol (M-A) reactions".[27]

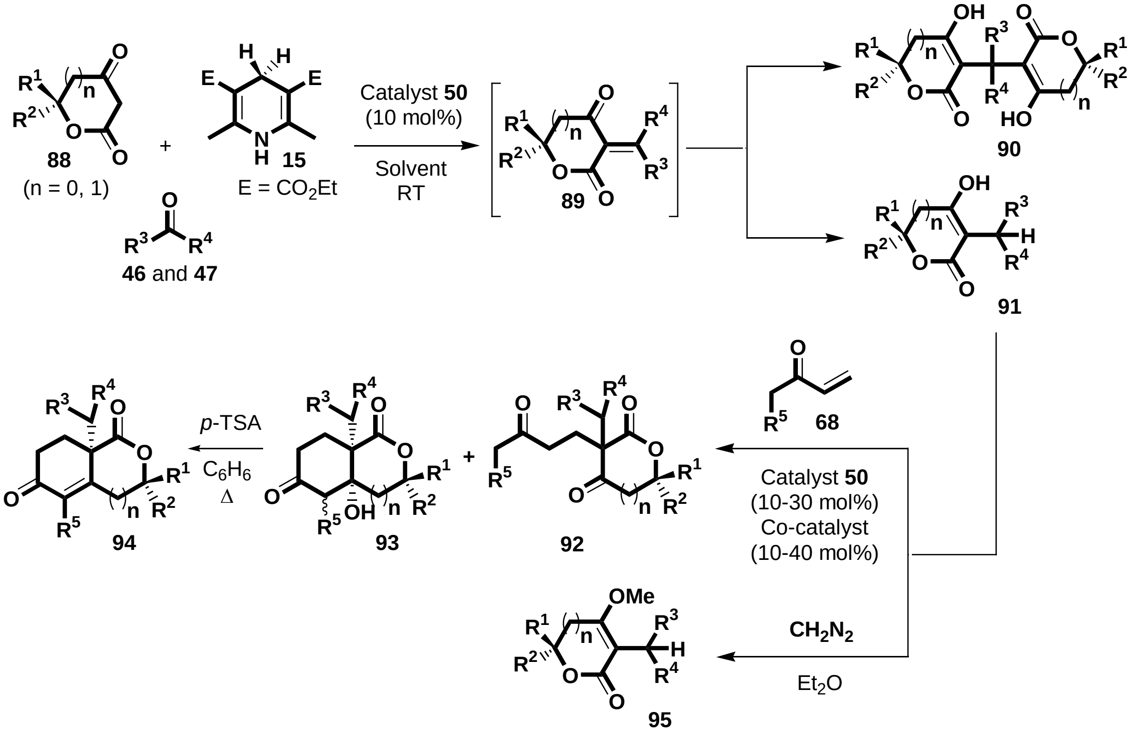
Recently Barbas, List and co-workers rediscovered the novel technology of amino acid-catalyzed intra-/inter-molecular aldol reactions of ketones/aldehydes with variety of carbonyls to provide a general route to a variety of aldol products in good yields with high enantioselectivity, which is known as Barbas-List aldol (BLA) reaction.[39,44,57] The advent of amino acid-catalyzed aldol reaction technology providing a high inspiration to scientific community to develop cellular type cascade reactions based on the in situ generated enamine/iminium chemistry.[39,44,57]

Chart 5: Natural and non-natural products library containing cascade TCRA and M-A compounds.



However, the amino acid-catalyzed intramolecular aldol reaction of diketo-lactones **92** is not known and resulting aldol products **93** and **94** are having a wide range of applications in natural products and pharmaceutical chemistry (see Chart 5 and Scheme 28) and also there is no direct asymmetric methodology available to prepare them by using the classical reaction strategies. Herein, we have reported a metal-free and novel technology for the asymmetric synthesis of highly substituted tetrahydro-isobenzofuran-1,5-diones **93/94** by using the two-step sequential combination of organocatalytic cascade TCRA and M-A reactions from commercially available cyclic β-keto-lactones **88**, aldehydes **46**/ketones **47**, organic hydride **15**, amines/amino acid **50** and alkyl vinyl ketones **68** (Scheme 28).

Scheme 28: Direct asymmetric cascade TCRA and M-A reactions.

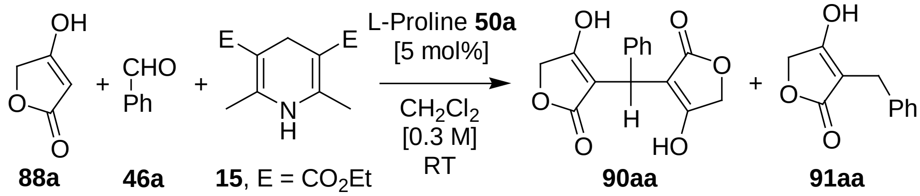


Over the last few years, we have been interested in an amino acid-catalyzed cascade TCRA reactions of CH-acids, aldehydes/ketones and organic hydride for the generation of reductive alkylation products via 1 x C-C/2 x C-H bonds formation in one-pot.[1,26,71] During our investigation for new reactive species for such TCRA processes and also for synthetic applications, we decided to explore the potential ability of the cyclic β-keto-lactones **88** as CH-acids to participate in an amino acid-catalyzed TCRA reaction with aldehydes **46**/ketones **47** and organic hydride **15** (see Scheme 28). Herein, we report our findings regarding these new TCRA reactions and their synthetic applications.

6.2 Results and discussion

***6.2.1 Amino acid-catalyzed TCRA reaction with tetronic acid: reaction optimization**:* We observed that the reaction of tetronic acid **88a** with in situ generated iminium ion from benzaldehyde **46a** under proline-catalysis would lead to bis-adduct **90aa** in 75% yield without olefin **89aa** formation (Table 26, entry 1) [In all compounds denoted **89xy**, **90xy**, **91xy**, **92xy**, **93xyz**, **94xyz** and **95xy**, **x** is incorporated from reactant CH acids **88**, **y** is incorporate from reactants aldehydes **46** and ketones **47** and **z** is incorporated from alkyl vinyl ketone]. However, when we used one equiv. of organic hydride **15** in cascade TCRA reaction of **88a** and **46a**, bis-adduct **90aa** was not detected and instead expected product **91aa** was obtained with 80% yield under the standard reaction conditions (Table 26, entry 2). The optimum conditions involved the use of 5 mol% catalyst **50a** and two equiv. of benzaldehyde **46a** in cascade TCRA reaction of **88a**, **46a** and **15** in CH_2Cl_2 at 25 °C for 5 h to furnish

Table 26: Optimization for the cascade TCRA reaction of **88a**, **46a** and **15**[a]



Entry	Aldehyde **46a** [equiv.]	H. ester **15** [equiv.]	Time [h]	Products yield [%][b]	
				90aa	**91aa**
1	2.0	–	24	75	–
2	1.0	1.0	24	–	80
3	**2.0**	**1.0**	**5**	–	**90**
4	3.0	1.0	2	–	90

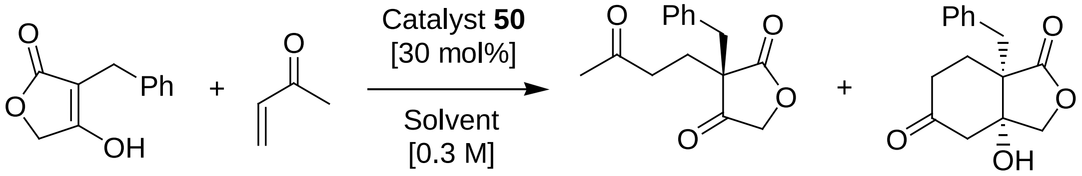
[a] Reactions were carried out in ethanol (0.3 M) with 2.0 to 3.0 equiv. of **46a** and 1.0 equiv. of **15** relative to the **88a** (0.3 mmol) in the presence of 5 mol% of catalyst **50a**. [b] Yield refers to the column purified product.

91aa in very good yield (Table 26, entry 3). TCRA product **91aa** is important intermediate for the total synthesis of caspase inhibitor (**W′**) and which is emphasizing the value of this TCRA approach to the pharmaceuticals.[69h] This interesting result represents a novel methodology for the preparation of 3-alkyl-tetronic acids **91** and a new reactivity for amino acid catalysis. The structure and regiochemistry of **91aa** was confirmed by ^{1}H NMR,^{13}C NMR [for example see Fig. 28] and mass analysis.

6.2.2 Asymmetric cascade M-A reaction with 3-benzyl-tetronic acid: reaction optimization

After successful synthesis of 3-benzyl-tetronic acid **91aa**, we initiated our preliminary studies of the asymmetric cascade M-A reactions by screening a number

Table 27: Optimization for the cascade M-A reaction of **91aa** and **68a**[a]



91aa **68a** **92aaa** **93aaa**

Entry	Catalyst **50** [30 mol%]	Solvent [0.3 M]	Time [h]	Products yield [%][b]		Products ee [%][c]	
				92aaa	**93aaa**	**92aaa**	**93aaa**
1	L-proline **50a**	DMSO	48	10	70	–23	–52 (–86)
2	D-proline **50g**	DMSO	48	10	50	21	53 (92)
3[d]	**Q-NH$_2$/TCA 50a'**	**THF**	**8**	**60**	**40**	**8**	**55 (92)**

[a] Reactions were carried out in solvent (0.3 M) with 3 equiv. of **68a** relative to the **91aa** (0.5 mmol) in the presence of 30-mol% of catalyst **50**. [b] Yield refers to the column-purified product. [c] ee determined by CSP HPLC analysis and values in parenthesis obtained from one quick crystallization of **93aaa** from *i*-PrOH at 25 °C. [d] Reactions were carried out in solvent (0.1 M) with 3 equiv. of **68a** relative to the **91aa** (0.5 mmol) in the presence of 10 mol% of **50a'** and 40 mol% of co-catalyst TCA.

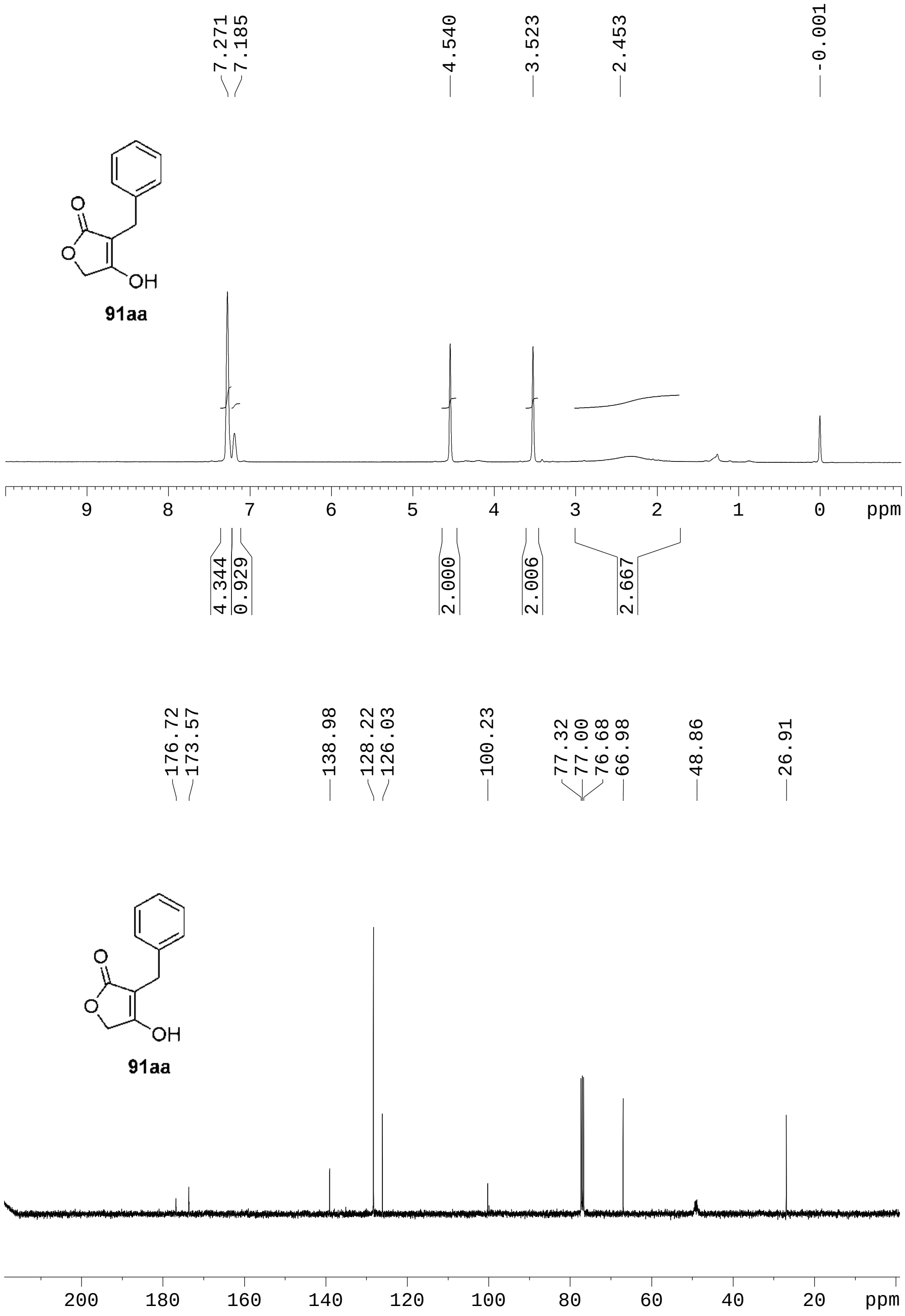


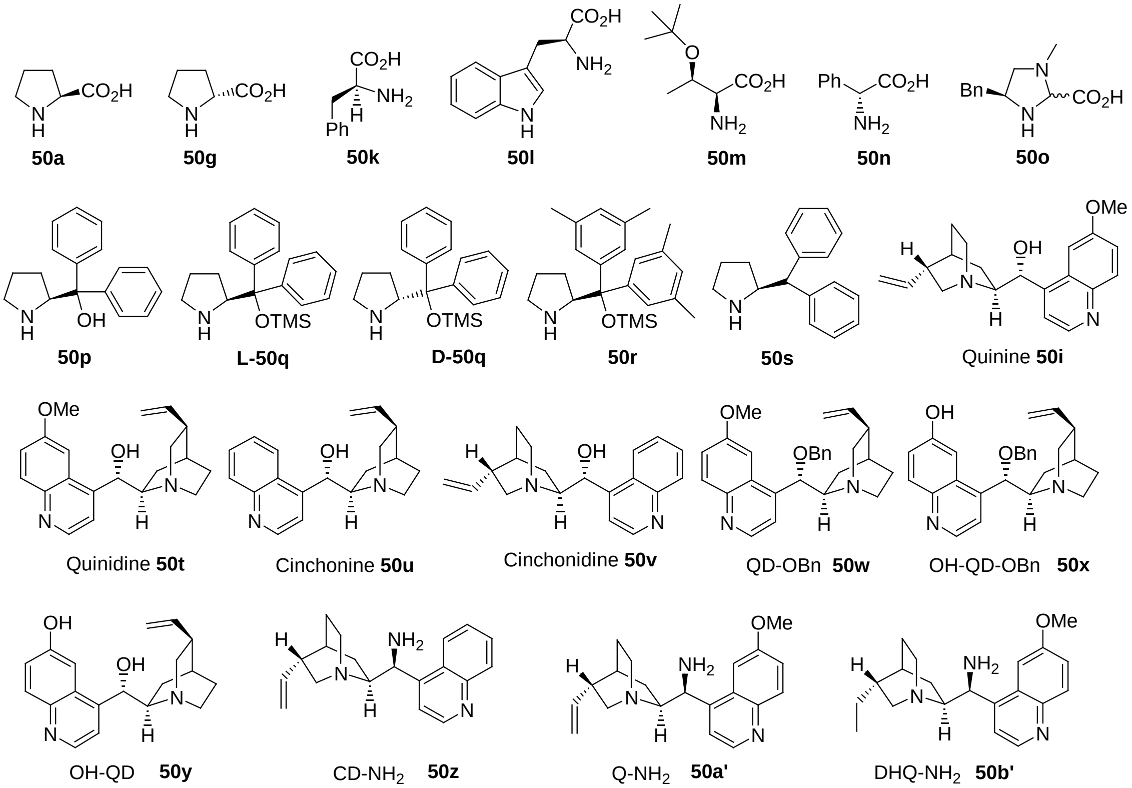
Figure-28: ^{1}H NMR and ^{13}C NMR Spectrum of product **91aa**.

of known and novel organocatalysts for the Michael-aldolization of **91aa** with 3 equiv. of methyl vinyl ketone **68a** and some representative results are shown in Table 27. Interestingly, cascade M-A reaction of **91aa** with 3 equiv. of methyl vinyl ketone **68a** in DMSO under 30 mol% of L-proline **50a**-catalysis furnished the Michael product (+)-**92aaa** in 10% yield with only 23% ee and cascade M-A product (–)-**93aaa** in 70% yield with 52% ee, which is enriched to 86% ee with 60-70% yield after one quick crystallization from isopropanol at 25 °C (Table 27, entry 1). Same reaction in DMSO under 30 mol% of D-proline **50g**-catalysis furnished the opposite enantiomer of Michael product (–)-**92aaa** in 10% yield with only 21% ee and cascade M-A product (+)-**93aaa** in 50% yield with 53% ee, which is enriched to 92% ee with 60-70% yield after one quick crystallization from isopropanol at 25 °C (Table 27, entry 2).

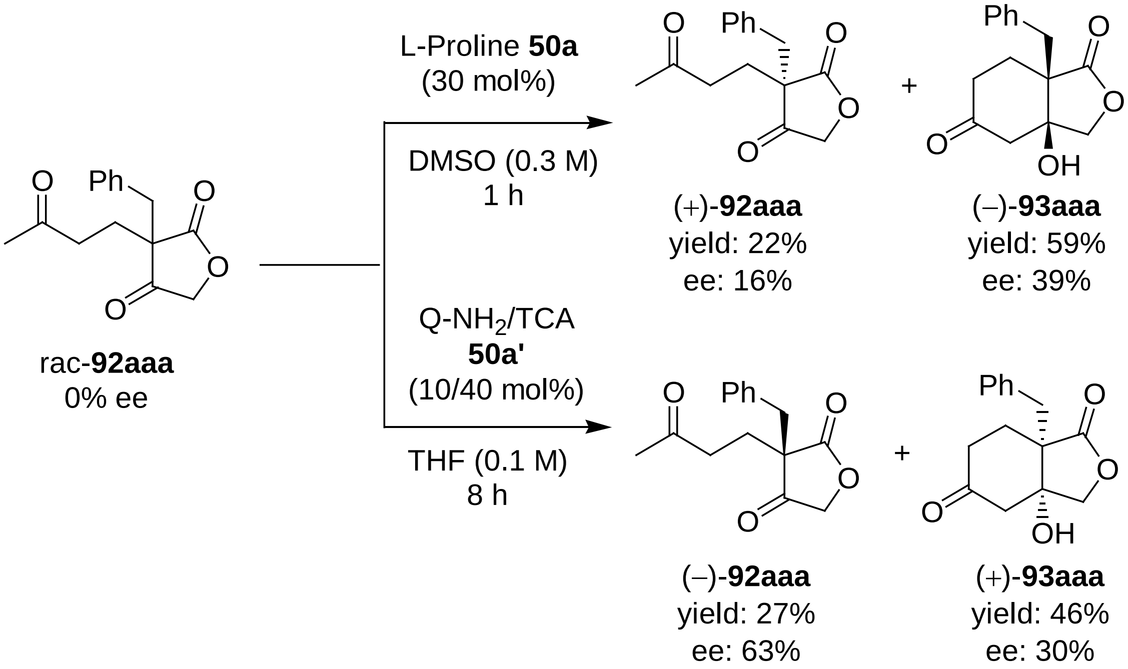
To further improvement of ee/yield of cascade products **92aaa**/**93aaa**, we also tested number of primary-/secondary-amino acids, chiral pyrrolidines and *tert*-amines based on cinchona alkaloids like L-phenylalanine **50k**, L-tryptophan **50l**, O^{t}Bu-L-threonine **50m**, D-amino-phenyl-acetic acid **50n**, 4-benzyl-1-methyl-imidazolidine-2-carboxylic acid **50o**, L-DPP **50p**, L-DPPOTMS **50q**, D-DPPOTMS **50q**, L-(3,5-Me$_2$)$_2$DPPOTMS **50r**, L-2-benzhydryl-pyrrolidine **50s**, quinine (Q) **50i**, quinidine (QD) **50t**, cinchonine (C) **50u**, cinchonidine (CD) **50v**, QD-OBn **50w**, OH-QD-OBn **50x**, OH-QD **50y**, CD-NH$_2$ **50z**, Q-NH$_2$ **50a'** and DHQ-NH$_2$ **50b'** as catalysts and TCA, TFA or 3,5-DNBA as co-catalysts for the cascade asymmetric M-A reaction of **91aa** with **68a** in different solvents as demonstrated in Chart 6. Among these catalysts **50k-b′** tested for cascade asymmetric M-A reaction, 10-mol% of 9-amino-9-deoxyepiquinine (Q-NH$_2$) **50a′** with 40-mol% of trichloroacetic acid (TCA) showed better results compared to other catalysts Table 27, entry 3[72] [For complete optimization of cascade M-A reaction see Annexure-I, Tables A1-A4]. Cascade M-A reaction of **91aa** and **68a** in THF under Q-NH$_2$/TCA **50a′**-catalysis furnished the Michael product (–)-**92aaa** in 60% yield with only 8% ee and cascade M-A product (+)-**93aaa** in 40% yield with 55% ee, which is enriched to

92% ee with 60-70% yield after one quick crystallization from isopropanol at 25 °C (Table 27, entry 3). We envisioned the optimized condition to be 25 °C in DMSO under 30 mol% L-proline **50a**-catalysis or at 25 °C in THF under 10-mol% Q-NH_2/TCA **50a′**-catalysis to furnish both enantiomers of highly substituted M-A product (–)-**93aaa** and (+)-**93aaa** in 70/40% yield with 86-92% ee respectively (Table 27). The absolute configuration of products (–)-/(+)-**93aaa** prepared under L-/D-proline-catalysis was established by comparison with the proline-catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction.[39,44,57]

Chart 6: Library of catalysts screened for the cascade asymmetric M-A reaction.



6.2.3 Observation of kinetic resolution in the asymmetric cascade Michael-aldol reactions: Next, we investigated the possibility of kinetic resolution in the amino acid **50a** and **50g** or amine/acid **50a′** catalyzed cascade asymmetric M-A reaction of **91aa** and **68a** at the optimized conditions, because ee of Michael adduct is not similar as compared to aldol product from cascade M-A reactions. Treatment of racemic (±)-**92aaa** with 30 mol% of (*S*)-**50a** in DMSO at 25 °C for 1 h furnished (–)-**93aaa** in 59% yield with 39% ee. This product was accompanied by recovered (+)-**92aaa** in 22% yield with 16% ee (see Scheme 29). In a similar manner, treatment of racemic (±)-**92aaa** with 10/40 mol% of Q-NH_2/TCA **50a′** in THF at 25 °C for 8 h resulted in the formation of (+)-**93aaa** in 46% yield with 30% ee and also recovered (–)-**92aaa** in 27% yield with 63% ee (see Scheme 29). Overall notable kinetic resolution was achieved by means of an amino acid **50a** or amine/acid **50a′**-catalysis in cascade M-A reactions at the ambient conditions. The products structure confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig 29-30] and mass analysis.



Scheme 29: Observation of kinetic resolution in the cascade M-A reaction.

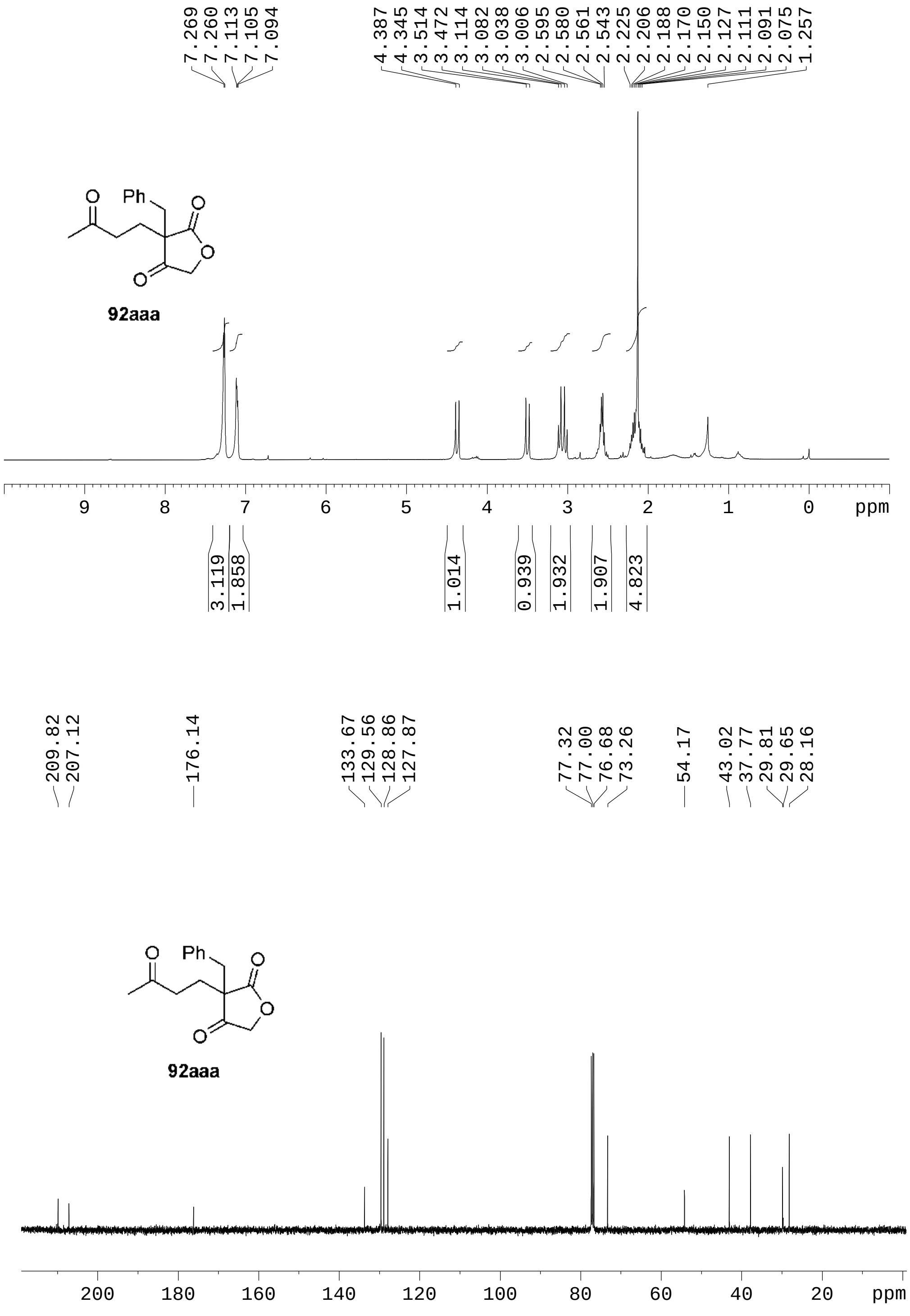


Figure-29: ^{1}H NMR and ^{13}C NMR Spectrum of product **92aaa**.

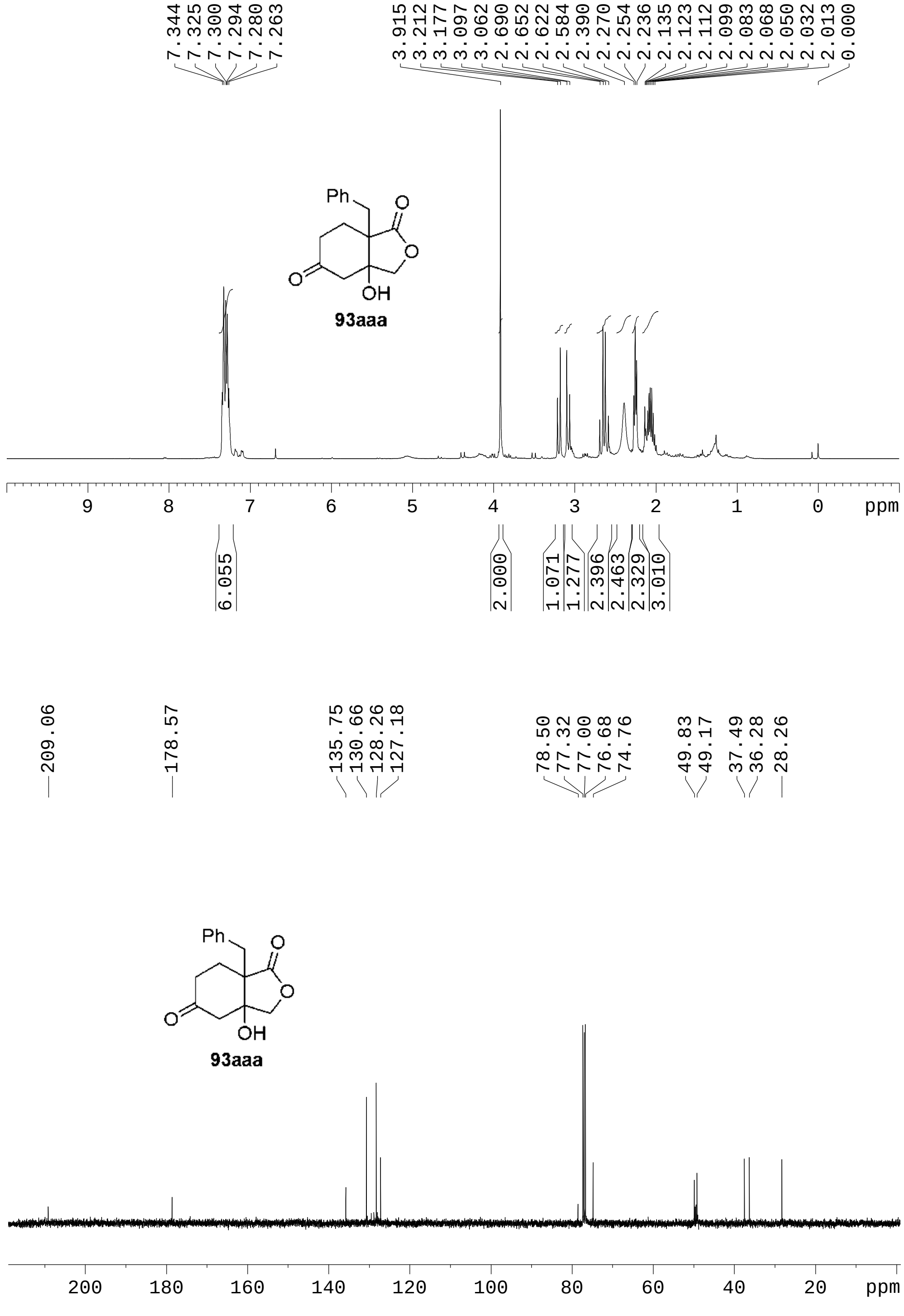


Figure-30: ^{1}H NMR and ^{13}C NMR Spectrum of product **93aaa**.

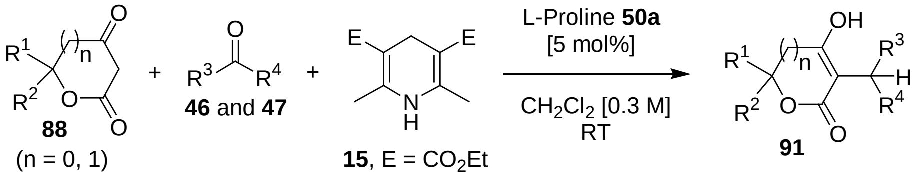
The pronounced kinetic resolution observed in the aldol reaction inspired us to study the enantioselective cascade Michael-aldol annulation reaction with variety of 3-alkyl-tetronic acids.

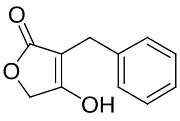
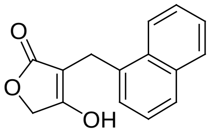
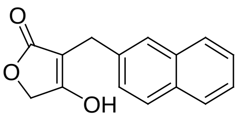
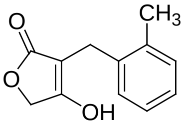
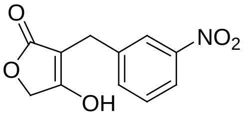
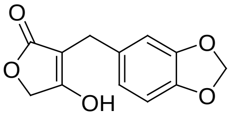
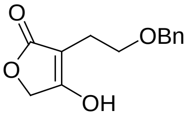
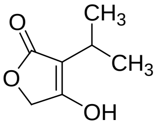
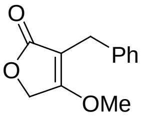
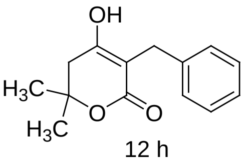
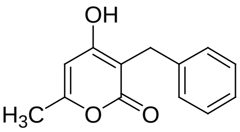
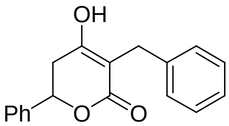
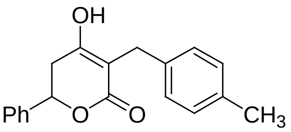
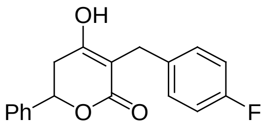
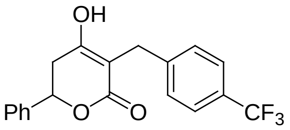
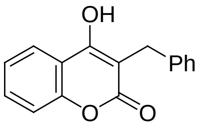
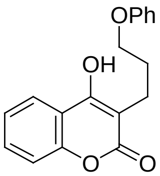
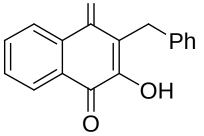
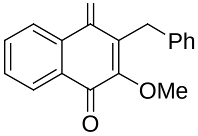
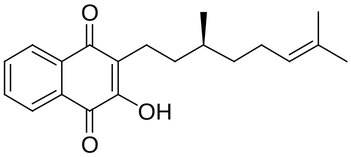
6.2.4 Diversity-oriented high-yielding synthesis of TCRA products 91aa-91fs′

With the optimized reaction conditions in hand, the scope of the amino acid- and amine/acid-catalyzed cascade TCRA and asymmetric M-A reactions was investigated. A series of functionalized cyclic β-keto-lactones **88a-f** were reacted with 3 equiv. of aldehydes **46a-x′**/ketone **47p** and 1 equiv. of organic hydride **15** catalyzed by 5 mol% of L-proline **50a** at 25 °C in CH_2Cl_2 (Table 28). TCRA reaction of tetronic acid **88a** and **15** with neutral, electron-withdrawing and electron-donating substituted benzaldehydes **46a-i** were generated expected products **91aa-ai** with excellent yields (Table 28).

Interestingly, TCRA reaction of benzyloxy acetaldehyde **46v′** with **88a** and **15** under **50a**-catalysis furnished the **91av′** as major product with 90% yield (Table 28). Fascinatingly, reaction of tetronic acid **88a** with acetone **47p** under **50a**-catalysis furnished the **91ap** as major single product (Table 28). Interestingly, TCRA reaction of substituted 4-hydroxy-pyran-2-ones **88b-e** with **46a-x′** and **15** under **50a**-catalysis furnished the expected 3-alkyl-4-hydroxy-pyran-2-ones **91** with very good yields (Table 28). In continuation, we also tested 2-hydroxy-[1,4]naphthoquinone **88f** as CH-acid source in TCRA reactions. Reaction of **88f** with **46a**/(*S*)-**46s**′ and **15** under **50a**-catalysis furnished the expected 3-alkyl-2-hydroxy-[1,4]naphthoquinones **91** with good yields as shown in Table 28. To test the reactivity of enolic OH in cascade TCRA products, we treated TCRA product **91aa** with 15 equiv. of ethereal diazomethane at 25 °C for 0.5-1.0 h to furnish the *O*-methylated product **95aa** in good yields through self-catalysis as shown in Table 28. Generality of the self-catalyzed chemoselective *O*-methylation was further confirmed by one more example using **91fa** to furnish the expected **95af** in 87% yield.

Table 28: High-yielding synthesis of cascade TCRA products **91**[a]



 3 h 90% [**91aa**]	 24 h 85% [**91ab**]	 3 h 90% [**91ac**]	 24 h 85% [**91au'**]
 17 h 70% [**91ao**]	 7 h 60% [**91ai**]	 0.5 h 90% [**91av'**]	 1 h 95% [**91ap**][b]
 1 h 50% [**95aa**][c]	 12 h 90% [**91ba**]	 2 h 90% [**91ca**]	 4 h 80% [**91da**]
 1 h 75% [**91de**]	 24 h 75% [**91dv**]	 12 h 90% [**91dw'**]	 2 h 90% [**91ea**]
 3 h 70% [**91ex'**]	 9 h 75% [**91fa**]	 1 h 87% [**95fa**][c]	 3 h 90% [**(*S*)-91fs'**]

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[a] Reactions were carried out in CH_2Cl_2 (0.3 M) with 3 equiv. of **46** or **47** relative to the **88** and **15** (0.5 mmol) in the presence of 5 mol% of catalyst **50a**. Yield refers to the column-purified product. [b] Acetone **47p** used as solvent and reagent. [c] TCRA compound **91** were reacted with 15 equiv. of ethereal diazomethane and stirred at 25 °C for 0.5-1 h.

Figure-31: ^{1}H NMR and ^{13}C NMR Spectrum of product **91ba**.

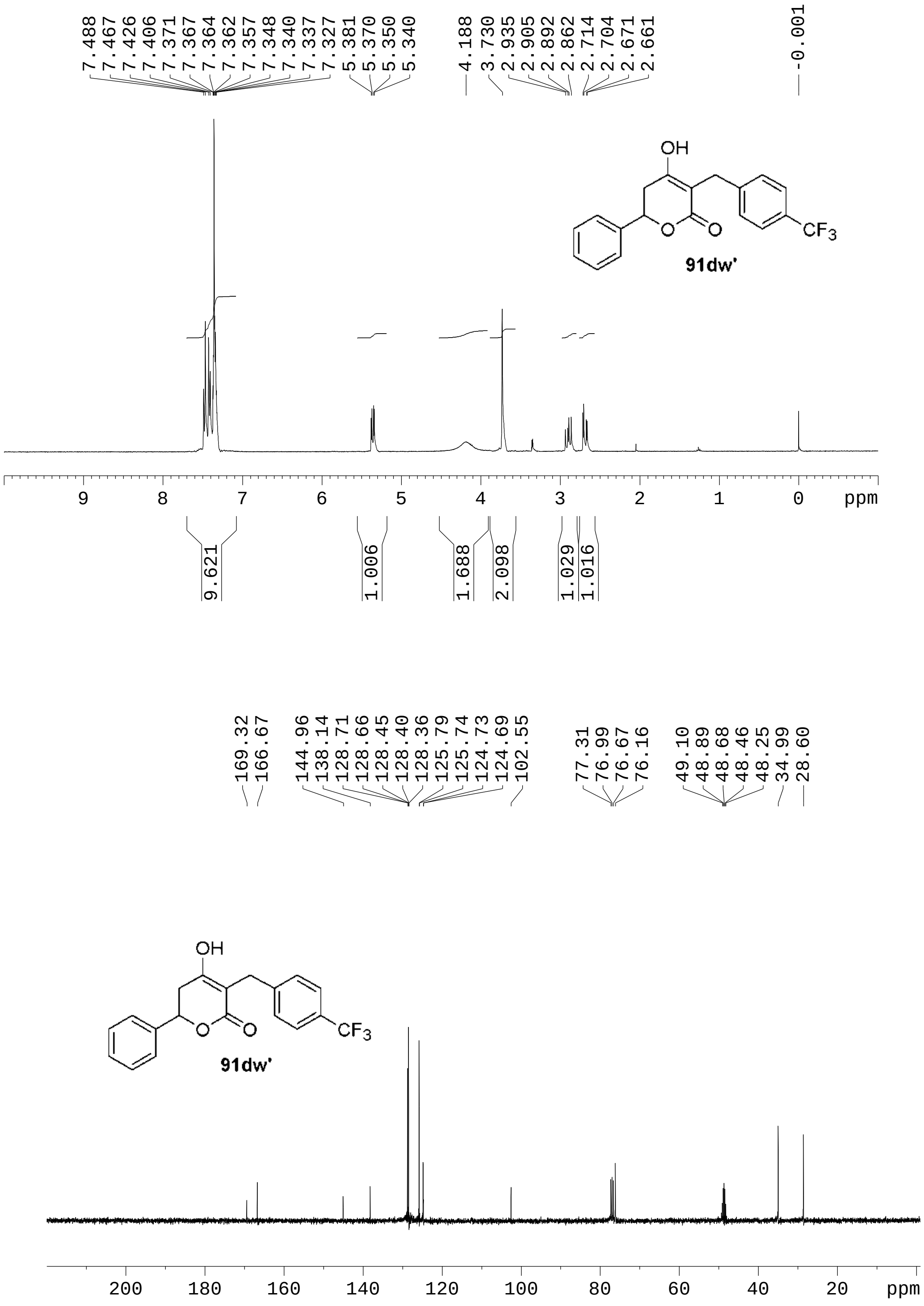


Figure-32: ^{1}H NMR and ^{13}C NMR Spectrum of product **91dw′**.

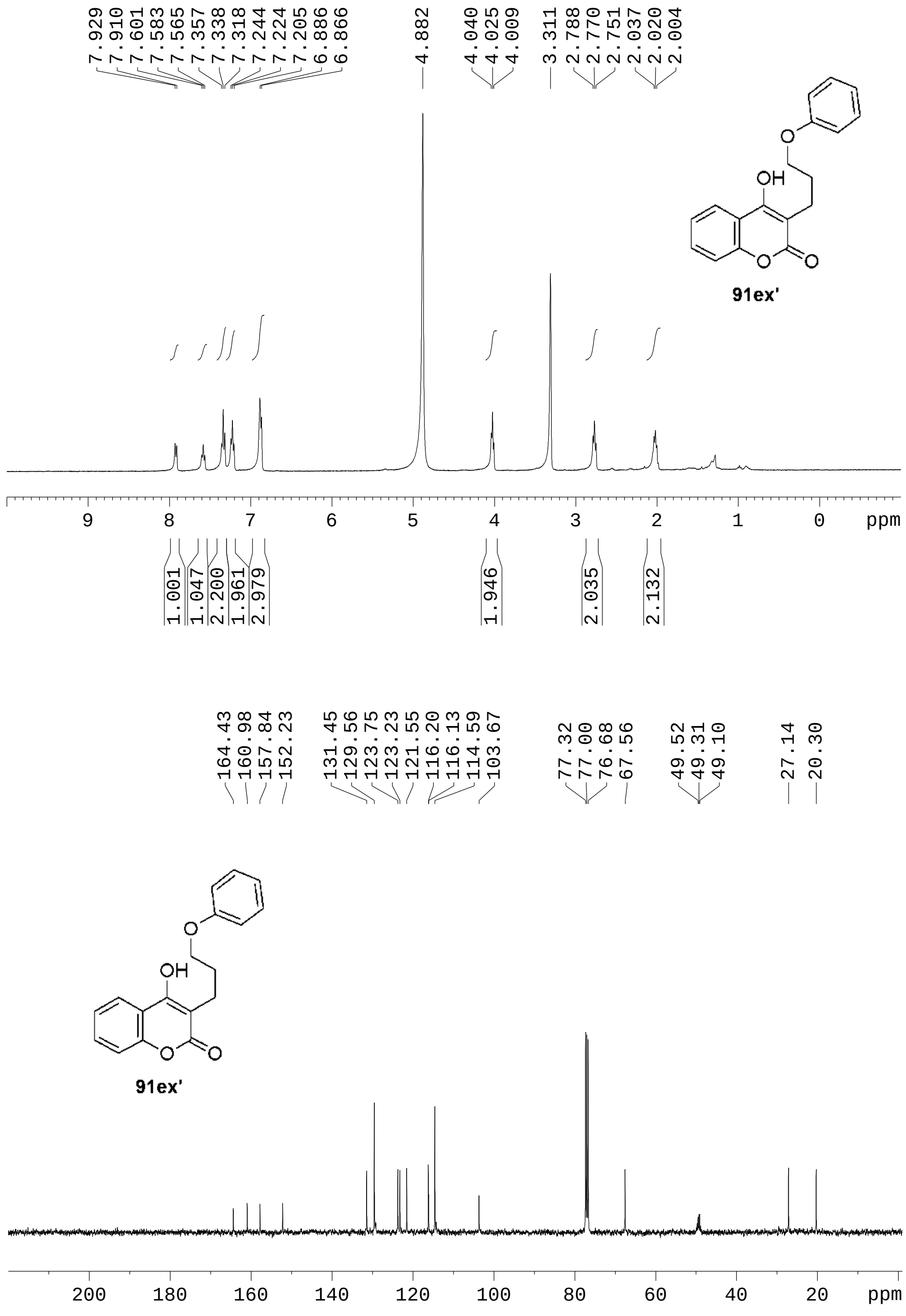


Figure-33: ^{1}H NMR and ^{13}C NMR Spectrum of product **91ex′**.

Figure-34: ^{1}H NMR and ^{13}C NMR Spectrum of product **95fa**.

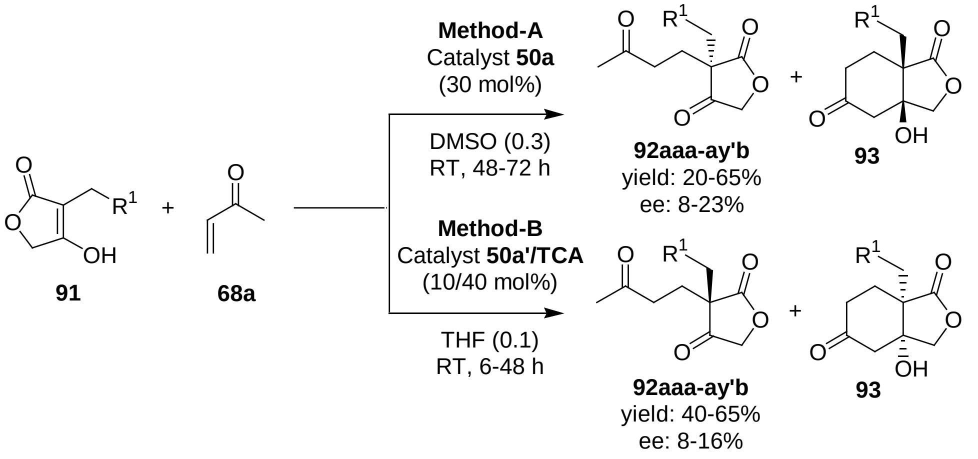
The results in Table 28 demonstrate the broad scope of this cascade TCRA methodology covering a structurally diverse group of cyclic β-keto-lactones **88a-f**, aldehydes **46a-s′** and ketone **47p** with many of the yields obtained being very good, or indeed better, than previously published two-step alkylation reactions.[70] TCRA product **91aa** and analogues **91ab-ap** are important compounds for the treating HIV and other retroviruses (**V′**),[69g] and also for the synthesis of caspase inhibitor (**W′**)[69h] and TCRA products **91ba-dw′** are directly useful compounds as HIV-1 and HIV-2 protease inhibitors, antiviral/antibacterial agents (**X′**),[69i-j] and hepatitis C virus polymerase inhibitor (**Y′**).[69k] TCRA products **91ea/ex′** and analogues are useful as inhibitors of vitamin K epoxide reductase (**Z′**),[69l] reducing the prothrombin content of the blood (**I**)[69m] and HIV-1 protease inhibitor (**B″**).[69n] Products **91fa**, **(*S*)-91fs′** and **95fa** are useful compounds as treating huntington's disease (**E″**),[69o] anti-bacterial, anti-viral, and pesticidal compounds (**F″**)[69p] emphasizing the value of this novel TCRA approach to the pharmaceuticals and agrochemicals. The products structure was confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 31-34] and mass analysis

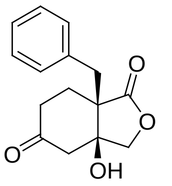
6.2.5 Applications of TCRA products

6.2.5.1 Diversity-oriented asymmetric synthesis of cascade M-A products 93aaa-93ay'a: With natural products synthesis and pharmaceutical applications in mind, we further extended the utilization of TCRA products in the asymmetric synthesis of functionalized tetrahydro-isobenzofuran-1,5-diones **93**/**94** via cascade M-A reactions of **91aa-ay′** and **68a-b** under **50a**- or **50a′**-catalysis in one-pot as shown in Table 29. All expected chiral tetrahydro-isobenzofuran-1,5-diones **93**/**94** were furnished in good yields with good to moderate ee’s from the reaction of **91** with **68** under **50a** or **50a′**-catalysis (see Table 29). Interestingly, Q-NH$_2$/TCA **50a′**-catalyzed M-A reaction of 4-hydroxy-3-naphthalen-1-ylmethyl-5*H*-furan-2-one **91ab** with 3 equiv. of freshly distilled methyl vinyl ketone **68a** in THF furnished the expected Michael-Aldol product (+)-**93aba** in 40% yield with 80% ee and which is accompanying with Michael adduct

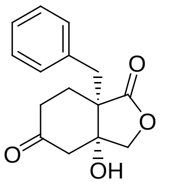
92aba in 60% yield with 13% ee at 25 °C for 6 h (Table 30, entry 3). For the synthesis of racemic products see Annexure-II, Tables A5-A7.

Table 29: Synthesis of chiral cascade M-A products **92**[a]

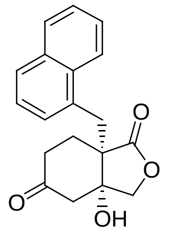




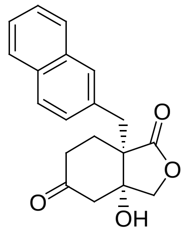
M-A: 48 h
(–)-**93aaa**
yield: 70%
ee: 52% (86%)[b]



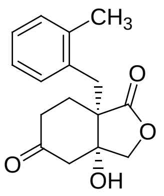
M-B: 8 h
(+)-**93aaa**
yield: 40%
ee: 55% (92%)[b]



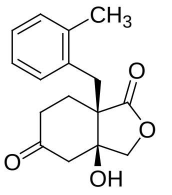
M-B: 6 h
(+)-**93aba**
yield: 40%
ee: 50% (80%)[b]



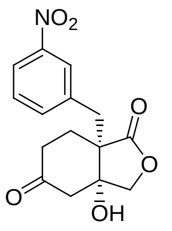
M-B: 6 h
(+)-**93aca**
yield: 40%
ee: 48% (70%)[b]



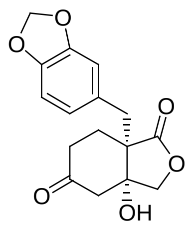
M-B: 48 h
(+)-**93au'a**
yield: 45%
ee: 60%



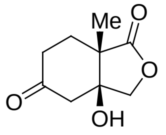
M-A: 72 h
(–)-**93au'a**
yield: 15%
ee: 50%



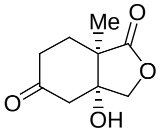
M-B: 48 h
(+)-**93aoa**
yield: 40%
ee: 50% (65%)[b]



M-B: 48 h
(+)-**93aia**
yield: 40%
ee: 40%



M-A: 24 h
(+)-**93ay'a**
yield: 45%
ee: 30%



M-B: 9 h
(–)-**93ay'a**
yield: 55%
ee: 34% (47%)[b]

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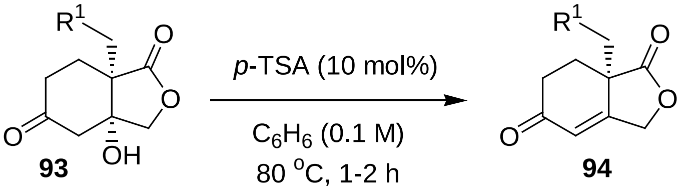
[a] Yield refers to the column-purified product. [b] ee determined by CSP HPLC analysis and values in paranthesis are obtained from one quick crystallization of **93** from i-PrOH at 25 °C.

Table 30: Synthesis of chiral bicyclic-ketones **94**[a]



Entry	R^1	Products	Yield (%)*[b]*	ee (%)*[c]*
1	Ph	(–)-**94aaa**	70	92
2	H	(–)-**94ay'a**	92	47
3	H	(+)-**94ay'a**	92	30

[a] Reactions were carried out in benzene (0.1 M) with 10 mol% of p-TSA as catalyst. [b] Yield refers to the column purified product. [c] ee determined by CSP HPLC analysis.

A series of 4-hydroxy-3-alkyl-5*H*-furan-2-one **91ac-ay′** were reacted with 3.0 equiv. of methyl vinyl ketone **68a** catalyzed by 30 mol% of L-proline **50a** at 25 °C in DMSO for 24-72 h or 10 mol% of Q-NH_2/TCA **50a′** at 25 °C in THF for 6-48 h (Table 29). All expected bicyclic-alcohols of M-A products **93aca-93ay′a** were obtained in good yields and ee's as shown in Table 29. Hydrolysis of bicyclic-alcohol (+)-**93aaa** obtained from **50a′** catalysis with *p*-TSA in C_6H_6 at 80 °C for 1-2 h furnished the expected bicyclic-ketone (–)-**94aaa** in 70% yield with 92% ee as shown in Table 30, entry 1. In a similar manner, we have prepared two more bicyclic-ketones (–)-**94ay′a/**(+)-**94ay′a** in 92% yield with 30-47% ee as shown in Table 30, entries 2-3.

6.2.5.2 Asymmetric synthesis of the key White intermediate for the synthesis of trisporic acids A-B:

Interestingly, L-proline **50a**-catalyzed cascade M-A reaction of 4-hydroxy-3-benzyl-5*H*-furan-2-one **91aa** with 3 equiv. of freshly distilled ethyl vinyl ketone **68b** in DMSO at

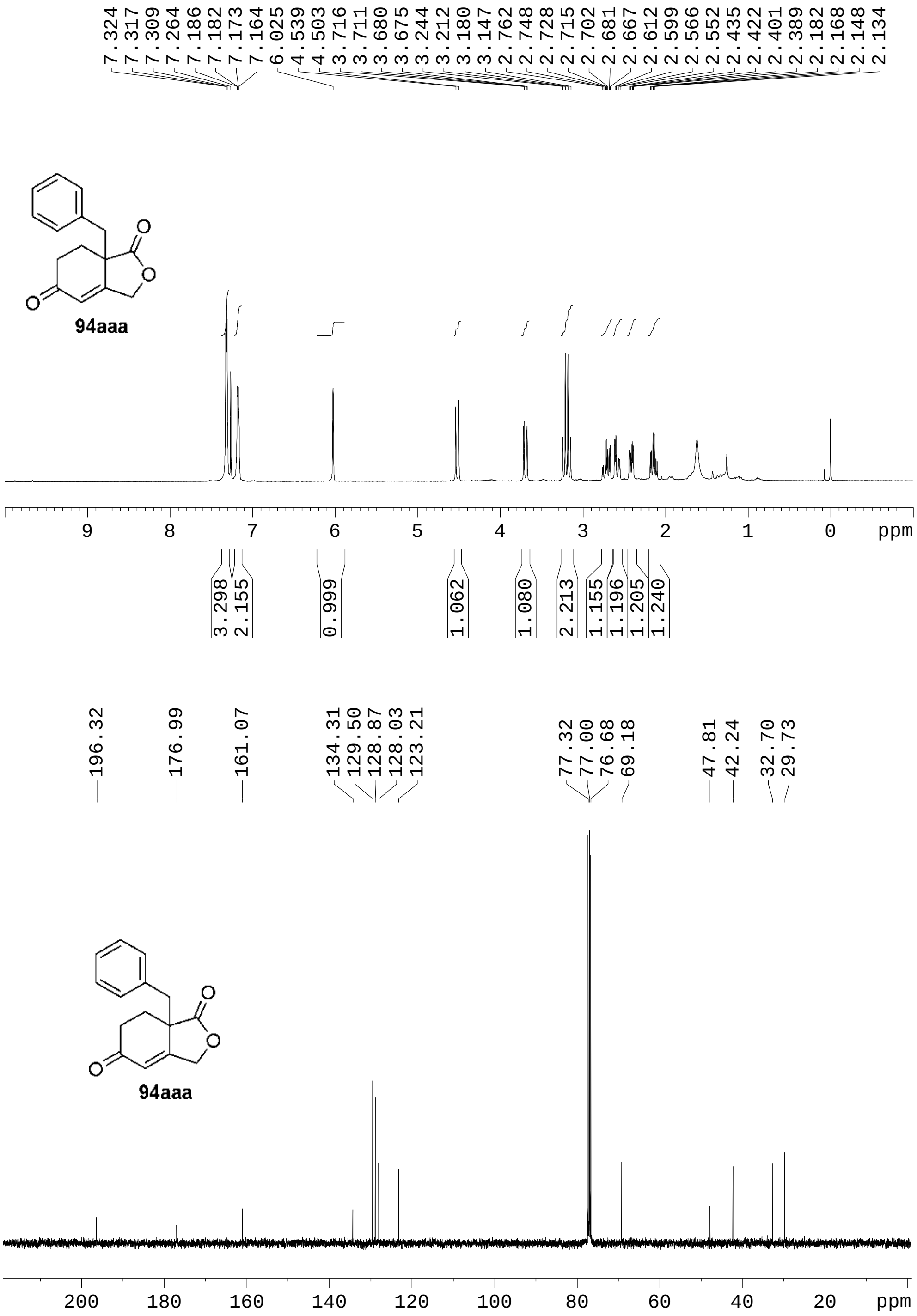


Figure-35: ^{1}H NMR and ^{13}C NMR Spectrum of product **94aaa**.

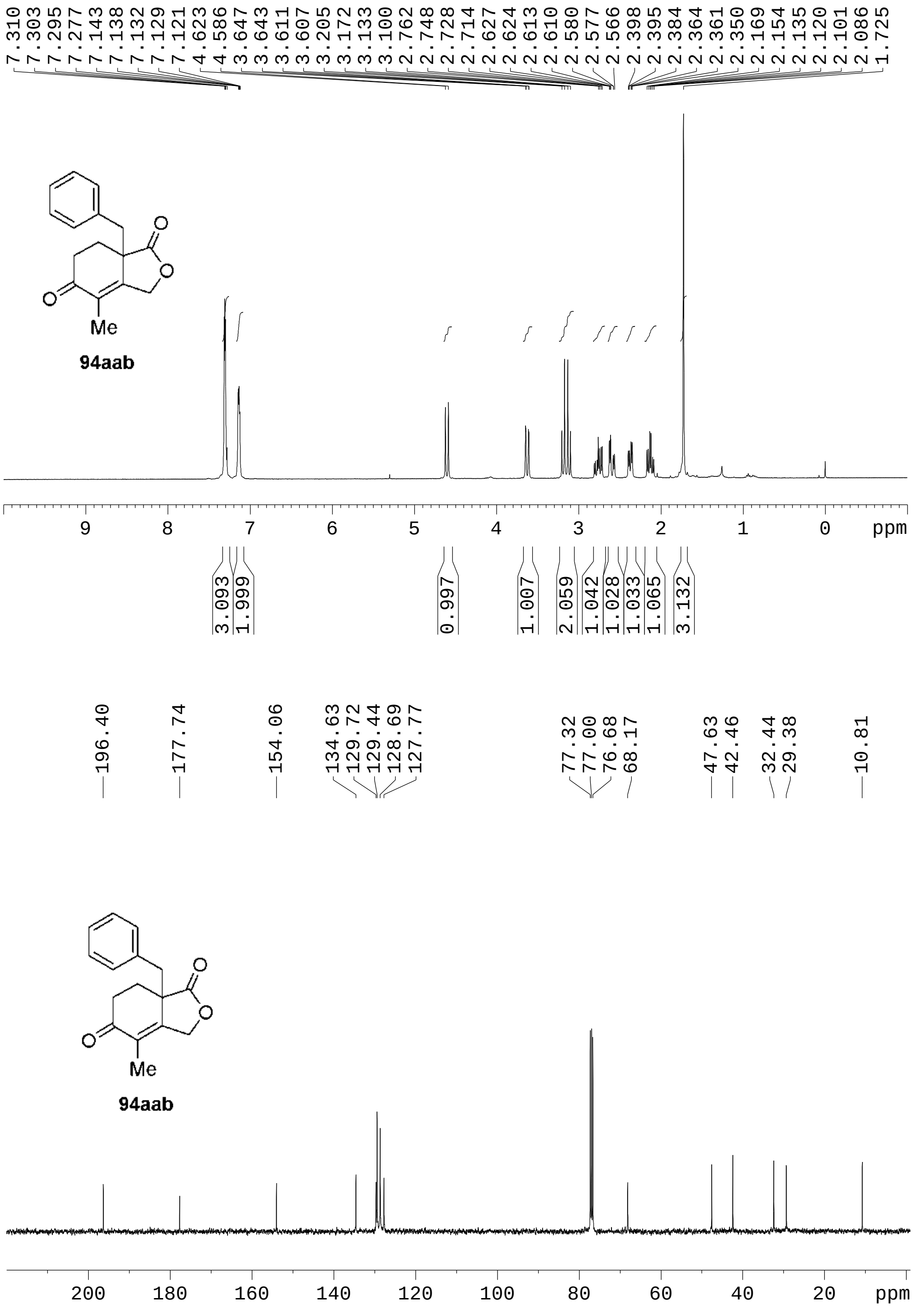
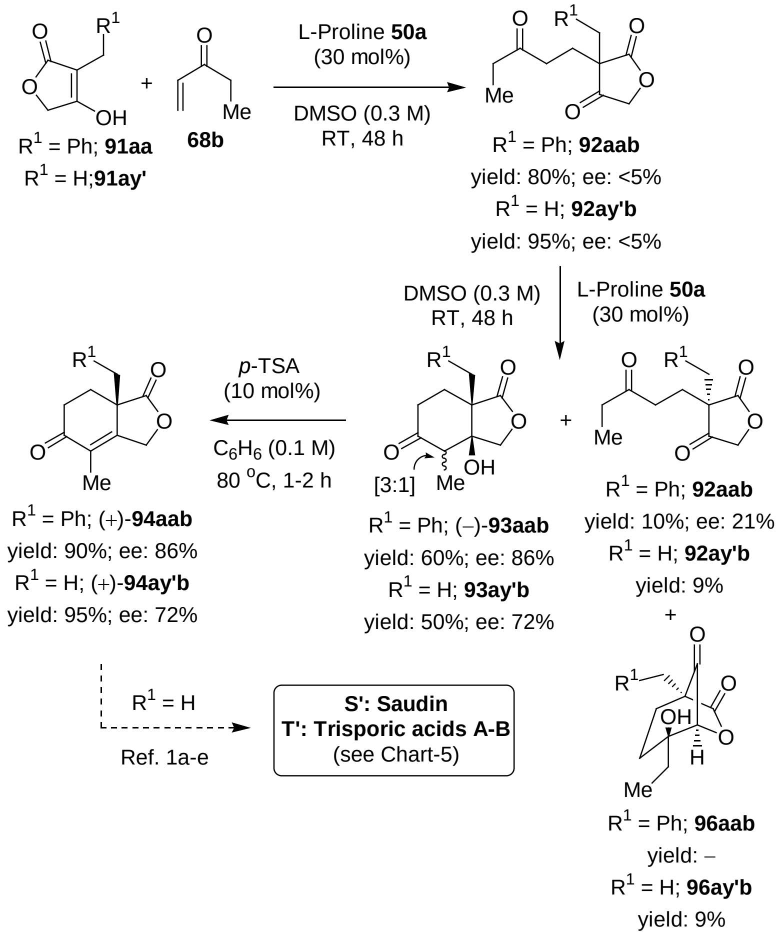


Figure-36: ^{1}H NMR and ^{13}C NMR Spectrum of product **94aab**.

25 °C for 48 h furnished the only Michael adduct **92aab** in 80% yield with <5% ee, which on further treatment with 30 mol% of L-proline **50a** in DMSO at 25 °C for 48 h furnished the expected cascade M-A product (–)-**93aab** in 60% yield with 86% ee through kinetic resolution and which is accompanying with unreacted Michael adduct **92aab** in 10% yield with 21% ee (see Scheme 30). In a similar manner, L-proline **50a**-catalyzed cascade M-A reaction of 4-hydroxy-3-methyl-5*H*-furan-2-one **91ay′** with 3 equiv. of freshly distilled ethyl vinyl ketone **68b** in DMSO at 25 °C for 48 h furnished the Michael adduct **92ay′b** in 95% yield with <5% ee, which on further treatment with

Scheme 30: Asymmetric synthesis of the key White intermediate and analogues for the chiral synthesis of trisporic acids **A–B**.

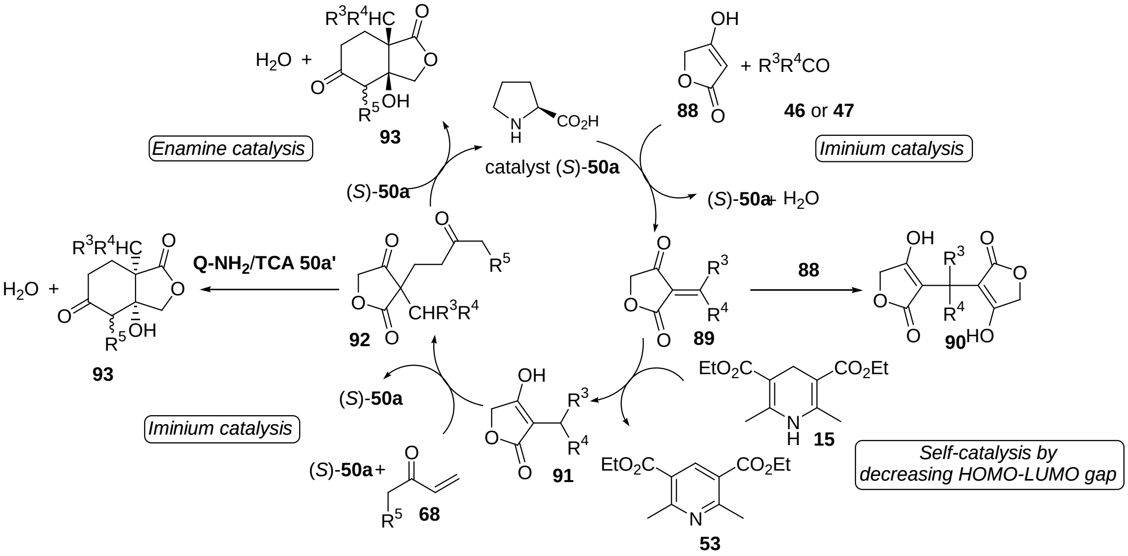


30 mol% of L-proline **50a** in DMSO at 25 °C for 48 h furnished the cascade M-A product **93ay′b** in 50% yield with 72% ee through kinetic resolution and which is accompanying with 1:1 mixture of unreacted Michael adduct **92ay′b** and new product **96ay′b** in 18% yield (see Scheme 30). Unfortunately, we are not able to separate these two compounds through column chromatography or chiral HPLC. Hydrolysis of chiral bicyclic-alcohols **93aab/93ay′b** under *p*-TSA-catalysis in C_6H_6 at 80 °C for 1-2 h furnished the expected bicyclic-ketones (+)-**94aab**/(+)-**94ay′b** in 90/95% yield with 86/72% ee, respectively as shown in Scheme 30.[73] The absolute configuration of products (+)-**94aab/**(+)-**94ay′b** were established by comparison with the Edmundo A. Rúveda's chiral resolution of the key White intermediate for the synthesis of trisporic acids **T′**.[73b] Chiral bicyclic-ketone (+)-**94ay′b** and their analogues would be suitable intermediates for the asymmetric total synthesis of natural products saudin **S′**, trisporic acids **T′**, anti-ulcerogenic compound (+)-cassiol and fraxinellonone and its related analogues as shown in Scheme 30.[69a-e,73]

6.2.6 Mechanistic Insights

The possible mechanism for L-proline- or Q-NH_2/TCA-catalyzed enantioselective synthesis of cascade products **91**, **92** and **93** through reaction of tetronic acid **88a**, aldehydes **46**/ketones **47**, Hantzsch ester **15** and alkyl vinyl ketone **68** is illustrated in Schemes 31 and 32. In the first step of cascade TCRA reaction, the catalyst (*S*)-**50a** activates component **46** or **47** by most likely iminium ion formation, which then selectively adds to the tetronic acid **88a** via a Mannich and retro-Mannich type reaction to generate active olefin **89**.[1] The following second step is hydrogenation of active olefin **89** by Hantzsch ester **15** to produce **91** through self-catalysis by decreasing HOMO-LUMO energy gap between **15** and **89** respectively.[1] In the subsequent third step or first step of cascade M-A reaction, Michael addition of **91** to alkyl vinyl ketone **68** via most likely iminium ion activation leads to the formation of Michael adduct **92** with less enantioselective fashion ($\leq$5% ee). In the fourth step, (*S*)-**50a** or Q-NH_2/TCA **50a′** catalyzed the asymmetric intramolecular aldol condensation of **92** via enamine catalysis and ee′s of the desired bicyclic-alcohols **93** were obtained through kinetic resolution.

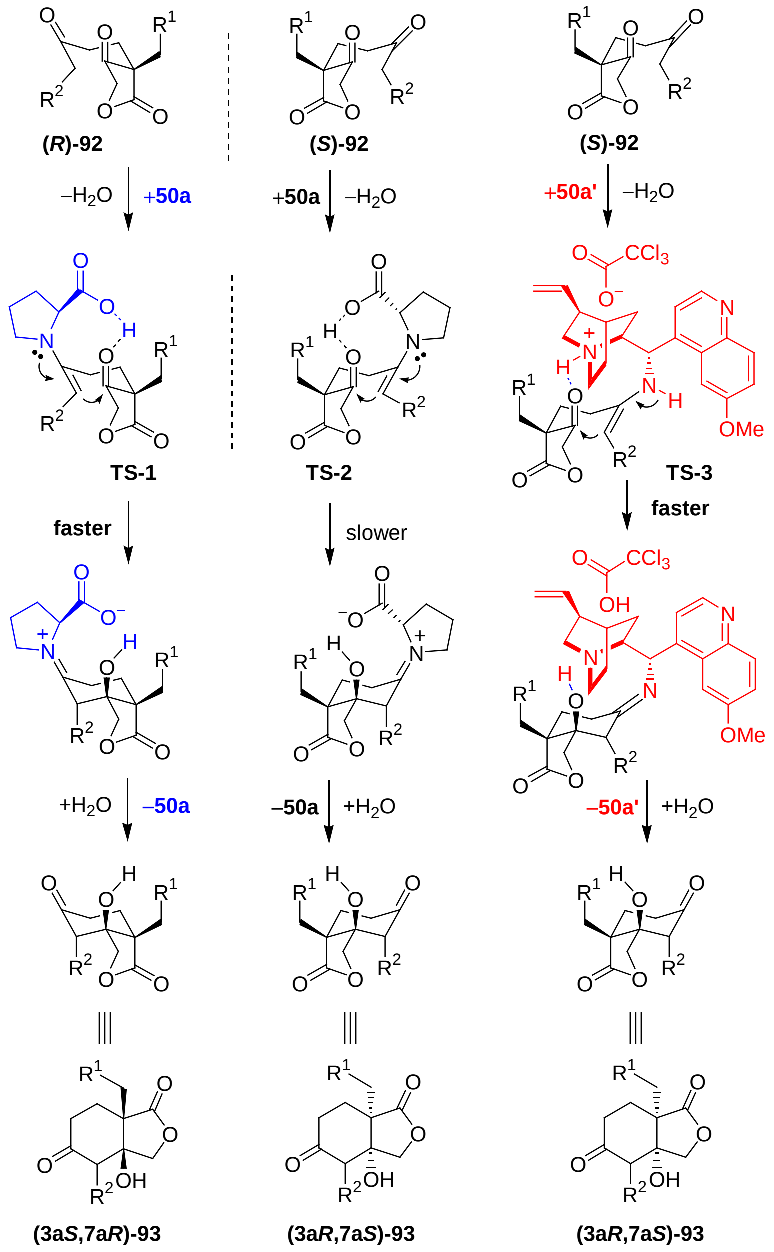
Scheme 31: Proposed catalytic cycle for the double cascade reactions.



The observed high enantioselectivity in cascade **93** products through kinetic resolution can be explained as illustrated in Scheme 32. L-Proline **50a**-catalyzed Michael addition of **91** to methyl vinyl ketone **68a** furnished the Michael adducts (*R*)-**92** and (*S*)-**92** with <5% ee, which on further reaction of amino acid (*S*)-**50a** with both ketones (*R*)-**92** and (*S*)-**92** generates the enamines with almost similar rates as shown in Scheme 32. Intramolecular aldol condensation of enamine generated from (*R*)-**92** will be a faster reaction compared to enamine generated from (*S*)-**92** as shown in **TS-1** and **TS-2** based on the strong/weak hydrogen bonding interactions, respectively (see Scheme 32).

In situ hydrolysis of imines generated from **TS-1** and **TS-2** with H_2O furnished the bicyclic-alcohols (3a*S*,7a*R*)-**93** and (3a*R*,7a*S*)-**93** respectively and observed high ee of (3a*S*,7a*R*)-**93** is directly due to the faster reaction rate in **TS-1**. In a similar manner, intramolecular aldol condensation of enamine generated from (*S*)-**92** with Q-NH_2/TCA **50a′** will be a faster reaction compared to enamine generated from (*R*)-**92** as shown in **TS-3** based on the hydrogen bonding interactions and steric hindrance, respectively (see Scheme 32).

Scheme 32: Proposed transition states for the asymmetric reactions.



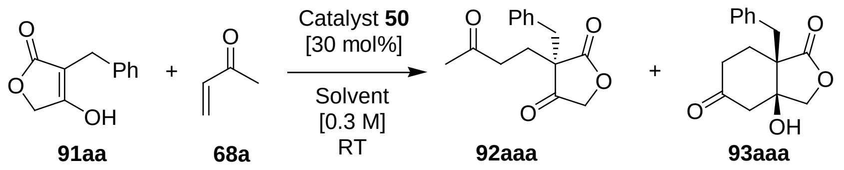
In situ hydrolysis of imine generated from **TS-3** with H_2O furnished the bicyclic-alcohol (3a*R*,7a*S*)-**93** and observed high ee of (3a*R*,7a*S*)-**93** is directly due to the faster reaction rate in **TS-3**. Stereoselective hydrogen bonding intereactions are main controlling factor than steric strain control in biomimetic cascade asymmetric M-A reactions, because ee of M-A product **93** is controled by co-catalyst in **50a′**-catalysis. Presently observed high enantioselectivity in cascade M-A reactions through kinetic resolution can be easily understood by rate differences in **TS-1** to **TS-3**, which may needs to get support from the high level DFT calculations.

6.3 Conclusions

In summary, first time we have developed the L-proline **50a-** or Q-NH_2/TCA **50a′**-catalyzed asymmetric cascade M-A reaction of 4-hydroxy-3-alkyl-5*H*-furan-2-ones with alkyl vinyl ketone at the ambient conditions. The asymmetric M-A reaction proceeds in good yields with high selectivity using L-proline or Q-NH_2/TCA as the catalyst through kinetic resolution. Furthermore, we have demonstrated the application of TCRA and M-A reactions in the synthesis of pharmaceutically useful molecules and natural products. Presently developed combination of cascade TCRA and M-A reactions will be suitable to synthesize library of **94ay′b** for the total synthesis of biologically importnant natural products and their analogues.

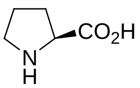
Annexure-1: Optimization of Cascade Asymmetric M-A Reaction

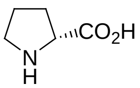
Table A1: Effect of Solvent and Amino acid on the Direct Amino acid Catalyzed Asymmetric Cascade M-A Reaction of 91aa and **68a**[a]

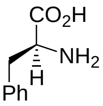


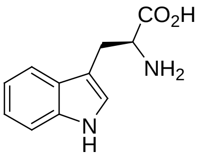
Entry	Catalyst	Solvent	Time [h]	Product **92aaa**		Product **93aaa**	
				Yield [%][b]	ee [%][c]	Yield [%][b]	ee [%][c]
1	**50a**	**DMSO**	**48**	**10**	**23**	**70**	**52**
2	**50a**	Toluene	72	38	0	55	ND
3	**50g**	**DMSO**	**48**	**10**	**-21**	**50**	**-53**
4	**50k**	DMSO	5	40	0	40	ND
5	**50k**	DMSO	6	10	0	79	0
6	**50l**	DMSO	24	31	0	65	ND
7	**50m**	DMSO	24	15	0	75	0
8	**50n**	DMSO	24	58	0	27	ND
9	**50o**	DMSO	168	50	0	31	ND
10	**50o**	Toluene	168	37	0	31	ND

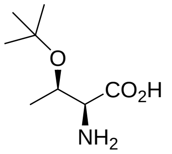
[a] Reactions were carried out in solvent [0.3 M] with 3.0 equiv. of freshly distilled **68a** in the presence of 30 mol% of catalyst **50**. [b] Yield refers to the column purified product. [c] Ee determined by HPLC analysis.

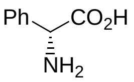

50a


50g


50k


50l


50m


50n

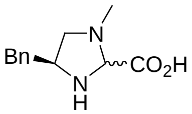
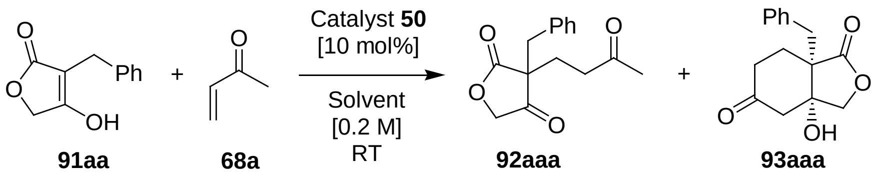
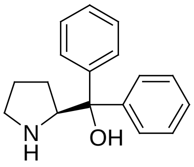

50o

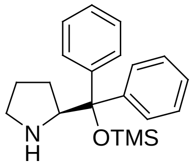
Table A2: Effect of Solvent and Pyrrolidine Catalysts on the Direct Amine Catalyzed Asymmetric Cascade M-A Reaction of **91aa** and **68a**[a]

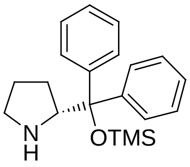


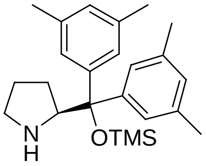
Entry	Catalyst	Solvent	Time [h]	Product **92aaa**		Product **93aaa**	
				Yield [%][b]	ee [%][c]	Yield [%][b]	ee [%][c]
1	**50p**	DMSO	48	60	0	–	–
2	**50p**	$C_6H_5CH_3$	36	74	0	–	–
3	**L-50q/PhCO$_2$H**	CH_2Cl_2	36	76	0	15	ND
4	**L-50q/PhCO$_2$H**	$C_6H_5CH_3$	10	77	0	10	ND
5	**D-50q**	DMSO	48	62	0	–	–
6	**D-50q**	$C_6H_5CH_3$	36	78	0	–	–
7	**50r/PhCO$_2$H**	$C_6H_5CH_3$	21	77	0	–	–
8	**50s/TFA**	CH_2Cl_2	168	<15	–	–	–

[a] Reactions were carried out in solvent [0.2 M] with 3.0 equiv. of freshly distilled **68a** in the presence of 10 mol% of catalyst **50** and 20 mol% of co-catalyst. [b] Yield refers to the column purified product. [c] Ee determined by HPLC analysis.


50p


L-50q


D-50q


50r

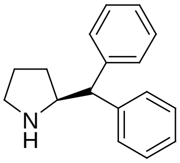
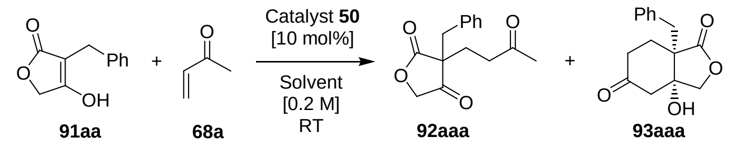
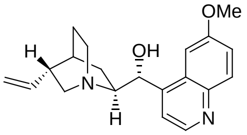

50s

Table A3: Effect of Solvent and 3^o-Amine on the Direct Amine-Catalyzed Asymmetric Cascade M-A Reaction of **91aa** and **68a**[a]

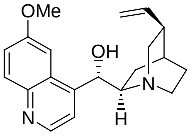


Entry	Catalyst	Solvent	Time [h]	Product **92aaa**		Product **93aaa**	
				Yield [%][b]	ee [%][c]	Yield [%][b]	ee [%][c]
1	**50i**	Toluene	24	71	0	–	–
2	**50t**	Toluene	24	80	0	–	–
3	**50u**	Toluene	12	80	0	–	–
4	**50v**	Toluene	12	80	0	–	–
5	**50w**	Toluene	48	70	5	–	–
6	**50x**	Toluene	19	80	2	–	–
7	**50y**	Toluene	24	82	0	–	–
8	**50z**	Toluene	48	73	0	–	–
9	**50a'**	Toluene	48	70	0	–	–
10	**50a'/TFA**	**Toluene**	**6**	**55**	**7**	**40**	**20**

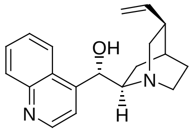
[a] Reactions were carried out in solvent [0.2 M] with 3.0 equiv. of freshly distilled **68a** in the presence of 10 mol% of catalyst **50** and 40 mol% of co-catalyst. [b] Yield refers to the column purified product. [c] Ee determined by HPLC analysis.



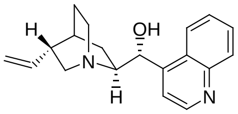
Quinine 50i



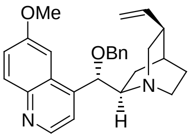
Quinidine 50t



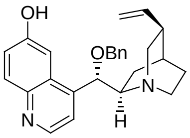
Cinchonine 50u



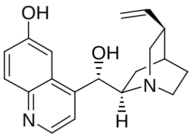
Cinchonidine 50v



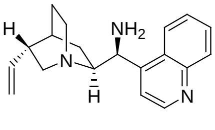
QD-OBn 50w



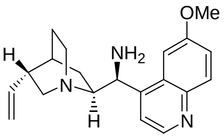
OH-QD-OBn 50x



OH-QD 50y

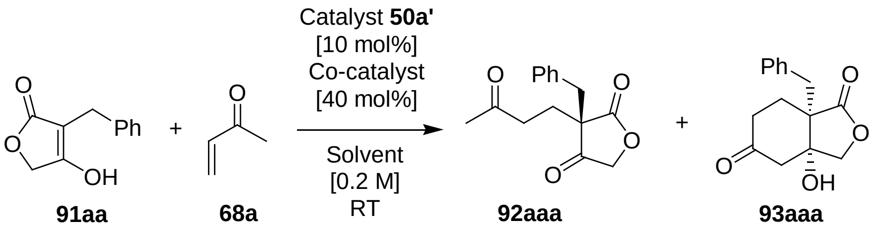


CD-NH_2 50z



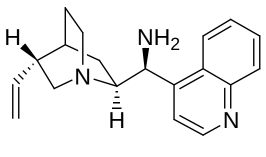
Q-NH_2 50a'

Table A4: Effect of Solvent and Co-catalyst on the Direct Q-NH_2-Catalyzed Asymmetric Cascade M-A Reaction of **91aa** and **68**a[a]

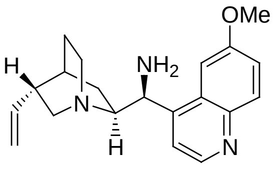


Entry	Catalyst/ Co-catalyst	Solvent	Time [h]	Product **92aaa**		Product **93aaa**	
				Yield [%][b]	ee [%][c]	Yield [%][b]	ee [%][c]
1	**50a'/TFA**	Toluene	6	55	7	40	20
2	**50a'/TFA**	CH_2Cl_2	4	75	11	–	–
3	**50a'/TFA**	**$CHCl_3$**	**10**	**71**	**13**	**19**	**58**
4	**50a'/TFA**	THF	3	50	9	40	43
5	**50a'/TFA**	DMSO	12	21	35	71	10
6	**50a'/TFA**	n-PrOH	24	23	54	44	1
7	**50a'/TFA**	i-PrOH	12	15	48	81	15
8	**50a'/TFA**	i-PrOH	8	25	69	44	17
9	**50a'/TFA**	**THF**	**8**	**60**	**8**	**40**	**55**
10	**50a'/3,5-DNBA**	THF	24	30	60	50	36
11	**50z/TFA**	THF	5	40	5	33	46
12	**50z/TCA**	**THF**	**6**	**60**	**2**	**20**	**61**
13	**50b'/TCA**	THF	120	45	8	35	57

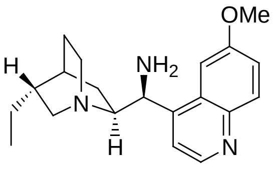
[a] Reactions were carried out in solvent [0.2 M] with 3.0 equiv. of freshly distilled **68a** in the presence of 10 mol% of catalyst **50** and 40 mol% of co-catalyst. [b] Yield refers to the column purified product. [c] Ee determined by HPLC analysis.



CD-NH$_2$ 50z



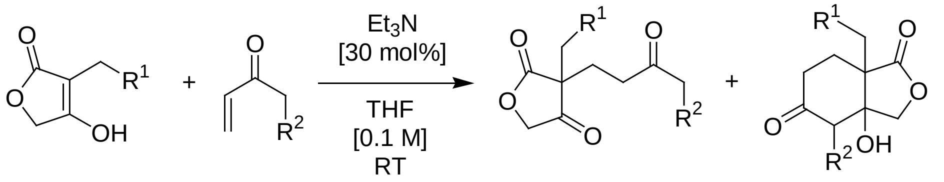
Q-NH$_2$ 50a'



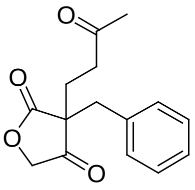
DHQ-NH$_2$ 50b'

Annexure-II: Synthesis of Racemic Products of 92-94

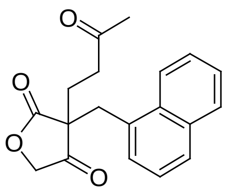
Table A5: Synthesis of Racemic Michael Adducts **92**[a][b]



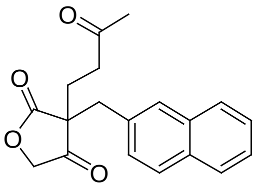
91 **68** **92** *cis*-**93** [10-20%]



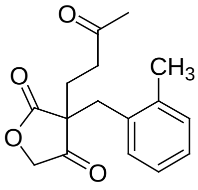
12 h
71% [**92aaa**]



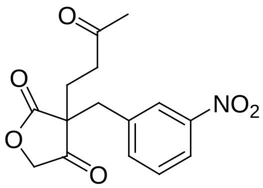
12 h
65% [**92aba**]



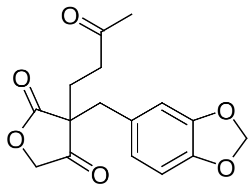
5 h
70% [**92aca**]



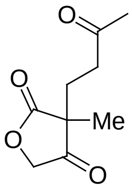
12 h
50% [**92au'a**]



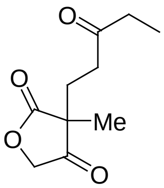
8 h
60% [**92aoa**]



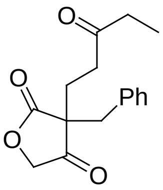
17 h
60% [**92aia**]



6 h
70% [**92ay'a**]



48 h
20% [**92ay'b**]



48 h
70% [**92aab**][c]

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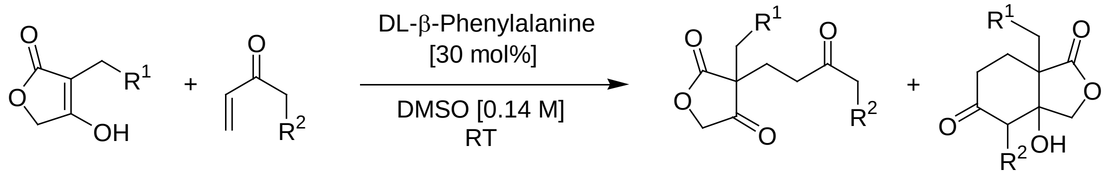
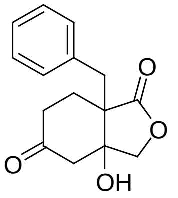
[a] Reactions were carried out in THF [0.1 M] with 3.0 equiv. of freshly distilled **68** in the presence of 30 mol% of Et_3N. [b] Yield refers to the column purified product. [c] Compound obtained from DL-proline-catalysis in DMSO at RT.

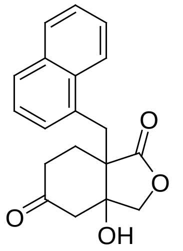
Table A6: Synthesis of Racemic Cascade Michael-Aldol Adducts **93**[a][b]



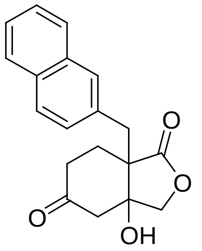
91 **68** **92** [10-20%] *cis*-**93**



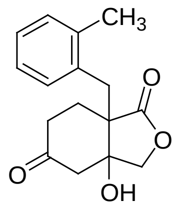
48 h
50% [*cis*-**93aaa**]



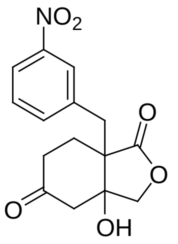
24 h
40% [*cis*-**93aba**]



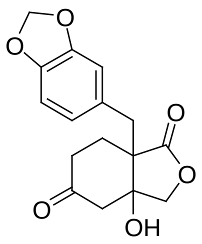
72 h
55% [*cis*-**93aca**]



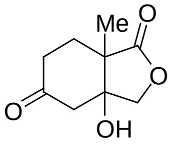
96 h
40% [*cis*-**93au'a**]



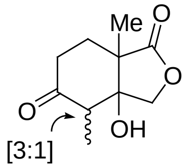
96 h
60% [*cis*-**93aoa**]



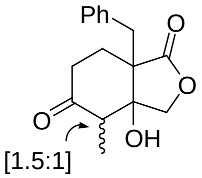
96 h
50% [*cis*-**93aia**]



12 h
30% [*cis*-**93ay'a**]



48 h
20% [*cis*-**93ay'b**][c]



48 h
70% [*cis*-**93aab**][d]

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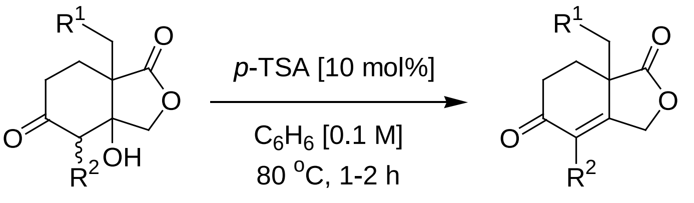
[a] Reactions were carried out in DMSO [0.14 M] with 3.0 equiv. of freshly distilled $_{68}$ in the presence of 30 mol% of DL-β-Phenylalanine. [b] Yield refers to the column purified product. [c] Compound obtained from Et_3N-catalysis.[d] Compound obtained from DL-proline-catalysis.

Table A7: Synthesis of Racemic Enones **94**[a]



93 **94**

Entry	R^1	R^2	Products yield [%][b] **94**	
1	Ph	H	**94aaa**	70
2	H	H	**94ay'a**	92
3	H	Me	**94ay'b**	90
4	Ph	Me	**94aab**	90

[a] Reactions were carried out in benzene (0.1 M) with 10 mol% of catalyst *p*-TSA as catalyst. [b] Yield refers to the column purified product.

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52. X-ray crystal data of **67bx**: $C_{15}H_{17}ClO_2$; MW = 264.74, monoclinic, space group C–2/c, with a = 21.065(11) Å, b = 5.735(3) Å, c = 24.155(13) Å, α = 90º, β = 108.357º, γ = 90º. CCDC-633529 contains the supplementary crystallographic data for this crystal structure.
53. X-ray crystal data of **67aa**: $C_{13}H_{14}O_2$; MW = 202.24, monoclinic, space group P–21/n, with a = 6.953(3) Å, b = 7.622(3) Å, c = 20.585(7) Å, α = 90º, β = 92.578º, γ = 90º. CCDC-633527 contains the supplementary crystallographic data for this crystal structure.
54. X-ray crystal data of **69aa**: $C_{17}H_{18}O_2$; MW = 254.31, Orthorhombic, space group P–21, with a = 7.1427(7) Å, b = 13.7344(13) Å, c = 13.9747(14) Å, α = 90º, β = 90º, γ = 90º. CCDC-633530 contains the supplementary crystallographic data for this crystal structure.
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65. X-ray crystal data of **82n**: $C_{12}H_{11}NO_4$; MW = 233.22, monoclinic, space group P–21/c, with a = 10.805(4) Å, b = 12.994(5) Å, c = 7.924(3) Å, α = 90º, β = 110.696º, γ = 90º. CCDC-674004 contains the supplementary crystallographic data for this crystal structure.
66. X-ray crystal data of **84a**: $C_{16}H_{16}O_2$; MW = 240.29, Orthorhombic, space group P–21, with a = 7.0365(9) Å, b = 11.9831(16) Å, c = 15.178(2) Å, α = 90º, β = 90º, γ = 90º. CCDC-674005 contains the supplementary crystallographic data for this crystal structure.

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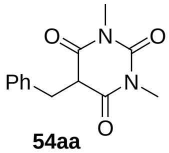
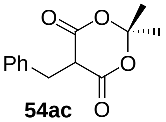
8. Experimental Section

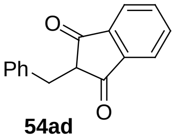
1a: Amine or Amino acid-catalyzed cascade olefination-hydrogenation reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde **46** or ketone **47**, 0.5 mmol of CH-acid **48** and 0.5 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst amine or amino acid **50** (0.025 mmol to 0.1 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1-5 and 7-9. The crude reaction mixture was directly loaded on silica gel column with or without aqueous work-up and pure cascade products **54** and **56** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).


54aa

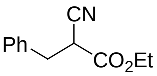
5-Benzyl-1,3-dimethyl-pyrimidine-2,4,6-trione (54aa): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 90 °C; IR (neat): ν_{max} 2924, 2852, 1687, 1450, 1381, 1288, 1105, 794, 752 and 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.23 (3H, m), 7.03 (2H, m) [Ar-*H*]; 3.77 (1H, t, *J* = 4.8 Hz), 3.46 (2H, d, *J* = 4.8 Hz), 3.12 (6H, s, 2 x N-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.2 (C, 2 x N-C=O), 150.9 (C, *C*=O), 135.1 (C), 128.8 (2 x CH), 128.6 (2 x CH), 127.8 (CH), 50.7 (CH), 37.8 (CH_2), 28.1 (2 x $CH_{3,}$ 2 x N-CH_3); LRMS: m/z 245.05 (M-H$^+$), calcd for $C_{13}H_{14}N_2O_3$ 246.1004.


54ac

5-Benzyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (54ac): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 62 °C; IR (KBr): ν_{max} 2982, 2932, 1720, 1689, 1593, 1444, 1379, 1292, 1043, 852, 771and 707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33-7.23 (5H, m) [Ar-*H*]; 3.77 (1H, t, *J* = 4.8 Hz), 3.49 (2H, d, *J* = 4.8 Hz), 1.73 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.3 (C, 2 x O-C=O), 137.2 (C), 129.7 (2 x CH), 128.6 (2 x CH), 127.2 (CH), 105.2 (C, O-*C*-O), 48.1 (CH), 32.1 (CH_2), 28.4 (CH_3), 27.2 (CH_3); LRMS: m/z 233.00 (M-H$^+$), calcd for $C_{13}H_{14}O_4$ 234.0892.


54ad

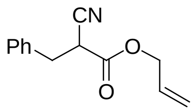
2-Benzyl-indan-1,3-dione (54ad): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 191 °C; IR (neat): ν_{max} 2982, 1716, 1597, 1444, 1371, 1284, 1253, 1107, 1043, 771, 756 and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88 (2H, m), 7.76 (2H, m), 7.12 (5H, m) [Ar-*H*]; 3.34 (3H, s, C*H* and C*H*$_2$Ph); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 199.9 (2 x C, O-C=O), 142.5 (2 x C), 137.0 (C), 135.5 (2 x CH), 129.5 (2 x CH), 128.2 (2 x CH), 126.6 (CH), 123.0 (2 x CH), 55.0 (CH), 32.2 (CH_2); LRMS: m/z 235.00 (M-H$^+$), calcd for $C_{16}H_{12}O_2$ 236.0837.


54af

2-Cyano-3-phenyl-propionic acid ethyl ester (54af): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3034, 2986, 2939, 2251 (C≡N), 1745 (O-C=O), 1604, 1496, 1263, 1082, 858, 750 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34-7.26 (5H, m) [Ar-*H*]; 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.71 (1H, dd, *J* = 8.0, 5.6

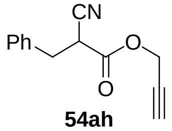
Hz), 3.30-3.16 (2H, dABq, *J* = 14.0, 6.0 Hz, Ph-CH_2), 1.26 (3H, t, *J* = 6.8 Hz, $\mathrm{OCH_2C}\mathit{H}_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.4 (C, O-C=O), 135.2 (C), 129.0 (2 x CH), 128.8 (2 x CH), 127.7 (CH), 116.1 (C, *C*≡N), 62.8 (CH_2, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 39.6 (CH), 35.7 ($CH_2$, $\mathrm{Ph}\mathit{C}\mathrm{H_2}$), 13.9 ($CH_3$, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$); LRMS: m/z 202.05 (M-H$^+$), calcd for $C_{12}H_{13}NO_2$ 203.0946.

2-Cyano-3-phenyl-propionic acid allyl ester (54ag): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3032, 2941, 2251 (C≡N), 1748 (O-C=O), 1649, 1605, 1497, 1455, 1271, 1190, 1082, 993, 941, 750 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39-7.28 (5H, m) [Ar-*H*]; 5.92-5.84(1H, m, $\mathrm{OCH_2C}\mathit{H}\mathrm{=CH_2}$), 5.35 (1H, d, *J* = 17.2 Hz, $\mathrm{OCH_2CH=C}\mathit{H}_2$), 5.30 (1H, d, *J* = 10.4 Hz, $\mathrm{OCH_2CH=C}\mathit{H}_2$), 4.69 (2H, d, *J* = 6.0 Hz, $\mathrm{OC}\mathit{H}_2\mathrm{CH=CH_2}$), 3.78 (1H, dd, *J* = 8.4, 6.0 Hz), 3.27 (2H, dABq, *J* = 14.0, 5.6 Hz, Ph-CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.2 (C, O-C=O), 135.2 (C), 130.6 (CH), 129.0 (2 x CH), 128.9 (2 x CH), 127.8 (CH), 119.7 (CH_2), 115.9 (C, *C*≡N), 67.2 (CH_2, $\mathrm{O}\mathit{C}\mathrm{H_2C=CH_2}$), 39.7 (CH), 35.8 ($CH_2$); LRMS: m/z 215.00 (M$^+$), calcd for $C_{13}H_{13}NO_2$ 215.10; Anal. calcd for $C_{13}H_{13}NO_2$ (215.10): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.548; H, 6.046; N, 6.517%.



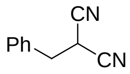
54ag

2-Cyano-3-phenyl-propionic acid prop-2-ynyl ester (54ah): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3291, 2939, 2253 (C≡N), 2131 (C≡C), 1755 (O-C=O), 1604, 1496, 1373, 1267, 1082, 1030 and 1001 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39-7.28 (5H, m) [Ar-*H*]; 4.79 (2H, s, $\mathrm{OC}\mathit{H}_2\mathrm{C{\equiv}CH}$), 3.81 (1H, dd, *J* = 8.4, 6.0 Hz), 3.28 (2H, dABq, *J* = 14.0, 6.0 Hz), 2.57 (1H, t, *J* = 2.4 Hz, $\mathrm{OCH_2C{\equiv}C}\mathit{H}$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.8 (C, O-C=O), 134.9 (C), 128.98 (2 x CH), 128.87 (2 x CH), 127.8 (CH), 115.5 (C, *C*≡N), 76.2 (CH, $\mathrm{CH_2C{\equiv}}\mathit{C}\mathrm{H}$), 76.1 (C, $\mathrm{CH_2}\mathit{C}\mathrm{{\equiv}CH}$), 53.9 ($CH_2$, $\mathrm{O}\mathit{C}\mathrm{H_2C{\equiv}CH}$), 39.7 (CH), 35.7 ($CH_2$, $\mathrm{Ph}\mathit{C}\mathrm{H_2}$); GCMS: m/z 213.00 (M$^+$), calcd for $C_{13}H_{11}NO_2$ 213.08; Anal. calcd for $C_{13}H_{11}NO_2$ (213.08): C, 73.22; H, 5.20; N, 6.57. Found: C, 73.379; H, 5.192; N, 6.452%.



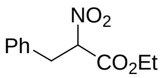
54ah

2-Benzyl-malononitrile (54aj): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 88 °C; IR (KBr): ν_{max} 3036, 2914, 2256 (C≡N), 1495, 1454, 1074, 1030, 748 and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.41-7.26 (5H, m) [Ar-*H*]; 3.91 (1H, t, *J* = 6.8 Hz, C*H*), 3.29 (2H, d, *J* = 6.8 Hz, $\mathrm{PhC}\mathit{H}_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 132.9 (C), 129.3 (2 x CH), 129.1 (2 x CH), 128.8 (CH), 112.1 (2 x C, *C*≡N), 36.7 (CH_2), 25.0 (CH). LRMS: m/z 155.10 (M-H$^+$), calcd for $C_{10}H_8N_2$ 156.0687.



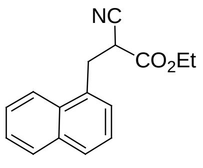
54aj

2-Nitro-3-phenyl-propionic acid ethyl ester (54ak): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2926, 1749 (O-C=O), 1560, 1456, 1373, 750 and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34-7.20 (5H, m) [Ar-*H*]; 5.33 (1H, dd, *J* = 9.2, 6.0 Hz), 4.28 (2H, q, *J* = 7.2 Hz, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 3.52 (2H, dABq, *J* = 14.8, 9.6 Hz, $\mathrm{PhC}\mathit{H}_2$), 1.28 (3H, t, *J* = 7.2 Hz, $\mathrm{OCH_2C}\mathit{H}_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.0 (C, O-C=O), 134.1



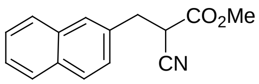
54ak

(C), 129.0 (2 x CH), 128.8 (2 x CH), 127.8 (CH), 89.2 (CH), 63.2 (CH_2, O*C*H_2CH_3), 36.2 (CH_2, Ph*C*H_2), 13.8 (CH_3, OCH_2*C*H_3); LRMS: m/z 222.05 (M-H^+), calcd for $C_{11}H_{13}NO_4$ 223.08.



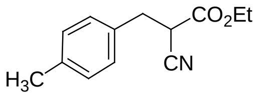
54bf

2-Cyano-3-naphthalen-1-yl-propionic acid ethyl ester (54bf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3053, 2984, 2251 (C≡N), 1744 (O-C=O), 1599, 1512, 1460, 1369, 1258, 1028, 856, 777 and 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93 (1H, d, *J* = 8.4 Hz), 7.87 (1H, d, *J* = 8.4 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.56-7.39 (4H, m) [Ar-*H*]; 4.22 (2H, q, *J* = 7.2 Hz, OC*H*$_2CH_3$), 3.89-3.80 (2H, m, ArC*H*$_2$), 3.52 (1H, dd, *J* = 15.6, 10.8 Hz, C*H*), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.6 (C, O-C=O), 133.9 (C), 131.1 (C), 131.0 (C), 129.2 (CH), 128.6 (CH), 127.8 (CH), 126.6 (CH), 125.9 (CH), 125.4 (CH), 122.4 (CH), 116.1 (C, *C*≡N), 62.9 (CH_2, O*C*H_2CH_3), 38.7 (CH), 33.0 (CH_2, Ar*C*H_2), 13.8 (CH_3, OCH_2*C*H_3); GCMS: m/z 253.10 (M^+), calcd for $C_{16}H_{15}NO_2$253.1103.



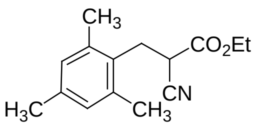
54ce

2-Cyano-3-naphthalen-2-yl-propionic acid methyl ester (54ce): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 54-56°C; IR (neat): ν_{max} 2955, 2251 (C≡N), 1749 (O-C=O), 1601, 1510, 1437, 1269, 1024, 897, 862, 816, 788 and 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (3H, m), 7.77 (1H, s), 7.50 (2H, m), 7.39 (1H, dd, *J* = 8.4, 1.72 Hz) [Ar-*H*]; 3.85 (1H, dd, *J* = 8.3, 5.7 Hz), 3.81 (3H, s, OC*H*$_3$), 3.44 (2H, dABq, *J* = 13.8, 5.7 Hz, ArC*H*$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.0 (C, O-C=O), 133.4 (C), 132.8 (C), 132.7 (C), 128.8 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 126.7 (CH), 126.4 (CH), 126.2 (CH), 116.1 (C, *C*≡N), 53.6 (CH_3, O*C*H_3), 39.5 (CH), 35.9 (CH_2, Ar*C*H_2); GCMS: m/z 239.0 (M^+), calcd for $C_{15}H_{13}NO_2$ 239.0946.



54ef

2-Cyano-3-p-tolyl-propionic acid ethyl ester (54ef): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2986, 2930, 2251 (C≡N), 1747 (O-C=O), 1616, 1516, 1028, 856 and 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (4H, s) [Ar-*H*]; 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2CH_3$), 3.70 (1H, dd, *J* = 8.4, 5.6 Hz), 3.22 (2H, dABq, *J* = 13.6, 5.6 Hz, PhC*H*$_2$), 2.36 (3H, s, PhC*H*$_3$), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.5 (C, O-C=O), 137.4 (C), 132.2 (C), 129.5 (2 x CH), 128.8 (2 x CH), 116.2 (C, *C*≡N), 62.8 (CH_2, O*C*H_2CH_3), 39.8 (CH), 35.3 (CH_2, Ph*C*H_2), 21.0 (CH_3), 13.9 (CH_3, OCH_2*C*H_3); LRMS: m/z 216.00 (M-H^+), calcd for $C_{13}H_{15}NO_2$ 217.1103.

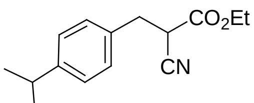


54ff

2-Cyano-3-(2,4,6-trimethyl-phenyl)-propionic acid ethyl ester (54ff): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 70°C; IR (KBr): ν_{max} 2988, 2916, 2247 (C≡N), 1728 (O-C=O), 1612, 1468, 1369, 1258, 854 and 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75 (2H, s) [Ar-*H*]; 4.15 (2H, q, *J* = 7.0 Hz, OC*H*$_2CH_3$), 3.52 (1H, dd, *J* =

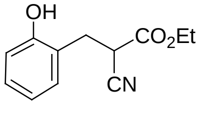
10.0, 6.0 Hz, C*H*), 3.17 (2H, dABq, *J* = 13.0, 6.0 Hz, PhC*H*$_2$), 2.29 (6H, s, 2 x C*H*$_3$), 2.13 (3H, s, C*H*$_3$), 1.19 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.0 (C, O-C=O), 137.1 (C), 136.7 (2 x C), 129.6 (2 x CH), 129.3 (C), 116.4 (C, *C*≡N), 63.0 (CH$_2$, O*C*H$_2$CH$_3$), 37.5 (CH), 29.4 (CH$_2$, Ph*C*H$_2$), 20.9 (CH$_3$, Ph*C*H$_3$), 19.9 (2 x CH$_3$, Ph*C*H$_3$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); GCMS: m/z 245.20 (M$^+$), calcd for $C_{15}H_{19}NO_2$ 245.1416; Anal. calcd for $C_{15}H_{19}NO_2$ (245.14): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.449; H, 7.861; N, 5.735%.

2-Cyano-3-(4-isopropyl-phenyl)-propionic acid ethyl ester (54gf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2962, 2251 (C≡N), 1747 (O-C=O), 1516, 1028 and 856 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.23 (4H, s) [Ar-*H*]; 4.23 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 3.72 (1H, dd, *J* = 8.8, 6.0 Hz), 3.24 (2H, dABq, *J* = 13.8, 6.8 Hz), 2.90 (1H, m, C*H*(C*H*$_3$)$_2$), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.27 (6H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.7 (C, O-C=O), 148.4 (C), 132.7 (C), 129.0 (2 x CH), 126.9 (2 x CH), 116.4 (C, *C*≡N), 62.8 (CH$_2$, O*C*H$_2$CH$_3$), 39.8 (CH), 35.4 (CH$_2$), 33.8 (CH), 24.0 (2 x CH$_3$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 246.15 (M+H$^+$), calcd for $C_{15}H_{19}NO_2$ 245.1416.



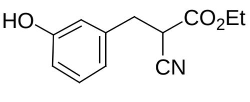
54gf

2-Cyano-3-(2-hydroxy-phenyl)-propionic acid ethyl ester (54kf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3408 (O-H), 2257 (C≡N), 1747 (O-C=O), 1597, 1506, 1041, 864 and 756 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.17 (1H, dt, *J* = 7.6, 1.6 Hz), 7.14 (1H, dd, *J* = 8.0, 1.6 Hz), 6.88 (1H, dt, *J* = 7.2, 1.2 Hz), 6.78 (1H, d, *J* = 8.0 Hz) [Ar-*H*]; 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.10 (1H, dd, *J* = 8.4, 6.8 Hz), 3.38 (1H, dd, *J* = 13.6, 6.8 Hz), 3.15 (1H, dd, *J* = 13.6, 8.4 Hz), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.3 (C, O-C=O), 154.2 (C), 131.2 (CH), 129.1 (CH), 121.8 (CH), 120.5 (C), 116.5 (C, *C*≡N), 115.4 (CH), 62.9 (CH$_2$, O*C*H$_2$CH$_3$), 37.4 (CH), 31.1 (CH$_2$, Ph*C*H$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); GCMS: m/z 219.0 (M$^+$), calcd for $C_{12}H_{13}NO_3$ 219.0895; Anal. calcd for $C_{12}H_{13}NO_3$ (219.09): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.732; H, 5.948; N, 6.654%.



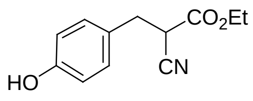
54kf

2-Cyano-3-(3-hydroxy-phenyl)-propionic acid ethyl ester (54lf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3443 (O-H), 2254 (C≡N), 1736 (O-C=O), 1591, 1458, 1269, 1030, 860 and 781 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.18 (1H, t, *J* = 8.6 Hz), 6.78 (3H, m) [Ar-*H*]; 6.67 (1H, br s, O*H*), 4.24 (2H, q, *J* = 7.12 Hz, OC*H*$_2$CH$_3$), 3.76 (1H, dd, *J* = 8.3, 5.8 Hz), 3.18 (2H, dABq, *J* = 13.8, 5.7 Hz), 1.27 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.6 (C, O-C=O), 156.1 (C), 136.7 (C), 130.0 (CH), 120.9 (CH), 116.0 (C, *C*≡N), 115.8 (CH), 114.8 (CH), 63.0 (CH$_2$, O*C*H$_2$CH$_3$), 39.5 (CH), 35.4 (CH$_2$, Ph*C*H$_2$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 220.15 (M+H$^+$), calcd for

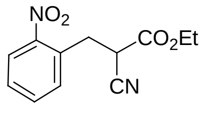


54lf

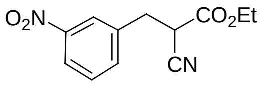
$C_{12}H_{13}NO_3$ 219.0895; Anal. calcd for $C_{12}H_{13}NO_3$ (219.09): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.669; H, 6.022; N, 6.447%.


54mf

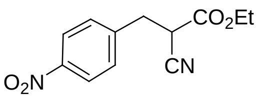
2-Cyano-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (54mf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3408 (O-H), 2986, 2939, 2255 (C≡N), 1743 (O-C=O), 1682, 1614, 1516, 1446, 1371, 1267, 1030, 839 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.12 (2H, d, *J* = 8.4 Hz), 6.79 (2H, d, *J* = 8.4 Hz) [Ar-*H*]; 6.60 (1H, br s, O*H*), 4.24 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.74 (1H, dd, *J* = 8.0, 5.6 Hz), 3.10 (2H, m, PhCH_2), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.9 (C, O-C=O), 155.7 (C), 130.3 (2 x CH), 126.8 (C), 116.5 (C, *C*≡N), 115.8 (2 x CH), 63.2 (CH$_2$, O*C*H$_2$CH$_3$), 40.1 (CH), 35.0 (CH$_2$, Ph*C*H$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); GCMS: m/z 219.0 (M$^+$), calcd for $C_{12}H_{13}NO_3$ 219.0895.


54nf

2-Cyano-3-(2-nitro-phenyl)-propionic acid ethyl ester (54nf): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 64°C; IR (neat): ν_{max} 2984, 2941, 2251 (C≡N), 1745 (O-C=O), 1610, 1578, 1348, 1026, 858, 788, 744 and 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, d, *J* = 8.4 Hz), 7.64 (1H, t, *J* = 7.6 Hz), 7.50 (2H, m) [Ar-*H*]; 4.26 (2H, q, *J* = 6.8 Hz, OCH_2CH$_3$), 4.14 (1H, dd, *J* = 9.6, 5.6 Hz), 3.68 (1H, dd, *J* = 13.6, 6.0 Hz), 3.26 (1H, dd, *J* = 13.6, 10.0 Hz), 1.30 (3H, t, *J* = 6.8 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.1 (C, O-C=O), 148.9 (C), 133.9 (CH), 133.6 (CH), 130.7 (C), 129.3 (CH), 125.5 (CH), 115.8 (C, *C*≡N), 63.2 (CH$_2$, O*C*H$_2$CH$_3$), 38.1 (CH), 33.4 (CH$_{2,}$ Ph*C*H$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 247.00 (M-H$^+$), calcd for $C_{12}H_{12}N_2O_4$ 248.0797; Anal. calcd for $C_{12}H_{12}N_2O_4$ (248.08): C, 58.06; H, 4.87; N, 11.29. Found: C, 58.080; H, 4.905; N, 11.368%.

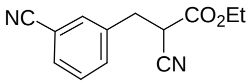

54of

2-Cyano-3-(3-nitro-phenyl)-propionic acid ethyl ester (54of): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 60 °C; IR (neat): ν_{max} 2986, 2941, 2253 (C≡N), 1745 (O-C=O), 1533, 1354, 1097, 856 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20-8.17 (2H, m), 7.67 (1H, d, *J* = 7.2 Hz), 7.55 (1H, t, *J* = 8.0 Hz) [Ar-*H*]; 4.26 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.82 (1H, dd, *J* = 8.0, 6.0 Hz), 3.32 (2H, dABq, *J* = 14.0, 6.0 Hz), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.9 (C, O-C=O), 148.5 (C), 137.2 (C), 135.4 (CH), 130.0 (CH), 124.1 (CH), 123.0 (CH), 115.5 (C, *C*≡N), 63.4 (CH$_2$, O*C*H$_2$CH$_3$), 39.0 (CH), 35.0 (CH$_2$, Ph*C*H$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 247.15 (M-H$^+$), calcd for $C_{12}H_{12}N_2O_4$ 248.0797; Anal. calcd for $C_{12}H_{12}N_2O_4$ (248.08): C, 58.06; H, 4.87; N, 11.29. Found: C, 58.074; H, 4.886; N, 11.500%.


54pf

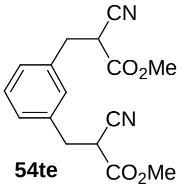
2-Cyano-3-(4-nitro-phenyl)-propionic acid ethyl ester (54pf): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 60 °C; IR (KBr): ν_{max} 2930, 2452, 2257 (C≡N), 1952, 1603, 1520, 1446, 1348, 1107, 1014, 885, 846, 754 and

711 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.22 (2H, d, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 8.4 Hz) [Ar-*H*]; 4.27 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 3.88 (1H, dd, *J* = 8.0, 6.0 Hz), 3.36 (2H, dABq, *J* = 14.0, 6.0 Hz), 1.28 (3H, t, *J* = 6.4 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 164.9 (C, O-C=O), 147.6 (C), 142.6 (C), 130.2 (2 x CH), 124.0 (2 x CH), 115.6 (C, *C*≡N), 66.9 (CH$_2$, O*C*H$_2$CH$_3$), 38.8 (CH), 35.0 (CH$_2$, Ph*C*H$_2$), 13.4 (CH$_3$, OCH$_2$*C*H$_3$); GCMS: m/z 248.0 (M$^+$), calcd for $C_{12}H_{12}N_2O_4$ 248.0797.



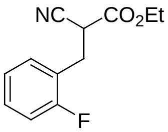
54qf

2-Cyano-3-(3-cyano-phenyl)-propionic acid ethyl ester (54qf): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 52-54 °C; IR (KBr): ν$_{max}$ 2984, 2908, 2251 (C≡N), 2228, 1734 (O-C=O), 1030, 860, 800 and 696 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.59-7.54 (3H, m), 7.46 (1H, t, *J* = 7.6 Hz) [Ar-*H*]; 4.21 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.79 (1H, dd, *J* = 8.0, 6.0 Hz), 3.21 (2H, dABq, *J* = 14.0, 5.8 Hz), 1.25 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.0 (C, O-C=O), 136.9 (C), 133.8 (CH), 132.7 (CH), 131.5 (CH), 129.8 (CH), 118.4 (C), 115.7 (C, *C*≡N), 112.9 (C, *C*≡N), 63.2 (CH$_2$, O*C*H$_2$CH$_3$), 39.0 (CH), 34.8 (CH$_2$, Ph*C*H$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 227.15 (M-H$^+$), calcd for $C_{13}H_{12}N_2O_2$ 228.0899; Anal. calcd for $C_{13}H_{12}N_2O_2$ (228.09): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.544; H, 5.323; N, 12.147%.



54te

2-Cyano-3-[3-(2-cyano-2-methoxycarbonyl-ethyl)-phenyl]-propionic acid methyl ester (54te): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 3018, 2959, 2251 (C≡N), 1746 (O-C=O), 1611, 1439, 1269, 1022, 775 and 706 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.34 (1H, t, *J* = 8.0 Hz), 7.22 (3H, m) [Ar-*H*]; 3.80 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.77 (2H, m, CH), 3.23 (2H, dABq, *J* = 13.6, 5.2 Hz), 3.20 (2H, dABq, *J* = 13.6, 5.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.8 (2 x C, O-C=O), 135.96 (C), 135.94 (C), 129.7 (CH), 129.46 (CH), 129.44 (CH), 128.51 (CH), 128.50 (CH), 115.9 (2 x C, *C*≡N), 53.6 (2 x CH$_3$, O*C*H$_3$), 39.34 (CH), 39.28 (CH), 35.45 (CH$_{2,}$ Ph*C*H$_2$), 35.41 (CH$_{2,}$ Ph*C*H$_2$); GCMS: m/z 299.9 (M$^+$), calcd for $C_{16}H_{16}N_2O_4$ 300.1110.

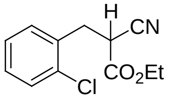


54uf

2-Cyano-3-(2-fluoro-phenyl)-propionic acid ethyl ester (54uf): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν$_{max}$ 2986, 2253 (C≡N), 1745 (O-C=O), 1618, 1587, 1493, 1033, 702 and 640 cm^{-1}; ^{1}H NMR (CDCl3) δ 7.30 (2H, m), 7.12 (1H, bt, *J* = 7.6 Hz), 7.07 (1H, bt, *J* = 8.6 Hz) [Ar-*H*]; 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.80 (1H, dd, *J* = 8.8, 6.4 Hz), 3.37 (1H, dd, *J* = 14.0, 6.4 Hz), 3.19 (1H, dd, *J* = 13.6, 8.8 Hz), 1.27 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); 13C NMR (CDCl$_3$, DEPT-135) δ 165.2 (C, O-*C*=O), 161.0 (C, d, *J* = 244.8 Hz, *C*-F), 131.4 (CH, d, *J* = 4.0 Hz), 129.7 (CH, d, *J* = 8.2 Hz), 124.4 (CH, d, *J* = 3.7 Hz), 122.3 (C, d, *J* = 15.2 Hz), 115.8 (C, *C*≡N), 115.5 (CH, d, *J* = 21.4 Hz), 62.9 (CH$_2$, O*C*H$_2$CH$_3$), 37.9 (CH, d, *J* = 6.4 Hz), 29.5 (CH$_2$, d, *J* = 10.0 Hz), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z

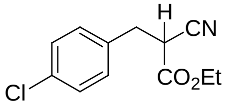
220.00 (M-H+), calcd for C $_{12}H_{12}FNO_2$ 221.0852; HRMS m/z 222.0924 (M+H$^+$), calcd for $C_{12}H_{12}FNO_2H$ 222.0930.

3-(2-Chloro-phenyl)-2-cyano-propionic acid ethyl ester (54wf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2988, 2251 (C≡N), 1745 (O-C=O), 1574, 1475, 1263, 1127, 860, 754 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.41-7.25 (4H, m) [Ar-*H*]; 4.28 (2H, q, *J* = 7.2 Hz, OC*H$_2$*CH$_3$), 3.90 (1H, t, *J* = 9.2 Hz), 3.51 (1H, dd, *J* = 13.6, 6.0 Hz, Ph-C*H$_2$*), 3.21 (1H, dd, *J* = 13.6, 6.0 Hz, Ph-C*H$_2$*), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H$_3$*); ^{13}C NMR (CDCl$_3$, DEPT135) δ 165.3 (C, O-C=O), 134.0 (C), 133.1 (C), 131.7 (CH), 129.8 (CH), 129.4 (CH), 127.3 (CH), 115.9 (C, *C*≡N), 63.0 (CH$_2$, OC*H$_2$*CH$_3$), 37.4 (CH), 33.8 (CH$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$).



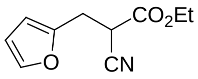
54wf

3-(4-Chloro-phenyl)-2-cyano-propionic acid ethyl ester (54yf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2922, 2251 (C≡N), 1730 (O-C=O), 1595, 1464, 1371, 1284, 1105, 808, 717 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.31 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 8.4 Hz) [Ar-*H*]; 4.28 (2H, q, *J* = 7.2 Hz, OC*H$_2$*CH$_3$), 3.70 (1H, t, *J* = 6.2 Hz), 3.27-3.14 (2H, m, Ph-C*H$_2$*), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H$_3$*); ^{13}C NMR (CDCl$_3$, DEPT135) δ 162.3 (C, O-C=O), 134.0 (C), 133.7 (C), 130.4 (2 x CH), 129.0 (2 x CH), 115.8 (C, *C*≡N), 63.0 (CH$_2$, OC*H$_2$*CH$_3$), 39.4 (CH), 35.0 (CH$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$).



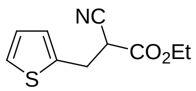
54yf

2-Cyano-3-furan-2-yl-propionic acid ethyl ester (54c′f): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2986, 2935, 2253 (C≡N), 1747 (O-C=O), 1608, 1026, 856 and 740 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.37 (1H, s), 6.33 (1H, s), 6.26 (1H, s) [Ar-*H*]; 4.27 (2H, q, *J* = 7.2 Hz, OC*H$_2$*CH$_3$), 3.84 (1H, t, *J* = 6.7 Hz), 3.32 (2H, m, PhC*H$_2$*), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H$_3$*); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.0 (C, O-C=O), 148.9 (C), 142.4 (CH), 115.7 (C, *C*≡N), 110.5 (CH), 108.3 (CH), 62.9 (CH$_2$, O*C*H$_2$CH$_3$), 36.9 (CH), 28.4 (CH$_2$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 192.00 (M-H$^+$), calcd for $C_{10}H_{11}NO_3$ 193.0739.



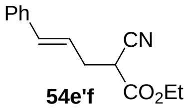
54c'f

2-Cyano-3-thiophen-2-yl-propionic acid ethyl ester (54d′f): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 3088, 2984, 2251 (C≡N), 1745 (O-C=O), 1593, 1261, 858, 713 and 596 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.23 (1H, d, *J* = 4.8 Hz), 7.00 (1H, m), 6.97 (1H, t, *J* = 4.0 Hz) [Ar-*H*]; 4.26 (2H, q, *J* = 7.2 Hz, OC*H$_2$*CH$_3$), 3.76 (1H, t, *J* = 6.0 Hz), 3.47 (2H, m), 1.29 (3H, t, *J* = 7.6 Hz, OCH$_2$C*H$_3$*); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.0 (C, O-*C*=O), 136.6 (C), 127.3 (CH), 127.2 (CH), 125.3 (CH), 115.8 (C, *C*≡N), 63.1 (CH$_2$, O*C*H$_2$CH$_3$), 39.8 (CH), 29.9 (CH$_2$), 13.9 (CH3, OCH$_2$*C*H$_3$); LRMS m/z 208.05



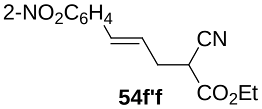
54d'f

(M−H$^+$), calcd for $C_{10}H_{11}NO_2S$ 209.0510; HRMS m/z 232.0405 (M+Na$^+$), calcd for $C_{10}H_{11}NO_2SNa$ 232.0408.



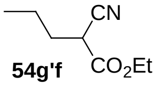
54e′f

2-Cyano-5-phenyl-pent-4-enoic acid ethyl ester (54e′f): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2930, 2249 (C≡N), 1743 (O-C=O), 1454, 1238 and 858 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (2H, d, *J* = 6.8 Hz), 7.31 (2H, t, *J* = 8.0 Hz), 7.25 (1H, t, *J* = 6.8 Hz) [Ar-*H*]; 6.59 (1H, d, *J* = 15.6 Hz), 6.18 (1H, dt, *J* = 15.6, 7.2 Hz), 4.28 (2H, q, *J* = 6.8 Hz, OCH_2CH_3), 3.62 (1H, t, *J* = 6.4 Hz), 2.86 (2H, t, *J* = 7.2 Hz), 1.31 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.5 (C, O-C=O), 136.3 (C), 135.0 (CH), 128.6 (2 x CH), 127.9 (CH), 126.4 (2 x CH), 122.4 (CH), 116.1 (C, *C*≡N), 62.9 (CH_2, OCH_2CH_3), 37.9 (CH), 33.3 (CH_2), 14.0 (CH_3, OCH_2CH_3); LCMS: m/z 228.00 (M-H$^+$), calcd for $C_{14}H_{15}NO_2$ 229.1103; Anal. calcd for $C_{14}H_{15}NO_2$ (229.11): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.293; H, 6.547; N, 6.256%.



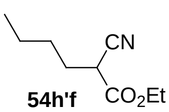
54f′f

2-Cyano-5-(2-nitro-phenyl)-pent-4-enoic acid ethyl ester (54f′f): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3069, 2928, 2872, 2251 (C≡N), 1743 (O-C=O), 1608, 1572, 1521, 968, 860 and 787 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.96 (1H, d, *J* = 8.0 Hz), 7.58 (2H, m), 7.45 (1H, m), 7.09 (1H, d, *J* = 15.56 Hz), 6.22 (1H, td, *J* = 15.6, 7.2 Hz), 4.31 (2H, q, *J* = 7.12 Hz, OCH_2CH_3), 3.69 (1H, t, *J* = 7.12 Hz), 2.92 (2H, t, *J* = 6.76 Hz), 1.33 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.2 (C, O-C=O), 147.6 (C), 133.3 (CH), 132.2 (C), 130.6 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 124.6 (CH), 115.9 (C, *C*≡N), 63.1 (CH_2, OCH_2CH_3), 37.6 (CH), 33.1 (CH_2), 14.0 (CH_3, OCH_2CH_3); LCMS: m/z 273.00 (M-H$^+$), calcd for $C_{14}H_{14}N_2O_4$ 274.10; Anal. calcd for $C_{14}H_{14}N_2O_4$ (274.10): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.480; H, 5.138; N, 10.103%.



54g′f

2-Cyano-pentanoic acid ethyl ester (54g′f): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2928, 2862, 2251 (C≡N), 1747 (O-C=O), 1464, 1371, 1257, 1030, 856 and 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.29 (2H, q, *J* = 7.13 Hz, OCH_2CH_3), 3.51 (1H, t, *J* = 6.9 Hz), 1.96 (2H, q, *J* = 7.6 Hz), 1.57 (2H, m), 1.35 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.01 (3H, t, *J* = 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.3 (C, O-C=O), 116.6 (C, *C*≡N), 62.7 (CH_2, OCH_2CH_3), 37.4 (CH), 31.8 (CH_2), 20.1 (CH_2), 14.0 (CH_3), 13.3 (CH_3, OCH_2CH_3); LRMS: m/z 156.0 (M+H$^+$), calcd for $C_8H_{13}NO_2$ 155.0946.

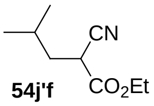


54h′f

2-Cyano-hexanoic acid ethyl ester (54h′f): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2942, 2249 (C≡N), 1747 (O-C=O), 1469, 1390, 1371, 1271, 1026, 927, 858 and 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.26 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.49 (1H, t, *J* = 7.0 Hz), 1.94 (2H, q, *J* = 7.2 Hz), 1.49 (2H, m), 1.40 (2H, m), 1.32 (3H, t, *J* = 6.8 Hz, OCH_2CH_3), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ

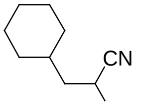
166.2 (C, O-C=O), 116.6 (C, *C*≡N), 62.7 (CH_2, O*C*H_2CH_3), 37.6 (CH), 29.6 (CH_2), 28.8 (CH_2), 21.9 (CH_2), 14.0 (CH_3), 13.6 (CH_3, OCH_2*C*H_3); GCMS: m/z 169.10 (M^+), calcd for $C_{10}H_{17}NO_2$ 169.1103.

2-Cyano-4-methyl-pentanoic acid ethyl ester (54j′f): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2964, 2249 (C≡N), 1747 (O-C=O), 1471, 1371, 1267 and 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (2H, q, *J* = 7.1 Hz, O*CH*$_2$$CH_3$), 3.36 (1H, dd, *J* = 9.12, 5.8Hz, CH), 1.74-1.60 (3H, m), 1.17 (3H, t, *J* = 7.16 Hz, OCH_2C*H*$_3$), 0.84 (3H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$), 0.82 (3H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.5 (C, O-C=O), 116.6 (C, *C*≡N), 62.7 (CH_2, O*C*H_2CH_3), 38.4 (CH_2), 36.0 (CH), 26.1 (CH), 22.4 (CH_3), 21.3 (CH_3), 14.0 (CH_3, OCH_2*C*H_3); GCMS: m/z 168.00 (M-H^+), calcd for $C_9H_{15}NO_2$ 169.1103.



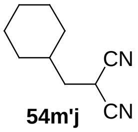
54j'f

2-Cyano-3-cyclohexyl-propionic acid ethyl ester (54m′f): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2928, 2852, 2249 (C≡N), 1745 (O-C=O), 1624, 1450, 1249, 1190, 1026 and 854 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.26 (2H, q, *J* = 7.2 Hz, O*CH*$_2$$CH_3$), 3.55 (1H, dd, *J* = 9.2, 6.4 Hz, CH), 1.89-1.66 (7H, m), 1.57-1.50 (1H, m), 1.32 (3H, t, *J* = 7.2 Hz), 1.36-1.10 (3H, m), 1.02-0.90 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.6 (C, O-C=O), 116.7 (C, *C*≡N), 62.7 (CH_2, O*C*H_2CH_3), 37.0 (CH_2), 35.3 (CH), 35.2 (CH), 33.0 (CH_2), 31.9 (CH_2), 26.2 (CH_2), 25.89 (CH_2), 25.77 (CH_2), 13.97 (CH_3, OCH_2*C*H_3); HRMS: m/z 232.1314 (M+Na^+), calcd for $C_{12}H_{19}NO_2Na$ 232.1313; Anal. calcd for $C_{12}H_{19}NO_2$ (209.1416): C, 68.87; H, 9.15; N, 6.69. Found: C, 68.781; H, 9.162; N, 6.655%.

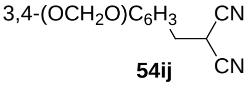


54m'f

2-Cyclohexylmethyl-malononitrile (54m′j): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2928, 2256 (C≡N), 1450 and 1352 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (1H, t, *J* = 7.7 Hz), 1.94 (2H, t, *J* = 7.3 Hz), 1.78-1.58 (6H, m), 1.36-1.14 (3H, m), 1.00 (2H, q, *J* = 11.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 112.9 (2 x C, *C*≡N), 37.8 (CH_2), 35.0 (CH), 32.1 (2 x CH_2), 26.0 (CH_2), 25.6 (2 x CH_2), 20.3 (CH); HRMS: m/z 201.1339 (M+K^+), calcd for $C_{10}H_{14}N_2K$ 201.0794; Anal. calcd for $C_{10}H_{14}N_2$ (162.1157): C, 74.03; H, 8.70; N, 17.27. Found: C, 74.020; H, 8.731; N, 17.410%.

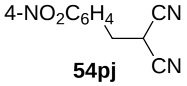


54m'j



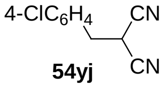
54ij

2-Benzo[1,3]dioxol-5-ylmethyl-malononitrile (54ij): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 78-80 °C; IR (KBr): ν_{max} 2934, 2251 (C≡N), 1608, 1446, 1039, 864 and 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83 (3H, m) [Ar-*H*]; 6.00 (2H, s, O*CH*$_2$O), 3.91 (1H, t, *J* = 6.8 Hz, CH), 3.21 (2H, d, *J* = 6.8 Hz, $ArCH_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 148.3 (C), 148.1 (C), 126.5 (C), 122.8 (CH), 113.2 (2 x C, *C*≡N), 109.3 (CH), 108.9 (CH), 101.5 (CH_2, O*C*H_2O), 36.4 (CH_2), 25.2 (CH); LRMS: m/z 199.00 (M-H^+), calcd for $C_{11}H_8N_2O_2$ 200.0586.



54pj

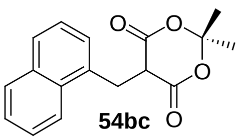
2-(4-Nitro-benzyl)-malononitrile (54pj): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 136-138 °C; IR (KBr): ν_{max} 3051, 2930, 2256 (C≡N), 1602, 1520, 1446, 1346, 1292, 885 and 754 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.31 (2H, d, *J* = 8.5 Hz), 7.56 (2H, d, *J* = 8.5 Hz), 4.05 (1H, t, *J* = 6.6 Hz), 3.43 (2H, d, *J* = 6.6 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 148.4 (C), 139.6 (C), 130.4 (2 x CH), 124.5 (2 x CH), 111.4 (2 x C, *C*≡N), 36.1 (CH$_2$), 24.4 (CH); LRMS: m/z 200.00 (M-H$^+$), calcd for $C_{10}H_7N_3O_2$ 201.0538.



54yj

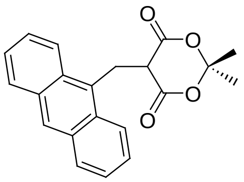
2-(4-Chloro-benzyl)-malononitrile (54yj): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 60 °C; IR (KBr): ν_{max} 2926, 2256 (C≡N), 1599, 1494, 1412, 1257, 848 and 711 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.41 (2H, d, *J* = 8.0 Hz), 7.29 (2H, d, *J* = 8.0 Hz), 3.95 (1H, t, *J* = 6.8 Hz), 3.28 (2H, d, *J* = 6.8 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 134.9 (C), 131.2 (C), 130.6 (2 x CH), 129.6 (2 x CH), 111.9 (2 x C, *C*≡N), 35.9 (CH$_2$), 24.8 (CH); LRMS: m/z 189.00 (M-H$^+$), calcd for $C_{10}H_7ClN_2$ 190.0298.

2,2-Dimethyl-5-naphthalen-1-ylmethyl-[1,3]dioxane-4,6-dione (54bc): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (neat): ν_{max} 2926, 1749 (O-C=O), 1385, 1294, 1070, 1016, 945, 788 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.07 (1H, d, *J* = 8.4 Hz), 7.89 (1H, d, *J* = 8.4 Hz), 7.79 (1H, d, *J* = 8.4 Hz), 7.65 (1H, d, *J* = 8.4 Hz), 7.56 (1H, t, *J* = 8.4 Hz), 7.50 (1H, t, *J* = 8.4 Hz), 7.44 (1H, t, *J* = 8.4 Hz) [Ar-*H*]; 3.93 (2H, d, *J* = 5.2 Hz, C*H*$_2$), 3.78 (1H, t, *J* = 5.2 Hz, C*H*), 1.70 (3H, s, C*H*$_3$), 1.69 (3H, s, C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT135) δ 165.3 (C, 2 x O-C=O), 134.1 (C), 133.9 (C), 131.2 (C), 129.2 (CH), 128.4 (CH), 127.9 (CH), 126.7 (CH), 125.7 (CH), 125.5 (CH), 122.8 (CH), 105.0 (C, O-*C*-O), 47.7 (CH), 28.8 (CH$_2$), 28.6 (CH$_3$), 26.5 (CH$_3$); LRMS: m/z 283.05 (M-H$^+$), calcd $C_{17}H_{16}O_4$ 284.1049.



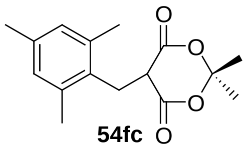
54bc

5-Anthracen-9-ylmethyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (54dc): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 140 °C; IR (KBr): ν_{max} 2924, 2876, 1736, 1311, 1203, 1068, 1033, 958, 908, 883, 796 and 729 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.45 (3H, d, *J* = 8.4 Hz), 8.03 (2H, d, *J* = 8.4 Hz), 7.57 (2H, br dt, *J* = 8.0, 1.2 Hz), 7.48 (2H, br dt, *J* = 8.0, 1.2 Hz) [Ar-*H*]; 4.50 (2H, d, *J* = 5.2 Hz), 3.97 (1H, t, *J* = 5.2 Hz), 1.77 (3H, s, CH$_3$), 1.64 (3H, s, CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.2 (2 x C, O-C=O), 131.5 (2 x C), 130.5 (C), 129.9 (2 x C), 129.4 (2 x CH), 127.5 (CH), 126.3 (2 x CH), 125.0 (2 x CH), 124.3 (2 x CH), 104.9 (C, O-C-O), 49.2 (CH), 28.8 (CH$_2$), 26.3 (CH$_3$), 23.9 (CH$_3$); LCMS: m/z 333.15 (M-H$^+$), calcd for $C_{21}H_{18}O_4$ 334.1205.



54dc

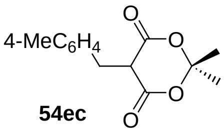
5-(2,4,6-Trimethyl-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (54fc): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν_{max} 2986, 1770 (O-C=O), 1394, 1043 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.87 (2H, s, Ar-



54fc

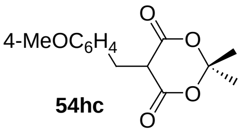
H), 3.67 (1H, t, *J* = 6.0 Hz, C*H*), 3.45 (2H, d, *J* = 6.0 Hz, $\mathrm{C}H_2$), 2.38 (6H, s, 2 x $\mathrm{C}H_3$), 2.26 (3H, s, $\mathrm{C}H_3$) [Ar-$C\mathrm{H}_3$]; 1.79 (3H, s, $\mathrm{C}H_3$), 1.76 (3H, s, $\mathrm{C}H_3$); ^{13}C NMR ($\mathrm{CDCl_3}$, DEPT135) δ 165.1 (C, 2 x O-C=O), 136.9 (2 x C), 136.3 (C), 131.8 (C), 129.3 (2 x CH), 104.9 (C, O-*C*-O), 47.1 (CH), 28.7 ($\mathrm{CH_2}$), 26.7 ($\mathrm{CH_3}$), 26.3 ($\mathrm{CH_3}$), 20.7 ($\mathrm{CH_3}$, Ar-$C\mathrm{H}_3$), 20.1 (2 x $\mathrm{CH_3}$, Ar-$C\mathrm{H}_3$); GCMS: m/z 276.13 ($\mathrm{M^+}$), 276.13, calcd $\mathrm{C_{16}H_{20}O_4}$ 276.1362.

2,2-Dimethyl-5-(4-methyl-benzyl)-[1,3]dioxane-4,6-dione (54ec): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 98 °C; IR (KBr): ν_{max} 3427, 2926, 1788, 1732, 1597,1518, 1442, 1277, 1203, 1114, 1060, 1024, 941, 912, 794 and 713 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.20 (2H, d, *J* = 8.0 Hz), 7.09 (2H, d, *J* = 8.0 Hz) [Ar-*H*]; 3.73 (1H, t, *J* = 4.8 Hz), 3.45 (2H, d, *J* = 4.8 Hz), 2.31 (3H, s, Ar$\mathrm{C}H_3$), 1.73 (3H, s, $\mathrm{C}H_3$), 1.50 (3H, s, $\mathrm{C}H_3$); ^{13}C NMR ($\mathrm{CDCl_3}$, DEPT-135) δ 165.3 (2 x C, O-C=O), 136.8 (C), 134.1 (C), 129.6 (2 x CH), 129.3 (2 x CH), 105.2 (C, O-C-O), 48.3 (CH), 31.8 ($\mathrm{CH_2}$), 28.5 ($\mathrm{CH_3}$), 27.3 ($\mathrm{CH_3}$), 21.0 ($\mathrm{CH_3}$); LRMS: m/z 247.05 ($\mathrm{M\text{-}H^+}$), calcd for $\mathrm{C_{14}H_{16}O_4}$ 248.1049.



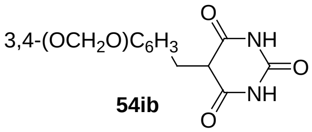
54ec

5-(4-Methoxy-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (54hc): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (KBr): ν_{max} 2930, 1745, 1701, 1610, 1510, 1458, 1032, 945, and 833 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.24 (2H, d, *J* = 8.8 Hz), 6.82 (2H, d, *J* = 8.8 Hz) [Ar-*H*]; 3.77 (3H, s, $\mathrm{OC}H_3$), 3.72 (1H, t, *J* = 4.8 Hz), 3.44 (2H, d, *J* = 5.2 Hz), 1.72 (3H, s, $\mathrm{C}H_3$), 1.48 (3H, s, $\mathrm{C}H_3$); ^{13}C NMR ($\mathrm{CDCl_3}$, DEPT-135) δ 165.4 (2 x C, O-C=O), 158.8 (C), 131.0 (2 x CH), 129.0 (C), 113.8 (2 x CH), 105.2 (C, O-C-O), 55.2 (C, $\mathrm{O}C\mathrm{H_3}$), 48.3 (CH), 31.5 ($\mathrm{CH_2}$), 28.4 ($\mathrm{CH_3}$), 27.4 ($\mathrm{CH_3}$); LRMS: m/z 263.00 ($\mathrm{M\text{-}H^+}$), calcd for $\mathrm{C_{14}H_{16}O_5}$ 264.0998.



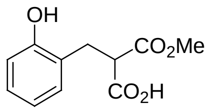
54hc

5-Benzo[1,3]dioxol-5-ylmethyl-pyrimidine-2,4,6-trione (54ib): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 210 °C; IR (KBr): ν_{max} 3223, 3096, 1714 (HN-C=O), 1504, 1440, 1356, 1248, 1039, 802 and 623 $\mathrm{cm^{-1}}$; ^{1}H NMR (DMSO-$\mathrm{D_6}$) δ 11.2 (2H, br s, 2 x N*H*), 6.78 (1H, d, *J* = 7.6 Hz), 6.67-6.56 (2H, m) [Ar-*H*]; 5.95 (2H, s, $\mathrm{OC}H_2\mathrm{O}$), 4.00-3.80 (1H, br s, C*H*), 3.16 (2H, br s, $\mathrm{ArC}H_2$); ^{13}C NMR (DMSO-$\mathrm{D_6}$, DEPT-135) δ 170.4 (2 x C, N-C=O), 151.0 (C, $\mathrm{(HN)_2}C$=O), 147.4 (C, O-*C*-O), 146.2 (C, O-*C*-O), 131.2 (C), 122.3 (CH), 109.6 (CH), 108.5 (CH), 101.2 ($\mathrm{CH_2}$, $\mathrm{O}C\mathrm{H_2O}$), 49.9 ($\mathrm{CH_2}$, $\mathrm{Ph}C\mathrm{H_2}$), 40.1 (CH); LRMS: m/z 261.00 ($\mathrm{M\text{-}H^+}$), calcd for $\mathrm{C_{12}H_{10}N_2O_5}$ 262.0590; Anal. calcd for $\mathrm{C_{12}H_{10}N_2O_5}$ (262.06): C, 54.97; H, 3.84; N, 10.68. Found: C, 55.019; H, 3.844; N, 10.573%.



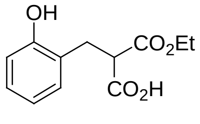
54ib

2-(2-Hydroxy-benzyl)-malonic acid monomethyl ester (54km): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3421, 2981, 1737, 1723 (O-C=O, $\mathrm{CO_2Et}$), 1710 (O-C=O, $\mathrm{CO_2H}$), 1495, 1259, 1234, 1153, 1101 and 755



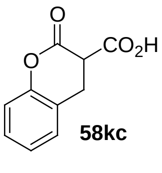
54km

cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.51 (2H, bs, CO$_2$*H*, O-*H*), 7.10 (2H, m), 6.84-6.78 (2H, m) [Ar-*H*]; 3.89 (1H, t, *J* = 7.2 Hz, C*H*), 3.70 (3H, s, OC*H*$_3$), 3.21 (2H, d, *J* = 7.6 Hz, ArC*H*$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 173.8 (C, *C*O$_2$Me), 170.4 (C, *C*O$_2$H), 154.1 (C), 131.0 (CH), 128.5 (CH), 123.8 (C), 120.8 (CH), 116.4 (CH), 53.0 (CH$_3$, O*C*H$_3$), 52.0 (CH), 29.5 (CH$_2$).; To a magnetically stirred ice-cold solution of malonic acid monomethyl ester **54km** (0.100 g) in ether (3 ml) was added an ice-cold ethereal diazomethane solution (excess, prepared from 1.5 gm of *N*-nitroso-*N*-methylurea and 15 ml of 60% aqueous KOH solution and 10 ml of ether) and stirred for 0.5 h at the same temperature. Careful evaporation of the excess diazomethane and solvent followed by purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 1:5) as eluent furnished the malonic acid dimethyl ester (95%) as oil. **2-(2-Hydroxy-benzyl)-malonic acid dimethyl ester:** Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3431 (O-H), 2954, 2924, 1737, 1725, 1712, 1459, 1439, 1351, 1234, 1154 and 755 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.13-7.08 (2H, m), 6.84 (2H, br t, *J* = 8.0 Hz) [Ar-*H*]; 6.69 (1H, bs, O*H*), 3.83 (1H, dt, *J* = 7.2, 2.0 Hz), 3.723 (3H, s, OC*H*$_3$), 3.72 (3H, s, OC*H*$_3$), 3.19 (2H, dd, *J* = 7.2, 2.0 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 170.2 (2 x C, *C*O$_2$Me), 154.2 (C), 131.0 (CH), 128.5 (CH), 124.1 (C), 120.8 (CH), 116.8 (CH), 52.8 (2 x CH$_3$, O*C*H$_3$), 52.5 (CH), 29.3 (CH$_2$); LRMS: m/z 237.00 (M-H$^+$), calcd for C$_{12}$H$_{14}$O$_5$ 238.0841.



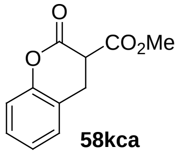
54kn

2-(2-Hydroxy-benzyl)-malonic acid monoethyl ester (54kn): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3433, 2981, 1737, 1722 (O-C=O, CO$_2$Et), 1710 (O-C=O, CO$_2$H), 1459, 1371, 1234, 1101 and 755 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.36 (2H, bs, CO$_2$*H*, O-*H*), 7.10 (2H, t, *J* = 8.0 Hz), 6.85-6.80 (2H, m) [Ar-*H*]; 4.21-4.13 (2H, m, OC*H*$_2$CH$_3$), 3.87 (1H, t, *J* = 8.0 Hz, C*H*), 3.09 (2H, d, *J* = 8.0 Hz, ArC*H*$_2$), 1.21 (3H, t, *J* = 8.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 174.1 (C, *C*O$_2$H), 170.1 (C, *C*O$_2$Et), 154.2 (C), 131.1 (CH), 128.5 (CH), 123.9 (C), 120.8 (CH), 116.5 (CH), 62.2 (CH$_2$, O*C*H$_2$CH$_3$), 52.3 (CH), 29.5 (CH$_2$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 239.00 (M+H$^+$), calcd for C$_{12}$H$_{14}$O$_5$ 238.0841; Anal. calcd for C$_{12}$H$_{14}$O$_5$ (238.08): C, 60.50; H, 5.92. Found: C, 60.503; H, 5.913 %.



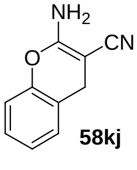
58kc

2-Oxo-chroman-3-carboxylic acid (58kc): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 120 °C; IR (neat): ν_{max} 3627 (CO$_2$H), 2966, 1778, 1775, 1690, 1218 and 1157 cm^{-1}; ^{1}H NMR (DMSO-D$_6$) δ 6.43 (2H, m), 6.20 (2H, m) [Ar-*H*]; 3.32 (1H, br s, C*H*), 3.07 (2H, br s, C*H*$_2$); ^{13}C NMR (DMSO-D$_6$, DEPT-135) δ 169.6 (C, O-*C*=O), 165.5 (C, O-*C*=O), 151.5 (C), 129.1 (CH), 128.7 (CH), 125.0 (CH), 122.0 (C), 116.6 (CH), 46.3 (CH), 27.0 (CH$_2$); Anal. calcd for C$_{10}$H$_8$O$_4$ (192.04): C, 62.50; H, 4.20. Found: C, 62.553; H, 4.224 %.



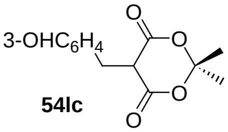
58kca

2-Oxo-chroman-3-carboxylic acid methyl ester (58kca): To a magnetically stirred ice-cold solution of acid **58kc** (0.134 g) in ether (3 ml) was added an ice-cold ethereal diazomethane solution (excess, prepared from 1.5 gm of *N*-nitroso-*N*-methylurea and 15 ml of 60% aqueous KOH solution and 10 ml of ether) and stirred for 0.5 h at the same temperature. Careful evaporation of the excess diazomethane and solvent followed by purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 1:5) as eluent furnished the ester **58kca** (95%) as white solid. Mp 88 °C; IR (neat): ν_{max} 2974, 1765, 1737, 1731, 1458, 1440, 1353, 1253, 1241, 1220, 1181, 1146, 778 and 760 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.27 (1H, t, *J* = 7.6 Hz), 7.22 (1H, d, *J* = 7.2 Hz), 7.12 (1H, t, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 8.4 HZ) [Ar-*H*]; 3.77 (1H, dd, *J* = 8.8, 6.0 Hz), 3.76 (3H, s, OC*H*$_3$), 3.42 (1H, dd, *J* = 16.0, 9.2 Hz), 3.18 (1H, dd, *J* = 16.0, 6.0 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.9 (C, O-*C*=O), 164.6 (C, O-*C*=O), 151.5 (C), 128.6 (CH), 128.2 (CH), 124.8 (CH), 120.6 (C), 116.7 (CH), 52.9 (CH$_3$, O*C*H$_3$), 46.1 (CH), 27.1 (CH$_2$); LRMS: m/z 205.00 (M-H$^+$), calcd for $C_{11}H_{10}O_4$ 206.0579; Anal. calcd for $C_{11}H_{10}O_4$ (206.06): C, 64.07; H, 4.89. Found: C, 64.038; H, 4.916 %.



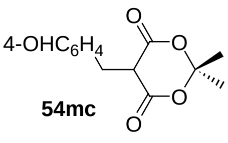
58kj

2-Amino-4H-chromene-3-carbonitrile (58kj): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 126 °C; IR (neat): ν_{max} 3447 (N*H*$_2$), 3332 (N*H*$_2$), 2191, 1664, 1659, 1608, 1581, 1492, 1457, 1410, 1266, 1229, 1184 and 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.23-7.15 (1H, m), 7.15-7.04 (2H, m), 6.92 (1H, d, *J* = 8.0 Hz) [Ar-*H*]; 4.65 (2H, br s, N*H*$_2$), 3.52 (2H, s, C*H*$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 160.1 (C), 149.3 (C), 128.6 (CH), 127.9 (CH), 124.7 (CH), 120.4 (C), 118.9 (C), 116.3 (CH), 53.4 (C), 23.8 (CH$_2$); Anal. calcd for $C_{10}H_8N_2O$ (172.06): C, 69.76; H, 4.68; N, 16.27. Found: C, 69.749; H, 4.680; N, 16.480 %.



54lc

5-(3-Hydroxy-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (54lc): Purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 116 °C; IR (neat): ν_{max} 3369, 1777, 1736 (O-C=O), 1730, 1601, 1460, 1399, 1354, 1320, 1227, 1199, 1084, 1066, 959, 877 and 782 cm^{-1}; ^{1}H NMR (DMSO-D$_6$) δ 8.4 (1H, br s, O*H*), 6.13 (1H, m), 5.73 (3H, m) [Ar-*H*]; 3.82 (1H, s, C*H*), 2.30 (2H, d, *J* = 4.0 Hz), 0.88 (3H, s, C*H*$_3$), 0.67 (3H, s, C*H*$_3$); ^{13}C NMR (DMSO-D$_6$, DEPT-135) δ 166.2 (2 x C, O-C=O), 157.6 (C), 139.7 (C), 129.5 (CH), 120.1 (CH), 116.5 (CH), 113.8 (CH), 105.4 (C, O-C-O), 47.1 (CH), 31.6 (CH$_2$), 28.3 (CH$_3$), 26.7 (CH$_3$); LRMS: m/z 249.00 (M-H$^+$), calcd for $C_{13}H_{14}O_5$ 250.0841; Anal. calcd for $C_{13}H_{14}O_5$ (250.08): C, 62.39; H, 5.64. Found: C, 62.476; H, 5.666 %.

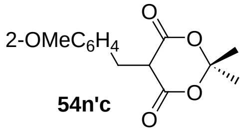


54mc

5-(4-Hydroxy-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (54mc): Purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 118 °C; IR (neat): ν_{max} 3347, 1780, 1727 (O-C=O), 1493, 1357, 1306, 1205, 1176, 1073 and

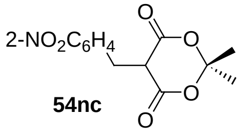
734 cm^{-1}; ^{1}H NMR (DMSO-D$_6$) δ 8.32 (1H, br s, O*H*), 6.12 (2H, d, *J* = 7.92 Hz), 5.73 (2H, d, *J* = 7.96 Hz) [Ar-*H*]; 3.76 (1H, br s, C*H*), 2.28 (2H, br s), 0.86 (3H, s, C*H*$_3$), 0.63 (3H, s, C*H*$_3$); ^{13}C NMR (DMSO-D$_6$, DEPT-135) δ 166.2 (2 x C, O-C=O), 156.4 (C), 130.8 (2 x CH), 128.3 (C), 115.4 (2 x CH), 105.3 (C, O-C-O), 47.8 (CH), 31.0 (CH$_2$), 28.3 (CH$_3$), 26.8 (CH$_3$); LRMS: m/z 249.00 (M-H$^+$), calcd for $C_{13}H_{14}O_5$ 250.0841; Anal. calcd for $C_{13}H_{14}O_5$ (250.08): C, 62.39; H, 5.64. Found: C, 62.345; H, 5.655 %.

5-(2-Methoxy-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (54n'c): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 118 °C; IR (KBr): ν_{max} 2928, 2874, 1784, 1749 (O-C=O), 1602, 1496, 1388, 1068, 1016, 949 and 763 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.34 (1H, br d, *J* = 7.6 Hz), 7.23 (1H, br t, *J* = 8.0 Hz), 6.92 (1H, br t, *J* = 7.2 Hz), 6.85 (1H, br d, *J* = 8.4 Hz) [Ar-*H*]; 4.02 (1H, t, *J* = 6.0 Hz), 3.82 (3H, s, OC*H*$_3$), 3.39 (2H, d, *J* = 5.6 Hz), 1.76 (3H, s, C*H*$_3$), 1.72 (3H, s, C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.3 (2 x C, O-C=O), 157.1 (C), 131.8 (CH), 128.3 (CH), 125.7 (C), 120.6 (CH), 110.2 (CH), 104.8 (C, O-C-O), 55.2 (CH$_3$, O*C*H$_3$), 46.1 (CH), 28.6 (CH$_3$), 28.0 (CH$_2$), 26.5 (CH$_3$); LRMS: m/z 263.00 (M-H$^+$), calcd for $C_{14}H_{16}O_5$ 264.0998; Anal. calcd for $C_{14}H_{16}O_5$ (264.0998): C, 63.63; H, 6.10. Found: C, 63.586; H, 6.136 %.



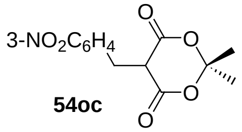
54n'c

2,2-Dimethyl-5-(2-nitro-benzyl)-[1,3]dioxane-4,6-dione (54nc): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν_{max} 3501, 2922, 1780, 1741, 1641, 1525, 1448, 1358, 1197, 1062, 945, 912, 860, 808, 785 and 734 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.01 (1H, d, *J* = 8.4 Hz), 7.77 (1H, d, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 7.2 Hz), 7.44 (1H, t, *J* = 8.0 Hz) [Ar-*H*]; 4.20 (1H, t, *J* = 5.6 Hz), 3.65 (2H, d, *J* = 5.6 Hz), 1.82 (3H, s, CH$_3$), 1.78 (3H, s, CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 164.6 (2 x C, O-C=O), 149.3 (C), 134.8 (CH), 133.3 (CH), 133.0 (C), 128.4 (CH), 125.0 (CH), 105.3 (C, O-C-O), 47.7 (CH), 29.3 (CH$_2$), 28.7 (CH$_3$), 26.1 (CH$_3$); LRMS: m/z 278.00 (M-H$^+$), calcd for $C_{13}H_{13}NO_6$ 279.0743.



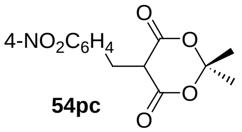
54nc

2,2-Dimethyl-5-(3-nitro-benzyl)-[1,3]dioxane-4,6-dione (54oc): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 129 °C; IR (KBr): ν_{max} 2926, 1778, 1736, 1531, 1350, 1315, 1277, 1197, 1066, 1022, 952, 922, 873, 815 and 740 cm^{-1}; ^{1}H NMR (DMSO-D$_6$) δ 8.22 (1H, br s), 8.08 (1H, d, *J* = 7.6 Hz), 7.77 (1H, br s), 7.58 (1H, t, *J* = 8.0 Hz) [Ar-*H*]; 4.89 (1H, br s, C*H*), 3.43 (2H, br s, ArC*H*$_2$), 1.84 (3H, s, CH$_3$), 1.65 (3H, s, CH$_3$); ^{13}C NMR (DMSO-D$_6$, DEPT-135) δ 165.3 (2 x C, O-C=O), 147.5 (C), 140.7 (C), 136.3 (CH), 129.3 (CH), 123.9 (CH), 121.2 (CH), 105.0 (C, O-C-O), 46.7 (CH), 30.6 (CH$_2$), 27.8 (CH$_3$), 25.8 (CH$_3$); LRMS: m/z 278.25 (M-H$^+$), calcd for $C_{13}H_{13}NO_6$ 279.0743.



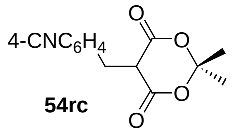
54oc

2,2-Dimethyl-5-(4-nitro-benzyl)-[1,3]dioxane-4,6-dione (54pc): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 120 °C; IR (KBr): ν_{max} 3427,



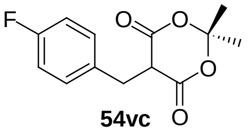
54pc

2926, 1778, 1732, 1664, 1346, 1064, 943, 858, 802 and 758 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.15 (2H, d, *J* = 8.8 Hz), 7.54 (2H, d, *J* = 7.2 Hz) [Ar-*H*]; 3.84 (1H, t, *J* = 4.8 Hz), 3.58 (2H, d, *J* = 4.8 Hz), 1.80 (3H, s, CH$_3$), 1.69 (3H, s, CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 164.6 (2 x C, O-C=O), 147.1 (C), 144.7 (C), 130.8 (2 x CH), 123.6 (2 x CH), 105.4 (C, O-C-O), 47.6 (CH), 31.4 (CH$_2$), 28.3 (CH$_3$), 26.9 (CH$_3$); LRMS: m/z 278.20 (M-H$^+$), calcd for $C_{13}H_{13}NO_6$ 279.0743.



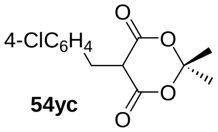
54rc

4-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-benzonitrile (54rc): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν$_{max}$ 2926, 2854, 2226 (C≡N), 1778, 1734, 1340, 1066 and 941 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.59 (2H, d, *J* = 8.4 Hz), 7.47 (2H, d, *J* = 8.4 Hz) [Ar-*H*]; 3.78 (1H, t, *J* = 4.4 Hz), 3.53 (2H, d, *J* = 4.4 Hz), 1.78 (3H, s, C*H*$_3$), 1.65 (3H, s, C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 164.7 (2 x C, O-C=O), 142.6 (C), 132.3 (2 x CH), 130.7 (2 x CH), 118.6 (C, C≡N), 111.2 (C), 105.4 (C, O-C-O), 47.7 (CH), 31.7 (CH$_2$), 28.4 (CH$_3$), 26.9 (CH$_3$); LRMS: m/z 258.05 (M-H$^+$), calcd for $C_{14}H_{13}NO_4$ 259.0845.



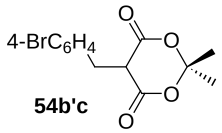
54vc

5-(4-Fluoro-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (54vc): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν$_{max}$ 2926, 1786 and 1739 (O-C=O), 1602, 1512, 1456, 1381, 1222, 1059, 949, 910, 837, 796 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.29 (2H, m), 6.96 (2H, t, *J* = 8.8 Hz) [Ar-*H*]; 3.75 (1H, t, *J* = 4.8 Hz, C*H*), 3.45 (2H, d, *J* = 4.8 Hz, C*H*$_2$), 1.73 (3H, s, C*H*$_3$), 1.53 (3H, s, C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT135) δ 165.1 (C, 2 x O-C=O), 161.9 (C, d, *J* = 244.3 Hz, *C*-F), 132.7 (C, d, *J* = 3.4 Hz), 131.5 (2 x CH, d, *J* = 7.9 Hz), 115.3 (2 x CH, *J* = 21.1 Hz), 105.2 (C, O-*C*-O), 48.1 (CH), 31.2 (CH$_2$), 28.3 (CH$_3$), 27.2 (CH$_3$); LRMS: m/z 251.15 (M-H$^+$), calcd $C_{13}H_{13}FO_4$ 252.0798.



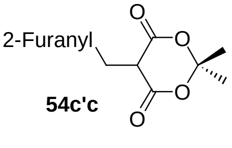
54yc

5-(4-Chloro-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (54yc): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 120 °C; IR (KBr): ν$_{max}$ 2926, 1734, 1494, 1381, 1288, 1109, 1059, 1012, 951, 910, 825, 792 and 707 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.26 (4H, m) [Ar-*H*]; 3.74 (1H, t, *J* = 4.8 Hz, C*H*), 3.46 (2H, d, *J* = 4.8 Hz, ArC*H*$_2$), 1.75 (3H, s, CH$_3$), 1.58 (3H, s, CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.0 (2 x C, O-C=O), 135.5 (C), 133.1 (C), 131.3 (2 x CH), 128.7 (2 x CH), 105.2 (C, O-C-O), 48.0 (CH), 31.3 (CH$_2$), 28.4 (CH$_3$), 27.2 (CH$_3$); LRMS: m/z 267.00 (M-H$^+$), calcd for $C_{13}H_{13}ClO_4$ 268.0502.



54b′c

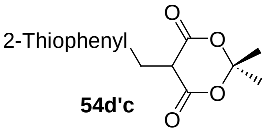
5-(4-Bromo-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (54b′c): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 128 °C; IR (KBr): ν$_{max}$ 2928, 1741, 1660, 1491, 1383, 1060, 1006, 937, 910 and 781 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.41 (2H, d, *J* = 8.4 Hz), 7.22 (2H, d, *J* = 8.4 Hz) [Ar-*H*]; 3.74 (1H, t, *J* = 4.8 Hz), 3.44 (2H, d, *J* = 4.8 Hz), 1.75 (3H, s, C*H*$_3$), 1.59 (3H, s, C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.0 (2 x C, O-C=O), 136.1 (C), 131.6 (4 x CH), 121.2 (C), 105.2 (C, O-C-O), 47.9 (CH),



54c'c

31.3 (CH_2), 28.4 (CH_3), 27.1 (CH_3); LRMS: m/z 312.10 (M^+), 314.10 (M^++2), calcd for $C_{13}H_{13}BrO_4$ 311.9997.

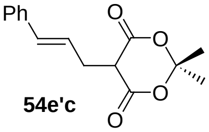
5-Furan-2-ylmethyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (54c′c): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν_{max} 2922, 1790, 1749, 1313, 1008, 945 and 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (1H, d, *J* = 1.20 Hz), 6.29 (1H, dd, *J* = 3.2, 2.0 Hz), 6.18 (1H, d, *J* = 2.8 Hz) [Ar-*H*]; 3.83 (1H, t, *J* = 3.6 Hz), 3.52 (2H, d, *J* = 3.6 Hz), 1.79 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.8 (2 x C, O-C=O), 150.5 (C), 141.6 (CH), 110.6 (CH), 107.8 (CH), 105.2 (C, O-C-O), 45.5 (CH), 29.7 (CH_2), 28.4 (CH_3), 27.1 (CH_3); LRMS: m/z 223.00 (M-H^+), calcd for $C_{11}H_{12}O_5$ 224.0685.



54d'c

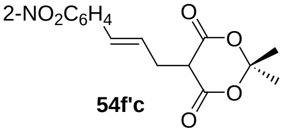
2,2-Dimethyl-5-thiophen-2-ylmethyl-[1,3]dioxane-4,6-dione (54d′c): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν_{max} 3001, 2926, 1784, 1747, 1342, 1296, 1203, 1072, 1012, 939 and 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.16 (1H, dd, *J* = 4.0, 1.20 Hz), 6.98 (1H, d, *J* = 2.4 Hz), 6.92 (1H, dd, *J* = 4.8, 3.2 Hz) [Ar-*H*]; 3.77 (1H, t, *J* = 4.4 Hz), 3.70 (2H, d, *J* = 4.4 Hz), 1.76 (3H, s, C*H*$_3$), 1.59 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.9 (2 x C, O-C=O), 138.1 (C), 127.9 (CH), 126.9 (CH), 125.1 (CH), 105.3 (C, O-C-O), 48.2 (CH), 28.4 (CH_2), 27.2 (CH_3), 26.4 (CH_3); LRMS: m/z 239.00 (M-H^+), calcd for $C_{11}H_{12}O_4S$ 240.0456.

1b: Amine/acid-catalyzed hydrogenation-olefination-hydrogenation reactions in one-pot: In an ordinary glass vial equipped with a magnetic stirring bar, to morpholine 50e (0.05 mmol, 5 mol%) and trifluoro-acetic acid (0.05 mmol, 5 mol%) were added and stirred at 25 °C for 10 minutes then THF solvent (4.0 mL), *trans*-cinnamaldehyde **25a** or *o*-nitrocinnamaldehyde **25b** (1.0 mmol) and Hantzsch ester **15** (1.0 mmol) were added and stirring was continued at the same temperature for the time indicated in Scheme 5. After completion of the hydrogenation, to the crude reaction mixture were added 1.0 equiv of Meldrum's acid **48c** and 1.0 equiv of Hantzsch ester **15** and stirring was continued at the same temperature for the time indicated in Scheme 5. The crude reaction mixture was worked up with aqueous $NaHCO_3$ and NH_4Cl solutions 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 **54** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



54e'c

2,2-Dimethyl-5-(3-phenyl-allyl)-[1,3]dioxane-4,6-dione (54e′c): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 90 °C; IR (KBr): ν_{max} 2924, 1743, 1315, 1205, 1068, 945, 787 and 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36-7.20 (5H, m) [Ar-*H*]; 6.60 (1H, d, *J* = 16.0 Hz, olefinic-*H*), 6.25 (1H, td, *J* = 16.0, 7.6 Hz, olefinic-*H*), 3.66 (1H, t, *J* = 4.8 Hz), 3.03 (2H, ddd, *J* = 7.2, 5.2, 1.2 Hz), 1.79 (3H, s, C*H*$_3$), 1.74 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.9 (2 x C, O-C=O), 136.7 (C), 134.7 (CH), 128.4 (2 x CH),

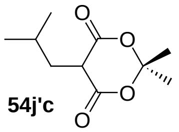


54f'c

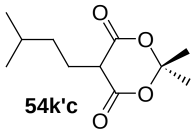
127.6 (CH), 126.3 (2 x CH), 123.9 (CH), 105.1 (C, O-C-O), 46.6 (CH), 29.6 (CH$_2$), 28.4 (CH$_3$), 26.9 (CH$_3$); LRMS: m/z 259.20 (M-H$^+$), calcd for $C_{15}H_{16}O_4$ 260.1049.

2,2-Dimethyl-5-[3-(2-nitro-phenyl)-allyl]-[1,3]dioxane-4,6-dione (54f′c): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 108 °C; IR (KBr): ν_{max} 2951, 2878, 1780, 1734, 1608, 1520, 1340, 1207, 829, 788 and 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.92 (1H, d, *J* = 8.4 Hz), 7.57-7.54 (2H, m), 7.40-7.36 (1H, m) [Ar-*H*]; 7.06 (1H, d, *J* = 16.0 Hz, olefinic-*H*), 6.31 (1H, td, *J* = 16.0, 7.2 Hz, olefinic-*H*), 3.71 (1H, t, *J* = 5.2 Hz), 3.07 (2H, br t, *J* = 6.8 Hz, PhCH=CHC*H*$_2$), 1.83 (3H, s, C*H*$_3$), 1.78 (3H, s, C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 164.7 (2 x C, O-C=O), 147.8 (C), 133.0 (CH), 132.6 (C), 129.9 (CH), 129.6 (CH), 128.8 (CH), 128.1 (CH), 124.5 (CH), 105.2 (C, O-C-O), 46.6 (CH), 29.4 (CH$_2$), 28.5 (CH$_3$), 26.8 (CH$_3$); LRMS: m/z 304.00 (M-H$^+$), calcd for $C_{15}H_{15}NO_6$ 305.0899; Anal. calcd for $C_{15}H_{15}NO_6$ (305.09): C, 59.01; H, 4.95; N, 4.59. Found: C, 59.018; H, 4.938; N, 4.437%.

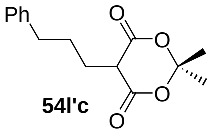
5-Isobutyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (54j′c): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (KBr): ν_{max} 2957, 1745, 1641, and 1211 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.44 (1H, t, *J* = 5.2 Hz), 1.99 (2H, m), 1.80 (3H, s, C*H*$_3$), 1.76 (3H, s, C*H*$_3$), 0.95 (6H, d, *J* = 6.0 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.0 (2 x C, O-C=O), 104.8 (C, O-C-O), 44.2 (CH), 35.4 (CH$_2$), 28.6 (CH), 26.9 (CH$_3$), 25.9 (CH$_3$), 22.1 (2 x CH$_3$); LRMS: m/z 199.10 (M-H$^+$), calcd for $C_{10}H_{16}O_4$ 200.1049.


54j'c

2,2-Dimethyl-5-(3-methyl-butyl)-[1,3]dioxane-4,6-dione (54k′c): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (Neat): ν_{max} cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.51 (1H, t, *J* = 5.2 Hz, C*H*), 2.11 (2H, m), 1.79 (3H, s, C*H*$_3$), 1.76 (3H, s, C*H*$_3$), 1.60 (1H, m), 1.35 (2H, m), 0.91 (6H, d, *J* = 6.4 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.6 (2 x C, O-C=O), 104.7 (C, O-C-O), 46.2 (CH), 35.3, 28.4, 28.1, 26.9, 24.6, 22.2 (2 x CH$_3$); LRMS: m/z 213.10 (M-H$^+$), calcd for $C_{11}H_{18}O_4$ 214.1205.

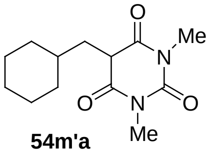

54k'c

2,2-Dimethyl-5-(3-phenyl-propyl)-[1,3]dioxane-4,6-dione (54l′c): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν_{max} 3364, 2926, 1784, 1750 and 1452 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.28-7.17 (5H, m), 3.47 (1H, t, *J* = 4.8 Hz), 2.69 (2H, t, *J* = 7.6 Hz), 2.17 (2H, m), 1.82 (2H, m), 1.74 (6H, s, 2 x C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.4 (2 x C, O-C=O), 141.5 (C), 128.39 (2 x CH), 128.36 (2 x CH), 125.9 (CH), 104.8 (C, O-C-O), 46.1 (CH), 35.8 (CH$_2$), 28.4 (CH$_2$), 28.1 (CH$_2$), 26.8 (CH$_3$), 26.3 (CH$_3$); LRMS: m/z 261.15 (M-H$^+$), calcd for $C_{15}H_{18}O_4$ 262.1205.



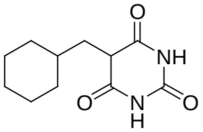
54l'c

5-Cyclohexylmethyl-1,3-dimethyl-pyrimidine-2,4,6-trione (54m′a): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 80 °C; IR (KBr): ν_{max} 3433, 2924, 2851, 1695, 1454, 1379, 1284 and 910 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ



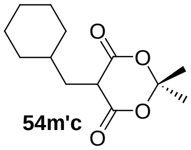
54m'a

3.50 (1H, t, *J* = 6.4 Hz), 3.30 (6H, s, 2 x N-CH_3), 1.94 (2H, t, *J* = 6.8 Hz), 1.72-1.63 (5H, m), 1.56-1.41 (1H, m), 1.26-1.18 (3H, m), 0.95-0.91 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.9 (2 x C, N-C=O), 151.7 (C, $N(CH_3)_2C=O$), 47.1 (CH), 38.9 (CH_2), 34.8 (CH), 32.8 (2 x CH_2), 28.5 (2 x CH_3, N-*C*H_3), 26.2 (CH_2), 25.9 (2 x CH_2); HRMS: m/z 253.1543 (M+H$^+$), calcd for $C_{13}H_{20}N_2O_3H$ 253.1552; Anal. calcd for $C_{13}H_{20}N_2O_3$ (253.16): C, 61.88; H, 7.99; N, 11.10. Found: C, 61.783; H, 8.036; N, 11.243%.



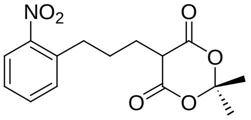
54m'b

5-Cyclohexylmethyl-pyrimidine-2,4,6-trione (54m′b): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 230 °C; IR (KBr): ν_{max} 3219, 3099, 2924, 2849, 1741, 1685, 1444,1369, 1344, 1213, 1051, 987 and 839 cm^{-1}; ^{1}H NMR (DMSO-D_6) δ 11.12 (2H, br s, 2 x N-*H*), 3.49 (1H, s, CH), 1.76 (2H, m), 1.58 (5H, m), 1.40 (1H, br s), 1.10 (3H, m), 0.82 (2H, m); ^{13}C NMR (DMSO-D_6, DEPT-135) δ 171.2 (2 x C, HN-C=O), 151.4 (C, $(NH)_2C=O$), 46.3 (CH), 35.6 (CH_2), 35.2 (CH), 32.9 (2 x CH_2), 26.4 (CH_2), 26.1 (2 x CH_2); HRMS: m/z 247.1065 (M+Na$^+$), calcd for $C_{11}H_{16}N_2O_3Na$ 247.1059; Anal. calcd for $C_{11}H_{16}N_2O_3$ (224.12): C, 58.91; H, 7.19; N, 12.49. Found: C, 58.954; H, 7.150; N, 12.427%.



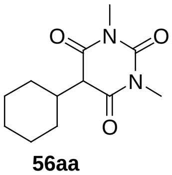
54m'c

5-Cyclohexylmethyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (54m′c): Purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 98 °C; IR (KBr): ν_{max} 2999, 1745, 1647, 1446, 1336, 1315, 1296, 1205, 1060, 1006 and 945 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.51 (1H, t, *J* = 5.6 Hz), 2.02 (2H, t, *J* = 6.40 Hz), 1.82 (3H, s, C*H*$_3$), 1.79 (3H, s, C*H*$_3$), 1.75-1.60 (6H, m), 1.29-1.16 (3H, m), 1.02-0.94 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.1 (2 x C, O-C=O), 104.8 (C, O-C-O), 43.6 (CH), 35.2 (CH), 33.9 (CH_2), 32.9 (2 x CH_2), 28.6 (CH_3), 26.9 (CH_3), 26.3 (CH_2), 26.0 (2 x CH_2); HRMS: m/z 241.1440 (M+H$^+$), calcd for $C_{13}H_{20}O_4H$ 241.1440; Anal. calcd for $C_{13}H_{20}O_4$ (240.14): C, 64.98; H, 8.39. Found: C, 65.059; H, 8.336%.



54p'c

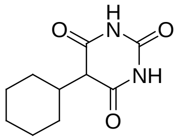
2,2-Dimethyl-5-[3-(2-nitro-phenyl)-propyl]-[1,3]dioxane-4,6-dione (54p′c): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 112 °C; IR (KBr): ν_{max} 2951, 2878, 1790, 1741, 1608, 1520, 1348, 1269, 1203, 987, 887, 788 and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.90 (1H, br d, *J* = 8.4 Hz), 7.53 (1H, br t, *J* = 7.6 Hz), 7.38 (1H, d, *J* = 8.0 Hz), 7.35 (1H, t, *J* = 7.6 Hz) [Ar-H]; 3.59 (1H, t, *J* = 4.8 Hz), 2.95 (2H, t, *J* = 8.0 Hz), 2.22-2.17 (2H, m), 1.92-1.86 (2H, m), 1.81 (3H, s, C*H*$_3$), 1.75 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.3 (C, O-*C*=O), 149.3 (C), 136.4 (C), 133.0 (CH), 131.8 (CH), 127.2 (CH), 124.7 (CH), 104.9 (C, O-*C*-O), 45.9 (CH), 32.5 (CH_2), 28.4 (CH_3), 27.5 (CH_2), 26.6 (CH_3), 25.8 (CH_2); LRMS m/z 306.05 (M-H$^+$), calcd for $C_{15}H_{17}NO_6$ 307.1056; Anal. calcd for $C_{15}H_{17}NO_6$ (307.11): C, 58.63; H, 5.58; N, 4.56. Found: C, 58.726; H, 5.560; N, 4.617%.



56aa

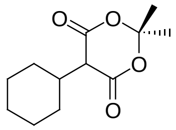
5-Cyclohexyl-1,3-dimethyl-pyrimidine-2,4,6-trione (56aa): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 95 °C; IR (KBr): ν_{max} 2935, 2914, 1718, 1658, 1444, 1369, 1257, 1113, 987 and 763 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.33 (1H, d, *J* = 3.6 Hz, CH), 3.29 (6H, s, 2 x N-C*H*$_3$), 2.19 (1H, m, C*H*), 1.76 (2H, m), 1.65 (3H, m), 1.25 (4H, m), 1.10 (1H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.5 (2 x C, N-C=O), 151.9 (C, (NMe)$_2$*C*=O), 55.5 (CH), 44.1 (CH), 29.9 (2 x CH$_2$), 28.3 (2 x CH$_3$, N-*C*H$_3$), 26.3 (2 x CH$_2$), 25.5 (CH$_2$); LRMS: m/z 237.10 (M-H$^+$), calcd for $C_{12}H_{18}N_2O_3$ 238.1317.

5-Cyclohexyl-pyrimidine-2,4,6-trione (56ab): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 230 °C; IR (KBr): ν_{max} 3209, 3070, 2939, 2860, 1757, 1685, 1554, 1442, 1358, 1217 and 821 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 12.48 (2H, s, 2 x N*H*), 4.41 (1H, d, *J* = 3.2 Hz), 3.30 (1H, m, CH), 2.97 (2H, br d, *J* = 12.0 Hz), 2.58-2.40 (4H, m), 2.28 (1H, m), 2.85 (3H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 170.2 (2 x C, N-C=O), 151.0 (C, (NH)$_2$*C*=O), 54.0 (CH), 41.5 (CH), 29.4 (2 x CH$_2$), 25.9 (2 x CH$_2$), 25.4 (CH$_2$); LRMS: m/z 209.00 (M-H$^+$), calcd for $C_{10}H_{14}N_2O_3$ 210.1004.



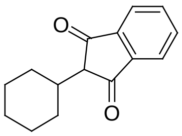
56ab

5-Cyclohexyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (56ac): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν_{max} 2934, 2854, 1780, 1738, 1315, 1308, 1213 and 955 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.32 (1H, d, *J* = 3.2 Hz, CH), 2.44-2.30 (1H, m), 1.74 (6H, s, 2 x C*H*$_3$), 1.68-1.62 (6H, m), 1.32-1.18 (4H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.3 (2 x C, O-C=O), 104.7 (C, O-C-O), 51.4 (CH), 39.6 (CH), 29.4 (2 x CH$_2$), 28.2 (CH$_3$), 27.7 (CH$_3$), 26.5 (2 x CH$_2$), 25.6 (CH$_2$); LRMS: m/z 225.10 (M-H$^+$), calcd for $C_{12}H_{18}O_4$ 226.1205.



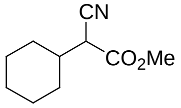
56ac

2-Cyclohexyl-indan-1,3-dione (56ad): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 70 °C; IR (KBr): ν_{max} 2924, 2854, 1709, 1593, 1452, 1350, 1275, 1047, 825 and 758 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.93 (2H, d, *J* = 8.8 Hz), 7.80 (2H, d, *J* = 6.0 Hz) [Ar-*H*]; 2.83 (1H, d, *J* = 4.0 Hz), 2.21 (1H, m), 1.70-1.50 (5H, m), 1.42 (2H, m), 1.30-1.08 (3H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 201.3 (2 x C, C=O), 142.8 (2 x C), 135.4 (2 x CH), 122.8 (2 x CH), 58.7 (CH), 39.3 (CH), 29.7 (2 x CH$_2$), 26.4 (2 x CH$_2$), 25.7 (CH$_2$); LRMS: m/z 227.10 (M-H$^+$), calcd for $C_{15}H_{16}O_2$ 228.1150.

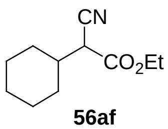


56ad

Cyano-cyclohexyl-acetic acid methyl ester (56ae): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2930, 2856, 2249 (C≡N), 1749 (O-C=O), 1452, 1257, and 1016 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.80 (3H, s, OC*H*$_3$), 3.39 (1H, d, *J* = 5.6 Hz, CH), 2.04 (1H, m), 1.78-1.61 (6H, m), 1.30-1.15 (4H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.3 (C, O-C=O), 115.6 (C, *C*≡N), 53.2 (CH$_3$, O*C*H$_3$), 44.4 (CH), 38.8 (CH), 31.0 (CH$_2$), 29.4 (CH$_2$), 25.7 (CH$_2$), 25.5 (CH$_2$), 25.4 (CH$_2$); LRMS: m/z 180.15 (M-H$^+$), calcd for $C_{10}H_{15}NO_2$ 181.1103.

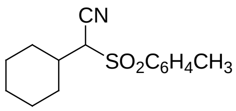


56ae



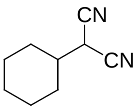
56af

Cyano-cyclohexyl-acetic acid ethyl ester (56af): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2932, 2856, 2251 (C≡N), 1745 (O-C=O), 1450, 1253, 1192 and 1028 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.36 (1H, d, *J* = 5.6 Hz), 2.03 (1H, m), 1.78-1.60 (6H, m), 1.30 (4H, m), 1.27 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.8 (C, O-C=O), 115.7 (C, *C*≡N), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 44.5 (CH), 38.8 (CH), 31.0 (CH$_2$), 29.3 (CH$_2$), 25.8 (CH$_2$), 25.5 (CH$_2$), 25.4 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 194.15 (M-H$^+$), calcd for $C_{11}H_{17}NO_2$ 195.1259.



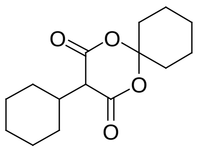
56ai

Cyclohexyl-(toluene-4-sulfonyl)-acetonitrile (56ai): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 80 °C; IR (KBr): ν_{max} 2924, 2854, 2249, 1595, 1448, 1323, 1170, 1149, 1086, 815 and 748 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.88 (2H, d, *J* = 8.0 Hz), 7.42 (2H, d, *J* = 8.0 Hz) [Ar-*H*]; 3.74 (1H, d, *J* = 3.6 Hz), 2.48 (3H, s, PhC*H*$_3$), 2.17 (1H, m), 1.82-1.60 (4H, m), 1.42-1.20 (6H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 146.3 (C), 134.2 (C), 130.2 (2 x CH), 129.1 (2 x CH), 113.2 (C, *C*≡N), 63.5 (CH), 36.0 (CH), 32.2 (CH$_2$), 29.4 (CH$_2$), 26.0 (CH$_2$), 25.32 (CH$_2$), 25.30 (CH$_2$), 21.8 (CH$_3$); LRMS: m/z 276.0 (M-H$^+$), calcd $C_{15}H_{19}NO_2S$ 277.1136; HRMS: m/z 300.1026 (M+Na$^+$), calcd for $C_{15}H_{19}NO_2SNa$ 300.1034.



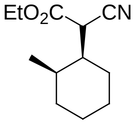
56aj

2-Cyclohexyl-malononitrile (56aj): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2932, 2858, 2254, 1452, 1319, 1224, 1170, 1062 and 892 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.58 (1H, d, *J* = 5.6 Hz), 1.96 (3H, m), 1.85 (2H, m), 1.73 (1H, m), 1.33-1.17 (5H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 111.9 (2 x C, *C*≡N), 39.3 (CH), 29.9 (2 x CH$_2$), 29.3 (CH), 25.2 (2 x CH$_2$), 25.0 (CH$_2$); LRMS: m/z 147.05 (M-H$^+$), calcd for $C_9H_{12}N_2$ 148.1000.



56ao

3-Cyclohexyl-1,5-dioxa-spiro[5.5]undecane-2,4-dione (56ao): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 134 °C; IR (KBr): ν_{max} 2935, 2874, 1784, 1739, 1450, 1302, 1209, 995 and 933 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.35 (1H, d, *J* = 2.8 Hz), 2.39 (1H, m), 1.93 (4H, m), 1.76 (4H, m), 1.70-1.60 (7H, m), 1.49 (2H, m), 1.30-1.17 (3H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.3 (2 x C, O-*C*=*O*), 105.5 (C, O-C-O), 51.7 (CH), 39.6 (CH), 36.89 (CH$_2$), 36.7 (CH$_2$), 29.4 (2 x CH$_2$), 26.5 (2 x CH$_2$), 25.5 (CH$_2$), 24.0 (CH$_2$), 22.4 (CH$_2$), 21.7 (CH$_2$); LRMS: m/z 265.20 (M-H$^+$), calcd $C_{15}H_{22}O_4$ 266.1518; HRMS: m/z 267.1599 (M+H$^+$), 289.1417 (M+Na$^+$), calcd for $C_{15}H_{22}O_4H$ 267.1596, $C_{15}H_{22}O_4Na$ 289.1416.

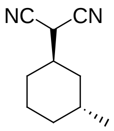


56bf

Cyano-(2-methyl-cyclohexyl)-acetic acid ethyl ester (56bf): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2930, 2856, 2249, 1745 (O-C=O), 1448, 1369, 1253, 1192, 1028 and 854 cm^{-1}; ^{1}H NMR (CDCl$_3$, 3.3:1 ratio of isomers, major isomer) δ 4.28 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.84 (1H, d, *J* = 3.6 Hz), 1.79-1.70

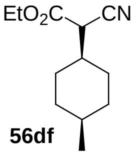
(4H, m), 1.57 (1H, m), 1.32 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.30 (3H, m), 0.97 (3H, d, *J* = 6.4 Hz), 0.85 (1H, m); ^{13}C NMR (CDCl$_3$, DEPT-135, 3.3:1 ratio of isomers, major isomer) δ 166.5 (C, O-C=O), 115.1 (C, *C*≡N), 62.6 (CH$_2$, O*C*H$_2$CH$_3$), 45.1 (CH), 41.4 (CH), 35.1 (CH$_2$), 34.6 (CH), 28.3 (CH$_2$), 25.8 (CH$_2$), 25.7 (CH$_2$), 19.7 (CH$_3$), 14.0 (CH$_3$); LRMS: m/z 208.15 (M-H$^+$), calcd for $C_{12}H_{19}NO_2$ 209.1416.

(–)-(1*R*, 3*R*)-2-(3-Methyl-cyclohexyl)-malononitrile (56cj): Purified by column chromatography using EtOAc/hexane and isolated as liquid. $[\alpha]_D^{25}$ = –2.403° (*c* = 0.5 g/100 mL, CHCl$_3$); IR (neat): ν_{max} 2930, 2860, 2254, 1460, 1381, 1217 and 1055 cm^{-1}; ^{1}H NMR (CDCl$_3$, 3.0:1 ratio of isomers, major isomer) δ 3.64 (1H, d, *J* = 7.6 Hz, CH), 2.32-2.27 (1H, m), 1.98-1.85 (2H, m), 1.68-1.41 (6H, m), 1.38-1.33 (1H, m), 0.98 (3H, d, *J* = 7.2 Hz, CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135, 3.0:1 ratio of isomers, major isomer) δ 112.2 (C, *C*≡N), 112.1 (C, *C*≡N), 35.6 (CH), 35.0 (CH$_2$), 31.5 (CH), 29.2 (CH), 28.2 (CH$_2$), 26.9 (CH$_2$), 19.7 (CH$_3$), 19.0 (CH$_2$); LRMS: m/z 161.10 (M-H$^+$), calcd for $C_{10}H_{14}N_2$ 162.1157; Anal. calcd for $C_{10}H_{14}N_2$ (162.12): C, 74.03; H, 8.70; N, 17.27. Found: C, 74.062; H, 8.721; N, 17.486%.



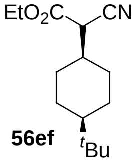
56cj

Cyano-(4-methyl-cyclohexyl)-acetic acid ethyl ester (56df): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2930, 2858, 2249, 1745 (O-C=O), 1450, 1369, 1251, 1192, 1030 and 854 cm^{-1}; ^{1}H NMR (CDCl$_3$, 3.4:1 ratio of isomers, major isomer) δ 4.22 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.43 (1H, d, *J* = 7.6 Hz), 2.12 (1H, m), 1.76 (1H, m), 1.67-1.37 (6H, m), 1.37 (2H, m), 1.27 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$), 0.91 (3H, d, *J* = 6.8 Hz, CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135, 3.4:1 ratio of isomers, major isomer) δ 165.9 (C, O-C=O), 115.9 (C, *C*≡N), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 42.8 (CH), 37.8 (CH), 30.4 (CH$_2$), 30.3 (CH$_2$), 27.9 (CH), 25.8 (CH$_2$), 24.9 (CH$_2$), 18.6 (CH$_3$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 208.15 (M-H$^+$), calcd for $C_{12}H_{19}NO_2$ 209.1416.



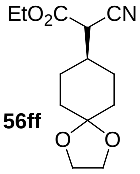
56df

(4-tert-Butyl-cyclohexyl)-cyano-acetic acid ethyl ester (56ef): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2945, 2868, 2247, 1747 (O-C=O), 1602, 1456, 1367, 1251, 1180, 1095, 1035 and 846 cm^{-1}; ^{1}H NMR (CDCl$_3$, 6.0:1 ratio of isomers, major isomer) δ 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.60 (1H, d, *J* = 11.6 Hz), 2.38 (1H, d, *J* = 5.2 Hz), 2.10 (1H, d, *J* = 11.6 Hz), 1.60 (5H, m), 1.31 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.06 (3H, m), 0.84 (9H, s, 3 x CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135, 6.0:1 ratio of isomers, major isomer) δ 166.2 (C, O-C=O), 116.6 (C, *C*≡N), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 47.7 (CH), 38.8 (CH), 34.7 (CH), 32.5 (C), 28.8 (CH$_2$), 28.0 (CH$_2$), 27.3 (3 x CH$_3$, *t*-Bu), 21.5 (CH$_2$), 21.2 (CH$_2$), 14.0 (CH$_3$); LRMS: m/z 250.25 (M-H$^+$), calcd for $C_{15}H_{25}NO_2$ 251.1885.



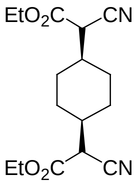
56ef

Cyano-(1,4-dioxa-spiro[4.5]dec-8-yl)-acetic acid ethyl ester (56ff): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2939, 2885, 2249, 1741 (O-C=O), 1446, 1371, 1336, 1105, 1033 and 927 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ



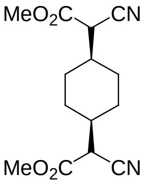
56ff

4.29 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.96 (4H, s, OC*H*$_2$C*H*$_2$O), 3.40 (1H, d, *J* = 6.4 Hz), 2.10 (1H, m), 1.87-1.74 (4H, m), 1.68-1.50 (4H, m), 1.34 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.6 (C, O-C=O), 115.4 (C, *C*≡N), 107.6 (C, O-C-O), 64.4 (CH$_2$), 64.3 (CH$_2$) [O*C*H$_2$*C*H$_2$O]; 62.7 (CH$_2$, O*C*H$_2$CH$_3$), 43.5 (CH), 37.5 (CH), 34.1 (CH$_2$), 33.9 (CH$_2$), 28.2 (CH$_2$), 26.9 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); HRMS: m/z 254.1377 (M+H$^+$), calcd for $C_{13}H_{19}NO_4H$ 254.1392.



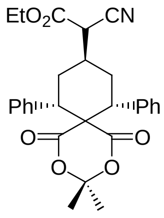
56gf

Cyano-[4-(cyano-ethoxycarbonyl-methyl)-cyclohexyl]-acetic acid ethyl ester (56gf): Purified by column chromatography using EtOAc/hexane and isolated as oil. ^{1}H NMR (CDCl$_3$, 10.0:1 ratio of isomers, major isomer) δ 4.27 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 3.52 (2H, d, *J* = 8.4 Hz), 2.29 (2H, m), 1.78-1.56 (8H, m), 1.32 (6H, t, *J* = 7.2 Hz, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135, 10.0:1 ratio of isomers, major isomer) δ 165.5 (2 x C, O-C=O), 115.6 (2 x C, *C*≡N), 62.9 (2 x CH$_2$, 2 x O*C*H$_2$CH$_3$), 41.2 (2 x CH), 35.9 (2 x CH), 25.9 (CH$_2$), 25.8 (CH$_2$), 25.6 (CH$_2$), 25.5 (CH$_2$), 14.0 (2 x CH$_3$, 2 x OCH$_2$*C*H$_3$); LRMS: m/z 305.00 (M-H$^+$), calcd for $C_{16}H_{22}N_2O_4$ 306.1580; Anal. calcd for $C_{16}H_{22}N_2O_4$ (306.16): C, 62.73; H, 7.24; N, 9.14. Found: C, 62.739; H, 7.243; N, 9.267 %.



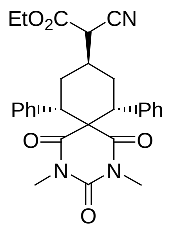
56ge

Cyano-[4-(cyano-methoxycarbonyl-methyl)-cyclohexyl]-acetic acid methyl ester (56ge): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2937, 2249, 1747 (O-C=O), 1456, 1259, 1020, 939, 842 and 775 cm^{-1}; ^{1}H NMR (CDCl$_3$, 10.0:1 ratio of isomers, major isomer) δ 3.79 (6H, s, 2 x OC*H*$_3$), 3.52 (2H, dd, *J* = 8.8, 1.6 Hz), 2.28-2.25 (2H, m), 1.77-1.48 (8H, m); ^{13}C NMR (CDCl$_3$, DEPT-135, 10.0:1 ratio of isomers, major isomer) δ 166.0 (2 x C, O-C=O), 115.5 (2 x C, *C*≡N), 53.4 (2 x CH$_3$, 2 x O*C*H$_3$), 41.0 (2 x CH), 35.9 (2 x CH), 25.84 (CH$_2$), 25.80 (CH$_2$), 25.5 (CH$_2$), 25.4 (CH$_2$); LRMS: m/z 277.05 (M-H$^+$), calcd for $C_{14}H_{18}N_2O_4$ 278.1267; Anal. calcd for $C_{14}H_{18}N_2O_4$ (278.12): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.439; H, 6.526; N, 10.079 %.



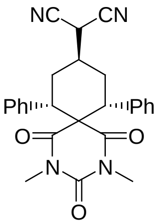
56hf

Cyano-(3,3-dimethyl-1,5-dioxo-7,11-diphenyl-2,4-dioxa-spiro[5.5]undec-9-yl)-acetic acid ethyl ester (56hf): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 170 °C; IR (KBr): ν_{max} 3034, 2980, 2868, 2249 (C≡N), 1734 (O-C=O), 1601, 1494, 1458, 1375, 1068, 1030, 900, 860 and 767 cm^{-1}; ^{1}H NMR (CDCl$_3$, 10.0:1 ratio of isomers, major isomer) δ 7.33-7.19 (10H, m, 2 x Ph-*H*); 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.16 (1H, d, *J* = 11.6 Hz), 3.72 (1H, dd, *J* = 13.6, 3.2 Hz), 3.67 (1H, dd, *J* = 14.0, 3.2 Hz), 3.18 (1H, dt, *J* = 14.8, 4.8 Hz), 3.10 (1H, dt, *J* = 14.8, 4.8 Hz), 2.97 (1H, m), 2.21 (1H, br d, *J* = 13.6 Hz), 1.72 (1H, br d, *J* = 13.6 Hz), 1.24 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 0.50 (6H, s, 2 x CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135, 10.0:1 ratio of isomers, major isomer) δ 169.3 (C, O-C=O), 165.6 (C, O-C=O), 164.8 (C, O-C=O), 138.3 (C), 138.2 (C), 129.0 (4 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 128.4 (CH), 128.0 (CH), 116.0 (C, *C*≡N), 106.0 (C, O-C-O), 62.9 (CH$_2$, O*C*H$_2$CH$_3$), 61.1 (C), 44.98 (CH), 44.7 (CH), 38.9 (CH), 35.2 (CH), 28.4 (CH_2), 28.2 (2 x CH_3), 27.7 (CH_2), 13.9 (CH_3, OCH_2CH_3); LRMS: m/z 474.25 ($M-H^+$), calcd for $C_{28}H_{29}NO_6$ 475.1995; HRMS: m/z 498.1908 ($M+Na^+$), calcd for $C_{28}H_{29}NO_6Na$ 498.1893.



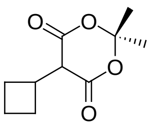
56if

Cyano-(2,4-dimethyl-1,3,5-trioxo-7,11-diphenyl-2,4-diaza-spiro[5.5]undec-9-yl)-acetic acid ethyl ester (56if): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 106 °C; IR (KBr): ν_{max} 3030, 2928, 2245, 1741 (O-C=O), 1676, 1442, 1381, 1259, 1024, 848 and 758 cm^{-1}; ^1H NMR ($CDCl_3$, 10.0:1 ratio of isomers, major isomer) δ 7.18 (6H, m), 7.05 (4H, m) [Ar-*H*]; 4.23 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.25-4.18 (1H, m, CH), 3.72 (2H, m), 3.16 (2H, m), 2.98 (1H, m), 2.92 (3H, s, N-CH_3), 2.87 (3H, s, N-CH_3), 2.18 (1H, br d, *J* = 14.4 Hz), 1.69 (1H, br d, *J* = 14.4 Hz), 1.22 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 10.0:1 ratio of isomers, major isomer) δ 171.4 (C, O-C=O), 168.4 (C, O-C=O), 165.5 (C, O-C=O), 149.5 (C, O-C=O), 138.1 (C), 137.9 (C), 128.5 (4 x CH), 128.1 (CH), 128.0 (CH), 127.6 (2 x CH), 127.5 (2 x CH), 116.0 (C, *C*≡N), 62.7 (CH_2, OCH_2CH_3), 61.1 (C), 45.1 (CH), 44.7 (CH), 38.8 (CH), 35.2 (CH), 28.2 (CH_2), 28.0 (CH_3, N-CH_3), 27.5 (CH_3, N-CH_3), 27.4 (CH_2), 13.8 (CH_3, OCH_2CH_3); LRMS: m/z 486.20 ($M-H^+$), calcd for $C_{28}H_{29}N_3O_5$ 487.2107; HRMS: m/z 510.2022 ($M+Na^+$), calcd for $C_{28}H_{29}N_3O_5Na$ 510.2005.



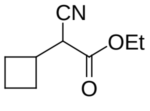
56ij

2-(2,4-Dimethyl-1,3,5-trioxo-7,11-diphenyl-2,4-diaza-spiro[5.5]undec-9-yl)-malononitrile (56ij): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 186 °C; IR (KBr): ν_{max} 3063, 3034, 2256, 1743 (N-C=O), 1680, 1602, 1439, 1265, 1205, 850 and 734 cm^{-1}; ^1H NMR ($CDCl_3$, 6.0:1 ratio of isomers, major isomer) δ 7.25 (6H, m), 7.06 (4H, m) [Ar-*H*]; 4.49 (1H, d, *J* = 11.6 Hz), 3.61 (2H, dd, *J* = 14.0, 3.2 Hz), 3.28 (2H, dt, *J* = 14.8, 5.2 Hz), 3.03 (1H, m), 2.95 (3H, s, N-CH_3), 2.90 (3H, s, N-CH_3), 2.16 (2H, br d, *J* = 14.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 6.0:1 ratio of isomers, major isomer) δ 171.4 (C, N-C=O), 168.4 (C, N-C=O), 149.5 (C, $(NMe)_2C$=O), 137.3 (2 x C), 128.8 (4 x CH), 128.6 (2 x CH), 127.7 (4 x CH), 112.2 (2 x C, *C*≡N), 61.1 (C), 44.7 (2 x CH), 36.4 (CH), 28.3 (CH_3, N-CH_3), 27.7 (CH_3, N-CH_3), 27.4 (2 x CH_2), 24.9 (CH); LRMS: m/z 439.10 ($M-H^+$), calcd for $C_{26}H_{24}N_4O_3$ 440.1848; Anal. calcd for $C_{26}H_{24}N_4O_3$ (440.18): C, 70.89; H, 5.49; N, 12.72. Found: C, 71.002; H, 5.488; N, 12.457%.

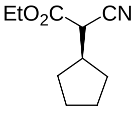


56jc

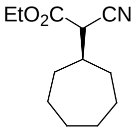
5-Cyclobutyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (56jc): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 96 °C; IR (KBr): ν_{max} 3506, 2999, 2947, 1792 1743, 1462, 1379, 1325, 1259, 1155 and 997 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.46 (1H, d, *J* = 8.4 Hz), 2.99 (1H, sextet, *J* = 8.4 Hz), 2.35-2.26 (2H, m), 2.20-2.05 (2H, m), 2.05-1.80 (2H, m), 1.79 (3H, s, CH_3), 1.74 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.8 (2 x C, 2 x O-C=O), 104.9 (C, O-*C*-O), 50.9 (CH), 34.6 (CH), 28.7 (CH_3), 28.1 (2 x CH_2), 27.1 (CH_3), 19.2 (CH$_2$); HRMS: m/z 199.0962 (M+H$^+$), calcd for $C_{10}H_{14}O_4$ 198.0970; Anal. calcd for $C_{10}H_{14}O_4$ (198.09): C, 60.59; H, 7.12. Found: C, 60.702; H, 7.117%.


56jf

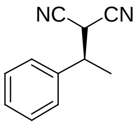
Cyano-cyclobutyl-acetic acid ethyl ester (56jf): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2986, 2945, 2870, 2249, 1745 (O-C=O), 1631, 1446, 1369, 1249 1024 and 914 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.50 (1H, d, *J* = 7.2 Hz), 2.93 (1H, sextet, *J* = 8.0 Hz), 2.22-2.10 (2H, m), 2.10-1.98 (2H, m), 1.98-1.85 (2H, m), 1.31 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.3 (C, O-C=O), 115.5 (C, *C*≡N), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 43.0 (CH), 35.1 (CH), 26.4 (CH$_2$), 25.7 (CH$_2$), 17.7 (CH$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); HRMS: m/z 190.0843 (M+Na$^+$), calcd for $C_9H_{13}NO_2Na$ 190.0844.


56kf

Cyano-cyclopentyl-acetic acid ethyl ester (56kf): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2961, 2874, 2253, 1745 (O-C=O), 1618, 1452, 1369, 1269, 1201 and 1032 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.48 (1H, d, *J* = 7.2 Hz), 2.47 (1H, sextet, *J* = 7.6 Hz), 1.85 (2H, m), 1.70 (2H, m), 1.59 (2H, m), 1.40 (2H, m), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.0 (C, O-C=O), 116.0 (C, *C*≡N), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 42.5 (CH), 40.1 (CH), 30.6 (CH$_2$), 29.7 (CH$_2$), 25.0 (CH$_2$), 24.9 (CH$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 180.00 (M-H$^+$), calcd for $C_{10}H_{15}NO_2$ 181.1103.

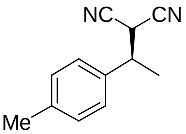

56lf

Cyano-cycloheptyl-acetic acid ethyl ester (56lf): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2930, 2858, 2249, 1743 (O-C=O), 1593, 1462, 1369, 1251, 1028 and 854 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.40 (1H, d, *J* = 5.2 Hz), 2.21 (1H, m), 1.72 (5H, m), 1.60-1.20 (7H, m), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.9 (C, O-C=O), 115.9 (C, *C*≡N), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 45.1 (CH), 40.4 (CH), 32.9 (CH$_2$), 30.8 (CH$_2$), 27.7 (CH$_2$), 27.5 (CH$_2$), 26.1 (CH$_2$), 25.9 (CH$_2$), 13.9 (CH$_3$); LRMS: m/z 208.15 (M-H$^+$), calcd for $C_{12}H_{19}NO_2$ 209.1416.


56mj

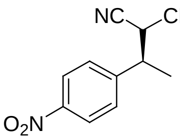
2-(1-Phenyl-ethyl)-malononitrile (56mj): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3067, 3034, 2980, 2908, 2254 (C≡N), 1718, 1597, 1496, 1371, 1286, 1045, 844 and 773 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.45-7.28 (5H, m) [Ar-*H*]; 3.88 (1H, d, *J* = 6.4 Hz), 3.48 (1H, quintet, *J* = 6.8 Hz), 1.67 (3H, d, *J* = 7.2 Hz, PhCHC*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 138.2 (C), 129.3 (2 x CH), 128.9 (CH), 127.2 (2 x CH), 111.9 (C, *C*≡N), 111,7 (C, *C*≡N), 41.2 (CH), 31.2 (CH), 17.7 (CH$_3$); LRMS: m/z 169.05 (M-H$^+$), calcd for $C_{11}H_{10}N_2$ 170.0844.

2-(1-p-Tolyl-ethyl)-malononitrile (56nj): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2924, 2254 (C≡N), 1608, 1454, 1269, 815 and 727

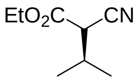

56nj

cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.24 (4H, s, Ph-*H*); 3.85 (1H, d, *J* = 6.4 Hz), 3.45 (1H, m), 2.40 (3H, s, PhC*H*$_3$), 1.65 (3H, d, *J* = 7.2 Hz, PhCHC*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 138.7 (C), 135.2 (C), 129.9 (2 x CH), 127.1 (2 x CH), 112.1 (C, *C*≡N), 111.8 (C, *C*≡N), 40.9 (CH), 31.3 (CH), 21.1 (CH$_3$), 17.8 (CH$_3$); LRMS: m/z 183.00 (M-H$^+$), calcd for $C_{12}H_{12}N_2$ 184.1000.

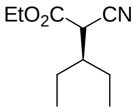
2-[1-(4-Nitro-phenyl)-ethyl]-malononitrile (56oj): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 72 °C; IR (neat): ν_{max} 2976, 2912, 2253 (C≡N), 1606, 1520, 1352, 860 and 738 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.28 (2H, d, *J* = 8.4 Hz), 7.58 (2H, d, *J* = 8.4 Hz) [Ar-*H*]; 4.05 (1H, d, *J* = 6.0 Hz), 3.64-3.61 (1H, quintet, *J* = 6.7 Hz), 1.70 (3H, d, *J* = 7.0 Hz, PhCHC*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 148.1 (C), 145.2 (C), 128.7 (2 x CH), 124.4 (2 x CH), 111.5 (C, *C*≡N), 111.4 (C, *C*≡N), 40.7 (CH), 30.6 (CH), 17.7 (CH$_3$); LRMS: m/z 214.00 (M-H$^+$), calcd for $C_{11}H_9N_3O_2$ 215.0695; Anal. calcd for $C_{11}H_9N_3O_2$ (215.07): C, 61.39; H, 4.22; N, 19.53. Found: C, 61.375; H, 4.216; N, 19.573%.


56oj

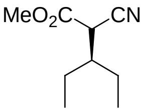
2-Cyano-3-methyl-butyric acid ethyl ester (56pf): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2970, 2937, 2249, 1745 (O-C=O), 1462, 1253, 1097, 1028 and 854 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.38 (1H, d, *J* = 4.8 Hz), 2.40 (1H, m), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.11 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 1.08 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.8 (C, O-C=O), 115.4 (C, *C*≡N), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 42.2 (CH), 29.9 (CH), 20.6 (CH$_3$), 18.7 (CH$_3$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 154.10 (M-H$^+$), calcd for $C_8H_{13}NO_2$ 155.0946.


56pf

2-Cyano-3-ethyl-pentanoic acid ethyl ester (56qf): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2970, 2879, 2249, 1745 (O-C=O), 1464, 1369, 1265 and 1028 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.28 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.60 (1H, d, *J* = 4.4 Hz), 1.99 (1H, m), 1.63-1.38 (4H, m), 1.32 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 0.96 (3H, t, *J* = 8.0 Hz, CH$_2$C*H*$_3$), 0.94 (3H, t, *J* = 7.6 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.5 (C, O-C=O), 115.6 (C, *C*≡N), 62.6 (CH$_2$, O*C*H$_2$CH$_3$), 42.5 (CH), 41.4 (CH), 24.14 (CH$_2$), 24.11 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$), 11.2 (CH$_3$, CH$_2$*C*H$_3$), 11.1 (CH$_3$, CH$_2$*C*H$_3$); LRMS: m/z 182.00 (M-H$^+$), calcd for $C_{10}H_{17}NO_2$ 183.1259.

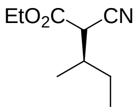

56qf

2-Cyano-3-ethyl-pentanoic acid methyl ester (56qe): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2966, 2934, 2249, 1749 (O-C=O), 1462, 1385, 1018 and 927 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.81 (3H, s, OC*H*$_3$), 3.62 (1H, d, *J* = 4.8 Hz), 1.98 (1H, m), 1.65-1.36 (4H, m), 0.95 (3H, t, *J* = 7.6 Hz, CH$_2$C*H*$_3$), 0.93 (3H, t, *J* = 7.6 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.0 (C, O-C=O), 115.4 (C,


56qe

C≡N), 53.2 (CH$_{3,}$ O*C*H$_3$), 42.5 (CH), 41.2 (CH), 24.1 (2 x CH$_2$), 11.2 (CH$_3$), 11.1 (CH$_3$); LRMS: m/z 168.00 (M-H$^+$), calcd for $C_9H_{15}NO_2$ 169.1103; HRMS: m/z 192.1002 (M+Na$^+$), calcd $C_9H_{15}NO_2Na$ 192.1000.

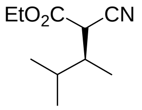
2-Cyano-3-methyl-pentanoic acid ethyl ester (56rf): Purified by column chromatography using



56rf

EtOAc/hexane and isolated as liquid. IR (neat): ν$_{max}$ 2970, 2249 (C≡N), 1745 (O-C=O), 1614, 1460, 1255 and 1028 cm^{-1}; ^{1}H NMR (CDCl$_{3,}$ 1.6:1 ratio of isomers) δ 4.26 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 3.54 (1H, d, *J* = 4.4 Hz), 3.41 (1H, d, *J* = 5.2 Hz), 2.14 (2H, m), 1.46 (4H, m), 1.30 (6H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.07 (3H, d, *J* = 7.2 Hz), 1.03 (3H, d, *J* = 7.2 Hz), 0.93 (3H, t, *J* = 7.2 Hz), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, 1.6:1 ratio of isomers) δ 166.1 (C, O-C=O), 165.8 (C, O-C=O), 115.7 (C, *C*≡N), 115.2 (C, *C*≡N), 62.5 (CH$_{2,}$ O*C*H$_2$CH$_3$), 62.4 (CH$_2$, O*C*H$_2$CH$_3$), 44.3 (CH), 43.3 (CH), 36.1 (2 x CH), 27.6 (CH$_2$), 26.1 (CH$_2$), 17.1 (CH$_3$), 16.0 (CH$_3$), 13.9 (2 x CH$_{3,}$ OCH$_2$*C*H$_3$), 11.3 (CH$_3$), 11.1 (CH$_3$); LRMS: m/z 168.10 (M-H$^+$), calcd for $C_9H_{15}NO_2$ 169.1103.

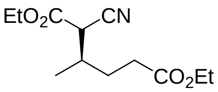
2-Cyano-3,4-dimethyl-pentanoic acid ethyl ester (56sf): Purified by column chromatography using



56sf

EtOAc/hexane and isolated as liquid. IR (neat): ν$_{max}$ 2968, 2249 (C≡N), 1747 (O-C=O), 1622, 1467, 1371, 1251, 1116 and 1030 cm^{-1}; ^{1}H NMR (CDCl$_{3,}$ 2:1 ratio of isomers) δ 4.25 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 3.63 (1H, d, *J* = 4.4 Hz), 3.38 (1H, d, *J* = 8.0 Hz), 2.09 (1H, m), 1.96 (2H, m), 1.66 (1H, m), 1.30 (6H, t, *J* = 7.2 Hz, 2 x OCH$_2$C*H*$_3$), 1.04 (3H, d, *J* = 6.8 Hz), 0.96 (12H, m, 4 x CH$_3$, 2 x (C*H*$_3$)$_2$CH), 0.88 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, 2:1 ratio of isomers) δ 166.5 (C, O-C=O), 166.0 (C, O-C=O), 116.2 (C, *C*≡N), 115.5 (C, *C*≡N), 62.6 (CH$_{2,}$ O*C*H$_2$CH$_3$), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 42.7 (CH), 42.1 (CH), 40.7 (CH), 40.2 (CH), 31.2 (CH), 29.9 (CH), 21.1 (CH$_3$), 20.7 (CH$_3$), 19.3 (CH$_3$), 17.0 (CH$_3$), 14.0 (CH$_{3,}$ OCH$_2$*C*H$_3$), 13.9 (CH$_{3,}$ OCH$_2$*C*H$_3$), 13.8 (CH$_3$), 13.0 (CH$_3$); LRMS: m/z 182.15 (M-H$^+$), calcd for $C_{10}H_{17}NO_2$ 183.1259.

2-Cyano-3-methyl-hexanedioic acid diethyl ester (56tf): Purified by column chromatography using

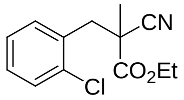


56tf

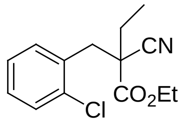
EtOAc/hexane and isolated as liquid. IR (neat): ν$_{max}$ 2984, 2932, 2251, 1739 (O-C=O), 1462, 1371, 1097, 1028 and 856 cm^{-1}; ^{1}H NMR (CDCl$_{3,}$ 1.4:1 ratio of isomers) δ 4.25 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 4.11 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 3.55 (1H, d, *J* = 4.4 Hz), 3.45 (1H, d, *J* = 5.2 Hz), 2.40-2.25 (5H, m), 1.87-1.61 (5H, m), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.24 (6H, t, *J* = 7.2 Hz, 2 x OCH$_2$C*H*$_3$), 1.11 (3H, d, *J* = 7.2 Hz), 1.06 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, 1.4:1 ratio of isomers) δ 172.5 (C, O-C=O), 172.4 (C, O-C=O), 165.6 (C, O-C=O), 165.4 (C, O-C=O), 115.3 (C, *C*≡N), 114.9 (C, *C*≡N), 62.7 (2 x CH$_2$, 2 x O*C*H$_2$CH$_3$), 60.6 (CH$_2$, O*C*H$_2$CH$_3$), 60.5 (CH$_2$, O*C*H$_2$CH$_3$), 44.2 (CH), 43.6 (CH), 33.8 (CH), 33.7 (CH), 31.6 (CH$_2$), 31.4 (CH$_2$), 29.7 (CH$_2$), 28.1 (CH$_2$), 17.3

(CH_3), 15.9 (CH_3), 14.1 (2 x CH_3, 2 x OCH_2CH_3), 13.9 (2 x CH_3, 2 x OCH_2CH_3); LRMS: m/z 240.05 ($M-H^+$), calcd for $C_{12}H_{14}NO_4$ 241.1314.

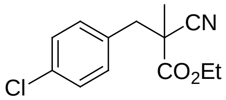
2. Proline-Cs_2CO_3 or K_2CO_3-catalyzed olefination-hydrogenation-alkylation reactions in one-pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde **46** or ketone **47**, 0.5 mmol of CH-acid **48** and 0.5 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst proline **50a** (0.1 mmol) was added and the reaction mixture was stirred at 25 °C for 1-96 h then R^4CH_2I or R^4CH_2Br 49 (2.5 mmol) and K_2CO_3 or Cs_2CO_3 (0.4 g) was added and stirring continued at the same temperature for 7-24 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 **55** and **57** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).


55wfa

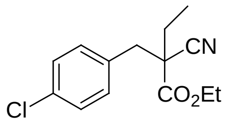
3-(2-Chloro-phenyl)-2-cyano-2-methyl-propionic acid ethyl ester (55wfa): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2988, 2245 (C≡N), 1743 (O-C=O), 1572, 1446, 1381, 1263, 1016, 858, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (2H, m), 7.25 (2H, m) [Ar-*H*]; 4.26 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.37 (2H, s, Ph-CH_2), 1.64 (3H, s, CH_3), 1.27 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT135) δ 168.2 (C, O-C=O), 135.0 (C), 132.3 (C), 131.7 (CH), 129.8 (CH), 129.2 (CH), 127.0 (CH), 119.5 (C, *C*≡N), 63.0 (CH_2, OCH_2CH_3), 44.6 (C), 39.3 (CH_2), 22.7 (CH_3), 13.8 (CH_3, OCH_2CH_3); LRMS: m/z 252.20 ($M+H^+$), calcd $C_{13}H_{14}NO_2Cl$ 251.0713.


55wfb

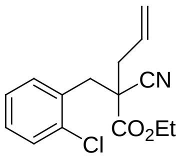
2-(2-Chloro-benzyl)-2-cyano-butyric acid ethyl ester (55wfb): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2978, 2245 (C≡N), 1741 (O-C=O), 1595, 1572, 1475, 1390, 1242, 1024, 856, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (2H, m), 7.25 (2H, m) [Ar-*H*]; 4.24 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.36 (2H, AB q, *J* = 14.4 Hz, Ph-CH_2), 2.16 (1H, dq, *J* = 14.8, 7.6 Hz), 1.88 (1H, dq, *J* = 14.8, 7.6 Hz), 1.24 (3H, t, *J* = 7.2 Hz, CH_3, OCH_2CH_3), 1.10 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT135) δ 168.4 (C, O-C=O), 135.0 (C), 132.5 (C), 131.4 (CH), 129.8 (CH), 129.1 (CH), 126.9 (CH), 118.6 (C, *C*≡N), 62.8 (CH_2, OCH_2CH_3), 51.4 (C), 38.8 (CH_2), 30.5 (CH_2), 13.9 (CH_3, OCH_2CH_3), 9.8 (CH_3); LRMS: m/z 266.15 ($M+H^+$), calcd $C_{14}H_{16}NO_2Cl$ 265.0870.


55yfa

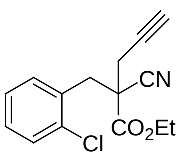
3-(4-Chloro-phenyl)-2-cyano-2-methyl-propionic acid ethyl ester (55yfa): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2986, 2245 (C≡N), 1743 (O-C=O), 1599, 1456, 1381, 1265, 1120, 1095, 846, 825, 719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz) [Ar-*H*]; 4.19 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.20 (1H, d, J = 13.6 Hz, Ph-CH_2), 2.99 (1H, d, J = 13.6 Hz, Ph-CH2), 1.61 (3H, s, CH_3), 1.23 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT135) δ 168.7 (C, O-C=O), 133.9 (C), 132.7 (C), 131.3 (2 x CH), 128.7 (2 x CH), 119.4 (C, *C*≡N), 62.9 (CH$_2$, OC*H*$_2$CH$_3$), 45.2 (C), 42.8 (CH$_2$), 23.2 (CH$_3$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 252.15 (M+H$^+$), calcd $C_{13}H_{14}NO_2Cl$ 251.0713.


55yfb

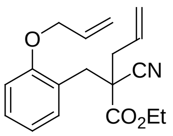
2-(4-Chloro-benzyl)-2-cyano-butyric acid ethyl ester (55yfb): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 2976, 2245 (C≡N), 1741 (O-C=O), 1597, 1493, 1460, 1390, 1369, 1242, 1095, 842, 717 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.30 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.0 Hz) [Ar-*H*]; 4.18 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.16 (1H, d, *J* = 13.6 Hz, Ph-C*H*$_2$), 3.02 (1H, d, *J* = 13.6 Hz, Ph-C*H*$_2$), 2.06 (1H, dq, *J* = 14.4, 7.2 Hz), 1.88 (1H, dq, *J* = 14.4, 7.2 Hz), 1.20 (3H, t, *J* = 7.2 Hz, C*H*$_3$, OCH$_2$C*H*$_3$), 1.10 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (CDCl$_3$, DEPT135) δ 168.4 (C, O-C=O), 133.4 (C), 132.8 (C), 131.2 (2 x CH), 128.7 (2 x CH), 118.6 (C, *C*≡N), 62.7 (CH$_2$, OC*H*$_2$CH$_3$), 52.3 (C), 42.1 (CH$_2$), 31.0 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$), 9.7 (CH$_3$); LRMS: m/z 266.55 (M+H$^+$), calcd $C_{14}H_{16}NO_2Cl$ 265.0870.


55wfc

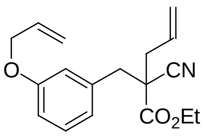
2-(2-Chloro-benzyl)-2-cyano-pent-4-enoic acid ethyl ester (55wfc): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 2928, 2229 (C≡N), 1734 (O-C=O), 1608, 1469, 1369, 1259, 1205, 1089, 748 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.40 (2H, m), 7.25 (2H, m) [Ar-*H*]; 5.85 (1H, m, olefinic-*H*), 5.26 (2H, m, olefinic-*H*), 4.21 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.37 (2H, AB q, *J* = 14.0 Hz, Ph-C*H*$_2$), 2.82 (1H, dd, *J* = 14.0, 7.6 Hz), 2.56 (1H, dd, *J* = 14.0, 7.6 Hz), 1.22 (3H, t, *J* = 7.2 Hz, C*H*$_3$, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT135) δ 167.8 (C, O-C=O), 134.9 (C), 132.2 (C), 131.4 (CH), 130.5 (CH), 129.8 (CH), 129.1 (CH), 126.9 (CH), 121.1 (CH$_2$), 118.1 (C, *C*≡N), 62.9 (CH$_2$, OC*H*$_2$CH$_3$), 50.2 (C), 41.0 (CH$_2$), 38.4 (CH$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 300.08 (M+Na$^+$), calcd $C_{15}H_{16}NO_2ClNa$ 300.0700.


55wfd

2-(2-Chloro-benzyl)-2-cyano-pent-4-ynoic acid ethyl ester (55wfd): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 3294, 2984, 2251 (C≡N), 1745 (O-C=O), 1475, 1444, 1236, 1062, 856 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.43 (2H, m), 7.27 (2H, m) [Ar-*H*]; 4.27 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.52 (1H, d, *J* = 14.4 Hz, Ph-C*H*$_2$), 3.40 (1H, d, *J* = 14.4 Hz, Ph-C*H*$_2$), 2.95 (1H, dd, *J* = 14.8, 2.0 Hz), 2.76 (1H, dd, *J* = 14.8, 2.0 Hz), 2.25 (1H, t, *J* = 2.8 Hz, CH$_2$C≡C-*H*), 1.22 (3H, t, *J* = 7.2 Hz, C*H*$_3$, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT135) δ 166.9 (C, O-C=O), 134.9 (C), 131.8 (CH), 131.6 (C), 129.8 (CH), 129.4 (CH), 127.0 (CH), 117.5 (C, *C*≡N), 76.9 (C, CH$_2$*C*≡C-H), 73.3 (CH, CH$_2$C≡*C*-H), 63.4 (CH$_2$, OC*H*$_2$CH$_3$), 49.4 (C), 37.7 (CH$_2$), 26.6 (CH$_2$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 298.06 (M+Na$^+$), calcd $C_{15}H_{14}NO_2ClNa$ 298.0600.

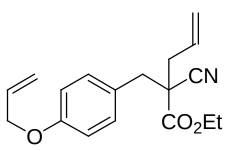

55kfc

2-(2-Allyloxy-benzyl)-2-cyano-pent-4-enoic acid ethyl ester (55kfc): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν_{max} 3080, 2982, 2930, 2245 (C≡N), 1741 (O-C=O), 1645, 1602, 1494, 1454, 1246, 1120, 1020, 929, 860 and 756 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.24 (1H, t, *J* = 8.0 Hz), 7.23 (1H, d, *J* = 8.0 Hz), 6.91 (1H, t, *J* = 7.6 Hz), 6.87 (1H, d, *J* = 8.4 Hz) [Ar-H]; 6.13-6.03 (1H, m, olefinic-*H*), 5.83 (1H, m, olefinic-*H*), 5.43 (1H, d, *J* = 17.2 Hz), 5.30-5.21 (3H, m, olefinic-*H*), 4.55 (2H, d, *J* = 4.60 Hz, OC*H*$_2$CH=CH$_2$), 4.21-4.15 (2H, m, OC*H*$_2$CH$_3$), 3.35 (1H, d, *J* = 13.5 Hz), 3.18 (1H, d, *J* = 13.59 Hz), 2.78 (1H, dd, *J* = 13.76, 7.39 Hz), 2.53 (1H, dd, *J* = 13.72, 7.01 Hz), 1.22 (3H, t, *J* = 7.05 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.4 (C, O-*C*=O), 156.9 (C), 133.3 (CH), 131.5 (CH), 131.2 (CH), 129.2 (CH), 123.0 (C), 120.7 (CH$_2$), 120.6 (CH), 118.6 (C, *C*≡N), 117.3 (CH$_2$), 111.8 (CH), 69.0 (CH$_2$, O*C*H$_2$CH=CH$_2$), 62.6 (CH$_2$, O*C*H$_2$CH$_3$), 50.5 (C), 41.0 (CH$_2$), 35.9 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 322.1419 (M+Na$^+$), calcd for C$_{18}$H$_{21}$NO$_3$ Na 322.1419.



55lfc

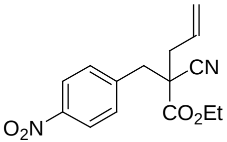
2-(3-Allyloxy-benzyl)-2-cyano-pent-4-enoic acid ethyl ester (55lfc): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν_{max} 3082, 2982, 2930, 2245 (C≡N), 1741 (O-C=O), 1645, 1601, 1494, 1454, 1248, 1020, 929 and 756 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.21 (1H, t, *J* = 8.1 Hz), 6.85 (3H, m) [Ar-H]; 6.07-5.99 (1H, m, olefinic-*H*), 5.88-5.79 (1H, m, olefinic-*H*), 5.43 (1H, d, *J* = 17.2 Hz, olefinic-*H*), 5.28-5.24 (3H, m, olefinic-*H*), 4.52 (2H, d, *J* = 5.40 Hz, OC*H*$_2$CH=CH$_2$), 4.16 (2H, q, *J* = 7.12 Hz, OC*H*$_2$CH$_3$), 3.17 (1H, d, *J* = 13.56 Hz), 3.03 (1H, d, *J* = 13.56 Hz), 2.73 (1H, dd, *J* = 13.72, 7.32 Hz), 2.57 (1H, dd, *J* = 13.72, 7.00 Hz), 1.18 (3H, t, *J* = 7.16 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.0 (C, O-*C*=O), 158.7 (C), 135.5 (C), 133.7, 130.6, 129.5, 122.4, 121.0 (CH), 118.6 (C, *C*≡N), 117.7, 116.3, 114.4, 68.8 (CH$_2$, O*C*H$_2$CH=CH$_2$), 62.7 (CH$_2$, O*C*H$_2$CH$_3$), 51.1 (C), 42.5 (CH$_2$), 41.4 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 300.10 (M+H$^+$), calcd for C$_{18}$H$_{21}$NO$_3$ 299.1521; Anal. calcd for C$_{18}$H$_{21}$NO$_3$ (299.15): C, 72.22; H, 7.07; N, 4.68. Found: C, 72.207; H, 7.044; N, 4.783%.



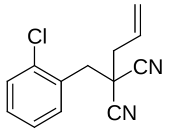
55mfc

2-(4-Allyloxy-benzyl)-2-cyano-pent-4-enoic acid ethyl ester (55mfc): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν_{max} 3082, 2984, 2930, 2245 (C≡N), 1739 (O-C=O), 1695, 1610, 1512, 1244, 1022, 929 and 837 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.18 (2H, d, *J* = 8.28 Hz), 6.85 (2H, d, *J* = 8.40 Hz) [Ar-H]; 6.04-6.00 (1H, m, OCH$_2$C*H*=CH$_2$), 5.84-5.80 (1H, m, OCH$_2$C*H*=CH$_2$), 5.39 (1H, d, *J* = 17.53 Hz, OCH$_2$CH=C*H*$_2$), 5.28-5.23 (3H, m, olefinic-*H*), 4.51 (2H, d, *J* = 4.72 Hz, OC*H*$_2$CH=CH$_2$), 4.14 (2H, q, *J* = 6.92 Hz, OC*H*$_2$CH$_3$), 3.14 (1H, d, *J* = 13.70 Hz), 3.00 (1H, d, *J* = 13.70 Hz), 2.71 (1H, dd, *J* = 13.70, 7.4 Hz), 2.55 (1H, dd, *J* = 11.90, 5.30 Hz), 1.17 (3H, t, *J* = 7.00 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.0 (C, O-*C*=O), 158.2 (C), 133.1 (CH), 130.9 (2 x CH), 130.5 (CH), 126.2 (C), 120.8 (CH$_2$), 118.6 (C, *C*≡N), 117.6 (CH$_2$), 114.7 (2 x CH), 68.7 (CH$_2$, O*C*H$_2$CH=CH$_2$), 62.5 (CH$_2$, O*C*H$_2$CH$_3$), 53.4 (C), 41.7 (CH$_2$), 41.1 (CH$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$);

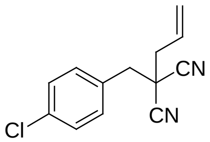
LRMS m/z 300.10 (M+H$^+$), calcd for $C_{18}H_{21}NO_3$ 299.1521; Anal. calcd for $C_{18}H_{21}NO_3$ (299.15): C, 72.22; H, 7.07; N, 4.68. Found: C, 72.211; H, 7.049; N, 4.849%.


55pfc

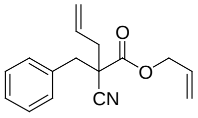
2-Cyano-2-(4-nitro-benzyl)-pent-4-enoic acid ethyl ester (55pfc): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν$_{max}$ 2972, 2930, 2247 (C≡N), 1743 (O-C=O), 1602, 1493 and 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (2H, d, *J* = 8.8 Hz), 7.47 (2H, d, *J* = 8.40 Hz) [Ar-H]; 5.88-5.82 (1H, m, olefinic-*H*), 5.32 (1H, br s, olefinic-*H*), 5.28 (1H, dd, *J* = 7.2, 1.2 Hz), 4.17 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 3.32 (1H, d, *J* = 13.6 Hz), 3.14 (1H, d, *J* = 13.6 Hz), 2.78 (1H, dd, *J* = 13.6, 7.6 Hz), 2.62 (1H, dd, *J* = 13.60, 7.2 Hz), 1.19 (3H, t, *J* = 7.20 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.5 (C, O-*C*=O), 141.6 (C), 131.0 (2 x CH), 129.9 (CH), 123.8 (2 x CH), 121.7 (CH$_2$, CH=*C*H$_2$), 117.9 (C, *C*≡N), 63.1 (CH$_2$, O*C*H$_2$CH$_3$), 50.7 (C), 41.8 (CH$_2$), 41.7 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); GCMS m/z 288.1 (M$^+$), calcd for $C_{15}H_{16}N_2O_4$ 288.11; Anal. calcd for $C_{15}H_{16}N_2O_4$ (288.11): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.588; H, 5.569; N, 9.667%.


55wjc

2-Allyl-2-(2-chloro-benzyl)-malononitrile (55wjc): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν$_{max}$ 2986, 2200 (C≡N), 1903, 1647, 1491, 1452, 1273 and 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (1H, m), 7.50 (1H, m), 7.35 (2H, m) [Ar-H]; 5.93 (1H, m, olefinic-*H*), 5.45 (2H, m, olefinic-*H*), 3.49 (2H, s, ArC*H*$_2$), 2.80 (2H, d, *J* = 7.2 Hz, C*H*$_2$CH=CH$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 135.1 (C), 131.8 (CH), 130.23 (CH), 130.20 (CH), 130.1 (C), 128.5 (CH), 127.4 (CH), 123.4 (CH$_2$), 114.7 (2 x C, *C*≡N), 41.4 (CH$_2$), 38.8 (CH$_2$), 38.5 (C); GCMS m/z 230 (M$^+$), calcd for $C_{13}H_{11}ClN_2$ 230.06; Anal. calcd for $C_{13}H_{11}ClN_2$ (230.06): C, 67.68; H, 4.81; N, 12.14. Found: C, 67.802; H, 4.820; N, 12.621%.

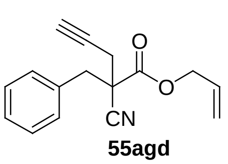

55yjc

2-Allyl-2-(4-chloro-benzyl)-malononitrile (55yjc): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 72 °C; IR (KBr): ν$_{max}$ 2989, 2924, 2847, 2249 (C≡N), 1647, 1599, 1493, 1450, 1097, 1016, 989, 939 and 841 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (2H, d, *J* = 8.4 Hz), 7.31 (2H, d, *J* = 7.2 Hz) [Ar-H]; 5.99-5.89 (1H, m, C*H*=CH$_2$), 5.48-5.41 (2H, m, CH=C*H*$_2$), 3.17 (2H, s, ArC*H*$_2$), 2.71 (2H, d, *J* = 7.2 Hz, C*H*$_2$CH=CH$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 135.0 (C), 131.5 (2 x CH), 130.3 (C), 129.2 (2 x CH), 128.3 (CH), 123.6 (CH$_2$, CH=*C*H$_2$), 114.6 (2 x C, *C*≡N), 41.9 (CH$_2$), 41.3 (CH$_2$), 39.1 (C); GCMS m/z 230 (M$^+$), calcd for $C_{13}H_{11}ClN_2$ 230.06; Anal. calcd for $C_{13}H_{11}ClN_2$ (230.06): C, 67.68; H, 4.81; N, 12.14. Found: C, 67.633; H, 4.791; N, 12.131%.


55agc

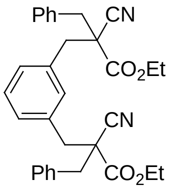
2-Benzyl-2-cyano-pent-4-enoic acid allyl ester (55agc): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν$_{max}$ 3086, 2928, 2245 (C≡N), 1745 (O-C=O), 1645, 1496, 1452 and 1221 cm^{-1}; ^{1}H NMR

(CDCl$_3$) δ 7.37-7.28 (5H) [Ar-H]; 5.93-5.74 (2H, m, 2 x C*H*=CH$_2$), 5.32-5.22 (4H, m, 2 x CH=C*H*$_2$), 4.64-4.55 (2H, m, OC*H*$_2$CH=CH$_2$), 3.23 (1H, d, *J* = 13.52 Hz), 3.11 (1H, d, *J* = 13.52 Hz), 2.78 (1H, dd, *J* = 13.7, 7.40 Hz, C*H*$_2$CH=CH$_2$), 2.61 (1H, dd, *J* = 13.7, 7.10 Hz, C*H*$_2$CH=CH$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.8 (C, O-*C*=O), 134.0 (C), 130.7 (CH, *C*H=CH$_2$), 130.5 (CH, *C*H=CH$_2$), 130.0 (2 x CH), 128.6 (2 x CH), 127.9 (CH), 121.2 (CH$_2$, CH=*C*H$_2$), 119.4 (CH$_2$, CH=*C*H$_2$), 118.4 (C, *C*≡N), 67.0 (CH$_2$, OC*H*$_2$CH=CH$_2$), 51.3 (C), 42.5 (CH$_2$), 41.4 (CH$_2$, *C*H$_2$CH=CH$_2$); HRMS m/z 278.1158 (M+Na$^+$), calcd for $C_{16}H_{17}NO_2Na$ 278.1157.



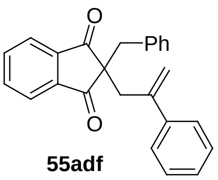
55agd

2-Benzyl-2-cyano-pent-4-ynoic acid allyl ester (55agd): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν$_{max}$ 3294, 3034, 2935, 2247 (C≡N), 1745 (O-C=O), 1649, 1604, 1201, 1086, 1053, 941 and 742 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.38-7.30 (5H, m) [Ar-H]; 5.87-5.78 (1H, m, C*H*=CH$_2$), 5.32 (1H, dd, *J* = 17.0, 1.0 Hz, CH=C*H*$_2$), 5.27 (1H, br d, *J* = 10.4 Hz, CH=C*H*$_2$), 4.65 (2H, m, OC*H*$_2$CH=CH$_2$), 3.29 (2H, s, PhC*H*$_2$), 2.76 (2H, dABq, *J* = 16.70, 2.50 Hz, C*H*$_2$C≡CH), 2.29 (1H, t, *J* = 2.44 Hz, CH$_2$C≡C*H*); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.8 (C, O-*C*=O), 133.4 (C), 130.6 (CH, *C*H=CH$_2$), 130.0 (2 x CH), 128.7 (2 x CH), 128.2 (CH), 119.6 (CH$_2$, CH=*C*H$_2$), 117.8 (C, *C*≡N), 76.8 (C, CH$_2$*C*≡CH), 73.7 (CH, CH$_2$C≡*C*H), 67.4 (CH$_2$, O*C*H$_2$CH=CH$_2$), 50.0 (C), 41.4 (CH$_2$), 26.5 (CH$_2$, *C*H$_2$C≡CH); HRMS m/z 276.1000 (M+Na$^+$), calcd for $C_{16}H_{15}NO_2Na$ 276.1000.



55tfe

2-Benzyl-3-[3-(2-benzyl-2-cyano-2-ethoxycarbonyl-ethyl)-phenyl]-2-cyano-propionic acid ethyl ester (55tfe): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν$_{max}$ 3032, 2984, 2934, 2245 (C≡N), 1739 (O-C=O), 1606, 1496, 1454, 1369, 1228, 1099, 856, 744 and 702 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.36-7.28 (14H, m) [Ar-H]; 4.04 (4H, q, *J* = 7.20 Hz, OC*H*$_2$CH$_3$); 3.35 (2H, br d, *J* = 9.20 Hz), 3.32 (2H, br d, *J* = 9.2 Hz), 3.14 (2H, br s), 3.10 (2H, br s), 1.02 (3H, t, *J* = 7.20 Hz, OCH$_2$C*H*$_3$), 1.00 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.0 (C, O-*C*=O), 168.0 (C, O-*C*=O), 134.6 (C), 134.5 (C), 134.1 (C), 134.0 (C), 132.03 (CH), 132.0 (CH), 130.03 (2 x CH), 130.01 (2 x CH), 129.6 (2 x CH), 128.91 (CH), 128.86 (CH), 128.59 (2 x CH), 127.93 (CH), 127.90 (CH), 118.54 (C, *C*≡N), 118.51 (C, *C*≡N), 62.71 (CH$_2$, O*C*H$_2$CH$_3$), 62.70 (CH$_2$, O*C*H$_2$CH$_3$), 53.0 (2 x C), 43.5 (CH$_2$), 43.25 (CH$_2$), 43.02 (2 x CH$_2$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$), 13.70 (CH$_3$, OCH$_2$*C*H$_3$); GCMS m/z 508.20 (M$^+$), calcd for $C_{32}H_{32}N_2O_4$ 508.2362; Anal. calcd for $C_{32}H_{32}N_2O_4$ (508.24): C, 75.57; H, 6.34; N, 5.51. Found: C, 75.600; H, 6.358; N, 5.546%.

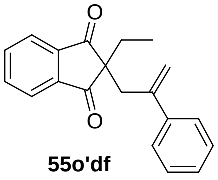


55adf

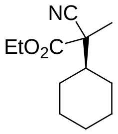
2-Benzyl-2-(2-phenyl-allyl)-indan-1,3-dione (55adf): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 58 °C; IR (KBr): ν$_{max}$ 3074, 2924, 1739, 1705, 1593, 1493, 1444, 1356, 1248, 1028 and 912 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 7.54-7.49 (4H, m), 7.13-6.94 (8H, m), 6.84 (2H, m) [Ar-H]; 5.05 (1H, s), 5.02 (1H, s) [C=C*H*$_2$]; 3.24 (2H, br s), 3.23 (2H, br s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 202.8 (2 x C, *C*=O), 144.0 (C), 142.6 (2 x C), 140.1 (C), 135.3 (C), 134.8 (2 x CH), 130.0 (2 x CH), 127.9 (2 x CH), 127.7 (2 x CH), 127.4 (CH), 126.8 (2 x CH), 126.5 (CH), 122.2 (2 x CH), 118.4 (CH_2), 60.7 (C), 42.0 (CH_2), 41.1 (CH_2); HRMS m/z 375.1345 (M+Na$^+$), calcd for $C_{25}H_{20}O_2Na$ 375.1361.

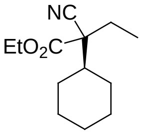
2-Ethyl-2-(2-phenyl-allyl)-indan-1,3-dione (55o′df): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 55 °C; IR (KBr): ν_{max} 2966, 2930, 1741, 1701, 1593, 1454, 1361, 1251, 914, 781 and 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.69-7.63 (4H, m), 7.09 (1H, t, *J* = 7.6 Hz), 7.01 (2H, t, *J* = 7.6 Hz), 6.80 (2H, d, *J* = 7.2 Hz) [Ar-H]; 4.98 (1H, br s), 4.97 (1H, br s) [C=CH_2]; 3.08 (2H, s), 1.93 (2H, q, *J* = 7.6 Hz, C*H*$_2$$CH_3$), 0.65 (3H, t, *J* = 7.6 Hz, CH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.8 (2 x C, *C*=O), 144.4 (C), 142.8 (2 x C), 140.2 (C), 135.1 (2 x CH), 127.7 (2 x CH), 127.5 (CH), 126.9 (2 x CH), 122.4 (2 x CH), 118.2 (CH_2), 59.5 (C), 41.7 (CH_2), 28.6 (CH_2), 9.1 (CH_3); HRMS m/z 313.1201 (M+Na$^+$), calcd for $C_{20}H_{18}O_2Na$ 313.1204.


55o'df

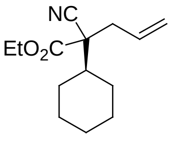
Cyano-cyclohexyl-methyl-acetic acid ethyl ester (57afa): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2934, 2858, 2239, 1741 (O-C=O), 1452, 1381, 1242, 1116 and 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 1.80 (4H, m), 1.66 (2H, m), 1.52 (3H, s, CH_3), 1.33 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$), 1.31-1.13 (5H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.5 (C, O-C=O), 119.3 (C, *C*≡N), 62.4 (CH_2, O*C*H$_2$$CH_3$), 48.99 (C), 44.2 (CH), 28.9 (CH_2), 27.2 (CH_2), 25.9 (2 x CH_2), 25.6 (CH_2), 20.7 (CH_3), 14.0 (CH_3, OCH_2*C*H$_3$); LRMS: m/z 210.20 (M+H$^+$), calcd for $C_{12}H_{19}NO_2$ 209.1416; HRMS: m/z 232.1303 (M+Na$^+$), calcd for $C_{12}H_{19}NO_2Na$ 232.1313.


57afa

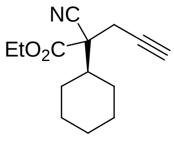
2-Cyano-2-cyclohexyl-butyric acid ethyl ester (57afb): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2934, 2856, 2241, 1739 (O-C=O), 1452, 1232, 1157, 1124 and 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.26 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 1.98-1.93 (1H, m), 1.90-1.76 (5H, m), 1.67 (1H, br d, *J* = 9.6 Hz), 1.57 (1H, br d, *J* = 12.0 Hz), 1.32 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$), 1.27-1.19 (5H, m), 1.02 (3H, t, *J* = 7.6 Hz, CH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.1 (C, O-C=O), 118.6 (C, *C*≡N), 62.3 (CH_2, O*C*H$_2$$CH_3$), 56.3 (C), 44.0 (CH), 29.3 (CH_2), 28.3 (CH_2), 27.6 (CH_2), 26.0 (2 x CH_2), 25.7 (CH_2), 14.2 (CH_3, OCH_2*C*H$_3$), 9.9 (CH_3, CH_2*C*H$_3$); LRMS: m/z 224.25 (M+H$^+$), calcd $C_{13}H_{21}NO_2$ 223.1572; HRMS: m/z 246.1465 (M+Na$^+$), calcd for $C_{13}H_{21}NO_2Na$ 246.1470.


57afb

2-Cyano-2-cyclohexyl-pent-4-enoic acid ethyl ester (57afc): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3082, 2934, 2856, 2243, 1741 (O-C=O), 1643, 1450, 1369, 1222, 1155, 1032, 927 and 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ

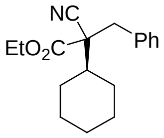

57afc

5.82-5.72 (1H, m, olefinic-*H*), 5.22-5.16 (2H, m, olefinic-*H*), 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.64 (1H, dd, *J* = 13.6, 6.8 Hz), 2.52 (1H, dd, *J* = 13.6, 8.0 Hz), 1.90-1.70 (4H, m), 1.67 (1H, br d, J = 10.4 Hz), 1.57 (1H, br d, J = 10.4 Hz), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.30-1.10 (5H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.5 (C, O-C=O), 131.0 (CH, *C*H=CH$_2$), 120.4 (CH$_2$, CH=*C*H$_2$), 118.2 (C, *C*≡N), 62.3 (CH$_2$, O*C*H$_2$CH$_3$), 55.2 (C), 43.7 (CH), 39.0 (CH$_2$), 29.1 (CH$_2$), 27.5 (CH$_2$), 25.9 (2 x CH$_2$), 25.6 (CH$_2$), 14.1 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 235.10 (M$^+$), calcd for $C_{14}H_{21}NO_2$ 235.1572; HRMS: m/z 258.1473 (M+Na$^+$), calcd for $C_{14}H_{21}NO_2Na$ 258.1470.



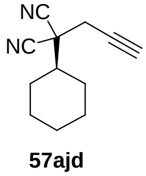
57afd

2-Cyano-2-cyclohexyl-pent-4-ynoic acid ethyl ester (57afd): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3287, 2934, 2858, 2247, 2125, 1743 (O-C=O), 1450, 1369, 1219, 1043, 896 and 858 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.29 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.76 (2H, dABq, *J* = 16.8, 2.0 Hz, *C*H$_2$C≡CH), 2.16 (1H, t, *J* = 2.0 Hz, CH$_2$C≡C*H*), 1.87-1.70 (5H, m), 1.67 (1H, br d, *J* = 10.8 Hz), 1.60 (1H, br d, *J* = 10.8 Hz), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.29-1.16 (4H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.7 (C, O-C=O), 117.6 (C, *C*≡N), 77.3 (C, CH$_2$*C*≡CH), 72.7 (CH, CH$_2$C≡*C*H), 62.8 (CH$_2$, O*C*H$_2$CH$_3$), 54.4 (C), 43.4 (CH), 28.8 (CH$_2$), 27.6 (CH$_2$), 25.8 (2 x CH$_2$), 25.5 (CH$_2$), 25.1 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); GCMS: m/z 233.00 (M$^+$), calcd for $C_{14}H_{19}NO_2$ 233.1416; HRMS: m/z 256.1323 (M+Na$^+$), calcd for $C_{14}H_{19}NO_2Na$ 256.1313.



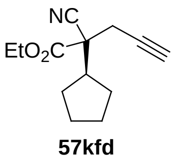
57afe

Benzyl-cyano-cyclohexyl-acetic acid ethyl ester (57afe): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3034, 2932, 2856, 2243, 1738 (O-C=O), 1604, 1496, 1369, 1265, 1089, 1035, 858 and 744 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.28 (5H, s, Ph-*H*), 4.03 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.21 (1H, d, *J* = 13.6 Hz), 3.03 (1H, d, *J* = 12.8 Hz), 2.05-1.96 (2H, m), 1.90 (1H, m), 1.80 (1H, m), 1.72 (1H, br d, *J* = 10.4 Hz), 1.59 (1H, br d, *J* = 12.4 Hz), 1.50-1.10 (5H, m), 1.04 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.4 (C, O-C=O), 134.7 (C), 129.8 (2 x CH), 128.4 (2 x CH), 127.5 (CH), 118.3 (C, *C*≡N), 62.2 (CH$_2$, O*C*H$_2$CH$_3$), 57.2 (C), 44.7 (CH), 40.8 (CH$_2$), 29.3 (CH$_2$), 27.6 (CH$_2$), 25.9 (CH$_2$), 25.8 (CH$_2$), 25.7 (CH$_2$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 285.00 (M$^+$), calcd for $C_{18}H_{23}NO_2$ 285.1729; HRMS: m/z 308.1632 (M+Na$^+$), calcd for $C_{18}H_{23}NO_2Na$ 308.1626.



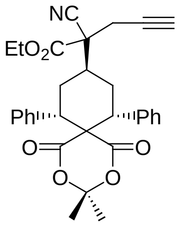
57ajd

2-Cyclohexyl-2-prop-2-ynyl-malononitrile (57ajd): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3294, 2935, 2860, 2251, 1452, 1302, 1261, 1078, 985 and 738 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.93 (2H, d, *J* = 2.8 Hz, C*H*$_2$C≡CH), 2.37 (1H, t, *J* = 2.8 Hz, CH$_2$C≡C*H*), 2.01 (4H, m), 1.90 (2H, m), 1.74 (1H, br d, *J* = 11.2 Hz), 1.33-1.18 (4H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 114.1 (2 x C, *C*≡N), 74.9 (CH, C≡*C*H), 74.6 (C, *C*≡CH), 42.5 (CH), 42.2 (C), 28.0 (2 x CH$_2$), 25.9 (CH$_2$), 25.4 (2 x CH$_2$), 25.1 (CH$_2$); HRMS: m/z 209.1064 (M+Na$^+$), calcd for $C_{12}H_{14}N_2$ Na 209.1055.

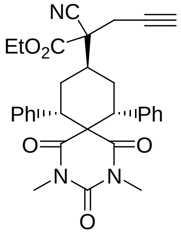


57kfd

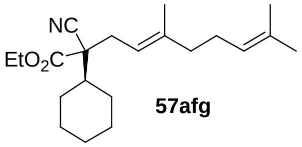
2-Cyano-2-cyclopentyl-pent-4-ynoic acid ethyl ester (57kfd): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3292, 2961, 2872, 2247, 1747 (O-C=O), 1456, 1369, 1224, 1097, 1049 and 858 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.32 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.78 (2H, dABq, *J* = 14.0, 2.8 Hz), 2.43-2.33 (1H, m), 2.18 (1H, t, *J* = 2.8 Hz, CH$_2$C≡C*H*), 1.87 (1H, m), 1.74 (3H, m), 1.60-1.40 (4H, m), 1.35 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.7 (C, O-C=O), 117.5 (C, *C*≡N), 77.3 (C, *C*≡CH), 72.6 (CH, C≡*C*H), 62.9 (CH$_{2,}$ O*C*H$_2$CH$_3$), 53.7 (C), 45.5 (CH), 28.9 (CH$_2$), 28.2 (CH$_2$), 26.7 (CH$_2$), 25.0 (CH$_2$), 24.90 (CH$_2$), 14.1 (CH$_{3,}$ OCH$_2$*C*H$_3$); LRMS: m/z 220.15 (M+H$^+$), calcd for C$_{13}$H$_{17}$NO$_2$ 219.1259; HRMS: m/z 242.1143 (M$^+$), calcd for C$_{13}$H$_{17}$NO$_2$ 242.1157.


57hfd

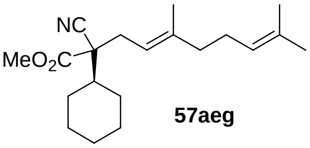
2-Cyano-2-(3,3-dimethyl-1,5-dioxo-7,11-diphenyl-2,4-dioxa-spiro[5.5]undec-9-yl)-pent-4-ynoic acid ethyl ester (57hfd): Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 175 °C; IR (KBr): ν_{max} 3296, 2939, 1734 (O-C=O), 1494, 1456, 1377, 1288, 1230, 1066, 896 and 765 cm^{-1}; ^{1}H NMR (CDCl$_3$, 10:1 ratio of isomers, major isomer) δ 7.31-7.19 (10H, m, 2 x Ph-*H*), 4.43 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.10 (1H, dd, *J* = 14.0, 3.2 Hz), 4.00 (1H, dd, *J* = 14.0, 3.6 Hz), 3.13 (2H, m), 2.94 (2H, d, *J* = 3.0 Hz), 2.88 (1H, m), 2.29 (1H, br d, *J* = 15.6 Hz), 2.22 (1H, t, *J* = 3.0 Hz, CH$_2$C≡C*H*), 1.93 (1H, br d, *J* = 15.6 Hz), 1.38 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 0.5 (6H, br s, 2 x CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135, 10:1 ratio of isomers, major isomer) δ 168.7 (C, O-C=O), 168.1 (C, O-C=O), 165.3 (C, O-C=O), 138.8 (C), 138.7 (C), 129.0 (2 x CH), 128.9 (2 x CH), 128.6 (4 x CH), 128.2 (CH), 128.1 (CH), 119.0 (C, *C*≡N), 105.7 (C, O-*C*-O), 76.8 (C, *C*≡CH), 73.4 (CH, C≡*C*H), 63.8 (CH$_{2,}$ O*C*H$_2$CH$_3$), 60.6 (C), 51.3 (C), 45.1 (2 x CH), 38.5 (CH), 28.2 (2 x CH$_3$), 27.3 (CH$_2$), 27.1 (CH$_2$), 26.8 (CH$_2$), 14.0 (CH$_{3,}$ OCH$_2$*C*H$_3$); LRMS: m/z 512.25 (M-H$^+$), calcd for C$_{31}$H$_{31}$NO$_6$ 513.22; HRMS: m/z 536.2059 (M+Na$^+$), calcd for C$_{31}$H$_{31}$NO$_6$Na 536.2049.


57ifd

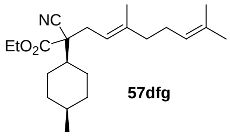
2-Cyano-2-(2,4-dimethyl-1,3,5-trioxo-7,11-diphenyl-2,4-diaza-spiro[5.5]undec-9-yl)-pent-4-ynoic acid ethyl ester (57ifd): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (KBr): ν_{max} 3287, 3063, 2934, 2858, 2245, 1739 (N-C=O), 1682, 1448, 1377, 1226, 1028, 850 and 756 cm^{-1}; ^{1}H NMR (CDCl$_3$, 10:1 ratio of isomers, major isomer) δ 7.19-7.03 (10H, m, 2 x Ph-*H*), 4.43 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.13 (1H, dd, *J* = 14.0, 3.6 Hz), 4.04 (1H, dd, *J* = 14.0, 3.6 Hz), 3.11 (2H, m), 2.93 (2H, d, *J* = 2.4 Hz, C*H*$_2$C≡CH), 2.91 (3H, s, N-C*H*$_3$), 2.85 (3H, s, N-C*H*$_3$), 2.91-2.85 (1H, m, C*H*), 2.24 (1H, br dd, *J* = 15.2, 3.2 Hz), 2.22 (1H, t, *J* = 2.4 Hz, CH$_2$C≡C*H*), 1.86 (1H, br dd, *J* = 15.2, 3.2 Hz), 1.36 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135, 10:1 ratio of isomers, major isomer) δ 171.1 (C, O-C=O), 168.8 (C, N-C=O), 168.1 (C, N-C=O), 149.7 (C, N-C=O), 138.7 (C), 138.6 (C), 128.5 (2 x CH), 128.4 (2 x CH), 128.0 (CH), 127.99 (CH), 127.6 (2 x CH), 127.5 (2 x CH), 118.99 (C, *C*≡N), 76.8 (C, *C*≡CH), 73.3 (CH, C≡*C*H), 63.5 (CH_2, O*C*H_2CH_3), 60.8 (C), 51.4 (C), 45.5 (CH), 45.4 (CH), 38.6 (CH), 28.0 (CH_3, N-*C*H_3), 27.6 (CH_3, N-*C*H_3), 27.2 (CH_2), 26.99 (CH_2), 26.9 (CH_2), 13.8 (CH_3, OCH_2*C*H_3); LRMS: m/z 526.30 ($M+H^+$), calcd for $C_{31}H_{31}N_3O_5$ 525.23; HRMS: m/z 548.2144 ($M+Na^+$), calcd for $C_{31}H_{31}N_3O_5Na$ 548.2161.


57afg

2-Cyano-2-cyclohexyl-5,9-dimethyl-deca-4,8-dienoic acid ethyl ester (57afg): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2930, 2856, 1741 (O-C=O), 1450, 1375, 1224, 1097 and 862 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (1H, m, olefinic-*H*), 5.07 (1H, br s, olefinic-*H*), 4.23 (2H, m, O*C*H_2CH_3), 2.59 (2H, dABq, *J* = 14.4, 6.8 Hz), 2.07-1.70 (10H, m), 1.68 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.30-1.20 (5H, m), 1.30 (3H, t, *J* = 7.2 Hz, OCH_2C*H_3*); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.9 (C, O-C=O), 140.7 (C), 131.6 (C), 123.8 (CH), 118.6 (C, *C*≡N), 116.7 (CH), 62.1 (CH_2, O*C*H_2CH_3), 55.4 (C), 43.8 (CH), 39.8 (CH_2), 33.6 (CH_2), 29.2 (CH_2), 27.7 (CH_2), 26.5 (CH_2), 25.98 (CH_2), 25.96 (CH_2), 25.7 (CH_2), 25.6 (CH_3), 17.7 (CH_3), 16.4 (CH_3), 14.2 (CH_3, OCH_2*C*H_3); LRMS: m/z 354.30 (M+Na), calcd for $C_{21}H_{33}NO_2Na$ 354.25; HRMS: m/z 354.2413 ($M+Na^+$), calcd for $C_{21}H_{33}NO_2Na$ 354.2409.


57aeg

2-Cyano-2-cyclohexyl-5,9-dimethyl-deca-4,8-dienoic acid methyl ester (57aeg): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2928, 2856, 2241, 1745 (O-C=O), 1450, 1377, 1228, 1064 and 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.13 (1H, t, *J* = 7.2 Hz), 5.06 (1H, br s) [olefinic-*H*]; 3.75 (3H, s, O*C*H_3), 2.58 (2H, dABq, *J* = 14.0, 6.8 Hz), 2.01 (4H, m), 1.84 (4H, m), 1.67-1.51 (1H, m), 1.67 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.35-1.15 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.5 (C, O-C=O), 141.0 (C), 131.6 (C), 123.7 (CH), 118.6 (C, *C*≡N), 116.7 (CH), 55.4 (C), 52.8 (CH_3, O*C*H_3), 43.8 (CH), 39.8 (CH_2), 33.6 (CH_2), 29.2 (CH_2), 27.6 (CH_2), 26.04 (CH_2), 25.94 (CH_2), 25.92 (CH_2), 25.7 (CH_2), 25.6 (CH_3), 17.6 (CH_3), 16.2 (CH_3); LRMS: m/z 318.30 ($M+H^+$), calcd for $C_{20}H_{31}NO_2$ 317.24; HRMS: m/z 340.2254 ($M+Na^+$), calcd for $C_{20}H_{31}NO_2$ Na 340.2252.

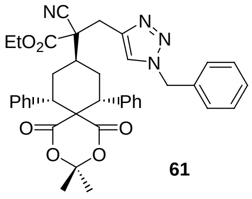

57dfg

2-Cyano-5,9-dimethyl-2-(4-methyl-cyclohexyl)-deca-4,8-dienoic acid ethyl ester (57dfg): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 2934, 2854, 2241, 1739 (O-C=O), 1668, 1448, 1379, 1300, 1222, 1097, 1049 and 862 cm^{-1}; ^1H NMR ($CDCl_3$, 3.0:1 ratio of isomers, major isomer) δ 5.14 (1H, t, *J* = 7.2 Hz), 5.04 (1H, t, *J* = 6.8 Hz) [olefinic-*H*]; 4.23-4.17 (2H, m), 2.54 (2H, dABq, *J* = 14.0, 7.6 Hz), 2.06-1.50 (12H, m), 1.67 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.30 (3H, t, *J* = 7.6 Hz, OCH_2C*H_3*), 0.97 (3H, d, *J* = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 3.0:1 ratio of isomers, major isomer) δ 169.0 (C, O-C=O), 140.8 (C), 131.6 (C), 123.8 (CH), 118.6 (C,

C≡N), 116.8 (CH), 62.2 (CH$_2$, O*C*H$_2$CH$_3$), 55.4 (C), 44.1 (CH), 39.8 (CH$_2$), 33.6 (CH$_2$), 31.22 (CH$_2$), 31.20 (CH$_2$), 26.5 (CH$_2$), 26.4 (CH$_3$), 25.7 (CH), 23.2 (CH$_2$), 21.7 (CH$_2$), 17.6 (CH$_3$), 17.0 (CH$_3$), 16.4 (CH$_3$), 14.2 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: m/z 368.35 (M+Na$^+$), calcd for $C_{22}H_{35}NO_2Na$ 368.27; HRMS: m/z 368.2575 (M+Na$^+$), calcd for $C_{22}H_{35}NO_2Na$ 368.2565.

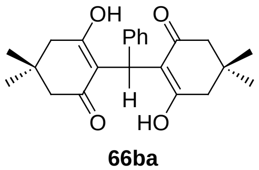
3. Amino acid-catalyzed olefination-hydrogenation-hydrolysis reactions in one-pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde **46a**, 0.5 mmol of Meldrum's acid **48c** and 0.5 mmol of Hantzsch ester **15** was added 1.0 mL of EtOH, and then the catalyst amino acid **50a** (0.1 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 2. To the crude reaction mixture added 0.5 mL of HCO_2H, 1.8 mL of NEt_3 and stirred at 120 °C for the 12 h. The crude reaction mixture was worked up with aqueous $NaHCO_3$ and NH_4Cl solutions 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 **59ac** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4. $CuSO_4$/Cu-Catalyzed Huisgen cycloaddition Reaction: For the synthesis of highly functionalized-triazole **61**, reactants O/H/A-cascade product **57hfd** (0.22 mmol), benzyl azide **60** (0.44 mmol), $CuSO_4$ (0.22 mmol, 35 mg) and Cu wire (23 mg) in ethanol (1.0 mL) was taken in an ordinary glass vial equipped with a magnetic stirring bar and stirred at 25 °C for the time indicated in Scheme 8. The crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure triazole **61** was obtained by flash column chromatography (silica gel, mixture of hexane/ethyl acetate).



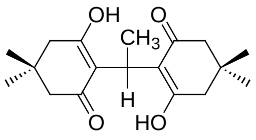
61

(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-cyano-(3,3-dimethyl-1,5-dioxo-7,11-diphenyl-2,4-dioxa-spiro[5.5]undec-9-yl)-acetic acid ethyl ester (61): Purified by column chromatography using EtOAc/hexane and isolated as solid. IR (neat): ν_{max} 2935, 2243, 1732 (O-C=O), 1552, 1454, 896 and 869 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.53 (1H, s, olefinic-*H*), 7.40-7.20 (15H, m, 3 x Ph-*H*), 5.52 (2H, br s, N-C*H*$_2$Ph), 4.28 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.22 (1H, dd, *J* = 14.4, 4.0 Hz), 4.10 (1H, m), 3.49-3.39 (2H, q, *J* = 14.4 Hz), 3.20-3.06 (2H, m), 2.83 (1H, br s), 2.31 (1H, br d, *J* =15.6 Hz), 1.98 (1H, br d, *J* = 15.6 Hz), 1.25 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$), 0.53 (3H, s, C*H*$_3$), 0.50 (3H, s, C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.7 (C, O-C=O), 168.4 (C, O-C=O), 165.2 (C, O-C=O), 141.3 (C), 138.8 (2 x C), 134.5 (C), 129.0 (2 x CH), 128.85 (2 x CH), 128.82 (2 x CH), 128.6 (3 x CH), 128.5 (2 x CH), 128.08 (CH), 128.03 (CH), 127.8 (2 x CH), 122.7 (CH), 119.7 (C, *C*≡N), 105.6 (C, O-C-O), 63.4 (CH$_2$, O*C*H$_2$CH$_3$), 60.8 (C), 54.0 (CH$_2$), 52.6 (C), 45.1 (CH), 44.9 (CH), 38.8 (CH), 33.2 (CH$_2$), 28.2 (CH$_3$), 28.1 (CH$_3$), 27.2 (CH$_2$), 26.8 (CH$_2$), 13.7 (CH$_3$, OCH$_2$*C*H$_3$); HRMS: m/z 669.2704 (M+Na$^+$), calcd for $C_{31}H_{38}N_4O_6Na$ 669.2689.



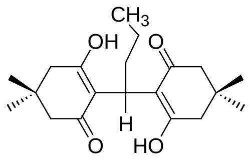
66ba

2,2'-Phenylmethylene-bis-[5,5-dimethyl-1,3-cyclohexanedione] (66ba): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 198 °C; ^{1}H NMR ($CDCl_3$) δ 11.90 (2H, br s, 2 x OH), 7.26 (2H, t, *J* = 7.6 Hz), 7.16 (1H, t, *J* = 7.6 Hz), 7.10 (2H, d, *J* = 7.6 Hz) [Ar-H]; 5.54 (1H, s), 2.48-2.28 (8H, m, 4 x CH_2), 1.23 (6H, s, 2 x CH_3), 1.09 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 190.4 (C, C=O), 189.3 (C, C=O), 138.0 (C), 128.1 (2 x CH), 126.7 (2 x CH), 125.7 (CH), 115.5 (2 x C), 47.0 (2 x CH_2), 46.3 (2 x CH_2), 32.6 (CH), 31.3 (2 x C), 29.6 (2 x CH_3), 27.3 (2 x CH_3).



66bo'

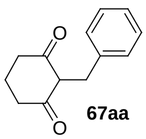
2,2'-methylmethylene-bis-[5,5-dimethyl-1,3-cyclohexanedione] (66bo'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 132 °C; ^{1}H NMR ($CDCl_3$) δ 12.56 (1H, s, OH), 11.60 (1H, br s, OH), 4.19 (1H, q, *J* = 7.2 Hz), 2.32 (8H, m, 4 x CH_2), 1.53 (3H, d, *J* = 7.2 Hz), 1.09 (12H, s, 4 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 189.6 (C, C=O), 189.4 (C, C=O), 117.6 (2 x C), 47.0 (2 x CH_2), 46.1 (2 x CH_2), 31.2 (2 x C), 29.7 (2 x CH_3), 26.5 (2 x CH_3), 23.5 (CH), 15.6 (CH_3).



66bh'

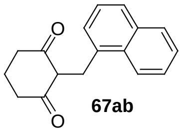
2,2'-propylmethylene-bis-[5,5-dimethyl-1,3-cyclohexanedione] (66bh'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 133 °C; ^{1}H NMR ($CDCl_3$) δ 12.54 (1H, s, OH), 11.60 (1H, br s, OH), 3.99 (1H, t, *J* = 8.0 Hz), 2.38-2.28 (8H, m, 4 x CH_2), 2.04 (2H, q, *J* = 7.7 Hz), 1.30-1.22 (2H, m), 1.11 (6H, s, 2 x CH_3), 1.10 (6H, s, 2 x CH_3), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 190.0 (C, C=O), 189.6 (C, C=O), 116.6 (2 x C), 47.0 (2 x CH_2), 46.2 (2 x CH_2), 31.2 (CH_2), 31.1 (2 x C), 29.9 (2 x CH_3), 29.3 (CH), 26.5 (2 x CH_3), 22.0 (CH_2), 13.8 (CH_3).

5. Amino Acid-Catalyzed Cascade Knoevenagel/Hydrogenation Reactions with Cyclohexane-1,3-Diones: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.5 mmol of the aldehyde **46**, 0.5 mmol of CH-acid **64a** or **64c** and 0.5 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst amino acid **50a** (0.10 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 15 and 16. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up, and pure cascade products **67** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



67aa

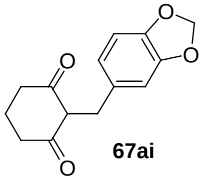
2-Benzyl-cyclohexane-1,3-dione (67aa): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 180 °C; IR (KBr): ν_{max} 2932, 2866, 1639, 1562, 1361, 1269, 1178 and 731 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.18-7.01 (5H, m) [Ar-H]; 4.60 (1H, bs, O-*H*), 3.55 (2H, s, PhC*H*$_2$), 2.34 (4H, t, *J* = 6.4 Hz, 2 x C*H*$_2$C=O), 1.85 (2H, quintet, *J* = 6.4 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 141.3 (C), 128.2 (2 x CH), 127.6 (2 x CH), 125.0 (CH), 115.3 (C), 32.5 (2 x CH_2), 27.2 (CH_2), 20.4 (CH_2); GCMS m/z 202.00, calcd for $C_{13}H_{14}O_2$ 202.2491.



67ab

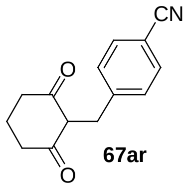
2-Naphthalen-1-ylmethyl-cyclohexane-1,3-dione (67ab): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 182 °C; IR (KBr): ν_{max} 3043, 2953, 1570, 1365, 1265, 1188, 1068, 1008, 856, 781 and 761 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.22 (1H, d, *J* = 8.4 Hz), 7.80 (1H, d, *J* = 7.6 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.45 (2H, m), 7.32 (1H, t, *J* = 8.8 Hz), 7.19 (1H, d, *J* = 7.2 Hz) [Ar-H]; 4.05 (2H, s, ArC*H₂*), 3.67 (1H, bs, O-*H*), 2.42 (4H, t, *J* = 8.0 Hz, 2 x C*H₂*C=O), 1.93 (2H, quintet, *J* = 8.0 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 136.1 (C), 133.6 (C), 132.2 (C), 128.2 (CH), 126.1 (CH), 125.4 (CH), 125.2 (CH), 125.1 (CH), 124.4 (CH), 123.9 (CH), 113.9 (C), 32.7 (2 x CH_2), 24.4 (CH_2), 20.6 (CH_2); LCMS m/z 251.95 (M - H^{+}), calcd for $C_{17}H_{16}O_2$ 252.3077; Anal. calcd for $C_{17}H_{16}O_2$ (252.3077): C, 80.93; H, 6.39. Found: C, 80.87; H, 6.38%.

2-Benzo[1,3]dioxol-5-ylmethyl-cyclohexane-1,3-dione (67ai): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 162 °C; IR (Neat): ν_{max} 3142, 2945, 1603, 1502, 1379, 1261, 1176, 1037, 1003, 918 and 775 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 6.77 (1H, s), 6.72 (1H, d, *J* = 8.0 Hz), 6.65 (1H, d, *J* = 8.0 Hz) [Ar-H]; 5.86 (2H, s, OC*H₂*O), 3.53 (2H, s, ArC*H₂*), 2.41 (4H, t, *J* = 6.4 Hz, 2 x C*H₂*C=O), 1.94 (2H, quintet, *J* = 6.4 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 147.0 (C), 145.0 (C), 135.4 (C), 121.1 (CH), 115.7 (C), 109.0 (CH), 107.6 (CH), 100.4 (CH_2, OCH_2O), 27.0 (CH_2), 20.6 (CH_2); GCMS m/z 246.15, calcd for $C_{14}H_{14}O_4$ 246.2586; Anal. calcd for $C_{14}H_{14}O_4$ (246.2586): C, 68.28; H, 5.73. Found: C, 68.251; H, 5.669%.



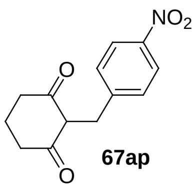
67ai

4-(2,6-Dioxo-cyclohexylmethyl)-benzonitrile (67ar): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 182 °C; IR (Neat): ν_{max} 2932, 2227 (CN), 1556, 1359, 1269, 1174, 1008, 551 and 484 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.48 (2H, br s), 7.37 (2H, br s) [Ar-H]; 3.65 (2H, s, ArC*H₂*), 2.43 (4H, br s, 2 x C*H₂*C=O), 1.95 (2H, br s); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 147.8 (C), 131.7 (2 x CH), 129.4 (2 x CH), 119.3 (C), 114.4 (C), 108.6 (C, CN), 32.6 (2 x CH_2), 27.8 (CH_2), 20.6 (CH_2); LRMS m/z 225.90 (M-H^{+}), calcd for $C_{14}H_{13}NO_2$ 227.2586; Anal. calcd for $C_{14}H_{13}NO_2$ (227.2586): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.925; H; 5.794; N, 6.151%.



67ar

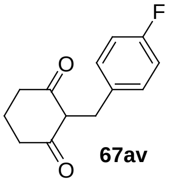
2-(4-Nitro-benzyl)-cyclohexane-1,3-dione (67ap): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 220 °C; IR (KBr): ν_{max} 3074, 1601, 1554, 1510, 1338, 1271, 1066, 850 and 802 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.06 (2H, d, *J* = 8.5 Hz), 7.32 (2H, d, *J* = 8.5 Hz) [Ar-H]; 3.70 (2H, br s, ArC*H₂*), 3.69 (1H, br s, O-*H*), 2.44 (4H, t, *J* = 4.0 Hz), 1.97 (2H, quintet, *J* = 8.0 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 150.0 (C), 145.6 (C),



67ap

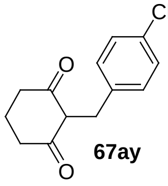
129.1 (2 x CH), 123.0 (2 x CH), 114.1 (C), 32.3 (2 x CH$_2$), 27.4 (CH$_2$), 20.4 (CH$_2$); LRMS m/z 246.85 (M-H$^+$), calcd for $C_{13}H_{13}NO_4$ 247.2467; Anal. calcd for $C_{13}H_{13}NO_4$ (247.2467): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.112; H; 5.307; N, 5.853%.

2-(4-Fluoro-benzyl)-cyclohexane-1,3-dione (67av): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 180 °C; IR (Neat): ν_{max} 2947, 1639, 1564, 1361, 1271, 1089, 821 and 771 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.18 (2H, dd, *J* = 5.8, 8.0 Hz), 6.85 (2H, dd, *J* = 8.7 Hz) [Ar-H]; 4.15 (1H, br s, O-H), 3.55 (2H, s, Ar-C*H*$_2$), 2.39 (4H, t, *J* = 6.0 Hz, 2 x C*H*$_2$C=O), 1.91 (2H, quintet, *J* = 6.4 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 160.9 (C, d, *J* = 241.0 Hz), 137.1 (C, d, *J* = 3.0 Hz), 129.7 (2 x CH, d, *J* = 8.0 Hz), 115.6 (C), 114.3 (2 x CH, d, *J* = 21.0 Hz), 32.6 (2 x CH$_2$, C*H*$_2$C=O), 26.6 (CH$_2$), 20.7 (CH$_2$); GCMS m/z 220.10, calcd for $C_{13}H_{13}FO_2$ 220.2395; Anal. calcd for $C_{13}H_{13}FO_2$ (220.2395): C, 70.90; H, 5.95. Found: C, 70.916; H, 5.924%.



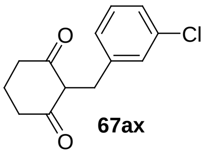
67av

2-(4-Chloro-benzyl)-cyclohexane-1,3-dione (67ay): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 188 °C; IR (KBr): ν_{max} 2935, 1637, 1560, 1363, 1089, 1007, 802, 547 and 488 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.14 (4H, m, Ar-*H*), 3.54 (2H, s, ArC*H*$_2$), 3.50 (1H, br s, O-*H*), 2.39 (4H, t, *J* = 6.0 Hz, 2 x C*H*$_2$C=O), 1.92 (2H, m); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 140.1 (C), 130.8 (C), 129.8 (2 x CH), 127.8 (2 x CH), 115.3 (C), 32.7 (2 x CH$_2$, C*H*$_2$C=O), 32.7 (2 x CH$_2$), 26.8 (CH$_2$), 20.6 (CH$_2$); Anal. calcd for $C_{13}H_{13}ClO_2$ (236.6938): C, 65.97; H, 5.54. Found: C, 65.904; H, 5.576%.



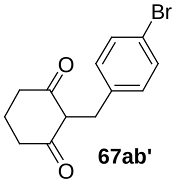
67ay

2-(3-Chloro-benzyl)-cyclohexane-1,3-dione (67ax): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 95 °C; IR (Neat): ν_{max} 2943, 1635, 1560, 1489, 1359, 1267, 1089, 802 and 752 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.22 (1H, s), 7.11-7.07 (3H, m) [Ar-H]; 3.59 (2H, s, ArC*H*$_2$), 2.42 (4H, t, *J* = 6.0 Hz, 2 x C*H*$_2$C=O), 2.17 (1H, br s, O-H), 1.95 (2H, quintet, *J* = 6.0 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 143.6 (C), 133.6 (C), 129.2 (CH), 128.5 (CH), 126.8 (CH), 125.5 (CH), 115.1(C), 27.2 (CH$_2$), 20.7 (CH$_2$); GCMS m/z 236.00, calcd for $C_{13}H_{13}ClO_2$ 236.6938; Anal. calcd for $C_{13}H_{13}ClO_2$ (236.6938): C, 65.97; H, 5.54. Found: C, 66.002; H, 5.529%.



67ax

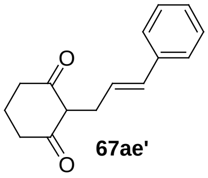
2-(4-Bromo-benzyl)-cyclohexane-1,3-dione (67ab): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 191 °C; IR (KBr): ν_{max} 2928, 1637, 1560, 1363, 1068, 796, 748 and 548 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.30 (2H, d, *J* = 8.0 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 3.55 (2H, s, ArC*H*$_2$), 2.40 (4H, t, *J* = 6.4 Hz, 2 x C*H*$_2$C=O), 1.94 (2H, m); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-



67ab'

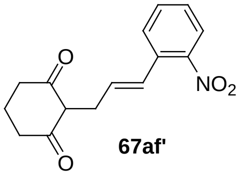
135] δ 140.6 (C), 130.8 (2 x CH), 130.3 (2 x CH), 118.9 (C), 115.2 (C), 26.9 (CH_2), 20.6 (CH_2); LRMS m/z 281.00 (M^+), calcd for $C_{13}H_{13}BrO_2$ 281.1451; Anal. calcd for $C_{13}H_{13}BrO_2$ (281.1451): C, 55.54; H, 4.66. Found: C, 55.575; H, 4.646%.

2-(3-Phenyl-allyl)-cyclohexane-1,3-dione (67ae′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 150 °C; IR (Neat): ν_{max} 3067, 2920, 2872, 1635, 1591, 1568, 1504, 1454, 1358, 1263, 1207, 1168, 1109, 1066, 1028, 993, 949, 887, 831 and 754 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.32 (2H, m), 7.24 (2H, t, *J* = 8.0 Hz), 7.14 (1H, t, *J* = 8.0 Hz) [Ar-H]; 6.39 (1H, d, *J* = 15.6 Hz), 6.22 (1H, td, *J* = 15.6, 6.4 Hz) [ArC*H*=C*H*CH_2]; 3.45 (1H, br s, O-H), 3.18 (2H, d, *J* = 6.4 Hz), 2.43 (4H, t, *J* = 5.6 Hz), 1.96 (2H, quintet, *J* = 6.4 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 137.8 (C), 129.4 (CH), 128.3 (CH), 128.2 (2 x CH), 126.5 (CH), 125.8 (2 x CH), 113.9 (C), 25.1 (CH_2), 20.6 (CH_2); Anal. calcd for $C_{15}H_{16}O_2$ (228.1150): C, 78.92; H, 7.06. Found: C, 78.851; H, 7.055%.



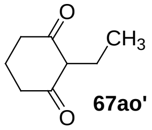
67ae'

2-[3-(2-Nitro-phenyl)-allyl]-cyclohexane-1,3-dione (67af′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 170 °C; IR (Neat): ν_{max} 2918, 1564, 1365, 1267, 1190, 1126, 985 and 596 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.84 (1H, d, *J* = 8.4 Hz), 7.61 (1H, d, *J* = 5.2 Hz), 7.52 (1H, t, *J* = 7.6 Hz), 7.32 (1H, t, *J* = 7.6 Hz) [Ar-H]; 6.80 (1H, d, *J* = 15.6 Hz), 6.30 (1H, td, *J* = 15.6, 6.4 Hz) [ArC*H*=C*H*CH_2]; 3.22 (2H, d, *J* = 6.4 Hz), 2.46 (4H, t, *J* = 5.6 Hz), 2.00 (2H, quintet, *J* = 6.0 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 147.4 (C), 134.1 (CH), 133.1 (C), 132.5 (CH), 128.0 (CH), 126.9 (CH), 123.9 (CH), 123.85 (CH), 112.9 (C), 25.0 (CH_2), 20.5 (CH_2); Anal. calcd for $C_{15}H_{15}NO_4$ (273.1001): C, 65.92; H, 5.53; N, 5.13. Found: C, 65.979; H, 5.509; N, 5.278%.



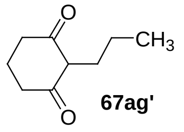
67af'

2-Ethyl-cyclohexane-1,3-dione (67ao′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 180 °C; IR (KBr): ν_{max} 3452, 2947, 1734, 1705, 1572, 1366 and 1103 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 2.40 (4H, t, *J* = 6.4 Hz, $CH_2C{=}O$), 2.27 (2H, q, *J* = 7.6 Hz), 2.19 (1H, s, O-H), 1.95 (2H, quintet, *J* = 6.4 Hz), 0.94 (3H, t, *J* = 7.6 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 117.7 (C), 32.7 (2 x CH_2, $CH_2C{=}O$), 20.7 (CH_2), 14.9 (CH_2), 13.0 (CH_3); **^{1}H NMR ($CDCl_3$, 1:1 keto-enol isomers)** δ 3.30 (1H, t, *J* = 6.0 Hz); 2.68-2.55 (4H, m, 2 x $CH_2C{=}O$), 2.45 (4H, t, *J* = 6.4 Hz, 2 x $CH_2C{=}O$), 2.30 (2H, q, *J* = 7.6 Hz), 2.20 (1H, s, O-H), 2.19-2.00 (2H, m), 1.95 (2H, quintet, *J* = 6.4 Hz), 1.90-1.80 (2H, m), 0.98 (3H, t, *J* = 7.6 Hz, CH_2CH_3), 0.94 (3H, t, *J* = 7.6 Hz, CH_2CH_3); **^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 keto-enol isomers)** δ 205.3 (C, C=O), 117.7 (C), 68.8 (CH), 39.7 (2 x CH_2, $CH_2C{=}O$), 20.7 (CH_2), 18.1

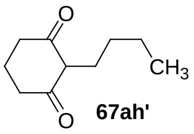


67ao'

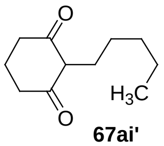
(CH$_2$), 17.0 (CH$_2$), 15.0 (CH$_2$), 13.2 (CH$_3$), 11.9 (CH$_3$); Anal. calcd for $C_8H_{12}O_2$ (140.1797): C, 68.54; H, 8.63. Found: C, 68.602; H, 8.609%.


67ag'

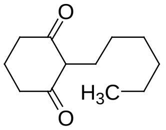
2-Propyl-cyclohexane-1,3-dione (67ag′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 131 °C; IR (KBr): ν_{max} 3439, 2962, 1709, 1566, 1367, 1296, 1197, 1030, 962 and 868 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 4.13 (1H, br s, O-H), 2.40 (4H, t, *J* = 6.4 Hz), 2.22 (2H, t, *J* = 6.4 Hz), 1.94 (2H, quintet, *J* = 6.4 Hz), 1.35 (2H, sextet, *J* = 7.6 Hz), 0.88 (3H, t, *J* = 7.2 Hz); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 116.1 (C), 32.7 (2 x CH$_2$, CH$_2$C=O), 23.5 (CH$_2$), 21.5 (CH$_2$), 20.7 (CH$_2$), 13.7 (CH$_3$); Anal. calcd for $C_9H_{14}O_2$ (154.2063): C, 70.10; H, 9.15. Found: C, 70.122; H, 9.15%.


67ah'

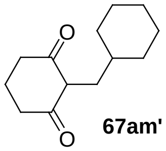
2-Butyl-cyclohexane-1,3-dione (67ah′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 116 °C; IR (KBr): ν_{max} 3443, 2959, 1711, 1601, 1388 and 1030 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 2.41 (4H, t, *J* = 6.4 Hz, CH$_2$C=O), 2.25 (2H, t, *J* = 7.0 Hz), 1.94 (2H, quintet, *J* = 6.4 Hz), 1.30 (4H, m), 0.90 (3H, t, *J* = 6.4 Hz); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 116.4 (C), 30.7 (CH$_2$), 22.6 (CH$_2$), 21.4 (CH$_2$), 20.7 (CH$_2$), 13.6 (CH$_3$); Anal. calcd for $C_{10}H_{16}O_2$ (168.2328): C, 71.39; H, 9.59. Found: C, 71.458; H, 9.581%.


67ai'

2-Pentyl-cyclohexane-1,3-dione (67ai′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 93 °C; IR (KBr): ν_{max} 3497, 2961, 2864, 1738, 1714, 1595 and 1388 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 3.8 (1H, br s, O-H), 2.40 (4H, t, *J* = 8.0 Hz, 2 x CH$_2$C=O), 2.24 (2H, t, *J* = 8.0 Hz), 1.89 (2H, quintet, *J* = 8.0 Hz), 1.40-1.20 (6H, m), 0.87 (3H, t, *J* = 8.0 Hz); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 116.6 (C), 32.8 (2 x CH$_2$, CH$_2$C=O), 31.8 (CH$_2$), 28.3 (CH$_2$), 22.6 (CH$_2$), 21.7 (CH$_2$), 20.8 (CH$_2$), 13.9 (CH$_3$); LRMS m/z 183.20 (M+H$^+$), calcd for $C_{11}H_{18}O_2$ 182.2594.


67ap'

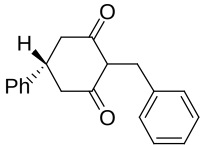
2-Hexyl-cyclohexane-1,3-dione (67ap′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 2939, 2874, 1734, 1705, 1574, 1367, 1269, 1103 and 721 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 2.44 (4H, t, *J* = 6.4 Hz, 2 x CH$_2$C=O), 2.26 (2H, t, *J* = 6.4 Hz), 1.94 (2H, quintet, *J* = 6.4 Hz), 1.27 (8H, br s), 0.85 (3H, t, *J* = 6.8 Hz); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 116.6 (C), 33.0 (2 x CH$_2$, CH$_2$C=O), 31.8 (CH$_2$), 29.4 (CH$_2$), 28.6 (CH$_2$), 22.6 (CH$_2$), 21.8 (CH$_2$), 20.8 (CH$_2$), 14.0 (CH$_3$).


67am'

2-Cyclohexylmethyl-cyclohexane-1,3-dione (67am′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 174 °C; IR (KBr): ν_{max} 2916, 2849, 1635, 1587, 1564, 1365, 1267, 1072, 985, 856 and 733 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 3.98 (1H, br s, O-H), 2.36 (4H, t, *J* = 6.0 Hz 2 x

$CH_2C=O$), 2.09 (2H, d, *J* = 7.2 Hz), 1.88 (2H, quintet, *J* = 6.0 Hz), 1.55 (5H, m), 1.33 (1H, m), 1.11 (3H, m), 0.85 (2H, m); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 114.9 (C), 37.1 (CH), 33.1 (2 x CH_2), 29.0 (CH_2), 26.6 (CH_2), 26.4 (2 x CH_2), 20.8 (CH_2); GCMS m/z 208.20, calcd for $C_{13}H_{20}O_2$ 208.2967; Anal. calcd for $C_{13}H_{20}O_2$ (208.2967): C, 74.96; H, 9.68. Found: C, 74.972; H, 9.66%.

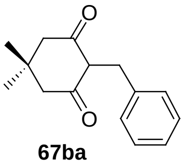
2-Benzyl-5-phenyl-cyclohexane-1,3-dione (67ca): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 150 °C; IR (Neat): ν_{max} 3024, 2930, 1635, 1579, 1543, 1381, 1338, 1242, 1103, 1070, 1030, 860 and 760 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.26-7.09 (10H, m) [Ar-H]; 4.0 (1H, br s, O-H), 3.65 (2H, s, PhC*H*$_2$), 3.31 (1H, quintet, *J* = 8.0 Hz), 2.64 (4H, d, *J* = 8.0 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 142.7 (C), 141.3 (C), 128.5 (2 x CH), 128.4 (2 x CH), 127.8 (2 x CH), 126.8 (CH), 126.5 (2 x CH), 125.2 (CH), 115.3 (C), 39.9 (2 x CH_2), 38.8 (CH), 27.4 (CH_2); GCMS m/z 278.15, calcd for $C_{19}H_{18}O_2$ 278.3450; Anal. calcd for $C_{19}H_{18}O_2$ (278.3450): C, 81.99; H, 6.52. Found: C, 82.018; H, 6.509%.



67ca

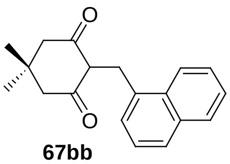
6. General Experimental Procedures for the Cascade Reactions: Amino Acid-Catalyzed Cascade Knoevenagel/Hydrogenation Reactions with Dimedone: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde **46**, 0.5 mmol of CH-acid **64b** and 0.5 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst amino acid **50a** (0.10 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 12, 13 and 14. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up, and pure cascade products **67** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2-Benzyl-5,5-dimethyl-cyclohexane-1,3-dione (67ba): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 118 °C; IR (Neat): ν_{max} 3414, 3026, 2957, 1635, 1585, 1556, 1377, 1309, 1249, 1190, 1074, 825 and 783 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.20 (4H, m), 7.11 (1H, t, *J* = 6.8 Hz) [Ar-H]; 3.63 (2H, s, PhC*H*$_2$), 3.09 (1H, br s, O-H), 2.29 (4H, s, 2 x C*H*$_2$C=O), 1.05 (6H, s, 2 x CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 141.3 (C), 128.3 (2 x CH), 127.9 (2 x CH), 125.3 (CH), 114.2 (C), 31.9 (C), 28.2 (2 x CH_3), 27.3 (CH_2); LRMS m/z 229.15 (M-H$^+$), calcd for $C_{15}H_{18}O_2$ 230.3022.



67ba

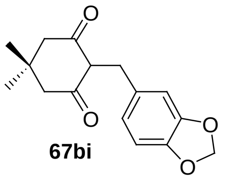
5,5-Dimethyl-2-naphthalen-1-ylmethyl-cyclohexane-1,3-dione (67bb): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 180 °C; IR (KBr): ν_{max} 2957, 2876, 1647, 1568, 1385, 1309, 1248, 1041 and 887 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.19 (1H, m), 7.80 (1H, d, *J* = 7.6 Hz), 7.65 (1H, d, *J* = 8.0 Hz), 7.45 (2H, m), 7.32 (1H, t, *J* = 8.0 Hz), 7.21 (1H, d, *J* =



67bb

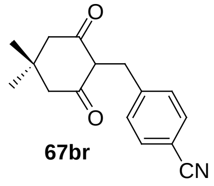
8.0 Hz) [Ar-H]; 4.07 (2H, s, ArC*H*$_2$), 2.30 (4H, s, 2 x C*H*$_2$C=O), 1.03 (6H, s, 2 x CH$_3$); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 136.2 (C), 133.6 (C), 132.2 (C), 128.3 (CH), 126.2 (CH), 125.4 (CH), 125.3 (CH), 125.2 (CH), 124.6 (CH), 124.0 (CH), 112.7 (C), 54.2 (2 x CH$_2$), 31.8 (C), 28.3 (2 x CH$_3$), 24.6 (CH$_2$); **^{1}H NMR (CDCl$_3$, 1:1 keto-enol isomers)** δ 8.10 (1H, m), 7.88 (3H, m), 7.77 (3H, m), 7.55 (1H, m), 7.50 (3H, m), 7.38 (3H, m) [Ar-H]; 4.16 (2H, s, ArC*H*$_2$), 3.71 (2H, s, ArC*H*$_2$), 2.64 (2H, d, *J* = 13.2 Hz), 2.50 (2H, d, *J* = 13.2 Hz), 2.31 (4H, s, 2 x C*H*$_2$C=O), 1.18 (3H, s, CH$_3$), 1.07 (6H, s, 2 x CH$_3$), 0.89 (3H, s, CH$_3$); **^{13}C NMR (CDCl$_3$, 1:1 keto-enol isomers, DEPT-135)** δ 202.9 (C, C=O), 136.3 (C), 135.7 (C), 134.1 (C), 133.9 (C), 132.0 (C), 132.0 (C), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 127.0 (CH), 126.3 (CH), 126.1 (2 x CH), 125.6 (CH), 125.5 (CH), 125.47 (CH), 125.2 (CH), 124.2 (CH), 123.2 (CH), 112.7 (C), 68.4 (CH), 54.4 (2 x CH$_2$), 31.8 (C), 31.0 (C), 30.4 (CH$_3$), 28.3 (2 x CH$_3$), 26.1 (CH$_3$), 25.8 (CH$_2$), 23.9 (CH$_2$); LRMS m/z 281.20 (M+H$^+$), calcd for $C_{19}H_{20}O_2$ 280.3609.

2-Benzo[1,3]dioxol-5-ylmethyl-5,5-dimethyl-cyclohexane-1,3-dione (67bi): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 191 °C; IR (KBr): ν$_{max}$ 2934, 1635 (C=O), 1558, 1379, 1311, 1249, 1041, 812 and 763 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 6.75 (1H, s), 6.71 (1H, dd, *J* = 8.4, 1.2 Hz), 6.65 (1H, d, *J* = 8.4 Hz) [Ar-H]; 5.86 (2H, s, OC*H*$_2$O), 4.00 (1H, br s, O-H), 3.53 (2H, s), 2.30 (4H, s, 2 x C*H*$_2$C=O), 1.05 (6H, s, 2 x CH$_3$); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 146.9 (C), 144.9 (C), 135.4 (C), 120.9 (CH), 114.3 (C), 108.8 (CH), 107.5 (CH), 100.3 (CH$_2$, OCH$_2$O), 31.7 (C), 28.0 (2 x CH$_3$), 26.8 (CH$_2$); LRMS m/z 274.05, calcd for $C_{16}H_{18}O_4$ 274.3117; Anal. calcd for $C_{16}H_{18}O_4$ (274.3117): C, 70.06; H, 6.61. Found: C, 70.083; H, 6.606%.

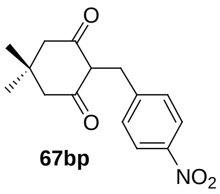


67bi

4-(4,4-Dimethyl-2,6-dioxo-cyclohexylmethyl)-benzonitrile (67br): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 186 °C; IR (KBr): ν$_{max}$ 3055, 2935, 2227, 1639, 1601, 1558, 1363, 1269, 1066, 922, 856 and 761 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 7.49 (2H, d, *J* = 8.0 Hz), 7.35 (2H, d, *J* = 8.0 Hz) [Ar-H]; 3.66 (2H, s, ArC*H*$_2$), 2.29 (5H, s, 2 x C*H*$_2$C=O and O-*H*), 1.04 (6H, s, 2 x CH$_3$); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 147.7 (C), 131.8 (2 x CH), 129.3 (2 x CH), 119.3 (C), 113.3 (C), 108.8 (C, CN), 32.0 (C), 28.3 (2 x CH$_3$), 27.8 (CH$_2$); LRMS m/z 254.05 (M-H$^+$), calcd for $C_{16}H_{17}NO_2$ 255.3117; Anal. calcd for $C_{16}H_{17}NO_2$ (255.3117): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.293; H; 6.711; N, 5.608%.



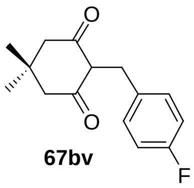
67br



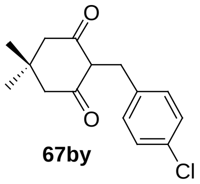
67bp

5,5-Dimethyl-2-(4-nitro-benzyl)-cyclohexane-1,3-dione (67bp): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 183 °C; IR (KBr): ν$_{max}$ 2961, 2866, 1635, 1556, 1377, 1249, 1037, 731 and 692 cm^{-1}; ^{1}H

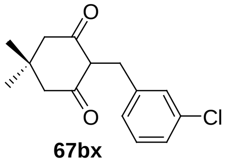
NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.06 (2H, d, *J* = 8.8 Hz), 7.40 (2H, d, *J* = 8.8 Hz) [Ar-H]; 3.70 (2H, s, $ArCH_2$), 2.30 (4H, s, 2 x C*H*$_2$C=O), 2.05 (1H, br s, O-H), 1.04 (6H, s, 2 x CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 149.9 (C), 145.9 (C), 129.3 (2 x CH), 123.2 (2 x CH), 113.3 (C), 32.0 (C), 28.3 (2 x CH_3), 27.6 (CH_2); LRMS m/z 274.00 (M-H^+), calcd for $C_{15}H_{17}NO_4$ 275.2998; Anal. calcd for $C_{15}H_{17}NO_4$ (275.2998): C, 65.44; H, 6.22; N, 5.09. Found: C, 65.716; H; 6.283; N, 4.904%.


67bv

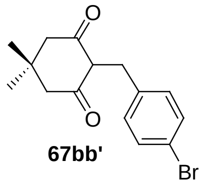
2-(4-Fluoro-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (67bv): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 160 °C; IR (KBr): ν_{max} 2962, 2874, 1556, 1508, 1377, 1249, 1033, 852 and 769 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.18 (2H, dd, *J* = 8.4, 5.6 Hz), 6.87 (2H, t, *J* = 8.4 Hz) [Ar-H]; 3.58 (2H, s, $ArCH_2$), 2.28 (4H, s, 2 x C*H*$_2$C=O), 1.03 (6H, s, 2 x CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 161.0 (C, d, *J* = 240.8 Hz), 137.0 (C, d, *J* = 3.0 Hz), 129.7 (2 x CH, d, *J* = 7.6 Hz), 114.6 (2 x CH, d, *J* = 21.0 Hz), 114.3 (C), 31.9 (C), 28.3 (2 x CH_3), 26.6 (CH_2); LRMS m/z 248.00 (M^+), calcd for $C_{15}H_{17}FO_2$ 248.2927; Anal. calcd for $C_{15}H_{17}FO_2$ (248.2927): C, 72.56; H, 6.90. Found: C, 72.567; H, 6.973%.


67by

2-(4-Chloro-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (67by): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 188 °C; IR (Neat): ν_{max} 2932, 2866, 1633, 1554, 1375, 1309, 1249, 1037, 814 and 763 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.12 (4H, m, Ar-H), 3.53 (2H, s, $ArCH_2$), 2.24 (4H, s, 2 x C*H*$_2$C=O), 0.99 (6H, s, 2 x CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 140.1 (C), 130.8 (C), 129.8 (2 x CH), 127.9 (2 x CH), 114.0 (C), 31.9 (C), 28.2 (2 x CH_3), 26.7 (CH_2); LRMS m/z 264.00 (M^+), calcd for $C_{15}H_{17}ClO_2$ 264.7470; Anal. calcd for $C_{15}H_{17}ClO_2$ (264.7470): C, 68.05; H, 6.47. Found: C, 68.05; H, 6.54%.

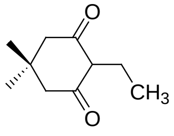

67bx

2-(3-Chloro-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (67bx): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 175 °C; IR (Neat): ν_{max} 2961, 1633, 1554, 1375, 1309, 1091, 1037, 814 and 763 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.20-7.07 (4H, m, Ph-*H*), 3.60 (2H, s), 2.30 (4H, s, 2 x C*H*$_2$CO), 1.03 (6H, s, 2 x CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 205.1 (C, C=O), 143.7 (C), 133.5 (C), 129.1 (CH), 128.4 (CH), 126.7 (CH), 125.4 (CH), 113.5 (C), 46.5 (CH_2, 2 x CH_2C=O), 31.9 (C), 28.2 (2 x CH_3), 27.1 (CH_2); Anal. calcd for $C_{15}H_{17}ClO_2$ (264.7470): C, 68.05; H, 6.47. Found: C, 68.24; H, 6.44%.


67bb'

2-(4-Bromo-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (67bb): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 204 °C; IR (Neat): ν_{max} 2959, 2874, 1631, 1583, 1554, 1373, 1309, 1249, 1035, 812 and 761 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.28 (2H, d, *J* = 8.4 Hz), 7.09 (2H, d, *J* = 8.4 Hz) [Ar-H]; 3.53 (2H, s), 2.87 (1H, br s, O-H), 2.25 (4H, s, 2 x C*H$_2$*C=O), 1.00 (6H, s, 2 x CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 140.6 (C), 130.9 (2 x CH), 130.2 (2 x CH), 118.9 (C), 113.9 (C), 31.9 (C), 28.2 (2 x CH_3), 26.8 (CH_2).

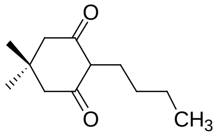
2-Ethyl-5,5-dimethyl-cyclohexane-1,3-dione (67bo'): Purified by column chromatography using



67bo'

EtOAc/hexane and isolated as a solid. Mp 152 °C; IR (KBr): ν_{max} 3460, 2964, 1732, 1699, 1639, 1371, 1107 and 1059 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 3.38 (1H, br s, O-H), 2.27 (6H, m), 1.05 (6H, s, 2 x CH_3), 0.94 (3H, t, *J* = 7.6 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 116.4 (C), 53.7 (2 x CH_2), 31.8 (C), 28.1 (2 x CH_3), 14.8 (CH_2), 13.0 (CH_3); LRMS m/z 167.00 (M-H$^+$), calcd for $C_{10}H_{16}O_2$ 168.2328; Anal. calcd for $C_{10}H_{16}O_2$ (168.2328): C, 71.39; H, 9.59. Found: C, 71.35; H, 9.58%.

2-Butyl-5,5-dimethyl-cyclohexane-1,3-dione (67bh'): Purified by column chromatography using



67bh'

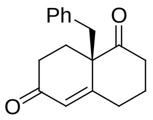
EtOAc/hexane and isolated as a solid. Mp 160 °C; IR (KBr): ν_{max} 3435, 2959, 1736, 1705, 1564, 1386, 1205, 1114 and 599 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 2.26 (6H, m), 1.32 (4H, m), 1.05 (6H, s, 2 x CH_3), 0.90 (3H, t, *J* = 8.0 Hz, CH_2C*H$_3$*); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 205.0 (C, C=O), 115.0 (C), 52.0 (2 x CH_2), 31.8 (C), 30.7 (CH_2), 28.0 (2 x CH_3), 22.5 (CH_2), 21.1 (CH_2), 13.8 (CH_3); Anal. calcd for $C_{12}H_{20}O_2$ (196.2860): C, 73.43; H, 10.27. Found: C, 73.453; H, 10.306%.

7. Amino Acid-Catalyzed Robinson Annulation Reaction: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of 2-alkyl-cyclohexane-1,3-diones **67** and 3.0 mmol of methyl vinyl ketone **68a** was added 3.0 mL of DMF solvent, and then the catalyst proline **50a** (0.3 mmol) was added and the reaction mixture was stirred at 25 °C for 5 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 products **69** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

8. Amino Acid-Catalyzed One-Pot Double Cascade Knoevenagel/Hydrogenation/Robinson Annulation Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 5.0 mmol of the aldehyde **46**, 1.0 mmol of CH-acid **64a** and 1.0 mmol of Hantzsch ester **15** was added 2.0 mL of dichloromethane, and then the catalyst amino acid **50a** (0.2 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 19. After evaporation of the solvent completely, to the crude reaction mixture added 3.0 mmol of methyl vinyl ketone **68a**, 3.0 mL of DMF solvent and 0.30 mmol of L-proline **50a** and the reaction mixture was stirred at 25 °C for 5 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 products **69**, **70** and **73** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

9. General Procedure for Dehydration of 8a-Alkyl-4a-Hydroxy-Hexahydro-Naphthalene-1,6-Diones 70: Method (1): A solution of alcohol compound **70** (0.5 mmol) and 1N $HClO_4$ (1.5 mmol) in DMSO (1.5 ml) was stirred at 90 °C for 24 h. After cooling, the reaction mixture washed with water 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 products **69** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate). **Method (2):** A solution of alcohol compound **70** (0.5 mmol) and *p*-TSA (0.15 mmol) in benzene (1.5 mL) was stirred at 80 °C for 2 h. After cooling, the reaction mixture washed with aqueous sodium bicarbonate 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 products **69** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

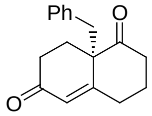
(+)-8a-Benzyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione (69aa): Purified by column



(+)-69aa

chromatography using EtOAc/hexane and isolated as a solid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 0.5 mL/min, λ = 254 nm), t_R = 64.54 min (minor), t_R = 72.12 min (major). **$[\alpha]_D^{25}$ = +114.0° (*c* = 1.12 g/100 mL, $CHCl_3$, >97% ee)**; Mp 100 °C; IR (Neat): ν_{max} 3065, 3030, 2964, 1707, 1668, 1612, 1496, 1352, 1074, 765 and 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (3H, m), 7.03 (2H, m) [Ar-H]; 5.96 (1H, s, olefinic-*H*), 3.18 (2H, AB q, *J* = 13.6 Hz), 2.75-2.50 (4H, m), 2.45-2.22 (2H, m), 2.22-1.93 (3H, m), 1.80-1.60 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.9 (C), 198.1 (C), 164.9 (C), 135.5 (C), 129.5 (2 x CH), 128.5 (2 x CH), 127.5 (CH), 126.9 (CH), 55.8 (C), 42.7 (CH_2), 39.1 (CH_2), 33.6 (CH_2), 32.6 (CH_2), 27.5 (CH_2), 23.0 (CH_2); Anal. calcd for $C_{17}H_{18}O_2$ (254.3236): C, 80.28; H, 7.13. Found: C, 80.287; H, 7.152%.

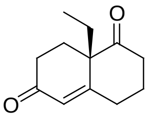
(–)-8a-Benzyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione (69aa): Purified by column



(–)-69aa

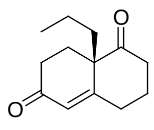
chromatography using EtOAc/hexane and isolated as a solid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 0.5 mL/min, λ = 254 nm), t_R = 64.54 min (major), t_R = 72.12 min (minor).. **$[\alpha]_D^{25}$ = –80.4° (*c* = 1.40 g/100 mL, $CHCl_3$, 80% ee).**

(+)-8a-Ethyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione (69ao'): Purified by column

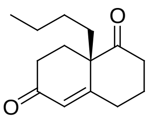


(+)-69ao'

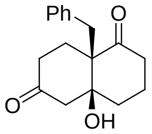
chromatography using EtOAc/hexane and isolated as a liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 41.67 min (major), t_R = 68.63 min (minor). **$[\alpha]_D^{25}$ = +4.0° (*c* = 0.5 g/100 mL, $CHCl_3$, 75% ee)**; IR (Neat): ν_{max} 3408, 2961, 1712, 1666, 1616, 1460, 1356, 1266, 1082, 1022 and 912 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 5.89 (1H, s, olefinic-*H*), 2.81 (1H, dt, J = 14.0, 4.8 Hz), 2.66 (1H, dt, J = 14.8, 6.0 Hz), 2.55-2.30 (4H, m), 2.30-2.10 (2H, m), 2.10-1.90 (2H, m), 1.90-1.75 (1H, m), 1.75-1.60 (1H, m), 0.88 (3H, t, J = 7.6 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 210.0 (C), 198.3 (C), 166.2 (C), 126.1 (CH), 55.1 (C), 38.3 (CH$_2$), 33.4 (CH$_2$), 31.8 (CH$_2$), 28.2 (CH$_2$), 24.8 (CH$_2$), 23.4 (CH$_2$), 8.8 (CH$_3$); LRMS m/z 192.95 (M+H$^+$), calcd for $C_{12}H_{16}O_2$ 192.2542.


(+)-69ag'

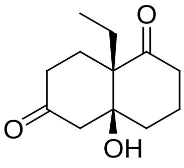
(+)-8a-Propyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione (69ag') Purified by column chromatography using EtOAc/hexane and isolated as a liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 28.38 min (major), t_R = 36.00 min (minor). **$[\alpha]_D^{25}$ = +46.0° (c = 0.375 g/100 mL, CHCl$_3$, 73% ee)**; IR (Neat): ν_{max} 3408, 2964, 1711, 1664, 1616, 1460, 1356, 1267, 1022 and 869 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 5.86 (1H, s, olefinic-*H*), 2.82 (1H, dt, J = 14.0, 4.8 Hz), 2.68 (1H, dt, J = 14.8, 6.0 Hz), 2.55-2.32 (3H, m), 2.33-2.10 (3H, m), 2.05 (1H, dt, J = 13.6, 6.0 Hz), 1.95-1.60 (3H, m), 1.43-1.20 (1H, m), 1.10 (1H, m), 0.92 (3H, t, J = 7.6 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 210.2 (C), 198.4 (C), 166.2 (C), 126.1 (CH), 55.1 (C), 38.4 (CH$_2$), 37.6 (CH$_2$), 33.6 (CH$_2$), 31.9 (CH$_2$), 25.6 (CH$_2$), 23.5 (CH$_2$), 17.8 (CH$_2$), 14.3 (CH$_3$); Anal. calcd for $C_{13}H_{18}O_2$ (206.2808): C, 75.69; H, 8.80. Found: C, 75.679; H, 8.793%.


(+)-69ah'

(+)-8a-Butyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione (69ah') Purified by column chromatography using EtOAc/hexane and isolated as a liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 109.29 min (minor), t_R = 116.81 min (major). **$[\alpha]_D^{25}$ = +46.1° (c = 0.425 g/100 mL, CHCl$_3$, 75% ee);** IR (Neat): ν_{max} 3402, 2964, 1712, 1664, 1616, 1460, 1356, 1265, 1178, 1022 and 910 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 5.87 (1H, s, olefinic-*H*), 2.81 (1H, dt, J = 13.6, 3.6 Hz), 2.67 (1H, dt, J = 14.4, 6.0 Hz), 2.55-2.35 (3H, m), 2.30-2.13 (2H, m), 2.05 (1H, m), 1.95 (1H, m), 1.82-1.64 (3H, m), 1.36-1.28 (3H, m), 1.09-1.02 (1H, m), 0.91 (3H, t, J = 6.8 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 210.2 (C), 198.4 (C), 166.2 (C), 126.1 (CH), 54.9 (C), 38.3 (CH$_2$), 35.2 (CH$_2$), 33.6 (CH$_2$), 31.9 (CH$_2$), 26.5 (CH$_2$), 25.6 (CH$_2$), 23.5 (CH$_2$), 22.9 (CH$_2$), 13.8 (CH$_3$); Anal. calcd for $C_{14}H_{20}O_2$ (220.3074): C, 76.33; H, 9.15. Found: C, 76.386; H, 9.152%.


70aa

8a-Benzyl-4a-hydroxy-hexahydro-naphthalene-1,6-dione (70aa): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (KBr): ν_{max} 3377, 3036, 2955, 1709, 1685, 1494, 1394, 978, 864, 775 and 715 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.25 (4H, m), 7.00 (2H, m) [Ph-*H*]; 3.42 (1H, d, J = 14.0 Hz), 3.13-3.0 (2H, m), 2.63 (1H, d, J = 14.0 Hz), 2.55-2.44 (3H, m), 2.39-2.00 (5H, m), 2.00-1.60 (2H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 211.5 (C, C=O), 211.1 (C, C=O), 136.2 (C), 129.7 (2 x CH), 128.3 (2 x CH), 126.9 (CH), 80.2 (C, C-OH), 58.2 (C), 51.2 (CH_2), 39.8 (CH_2), 38.3 (CH_2), 37.1 (CH_2), 34.6 (CH_2), 27.6 (CH_2), 20.8 (CH_2).

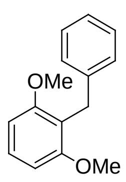


70ao'

8a-Ethyl-4a-hydroxy-hexahydro-naphthalene-1,6-dione (70ao'): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. ^{1}H NMR ($CDCl_3$) δ 2.65-1.60 (14H, m), 0.79 (3H, t, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.2 (C, C=O), 210.9 (C, C=O), 80.4 (C, C-OH), 57.6 (C), 51.1 (CH_2), 38.4 (CH_2), 36.9 (CH_2), 34.7 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 20.5 (CH_2), 7.7 (CH_3).

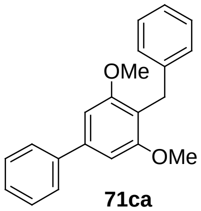
10. General Procedure for Aromatization of 2-Alkyl-Cyclohexane-1,3-Dione compounds: A solution of 2-alkyl-cyclohexane-1,3-dione compound **67** (1.0 mmol) and iodine (2.0 mmol) in methanol was refluxed for 24 h. After cooling, the reaction mixture washed with aqueous sodium thiosulphate, brine solution, 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 products **71** and **72** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2-Benzyl-1,3-dimethoxy-benzene (71aa): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 56 °C; IR (Neat): ν_{max} 3082, 3061, 2999, 1595, 1493, 1473, 1257, 1107, 767 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30-7.00 (6H, m), 6.52 (2H, d, J = 8.0 Hz), 4.01 (2H, s, ArCH_2), 3.75 (6H, s, 2 x OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 158.3 (C), 141.8 (C), 128.5 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 125.3 (CH), 117.7 (C), 103.8 (2 x CH), 55.6 (2 x CH_3, OCH_3), 28.7 (CH_2); GCMS m/z 228.20, calcd for $C_{15}H_{16}O_2$ 228.2863.



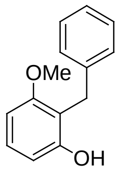
71aa

4-Benzyl-3,5-dimethoxy-biphenyl (71ca): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 90 °C; IR (Neat): ν_{max} 2995, 2932, 1589, 1570, 1491, 1458, 1404, 1323, 1253, 1195, 1037, 879, 835 and 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (2H, m), 7.53 (2H, m), 7.43 (3H, m), 7.34 (2H, m), 7.24 (1H, m), 6.87 (2H, s) [Ar-H]; 4.18 (2H, s, ArCH_2), 3.96 (6H, s, 2 x OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 158.5 (2 x C), 141.91 (C), 141.88 (C), 141.01 (C), 128.8 (2 x CH), 128.7 (2 x CH), 128.1 (2 x CH), 127.4 (CH), 127.2 (2 x CH), 125.5 (CH), 116.9 (C), 103.2 (2 x CH), 55.9 (2 x CH_3, OCH_3), 28.8 (CH_2); GCMS m/z 304.20, calcd for $C_{21}H_{20}O_2$ 304.3823; Anal. calcd for $C_{21}H_{20}O_2$ (304.3823): C, 82.86; H, 6.62. Found: C, 82.789; H, 6.651%.



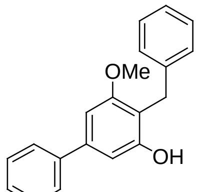
71ca

2-Benzyl-3-methoxy-phenol (72aa): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (Neat): ν_{max} 3526, 3026, 2939, 1597, 1494, 1469, 1086, 771 and 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30-7.25 (4H, m), 7.20 (1H, m), 7.11 (1H, t, J = 8.0 Hz), 6.56 (1H, d, J = 8.0 Hz), 6.48 (1H, d, J = 8.0 Hz) [Ar-H]; 4.81 (1H, s, OH), 4.08 (2H, s, ArCH_2), 3.85 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 158.6 (C), 154.7 (C), 140.5



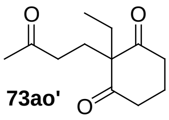
72aa

(C), 128.4 (4 x CH), 127.5 (CH), 125.9 (CH), 115.6 (C), 108.6 (CH), 103.4 (CH), 55.8 (CH_3, O*C*H_3), 28.7 (CH_2); GCMS m/z 214.20, calcd for $C_{14}H_{14}O_2$ 214.2598.



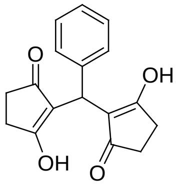
72ca

4-Benzyl-5-methoxy-biphenyl-3-ol (72ca): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 80 °C; IR (KBr): ν_{max} 3501, 3441, 2914, 1589, 1570, 1520, 1456, 1404, 1350, 1265, 1089, 968, 835 and 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (2H, m), 7.38 (2H, m), 7.35-7.23 (5H, m), 7.12 (1H, m), 6.70 (1H, s), 6.60 (1H, s) [Ar-H]; 4.96 (1H, s, OH), 4.05 (2H, s, ArC*H_2*), 3.83 (3H, s, OC*H_3*); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 158.7 (C), 154.8 (C), 141.0 (C), 140.95 (C), 140.54 (C), 128.6 (2 x CH), 128.40 (2 x CH), 128.36 (2 x CH), 127.3 (CH), 126.9 (2 x CH), 125.9 (CH), 114.7 (C), 107.6 (CH), 102.6 (CH), 55.8 (CH_3, O*C*H_3), 28.6 (CH_2); Anal. calcd for $C_{20}H_{18}O_2$ (290.3557): C, 82.73; H, 6.25. Found: C, 82.685; H, 6.254%.



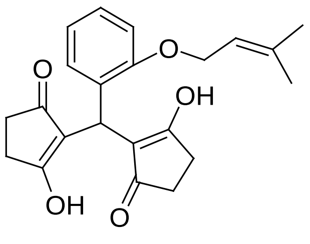
73ao'

2-Ethyl-2-(3-oxo-butyl)-cyclohexane-1,3-dione (73ao'): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. ^1H NMR ($CDCl_3$) δ 2.58 (4H, t, *J* = 6.4 Hz), 2.26 (2H, t, *J* = 6.4 Hz), 2.05 (3H, s, C*H_3*CO), 1.95-1.85 (4H, m), 1.74 (2H, q, *J* = 7.2 Hz), 0.72 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.0 (2 x C, 2 x C=O), 207.8 (C, C=O), 68.4 (C), 38.5 (3 x CH_2), 29.8 (CH_3), 29.3 (CH_2), 26.6 (CH_2), 17.1 (CH_2), 9.0 (CH_3).



80a

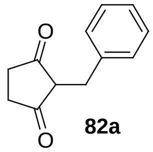
2,2'-Phenylmethylene-bis-[1,3-cyclopentanedione] (80a): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 186 °C; IR (Neat): ν_{max} 3376, 2921, 1659, 1547, 1411, 1239 and 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.77 (2H, br s, 2 x O-H), 7.21-7.09 (5H, m) [Ar-H]; 5.33 (1H, s, PhC*H*), 2.58 (8H, s, 4 x CH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 200.1 (2 x C, C=O), 139.6 (C), 128.3 (2 x CH), 126.9 (2 x CH), 126.3 (CH), 118.5 (2 x C), 30.5 (4 x CH_2), 30.0 (CH); LCMS m/z 285.00 ($M+H^+$), calcd for $C_{17}H_{16}O_4H$ 285.1049; Anal. calcd for $C_{17}H_{16}O_4$ (284.1049): C, 71.82; H, 5.67. Found: C, 71.731; H, 5.652%.



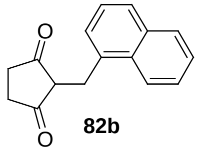
80t'

2,2'-Dicyclopentane-1,3-dione-methyl-2-(3-methyl-but-2-enyloxy)-benzene (80t'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 140 °C; IR (Neat): ν_{max} 2924, 2723, 1659, 1590, 1412, 1354, 1275, 1226, 1118, 1020 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (2H, br s, 2 x OH), 7.26 (1H, d, *J* = 7.2 Hz), 7.13 (1H, t, *J* = 8.0 Hz), 6.85 (1H, t, *J* = 7.6 Hz), 6.77 (1H, d, *J* = 8.0 Hz) [Ar-H]; 5.42 (1H, t, *J* = 6.4 Hz, olefinic-*H*), 5.37 (1H, s, PhC*H*), 4.45 (2H, d, *J* = 6.8 Hz, OC*H_2*CH=CMe_2), 2.53 (8H, br s, 4 x CH_2), 1.77 (3H, s, CH_3), 1.70 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 199.4 (2 x C, C=O), 155.8 (C), 137.5 (C), 128.34 (CH), 128.2 (C, OCH_2CH=*C*Me_2), 127.7 (CH), 120.3 (CH), 119.8 (CH), 117.9 (2 x C), 111.6 (CH), 65.1 (CH_2, O*C*H_2CH=CMe$_2$), 30.4 (4 x CH_2), 25.7 (CH), 25.6 (CH_3), 18.1 (CH_3); LCMS m/z 369.00 ($M+H^+$), calcd for $C_{22}H_{24}O_5H$ 369.1624; Anal. calcd for $C_{22}H_{24}O_5$ (368.1624): C, 71.72; H, 6.57. Found: C, 71.668; H, 6.575%.

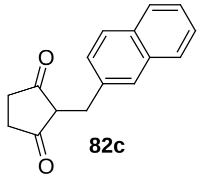
11. Amino Acid-Catalyzed Cascade Olefination/Hydrogenation Reactions with Cyclopentane-1,3-Dione: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **46**, 0.3 mmol of CH-acid **78** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst amino acid **50a** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 21 to 23. The crude reaction mixture was directly loaded on silica gel column with or without aqueous work-up and pure cascade products **82** and **83** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).


82a

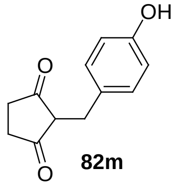
2-Benzyl-cyclopentane-1,3-dione (82a): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 180 °C; IR (Neat): ν_{max} 2923, 1571, 1565, 1473, 1434, 1396, 1368, 1321 and 1257 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.26-7.20 (4H, m), 7.15-7.13 (1H, m) [Ar-H]; 3.46 (2H, s, PhC*H*$_2$), 2.46 (4H, s); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 140.0 (C), 128.3 (2 x CH), 128.1 (2 x CH), 125.6 (CH), 117.3 (C), 30.2 (2 x CH_2), 26.7 (CH_2); HRMS m/z 211.0728 ($M+Na^+$), calcd for $C_{12}H_{12}O_2Na$ 211.0735.


82b

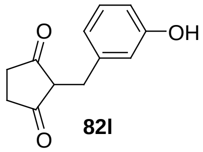
2-Naphthalen-1-ylmethyl-cyclopentane-1,3-dione (82b): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 205 °C; IR (Neat): ν_{max} 2971, 1569, 1365, 1259, 1179 and 779 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.23 (1H, d, *J* = 8.4 Hz), 7.82 (1H, d, *J* = 7.6 Hz), 7.69 (1H, t, *J* = 5.2 Hz), 7.51-7.45 (2H, m), 7.36 (2H, m) [Ar-H]; 3.90 (2H, s, ArC*H*$_2$), 2.47 (4H, s, 2 x C*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 135.1 (C), 133.5 (C), 131.8 (C), 128.2 (CH), 126.4 (CH), 125.7 (CH), 125.4 (CH), 125.2 (CH), 125.1 (CH), 124.0 (CH), 116.0 (C), 30.1 (2 x CH_2), 24.0 (CH_2); HRMS m/z 261.0882 ($M+Na^+$), calcd for $C_{16}H_{14}O_2Na$ 261.0891.


82c

2-Naphthalen-2-ylmethyl-cyclopentane-1,3-dione (82c): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 220 °C; IR (Neat): ν_{max} 2923, 2854, 2658, 1573, 1430, 1376, 1260, 1178, 1034, 818 and 754 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.76-7.67 (4H, m), 7.43-7.30 (3H, m) [Ar-H]; 3.63 (2H, s, ArC*H*$_2$), 2.50 (4H, s, 2 x C*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 137.6 (C), 133.4 (C), 131.8 (C), 127.5 (CH), 127.3 (3 x CH), 126.1 (CH), 125.5 (CH), 124.8 (CH), 117.1 (C), 30.2 (2 x CH_2), 26.8 (CH_2); HRMS m/z 261.0880 ($M+Na^+$), calcd for $C_{16}H_{14}O_2Na$ 261.0891.

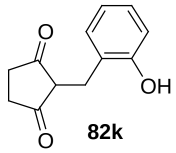

82m

2-(4-Hydroxy-benzyl)-cyclopentane-1,3-dione (82m): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 194 °C; IR (Neat): ν_{max} 3243, 1578, 1433, 1366, 1258, 1237, 1174, 1028 and 820 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.07 (2H, d, *J* = 8.4 Hz), 6.69 (2H, d, *J* = 8.4 Hz) [Ar-H]; 3.36 (2H, s, ArC*H*$_2$), 2.46 (4H, s, 2 x C*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 154.4 (C), 131.1 (C), 129.1 (2 x CH), 117.7 (C), 114.8 (2 x CH), 30.1 (2 x CH_2), 25.7 (CH_2); HRMS m/z 227.0688 (M+Na$^+$), calcd for $C_{12}H_{12}O_3Na$ 227.0684.



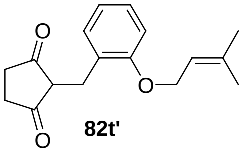
82l

2-(3-Hydroxy-benzyl)-cyclopentane-1,3-dione (82l): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 160 °C; IR (Neat): ν_{max} 3406, 3152, 2924, 1664, 1375, 1262, 1240, 1161 and 692 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.05 (1H, t, *J* = 8.0 Hz), 6.74 (1H, d, *J* = 7.6 Hz), 6.71 (1H, br s), 6.62 (1H, dd, *J* = 8.0, 1.6 Hz) [Ar-H]; 3.38 (2H, s, ArC*H*$_2$), 2.46 (4H, s, 2 x C*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 156.4 (C), 141.5 (C), 129.1 (CH), 119.8 (CH), 117.2 (C), 115.1 (CH), 112.7 (CH), 30.2 (2 x CH_2), 26.5 (CH_2); HRMS m/z 227.0679 (M+Na$^+$), calcd for $C_{12}H_{12}O_3Na$ 227.0684.



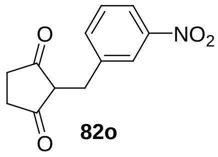
82k

2-(2-Hydroxy-benzyl)-cyclopentane-1,3-dione (82k): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 156 °C; IR (Neat): ν_{max} 3237, 2923, 1727, 1584, 1540, 1372, 1301, 1260, 1174, 1101 and 661 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* = 7.2 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 6.81 (1H, t, *J* = 7.2 Hz) [Ar-H]; 3.42 (2H, s, ArC*H*$_2$), 2.47 (4H, s, 2 x C*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 197.5 (C, *C*=O), 153.7 (C), 130.6 (CH), 127.7 (CH), 126.6 (C), 120.6 (CH), 117.8 (C), 116.7 (CH), 30.1 (2 x CH_2), 21.7 (CH_2); HRMS m/z 227.0685 (M+Na$^+$), calcd for $C_{12}H_{12}O_3Na$ 227.0686.



82t'

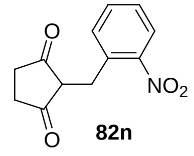
2-[2-(3-Methyl-but-2-enyloxy)-benzyl]-cyclopentane-1,3-dione (82t) Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 95 °C; IR (Neat): ν_{max} 2924, 1570, 1432, 1374, 1324, 1262, 1244, 1223, 1190, 1108, 1021 and 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.22 (1H, s, O-*H*), 7.35 (1H, dd, *J* = 7.6, 1.6 Hz), 7.20 (1H, dt, *J* = 8.0, 1.6 Hz), 6.96 (2H, m) [Ar-H]; 5.59 (1H, t, *J* = 7.2 Hz, OCH$_2$C*H*=CMe$_2$), 4.65 (2H, d, *J* = 7.2 Hz, OC*H*$_2$CH=CMe$_2$), 3.45 (2H, s, ArC*H*$_2$), 2.45-2.39 (4H, m), 1.86 (3H, s, CH_3), 1.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.4 (C, *C*=O), 184.2 (C), 154.6 (C), 141.5 (C), 131.4 (CH), 128.5 (C), 127.7 (CH), 122.5 (CH), 117.7 (CH), 117.5 (C), 112.5 (CH), 66.1 (CH_2, O*C*H$_2$CH=CMe$_2$), 33.7 (CH_2), 26.5 (CH_2), 25.9 (CH_3), 21.2 (CH_2), 18.2 (CH_3); HRMS m/z 295.1299 (M+Na$^+$), calcd for $C_{17}H_{20}O_3Na$ 295.1310.



82o

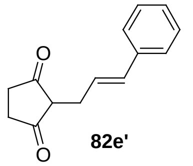
2-(3-Nitro-benzyl)-cyclopentane-1,3-dione (82o): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 202 °C; IR

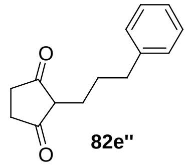
(Neat): ν_{max} 2922, 1620, 1559, 1523, 1427, 1354, 1295, 1259, 1164, 1084, 1027, 802 and 716 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.09 (1H, s), 8.00 (1H, d, *J* = 7.6 Hz), 7.62 (1H, d, *J* = 7.6 Hz), 7.40 (1H, t, *J* = 8.0 Hz) [Ar-H]; 3.56 (2H, s, ArC*H*$_2$), 2.52 (4H, s, 2 x C*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 148.1 (C), 142.3 (C), 135.0 (CH), 128.9 (CH), 123.2 (CH), 120.8 (CH), 115.9 (C), 30.3 (2 x CH_2), 26.5 (CH_2); HRMS m/z 256.0591, calcd for $C_{12}H_{11}NO_4Na$ 256.0586.



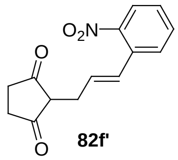
82n

2-(2-Nitro-benzyl)-cyclopentane-1,3-dione (82n): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 190 °C; IR (Neat): ν_{max} 2550, 1570, 1521, 1339, 1257, 1189, 1036, 844 and 727 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.86 (1H, d, *J* = 8.0 Hz), 7.48 (1H, t, *J* = 7.2 Hz), 7.31 (2H, m) [Ar-H]; 3.81 (2H, s, ArC*H*$_2$), 2.53 (4H, s, 2 x C*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 149.2 (C), 134.1 (C), 132.5 (CH), 130.8 (CH), 126.6 (CH), 124.0 (CH), 114.4 (C), 30.0 (2 x CH_2), 23.4 (CH_2); HRMS m/z 234.0755, calcd for $C_{12}H_{11}NO_4H$ 234.0766.

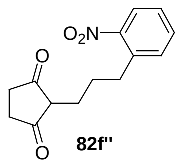

82e'


82e''

2-(3-Phenyl-allyl)-cyclopentane-1,3-dione (82e′) and 2-(3-Phenyl-propyl)-cyclopentane-1,3-dione (82e″): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (Neat): ν_{max} 2928, 1724, 1609, 1520, 1435, 1401, 1375, 1255, 1158, 827 and 751 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops), 2:1 ratio of O/H product **82e′** and completely reduced product **82e″**, major product **82e′**] δ 7.30-7.17 (5H, m) [Ar-H]; 6.39 (1H, d, *J* = 16.0 Hz), 6.29 (1H, td, *J* = 15.6, 6.8 Hz) [PhC*H*=C*H*CH$_2$]; 3.04 (2H, d, *J* = 6.0 Hz), 2.48 (4H, s, 2 x CH_2); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135, 2:1 ratio of O/H product **82e′** and completely reduced product **82e″**, major product **82e′**] δ 137.5 (C), 130.1 (CH), 128.3 (2 x CH), 126.80 (CH), 126.76 (CH), 125.9 (2 x CH), 115.8 (C), 30.4 (2 x CH_2), 24.3 (CH_2).; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops), 2:1 ratio of O/H product **82e′** and completely reduced product **82e″**, minor product **82e″**] δ 7.33-7.10 (5H, m) [Ar-H]; 2.59 (2H, t, *J* = 8.0 Hz), 2.43 (4H, s, 2 x CH_2), 2.19 (2H, t, *J* = 8.0 Hz), 1.74 (2H, quintet, *J* = 8.0 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135, 2:1 ratio of O/H product **82e′** and completely reduced product **82e″**, minor product **82e″**] δ 142.5 (C), 128.4 (CH), 128.1 (2 x CH), 125.5 (2 x CH), 117.8 (C), 35.7 (CH_2), 30.4 (2 x CH_2), 29.4 (CH_2), 20.7 (CH_2); HRMS (Q-top) m/z 215.1016 and 217.1190, calcd for $C_{14}H_{14}O_2H$ 215.1072 and $C_{14}H_{16}O_2H$ 217.1229.



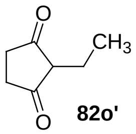
82f'



82f''

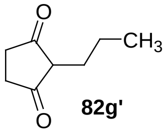
2-[3-(2-Nitro-phenyl)-allyl]-cyclopentane-1,3-dione (82f') and 2-[3-(2-Nitro-phenyl)-propyl]-cyclopentane-1,3-dione (82f''): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (Neat): ν_{max} 3326, 2927, 1624, 1524, 1344, 1255, 1176 and 750 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops), 2:1 ratio of O/H product **82f'** and completely reduced product **82f''**, major product **82f'**] δ 7.85 (1H, d, *J* = 8.4 Hz), 7.57 (1H, d, *J* = 8.0 Hz), 7.50 (1H, t, *J* = 7.2 Hz), 7.32 (1H, t, *J* = 7.6 Hz) [Ar-H]; 6.83 (1H, d, *J* = 16.0 Hz), 6.28 (1H, td, *J* = 15.2, 6.4 Hz) [ArC*H*=C*H*CH$_2$]; 3.11 (2H, d, *J* = 6.4 Hz), 2.53 (4H, s, 2 x CH$_2$); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135, 2:1 ratio of O/H product **82f'** and completely reduced product **82f''**, major product **82f'**] δ 147.4 (C), 133.2 (C), 132.9 (CH), 132.8 (CH), 128.5 (CH), 127.4 (CH), 125.0 (CH), 124.2 (CH), 115.0 (C), 30.3 (2 x CH$_2$), 24.5 (CH$_2$).; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops), 2:1 ratio of O/H product **82f'** and completely reduced product **82f''**, minor product **82f''**] δ 7.85 (1H, d, *J* = 8.4 Hz), 7.50 (1H, t, *J* = 7.2 Hz), 7.38 (1H, d, *J* = 8.0 Hz), 7.32 (1H, t, *J* = 7.6 Hz) [Ar-H]; 2.84 (2H, t, *J* = 8.0 Hz), 2.48 (4H, s, 2 x CH$_2$), 2.23 (2H, t, *J* = 8.0 Hz), 1.76 (2H, quintet, *J* = 8.0 Hz); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135, 2:1 ratio of O/H product **82f'** and completely reduced product **82f''**, minor product **82f''**] δ 149.1 (C), 137.3 (C), 132.7 (CH), 131.7 (CH), 126.6 (CH), 124.3 (CH), 117.1 (C), 32.3 (CH$_2$), 30.3 (2 x CH$_2$), 28.5 (CH$_2$), 20.6 (CH$_2$); HRMS (Q-top) m/z 260.0845 and 262.1007, calcd for $C_{14}H_{13}NO_4H$ 260.0923 and $C_{14}H_{15}NO_4H$ 262.1079.

2-Ethyl-cyclopentane-1,3-dione (82o′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 166 °C; IR (Neat): ν_{max} 2971, 2931, 1530, 1545, 1348, 1267 and 1108 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 2.46 (4H, s, 2 x C*H$_2$*), 2.14 (2H, q, *J* = 7.2 Hz, C*H$_2$*CH$_3$), 0.99 (3H, t, *J* = 7.6 Hz, CH$_2$C*H$_3$*); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 119.6 (C), 30.1 (2 x CH$_2$), 14.0 (CH$_2$), 12.3 (CH$_3$); HRMS m/z 149.0571 (M+Na$^+$), calcd for $C_7H_{10}O_2Na$ 149.0578.



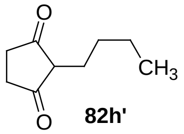
82o'

2-Propyl-cyclopentane-1,3-dione (82g′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 174 °C; IR (Neat): ν_{max} 2951, 2870, 1547, 1535, 1458, 1473, 1430, 1345, 1258, 1244, 1113 and 998 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 2.48 (4H, s, 2 x C*H$_2$*), 2.10 (2H, t, *J* = 7.2 Hz, C*H$_2$*CH$_2$CH$_3$), 1.42 (2H, sextet, *J* = 7.2 Hz, CH$_2$C*H$_2$*CH$_3$), 0.88 (3H, t, *J* = 7.2 Hz, CH$_2$CH$_2$C*H$_3$*); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 118.2 (C), 30.3 (2 x CH$_2$), 22.8 (CH$_2$), 22.1 (CH$_2$), 13.8 (CH$_3$); HRMS m/z 141.0922 (M+H$^+$), calcd for $C_8H_{12}O_2H$ 141.0915.



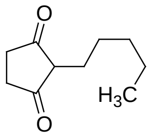
82g'

2-Butyl-cyclopentane-1,3-dione (82h′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 150 °C; IR (Neat): ν_{max} 2930, 2856, 1547, 1530, 1427, 1344, 1279, 1257, 1206, 1119 and 998 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 2.48 (4H, s, 2 x C*H$_2$*), 2.13 (2H, t, *J* = 7.6 Hz, C*H$_2$*CH$_2$CH$_2$CH$_3$), 1.40-1.26 (4H, m, CH$_2$C*H$_2$*C*H$_2$*CH$_3$), 0.89 (3H, t, *J* = 7.2 Hz, CH$_2$CH$_2$CH$_2$C*H$_3$*); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 118.5 (C), 30.2 (2 x CH$_2$), 30.1 (CH$_2$), 22.6 (CH$_2$), 20.7 (CH$_2$), 13.8 (CH$_3$); HRMS m/z 155.1078 (M+H$^+$), calcd for $C_9H_{14}O_2H$ 155.1072.



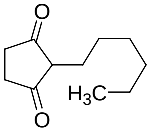
82h'

2-Pentyl-cyclopentane-1,3-dione (82i′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 136 °C; IR (Neat): ν_{max} 2929, 2861, 1531, 1456, 1428, 1342, 1262, 1194, 1122, 999 and 663 cm^{-1}; ^{1}H NMR [$\mathrm{CDCl_3}$ + $\mathrm{CD_3OD}$ (three drops)] δ 2.46 (4H, br s, 2 x $\mathrm{C}\mathit{H}_2$), 2.11 (2H, t, *J* = 8.0 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_2CH_2CH_2CH_3}$), 1.40 (2H, quintet, *J* = 7.6 Hz, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2CH_2CH_3}$), 1.33-1.24 (4H, m, $\mathrm{CH_2CH_2C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 0.87 (3H, t, *J* = 6.8 Hz, $\mathrm{CH_2CH_2CH_2CH_2C}\mathit{H}_3$); ^{13}C NMR [$\mathrm{CDCl_3}$ + $\mathrm{CD_3OD}$ (three drops), DEPT-135] δ 118.5 (C), 31.7 ($\mathrm{CH_2}$), 30.3 (2 x $\mathrm{CH_2}$), 27.6 ($\mathrm{CH_2}$), 22.4 ($\mathrm{CH_2}$), 20.9 ($\mathrm{CH_2}$), 13.9 ($\mathrm{CH_3}$); HRMS m/z 169.1224 (M+H$^+$), calcd for $\mathrm{C_{10}H_{16}O_2H}$ 169.1228.



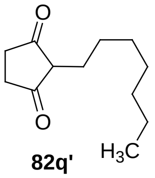
82i'

2-Hexyl-cyclopentane-1,3-dione (82p′): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 240 °C; IR (Neat): ν_{max} 2923, 2852, 1531, 1454, 1427, 1348, 1285, 1254, 1123, 1001 and 664 cm^{-1}; ^{1}H NMR [$\mathrm{CDCl_3}$ + $\mathrm{CD_3OD}$ (three drops)] δ 2.48 (4H, s, 2 x $\mathrm{C}\mathit{H}_2$), 2.12 (2H, t, *J* = 7.2 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_2CH_2CH_2CH_2CH_3}$), 1.38 (2H, quintet, *J* = 7.6 Hz, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2CH_2CH_2CH_3}$), 1.33-1.20 (6H, m, $\mathrm{CH_2CH_2C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 0.86 (3H, t, *J* = 6.8 Hz, $\mathrm{CH_2CH_2CH_2CH_2CH_2C}\mathit{H}_3$); ^{13}C NMR [$\mathrm{CDCl_3}$ + $\mathrm{CD_3OD}$ (three drops), DEPT-135] δ 118.4 (C), 31.6 ($\mathrm{CH_2}$), 30.4 (2 x $\mathrm{CH_2}$), 29.2 ($\mathrm{CH_2}$), 27.9 ($\mathrm{CH_2}$), 22.5 ($\mathrm{CH_2}$), 20.9 ($\mathrm{CH_2}$), 13.9 ($\mathrm{CH_3}$); LRMS m/z 183.00 (M+H$^+$), calcd for $\mathrm{C_{11}H_{18}O_2H}$ 183.1307; Anal. calcd for $\mathrm{C_{11}H_{18}O_2}$ (182.1307): C, 72.49; H, 9.95. Found: C, 72.584; H, 9.966%.



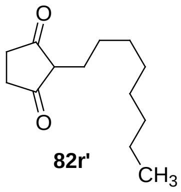
82p'

2-Heptyl-cyclopentane-1,3-dione (82q'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 128 °C; IR (Neat): ν_{max} 2927, 2852, 1532, 1456, 1426, 1344, 1276, 1253, 1123 and 998 cm^{-1}; ^{1}H NMR [$\mathrm{CDCl_3}$ + $\mathrm{CD_3OD}$ (three drops)] δ 2.46 (4H, s, 2 x $\mathrm{C}\mathit{H}_2$), 2.11 (2H, t, *J* = 8.0 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_2CH_2CH_2CH_2CH_2CH_3}$), 1.39 (2H, quintet, *J* = 6.8 Hz, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2CH_2CH_2CH_2CH_3}$), 1.26 (8H, br s, $\mathrm{CH_2CH_2C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 0.87 (3H, t, *J* = 6.8 Hz, $\mathrm{CH_2CH_2CH_2CH_2CH_2CH_2C}\mathit{H}_3$); ^{13}C NMR [$\mathrm{CDCl_3}$ + $\mathrm{CD_3OD}$ (three drops), DEPT-135] δ 118.3 (C), 31.7 ($\mathrm{CH_2}$), 30.2 (2 x $\mathrm{CH_2}$), 29.4 ($\mathrm{CH_2}$), 29.0 ($\mathrm{CH_2}$), 27.9 ($\mathrm{CH_2}$), 22.5 ($\mathrm{CH_2}$), 20.8 ($\mathrm{CH_2}$), 13.8 ($\mathrm{CH_3}$); HRMS m/z 197.1543 (M+H$^+$), calcd for $\mathrm{C_{12}H_{20}O_2H}$ 197.1541.



82q'

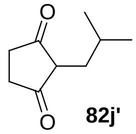
2-Octyl-cyclopentane-1,3-dione (82r'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 130 °C; IR (Neat): ν_{max} 2918, 2850, 1532, 1462, 1428, 1347, 1290, 1261, 1124, 999 and 664 cm^{-1}; ^{1}H NMR [$\mathrm{CDCl_3}$ + $\mathrm{CD_3OD}$ (three drops)] δ 2.46 (4H, s, 2 x $\mathrm{C}\mathit{H}_2$), 2.11 (2H, t, *J* = 7.2 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_2CH_2CH_2CH_2CH_2CH_2CH_3}$), 1.39 (2H, quintet, *J* = 6.8 Hz, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2CH_2CH_2CH_2CH_2CH_3}$), 1.26 (10H, br s, $\mathrm{CH_2CH_2C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 0.87 (3H, t, *J* = 6.8 Hz,



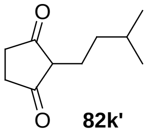
82r'

$\mathrm{CH_2CH_2CH_2CH_2CH_2CH_2CH_2C}H_3$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 118.4 (C), 31.8 (CH_2), 30.4 (2 x CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.9 (CH_2), 22.5 (CH_2), 20.9 (CH_2), 13.9 (CH_3); HRMS m/z 211.1697 (M+H$^+$), calcd for $C_{13}H_{22}O_2H$ 211.1698.

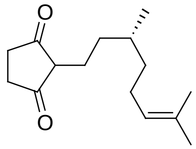
2-Isobutyl-cyclopentane-1,3-dione (82j'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 190 °C; IR (Neat): ν_{max} 2929, 2496, 1552, 1427, 1350, 1313, 1258, 1124 and 998 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 2.48 (4H, s, 2 x $\mathrm{C}H_2$), 2.00 (2H, d, *J* = 7.2 Hz, $\mathrm{C}H_2\mathrm{CHMe_2}$), 1.80 (1H, m, *J* = 6.8 Hz, $\mathrm{CH_2C}H\mathrm{Me_2}$), 0.85 [6H, d, *J* = 6.4 Hz, $\mathrm{CH_2CH(C}H_3)_2$]; ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 117.4 (C), 30.1 (2 x CH_2), 29.7 (CH_2), 27.2 (CH), 22.2 (2 x CH_3); LRMS m/z 155.00 (M+H$^+$), calcd for $C_9H_{14}O_2H$ 155.0994; Anal. calcd for $C_9H_{14}O_2$ (154.0994): C, 70.10; H, 9.15. Found: C, 70.162; H, 9.180%.

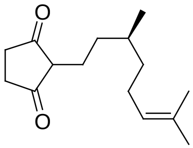

82j'

2-(3-Methyl-butyl)-cyclopentane-1,3-dione (82k'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 138 °C; IR (Neat): ν_{max} 2924, 2598, 1598, 1555, 1436, 1364, 1289, 1254 and 1128 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 2.47 (4H, s, 2 x $\mathrm{C}H_2$), 2.12 (2H, t, *J* = 8.0 Hz, $\mathrm{C}H_2\mathrm{CH_2CHMe_2}$), 1.51 (1H, m, *J* = 6.4 Hz, $\mathrm{CH_2CH_2C}H\mathrm{Me_2}$), 1.28 (2H, td, *J* = 12.4, 7.2 Hz, $\mathrm{CH_2C}H_2\mathrm{CHMe_2}$), 0.89 (6H, d, *J* = 6.4 Hz, $\mathrm{CH_2CH_2CH}Me_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 118.5 (C), 36.7 (CH_2), 30.2 (2 x CH_2), 27.9 (CH), 22.2 (2 x CH_3), 18.8 (CH_2); LRMS m/z 169.05 (M+H$^+$), calcd for $C_{10}H_{16}O_2H$ 169.11; Anal. calcd for $C_{10}H_{16}O_2$ (168.1150): C, 71.39; H, 9.59. Found: C, 71.392; H, 9.578%.


82k'

(–)-(3*R*)-2-(3,7-Dimethyl-oct-6-enyl)-cyclopentane-1,3-dione (82s'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. **[α]$_D^{25}$ = –5.029° (*c* = 1.075 g/100 mL, $CHCl_3$, 90%)**; Mp 70 °C; IR (Neat): ν_{max} 2922, 1566, 1473, 1368, 1289 and 1256 cm^{-1}; **^{1}H NMR [$CDCl_3$]** δ 5.08 (1H, d, *J* = 6.8 Hz), 2.56 (4H, s, 2 x $\mathrm{C}H_2$), 2.30-2.10 (2H, m), 2.08-1.80 (2H, m), 1.67 (3H, s, $\mathrm{C}H_3$), 1.59 (3H, s, $\mathrm{C}H_3$), 1.50-1.30 (3H, m), 1.30-1.20 (1H, m), 1.19-1.10 (1H, m), 0.89 (3H, d, *J* = 6.4 Hz, $\mathrm{C}H_3$); **^{13}C NMR [$CDCl_3$, DEPT-135]** δ 198.5 (C, C=O), 130.9 (C), 125.0 (CH), 118.7 (C), 36.9 (CH_2), 35.0 (CH_2), 32.6 (CH), 30.5 (single sharp peak, 2 x CH_2), 25.7 (CH_3), 25.5 (CH_2), 19.3 (CH_3), 18.7 (CH_2), 17.6 (CH_3); LRMS m/z 237.10 (M + H$^+$), calcd for $C_{15}H_{24}O_2H$ 237.18; Anal. calcd for $C_{15}H_{24}O_2$ (236.1776): C, 76.23; H, 10.24. Found: C, 76.217; H, 10.242%.; **^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)]** δ 5.09 (1H, d, *J* = 6.8 Hz), 2.47 (4H, s, 2 x $\mathrm{C}H_2$), 2.20-2.05 (2H, m), 2.05-1.85 (2H, m), 1.67 (3H, s, $\mathrm{C}H_3$), 1.59 (3H, s, $\mathrm{C}H_3$), 1.50-1.30 (3H, m), 1.30-1.20 (1H, m), 1.19-1.10 (1H, m), 0.90 (3H, d, *J* = 6.4 Hz, $\mathrm{C}H_3$); **^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135]** δ 130.8 (C),

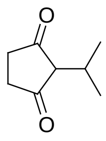

(*R*)-82s'


(*S*)-82s'

125.0 (CH), 118.6 (C), 36.9 (CH_2), 34.8 (CH_2), 32.4 (CH), 30.3 (broad peak, poor resolution, 2 x CH_2), 25.6 (CH_3), 25.4 (CH_2), 19.2 (CH_3), 18.6 (CH_2), 17.5 (CH_3).

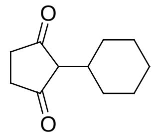
(□+)-(3*S*)-2-(3,7-Dimethyl-oct-6-enyl)-cyclopentane-1,3-dione (82s'): Purified by column chromatography using EtOAc/hexane and isolated as a solid. **$[\alpha]_D^{25}$ = +7.463° (*c* = 0.55 g/100 mL, $CHCl_3$, 96%)**; Mp 70 °C; IR (Neat): ν_{max} 2920, 1622, 1566, 1473, 1368, 1255, 1195, 1127, 904, 826 and 672 cm^{-1}; **^1H NMR [$CDCl_3$]** δ 5.08 (1H, d, *J* = 6.0 Hz), 2.56 (4H, s, 2 x C*H*$_2$), 2.30-2.10 (2H, m), 2.10-1.80 (2H, m), 1.66 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.50-1.30 (3H, m), 1.30-1.20 (1H, m), 1.20-1.05 (1H, m), 0.90 (3H, d, *J* = 6.0 Hz, CH_3); **^{13}C NMR [$CDCl_3$, DEPT-135]** δ 198.5 (C, C=O), 130.9 (C), 125.0 (CH), 118.7 (C), 36.9 (CH_2), 35.0 (CH_2), 32.5 (CH), 30.5 (2 x CH_2), 25.7 (CH_3), 25.5 (CH_2), 19.3 (CH_3), 18.7 (CH_2), 17.6 (CH_3); LRMS m/z 237.10 ($M+H^+$), calcd for $C_{15}H_{24}O_2H$ 237.18; Anal. calcd for $C_{15}H_{24}O_2$ (236.1776): C, 76.23; H, 10.24. Found: C, 76.240; H, 10.243%.

2-Isopropyl-cyclopentane-1,3-dione (83p): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 216 °C; IR (Neat): ν_{max} 2970, 2927, 2522, 1721, 1684, 1549, 1431, 1364, 1340, 1279 and 1120 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 2.74 (1H, heptet, *J* = 7.2 Hz, C*H*Me$_2$), 2.46 (4H, s, 2 x C*H*$_2$), 1.14 (6H, d, *J* = 7.2 Hz, 2 x CH_3, CH*Me*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 122.9 (C), 30.3 (2 x CH_2), 22.6 (CH, *C*HMe$_2$), 20.0 (2 x CH_3, CH*Me*$_2$); LRMS m/z 141.05 ($M+H^+$), calcd for $C_8H_{12}O_2H$ 141.08; Anal. calcd for $C_8H_{12}O_2$ (140.0837): C, 68.54; H, 8.63. Found: C, 68.578; H, 8.685%.



83p

2-Cyclohexyl-cyclopentane-1,3-dione (83a): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 230 °C; IR (Neat): ν_{max} 2930, 2854, 1552, 1440, 1382, 1350, 1282, 1255, 1140, 1096 and 654 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 2.43 (4H, s, 2 x C*H*$_2$), 2.38-2.35 (1H, m), 1.80-1.67 (5H, m), 1.50 (2H, m), 1.26 (3H, m); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 122.3 (C), 32.8 (CH), 30.5 (2 x CH_2), 29.7 (2 x CH_2), 26.7 (2 x CH_2), 25.9 (CH_2); LRMS m/z 181.10 ($M+H^+$), calcd for $C_{11}H_{16}O_2H$ 181.1150; Anal. calcd for $C_{11}H_{16}O_2$ (180.1150): C, 73.30; H, 8.95. Found: C, 73.365; H, 8.919%.

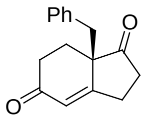


83a

12. Amino Acid-Catalyzed Robinson Annulation Reaction: In ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-alkyl-cyclopentane-1,3-diones **82** and 0.9 mmol of methyl vinyl ketone **68a** was added 1.0 mL of DMSO solvent, and then the catalyst proline **50a** (0.09 mmol, 30 mol%) was added and the reaction mixture was stirred at 25 °C for 6 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 products **85** and **86** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

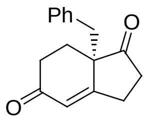
13. Amino Acid-Catalyzed One-Pot Double Cascade Olefination/Hydrogenation/Robinson Annulation Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **46**, 0.3 mmol of CH-acid **78** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of dichloromethane, and then the catalyst amino acid **50a** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 25. After evaporation of the solvent completely, to the crude reaction mixture added 0.9 mmol of methyl vinyl ketone **68a**, 1.0 mL of DMSO solvent and 0.09 mmol of L-proline **50a** and the reaction mixture was stirred at room temperature for the 6 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 products **85** and **86** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

14. General Procedure for the Dehydration of 7a-Alkyl-3a-Hydroxy-Hexahydro-Indene-1,5-Diones 85: A solution of alcohol compound **85** (0.2 mmol) and 1N $HClO_4$ (0.4 mmol) in DMSO (1.0 ml) stirred at 90 °C for 0.5 to 1 h. After cooling, the reaction mixture washed with water 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 products **84** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



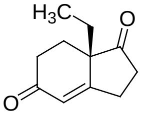
(+)-84a

(+)-7a-Benzyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione (84a): Purified by column chromatography using EtOAc/hexane and isolated as a solid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 0.5 mL/min, λ = 254 nm), t_R = 61.6 min (major), t_R = 75.2 min (minor). **$[\alpha]_D^{25}$ = +241.3° (*c* = 0.80 g/100 mL, $CHCl_3$, 90.6% ee)**; Mp 154 °C; IR (Neat): ν_{max} 2925, 1729, 1664, 1453, 1406, 1250, 1208, 1077, 754 and 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (3H, m), 7.08 (2H, m) [Ar-H]; 6.06 (1H, s, olefinic-*H*), 3.06 (2H, AB q, *J* = 12.8 Hz), 2.60-2.40 (3H, m), 2.30-2.22 (3H, m), 2.10-2.01 (1H, m), 1.84 (1H, dt, *J* = 13.6, 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 217.5 (C, C=O), 198.0 (C, C=O), 169.2 (C), 135.5 (C), 129.6 (2 x CH), 128.6 (2 x CH), 127.5 (CH), 125.1 (CH), 54.1 (C), 42.4 (CH_2), 36.9 (CH_2), 32.8 (CH_2), 29.2 (CH_2), 28.1 (CH_2); LRMS m/z 241.00 ($M+H^+$), calcd for $C_{16}H_{16}O_2H$ 241.1150; Anal. calcd for $C_{16}H_{16}O_2$ (240.1150): C, 79.97; H, 6.71. Found: C, 79.924; H, 6.718%.



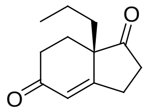
(–)-84a

(–)-7a-Benzyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione (84a): Purified by column chromatography using EtOAc/hexane and isolated as a solid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 0.5 mL/min, λ = 254 nm), t_R = 61.6 min (minor), t_R = 75.2 min (major). **$[\alpha]_D^{25}$ = –293.6° (*c* = 0.960 g/100 mL, $CHCl_3$, 90.2% ee)**.



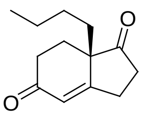
(+)-84o'

(+)-7a-Ethyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione (84o'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 62.0 min (minor), t_R = 89.0 min (major). **$[\alpha]_D^{25}$ = +125.8° (*c* = 0.16 g/100 mL, $CHCl_3$, 90% ee)**; IR (Neat): ν_{max} 2973, 2953, 1732, 1658, 1651, 1465, 1364, 1217, 1147 and 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (1H, s, olefinic-*H*), 3.10-2.93 (1H, m), 2.85-2.67 (2H, m), 2.47-2.38 (2H, m), 2.27 (1H, ddd, *J* = 14.0, 4.8, 2.4 Hz), 1.79-1.70 (4H, m), 0.98 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.8 (C, C=O), 198.1 (C, C=O), 170.1 (C), 124.1 (CH), 52.6 (C), 35.8 (CH_2), 32.6 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 25.8 (CH_2), 8.9 (CH_3); LRMS m/z 179.00 ($M+H^+$), calcd for $C_{11}H_{14}O_2H$ 179.0994; Anal. calcd for $C_{11}H_{14}O_2$ (178.0994): C, 74.13; H, 7.92. Found: C, 74.195; H, 7.928%.



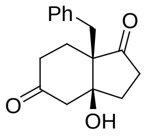
(+)-84g'

(+)-7a-Propyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione (84g'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 25.0 min (major), t_R = 36.1 min (minor). **$[\alpha]_D^{25}$ = +225.83° (*c* = 0.36 g/100 mL, $CHCl_3$, 94% ee)**; IR (Neat): ν_{max} 2960, 2933, 2873, 1741, 1666, 1443, 1357, 1211 and 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (1H, s, olefinic-*H*), 3.05-2.90 (1H, m), 2.85-2.65 (2H, m), 2.54-2.38 (2H, m), 2.28-2.23 (1H, m), 1.80-1.60 (3H, m), 1.45-1.32 (3H, m), 0.91 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 216.1 (C, C=O), 198.2 (C, C=O), 170.1 (C), 124.1 (CH), 52.5 (C), 36.5 (CH_2), 35.9 (CH_2), 32.7 (CH_2), 27.0 (CH_2), 26.6 (CH_2), 17.9 (CH_2), 14.3 (CH_3); LRMS m/z 193.00 ($M+H^+$), calcd for $C_{12}H_{16}O_2H$ 193.1150; Anal. calcd for $C_{12}H_{16}O_2$ (192.1150): C, 74.97; H, 8.39. Found: C, 74.885; H, 8.406%.



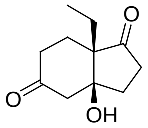
(+)-84h'

(+)-7a-Butyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione (84h'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 20.0 min (major), t_R = 25.2 min (minor). **$[\alpha]_D^{25}$ = +148.3° (*c* = 0.32 g/100 mL, $CHCl_3$, 94.3% ee)**; IR (Neat): ν_{max} 2957, 2933, 2869, 1742, 1666, 1461, 1358, 1246, 1209 and 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (1H, s, olefinic-*H*), 3.03-2.93 (1H, m), 2.85-2.67 (2H, m), 2.53-2.37 (2H, m), 2.25 (1H, dd, *J* = 14.2, 5.2 Hz), 1.80-1.62 (4H, m), 1.40-1.24 (4H, m), 0.90 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 216.0 (C, C=O), 198.2 (C, C=O), 170.1 (C), 124.1 (CH), 52.4 (C), 35.9 (CH_2), 34.1 (CH_2), 32.8 (CH_2), 27.0 (CH_2), 26.59 (CH_2), 26.57 (CH_2), 23.0 (CH_2), 13.8 (CH_3); LRMS m/z 207.00 ($M+H^+$), calcd for $C_{13}H_{18}O_2H$ 207.1307; Anal. calcd for $C_{13}H_{18}O_2$ (206.1307): C, 75.69; H, 8.80. Found: C, 75.613; H, 8.794%.



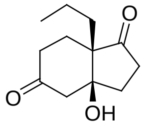
85a

7a-Benzyl-3a-hydroxy-hexahydro-indene-1,5-dione (85a): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 128 °C IR (Neat): ν_{max} 3409 (O-H), 2925, 1723, 1715, 1447, 1288, 1155, 1080, 1056, 758 and 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26 (5H, m) [Ph-*H*]; 3.07 (2H, AB q, J = 14.0 Hz, C*H*$_2$Ph), 2.65-2.57 (3H, m), 2.51-2.37 (2H, m), 2.15 (2H, t, J = 6.8 Hz), 2.10-2.04 (1H, m), 1.98-1.91 (1H, m), 1.84 (2H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 216.8 (C, C=O), 209.3 (C, C=O), 136.7 (C), 130.5 (2 x CH), 128.3 (2 x CH), 127.0 (CH), 82.0 (C, *C*-OH), 56.4 (C), 51.2 (CH_2), 37.1 (CH_2), 36.8 (CH_2), 34.2 (CH_2), 33.4 (CH_2), 27.4 (CH_2); LRMS m/z 259.00 (M+H$^+$), calcd for $C_{16}H_{18}O_3H$ 259.1256; Anal. calcd for $C_{16}H_{18}O_3$ (258.1256): C, 74.39; H, 7.02. Found: C, 74.406; H, 7.006%.



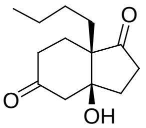
85o'

7a-Ethyl-3a-hydroxy-hexahydro-indene-1,5-dione (85o'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. IR (Neat): ν_{max} 3456 (O-H), 2967, 2883, 1721, 1714, 1464, 1411, 1292, 1231, 1138 and 1062 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.65-2.46 (4H, m), 2.40-2.22 (3H, m), 2.20-2.08 (2H, m), 2.05-1.94 (1H, m), 1.85-1.76 (2H, m), 1.74-1.64 (1H, m), 0.97 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 217.2 (C, C=O), 209.6 (C, C=O), 82.3 (C, C-OH), 55.3 (C), 51.1 (CH_2), 37.1 (CH_2), 34.3 (CH_2), 33.2 (CH_2), 25.8 (CH_2), 22.9 (CH_2), 8.2 (CH_3); LRMS m/z 197.00 (M+H$^+$), calcd for $C_{11}H_{16}O_3H$ 197.1099; Anal. calcd for $C_{11}H_{16}O_3$ (196.1099): C, 67.32; H, 8.22. Found: C, 67.347; H, 8.259%.



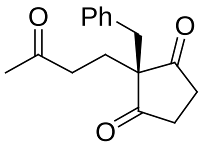
85g'

3a-Hydroxy-7a-propyl-hexahydro-indene-1,5-dione (85g'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. IR (Neat): ν_{max} 3448 (O-H), 2960, 2930, 1720, 1715, 1414, 1211 and 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.63-2.46 (4H, m), 2.39-2.24 (3H, m), 2.20-2.05 (2H, m), 2.00-1.94 (1H, m), 1.95-1.75 (1H, m), 1.70-1.56 (2H, m), 1.48-1.33 (2H, m), 0.94 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 217.4 (C, C=O), 209.4 (C, C=O), 82.3 (C, C-OH), 55.3 (C), 51.0 (CH_2), 37.2 (CH_2), 34.3 (CH_2), 33.2 (CH_2), 32.5 (CH_2), 26.4 (CH_2), 17.1 (CH_2), 14.8 (CH_3); LRMS m/z 211.00 (M+H$^+$), calcd for $C_{12}H_{18}O_3H$ 211.1256; Anal. calcd for $C_{12}H_{18}O_3$ (210.1256): C, 68.54; H, 8.63. Found: C, 68.526; H, 8.619%.



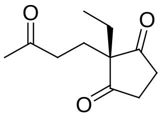
85h'

7a-Butyl-3a-hydroxy-hexahydro-indene-1,5-dione (85h'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. IR (Neat): ν_{max} 3452 (O-H), 2957, 2868, 1720, 1715, 1651, 1413, 129, 1178 and 1099 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.94 (1H, br s, O-H), 2.63-2.45 (3H, m), 2.40-2.26 (3H, m), 2.21-2.07 (2H, m), 2.00-1.93 (1H, m), 1.87-1.77 (1H, m), 1.73-1.53 (2H, m), 1.43-1.21 (4H, m), 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 217.4 (C, C=O), 209.6 (C, C=O), 82.2 (C, *C*-OH), 55.2 (C), 51.0 (CH_2), 37.2 (CH_2), 34.3 (CH_2), 33.2 (CH_2), 30.0 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 23.4 (CH_2), 13.9 (CH_3); LRMS m/z 225.00 (M+H$^+$), calcd for $C_{13}H_{20}O_3H$ 224.1412; Anal. calcd for $C_{13}H_{20}O_3$ (224.1412): C, 69.61; H, 8.99. Found: C, 69.690; H, 8.969%.



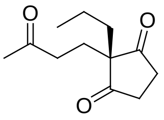
86a

2-Benzyl-2-(3-oxo-butyl)-cyclopentane-1,3-dione (86a): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 114 °C. IR (Neat): ν_{max} 2922, 2852, 1721, 1713, 1448, 1407, 1374, 1167, 758 and 707 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.24-7.21 (3H, m), 7.04-7.01 (2H, m) [Ph-*H*]; 2.93 (2H, s, C*H*$_2$Ph), 2.54 (2H, AB q, *J* = 6.8 Hz), 2.45 (2H, t, *J* = 7.2 Hz), 2.10 (3H, s, CH$_3$), 2.00 (2H, t, *J* = 7.2 Hz), 1.96 (2H, AB q, *J* = 6.8 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 217.1 (2 x C, C=O), 207.6 (C, C=O), 135.1 (C), 129.7 (2 x CH), 128.6 (2 x CH), 127.3 (CH), 61.1 (C), 42.9 (CH$_2$), 37.8 (CH$_2$), 36.3 (2 x CH$_2$), 29.9 (CH$_3$), 28.4 (CH$_2$); LRMS m/z 259.00 (M+H$^+$), calcd for $C_{16}H_{18}O_3H$ 259.1256; Anal. calcd for $C_{16}H_{18}O_3$ (258.1256): C, 74.39; H, 7.02. Found: C, 74.403; H, 7.073%.



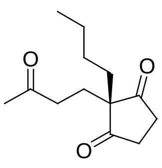
86o'

2-Ethyl-2-(3-oxo-butyl)-cyclopentane-1,3-dione (86o'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. IR (Neat): ν_{max} 2971, 2927, 1720, 1713, 1418, 1364, 1255, 1170 and 1089 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.88-2.66 (4H, m), 2.42 (2H, t, *J* = 6.8 Hz), 2.10 (3H, s, CH$_3$), 1.88 (2H, t, *J* = 7.2 Hz), 1.65 (2H, q, *J* = 7.2 Hz), 0.80 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 216.1 (2 x C, C=O), 207.9 (C, C=O), 59.7 (C), 37.5 (CH$_2$), 35.6 (2 x CH$_2$), 29.9 (CH$_3$), 28.0 (CH$_2$), 26.4 (CH$_2$), 8.7 (CH$_3$); LRMS m/z 197.00 (M+H$^+$), calcd for $C_{11}H_{16}O_3H$ 197.1099; Anal. calcd for $C_{11}H_{16}O_3$ (196.1099): C, 67.32; H, 8.22. Found: C, 67.322; H, 8.217%.



86g'

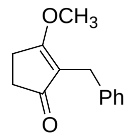
2-(3-Oxo-butyl)-2-propyl-cyclopentane-1,3-dione (86g'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. IR (Neat): IR (Neat): ν_{max} 2962, 2932, 2875, 1720, 1715, 1420, 1364, 1170 and 1098 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.82-2.64 (4H, m), 2.42 (2H, t, *J* = 7.2 Hz), 2.09 (3H, s, CH$_3$), 1.88 (2H, t, *J* = 7.2 Hz), 1.58 (2H, m), 1.16 (2H, m), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 216.3 (2 x C, C=O), 207.8 (C, C=O), 59.4 (C), 37.6 (CH$_2$), 37.1 (CH$_2$), 35.6 (2 x CH$_2$), 29.9 (CH$_3$), 27.1 (CH$_2$), 17.8 (CH$_2$), 14.3 (CH$_3$); LRMS m/z 211.00 (M+H$^+$), calcd for $C_{12}H_{18}O_3H$ 211.1256; Anal. calcd for $C_{12}H_{18}O_3$ (210.1256): C, 68.54; H, 8.63. Found: C, 68.549; H, 8.658%.



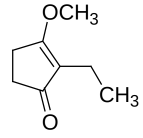
86h'

2-Butyl-2-(3-oxo-butyl)-cyclopentane-1,3-dione (86h'): Purified by column chromatography using EtOAc/hexane and isolated as an oil. IR (Neat): ν_{max} 2958, 2932, 2870, 1720, 1715, 1652, 1420, 1366, 1170 and 1100 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.85-2.65 (4H, m), 2.42 (2H, t, *J* = 7.2 Hz), 2.09 (3H, s, CH$_3$), 1.88 (2H, t, *J* = 7.2 Hz), 1.58 (2H, m), 1.30-1.20 (2H, m), 1.13-1.07 (2H, m), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 216.3 (2 x C, C=O), 207.8 (C, C=O), 59.3 (C), 37.6 (CH$_2$), 35.6 (2 x CH$_2$), 34.8 (CH$_2$), 29.9 (CH$_3$), 27.1 (CH$_2$), 26.5 (CH$_2$), 23.0 (CH$_2$), 13.6 (CH$_3$); LRMS m/z 225.00 (M+H$^+$), calcd for $C_{13}H_{20}O_3H$ 225.1412; Anal. calcd for $C_{13}H_{20}O_3$ (224.1412): C, 69.61; H, 8.99. Found: C, 69.626; H, 9.015%.

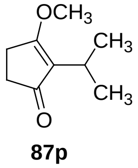
15. General Procedure for the Direct Organocatalytic One-Pot Synthesis of 2-Alkyl-3-Methoxy-Cyclopent-2-enones 87: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **46**, 0.3 mmol of CH-acid **78** and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of dichloromethane, and then the catalyst amino acid **50a** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 23. After evaporation of the solvent completely, to the crude reaction mixture added an excess ethereal solution of diazomethane and the reaction mixture was stirred at room temperature for the 0.5 h. After evaporation of the solvent and excess diazomethane completely in fume hood, the crude reaction mixture was directly loaded on silica gel column with or without aqueous work-up and pure one-pot products **87** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).


87a

2-Benzyl-3-methoxy-cyclopent-2-enone (87a): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν_{max} 3027, 2919, 1685, 1623 (C=O), 1358, 1258, 1087, 1041 and 962 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26-7.20 (4H, m), 7.17-7.13 (1H, m) [Ar-H]; 3.92 (3H, s, $OC\mathit{H}_3$), 3.45 (2H, s, $PhC\mathit{H}_2$), 2.64 (2H, t, J = 4.8 Hz), 2.44 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.1 (C, C=O), 185.0 (C), 140.1 (C), 128.4 (2 x CH), 128.1 (2 x CH), 125.7 (CH), 119.8 (C), 56.4 (CH_3, OCH_3), 33.4 (CH_2), 27.1 (CH_2), 24.5 (CH_2); LCMS m/z 203.10 ($M+H^+$), calcd for $C_{13}H_{14}O_2H$ 203.0994; Anal. calcd for $C_{13}H_{14}O_2$ (202.0994): C, 77.20; H, 6.98. Found: C, 77.334; H, 6.966%.

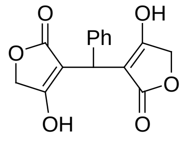

87o'

2-Ethyl-3-methoxy-cyclopent-2-enone (87o'): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν_{max} 3471, 2966, 1683, 1621 (C=O), 1614, 1462, 1360, 1268, 1123, 1016, 914 and 618 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.95 (3H, s, $OC\mathit{H}_3$), 2.66 (2H, br t, J = 4.4 Hz), 2.43 (2H, br t, J = 4.4 Hz), 2.14 (2H, q, J = 7.6 Hz, $C\mathit{H}_2CH_3$), 0.98 (3H, t, J = 7.6 Hz, $CH_2C\mathit{H}_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.8 (C, C=O), 184.3 (C), 122.1 (C), 56.2 (CH_3, OCH_3), 33.4 (CH_2), 24.4 (CH_2), 14.4 (CH_2), 12.5 (CH_3); LCMS m/z 141.15 ($M+H^+$), calcd for $C_8H_{12}O_2H$ 141.0837; Anal. calcd for $C_8H_{12}O_2$ (140.0837): C, 68.54; H, 8.63. Found: C, 68.536; H, 8.613%.


87p

2-Isopropyl-3-methoxy-cyclopent-2-enone (87p): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν_{max} 2960, 1681, 1612 (C=O), 1463, 1375, 1352, 1278, 1248, 1060 and 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.92 (3H, s, $OC\mathit{H}_3$), 2.74 (1H, heptet, J = 7.2 Hz, $C\mathit{H}Me_2$), 2.64-2.62 (2H, m), 2.41-2.39 (2H, m), 1.11 (6H, d, J = 7.2 Hz, 2 x CH_3, $CH\mathit{Me}_2$); ^{13}C NMR [$CDCl_3$, DEPT-135] δ 204.4 (C, C=O), 184.0 (C), 125.7 (C), 56.1 (CH_3, OCH_3), 33.5 (CH_2), 24.1 (CH_2), 22.8 (CH), 20.1 (2 x CH_3); LCMS m/z 155.10 ($M+H^+$), calcd for $C_9H_{14}O_2H$ 155.0994; Anal. calcd for $C_9H_{14}O_2$ (154.0994): C, 70.10; H, 9.15. Found: C, 70.070;H,9.164%

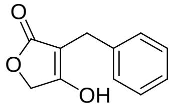
3,3'-(phenylmethanediyl)bis(4-hydroxyfuran-2(5*H*)-one) (90aa): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3418, 2934, 2544, 1721, 1644, 1445 and 1117 cm^{-1}; ^1H NMR [CD_3OD] δ 7.32 (2H, d, *J* = 7.6 Hz), 7.18 (2H, t, *J* = 7.2 Hz), 7.10 (1H, d, *J* = 7.2 Hz), 4.74 (1H, s), 4.48 (4H, s); ^{13}C NMR [CD_3OD, DEPT-135] δ 183.0 (2 x C), 181.0 (2 x C), 145.0 (C), 129.3 (2 x CH), 128.3 (2 x CH), 127.1 (CH), 100.6 (2 x C), 69.9 (2 x CH_2), 33.9 (CH); LCMS m/z 288.30 (M^+), calcd $C_{15}H_{12}O_6$ 288.0634; Anal. calcd for $C_{15}H_{12}O_6$ (288.0634): C, 62.50; H, 4.20. Found: C, 62.48; H, 4.25%.



90aa

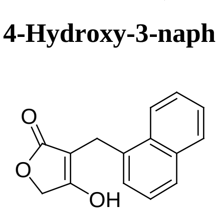
16. General Procedure for the Amino Acid-Catalyzed Cascade Three-Component Reductive Alkylation (TCRA) Reactions with Cyclic β-keto-Lactones: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the aldehyde **46**, 0.3 mmol of CH acid **88**, and 0.3 mmol of Hantzsch ester **15** was added 1.0 mL of solvent, and then the catalyst amino acid **50a** (0.015 mmol) was added, and the reaction mixture was stirred at 25 °C for the time indicated in Tables 28. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products **91aa-91fs′** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

3-Benzyl-4-hydroxy-5*H*-furan-2-one (91aa): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp.: 158 °C; IR (neat): ν_{max} 2984, 2683, 1589, 1446, 1392, 1099, 1026 and 759 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.27 (4H, s, Ph-*H*), 7.19 (1H, s, Ph-*H*), 4.54 (2H, s, OC*H*$_2$), 3.52 (2H, s, PhC*H*$_2$), 2.31 (1H, br s, O-H); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 176.7 (C, O-*C*=O), 173.6 (C), 139.0 (C), 128.2 (4 x CH), 126.0 (CH), 100.2 (C), 67.0 (CH_2), 26.9 (CH_2); LCMS m/z 191.05 ($M+H^+$), calcd $C_{11}H_{10}O_3$ 190.0630; HRMS m/z 213.0528 ($M+Na^+$), calcd $C_{11}H_{10}O_3Na$ 213.0528; Anal. calcd for $C_{11}H_{10}O_3$ (190.0630): C, 69.46; H, 5.30. Found: C, 69.38; H, 5.35%.



91aa

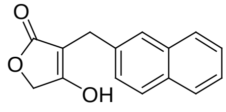
4-Hydroxy-3-naphthalen-1-ylmethyl-5*H*-furan-2-one (91ab): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 182 °C; IR (neat): ν_{max} 2968, 1706, 1658, 1600, 1318, 1110, 1044, 863 and 786 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.20 (1H, d, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 7.6 Hz), 7.69 (1H, d, *J* = 6.4 Hz), 7.55-7.40 (2H, m), 7.40-7.30 (2H, m), 4.53 (2H, s, OC*H*$_2$), 3.93 (2H, s, ArC*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ



91ab

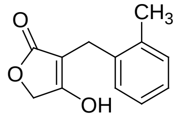
176.6 (C, O-*C*=O), 174.0 (C), 134.1 (C), 133.5 (C), 131.6 (C), 128.3 (CH), 126.7 (CH), 125.8 (CH), 125.6 (CH), 125.2 (CH), 125.15 (CH), 123.6 (CH), 99.1 (C), 66.8 (CH_2, O*C*H_2), 24.2 (CH_2, Ar*C*H_2); LCMS m/z 241.10 ($M+H^+$), calcd $C_{15}H_{12}O_3$ 240.0786; HRMS m/z 263.0692 ($M+Na^+$), calcd $C_{15}H_{12}O_3Na$ 263.0684; Anal. calcd for $C_{15}H_{12}O_3$ (240.0786): C, 74.99; H, 5.03. Found: C, 74.85; H, 5.08%.

4-Hydroxy-3-naphthalen-2-ylmethyl-5*H*-furan-2-one (91ac): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 136 °C; IR (neat): ν_{max} 2979, 1753, 1595, 1450 and 1095 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.76-7.68 (4H, m), 7.42-7.37 (3H, m), 4.56 (2H, s, OC*H*$_2$), 3.66 (2H, s, ArC*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 176.8 (C, O-*C*=O), 173.8 (C), 136.4 (C), 133.3 (C), 131.9 (C), 127.7 (CH), 127.3 (2 x CH), 126.9 (CH), 126.1 (CH), 125.7 (CH), 125.0 (CH), 100.0 (C), 67.0 (CH_2, O*C*H_2), 27.0 (CH_2, Ar*C*H_2); LCMS m/z 239.10 ($M-H^+$), calcd $C_{15}H_{12}O_3$ 240.0786; HRMS m/z 263.0683 ($M+Na^+$), calcd $C_{15}H_{12}O_3Na$ 263.0684; Anal. calcd for $C_{15}H_{12}O_3$ (240.0786): C, 74.99; H, 5.03. Found: C, 75.12; H, 5.08%.



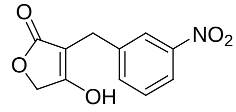
91ac

4-Hydroxy-3-(2-methyl-benzyl)-5*H*-furan-2-one (91au'): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 146 °C; IR (neat): ν_{max} 2987, 2662, 1716, 1603, 1391, 1092 and 1017 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.16-7.07 (4H, m), 4.53 (2H, s, OC*H*$_2$), 3.46 (2H, s, ArC*H*$_2$), 2.34 (3H, s, ArC*H*$_3$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 177.2 (C, O-*C*=O), 174.2 (C), 136.4 (C), 136.1 (C), 129.9 (CH), 128.3 (CH), 126.2 (CH), 125.7 (CH), 99.4 (C), 67.2 (CH_2, O*C*H_2), 24.4 (CH_2, Ar*C*H_2), 19.4 (CH_3, Ar*C*H_3); LCMS m/z 205.05 ($M+H^+$), calcd $C_{12}H_{12}O_3$ 204.0786; HRMS m/z 227.0692 ($M+Na^+$), calcd $C_{12}H_{12}O_3Na$ 227.0684; Anal. calcd for $C_{12}H_{12}O_3$ (204.0786): C, 70.57; H, 5.92. Found: C, 70.45; H, 5.98%.



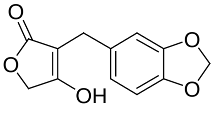
91au'

4-Hydroxy-3-(3-nitro-benzyl)-5*H*-furan-2-one (91ao): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 158 °C; IR (neat): ν_{max} 3417, 2963, 1721, 1492, 1441, 1246 and 1036 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.12 (1H, s), 8.04 (1H, d, *J* = 8.4 Hz), 7.65 (1H, d, *J* = 7.6 Hz), 7.45 (1H, t, *J* = 7.6 Hz), 4.63 (2H, s, OC*H*$_2$), 3.62 (2H, s, ArC*H*$_2$); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 176.3 (C, O-*C*=O), 174.4 (C), 148.0 (C), 141.0 (C), 134.8 (CH), 129.0 (CH), 123.0 (CH), 121.1 (CH), 98.7 (C), 67.0 (CH_2, O*C*H_2), 26.5 (CH_2, Ar*C*H_2); LCMS m/z 236.05 ($M+H^+$), calcd $C_{11}H_9NO_5$ 235.0481; HRMS m/z 258.0372 ($M+Na^+$), calcd $C_{11}H_9NO_5Na$ 258.0378; Anal. calcd for $C_{11}H_9NO_5$ (235.0481): C, 56.17; H, 3.86; N, 5.96. Found: C, 56.10; H, 3.82; N, 6.07%.



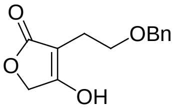
91ao

3-Benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-5*H*-furan-2-one (91ai): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 210 °C; IR (neat): ν_{max} 2686, 1622, 1447, 1399, 1245, 1034 and 788 cm^{-1}; ^{1}H NMR (DMSO-D_6) δ 5.62-5.59 (2H, m), 5.51-5.49 (1H, m), 4.76 (2H, s, OC*H*$_2$O), 3.46 (2H, s, C*H*$_2$O), 2.16 (2H, s, C*H*$_2$Ar); ^{13}C NMR (DMSO-D_6, DEPT-135) δ 175.4 (C, O-*C*=O), 174.4 (C), 147.6 (C), 145.8 (C), 133.8 (C), 121.3 (CH), 109.0 (CH), 108.4 (CH), 101.1 (CH$_2$, O*C*H$_2$O), 99.1 (C), 67.1 (CH$_2$, O*C*H$_2$), 26.6 (CH$_2$, Ar*C*H$_2$); LCMS m/z 235.10 (M+H$^+$), calcd $C_{12}H_{10}O_5$ 234.0528; HRMS m/z 257.0420 (M+Na$^+$), calcd $C_{12}H_{10}O_5Na$ 257.0426; Anal. calcd for $C_{12}H_{10}O_5$ (234.0528): C, 61.54; H, 4.30. Found: C, 61.48; H, 4.35%.



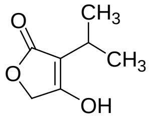
91ai

3-(2-Benzyloxy-ethyl)-4-hydroxy-5*H*-furan-2-one (91av'): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 80 °C; IR (neat): ν_{max} 3028, 2984, 1725, 1639, 1456, 1394, 1097, 1039, 749 and 696 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 7.31-7.16 (5H, m), 4.54 (2H, s, OC*H*$_2$Ph), 4.44 (2H, s, OC*H*$_2$), 3.66 (2H, t, *J* = 5.6 Hz, OC*H*$_2$CH$_2$), 2.44 (2H, t, *J* = 5.6 Hz, OCH$_2$C*H*$_2$); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 175.5 (C, O-*C*=O), 173.8 (C), 135.8 (C), 128.6 (2 x CH), 128.4 (CH), 128.1 (2 x CH), 98.4 (C), 73.6 (CH$_2$), 69.5 (CH$_2$), 66.6 (CH$_2$), 22.6 (CH$_2$); LCMS m/z 233.05 (M-H$^+$), calcd $C_{13}H_{14}O_4$ 234.0892; HRMS m/z 257.0789 (M+Na$^+$), calcd $C_{13}H_{14}O_4Na$ 257.0790; Anal. calcd for $C_{13}H_{14}O_4$ (234.0892): C, 66.66; H, 6.02. Found: C, 66.75; H, 6.08%.



91av'

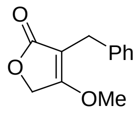
4-Hydroxy-3-isopropyl-5*H*-furan-2-one (91ap): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 110 °C; IR (neat): ν_{max} 2968, 1711, 1603, 1430, 1343, 1298, 1116 and 1040 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 4.52 (2H, s, OC*H*$_2$), 2.72 (1H, septet, *J* = 6.8 Hz, C*H*(CH$_3$)$_2$), 1.19 (6H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 176.4 (C, O-*C*=O), 172.1 (C), 105.3 (C), 66.3 (CH$_2$, O*C*H$_2$), 22.5 (CH), 20.0 (2 x CH$_3$); LCMS m/z 143.05 (M+H$^+$), calcd $C_7H_{10}O_3$ 142.0630; HRMS m/z 165.0526 (M+Na$^+$), calcd $C_7H_{10}O_3Na$ 165.0528; Anal. calcd for $C_7H_{10}O_3$ (142.0630): C, 59.14; H, 7.09. Found: C, 59.21; H, 7.03%.



91ap

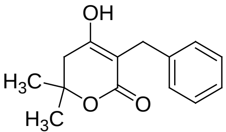
17. General Procedure for the Synthesis of 3-Benzyl-4-methoxy-5*H*-furan-2-one 95aa: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of 4-hydroxy-3-benzyl-5*H*-furan-2-one **91aa** in 1.0 mL of ether at 0 °C added an excess ethereal solution of diazomethane and the reaction mixture was stirred at room temperature for the 0.5 h. After evaporation of the solvent and excess diazomethane completely in fume hood, the crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure products **95aa** were obtained by column chromatography (silica gel, mixture of exane/ethyl acetate).

3-Benzyl-4-methoxy-5*H*-furan-2-one (95aa): Prepared following the procedure **17** and purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{mlax} 1749, 1667, 1457, 1381, 1105 and 1046 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.26-7.23 (4H, m), 7.19-7.17 (1H, m), 4.65 (2H, s, OC*H*$_2$), 3.89 (3H, s, OC*H*$_3$), 3.57 (2H, s, PhC*H*$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 174.6 (C, O-*C*=O), 173.2 (C), 138.9 (C), 128.4 (2 x CH), 128.2 (2 x CH), 126.2 (CH), 102.4 (C), 65.2 (CH$_2$, O*C*H$_2$), 57.6 (CH$_3$, O*C*H$_3$), 27.6 (CH$_2$, Ph*C*H$_2$); LCMS 205.05 m/z (M+H$^+$), calcd C$_{12}$H$_{12}$O$_3$ 204.0786; Anal. calcd for C$_{12}$H$_{12}$O$_3$ (204.0786): C, 70.57; H, 5.92. Found: C, 70.65; H, 5.88%.



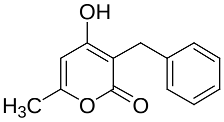
95aa

3-Benzyl-4-hydroxy-6,6-dimethyl-5,6-dihydro-pyran-2-one (91ba): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 130 °C; IR (neat): ν_{max} 2977, 2940, 2697, 1589, 1380, 1312, 1229 and 1108 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 7.24 (2H, d, *J* = 7.2 Hz), 7.19 (2H, t, *J* = 7.6 Hz), 7.09 (1H, *J* = 6.8 Hz), 4.72 (1H, br s, O-H), 3.62 (2H, s, PhC*H*$_2$), 2.55 (2H, s, RC*H*$_2$), 1.38 (6H, s, 2 x C*H*$_3$); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 169.2 (C, O-*C*=O), 165.1 (C), 140.4 (C), 127.8 (2 x CH), 127.4 (2 x CH), 125.0 (CH), 101.9 (C), 76.6 (C), 38.6 (CH$_2$), 28.1 (CH$_2$), 26.7 (2 x CH$_3$); LCMS m/z 233.05 (M+H$^+$), calcd C$_{14}$H$_{16}$O$_3$ 232.1099; HRMS m/z 255.0998 (M+Na$^+$), calcd C$_{14}$H$_{16}$O$_3$Na 255.0997; Anal. calcd for C$_{14}$H$_{16}$O$_3$ (232.1099): C, 72.39; H, 6.94. Found: C, 72.45; H, 6.88%.



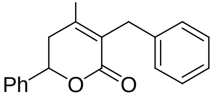
91ba

3-Benzyl-4-hydroxy-6-methyl-pyran-2-one (91ca): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 166 °C; IR (neat): ν_{max} 3133, 2684, 1639, 1588, 1446, 1401, 1251 and 828 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 7.31 (2H, d, *J* = 7.6 Hz), 7.21 (2H, t, *J* = 7.2 Hz), 7.13 (1H, t, *J* = 7.2 Hz), 5.96 (1H, s, olefinic-*H*), 3.74 (2H, s, PhC*H*$_2$), 2.12 (3H, s, C*H*$_3$); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 167.3 (C, O-*C*=O), 166.5 (C), 160.3 (C), 140.2 (C), 128.4 (2 x CH), 128.0 (2 x CH), 125.7 (CH), 102.0 (C), 100.7 (CH), 28.6 (CH$_2$), 19.4 (CH$_3$); LCMS m/z 217.10 (M+H$^+$), calcd C$_{13}$H$_{12}$O$_3$ 216.0786; HRMS m/z 239.0678 (M+Na$^+$), calcd C$_{13}$H$_{12}$O$_3$Na 239.0684; Anal. calcd for C$_{13}$H$_{12}$O$_3$ (216.0786): C, 72.21; H, 5.59. Found: C, 72.11; H, 5.63%.



91ca

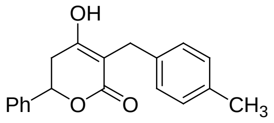
3-Benzyl-4-hydroxy-6-phenyl-5,6-dihydro-pyran-2-one (91da): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 136 °C; IR (neat): ν_{max} 2998, 2686, 1600, 1448, 1399, 1244, 1034 and 791 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 7.30-7.26 (7H, m), 7.19



91da

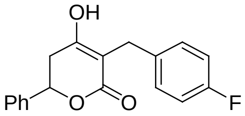
(2H, t, *J* = 7.2 Hz), 7.11 (1H, t, *J* = 7.2 Hz), 5.22 (1H, dd, *J* = 12.4, 4.0 Hz), 3.66 (2H, s, C*H*$_2$Ph), 2.79 (1H, dd, *J* = 13.6, 8.8 Hz), 2.59 (1H, dd, *J* = 17.2, 4.0 Hz); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 169.6 (C, O-*C*=O), 166.3 (C), 140.6 (C), 138.3 (C), 128.5 (2 x CH), 128.4 (3 x CH), 128.0 (2 x CH), 125.9 (2 x CH), 125.7 (CH), 103.4 (C), 76.2 (CH), 35.1 (CH$_2$), 28.8 (CH$_2$); LCMS m/z 281.10 (M+H$^+$), calcd $C_{18}H_{16}O_3$ 280.1099; HRMS m/z 303.0994 (M+Na$^+$), calcd $C_{18}H_{16}O_3Na$ 303.0997; Anal. calcd for $C_{18}H_{16}O_3$ (280.1099): C, 77.12; H, 5.75. Found: C, 77.32; H, 5.71%.

4-Hydroxy-3-(4-methyl-benzyl)-6-phenyl-5,6-dihydro-pyran-2-one (91de): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 146 °C; IR (neat): ν_{max} 3160, 1641, 1586, 1435, 1401, 1254, 1117 and 994 cm^{-1}; ^{1}H NMR (DMSO-D$_6$) δ 7.55-7.35 (5H, m), 7.15 (2H, d, *J* = 8.0 Hz), 7.08 (2H, d, *J* = 8.0 Hz), 5.49 (1H, dd, *J* = 12.0, 4.0 Hz), 3.57 (2H, s), 3.01 (1H, dd, *J* = 16.0, 12.0 Hz), 2.77 (1H, br dd, *J* = 16.0, 4.0 Hz), 2.29 (3H, s); ^{13}C NMR (DMSO-D$_6$, DEPT-135) δ 168.0 (C, O-*C*=O), 167.0 (C), 139.7 (C), 138.4 (C), 134.8 (C), 129.0 (2 x CH), 128.9 (2 x CH), 128.7 (CH), 128.6 (2 x CH), 126.9 (2 x CH), 102.4 (C), 75.7 (CH), 35.2 (CH$_2$), 28.6 (CH$_2$), 21.1 (CH$_3$); HRMS m/z 317.1154 (M+Na$^+$), calcd $C_{19}H_{18}O_3Na$ 317.1154; Anal. calcd for $C_{19}H_{18}O_3$ (294.1256): C, 77.53; H, 6.16. Found: C, 77.48; H, 6.21%.



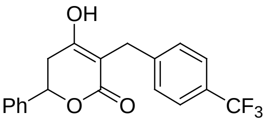
91de

3-(4-Fluoro-benzyl)-4-hydroxy-6-phenyl-5,6-dihydro-pyran-2-one (91dv): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 170 °C; IR (neat): ν_{max} 3038, 2649, 1594, 1506, 1396, 1221 and 1116 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 7.36-7.31 (5H, m), 7.28-7.25 (2H, m), 6.93-6.88 (2H, m), 5.33 (1H, dd, *J* = 12.0, 4.0 Hz), 3.64 (2H, s), 2.86 (1H, dd, *J* = 17.2, 12.4 Hz), 2.64 (1H, dd, *J* = 17.2, 4.0 Hz); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ 169.2 (C, O-*C*=O), 165.9 (C), 161.1 (*C*-F, d, *J* = 241.3 Hz), 138.4 (C), 136.4 (C, d, *J* = 5.1 Hz), 129.8 (2 x CH, d, *J* = 7.7 Hz), 128.5 (2 x CH), 128.4 (CH), 125.9 (2 x CH), 114.6 (2 x CH, d, *J* = 20.9 Hz), 103.6 (C), 76.2 (CH), 35.2 (CH$_2$), 28.0 (CH$_2$); LCMS m/z 299.15 (M+H$^+$), calcd $C_{18}H_{15}FO_3$ 298.1005; HRMS m/z 321.0902 (M+Na$^+$), calcd $C_{18}H_{15}FO_3Na$ 321.0903; Anal. calcd for $C_{18}H_{15}FO_3$ (298.1005): C, 72.47; H, 5.07. Found: C, 72.35; H, 5.11%.



91dv

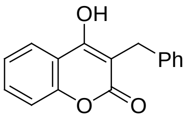
4-Hydroxy-6-phenyl-3-(4-trifluoromethyl-benzyl)-5,6-dihydro-pyran-2-one (91dw'): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 170 °C; IR (neat): ν_{max} 3058, 1592, 1366, 1327, 1236, 1111, 1063 and 920 cm^{-1}; ^{1}H NMR [CDCl$_3$ + CD$_3$OD (three drops)] δ 7.48 (2H, d, *J* = 8.0 Hz), 7.42 (2H, d, *J* = 8.0 Hz), 7.34-7.32 (5H, m), 5.36 (1H, dd, *J* = 12.0, 4.0 Hz), 4.16 (1H, br s, O-H), 3.73 (2H, s), 2.90 (1H, dd, *J* = 17.2, 12.0 Hz), 2.69 (1H, dd, *J* = 17.2, 4.0 Hz); ^{13}C NMR [CDCl$_3$ + CD$_3$OD (three drops), DEPT-135] δ



91dw'

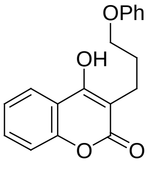
169.3 (C, O-*C*=O), 166.7 (C), 144.98 (C), 144.97 (C), 138.2 (C), 128.7 (2 x CH), 128.41 (2 x CH), 128.37 (CH), 127.7 (C, *C*F_3, q, *J* = 31.9 Hz), 125.8 (2 x CH), 124.7 (2 x CH, q, *J* = 3.8 Hz), 102.6 (C), 76.2 (CH), 35.0 (CH_2), 28.6 (CH_2); LCMS m/z 349.15 ($M+H^+$), calcd $C_{19}H_{15}F_3O_3$ 348.0973; HRMS m/z 371.0864 ($M+Na^+$), calcd $C_{19}H_{15}F_3O_3Na$ 371.0871; Anal. calcd for $C_{19}H_{15}F_3O_3$ (348.0973): C, 65.52; H, 4.34. Found: C, 65.58; H, 4.31%.

3-Benzyl-4-hydroxy-chromen-2-one (91ea): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 205 °C; IR (neat): ν_{max} 3101, 1656, 1608, 1494, 1394, 1263, 1181, 1110 and 754 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.89 (1H, d, *J* = 8.0 Hz), 7.52 (1H, t, *J* = 8.0 Hz), 7.33-7.26 (6H, m), 7.18 (1H, t, *J* = 7.2 Hz), 3.98 (2H, s), 2.25 (1H, br s, O-H); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 164.6 (C, O-*C*=O), 161.0 (C), 152.4 (C), 139.0 (C), 131.5 (CH), 128.3 (2 x CH), 128.2 (2 x CH), 126.1 (CH), 123.7 (CH), 123.0 (CH), 116.4 (CH), 116.3 (C), 104.5 (C), 29.3 (CH_2); LCMS m/z 253.10 ($M+H^+$), calcd $C_{16}H_{12}O_3$ 252.0786; HRMS m/z 275.0685 ($M+Na^+$), calcd $C_{16}H_{12}O_3Na$ 275.0684; Anal. calcd for $C_{16}H_{12}O_3$ (252.0786): C, 76.18; H, 4.79. Found: C, 76.11; H, 4.83%.



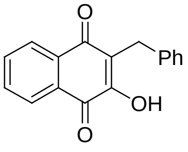
91ea

4-Hydroxy-3-(3-phenoxy-propyl)-chromen-2-one (91ex'): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 126 °C; IR (neat): ν_{max} 2979, 1667, 1601, 1381, 1231, 1107 and 757 cm^{-1}; ^1H NMR (CD_3OD) δ 7.92 (1H, d, *J* = 7.6 Hz), 7.58 (1H, t, *J* = 7.2 Hz), 7.34 (2H, t, *J* = 8.0 Hz), 7.22 (2H, t, *J* = 8.0Hz), 6.88 (3H, m), 4.02 (2H, t, *J* = 6.0 Hz), 2.77 (2H, t, *J* = 7.2 Hz), 2.02 (2H, quintet, *J* = 6.4 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 164.4 (C, O-*C*=O), 161.0 (C), 157.8 (C), 152.2 (C), 131.4 (CH), 129.6 (2 x CH), 123.8 (CH), 123.2 (CH), 121.6 (CH), 116.2 (CH), 116.1 (C), 114.6 (2 x CH), 103.7 (C), 67.6 (CH_2), 27.1 (CH_2), 20.3 (CH_2); LCMS 297.00 m/z ($M+H^+$), calcd $C_{18}H_{16}O_4$ 296.1049; Anal. calcd for $C_{18}H_{16}$O4 (296.1049): C, 72.96; H, 5.44. Found: C, 72.88; H, 5.51%.



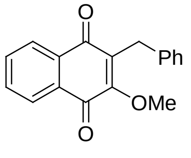
91ex'

2-Benzyl-3-hydroxy-[1,4]naphthoquinone (91fa): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 174 °C; IR (neat): ν_{max} 3340, 1658, 1642, 1590, 1369, 1346, 1274, 1221 and 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (1H, d, *J* = 7.6 Hz), 8.06 (1H, d, *J* = 7.6 Hz), 7.74 (1H, t, *J* = 7.6 Hz), 7.66 (1H, t, *J* = 7.6 Hz), 7.45 (1H, s, O-H), 7.39 (2H, d, *J* = 7.6 Hz), 7.26 (2H, dt, *J* = 7.6, 2.0 Hz), 7.19-7.16 (1H, m), 3.95 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.3 (C), 181.6 (C), 153.0 (C), 138.9 (C), 135.0 (CH), 132.9 (CH), 132.8 (C), 129.3 (C), 129.2 (CH), 128.4 (2 x CH), 126.9 (CH), 126.3 (2 x CH), 126.1 (CH), 123.0 (C), 29.1 (CH_2); LCMS m/z



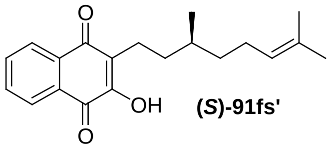
91fa

265.05 ($M+H^+$), calcd $C_{17}H_{12}O_3$ 264.0786; HRMS m/z 287.0686 ($M+Na^+$), calcd $C_{17}H_{12}O_3Na$ 287.0684; Anal. calcd for $C_{17}H_{12}O_3$ (264.0786): C, 77.26; H, 4.58. Found: C, 77.32; H, 4.51%.



95fa

2-Benzyl-3-methoxy-[1,4]naphthoquinone (95fa): Prepared following the procedure **17** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 72 °C; IR (neat): ν_{max} 2993, 1763, 1668, 1601, 1334, 1263, 1224, 961 and 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05-7.99 (2H, m), 7.69-7.62 (2H, m), 7.33 (2H, dd, *J* = 7.2, 1.2 Hz), 7.24 (2H, t, *J* = 7.2 Hz), 7.18 (1H, br t, *J* = 7.2 Hz), 4.12 (3H, s, OCH_3), 3.93 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 185.0 (C), 181.7 (C), 157.6 (C), 139.0 (C), 133.8 (CH), 133.6 (C), 133.2 (CH), 131.8 (C), 131.4 (C), 129.0 (2 x CH), 128.4 (2 x CH), 126.23 (CH), 126.19 (CH), 126.0 (CH), 61.1 (CH_3), 29.3 (CH_2); LCMS m/z 279.15 ($M+H^+$), calcd $C_{18}H_{14}O_3$ 278.0943; HRMS m/z 301.0845 ($M+Na^+$), calcd $C_{18}H_{14}O_3Na$ 301.0841; Anal. calcd for $C_{18}H_{14}O_3$ (278.0943): C, 77.68; H, 5.07. Found: C, 77.56; H, 5.12%.



(*S*)-91fs'

2-[(3*S*)-(+)-3,7-dimethyloct-6-en-1-yl]-3-hydroxynaphthalene-1,4-dione (91fs'): Prepared following the procedure **16** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 56 °C; **$[\alpha]^{25}_{D}$ = +3.5 (*c* 1.42, $CHCl_3$, >99% ee);** IR (neat): ν_{max} 3363, 1649, 1640, 1591, 1351, 1275, 1224 and 728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (1H, dd, *J* = 8.0, 1.2 Hz), 8.07 (1H, dd, *J* = 8.0, 1.2 Hz), 7.75 (1H, dt, *J* = 7.6, 1.6 Hz), 7.67 (1H, dt, *J* = 7.6, 1.6 Hz), 7.34 (1H, br s, O-H), 5.10 (2H, tt, *J* = 6.8, 1.2 Hz), 2.66-2.54 (2H, m), 2.07-1.91 (2H, m), 1.67 (3H, s), 1.60 (3H, s), 1.56-1.48 (2H, m), 1.45-1.33 (2H, m), 1.25-1.17 (1H, m), 0.98 (3H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.6 (C), 181.4 (C), 152.9 (C), 134.8 (CH), 133.0 (C), 132.8 (CH), 131.0 (C), 129.4 (C), 126.7 (CH), 126.0 (CH), 125.2 (C), 124.9 (CH), 36.8 (CH_2), 35.1 (CH_2), 32.7 (CH), 25.7 (CH_3), 25.4 (CH_2), 21.0 (CH_2), 19.4 (CH_3), 17.6 (CH_3); LCMS m/z 313.20 ($M+H^+$), calcd $C_{20}H_{24}O_3$ 312.1725; Anal. calcd for $C_{20}H_{24}O_3$ (312.1725): C, 76.89; H, 7.74. Found: C, 76.95; H, 7.70%.

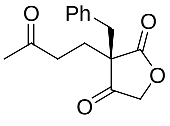
18. Preparation for Racemic Michael Products 92 with Triethylamine-Catalysis: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **91** and 0.9 mmol of alkyl vinyl ketone **68** with a catalytic amount of triethylamine in 1.0 mL of THF solvent and the reaction mixture was stirred at 25 °C for 6-48 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **92** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

19. Preparation of Racemic Cascade Michael-Aldol Products 93 with DL-β-Phenylalanine-Catalysis: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **91** and 0.9 mmol of alkyl vinyl ketone **68** with a catalytic amount of DL-β-phenylalanine in 1.0 mL of THF solvent and the reaction mixture was stirred at 25 °C for 6-48 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **93** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

20. Amino Acid-Catalyzed Asymmetric Cascade Michael-Aldol Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **91** and 0.9 mmol of methyl vinyl ketone **68a** was added 1.0 mL of DMSO solvent, and then the catalyst L-proline **50a** (0.09 mmol) was added, and the reaction mixture was stirred at 25 °C for 2 days. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure cascade M-A products **93** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

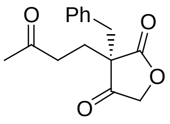
21. Q-NH_2/TCA-Catalyzed Asymmetric Cascade Michael-Aldol Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to Q-NH_2 **50a'** (0.05 mmol) and TCA (32 mg, 0.2 mmol) in THF (5.0 mL) were added and stirred at 25 °C for 10 minutes then 0.5 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **91** and 1.5 mmol of methyl vinyl ketone **68a** was added, and the reaction mixture was stirred at 25 °C for 6-48 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure cascade M-A products **93** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(3*R*)-(–)-3-benzyl-3-(3-oxobutyl)furan-2,4(3*H*,5*H*)-dione (92aaa): Prepared following the procedure **20** or **21** and purified by column chromatography using EtOAc/hexane and isolated as an oil; The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 80:20, flow rate 0.8 mL/min, λ = 220 nm), t_R = 15.2 min (minor), t_R = 17.4 min (major); **$[\alpha]^{25}_D$ = –5.2 (*c* 0.33, $CHCl_3$, 63.6% ee);** IR (neat): ν_{max} 2926, 1756, 1714 and 1173 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (3H, m), 7.10 (2H, m), 4.37 (1H, d, *J* = 16.8 Hz), 3.49 (1H, d, *J* = 16.8 Hz), 3.06 (2H, ABq, *J* = 12.8 Hz), 2.60-2.54 (2H, m), 2.23-2.09 (2H, m), 2.13 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.8 (C, *C*=O), 207.1 (C, *C*=O), 176.1 (C, O-*C*=O), 133.7 (C), 129.6 (2 x CH), 128.9 (2 x CH), 127.9 (CH), 73.3 (CH_2), 54.2 (C), 43.0 (CH_2), 37.8 (CH_2), 29.8 (CH_3), 28.2 (CH_2); LCMS m/z 261.15 (M+H^+), calcd $C_{15}H_{16}O_4$ 260.1049; HRMS m/z 283.0957 (M+Na^+), calcd $C_{15}H_{16}O_4Na$ 283.0946; Anal. calcd for $C_{15}H_{16}O_4$ (260.1049): C, 69.22; H, 6.20. Found: C, 69.35; H, 6.16%.



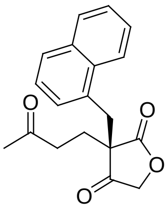
(–)-**92aaa**

(3*S*)-(+)-3-benzyl-3-(3-oxobutyl)furan-2,4(3*H*,5*H*)-dione (92aaa): Prepared following the procedure **20** or **21** and purified by column chromatography using EtOAc/hexane and isolated as



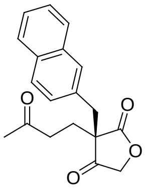
(+)-**92aaa**

an oil; The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 80:20, flow rate 0.8 mL/min, λ = 220 nm), t_R = 15.2 min (major), t_R = 17.4 min (minor); **$[\alpha]^{25}_{D}$ = +1.4 (*c* 0.5, $CHCl_3$, 16% ee).**



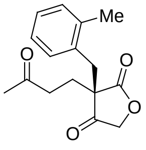
92aba

(3*R*)-3-Naphthalen-1-ylmethyl-3-(3-oxo-butyl)-furan-2,4-dione (92aba): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as an oil. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 80:20, flow rate 0.8 mL/min, λ = 220 nm), t_R = 16.0 min (major), t_R = 20.5 min (minor); ee = 13%.; IR (neat): ν_{max} 2925, 1753, 1710, 1369, 1228, 1051 and 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (1H, d, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 8.0 Hz), 7.77 (1H, d, *J* = 8.0 Hz), 7.53 (1H, t, *J* = 7.2 Hz), 7.47 (1H, t, *J* = 8.0 Hz), 7.38 (1H, t, *J* = 7.6 Hz), 7.32 (1H, d, *J* = 6.8 Hz), 4.23 (1H, d, *J* = 16.8 Hz), 3.65 (1H, d, *J* = 13.6 Hz), 3.53 (1H, d, *J* = 13.6 Hz), 3.24 (1H, d, *J* = 16.8 Hz), 2.61-2.55 (2H, m), 2.34-2.23 (2H, m), 2.14 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.6 (C, *C*=O), 207.1 (C, *C*=O), 176.2 (C, O-*C*=O), 133.8 (C), 131.4 (C), 130.0 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 126.5 (CH), 126.1 (CH), 125.3 (CH), 123.7 (CH), 73.3 (CH_2), 54.0 (C), 39.0 (CH_2), 37.9 (CH_2), 29.9 (CH_3), 28.3 (CH_2); HRMS m/z 333.1104 (M+Na^+), calcd $C_{19}H_{18}O_4Na$ 333.1103; Anal. calcd for $C_{19}H_{18}O_4$ (310.1205): C, 73.53; H, 5.85. Found: C, 73.65; H, 5.81%.



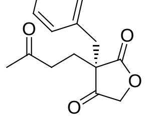
92aca

(3*R*)-3-Naphthalen-2-ylmethyl-3-(3-oxo-butyl)-furan-2,4-dione (92aca): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as an oil. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 80:20, flow rate 0.2 mL/min, λ = 220 nm), t_R = 108.7 min (major), t_R = 115.0 min (minor); ee = 11%.; IR (neat): ν_{max} 1753 and 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80-7.74 (3H, m), 7.58 (1H, s), 7.48-7.46 (2H, m), 7.21 (1H, dd, *J* = 8.4, 1.6 Hz), 4.34 (1H, d, *J* = 16.8 Hz), 3.46 (1H, d, *J* = 16.8 Hz), 3.23 (2H, ABq, *J* = 12.8 Hz), 2.62-2.57 (2H, m), 2.26-2.16 (2H, m), 2.14 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.8 (C, *C*=O), 207.1 (C, *C*=O), 176.2 (C, O-*C*=O), 133.2 (C), 132.6 (C), 131.2 (C), 128.68 (CH), 128.64 (CH), 127.9 (CH), 127.6 (CH), 127.2 (CH), 126.4 (CH), 126.3 (CH), 73.3 (CH_2), 54.2 (C), 43.0 (CH_2), 37.8 (CH_2), 29.9 (CH_3), 28.3 (CH_2); LCMS m/z 309.05 (M-H^+), calcd $C_{19}H_{18}O_4$ 310.1205; Anal. calcd for $C_{19}H_{18}O_4$ (310.1205): C, 73.53; H, 5.85. Found: C, 73.45; H, 5.89%.



92au'a

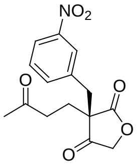
(3*R*)-3-(2-Methyl-benzyl)-3-(3-oxo-butyl)-furan-2,4-dione (92au'a): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as an oil; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/ethanol = 70:30, flow rate 1.0 mL/min, λ = 220 nm), t_R = 13.4 min (major), t_R = 14.6 min (minor); ee = 10%.; IR (neat): ν_{max} 1802 and 1755 cm^{-1}; ^1H NMR



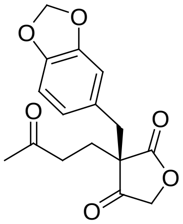
92au'a

(CDCl$_3$) δ 7.14-7.06 (4H, m), 4.36 (1H, d, *J* = 16.4 Hz), 3.55 (1H, d, *J* = 16.4 Hz), 3.15 (2H, ABq, *J* = 13.6 Hz), 2.62-2.47 (2H, m), 2.27 (3H, s, CH$_3$), 2.24-2.15 (2H, m), 2.12 (3H, s, CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 209.6 (C, *C*=O), 207.1 (C, *C*=O), 176.5 (C, O-*C*=O), 136.8 (C), 132.2 (C), 131.1 (CH), 129.6 (CH), 127.9 (CH), 126.3 (CH), 73.2 (CH$_2$), 53.7 (C), 39.3 (CH$_2$), 37.8 (CH$_2$), 29.8 (CH$_3$), 28.2 (CH$_2$), 19.5 (CH$_3$); LCMS m/z 275.15 (M+H$^+$), calcd $C_{16}H_{18}O_4$ 274.1205; HRMS m/z 297.1101 (M+Na$^+$), calcd $C_{16}H_{18}O_4Na$ 297.1103; Anal. calcd for $C_{16}H_{18}O_4$ (274.1205): C, 70.06; H, 6.61. Found: C, 70.12; H, 6.65%.

(3*S*)-3-(2-Methyl-benzyl)-3-(3-oxo-butyl)-furan-2,4-dione (92au'a): Prepared following the procedure **20** and purified by column chromatography using EtOAc/hexane and isolated as an oil; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/ethanol = 70:30, flow rate 1.0 mL/min, λ = 220 nm), t_R = 13.4 min (minor), t_R = 14.6 min (major); ee = 16%.

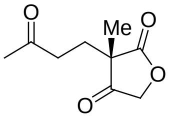

92aoa

(3*R*)-3-(3-Nitro-benzyl)-3-(3-oxo-butyl)-furan-2,4-dione (92aoa): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 88 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/ethanol = 70:30, flow rate 1.0 mL/min, λ = 220 nm), t_R = 44.0 min (minor), t_R = 50.1 min (major); ee = 15%.; IR (neat): ν_{max} 1750, 1712, 1531, 1355, 1076 and 1036 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.10 (1H, td, *J* = 7.2, 2.4 Hz), 7.93 (1H, br s), 7.46-7.45 (2H, m), 4.50 (1H, d, *J* = 17.2 Hz), 3.74 (1H, d, *J* = 17.2 Hz), 3.14 (2H, s), 2.67-2.53 (2H, m), 2.22-2.09 (2H, m), 2.12 (3H, s, CH$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 208.7 (C, *C*=O), 207.0 (C, *C*=O), 175.3 (C, O-*C*=O), 148.3 (C), 135.9 (C), 135.8 (CH), 129.8 (CH), 124.6 (CH), 122.9 (CH), 73.1 (CH$_2$), 53.4 (C), 40.9 (CH$_2$), 37.3 (CH$_2$), 29.8 (CH$_3$), 28.4 (CH$_2$); LCMS m/z 306.15 (M+H$^+$), calcd $C_{15}H_{15}NO_6$ 305.0899; HRMS m/z 328.0789 (M+Na$^+$), calcd $C_{15}H_{15}NO_6Na$ 328.0797; Anal. calcd for $C_{15}H_{15}NO_6$ (305.0899): C, 59.01; H, 4.95; N, 4.59. Found: C, 59.12; H, 4.88; N, 4.65%.


92aia

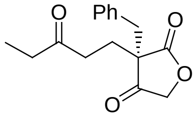
(3*R*)-3-Benzo[1,3]dioxol-5-ylmethyl-3-(3-oxo-butyl)-furan-2,4-dione (92aia): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp.: 114 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/ethanol = 80:20, flow rate 1.0 mL/min, λ = 220 nm), t_R = 17.7 min (major), t_R = 26.0 min (minor); ee = 8%.; IR (neat): ν_{max} 2944, 1749, 1717, 1492, 1447, 1250, 1224, 1040, 928 and 814 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.69 (1H, d, *J* = 8.0 Hz), 6.58-6.55 (2H, m), 5.93 (2H, s, OC*H*$_2$O), 4.42 (1H, d, *J* = 16.4 Hz), 3.69 (1H, d, *J* = 16.8 Hz), 2.98 (2H, ABq, *J* = 9.6 Hz), 2.58-2.53 (2H, m), 2.18-2.11 (1H, m), 2.13 (3H, s, CH$_3$), 2.09-2.03 (1H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 210.0 (C, *C*=O), 207.2 (C, *C*=O), 176.2 (C, O-*C*=O), 147.8 (C), 147.2 (C), 127.2 (C), 122.9 (CH), 109.9 (CH), 108.5 (CH), 101.2 (CH$_2$, O*C*H$_2$O), 73.4 (CH$_2$), 54.2 (C), 42.7 (CH$_2$), 37.7 (CH$_2$), 29.8 (CH$_3$), 28.1 (CH$_2$); LCMS m/z 303.10 (M-H$^+$), calcd $C_{16}H_{16}O_6$ 304.0947; HRMS m/z 327.0834 (M+Na$^+$), calcd

$C_{16}H_{16}O_6Na$ 327.0845; Anal. calcd for $C_{16}H_{16}O_6$ (304.0947): C, 63.15; H, 5.30. Found: C, 63.25; H, 5.28%.



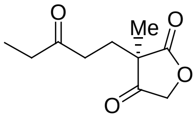
92ay'a

3-Methyl-3-(3-oxo-butyl)-furan-2,4-dione (92ay'a): Prepared following the procedure **20** or **21** and purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2922, 1756, 1712, 1099 and 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.64 (2H, ABq, *J* = 16.8 Hz), 2.51 (2H, t, *J* = 8.0 Hz), 2.08 (3H, s, CH_3), 2.03-1.91 (2H, m), 1.27 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.0 (C, *C*=O), 207.4 (C, *C*=O), 176.8 (C, O-*C*=O), 72.2 (CH_2), 46.4 (C), 37.2 (CH_2), 29.8 (CH_3), 28.1 (CH_2), 20.0 (CH_3); LCMS m/z 183.10 (M-H$^+$), calcd $C_9H_{12}O_4$ 184.0736; HRMS m/z 207.0630 (M+Na$^+$), calcd $C_9H_{12}O_4Na$ 207.0633.



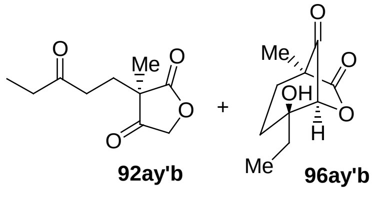
92aab

(3*S*)-3-benzyl-3-(3-oxopentyl)furan-2,4(3*H*,5*H*)-dione (92aab): Prepared following the procedure **20** and purified by column chromatography using EtOAc/hexane and isolated as an oil. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/iso-propanol = 85:15, flow rate 0.25 mL/min, λ = 220 nm), t_R = 48.2 min (minor), t_R = 51.8 min (major); IR (neat): ν_{max} 1799, 1755, 1713, 1078, 1047 and 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27-7.26 (3H, m), 7.10 (2H, d, *J* = 4.4 Hz), 4.38 (1H, d, *J* = 16.8 Hz), 3.49 (1H, d, *J* = 16.8 Hz), 3.06 (2H, ABq, *J* = 12.8 Hz), 2.59-2.48 (2H, m), 2.40 (2H, q, *J* = 7.2 Hz), 2.23-2.06 (2H, m), 1.02 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.0 (C, C=O), 209.8 (C, C=O), 176.2 (C, O-C=O), 133.6 (C), 129.5 (2 x CH), 128.8 (2 x CH), 127.8 (CH), 73.3 (CH_2), 54.2 (C), 43.1 (CH_2), 36.4 (CH_2), 35.8 (CH_2), 28.2 (CH_2), 7.5 (CH_3); LCMS m/z 275.00 (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, 70.18; H, 6.65%.



92ay'b

3-Methyl-3-(3-oxo-pentyl)-furan-2,4-dione (92ay'b): Prepared from amino acid catalysed procedure **20** and purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 1800, 1754, 1711, 1377 and 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.70 (2H, ABq, *J* = 16.8 Hz), 2.54 (2H, t, *J* = 7.6 Hz), 2.41 (2H, q, *J* = 7.2 Hz), 2.12-1.97 (2H, m), 1.33 (3H, s, CH_3), 1.03 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.3 (C, *C*=O), 209.0 (C, *C*=O), 176.8 (C, O-*C*=O), 72.3 (CH_2), 46.6 (C), 36.03 (CH_2), 35.94 (CH_2), 28.3 (CH_2), 20.4 (CH_3), 7.6 (CH_3); LCMS m/z 199.15 (M+H$^+$), calcd $C_{10}H_{14}O_4$ 198.0892; HRMS m/z 221.0787 (M+Na$^+$), calcd $C_{10}H_{14}O_4Na$ 221.0790.

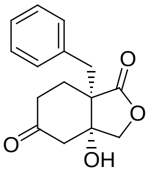


92ay'b **96ay'b**

1:1

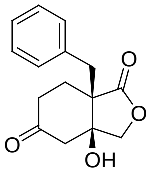
3-Methyl-3-(3-oxo-pentyl)-furan-2,4-dione (92ay'b) and 4-Ethyl-4-hydroxy-1-methyl-6-oxa-bicyclo[3.2.1]octane-7,8-dione (96ay'b): Prepared from the amino acid catalysed procedure and purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2936, 1805, 1758, 1711, 1377 and 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 1:1 mixture of **92ay'b/96ay'b**, data for **96ay'b**) δ 4.35

(1H, s), 2.57-2.53 (2H, m), 2.11-1.97 (2H, m), 1.84-1.73 (2H, m), 1.25 (3H, s), 1.00 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of **92ay'b/96ay'b**, data for **96ay'b**) δ 206.3 (C, *C*=O), 173.6 (C, O-*C*=O), 83.7 (CH), 80.1 (C), 51.2 (C), 35.2 (CH_2), 32.7 (CH_2), 30.4 (CH_2), 11.6 (CH_3), 6.6 (CH_3); LCMS m/z 199.15 ($M+H^+$), calcd $C_{10}H_{14}O_4$ 198.0892.



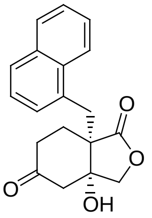
(+)-**93aaa**

(3a*R*,7a*S*)-(+)-7a-benzyl-3a-hydroxytetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (93aaa): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp. 152 °C.; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 80:20, flow rate 0.5 mL/min, λ = 220 nm), t_R = 20.9 min (minor), t_R = 23.8 min (major). **$[\alpha]^{25}_D$ = +16.2 (*c* 0.82, $CHCl_3$, 92% ee);** IR (neat): ν_{max} 3312, 1766, 1710, 1188, 1113, 1033 and 704 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.34-7.26 (5H, m), 3.92 (2H, s), 3.13 (2H, ABq, *J* = 14.0 Hz), 2.64 (2H, ABq, *J* = 15.6 Hz), 2.39 (1H, br s, O-H), 2.26 (2H, t, *J* = 6.4 Hz), 2.14-2.00 (2H, m); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 209.1 (C, *C*=O), 178.6 (C, O-*C*=O), 135.8 (C), 130.7 (2 x CH), 128.3 (2 x CH), 127.2 (CH), 78.5 (C), 74.8 (CH_2), 49.8 (C), 49.2 (CH_2), 37.5 (CH_2), 36.3 (CH_2), 28.3 (CH_2); HRMS m/z 283.0947 ($M+Na^+$), calcd $C_{15}H_{16}O_4Na$ 283.0946; Anal. calcd for $C_{15}H_{16}O_4$ (260.1049): C, 69.22; H, 6.20. Found: C, 69.15; H, 6.25%.



(–)-**93aaa**

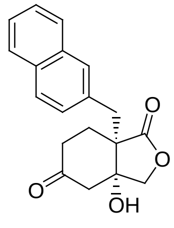
(3a*S*,7a*R*)-(+)-7a-benzyl-3a-hydroxytetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (93aaa): Prepared following the procedure **20** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp. 152 °C.; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 80:20, flow rate 0.5 mL/min, λ = 220 nm), t_R = 20.9 min (major), t_R = 23.8 min (minor). **$[\alpha]^{25}_D$ = –14.5 (*c* 1.71, $CHCl_3$, 86% ee)**.



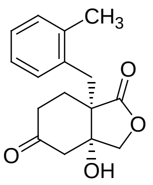
(+)-**93aba**

(3a*R*,7a*S*)-(+)-3a-hydroxy-7a-(naphthalen-1-ylmethyl)tetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (93aba): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp.: 174 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/EtOH = 80:20, flow rate 0.75 mL/min, λ = 220 nm), t_R = 30.6 min (major), t_R = 39.3 min (minor). **$[\alpha]^{25}_D$ = +24.4 (*c* 0.23, $CHCl_3$, 81% ee);** IR (neat): ν_{max} 3398, 1743, 1723, 1405, 1196, 1159, 1014 and 781 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.19 (1H, d, *J* = 8.4 Hz), 7.85 (1H, d, *J* = 8.4 Hz), 7.76 (1H, d, *J* = 8.4 Hz), 7.54-7.37 (4H, m), 4.23 (1H, d, *J* = 9.6 Hz), 4.00 (1H, d, *J* = 9.6 Hz), 3.67 (2H, ABq, *J* = 14.8 Hz), 3.04 (2H, s), 2.22-2.07 (2H, m), 2.02-1.89 (2H, m); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 209.1 (C, *C*=O), 178.5 (C, O-*C*=O), 133.8 (C), 132.9 (C), 132.1 (C), 129.2 (CH), 128.8 (CH), 128.0 (CH), 126.0 (CH), 125.5 (CH), 125.0 (CH), 123.8 (CH), 78.6 (C), 74.6 (CH_2), 49.9 (C), 48.9 (CH_2), 36.5 (CH_2), 31.6 (CH_2), 27.5 (CH_2); HRMS m/z

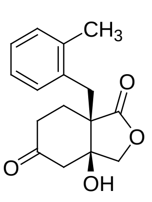
333.1119 (M+Na$^+$), calcd $C_{19}H_{18}O_4Na$ 333.1103; Anal. calcd for $C_{19}H_{18}O_4$ (310.1205): C, 73.53; H, 5.85. Found: C, 73.64; H, 5.80%.


(+)-**93aca**

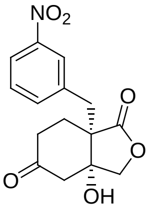
(3a*R*,7a*S*)-(+)-3a-hydroxy-7a-(naphthalen-2-ylmethyl)tetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (93aca): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 144 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/*i*-PrOH = 60:40, flow rate 0.5 mL/min, λ = 220 nm), t_R = 42.8 min (minor), t_R = 101.4 min (major). **$[\alpha]^{25}_D$ = +10.6 (*c* 0.34, $CHCl_{3,}$ 70.2% ee);** IR (neat): ν_{max} 3431, 3324, 1769, 1708, 1098 and 1014 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 7.79-7.76 (4H, m), 7.50-7.44 (3H, m), 3.93 (2H, ABq, *J* = 9.2 Hz), 3.36 (1H, d, *J* = 14.0 Hz), 3.24 (1H, d, *J* = 14.0 Hz), 2.64 (2H, ABq, *J* = 15.2 Hz), 2.27-2.24 (2H, m), 2.19-2.12 (1H, m), 2.07-2.02 (1H, m); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 209.1 (C, *C*=O), 178.9 (C, O-*C*=O), 133.4 (C), 133.1 (C), 132.3 (C), 129.4 (CH), 128.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.0 (CH), 125.7 (CH), 78.2 (C), 74.8 (CH_2), 49.9 (CH_2), 48.7 (C), 37.4 (CH_2), 36.2 (CH_2), 28.1 (CH_2); LCMS m/z 293.15 (M+H$^+$-H_2O), calcd $C_{19}H_{18}O_4$ 310.1205; Anal. calcd for $C_{19}H_{18}O_4$ (310.1205): C, 73.53; H, 5.85. Found: C, 73.61; H, 5.80%.


(+)-**93au'a**

(3a*R*,7a*S*)-(+)-3a-hydroxy-7a-(2-methylbenzyl)tetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (**93au'a):** Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 160 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, λ = 220 nm), t_R = 91.9 min (minor), t_R = 98.9 min (major); **$[\alpha]^{25}_D$ = +2.8 (*c* 0.666, $CHCl_{3,}$ 60.4% ee);** IR (neat): ν_{max} 3324, 1777, 1711, 1102 and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (1H, d, *J* = 6.4 Hz), 7.18-7.13 (3H, m), 4.15 (1H, d, *J* = 9.2 Hz), 4.02 (1H, d, *J* = 9.2 Hz), 3.54 (1H, br s, O-H), 3.19 (2H, ABq, *J* = 14.4 Hz), 2.70 (2H, ABq, *J* = 15.6 Hz), 2.36 (3H, s, CH_3), 2.33-2.28 (2H, m), 2.14-2.11 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.9 (C, *C*=O), 177.9 (C, O-*C*=O), 137.2 (C), 133.7 (C), 131.2 (CH), 130.9 (CH), 127.4 (CH), 125.9 (CH), 79.5 (C), 74.5 (CH_2), 49.7 (C), 49.6 (CH_2), 36.5 (CH_2), 33.3 (CH_2), 27.9 (CH_2), 19.9 (CH_3); LCMS m/z 275.15 (M+H$^+$), calcd $C_{16}H_{18}O_4$ 274.1205; HRMS m/z 297.1103 (M+Na$^+$), calcd $C_{16}H_{18}O_4Na$ 297.1103; Anal. calcd for $C_{16}H_{18}O_4$ (274.1205): C, 70.06; H, 6.61. Found: C, 70.12; H, 6.67%.

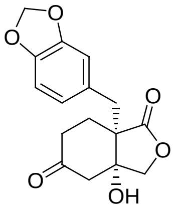

(–)-**93au'a**

(3a*S*,7a*R*)-(–)-3a-hydroxy-7a-(2-methylbenzyl)tetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (**93au'a):** Prepared following the procedure **20** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 160 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, λ = 220 nm), t_R = 91.9 min (major), t_R = 98.9 min (minor); **$[\alpha]^{25}_{D}$ = –2.5** (***c*** **0.2, $CHCl_3$, 50.0% ee**).



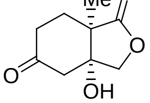
(+)-**93aoa**

(3a*R*,7a*S*)-(+)-3a-hydroxy-7a-(3-nitrobenzyl)tetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (93aoa): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 146 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/ethanol = 80:20, flow rate 1.0 mL/min, λ = 220 nm), t_R = 13.9 min (minor), t_R = 19.5 min (major). **$[\alpha]^{25}_{D}$ = +14.4 (*c* 0.833, $CHCl_3$, 65% ee);** IR (neat): ν_{max} 3363, 2500, 1761, 1712, 1532, 1353, 1117, 1028, 1008 and 657 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 8.27 (1H, s), 8.15 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 7.6 Hz), 7.55-7.50 (1H, m), 4.02 (1H, d, *J* = 9.2 Hz), 3.95 (1H, d, *J* = 9.2 Hz), 3.37 (1H, d, *J* = 14.0 Hz), 3.15 (1H, d, *J* = 14.0 Hz), 2.70 (2H, ABq, *J* = 15.6 Hz), 2.38-2.29 (2H, m), 2.11-2.03 (2H, m); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 208.4 (C, C=O), 178.4 (C, O-C=O), 147.6 (C), 137.9 (C), 136.9 (CH), 128.8 (CH), 125.4 (CH), 121.8 (CH), 77.4 (C), 74.9 (CH_2), 49.6 (C), 48.8 (CH_2), 36.4 (CH_2), 35.4 (CH_2), 27.4 (CH_2); LCMS m/z 306.15 (M+H$^+$), calcd $C_{15}H_{15}NO_6$ 305.0899; HRMS m/z 328.0804 (M+Na$^+$), calcd $C_{15}H_{15}NO_6Na$ 328.0797; Anal. calcd for $C_{15}H_{15}NO_6$ (305.0899): C, 59.01; H, 4.95; N, 4.59. Found: C, 58.92; H, 4.99; N, 4.52%.



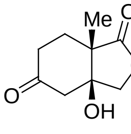
(+)-**93aia**

(3a*R*,7a*S*)-(+)-7a-(1,3-benzodioxol-5-ylmethyl)-3a-hydroxytetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (93aia): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 200 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/ethanol = 70:30, flow rate 1.0 mL/min, λ = 220 nm), t_R = 19.6 min (minor), t_R = 22.7 min (major). **$[\alpha]^{25}_{D}$ = +4.9 (*c* 1.11, $CHCl_3$, 40% ee);** IR (neat): ν_{max} 3372, 1736, 1726, 1493, 1249, 1197 and 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.86 (1H, s), 6.78 (2H, m), 5.95 (2H, s, OC*H*$_2$O), 3.93 (2H, ABq, *J* = 19.2 Hz), 3.09 (2H, ABq, *J* = 14.0 Hz), 2.67 (2H, ABq, *J* = 16.4 Hz), 2.31 (2H, t, *J* = 6.8 Hz), 2.12-2.07 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.5 (C), 178.4 (C), 147.7 (C), 146.9 (C), 129.1 (C), 123.7 (CH), 110.9 (CH), 108.3 (CH), 101.1 (CH_2, O*C*H$_2$O), 79.1 (C), 74.9 (CH_2), 50.0 (C), 49.4 (CH_2), 37.6 (CH_2), 36.2 (CH_2), 28.6 (CH_2); LCMS m/z 305.05 (M+H$^+$), calcd $C_{16}H_{16}O_6$ 304.0947; HRMS m/z 327.0847 (M+Na$^+$), calcd $C_{16}H_{16}O_6Na$ 327.0845; Anal. calcd for $C_{16}H_{16}O_6$ (304.0947): C, 63.15; H, 5.30. Found: C, 63.11; H, 5.34%.

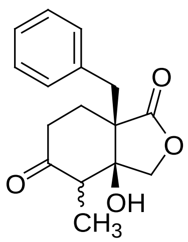


(–)-**93ay'a**

(3a*R*,7a*R*)-3a-Hydroxy-7a-methyl-tetrahydro-isobenzofuran-1,5-dione (93ay'a): Prepared following the procedure **21** and purified by column chromatography using EtOAc/hexane and isolated a solid. Mp 126 °C; The enantiomeric excess (ee) of **93ay'a** was determined via enone product **94ay'a** by chiral stationary phase HPLC analysis as shown below (see preparation of (–)-**94ay'a**); IR (neat): ν_{max} 3434, 1765, 1704, 1096 and 1013 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 4.16 (1H, d, *J* = 9.6 Hz), 4.06 (1H, d, *J* = 9.2 Hz), 3.00 (1H, br s, O-H), 2.64 (2H, ABq, *J* = 15.2 Hz), 2.51-2.32 (2H, m), 2.08-1.97 (2H, m), 1.38 (3H, s, CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 208.4 (C), 180.1 (C), 78.1 (C), 74.9 (CH_2), 47.7 (CH_2), 45.7 (C), 36.0 (CH_2), 30.1 (CH_2), 15.6 (CH_3); LCMS m/z 183.00 (M-H), calcd $C_9H_{12}O_4$ 184.0736; HRMS m/z 207.0624 (M+Na^+), calcd $C_9H_{12}O_4Na$ 207.0633.

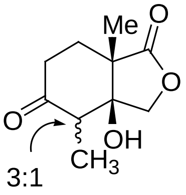

(+)-**93ay'a**

(3a*S*,7a*S*)-3a-Hydroxy-7a-methyl-tetrahydro-isobenzofuran-1,5-dione (93ay'a): Prepared following the procedure **20** and purified by column chromatography using EtOAc/hexane and isolated a solid. Mp 126 °C; The enantiomeric excess (ee) of **93ay'a** was determined via enone product **94ay'a** by chiral stationary phase HPLC analysis as shown below (see preparation of (+)-**94ay'a**); IR (neat): ν_{max} 3434, 1765, 1704, 1096 and 1013 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (three drops)] δ 4.16 (1H, d, *J* = 9.6 Hz), 4.06 (1H, d, *J* = 9.2 Hz), 3.00 (1H, br s, O-H), 2.64 (2H, ABq, *J* = 15.2 Hz), 2.51-2.32 (2H, m), 2.08-1.97 (2H, m), 1.38 (3H, s, CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135] δ 208.4 (C, *C*=O), 180.1 (C, O-*C*=O), 78.1 (C), 74.9 (CH_2), 47.7 (CH_2), 45.7 (C), 36.0 (CH_2), 30.1 (CH_2), 15.6 (CH_3); LCMS m/z 183.00 (M-H), calcd $C_9H_{12}O_4$ 184.0736; HRMS m/z 207.0624 (M+Na^+), calcd $C_9H_{12}O_4Na$ 207.0633.


(–)-93aab

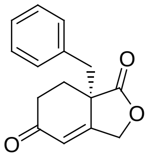
(3a*S*,7a*R*)-(–)-7a-benzyl-3a-hydroxy-4-methyltetrahydro-2-benzofuran-1,5(3*H*,4*H*)-dione (93aab): Prepared following the procedure **20** and purified by column chromatography using EtOAc/hexane and isolated as a solid. The enantiomeric excess (ee) of **93aab** was determined via enone product **94aab** by chiral stationary phase HPLC analysis as shown below (see preparation of (□+)-**94aab**); **[α]$^{25}_{D}$ = –4.2 (*c* 0.5, $CHCl_3$, 86% ee);** IR (neat): ν_{max} 3302, 1762, 1709, 1669, 1188, 1114 and 742 cm^{-1}; ^1H NMR [$CDCl_3$, 1.5:1 mixture of isomers] δ 7.54-7.52 (2H, m), 7.36-7.27 (6H, m), 7.25-7.22 (2H, m), 4.16 (1H, d, *J* = 9.2 Hz), 4.07 (1H, d, *J* = 10.4 Hz), 3.99 (1H, d, *J* = 10.4 Hz), 3.78 (1H, d, *J* = 9.6 Hz), 3.72 (1H, br s, O-H), 3.50 (1H, br s, O-H), 3.37 (1H, d, *J* = 14.0 Hz), 3.25 (1H, d, *J* = 14.4 Hz), 3.20 (1H, d, *J* = 14.0 Hz), 3.00 (1H, d, *J* = 14.0 Hz), 2.83 (1H, q, *J* = 6.8 Hz), 2.69 (1H, q, *J* = 6.4 Hz), 2.44-2.39 (2H, m), 2.27-2.18 (2H, m), 2.15-2.04 (3H, m), 1.80-1.72 (1H, m), 1.14 (3H, d, *J* = 6.4 Hz), 1.12 (3H, d, *J* = 6.8 Hz); ^{13}C NMR [$CDCl_3$, DEPT-135, 1.5:1 mixture of isomers] δ 210.8 (C, *C*=O), 208.9 (C, *C*=O), 179.7 (C, O-*C*=O), 178.1 (C, O-*C*=O), 136.3 (C), 135.2 (C), 130.8 (2 x CH), 130.4 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 127.2 (CH), 82.8 (C), 82.1 (C), 73.4 (CH_2), 72.1 (CH_2), 51.0 (C), 50.3 (C), 49.6 (CH), 48.7 (CH), 39.0 (CH_2), 36.4 (CH_2), 36.3 (CH_2), 35.7 (CH_2), 28.5 (CH_2), 27.7 (CH_2), 7.12 (CH_3), 7.08 (CH_3); LCMS m/z 273.35 (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, 70.12; H, 6.57%.

(3a*S*,7a*S*)-3a-Hydroxy-4,7a-dimethyl-tetrahydro-isobenzofuran-1,5-dione (93ay'b): Prepared following the procedure **20** and purified by column chromatography using

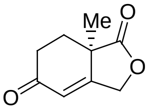

93ay'b

EtOAc/hexane and isolated as a solid. mp 144 °C; The enantiomeric excess (ee) of **93ay’b** was determined via enone product **94ay’b** by chiral stationary phase HPLC analysis as shown below (see preparation of **(+)-94ay’b**); IR (neat): ν_{max} 1666, 1602, 1496, 1381, 1233 and 757 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (three drops), 3:1 mixture of isomers] δ 4.24 (1H, d, *J* = 9.6 Hz), 4.14 (1H, d, *J* = 10.4 Hz), 4.06 (1H, d, *J* = 9.6 Hz), 3.99 (1H, d, *J* = 10.8 Hz), 3.42 (2H, br s, 2 x O-H), 2.75 (1H, q, *J* = 6.8 Hz), 2.63-2.55 (2H, m), 2.42-2.33 (3H, m), 2.31-2.24 (1H, m), 2.06-2.00 (1H, m), 1.94-1.87 (1H, m), 1.84 (1H, dt, *J* = 14.0, 4.0 Hz), 1.45 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.14 (3H, d, *J* = 7.2 Hz), 1.11 (3H, d, *J* = 7.2 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (three drops), DEPT-135, 3:1 mixture of isomers] δ 210.8 (C), 208.8 (C), 180.6 (C), 180.2 (C), 82.0 (C), 80.5 (C), 73.2 (CH_2), 72.6 (CH_2), 49.3 (CH), 49.2 (CH), 47.1 (C), 46.1 (C), 35.9 (CH_2), 35.8 (CH_2), 30.7 (CH_2), 29.5 (CH_2), 18.3 (CH_3), 13.7 (CH_3), 7.5 (CH_3), 6.7 (CH_3); LCMS m/z 199.15 ($M+H^+$), calcd $C_{10}H_{14}O_4$ 198.0892; HRMS m/z 221.0786 ($M+Na^+$), calcd $C_{10}H_{14}O_4Na$ 221.0790.

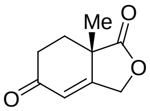
22. **General Procedure for the Hydrolysis of Cascade Michael-Aldol Products:** A solution of bicyclic alcohol compound **93** (0.5 mmol) and *p*-TSA (0.05 mmol) in dry benzene (3.0 mL) was stirred at 80 °C for 1 hr. After cooling, the reaction mixture washed with aqueous sodium bicarbonate solution 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 products **94** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).


(–)-**94aaa**

(7a*S*)-(–)-7a-benzyl-7,7a-dihydro-2-benzofuran-1,5(3*H*,6*H*)-dione(94aaa): Prepared following the procedure **22** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 160 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 29.4 min (minor), t_R = 46.5 min (major). **$[\alpha]^{25}_D$ = –342.7 (*c* 0.566, $CHCl_3$, 92.6% ee);** IR (neat): ν_{max} 2923, 1781, 1674, 1212, 1121, 1029 and 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32-7.31 (3H, m), 7.19-7.16 (2H, m), 6.02 (1H, s, olefinic-*H*), 4.52 (1H, d, *J* = 14.4 Hz), 3.70 (1H, dd, *J* = 14.4, 2.0 Hz), 3.20 (2H, ABq, *J* = 12.8 Hz), 2.76-2.67 (1H, m), 2.61-2.55 (1H, m), 2.41 (1H, dd, *J* = 13.6, 5.2 Hz), 2.14 (1H, dt, *J* = 13.6, 5.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.3 (C, C=O), 177.0 (C, O-C=O), 161.1 (C), 134.3 (C), 129.5 (2 x CH), 128.9 (2 x CH), 128.0 (CH), 123.2 (CH), 69.2 (CH_2), 47.8 (C), 42.2 (CH_2), 32.7 (CH_2), 29.7 (CH_2); LCMS m/z 243.05 ($M+H^+$), calcd $C_{15}H_{14}O_3$ 242.0943; HRMS m/z 265.0841 ($M+Na^+$), calcd $C_{15}H_{14}O_3Na$ 265.0841; Anal. calcd for $C_{15}H_{14}O_3$ (242.0943): C, 74.36; H, 5.82. Found: C, 74.45; H, 5.78%.

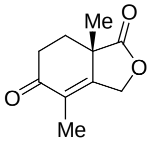

(–)-**94ay'a**

(7a*R*)-(–)-7a-methyl-7,7a-dihydro-2-benzofuran-1,5(3*H*,6*H*)-dione (94ay'a): Prepared following the procedure **22** and purified by column chromatography using EtOAc/hexane and isolated as an oil. The ee was determined by chiral-phase HPLC using a Daicel


(+)-**94ay'a**

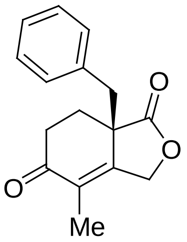
Chiralcel OJ-H column (hexane/ethanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 22.3 min (minor), t_R = 25.9 min (major). **$[\alpha]^{25}_{D}$ = –56.6 (*c* 0.416, $CHCl_3$, 47.4% ee);** IR (neat): ν_{max} 3147, 2684, 1786, 1665, 1638, 1448, 1401 and 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (1H, d, *J* = 0.8 Hz), 5.08 (1H, dd, *J* = 14.4, 2.0 Hz), 4.91 (1H, dd, *J* = 14.4, 0.8 Hz), 2.65-2.51 (2H, m), 2.26 (1H, ddd, *J* = 13.6, 4.8, 2.8 Hz), 2.11 (1H, dt, *J* = 13.2, 6.8 Hz), 1.55 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.3 (C, C=O), 177.4 (C, O-C=O), 161.5 (C), 122.3 (CH), 68.1 (CH_2), 41.3 (C), 32.6 (CH_2), 29.5 (CH_2), 20.8 (CH_3); LCMS 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, 65.12; H, 5.98%.

(*S*)-(+)-7a-methyl-7,7a-dihydro-2-benzofuran-1,5(3*H*,6*H*)-dione (94ay'a): Prepared following the procedure **22** and purified by column chromatography using EtOAc/hexane and isolated as an oil. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/ethanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 22.3 min (major), t_R = 25.9 min (minor). **$[\alpha]^{25}_{D}$ = +20.3 (*c* 0.583, $CHCl_3$, 30.0% ee)**.



(+)-**94ay'b**

(*S*)-(+)-4,7a-dimethyl-7,7a-dihydro-2-benzofuran-1,5(3*H*,6*H*)-dione (94ay'b): Prepared following the procedure **22** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 90 °C; The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column (hexane/ethanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.2 min (major), t_R = 19.2 min (minor). **$[\alpha]^{25}_{D}$ = +129.5 (*c* 0.666, $CHCl_3$, 72% ee);** IR (neat): ν_{max} 1780, 1668, 1353, 1185, 1103 and 1006 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.00 (2H, s), 2.68-2.53 (2H, m), 2.22 (1H, ddd, *J* = 13.2, 5.2, 2.4 Hz), 2.10 (1H, dt, *J* = 13.6, 6.0 Hz), 1.74 (3H, s, CH_3), 1.52 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.5 (C, C=O), 178.2 (C, O-C=O), 154.4 (C), 128.7 (C), 67.2 (CH_2), 41.2 (C), 32.4 (CH_2), 29.4 (CH_2), 21.1 (CH_3), 10.7 (CH_3); HRMS m/z 203.0688 ($M+Na^+$), calcd $C_{10}H_{12}O_3Na$ 203.0684.



(+)-**94aab**

(7a*R*)-(+)-7a-benzyl-4-methyl-7,7a-dihydro-2-benzofuran-1,5(3*H*,6*H*)-dione (94aab): Prepared from the hydrolysis procedure **22** and purified by column chromatography using EtOAc/hexane and isolated as a solid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/ethanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 13.5 min (major), t_R = 23.6 min (minor). **$[\alpha]^{25}_{D}$ = +169.4 (*c* 0.633, $CHCl_3$, 86% ee);** IR (neat): ν_{max} 1772, 1666, 1445, 1361, 1149, 1024 and 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31-7.30 (3H, m), 7.14-7.12 (2H, m), 4.60 (1H, d, *J* = 14.4 Hz), 3.63 (1H, dd, *J* = 14.4, 1.6 Hz), 3.15 (2H, ABq, *J* = 12.8 Hz), 2.81-2.71 (1H, m), 2.60 (1H, ddd, *J* = 18.8, 5.6, 0.8 Hz), 2.37 (1H, ddd, *J* = 13.6, 5.6, 1.2 Hz), 2.13 (1H, dt, *J* = 13.6, 6.0 Hz), 1.73 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.4 (C, *C*=O), 177.7 (C, O-*C*=O), 154.1 (C), 134.6 (C), 129.7 (C), 129.4 (2 x CH), 128.7 (2 x CH), 127.8 (CH), 68.2 (CH_2), 47.6 (C), 42.5

(CH_2), 32.4 (CH_2), 29.4 (CH_2), 10.8 (CH_3); LCMS m/z 257.00 ($M+H^+$), calcd $C_{16}H_{16}O_3$ 256.1099. Anal. calcd for $C_{16}H_{16}O_3$ (256.1099): C, 74.98; H, 6.29. Found: C, 74.85; H, 6.35%.