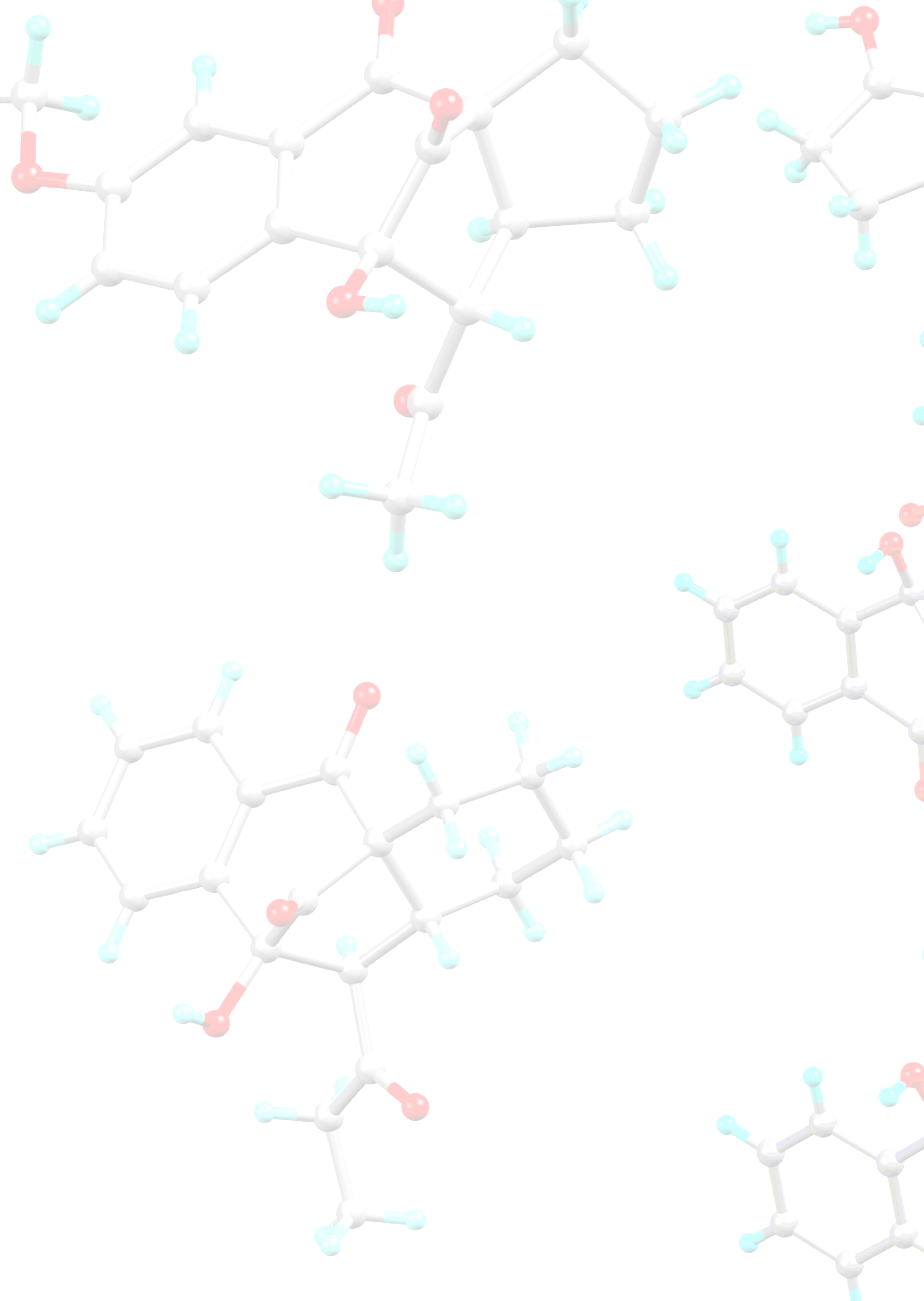


Ph.D
THESIS

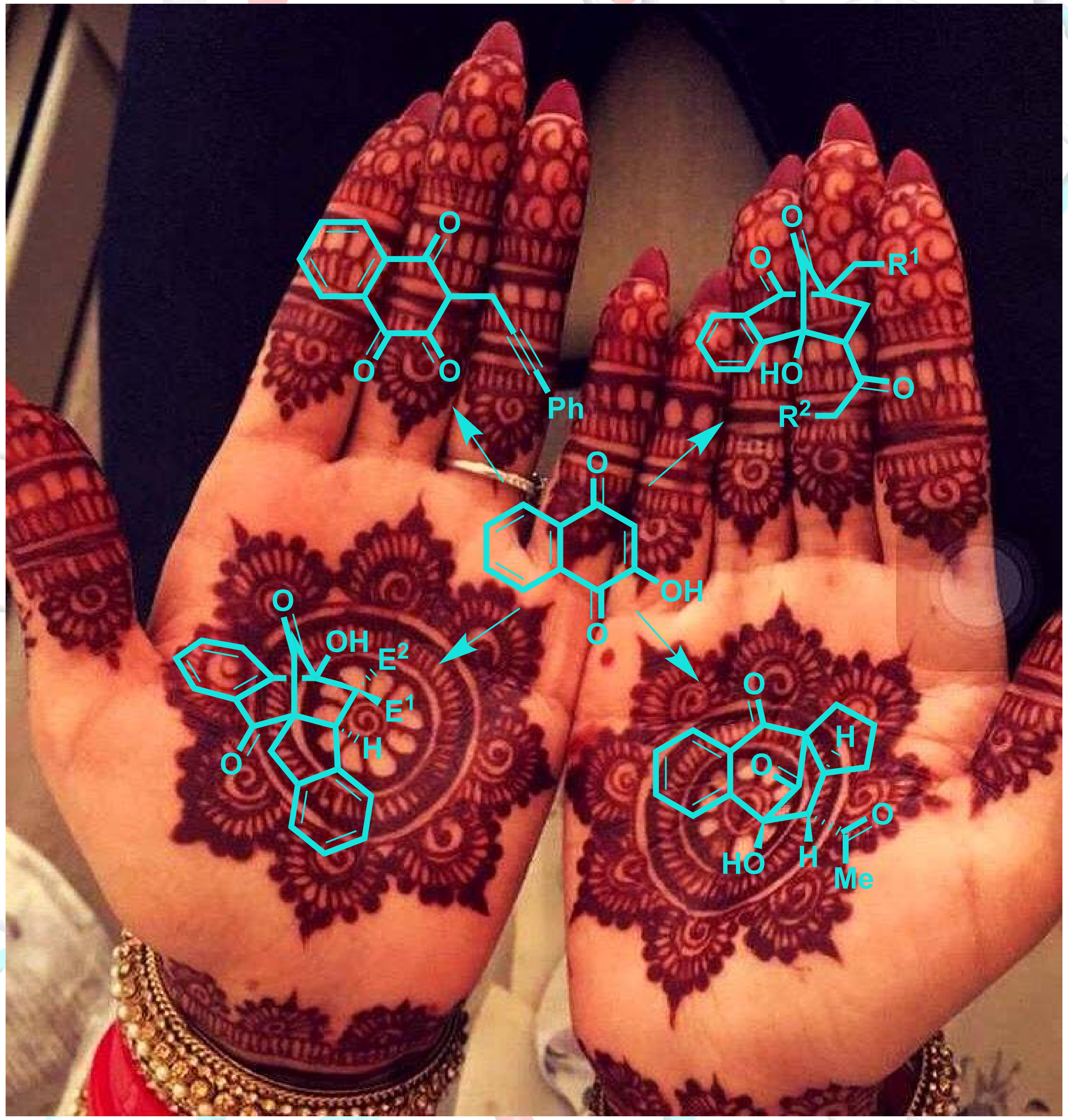
Lawsone as Synthon for the Discovery of
Organocatalytic Reactions

Md. Anif Pasha

Feb
2021

Ph.D. Thesis

Lawsone as Synthon for the Discovery of Organocatalytic Reactions



SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
INDIA

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Lawsone as Synthon for the Discovery of Organocatalytic Reactions

A
Thesis
Submitted for the Degree of

Doctor of Philosophy

By

MOHAMMED ANIF PASHA

(15CHPH29)

प्रतिष्ठित संस्थान
INSTITUTION OF EMINENCE
राष्ट्रीय अपेक्षाएँ, वैश्विक मानक
National Needs, Global Standards

SCHOOL OF CHEMISTRY
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HYDERABAD-500 046, INDIA.

FEBRUARY 2021

Thesis **DEDICATED** *to*

Parents **RAZIYA-ALLAUDDIN**

and

Sister **SHAHANAAZ**

DECLARATION

I hereby declare that the entire work embodied in this thesis entitled as ***"Lawsone as Synthon for the Discovery of Organocatalytic Reactions"*** *is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the guidance of* ***Prof. Dhevalapally B. Ramachary*** *and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted. I hereby agree that my thesis can be deposited in Shodhganga/INFLIBNET. This research work is free from Plagiarism and a report on plagiarism statistics from the University Librarian is enclosed.*

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Certificate

Certified that the work contained in the thesis entitled "**Lawsone as Synthon for the Discovery of Organocatalytic Reactions**" has been carried out by **Mr. Mohammed Anif Pasha** under my supervision and the same has not been submitted elsewhere for a degree.

This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for award of any degree or diploma.

Parts of the thesis have been:

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1. D. B. Ramachary, **Md. Anif Pasha**, and G. Thirupathi, *Angew. Chem. Int. Ed.* **2017**, *56*, 12930
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3. **Md. Anif Pasha**, A. V. Krishna, E. Ashok, D. B. Ramachary, *J. Org. Chem.* **2019**, *84*, 15399.
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2.	CY802	Chemistry Pedagogy (CY502: Advanced Organic Synthesis	3	Pass
3.	CY805	Instrumental Methods A	3	Pass
4.	CY573	Stereoselective Organic Synthesis	2	Pass
5.	CY580	Natural Products and Medicinal Chemistry	2	Pass

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Mohammed Anif Pasha

PREFACE

Lawsone is an important class of structural motifs, which is widely found in numerous natural and synthetic compounds. Lawsone and its isomeric forms are common core structure in biologically and structurally important molecules. Lawsone is the main key ingredient of henna extracts, which is traditionally used as a coloring agent for skin, hair and nails over many decades. Lawsone was used as a synthon for the synthesis of various pharmaceutically and biologically important molecules, lawsone is also used as starting material in a variety of reactions like C/O-alkylation, C-alkylation via the Michael addition, dimerization reactions, free radical alkylation of lawsone, synthesis of C-alkylated derivatives of lawsone by the Hooker oxidation, natural product synthesis, naphthoquinone fused chromone synthesis, xanthene synthesis via O-quinone methide, and heterocyclic compounds synthesis. The present thesis entitled ***"Lawsone as Synthon for the Discovery of Organocatalytic Reactions"*** *describes the utilization of lawsone for organocatalytic reactions to solve some of the problems in the synthetic organic chemistry, which are unsolved over decades and generate biologically, pharmaceutically active scaffolds from the small key intermediates. In all these 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.*

In continuation to the organocatalytic three-component reductive alkylation or reductive coupling reactions developed in our group, the first chapter illustrates an amine-catalyzed three-component reductive coupling protocol for the high-yielding, chemo- and regioselective propargylation on cyclic/acyclic CH-acid systems, which is an unsolved problem in synthetic organic chemistry over decades. It is an economical, efficient, catalytic, metal-free protocol where the variety of CH-acids and propargyl *aldehydes are employed as key ingredients under (S)-proline catalysis. Furthermore, these propargylated cyclic systems were transformed into functionally rich dihydropyrans and C-methylated propargylated cyclic systems, which are prolific synthons in natural products and medicinal chemistry.*

In the second chapter, we developed the 5-(enolexo)-exo-trig cyclization to synthesize pharmaceutically and structurally important bicyclo[3,2,1]octanes particularly methanobenzo[7]annulenes in very good yields with excellent enantio- and diastereoselectivities. To synthesize these skeletons an efficient, green and sustainable protocol is required. Herein, we accomplished those using simple starting materials like lawsone, aldehydes, alkyl vinyl ketones and a catalytic amount of chiral thiourea catalyst. This protocol ensues an unprecedented organocatalytic [3+2] cycloaddition reaction from readily accessible 2-alkyl-3-hydroxynaphthalene-1,4-diones and alkyl vinyl ketones via 5-(enolexo)-exo-trig cyclization. Furthermore, these methonobeno[7]annulens are transformed into functionally rich trihydroxy methanobenzo[7]annulenes.

In continuation to the development of intermolecular 5-(enolexo)-exo-trig cyclization reactions, the third chapter demonstrates the organocatalytic formal intramolecular [3+2]-cycloaddition reaction to accomplish structurally complex methanodibenzo[a,f]azulenes and methanobenzo[f]azulens in good yields with excellent selectivities. The resultant molecules are basic skeletons of important antibiotics and highlight the value of this formal intramolecular [3+2]-cycloaddition as a key protocol. A variety of lawsones, dialdehydes, CH-acids/Wittig reagents are employed as starting materials under the secondary amine-catalysis/self-catalysis. Furthermore, these methonodibenzo[a,f]azulenes are transformed into functionally rich bio-inspired methanobenzo[a,f]azulenes.

In the fourth chapter, we demonstrated the asymmetric synthesis of structurally and biologically important methanobenzo[f]azulenes with high molecular complexity in good yields with excellent enatio- and diastereoselectivities. In this protocol variety of *lawsones, aliphatic dialdehydes and Wittig reagents are employed as key starting materials under the chiral quinine thiourea catalysis. Furthermore, these chiral methonobeno[f]azulenes are transformed into functionally rich bio-inspired chiral methanobenzo[f]azulenes.*

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
Anal.	analysis
aq.	aqueous
Ar	aryl
Bn	benzyl
Bp	boiling point
br	broad
Bu	butyl
*t*Bu or ^{t}Bu	*tertiar*y-butyl
n-BuLi	*n*-butyl lithium
calcd.	calculated
cat.	catalytic
cm	centimeter
CS/H	Claisen-Schmidt/Henry
CS/I	Claisen-Schmidt/isomerisation
CSP	chiral stationary phase
DABCO	1,4-Diazabicyclo[2.2.2]octane
dABq	doublet of AB quartet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
ddd	doublet of doublet of doublet
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DMAP	dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplet
EDG	electron donating group
ee	enantiomeric excess
eq.	equation
equiv.	equivalent(s)
Et	ethyl
EtOH	ethyl alcohol
Et_2O	diethylether
EWG	electron withdrawing group
Fg	functional group
Fig.	figure
gm	gram (s)

h	hour (s)
Hz	hertz
Hex	hexyl
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
^{i}Pr	isopropyl
IR	infrared
$LiAlH_4$	lithium aluminum hydride
lit.	literature
m	multiplet
m-CPBA	*m*-chloro perbenzoic acid
M	molarity
Mp.	melting point
Me	methyl
mg	milligram (s)
mGluR1	metabotropic glutamate receptor 1
mL	milliliter
mmol	millimole
MW	microwave
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
OrgRC	organocatalytic reductive coupling
PCC	pyridinium chlorochromate
PET	positron emission tomography
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
TBHP	tertiary-butyl hydroperoxide
*t*BuOK	Potassium tertiarybutoxide
td	triplet of doublet
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulphonyl
UV	ultraviolet

Lawsone as Synthon for the Discovery of Organocatalytic Reactions

1.0 ABSTRACT

An amino acid-catalyzed three-component reductive coupling protocol has developed for the selective high-yielding synthesis of nearly fifty examples of propargylated cyclic/acyclic systems from the various propargyl aldehydes, cyclic/acyclic CH-acids, and Hantzsch ester at the ambient conditions. It is an economical, efficient, catalytic, metal-free protocol for the rapid gram-scale synthesis of propargylated cyclic/acyclic compounds, and many of these coupling compounds were purified by simple precipitation-filtration technique instead of column chromatography. Functionally rich propargylated cyclic-1,3-diketones were specifically transformed into dihydropyrans found in natural products and drugs through an annulative etherification reaction by using Lewis-acid (AgOTf) catalysis. Further, we developed the *C*-methylation reactions on propargylated cyclic-1,3-diketones, which are prolific synthons in natural products and medicinal chemistry.

In the second chapter, pharmaceutically and structurally important methanobenzo[7]annulenes were synthesized in excellent yields with excellent enantio- and diastereoselectivities through an unprecedented competitive organocatalytic formal [3+2]-cycloaddition or domino Michael/*5-(enolexo)-exo-trig* cyclization from the readily available 2-alkyl-3-hydroxynaphthalene-1,4-diones and alkyl vinyl ketones.

In the third chapter, lawsones were transformed into functionally rich, unique carbon skeleton of methanodibenzo[*a,f*]azulenes and methanobenzo[*f*]azulenes in a

single- or two-pot operation by using five organocatalytic sequential reactions in very good yields with excellent selectivities. These resultant molecules are basic skeletons of important antibiotics and highlight the value of this formal intramolecular [3+2]-cycloaddition as a key protocol.

In the fourth chapter, we demonstrated the asymmetric synthesis of structurally and biologically important methanobenzo[*f*]azulenes with high molecular complexity in good yields with excellent enatio- and diastereoselectivities. In this protocol variety of lawsones, aliphatic dialdehydes and Wittig reagents are employed as key starting materials under the chiral quinine thiourea catalysis. Furthermore, these chiral methonobeno[*f*]azulenes are transformed into functionally rich bio-inspired chiral methanobenzo[*f*]azulenes.

2.0 INTRODUCTION

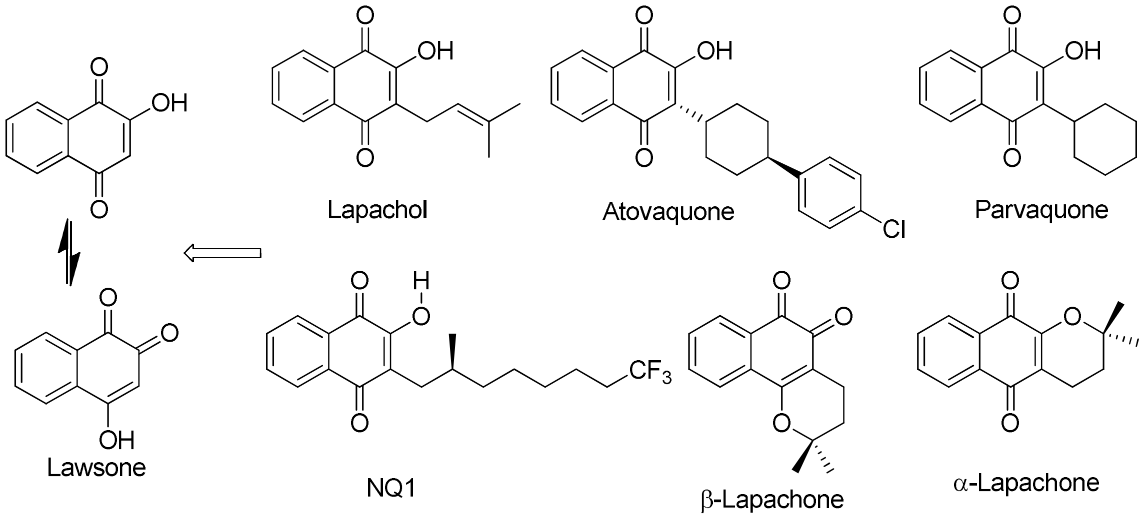


Figure 1: Selected natural compounds containing lawsone as core structure.

Quinones belong to a vital class of structural motifs, which are widely observed in several natural and synthetic compounds. Most of the natural and synthetic compounds with a quinone moiety are very important in several fields of chemistry, biochemistry and medicinal chemistry etc. Furthermore, synthetically or naturally available quinone moieties are possessing a hydroxyl group on quinone ring, namely lawsone and its isomeric forms found as a common core in biologically and structurally important molecules (Figure 1).[1]

Among several naphthoquinones, lawsone is the simplest form of naturally occurring naphthoquinone. Lawsone is also named as 2-hydroxy-1,4-naphthoquinone or hennotannic acid which is responsible for the red-dye pigment properties. The red-orange pigment (natural orange 6) is naturally obtained from the leaves of the henna plant.[1] The red-dye pigmentation properties of henna are due to the chemical reaction of lawsone with keratin protein. Lawsone undergoes Michael addition reaction with the keratin protein in skin, hair, and nails, which results in a dark stain to the hair, skin and nails. The stronger interaction between lawsone and keratin protein resulted in the darker stain for skin, hair and nails and eventually, the darker stain sheds with the decreasing concentration of lawsone.

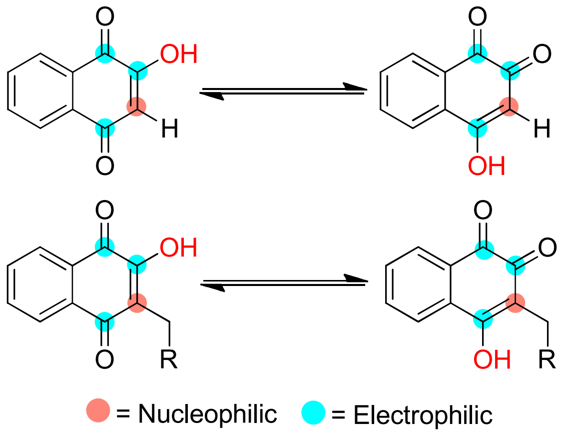


Figure 2: Reactivity pattern of lawsone.

Henna extracts are used as a traditional coloring agent for skin, hair, and nails since early times of humanity. The henna extracts are also used in various platforms like pharmaceutical, cosmetic, cloth dyeing, acts as an antiaging additive to vulcanized natural rubber, oxidation of chlorinated compounds, corrosion inhibition for steel etc. [1]

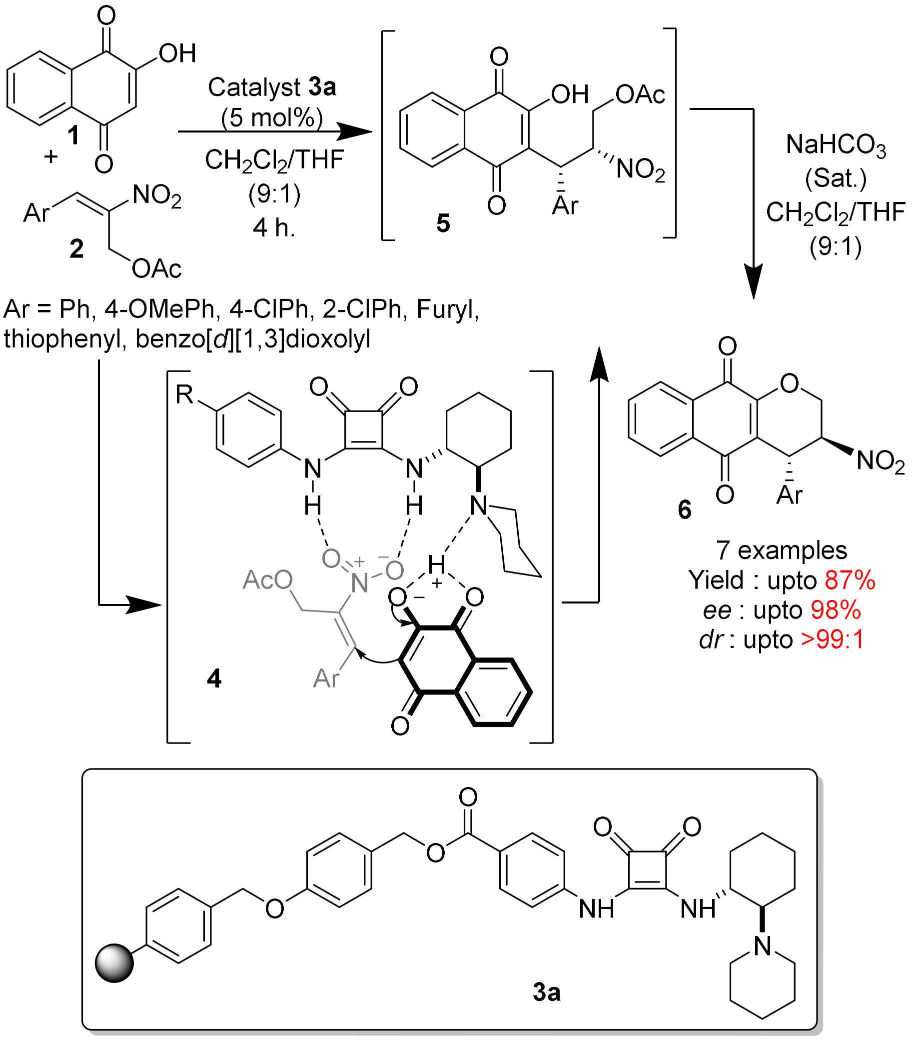
Since the beginning, researchers have been using lawsone as a starting material for the synthesis of various pharmaceutically and biologically important molecules. [1f] Generally, lawsone is functionally rich by having two carbonyl groups and one enolic hydroxyl group which makes lawsone so special among other substrates. Fascinatingly, lawsone acts as a nucleophile from an enolic position either as *O*-nucleophile or as *C*-nucleophile based on the reaction conditions applied, it also acts as an electrophile at carbonyl positions and this reactivity pattern is unaffected even if there is an alkyl/aryl substitution at the C-3 position (Figure 2). Due to this ambident nature of reactivity lawsone is widely used in synthetic organic chemistry.

In the last two decades, researchers are utilizing lawsone in many fields of chemistry such as synthetic, material, biological and pharmaceutical chemistry for the synthesis of important molecules which are of great importance to mankind.[1f] Particularly, lawsone is involved very much in chiral or achiral reactions like *C*/*O*-alkylation, *C*-alkylation *via* the Michael addition, dimerization, free radical alkylation of lawsone, *C*-alkylated derivatives of lawsone by the oxidation, natural product synthesis, naphthoquinone fused chromone synthesis, xanthenes synthesis *via O*-quinone methide, and heterocyclic compounds synthesis.[1f]

As our laboratory is working on the development of chemo-, regio-, enantio- and diastereoselective cycloaddition reactions for the one-pot synthesis of drug-like molecules through asymmetric organocatalysis, and in this thesis also reported the asymmetric reactions developed from the lawsone as starting material. To give the overview of lawsone reactivity, herein, we summarized the previous few selected research work where lawsone is utilized as a starting material for the asymmetric organo-metal/organocatalyzed reactions.

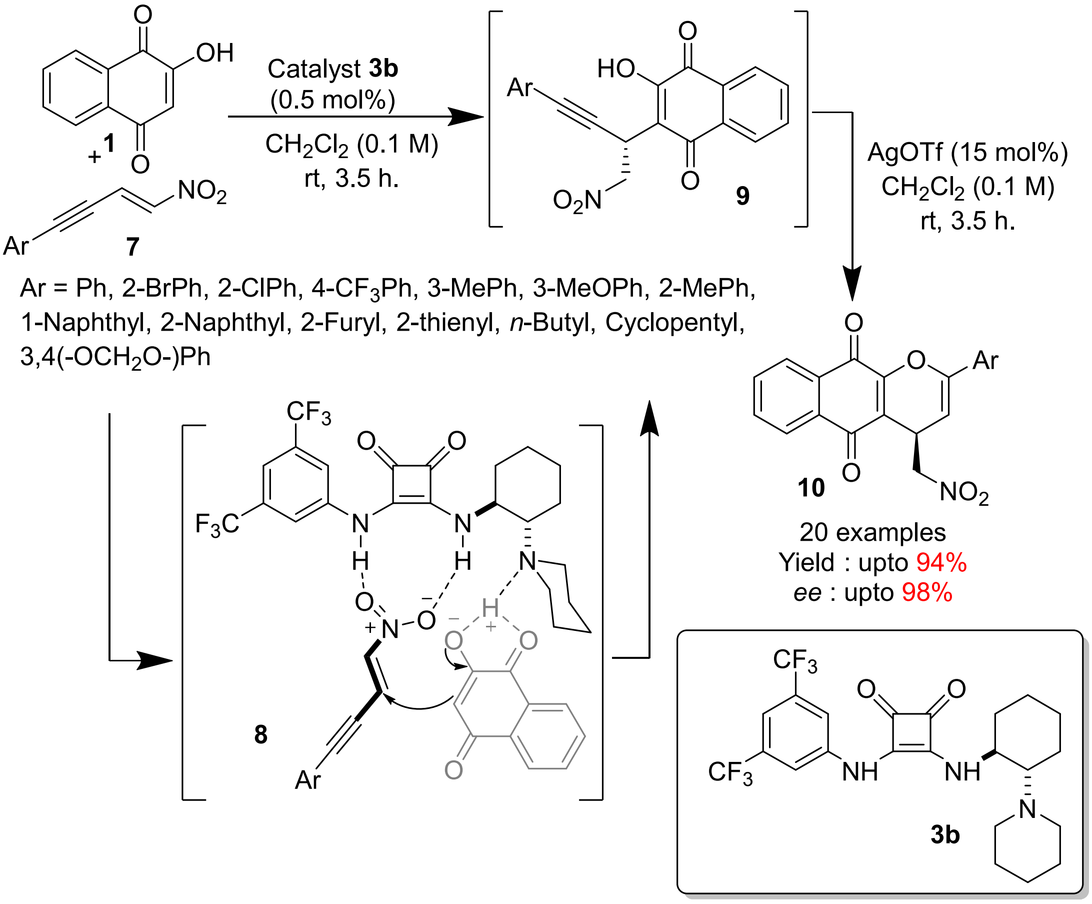
2.1: Previous Asymmetric Reactions Developed from the Lawsone:

In 2016, Pericas and co-workers adopted the flow technique for the asymmetric synthesis of pyranonaphthoquinone **6** through Michael addition on hydroxynaphthoquinone **1** with nitroalkene **2** (Scheme 1).[2a] In this protocol, the authors prepared a column in which polystyrene-supported squaramide catalyst **3a** was used. The solution of reactants and the solvents were passed through their respective channels which are connected to the polystyrene-supported squaramid catalyst **3a** column. Herein, the reaction was performed with 4.5 mmol of nitroalkene **2**, 1.1 equiv. of hydroxynaphthoquinone **1** and an optimal amount of catalyst **3a** (3.2 μmol, 5 mol%) was used in DCM/THF (9:1) solvent system with 0.2 mL/min flow rate. Furthermore, the second *oxa*-Michael cyclization reaction was performed with the out-stream collected in the prior transformation. It was directly used for the successive *oxa*-Michael cyclization reaction. Herein, saturated aq. $NaHCO_3$ solution was connected to the flow system and a 10 mL coil (ϕ = 0.8 mm, PTFE) as a reactor with a flow rate of 0.45 mL/min. Finally, high yields of pyranonaphthoquinone **6** with an excellent enantio- and diastereoselectivity were formed from the intermediate Michael adduct **5**. Furthermore, the squaramide **3a** initially interacts with nitroalkene **2** through two hydrogen bonds and the tertiary amine part of the catalyst activates the hydroxynaphthoquinone **1**. Consequently, as depicted in the *pre*-transition state **4**, lawsone **1** and nitroalkene **2** undergoes a *Si,Si*-facial attack and results in (2*S*,3*R*)-intermediate **5**, which is further converted into functionally rich pyranonaphthoquinones **6** (Scheme 1).[2a]



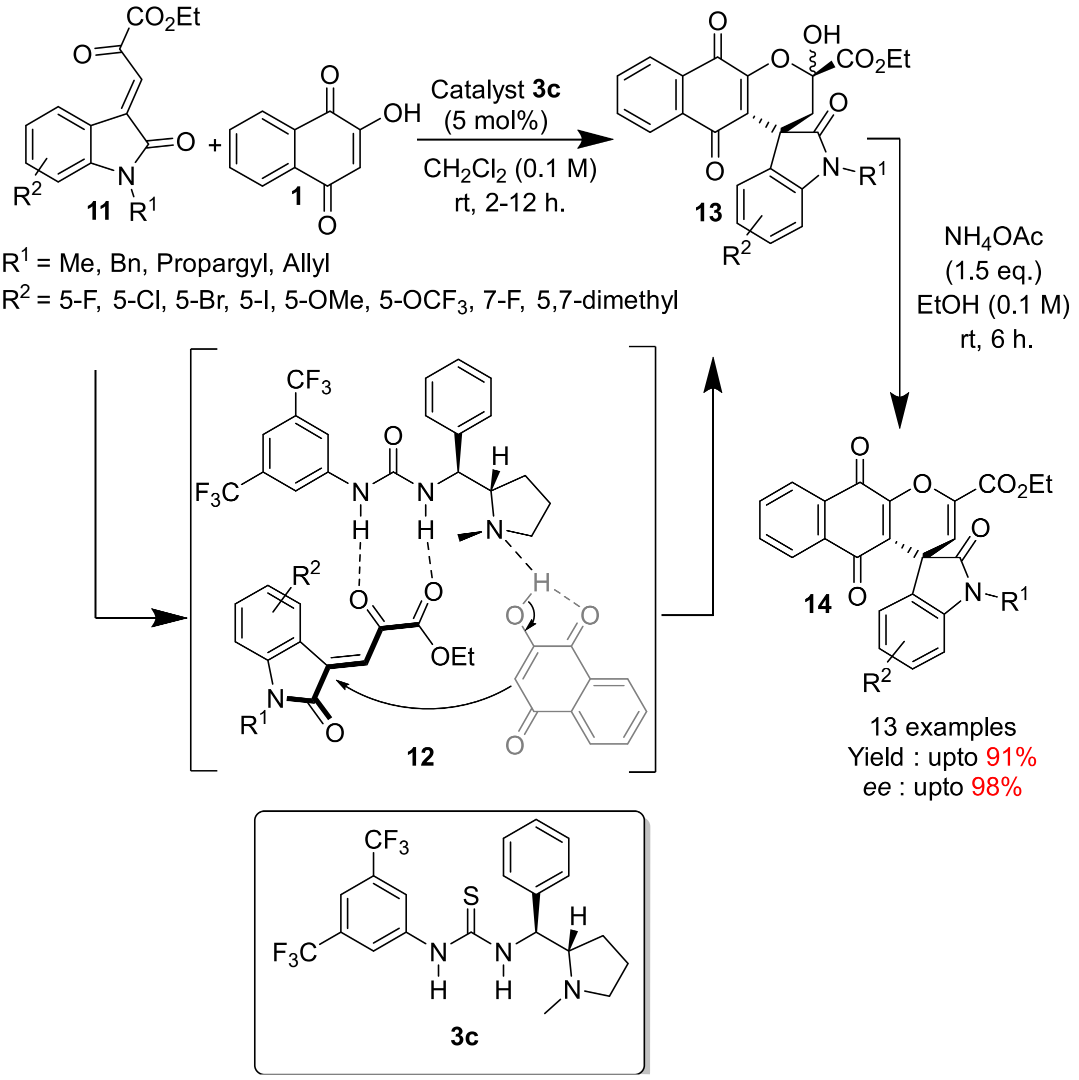
Scheme 1: Pericas's protocol for the synthesis of chiral pyranonaphthoquinone **6** from the lawsone.

Successively, Enders and co-workers in 2016 reported the enantioselective synthesis of pyranonaphthoquinones **10**, using hydroxynaphthoquinones **1** and alkyne-nitroalkene **7** in the presence of chiral bifunctional tertiary squaramide **3b** and AgOTf catalysts (Scheme 2).[2b] Initially, the hydroxynaphthoquinone **1** was treated with alkyne-nitroalkene **7** in DCM (0.2 M) solvent under the influence of chiral bifunctional tertiary amine squaramide catalyst **3b** (0.5 mol%) which furnishes the required Michael adduct **9** in high yield with excellent enantioselectivity.



Scheme 2: Enders protocol for the synthesis of pyranonaphthoquinones **10** from lawsone.

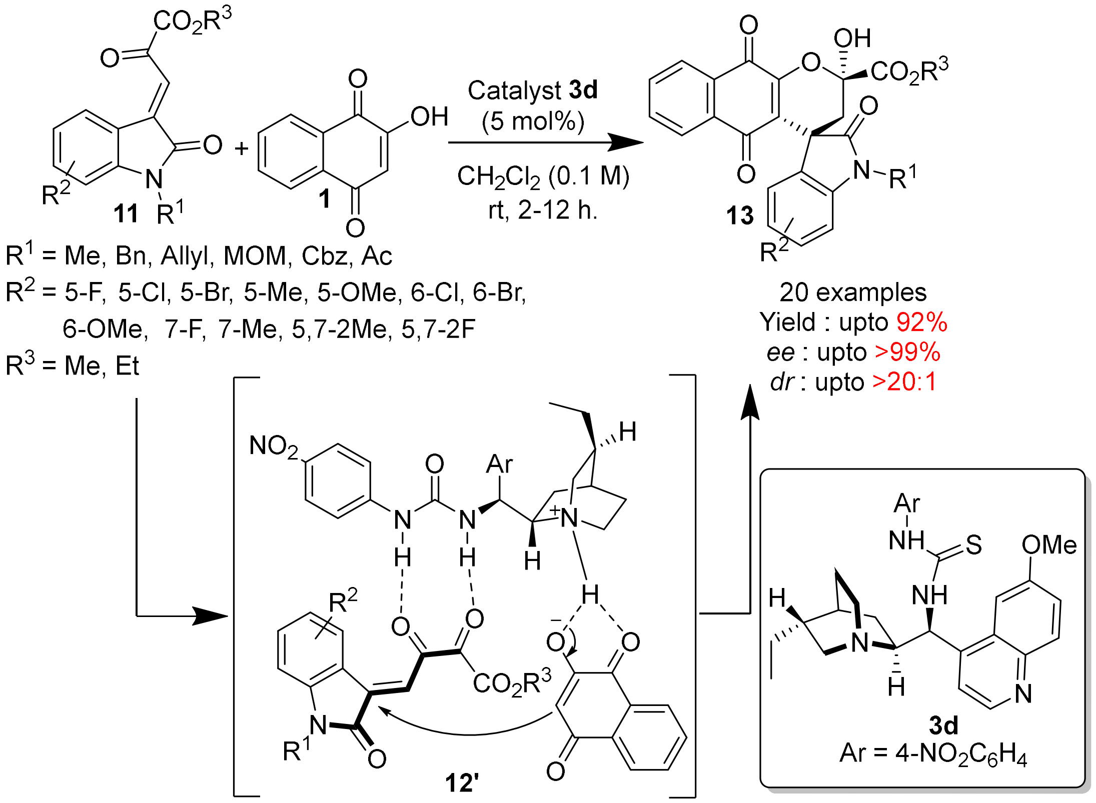
The formed Michael adduct **9** upon subsequent reaction with 15 mol% AgOTf in DCM undergoes hydroalkoxylation through the π-activation of the alkyne by silver metal and generates exclusively *6-endo-dig*-product **10**. In the catalytic cycle, chiral bifunctional tertiary amine catalyst **3b** synergistically interacts with alkyne-nitroalkene **7** by squaramide-*NH* through a double hydrogen bond and hydroxynaphthoquinone **1** interacts with tertiary amine part of the catalyst. Finally the favoured *Re,Re*-facial attack takes place to generate enantiomerically rich Michael adduct **9**. The alkyne group of Michael adduct **9** interacts with the silver catalyst through electrophilic activation which facilitates the *6-endo-dig* cyclization, resulted in pyranonaphthoquinone **10** in high yields with excellent enantioselectivity (Scheme 2).



Scheme 3: Kesavan's approach for the synthesis of chiral spiro-oxindole naphthoquinones **14** from lawsone.

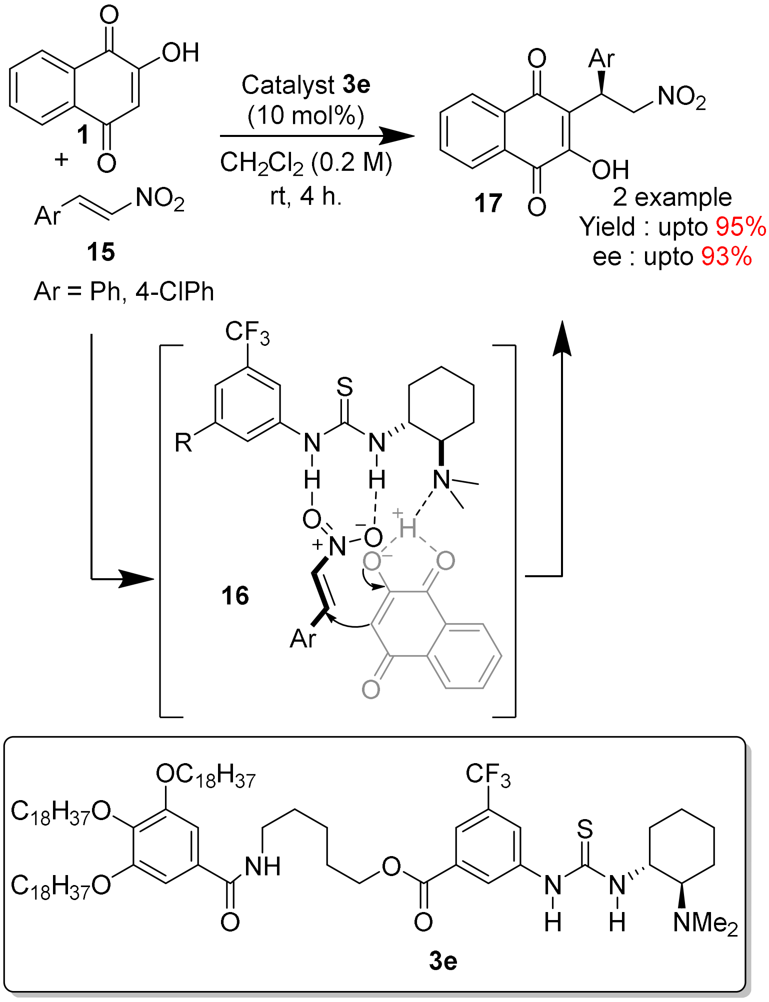
In 2016, Kesavan and co-workers elegantly explained an enantioselective organocatalytic synthesis of spiro-oxindole naphthoquinones **14** by reacting hydroxy naphthoquinone **1** with ketoester **11**, through a sequence of Michael/hemiketalization reactions using (*S*)-proline derived chiral bifunctional tertiary amine thiourea catalyst **3c** (Scheme 3).[2c] Herein, the authors performed a reaction with 1.0 equiv. of both hydroxyl naphthoquinone **1** and oxindole ketoester **11** in the presence of an optimal amount of chiral bifunctional tertiary amine thiourea catalyst **3c** in DCM solvent, results in the formation of a spiro-oxindole naphthoquinone hemiketal **13**, which further reacts with ammonium acetate to generate spiro-oxindole naphthoquinones **14** with excellent yields and enantioselectivity. Furthermore, as depicted in the *pre*-transition state **12**, oxindole ketoester **11** interacts with thiourea-*NH* through double hydrogen bond and hydroxynaphthoquinone **1** interacts with the tertiary amine part of the catalyst. Finally, the *Re* face of the oxindole ketoester **11** approaches the *Re* face of the hydroxyl naphthoquinone **1**. As a result of this approach, *Re,Re*-facial attack takes place to generate spiro-oxindole naphthoquinone **14** in excellent enantioselectivity (Scheme 3).[2c]

Similarly, Wang and co-workers in 2016 described the tandem enantioselective Michael/cyclization reaction between oxindole α-ketoester **11** and hydroxynaphthoquinone **1** using modularly designed cinchona derived thiourea catalyst **3d** to furnish spiro[oxindole-benzo[*g*]chromenedione] **13** in high yields with excellent enatio- and diastereoselectivity (Scheme 4).[2d] Herein, 1.2 equiv. of hydroxynaphthoquinone **1** is treated with 1.0 equiv. of oxindole α-ketoester **11** in the presence of 5 mol% quinine thiourea catalyst **3d** in DCM solvent for 12 h which furnishes spiro[oxindole-benzo[g]chromenedione] **13**. Furthermore, as depicted in the *pre*-transition state **12'** oxindole ketoester interacts with thiourea-*NH* through a double hydrogen bond and hydroxynaphthoquinone **1** interacts with the tertiary amine part of the catalyst. Finally, *Re* face of the oxindole α-ketoester **11** approaches the *Re* face of the hydroxyl naphthoquinone **1.** As a result of this approach *Re,Re*-facial attack takes place to generate spiro[oxindole-benzo[*g*]chromenedione] **13** with excellent enantioselectivity (Scheme 4). [2d]



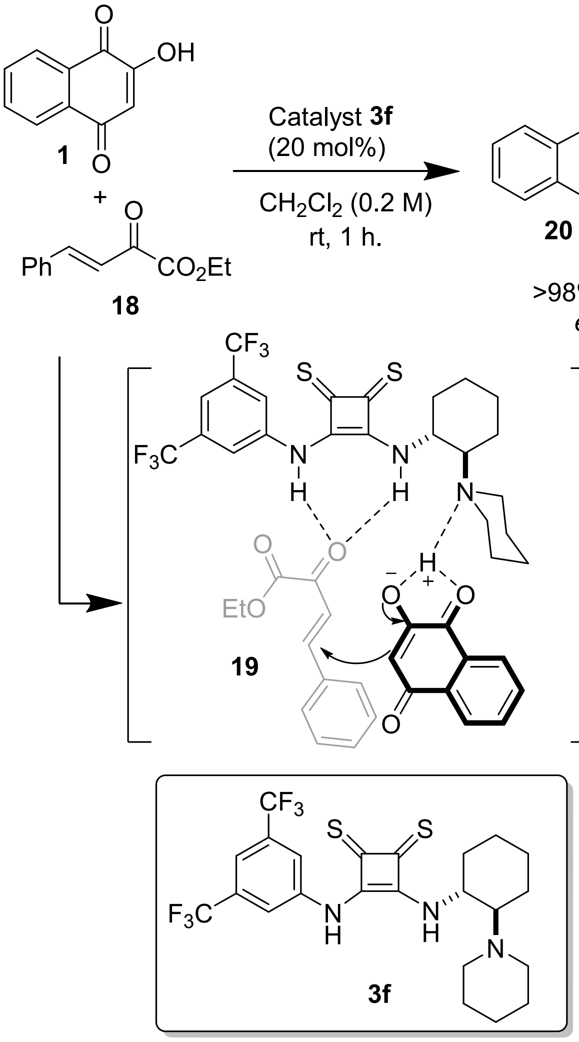
Scheme 4: Wang's approach for the synthesis of chiral spiro-oxindole naphthoquinones **13** from lawsone.

In 2018, Otaka and co-workers elegantly disclosed the use of recyclable thiourea-based chiral tertiary amine catalyst **3e** (Scheme 5).[2e] Herein, the authors developed an asymmetric organocatalyst containing a hydrophobic anchor which contributes to the main characteristics of the recyclable catalyst. Furthermore, this recyclable chiral bifunctional tertiary amine catalyst **3e** is highly soluble in non-polar/less polar solvents and sparingly soluble in polar solvents which shows a comparable performance when compared with the parent catalyst. The authors examined the asymmetric Michael reactions with the prepared recyclable catalyst, the Michael reaction between nitrostyrene **15** and hydroxynaphthoquinone **1** in the presence of 10% of catalyst **3e** in toluene solvent, reaction performed well at 30 °C and delivers the required Michael adduct **17** in good yields with excellent enantioselectivity. As represented in the *pre*-transition state **16**, nitrostyrene **15** interacts with thiourea-*NH* through hydrogen bond and the tertiary amine of the catalyst activates the enolic hydroxyl group of hydroxynaphthoquinone **1**. As a result of this synergistic activation *Re,Re*-facial attack takes place and that leads to high asymmetric induction in Michael adduct **17** (Scheme 5).[2e]



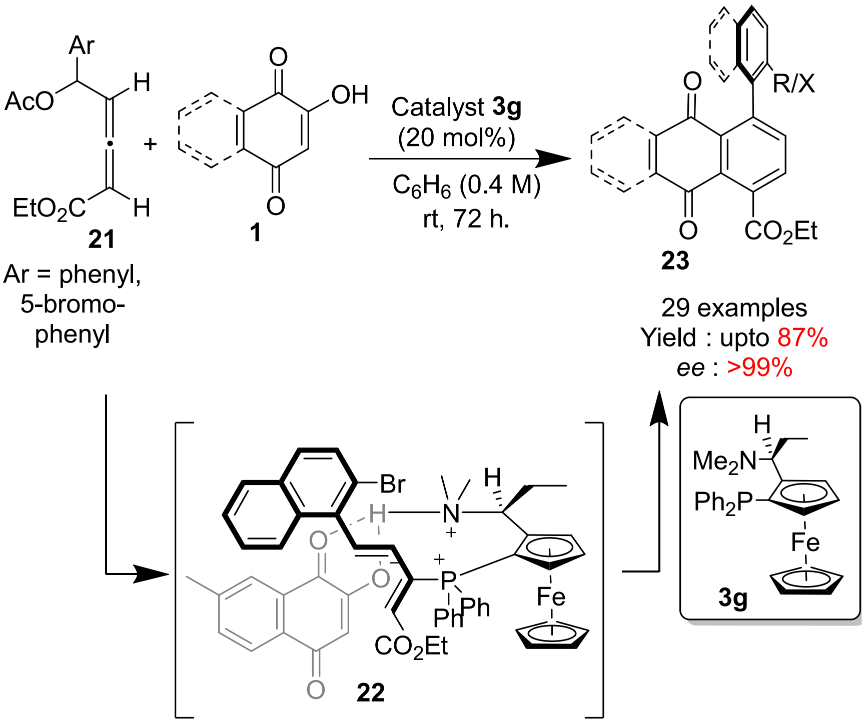
Scheme 5: Otaka's approach for Michael reactions using lawsone.

In 2018, Rawal and co-workers sophisticatedly explained the synthetic route for chiral Michael adduct **20** under the influence of thiosquaramide based chiral tertiary amine **3f** catalyst (Scheme 6).[2f] Herein, the authors developed a synthetic protocol for the tertiary amine thiosquaramide catalysts from dicyclopentyl dithiosquarate, their catalytic performance was demonstrated by several Michael/aza-Diels-Alder reactions.



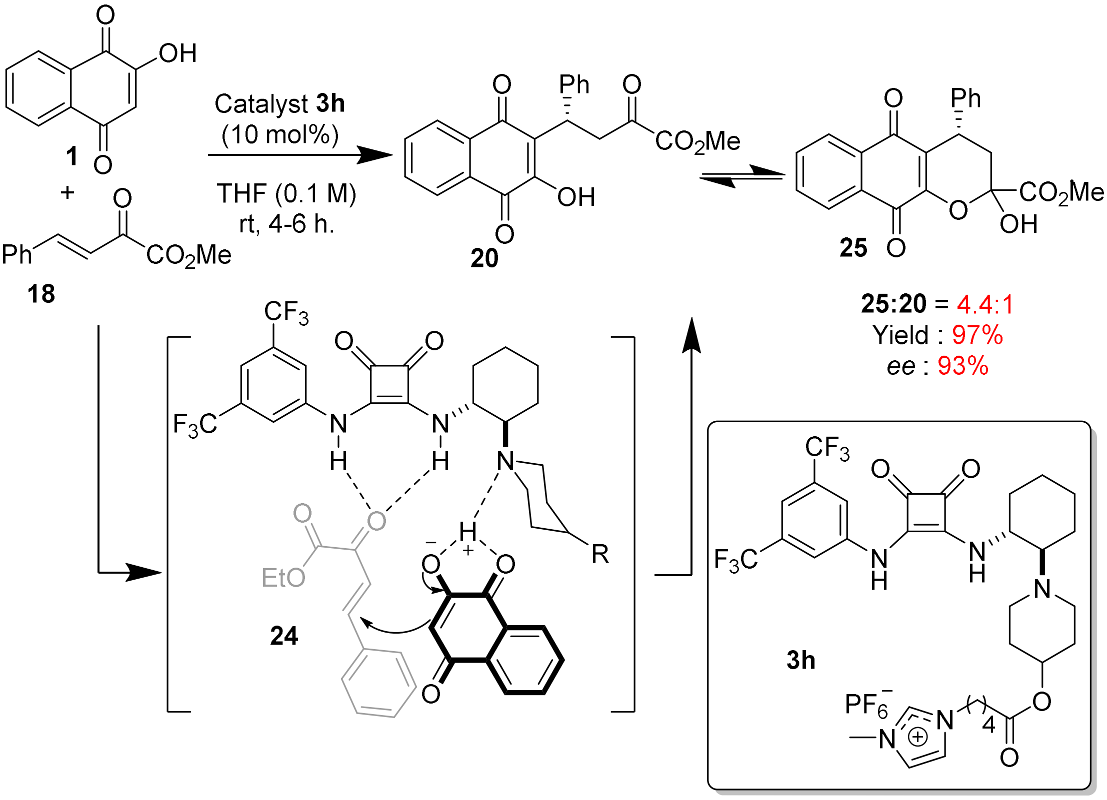
Scheme 6: Rawal's approach of using lawsone for the conjugate addition reaction.

The conjugate addition reaction between hydroxynaphthoquinone **1** and β,γ-unsaturated α-keto ester **18** in the presence of thiosquaramide catalyst **3f** in DCM solvent for 1 h furnishes the conjugate addition product **20** in moderate yields with excellent enantioselectivity. Furthermore, as shown in the *pre*-transition state **19**, *Re*-face of the β,γ-unsaturated α-keto ester **18** approaches the *Si*-face of the hydroxynaphthoquinone **1**, which leads to the *Re,Si*-facial attack to furnish the conjugated products **20** with excellent facial selectivity (Scheme 6).[2f]



***Scheme** 7*: Tong's approach for atroposelective [4+2]-annulation reactions using lawsone.

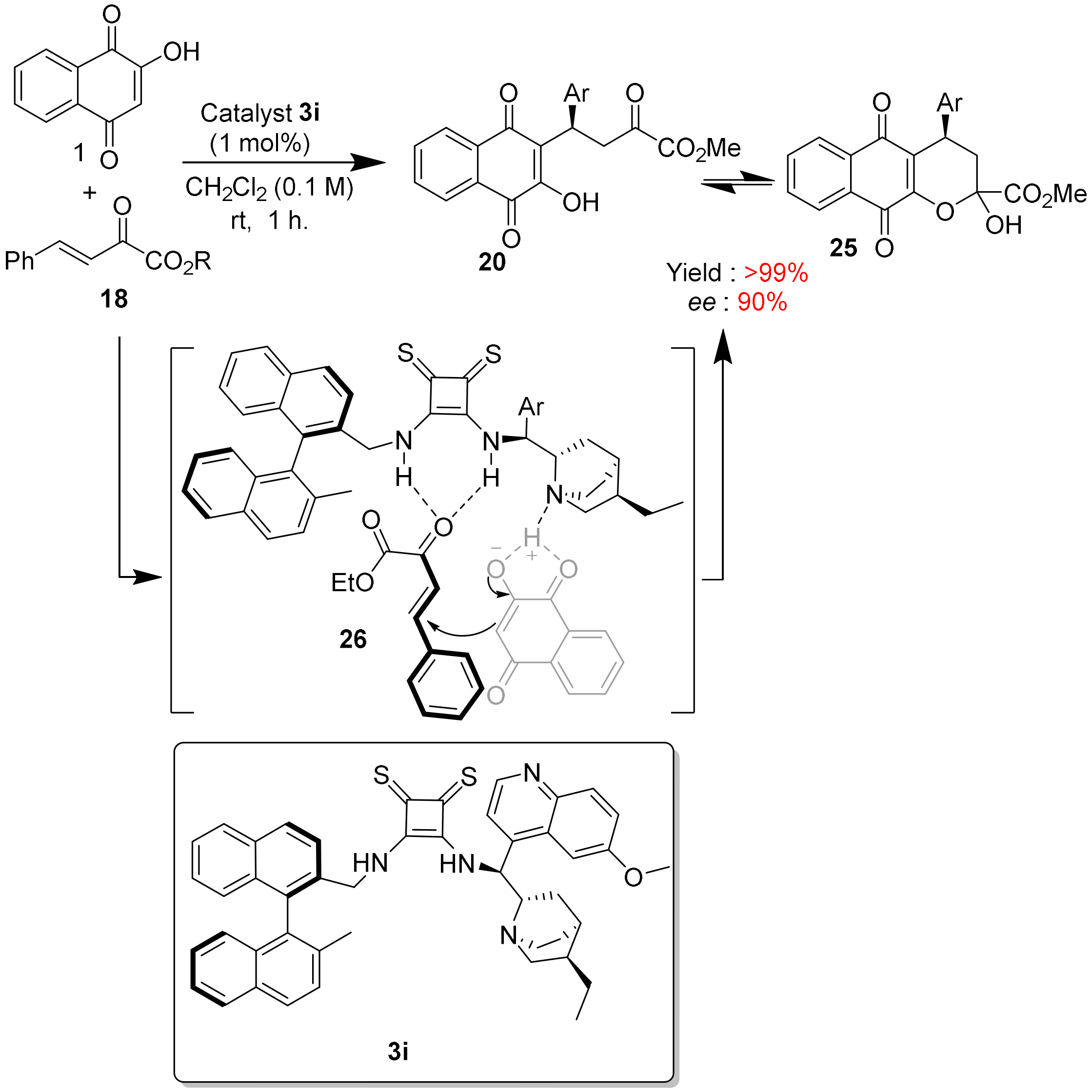
In 2019, Tong and co-workers strikingly described the phosphine-catalyzed atroposelective [4+2]-cycloaddition reactions between hydroxynaphthoquinone **1** and δ-acetoxy allenoates **21** with excellent yields and enantioselectivity (Scheme 7).[2g] Initially, the reaction was performed with commercially available hydroxynaphthoquinone **1** and δ-acetoxyallenoates **21** containing a phenyl group in the presence of PPh_3 catalyst in benzene solvent and the desired product **23** was obtained in moderate yield. After investigating different substituents and a variety of catalysts, the authors found that bromo-phenyl allenoates **21** and catalyst **3g** showed satisfying results. Furthermore, as represented in the *pre*-transition state **22**, the tertiary amine group of the catalyst interacts with hydroxynaphthoquinone **1** and the tertiary phosphine part of the catalyst interacts with allenoates **21**, which leads to the formation of phosphonium diene. Interestingly, the reaction proceeds in a pseudo-intramolecular fashion and generates atroposelective products **23** in moderate to good yields and moderate to excellent enantioselectivity (Scheme 7).[2g]



Scheme 8: Zlotin's approach for asymmetric Michael reaction using lawsone.

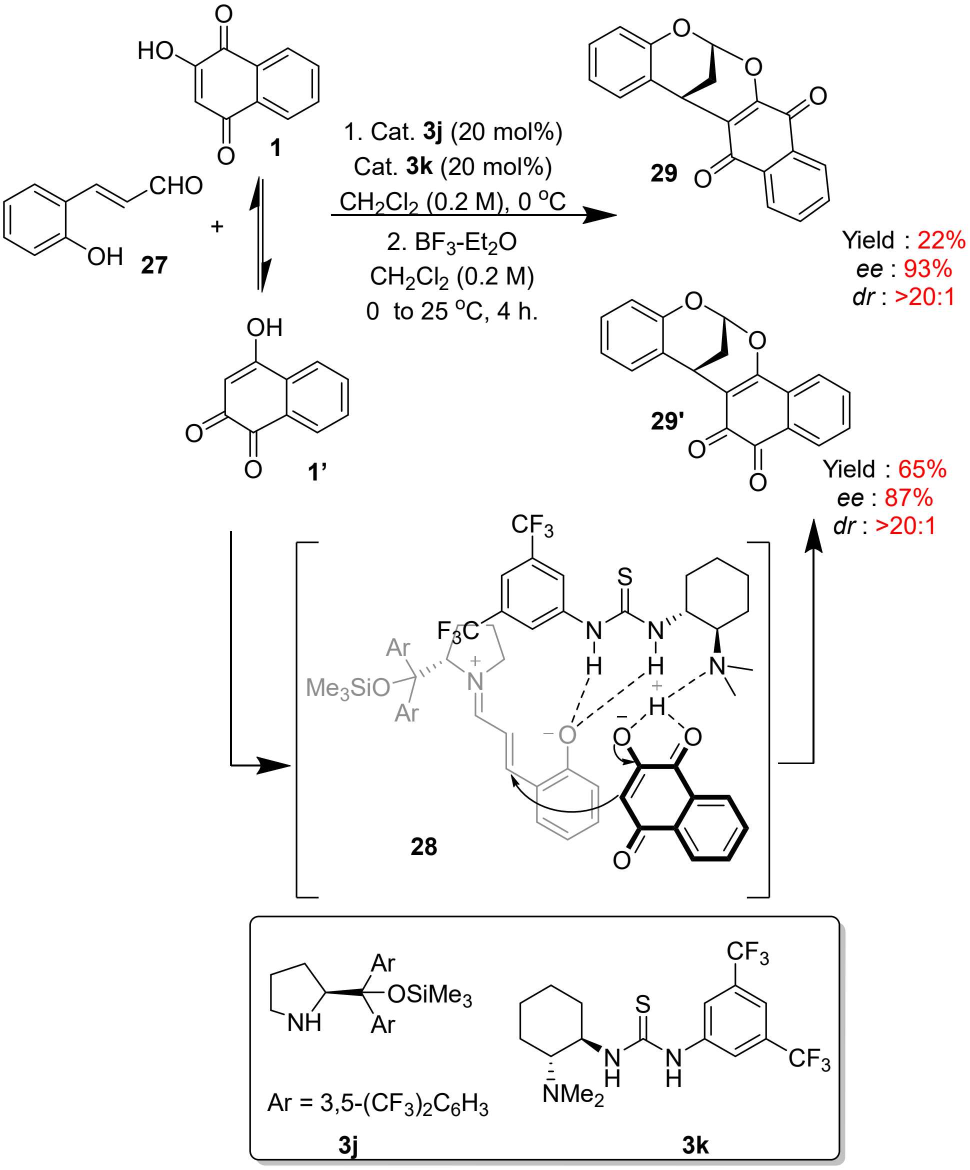
Successively, Zlotin and co-workers in 2019 enlighteningly explained a correlation between the equilibrium ratios of tautomeric products furnished in the asymmetric organocatalytic Michael reaction of hydroxynaphthoquinone **1** with β,γ-unsaturated α-keto ester **18** (Scheme 8).[2h] Particularly, the Michael addition reaction between hydroxynaphthoquinone **1** and β,γ-unsaturated α-keto ester **18** in the presence of squaramide catalyst **3h** in THF for 6 h furnishes the Michael addition product **20** which is in equilibrium with product **25**. Particularly, the higher electron-withdrawing nature of hydroxynaphthoquinone, leads to increase in the nucleophilicity of hydroxyl group of hydroxynaphthoquinone **1** and also increase in the electrophilicity of the carbonyl group in the β,γ-unsaturated α-keto ester **18**, which is the reason for the equilibrium between product **20** and **25**. Furthermore, as shown in the *pre*-transition state **24**, *Re*-face of the β,γ-unsaturated α-keto ester **18** approaches the *Si*-face of the hydroxynaphthoquinone **1**, which leads to the *Re,Si*-facial attack to furnish the Michael products **20** and **25** with excellent facial selectivity (Scheme 8).[2h]

Similarly, Kupai and co-workers in 2019 reported the successful use of binaphthyl-cinchona based thiosquaramide **3i** as a catalyst for asymmetric Michael addition reactions between hydroxynaphthoquinone **1** and β,γ-unsaturated α-keto ester **18** to furnish enantiomerically pure product **20**/**25** using 1.0 mol% catalyst loading in DCM solvent (Scheme 9).[2i] Furthermore, β,γ-unsaturated α-keto ester **18** interacts with squaramide-*NH* through double hydrogen bond and the tertiary amine part of the catalyst activates the hydroxynaphthoquinone **1**. As a result of this substrate-catalyst interactions *Si*,*Re*-facial attacks take place to furnish enantiomerically pure product **20**/**25** (Scheme 9).[2i]



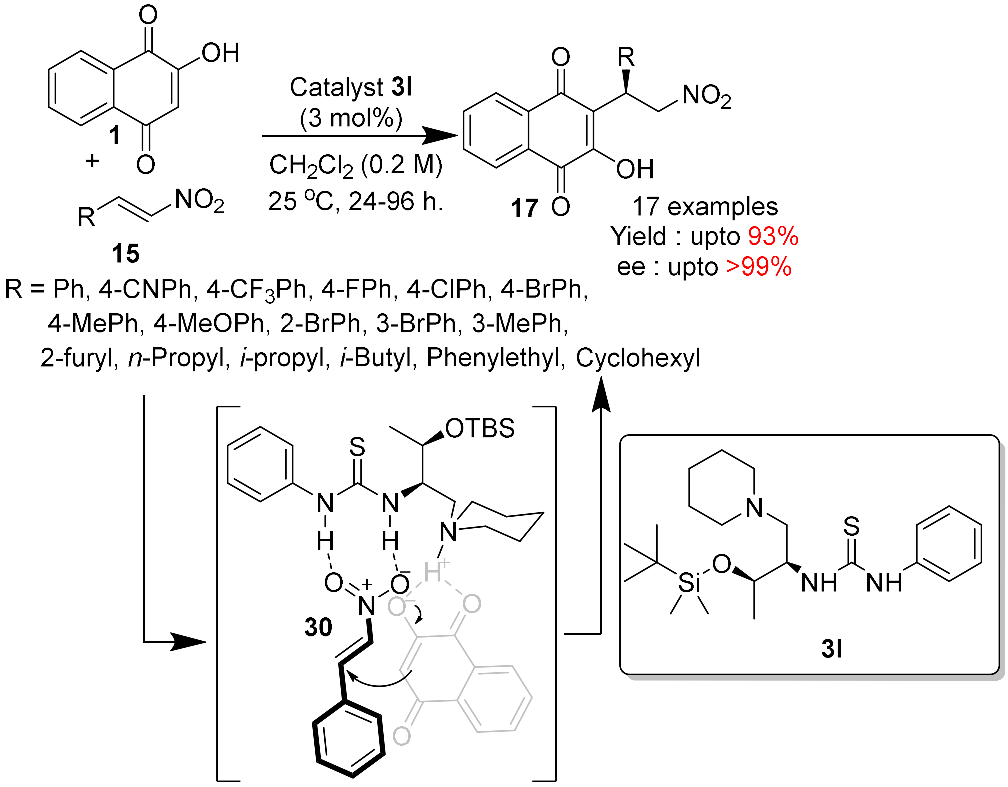
Scheme 9: Kupai's approach for asymmetric Michael addition reaction using lawsone.

Very recently Liu and co-workers successfully utilized the supra-molecular organocatalysis involving tertiary amine thiourea catalysis and iminium catalysis for asymmetric Michael addition and cyclization reactions (Scheme 10).[2k] In their work, 2-hydroxycinnamaldehyde **27** and hydroxynaphthoquinone **1** undergoes Michael addition reaction in the presence of 20 mol% of each **3j** and **3k** in DCM at 0 °C furnishes Michael adduct, which on further treatment with BF_3-Et_2O in DCM results in benzo fused 2,8-dioxabicyclo[3.3.1]nonane **29**/**29'** with moderate yield and good enantioselectivity.



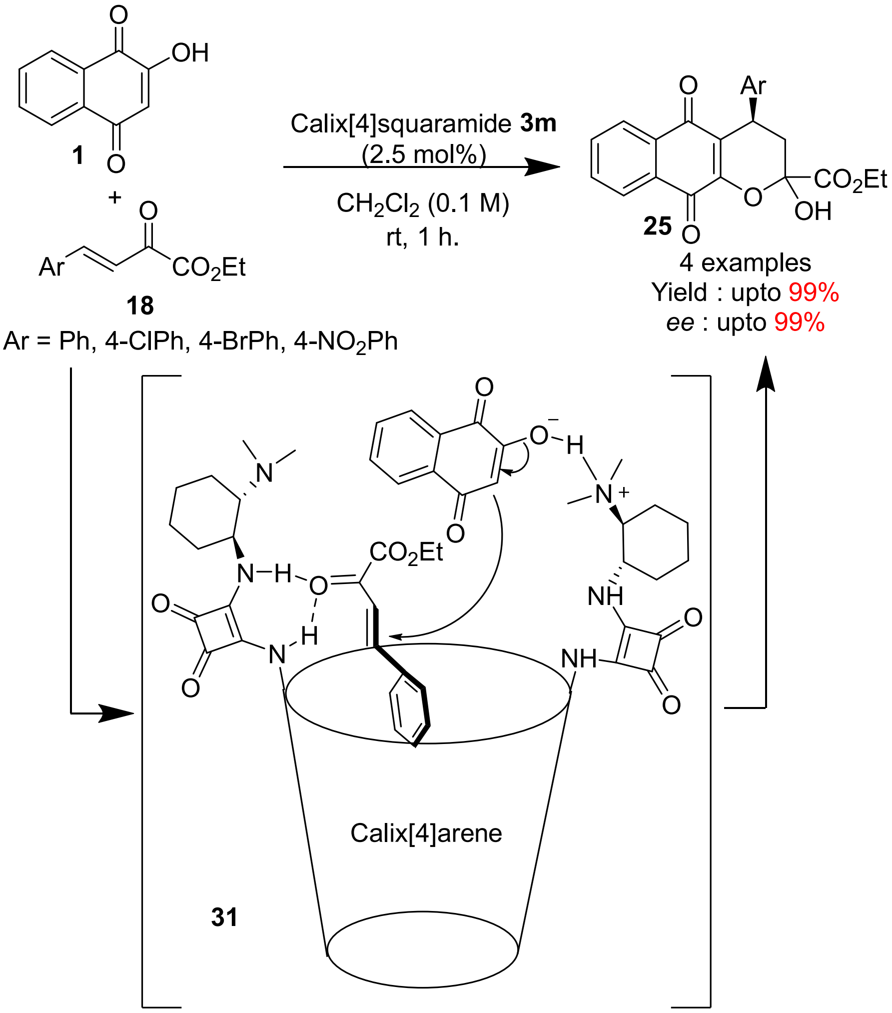
Scheme 10: Liu's approach of Michael addition/cyclization reactions using lawsone.

Furthermore, interaction of catalyst **3j** with 2-hydroxycinnamaldehyde **27** generates the iminium species meanwhile, tertiary amine interacts with hydroxynaphthoquinone **1** and the thiourea-*NH* part of the catalyst co-ordinate with iminium species with a double hydrogen bond. Finally *Re,Si*-facial attack takes place to generate enantiomerically pure product **29**/**29'** (Scheme 10).[2k]



Scheme 11: Zhang's approach for asymmetric Michael reaction using lawsone.

In 2020, Zhang and co-workers explained the enantioselective Michael addition reactions on hydroxynaphthoquinone **1** and β-nitrostyrene **15** under threonine-derived thiourea catalyst **3l** (Scheme 11).[2j] Herein, the authors performed a series of reactions with a variety of substituents on the threonine-derived catalyst. Based on their detailed investigation on catalysts and solvents effects, it is found that 3.0 mol% catalyst **3l** and 0.2 M toluene solvent are the optimal conditions for this Michael addition reaction. Furthermore, β-nitrostyrene **15** interacts with thiourea-*NH* through hydrogen bond and hydroxynaphthoquinone **1** interacts with tertiary amine part of the catalyst. Due to this orientation of the catalyst-substrate complex depicted in the *pre*-transition state **30**, *Si,Re*-facial attack takes place to furnish Michael adducts with good enantioselectivity (Scheme 11).[2j]



Scheme 12: Li's approach of asymmetric Michael reactions using lawsone.

In 2020, Li and co-workers beautifully explained the use of calix[4]arene-tethered squaramide catalyst **3m** for asymmetric Michael addition reactions. Herein, the authors developed calix[4]arene with the cavity of upper-rim functionality. The calix[4]arene squaramide catalyst **3m** has a synergistic action with help of calix[4]arene cavity and the chiral catalytic part which induces asymmetric induction (Scheme 12).[21] Furthermore, asymmetric Michael reaction between hydroxynaphthoquinone **1** and ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **18** in the presence of 2.5 mol% of **3m** performed well in DCM solvent at 20 °C and that furnishes the product **25** in good yields with good to excellent enantioselectivity. Particularly, as shown in the *pre*-transition state **31** the α-keto ester **18** interact with one of the squaramide-*NH* through double hydrogen bond and its benzene ring was held in proper orientation in the calix[4]arene cavity through π–π stacking interactions like host-guest interaction while hydroxynaphthoquinone gets activated by tertiary amine part of the catalyst. Finally, synergistic activation of calix[4]arene squaramide, facilitates the *Si,Si*-facial attack to deliver product **25** in excellent yields with excellent enantioselectivity (Scheme 12). [21]

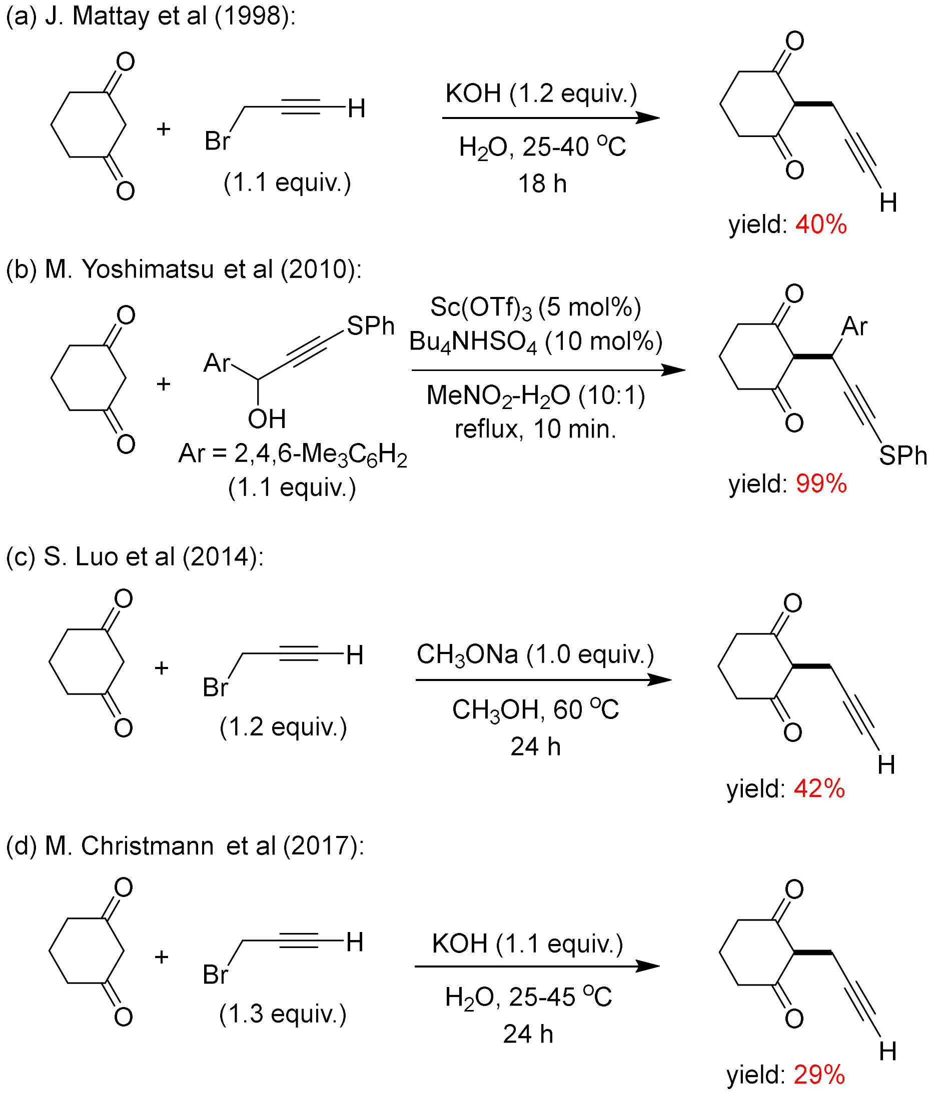
3. Organocatalytic Reductive Propargylation: Scope and Applications

3.1 Introduction

Reaction engineering is all about constructing different bonds in a highly selective, efficient and greener mode, which is a key supporting technique for the synthesis of structurally important molecules including natural products, drugs and materials.[4] One such reaction is the chemoselective propargylation of cyclic 1,3-diones at C-2 position. Owing to its numerous potential applications in the synthesis of drugs and natural products, chemoselective C-propargylation drew the attention of many research groups.[5]

In the previous methods, the C-2 selective propargylation was performed using base in solvent with or without phase transfer catalyst, but it suffered competition with *O*-propargylation. It is evident from the literature that many researchers succeeded in double propargylation at C-2 position of cyclic 1,3-diones.[5] But, when it comes to mono propargylation at C-2 position, it has always ended up in low yields and sometimes even failed in introducing the functionally rich propargyl groups. As of today, there is no perfect high-yielding protocol for C-2 selective mono propargylation of cyclic 1,3-diones.

Earlier in 1998, Mattay *et al.* and later in 2017, Christmann *et al.* reported mono propargylation of 1,3-cyclohexanedione with propargyl bromide induced by KOH at 25-45 °C in water with longer reaction times and poor yields (40% and 29% respectively, Scheme 13a/d).[6a,d] In 2010, Yoshimatsu *et al.* reported a regioselective mono propargylation of 1,3-cyclohexanedione using sterically crowded 3-sulfanylpropargyl alcohol catalyzed by the scandium triflate in $MeNO_2$-H_2O (10:1) at reflux conditions to furnish propargylated 1,3-diketone in good yields (Scheme 13b).[6b] Later, Luo *et al.* in 2014 reported the mono propargylation of 1,3-cyclohexanedione at C-2 position by using propargyl bromide, induced by sodium methoxide in methanol at 60 °C with longer reaction time and poor yield (42%, Scheme 13c).[6c] In these mono-propargylation methods, either the process lacks favourable yield or was performed only on some special substrates (Scheme 13).[6]


(a) J. Mattay et al (1998):

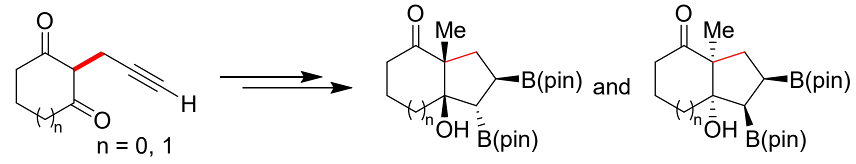
(b) M. Yoshimatsu et al (2010):

(c) S. Luo et al (2014):

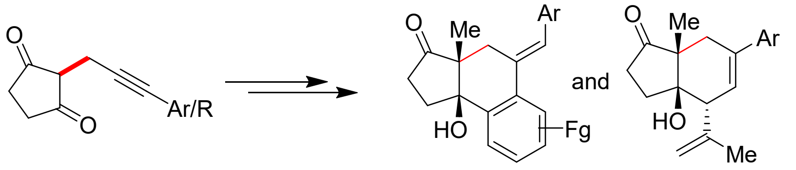
(d) M. Christmann et al (2017):

Scheme 13: Previous Reports on the Selective C-Propargylation of Cyclic-1,3-diketones

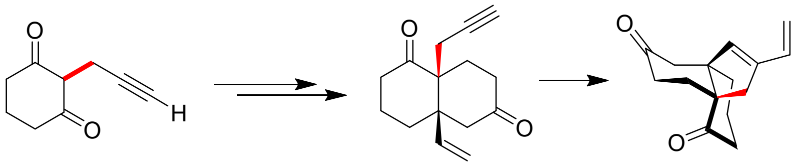
(a) Cu-catalyzed asymmetric borylative cyclization of alkynes with ketones: S. J. Meek et al (2019)



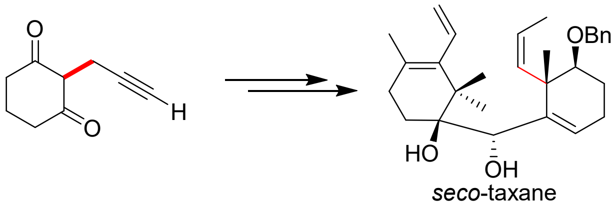
(b) Iridium- or Rhodium-catalyzed arylative cyclization of alkynones: H. W. Lam et al (2017 and 2014)



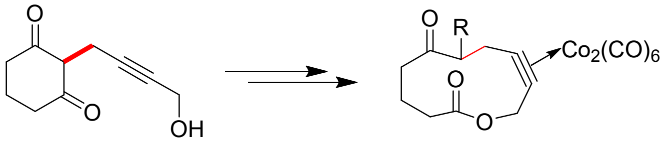
(c) Asymmetric synthesis of carbocyclic propellanes: M. Christmann et al (2017)



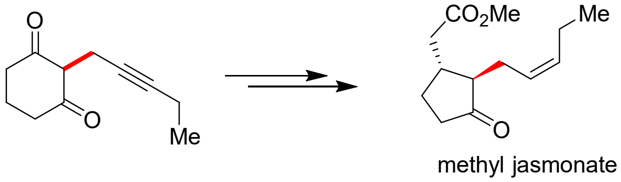
(d) Diastereoselective synthesis of a *seco*-taxane: J. Prunet et al (1999)



(e) Metal complexation in the synthesis of medium-ring acetylenic lactones: N. E. Schore et al (1992)



(f) A new synthesis of cyclopentenones, methyl jasmonate: G. Buchi et al (1971)



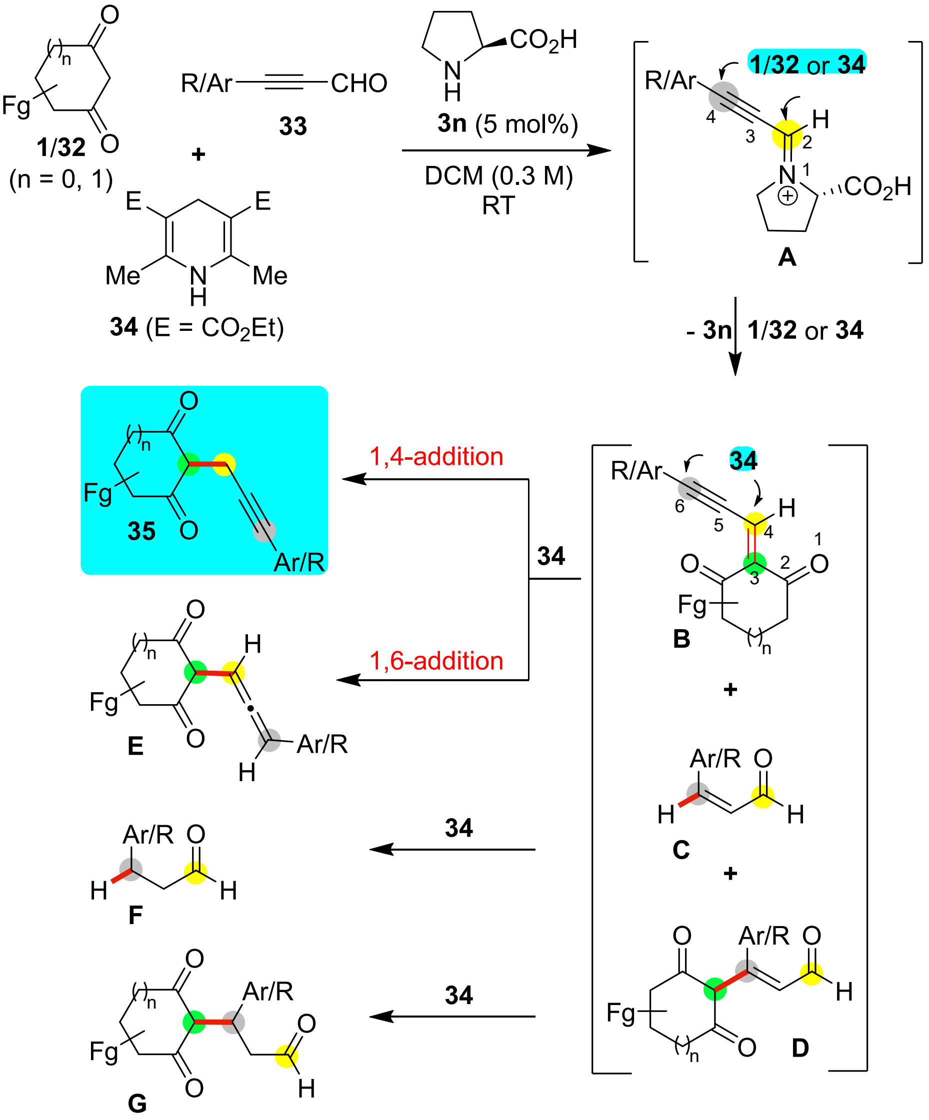
Scheme 14: Selected Applications from 2-(Prop-2-yn-1-yl)cyclic-1,3-diones as Synthons

The significance of the chemoselective mono propargylation on cyclic 1,3-diketones is comprehensible from the few reports enlisted in Scheme 14.[7] In 2019, Meek *et al.* reported the asymmetric borylative cyclization of alkynes with ketones by using propargylated cyclic 1,3-diones as starting materials (Scheme 14a).[7a] For the stereoselective racemic synthesis of complex carbocyclic compounds by Lam *et al.* in 2017/2014 and asymmetric synthesis of carbocyclic propellanes by Christmann *et al.* in 2017, the propargylated cyclic 1,3-diones were used as the key staring materials (Scheme 14b-c).[7b-d]

Later in 1999, Prunet *et al.* synthesized interesting seco-taxane from 2-methyl-2-propargylcyclohexane-1,3-dione (Scheme 14d).[7e] In 1992, Schore *et al.* synthesized metal-complexation with macrocyclic lactones starting from 2-(hydroxybutynyl) derivatives of 1,3-cyclohexanedione (Scheme 14e).[7f] In 1971, Buchi *et al.* reported the synthesis of methyl jasmonate which is a valuable raw material in modern perfumery, starting from simple mono propargylated 1,3-cyclohexanedione (Scheme 14f).[7g] By considering the shortcomings of the available procedures for the chemoselective mono propargylation on cyclic-1,3-diketones and the importance of the requirement for an efficient method (Scheme 13), we decided to take up the challenge of developing a simple protocol through which one can access various cyclic 1,3-diones possessing different functionalized propargyl groups at C-2 position (Scheme 15).

Our reaction design as depicted in Scheme 15 suggests that amino acid **3n** would catalyze three-component reductive coupling between cyclic 1,3-diones **1**/**32**, propargyl aldehydes **33** and Hantzsch ester **34** at the ambient conditions in DCM. First, amino acid (*S*)-proline **3n** would selectively react with propargyl aldehydes **33** to generate the iminium ion **A** formation by 1,2-addition. Secondly, in situ generated iminium ion **A** intermediate may undergo reaction with both of the nucleophiles **1**/**32** or/and **34** through 1,2- or 1,4-additon. In situ reaction of iminium ion **A** with cyclic 1,3-diones **1**/**32** can produce the intermediates **B** and **D** through 1,2-addition (Knoevenagel condensation) and 1,4-addition (Michael addition), respectively (see Scheme 15).

In a similar manner, reaction of iminium ion **A** with **34** can produce olefin-aldehydes **C** through 1,4-additon. Thirdly, reduction or transfer hydrogenation of intermediates **B** with Hantzsch ester **34** could result in the formation of products **35** or/and **E** through 1,4-addition or 1,6-addition, respectively. In a similar manner, reduction or transfer hydrogenation of other intermediates **C** and **D** with **34** could produce the products **F** and **G** through 1,4-addition, respectively.



Scheme 15: Reaction Design for the Chemoselective C-Propargylation of CH-Acids

Possible formation of four products **35**, **E**, **F**, and **G** from the three-component coupling reaction under the amino acid-catalysis made more challenging to investigate the selective synthesis of designed products (Scheme 15).[8]

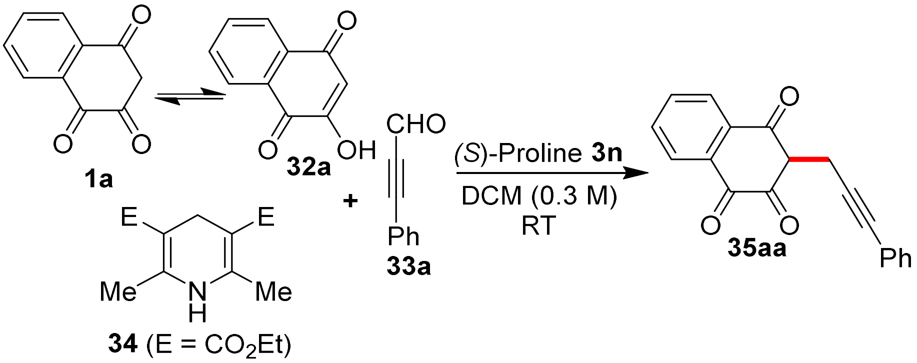
3.2 *Results and Discussions*

3.2.1 *Reaction optimization:*

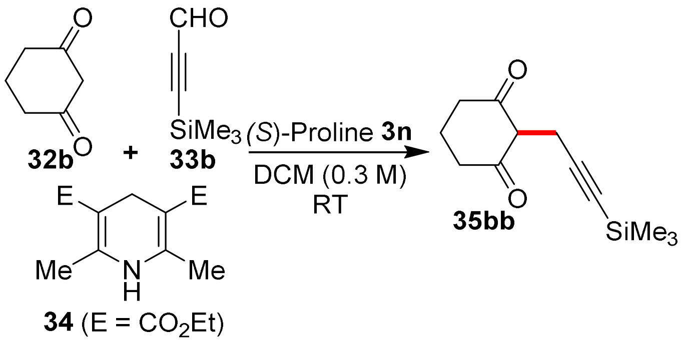
Based on the many applications of lawsone derivatives in medicinal to material chemistry,[3] we decided to investigate the three-component reductive coupling reaction by choosing 2-hydroxynaphoquione **1a/32a**, 3-phenylpropiolaldehydes **33a**, and Hantzsch ester **34** as the substrates. Accordingly, when we treated **1a/32a** with **33a** under (*S*)-proline **3n** catalysis, a Knoevenagel condensation product was formed, which upon further sequential treatment with Hantzsch ester **34** resulted in 96% of the reductive coupling product **35aa**.

Accordingly, when we treated **1a/32a** with **33a** under (*S*)-proline **3n** catalysis, a Knoevenagel condensation product was formed, which upon further sequential treatment with Hantzsch ester **34** resulted in 70% of the reductive coupling product **35aa** (not mentioned in Table 1). Surprisingly, when we performed one-pot reaction of 1.0 equiv. of **1a/32a**, 2.0 equiv. of **33a** and 1.0 equiv. of **34** in the presence of 20 mol% of (*S*)-proline **3n** in DCM at room temperature furnished the reductive coupling product **35aa** in 96% yields within 10 minutes respectively (Table 1, entry 1), which opened a new window for the 'three-component reductive propargylation' (TCRP) reaction. Notably, we are not observed formation of other possible products **Eaa**, **Faa**, **Gaa** and 3,3'-(3-phenylprop-2-yne-1,1-diyl)bis(2-hydroxynaphthalene-1,4-dione) in the above reaction. We proceeded with further optimization, by reducing the catalyst loading to 15, 10 and 5 mol%, which resulted in 96%, 98% and 97% yield of **35aa** with 15, 20 and 30 minutes of reaction times, respectively (Table 1, entries 2-4).

Table 1: Investigation of the Reductive Propargylation on Cyclic-1,3-dione **32a/b**.[a]



entry	**3n** (mol %)	*T* (min)	yield **35aa** (%)[b]
1	20	10	96
2	15	15	96
3	10	20	98
4	5	30	97
5[c]	5	180	89



entry	**3n** (mol %)	*T* (min)	yield **35bb** (%)[b]
6	20	5	93
7	15	35	90
8	10	50	90
9	5	60	93
10[c]	5	180	76
11[d]	5	300	70

[a]Reactions were carried out in DCM (1.0 mL) with 2.0 equiv of **33a** (0.6 mmol) and 1.0 equiv of **34** (0.3 mmol) relative to the **1a/32a** (0.3 mmol) in the presence of x mol% of (*S*)-**3n**. [b] Yield refers to the column-purified product.[c] 1.5 equiv amount of **33a**/**33b** used. [d] 1.0 equiv amount of **33b** used.

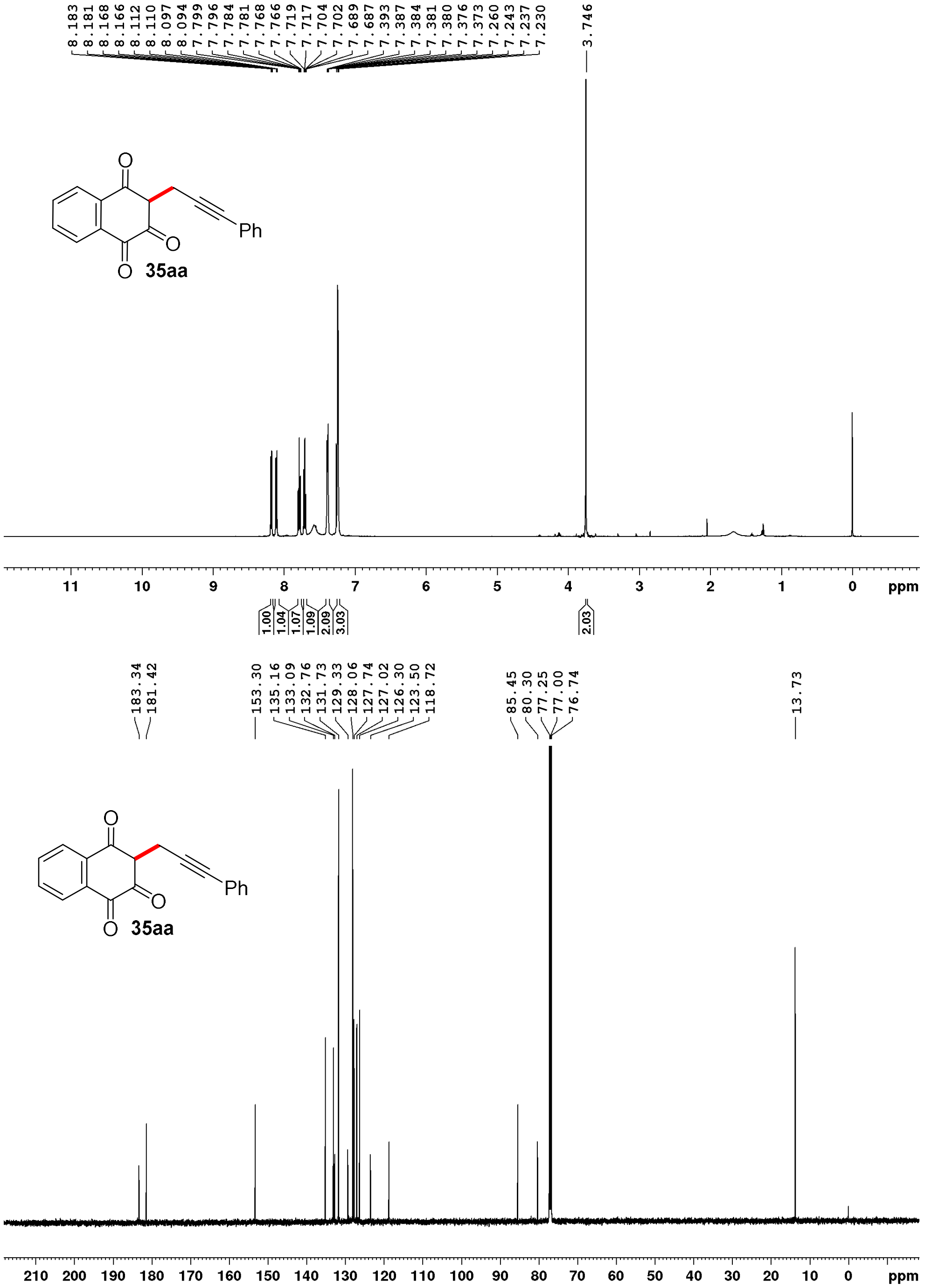


Figure 3: ^{1}H and ^{13}C spectra of the product **35aa**.

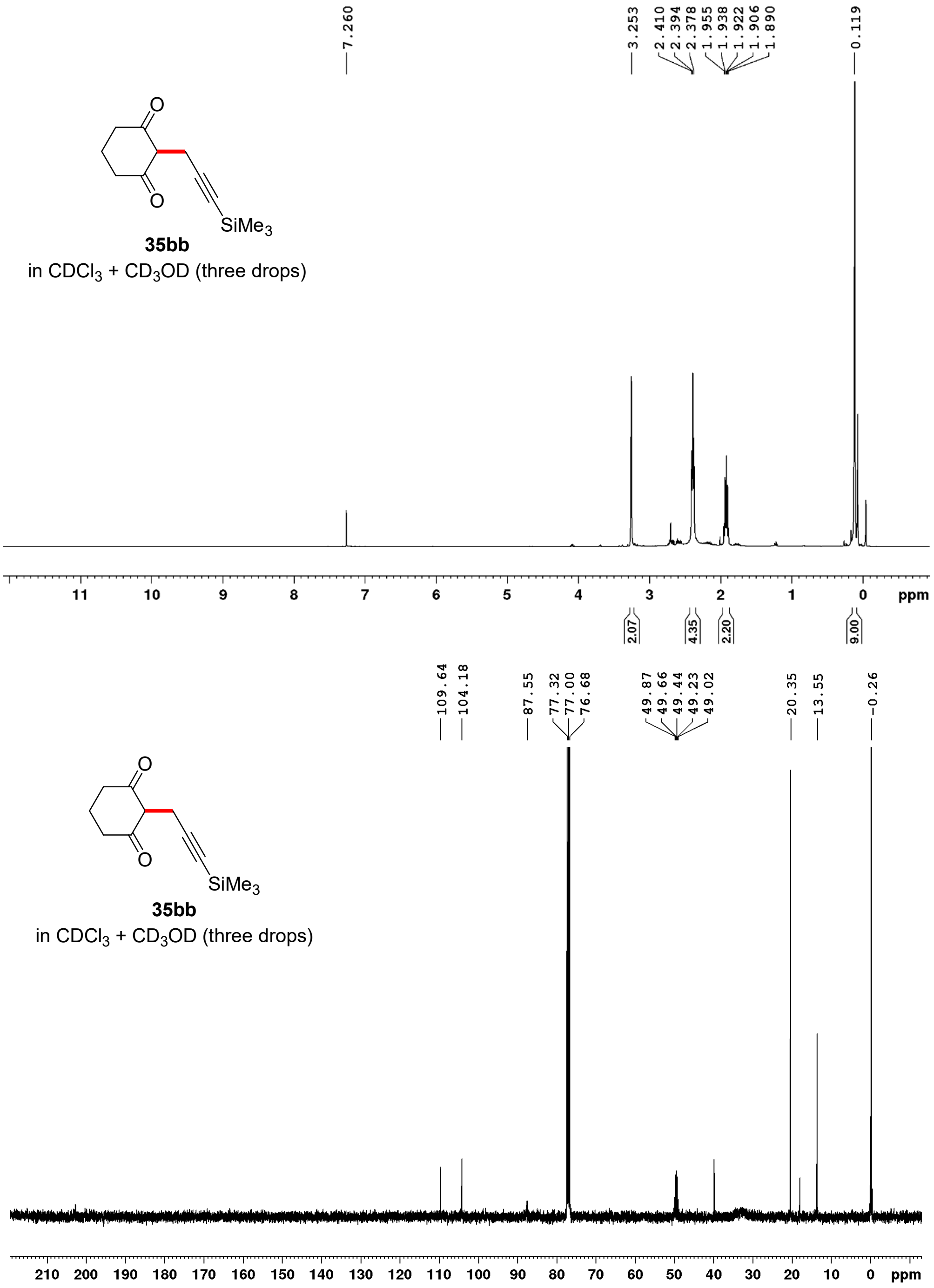


Figure 4: ^{1}H and ^{13}C spectra of the product **35bb**.

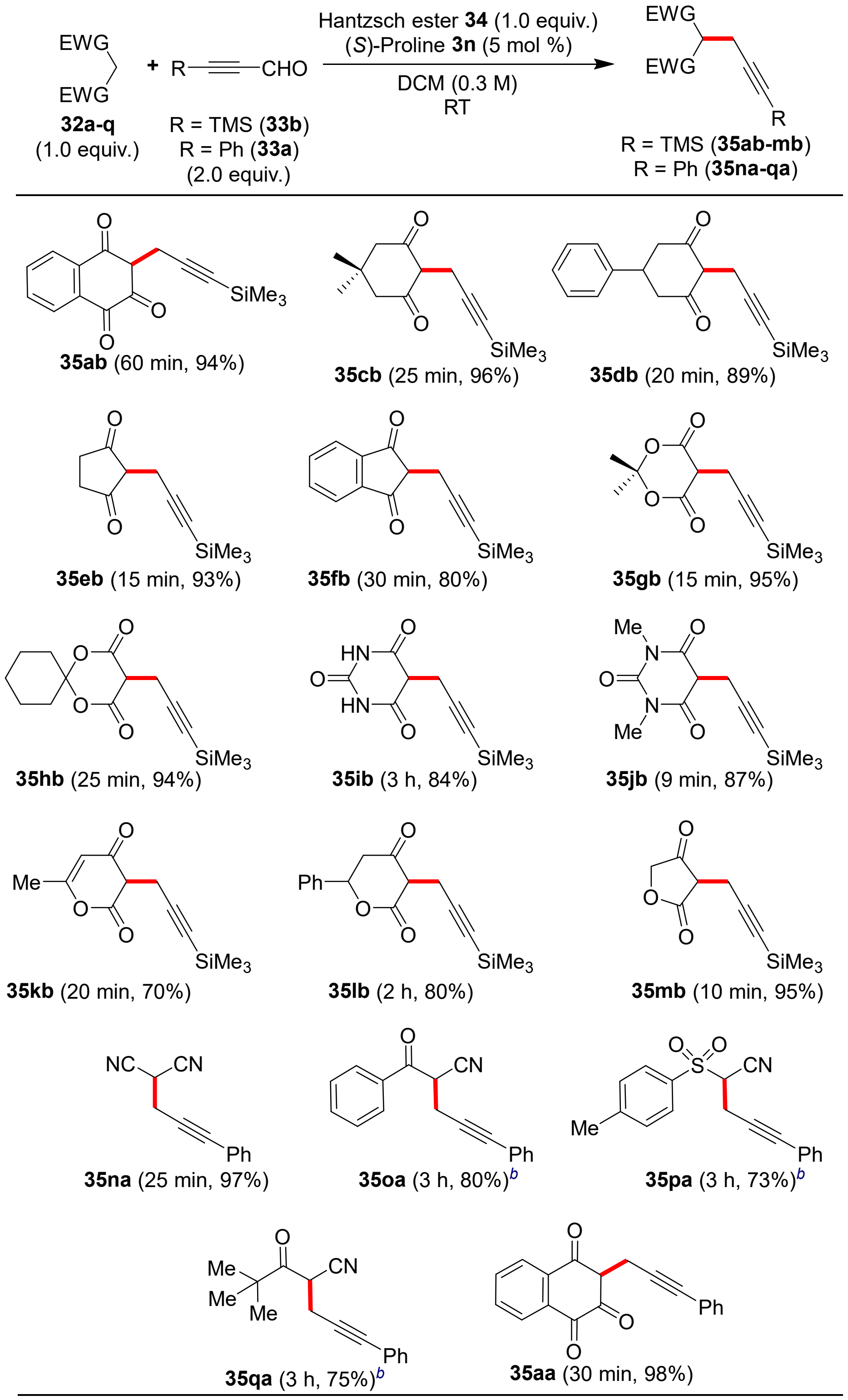
Though, there is no discernible effect of the catalyst loading on the reaction yield, it does have a visible effect on the reaction times which are inversely proportional to the catalyst loadings. As the reaction is satisfactorily facile in the presence of 5 mol% of catalyst **3n**, we considered it to be the optimal catalyst loading. Next, we tried to minimize the equivalents of **33a** (1.5 equiv. and 1.0 equiv.) which showed a negative impact on the reaction, with sluggish reaction times (180 min.) and yields 89%, which are comparatively low (Table 1, entries 5-6). Similarly, after understanding TCRP reactions on lawsone, we thought to simplify this three-component reductive coupling reaction by choosing 1,3-cyclohexanedione **32b**, 3-(trimethylsilyl)propiolaldehyde **33b** and Hantzsch ester **34** as the substrates and we observed the similar reactivity patterns as lawsone **1a/32a**.

Same time TCRP reaction of **32a** (0.3 mmol), **33a** (0.6 mmol) and **34** (0.3 mmol) in DCM at 25 °C under the 5 mol% of piperidine-catalysis for 45 minutes furnished the **35aa** in 87% yield and under the 10 mol% of piperidine-catalysis for 30 minutes furnished the **35aa** in 81% yield, respectively (results not shown in Table 1) and these results are inferior to (*S*)-**3n** catalysis. Thus, the optimization process came to an end inferring entry 4 of Table 1 to be the best optimized condition.

3.2.2 *Scope of TCRP reaction:*

With optimized conditions in hand, we continued our studies of three-component reductive propargylation on various CH-acids or active methylene compounds in order to prove the strength and generality of the coupling reaction (Table 2). The 3-(trimethylsilyl)propiolaldehyde **33b** reacted with various functionalized cyclic 1,3-diones **32a-q** under the (*S*)-proline **3n** catalysis in the presence of **34** to afford the corresponding reductive propargylation products **35ab-35mb** with good to excellent yields (Table 2). Many of these coupling reactions completed within the range of 9 min. to 60 min. and few of the reactions took 2-3 h may be due to the solubility issues.

Table 2: Substrate scope of the proposed design.[a]



35ab (60 min, 94%)

35cb (25 min, 96%)

35db (20 min, 89%)

35eb (15 min, 93%)

35fb (30 min, 80%)

35gb (15 min, 95%)

35hb (25 min, 94%)

35ib (3 h, 84%)

35jb (9 min, 87%)

35kb (20 min, 70%)

35lb (2 h, 80%)

35mb (10 min, 95%)

35na (25 min, 97%)

35oa (3 h, 80%)*b*

35pa (3 h, 73%)*b*

35qa (3 h, 75%)*b*

35aa (30 min, 98%)

[a] Reactions were carried out in DCM (1.0 mL) with 2.0 equiv of **33a**/**33b** (0.6 mmol) and 1.0 equiv of **34** (0.3 mmol) relative to the **32a-q** (0.3 mmol) in the presence of 5 mol% of (*S*)-**3n** and yield refers to the column-purified product. [b] Reaction performed in DCE at 50 °C.

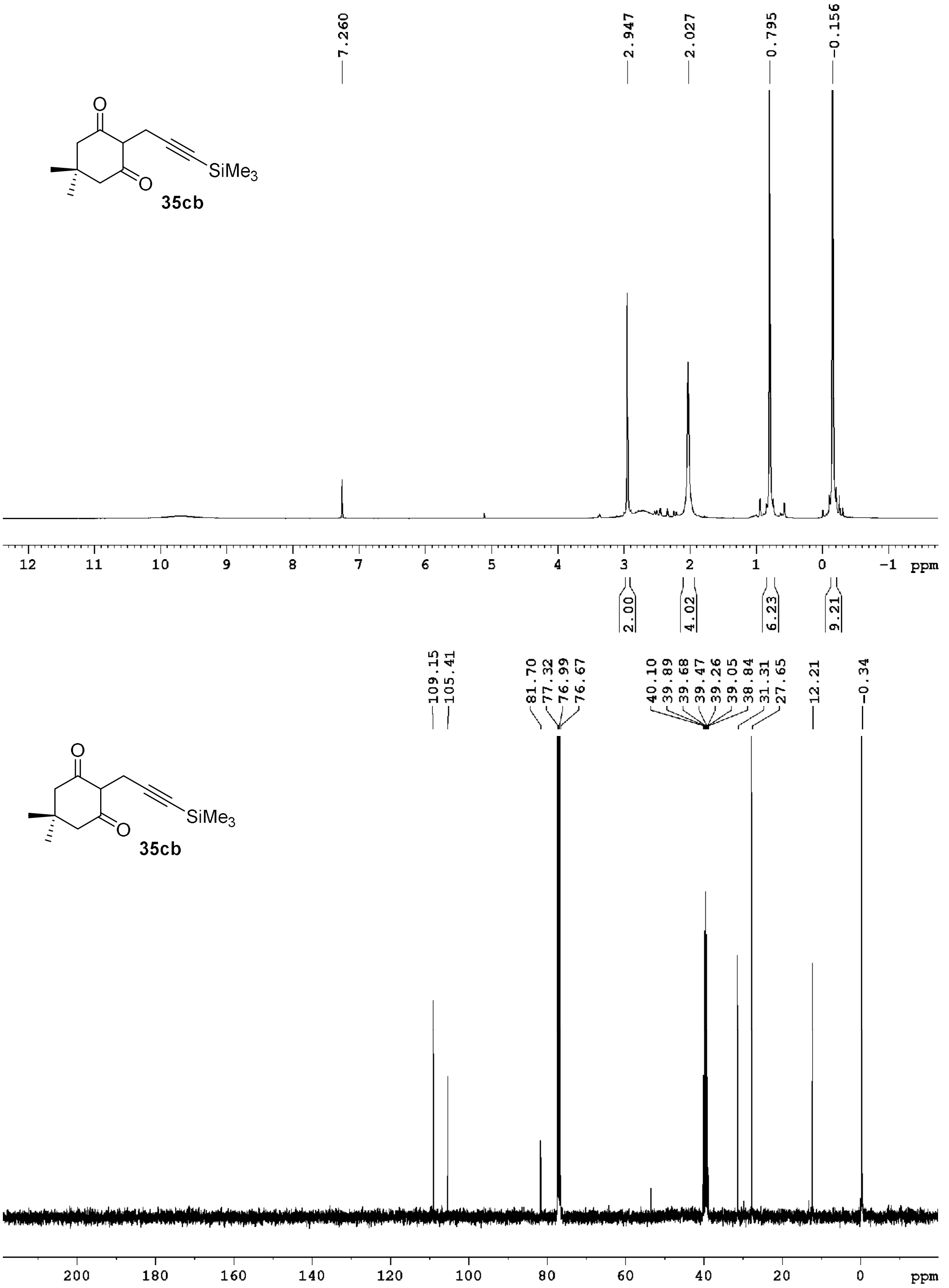


Figure 5: ^{1}H and ^{13}C spectra of the product **35cb**.

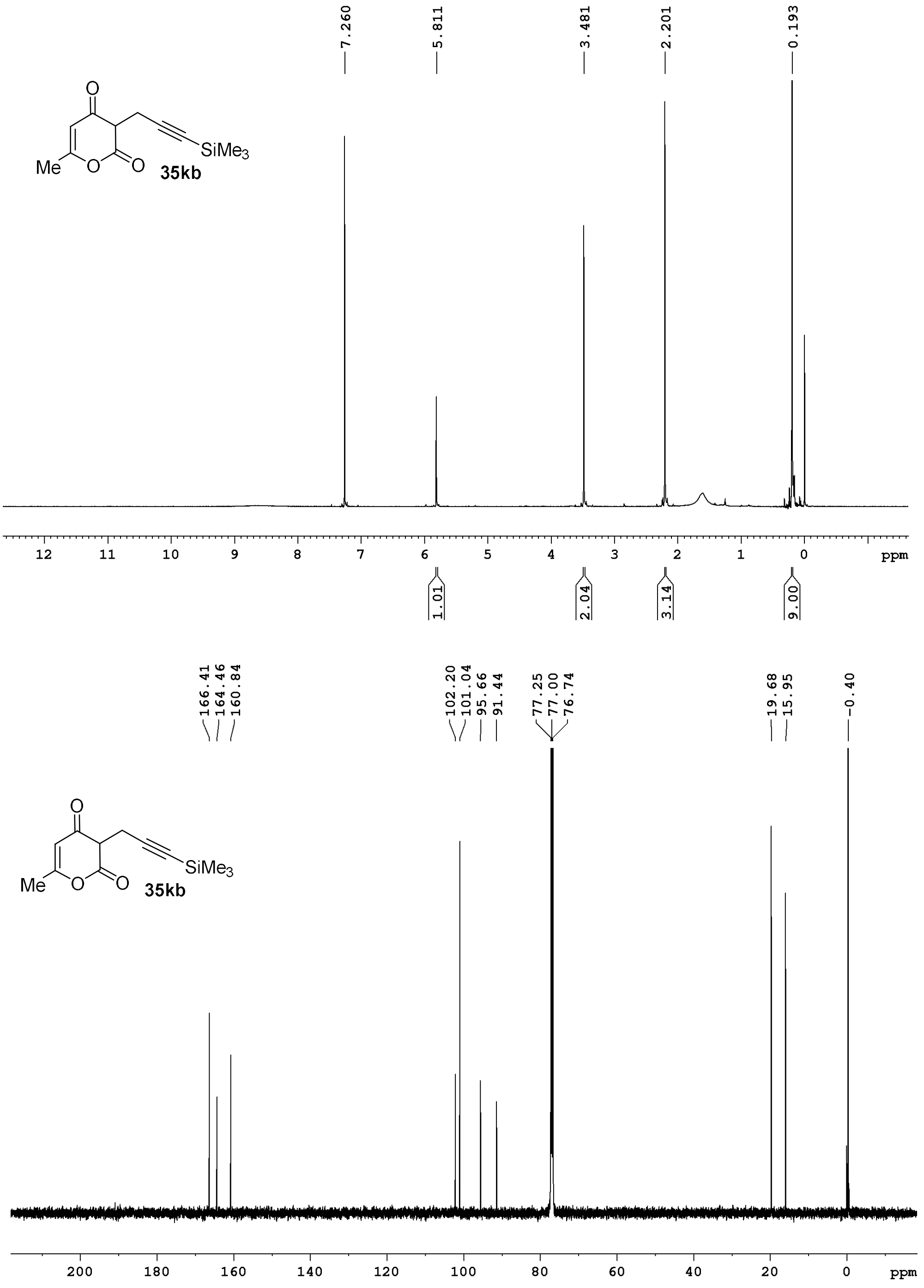


Figure 6: ^{1}H and ^{13}C spectra of the product **35kb**.

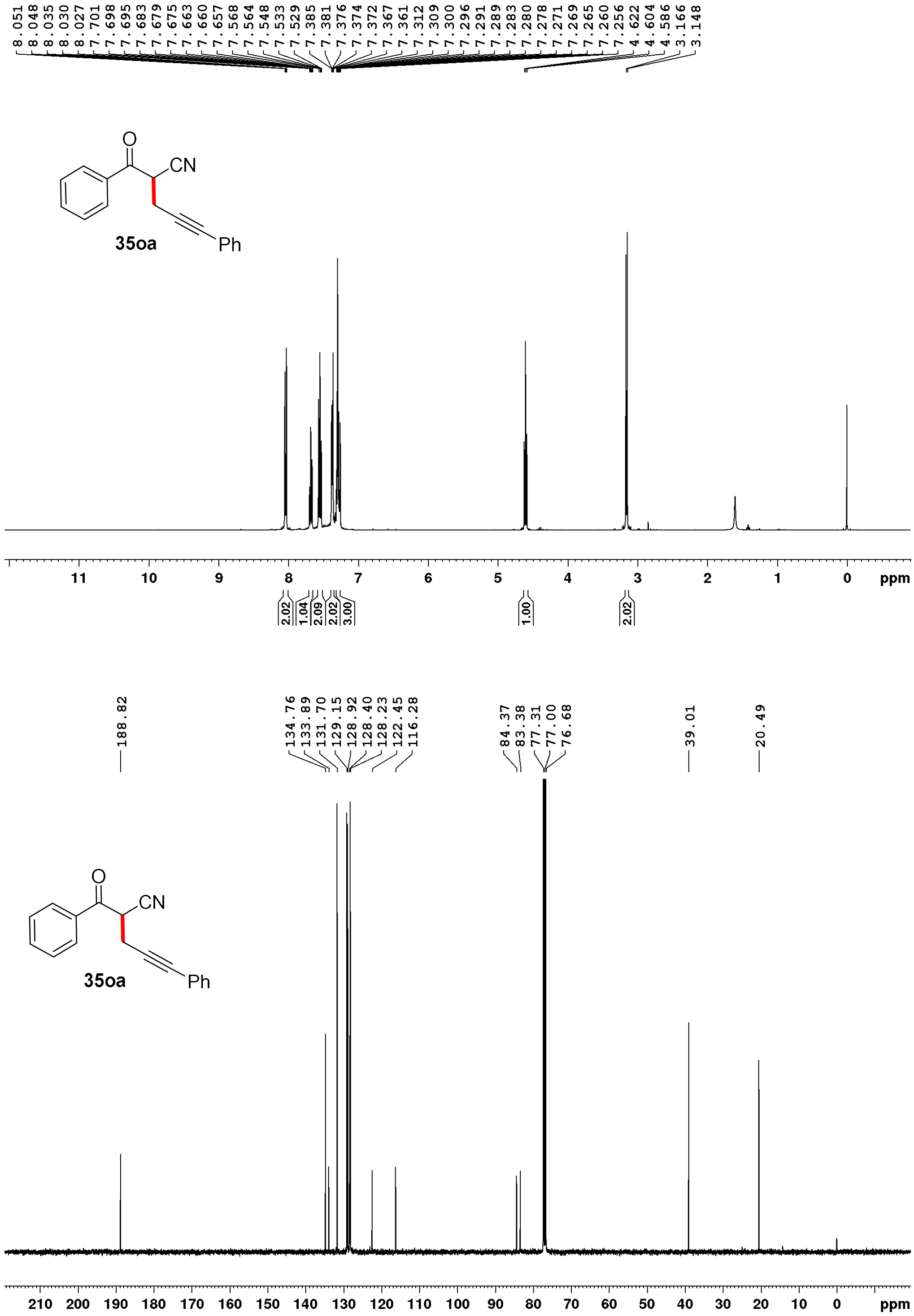


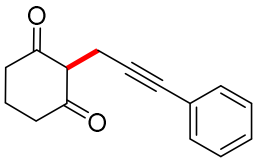
Figure 7: ^{1}H and ^{13}C spectra of the product **35oa**.

These results are showing that the coupling reaction is compatible with a variety of functionalities including ring size on the cyclic 1,3-dione **32a-m** substrates. The yield of the product **35kb** is comparatively low and reaction conversion is not 99% even after longer reaction times, which may be due to low reactivity of CH-acid **32k** as enolic double bond is in conjugation with internal double bond. To expand the CH-acids scope, we further carried out the coupling studies on different acyclic active methylene compounds (**32n-32q**) with **33a** or **33b** (Table 2). Surprisingly, reaction between malononitrile **32n**, **33b** and **34** under the **3n**-catalysis didn't furnished the coupling product **35nb** and even Knoevenagel product **Bnb** not formed may be due to the different electronic nature of substrates. Further when malononitrile **32n** reacted with 3-phenylpropiolaldehyde **33a** under the optimized condition, followed by treatment with **34** at the 25 °C for within 25 min. furnished the coupling product **35na** in 97% yield (Table 2). In a similar manner, treatment of the active methylene compounds **32o-32q** with **33a** and **34** under the **3n**-catalysis in DCM at 25 °C for longer reaction times didn't furnished the expected coupling **35oa-35qa** products. But the coupling products **35oa-35qa** were furnished in good yields from the corresponding substrates of **32o-32q** with **33a** and **34** under the **3n**-catalysis in DCE at 50 °C for 3 h as shown Table 2. Temperature has become key factor to provide the reductive coupling **35oa-35qa** products in good yields may be due to the less acidity of acyclic compounds **32o-q** compared to cyclic 1,3-diones **32a-m** (Table 2).[9]

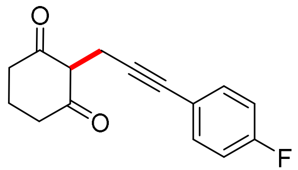
After successful understanding of the organocatalytic reductive propargylation of different CH-acids **32a-q** with **33a/33b**, we further shown interest to synthesize the library of 2-(3-aryl/alkylprop-2-yn-1-yl)cyclohexane-1,3-diones **35ba-bq** from the corresponding 3-aryl/alkylpropiolaldehydes **32a-q** and cyclohexane-1,3-dione **32b** (Table 3). Because there are numerous synthetic applications starting from the 2-(3-aryl/alkylprop-2-yn-1-yl)cyclohexane-1,3-diones **35ba-bq** (see Scheme 14).[5-7] The reported 2-(3-aryl/alkylprop-2-yn-1-yl)cyclohexane-1,3-diones **35ab-aq** were obtained in good to excellent yields through a coupling reaction of simple cyclohexane-1,3-dione **32b** with a variety of 3-aryl/alkylpropiolaldehydes (**33a-q**) containing halogen atoms, electron withdrawing, electron donating, neutral, and heteroatom substituted aryl moieties as well as achiral alkyl groups (Table 3).

Table 3: Scope of Reductive C-Propargylation with Cyclohexane-1,3-dione and Various 3-Aryl/Alkylpropiolaldehydes.[a]

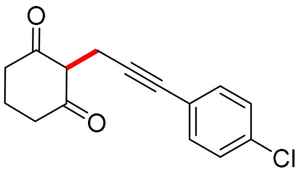
32b (1.0 equiv.) **33a-q** (2.0 equiv.) **35ba-bq**



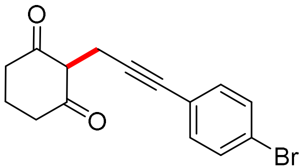
35ba (60 min, 85%)



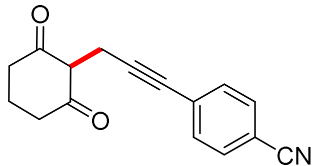
35bc (5 h, 85%)



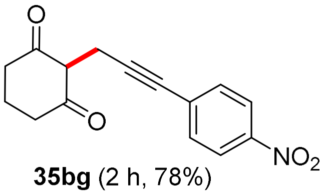
35bd (2 h, 95%)



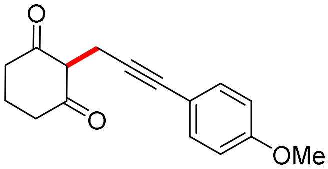
35be (2 h, 90%)



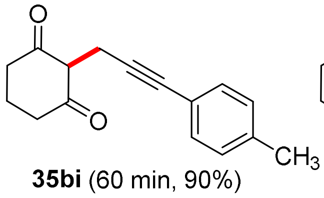
35bf (2.5 h, 95%)



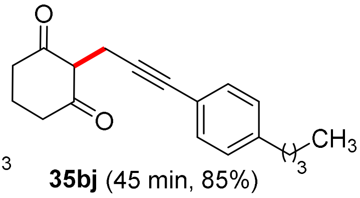
35bg (2 h, 78%)



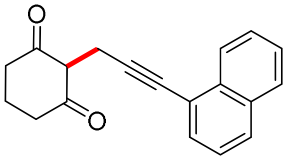
35bh (60 min, 90%)



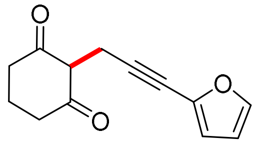
35bi (60 min, 90%)



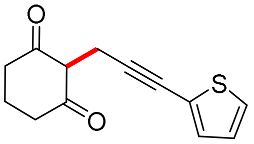
35bj (45 min, 85%)



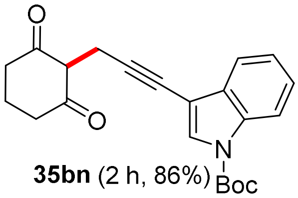
35bk (20 min, 95%)



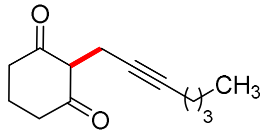
35bl (20 min, 90%)



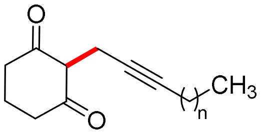
35bm (60 min, 88%)



35bn (2 h, 86%)



35bo (30 min, 85%)



n = 4; **35bp** (25 min, 92%)
n = 5; **35bq** (15 min, 92%)

[a] Reactions were carried out in DCM (1.0 mL) with 2.0 equiv of **33a-q** (0.6 mmol) and 1.0 equiv of **34** (0.3 mmol) relative to the **32b** (0.3 mmol) in the presence of 5 mol% of (*S*)-**3n** and yield refers to the product obtained from simple precipitation-filtration technique.

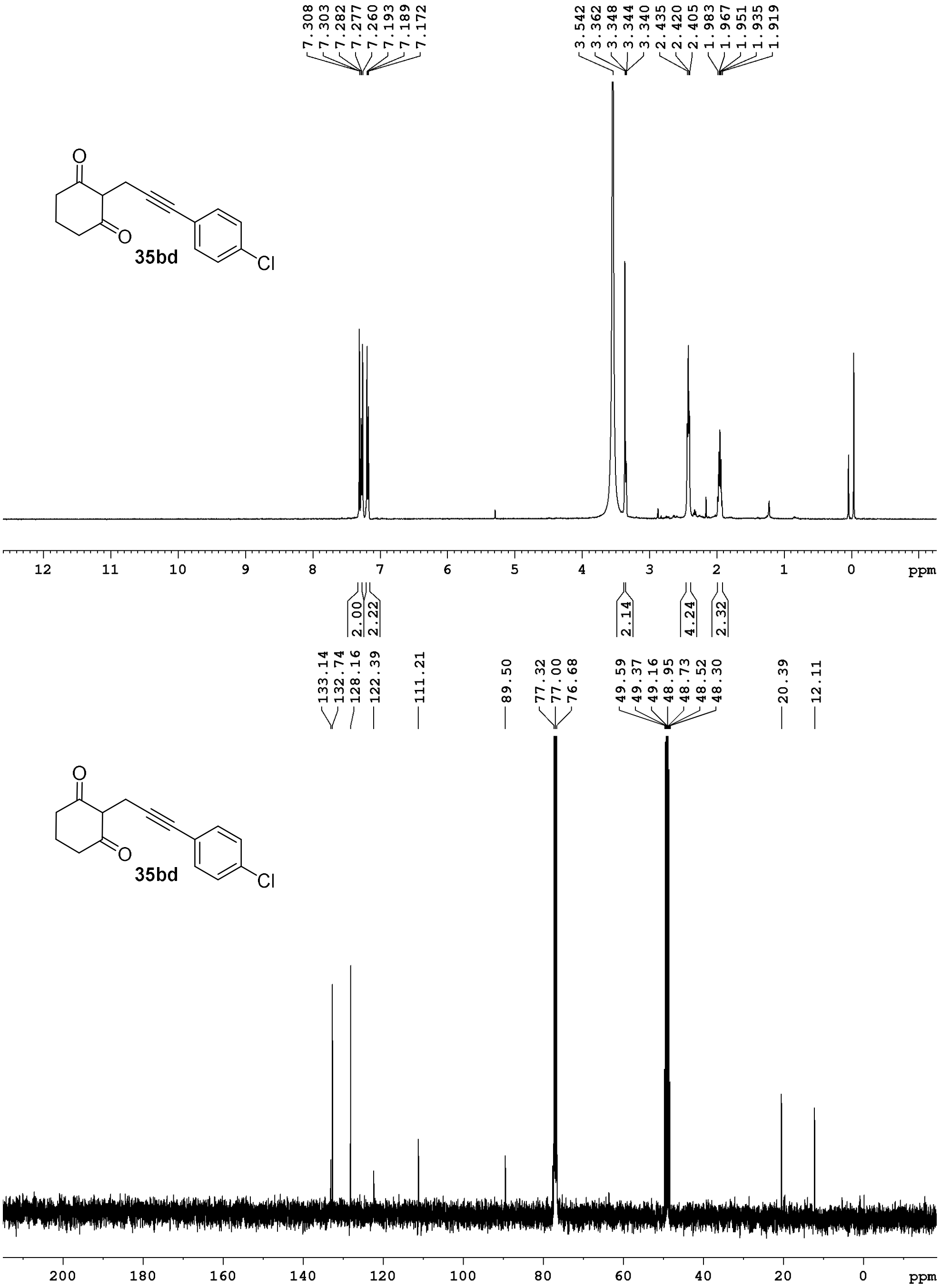


Figure 8: ^{1}H and ^{13}C spectra of the product **35bd**.

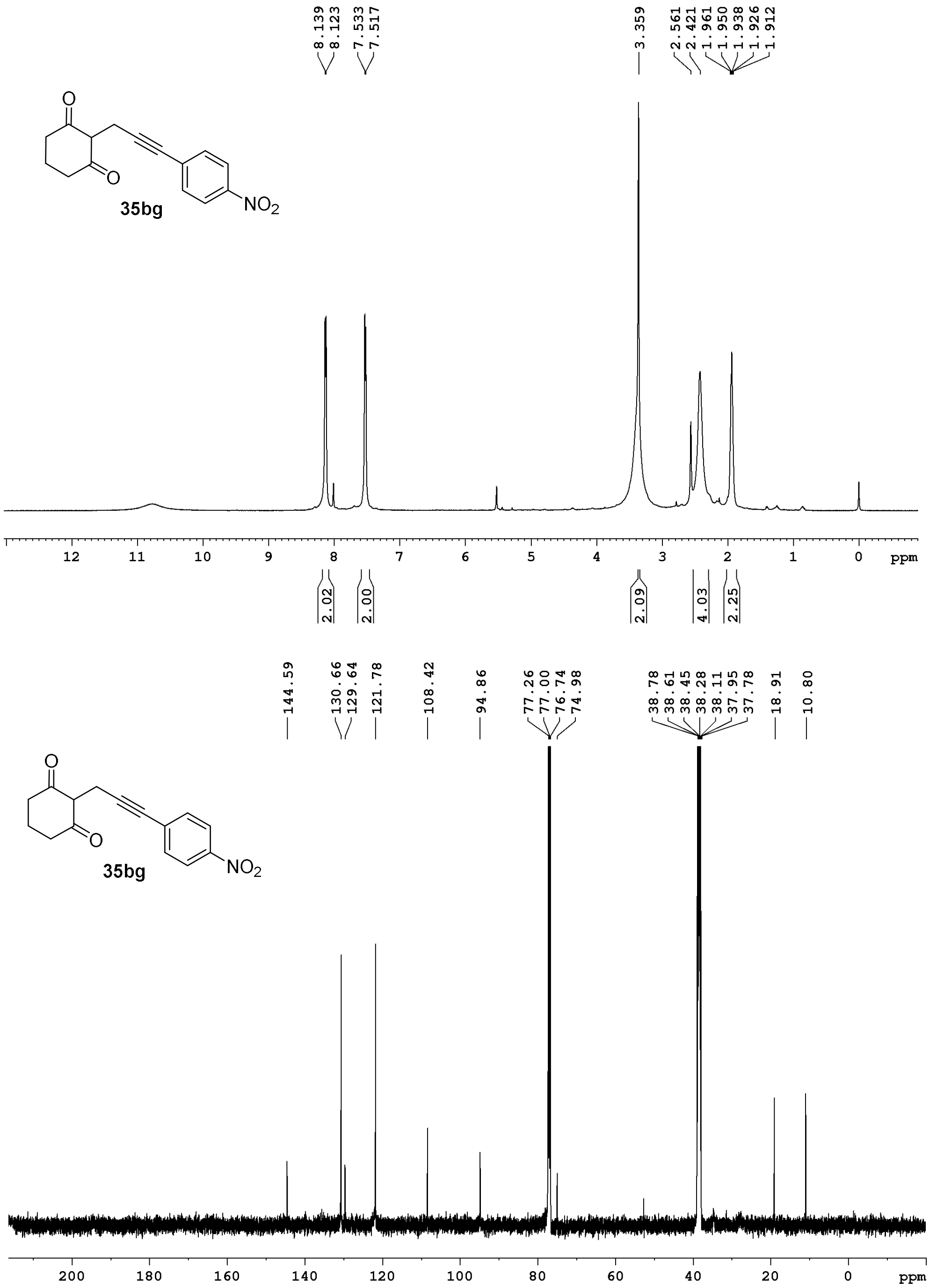


Figure 9: ^{1}H and ^{13}C spectra of the product **35bg**.

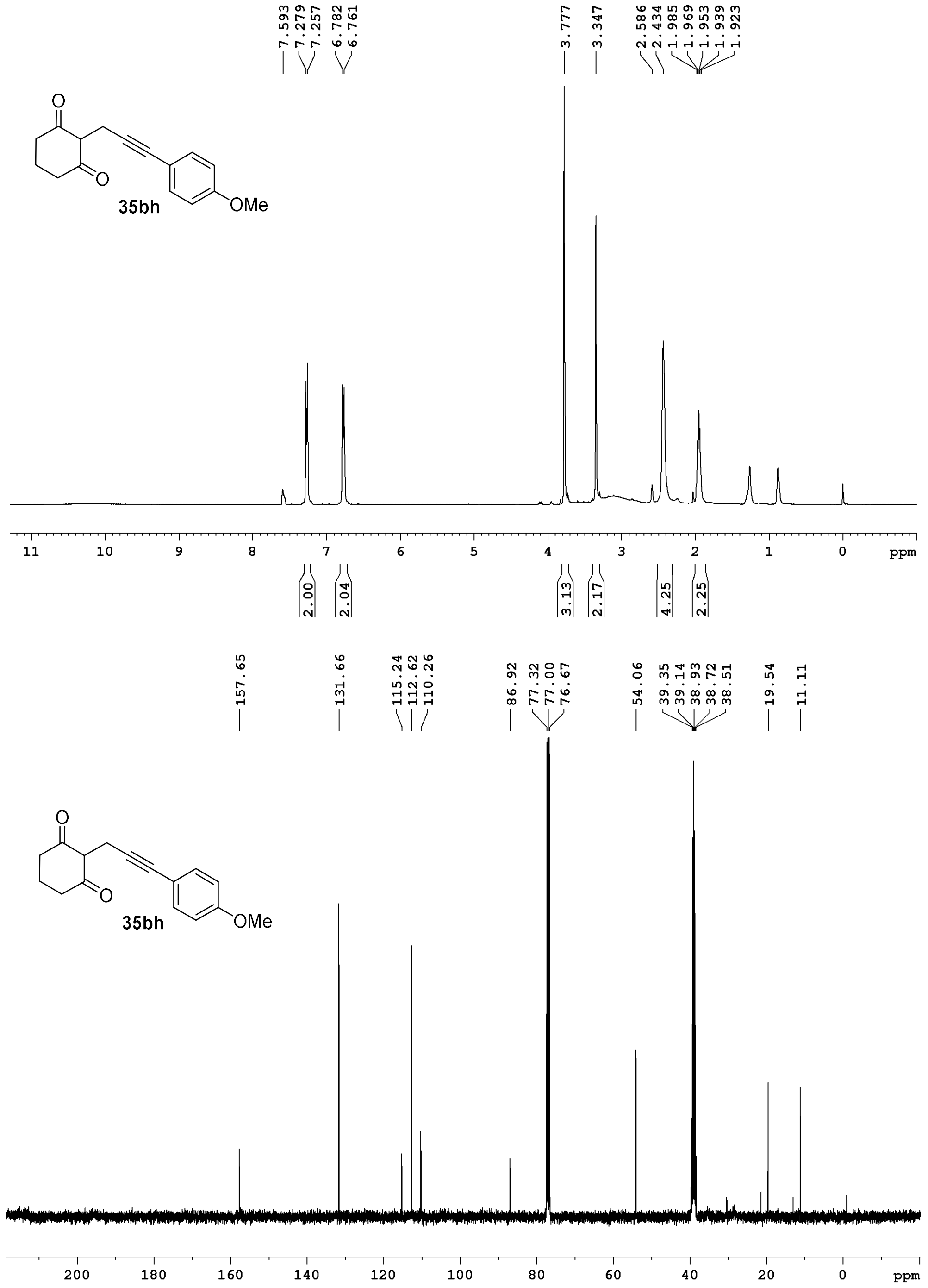


Figure 10: ^{1}H and ^{13}C spectra of the product **35bh**.

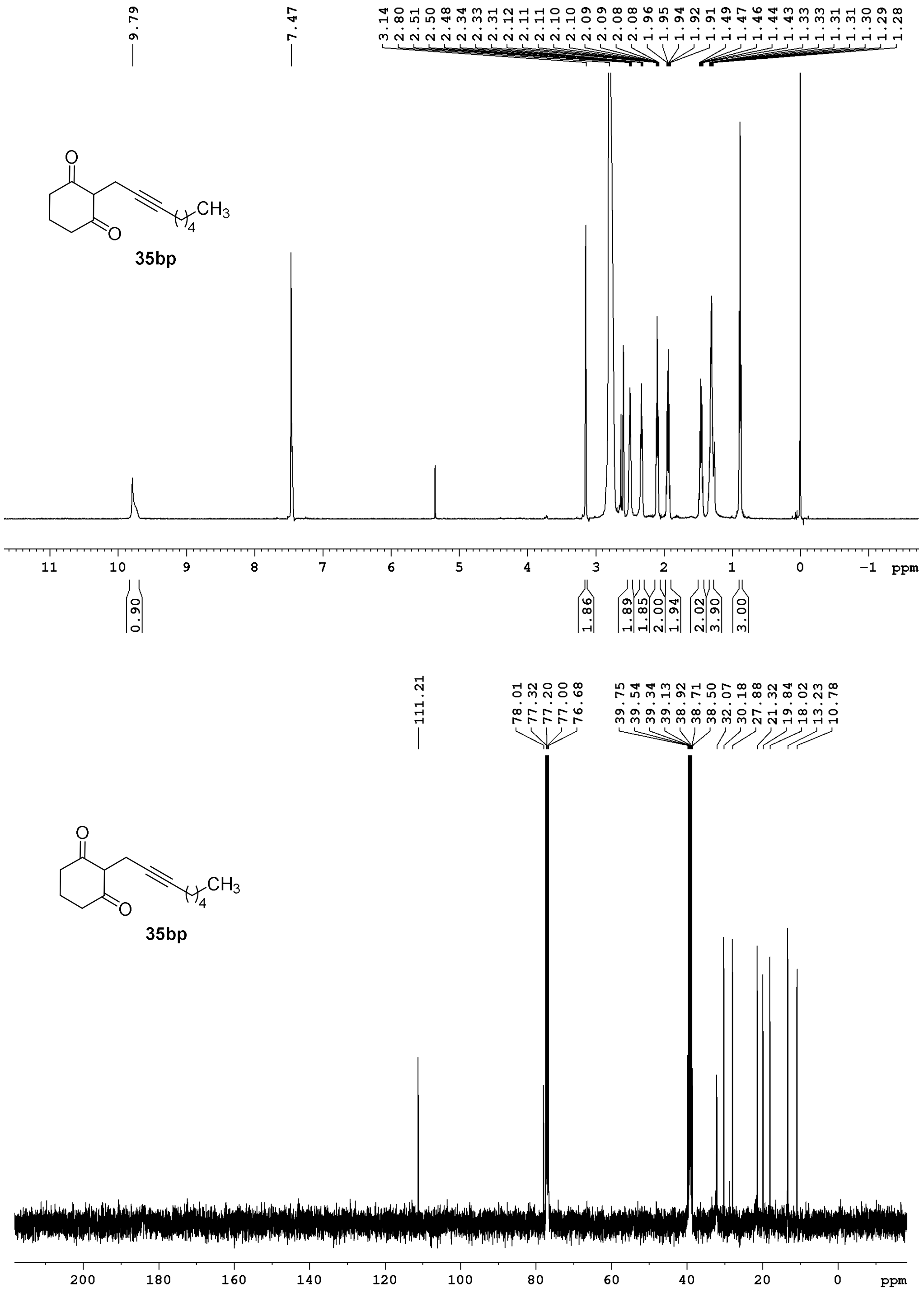


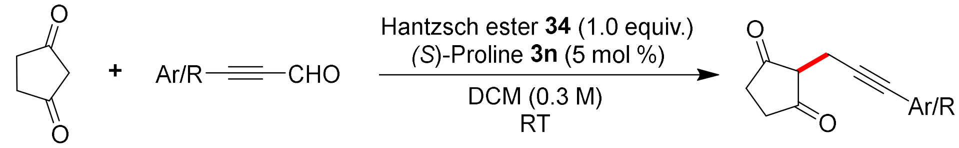
Figure 11: ^{1}H and ^{13}C spectra of the product **35bp**.

The organocatalytic three-component reductive coupling of **32b** with **33a** and 3 in DCM at 25 °C for 60 minutes followed by precipitation in cold 10% ethyl acetate in hexanes and quick filtration gave the analytically pure coupling product 2-(3-phenylprop-2-yn-1-yl)cyclohexane-1,3-dione **35ba** in 85% yield without further column purification (Table 3). Strikingly, the coupling reaction of **32b** with 4-halophenyl, 4-cyanophenyl, and 4-nitrophenyl substituted 3-arylpropiolaldehydes **33c-g** and **34** under the catalysis of **3n** in DCM at 25 °C for relatively longer reaction times (5.0-2.0 h) furnished the products **35bc-bg** in 95-78% yields (Table 3). Surprisingly, the reductive coupling reaction of 3-arylpropiolaldehydes **33h-k** containing 4-methoxyphenyl, 4-methylphenyl, 4-^{n}butylphenyl, and naphthalene-1-yl with **32b** and **34** under the catalysis of **3n** in DCM at 25 °C for shorter reaction times (60-20 min.) furnished the expected coupling products **35bh**-**bk** in excellent yields (90%, 90%, 85% and 95%, respectively, Table 3).

In a similar manner, the coupling reaction of 3-heteroarylpropiolaldehydes **33l**-**n** containing furan-2-yl, thiophen-2-yl, and *N*-Boc-indolyl-3-yl with **32b** and **34** under the catalysis of **3n** in DCM at 25 °C for 20 min. to 2.0 h furnished the coupling products **35bl**-**bn** in very good yields (90%, 88% and 86%, respectively, Table 3). Interestingly, the reductive coupling reaction of **32b** and **34** with the 3-alkylpropiolaldehydes **33o**-**q** containing *n*-butyl, *n*-pentyl, and *n*-hexyl under the catalysis of 4 at 25 °C for very short reaction times (30 min. to 15 min.) furnished the expected domino products **35bo**-**bq** in 85–92% yields (Table 3). All of these propargylated coupling products **35ba**-**bq** were isolated in pure form by using a unique and simple precipitation-filtration technique on reaction mixture avoiding tedious column chromatography.

After successful high-yielding synthesis of important library of 2-(3-aryl/alkylprop-2-yn-1-yl)cyclohexane-1,3-diones **35ba**-**bq** from the cyclohexane-1,3-dione **32b**, we further shown interest to investigate the similar library synthesis from cyclopentane-1,3-dione **32e** as corresponding synthon for reductive coupling reactions to show more applications (see Scheme 14).[2-4].

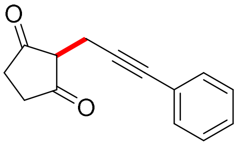
Table 4: Scope of Reductive C-Propargylation with Cyclopentane-1,3-dione and Various 3-Aryl/Alkylpropiolaldehydes.[a]



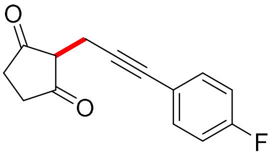
32e
(1.0 equiv.)

33a-q
(2.0 equiv.)

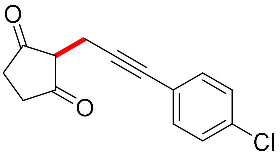
35ea-eq



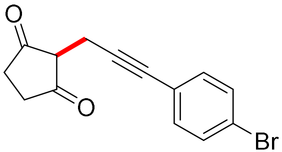
35ea (50 min, 95%)



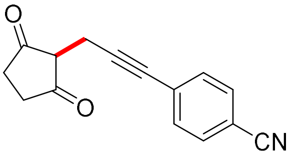
35ec (1.5 h, 95%)



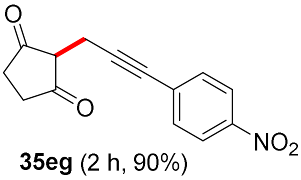
35ed (2 h, 95%)



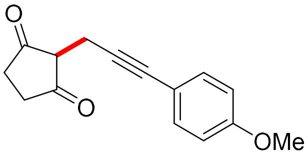
35ee (2 h, 93%)



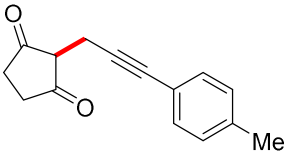
35ef (1.5 h, 95%)



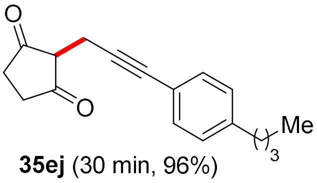
35eg (2 h, 90%)



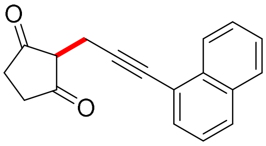
35eh (30 min, 88%)



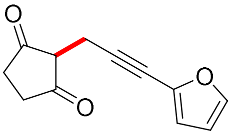
35ei (50 min, 95%)



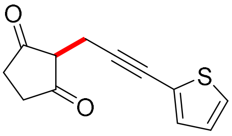
35ej (30 min, 96%)



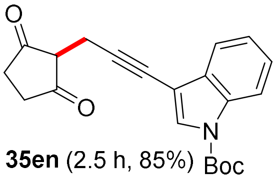
35ek (20 min, 95%)



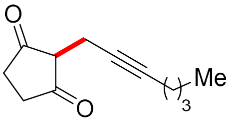
35el (20 min, 95%)



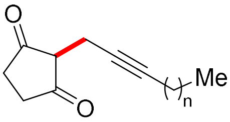
35em (1 h, 92%)



35en (2.5 h, 85%)



35eo (30 min, 80%)



n = 4; **35ep** (20 min, 90%)
n = 5; **35eq** (15 min, 95%)

[a] Reactions were carried out in DCM (1.0 mL) with 2.0 equiv of **33a-q** (0.6 mmol) and 1.0 equiv of **34** (0.3 mmol) relative to the **32e** (0.3 mmol) in the presence of 5 mol% of (*S*)-**3n** and yield refers to the product obtained from simple precipitation-filtration technique.

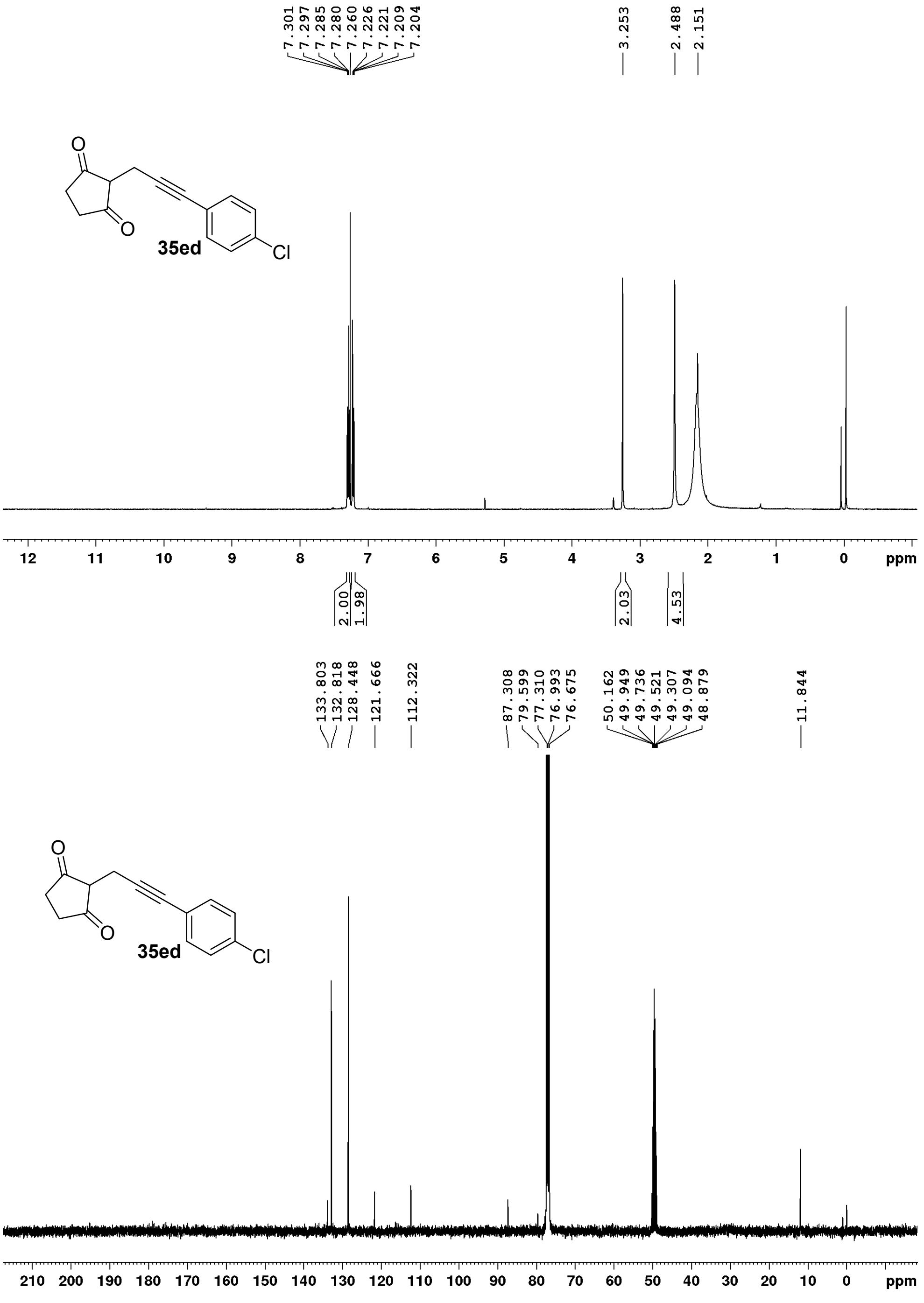


Figure 12: ^{1}H and ^{13}C spectra of the product **35ed**.

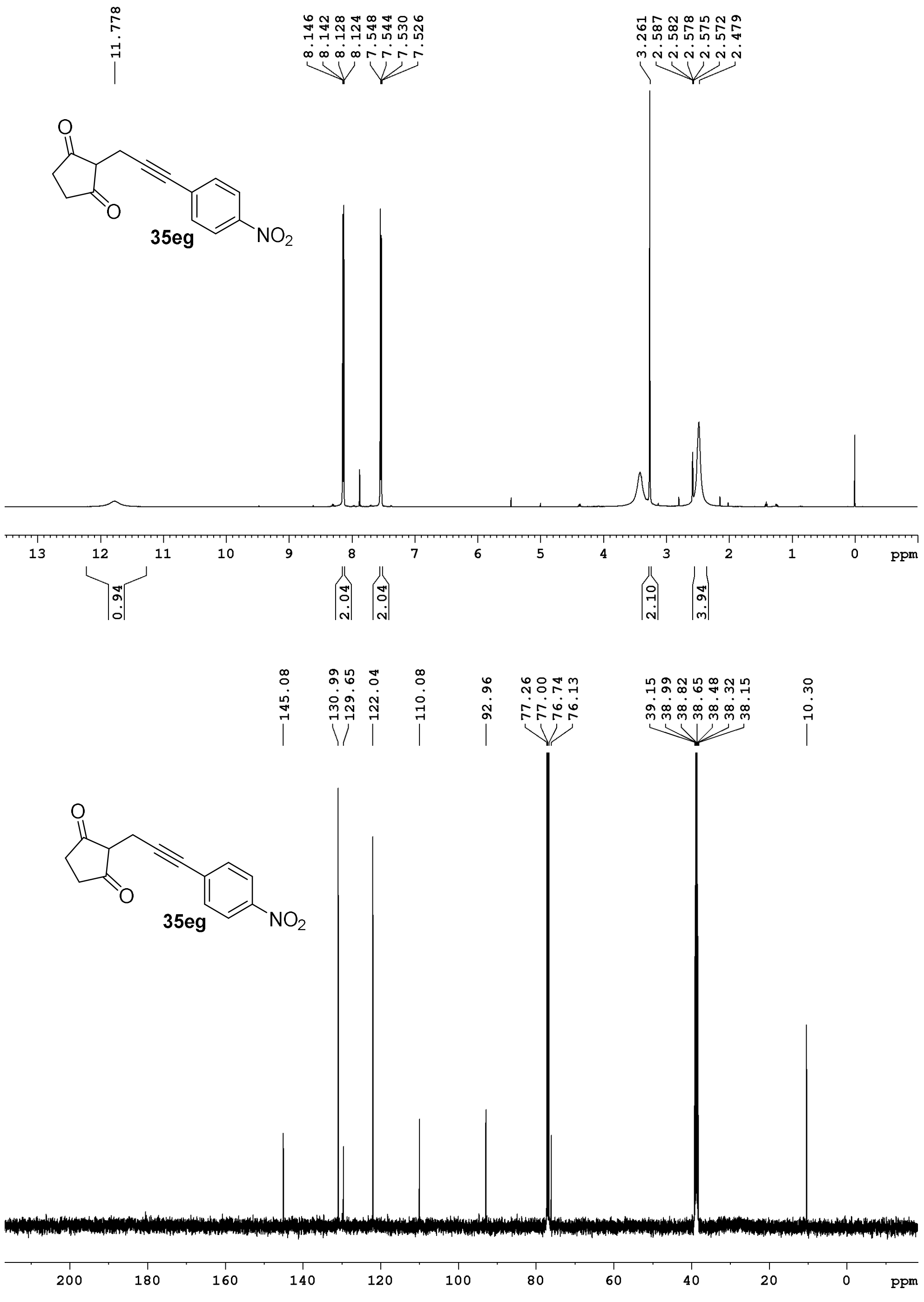


Figure 13: ^{1}H and ^{13}C spectra of the product **35eg**.

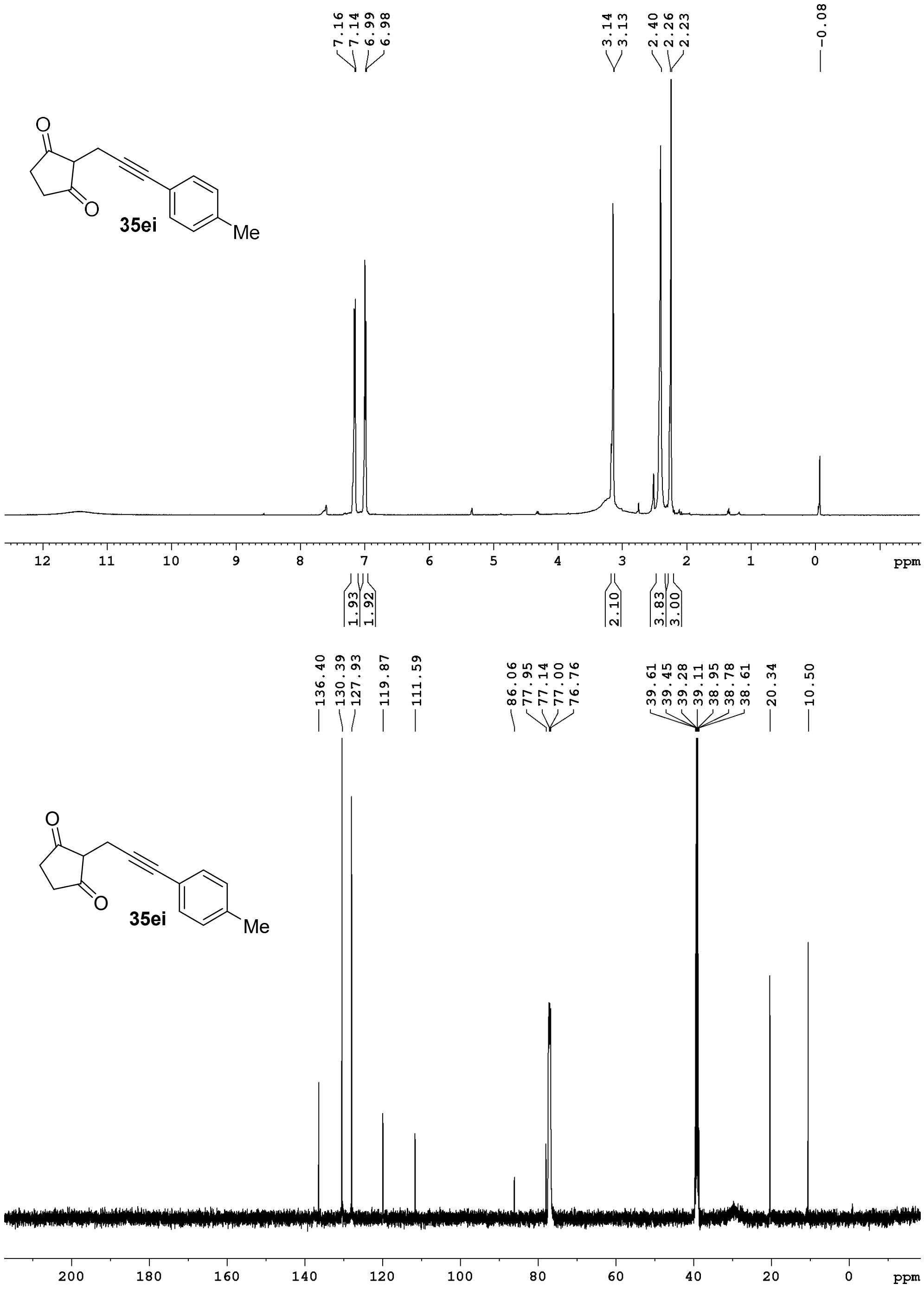


Figure 14: ^{1}H and ^{13}C spectra of the product **35ei**.

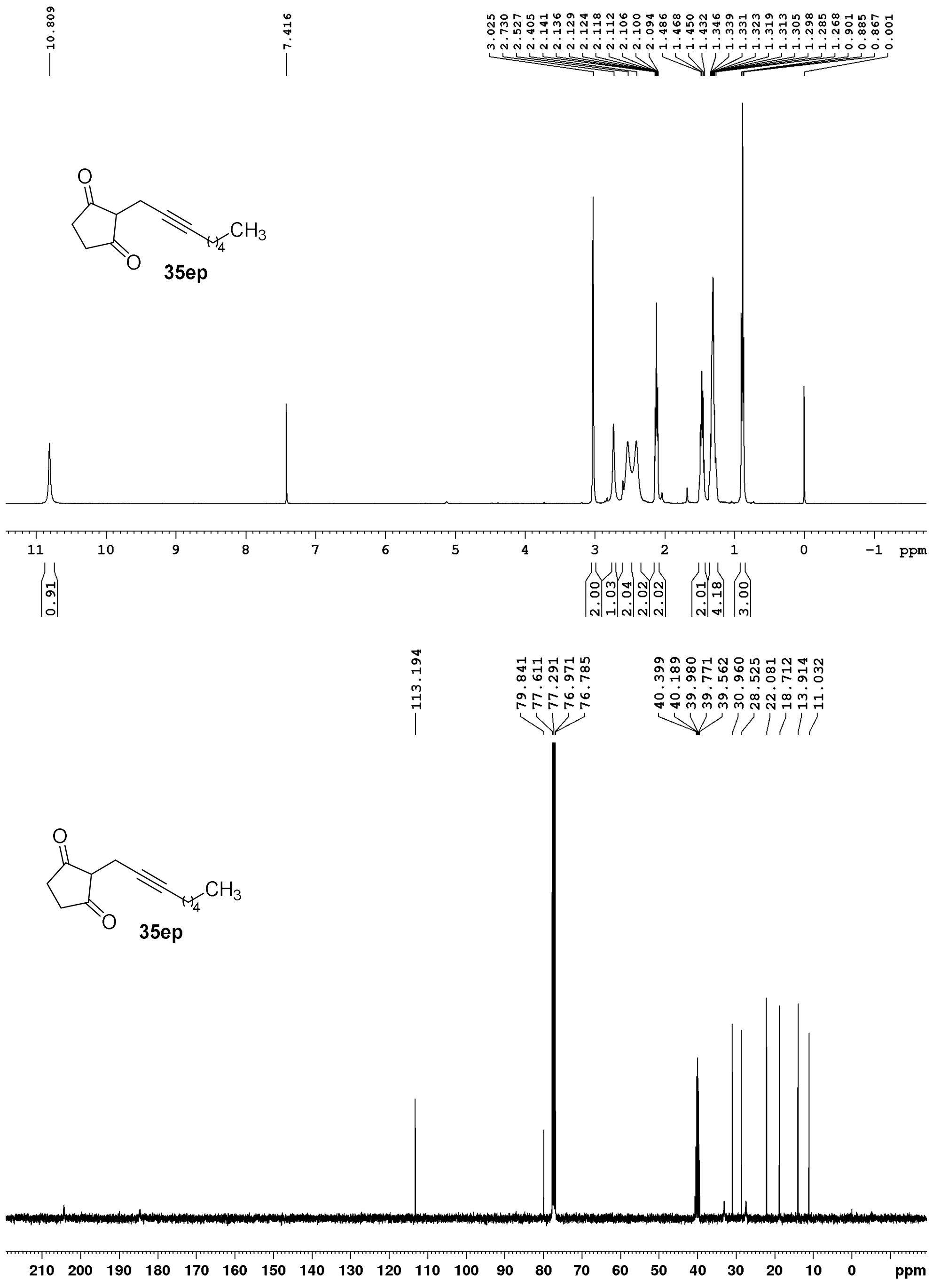
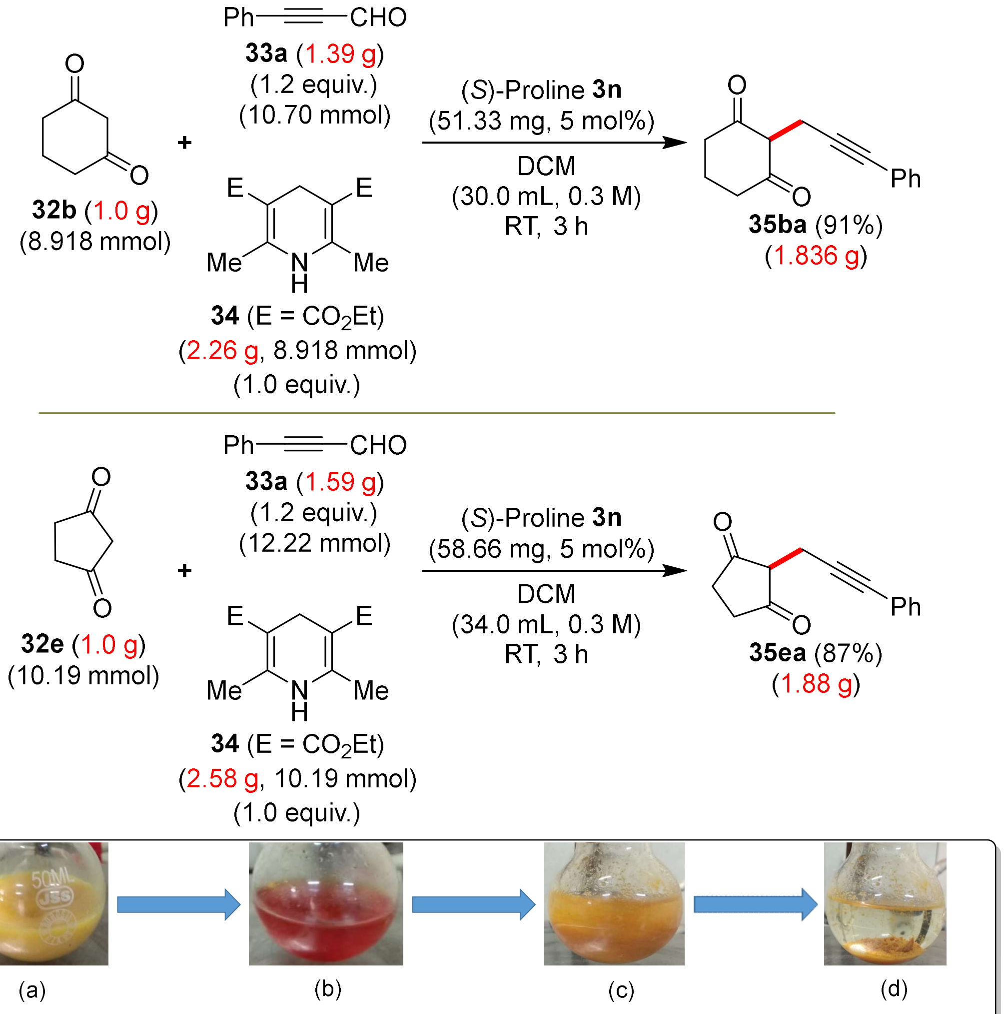


Figure 15: ^{1}H and ^{13}C spectra of the product **35ep**.

In a similar manner, 2-(3-aryl/alkylprop-2-yn-1-yl)cyclopentane-1,3-diones **35ea-eq** were obtained in excellent yields and shorter reaction times through a reductive coupling reaction of cyclopentane-1,3-dione **32e** with a variety of 3-aryl/alkylpropiolaldehydes (**33a-q**) containing halogen atoms, electron withdrawing, electron donating, neutral, and heteroatom substituted aryl moieties as well as alkyl groups (Table 4). Exceptionally, amino acid **3n** catalyzed three-component reductive coupling of cyclopentane-1,3-dione **32e** with phenyl, 4-halophenyl, 4-cyanophenyl, 4-nitrophenyl, 4-methoxyphenyl, 4-methylphenyl-, 4-^{n}butylphenyl-, naphthalene-1-yl, furan-2-yl, thiophen-2-yl, *N*-Boc-indolyl-3-yl, *n*-butyl, *n*-pentyl, and *n*-hexyl substituted 3-aryl/alkyl-propiolaldehydes **33a-q** and Hantzsch ester **34** in DCM at 25 °C for 15 min. to 2.5 h furnished the coupling products 2-(3-aryl/alkylprop-2-yn-1-yl)cyclopentane-1,3-diones **35ea-eq** in 80-96% yields as shown in Table 4. Formation of TCRP products **35bc-bg/35ec-eg** took longer reaction times compared to other products **35** (see Tables 3-4), may be due to the shift in the direction of the polarization of double bond between electron-withdrawing group substituted aryls or 1,3-dicarbonyls in the in situ generated Knoevenagel condensation intermediates **Bbc-bg/Bec-eg** (see Scheme 15), which delayed transfer hydrogenation. Herein, all of these coupling products were purified by simple precipitation of reaction mixture in cold 10% ethyl acetate in hexanes and followed by quick filtration gave the analytically pure coupling products **35eb-eq** straightway, in very good yields (Table 4).

3.2.3 Gram-scale synthesis of TCRP products:

In order to investigate the sustainability of the reductive coupling reaction in bulk scale, we planned grams scale reaction of cyclohexane-1,3-dione **32b** (1.0 g, 8.918 mmol) with reduced equivalents of 3-phenylpropiolaldehyde **33a** (1.39 g, 10.7 mmol, 1.2 equiv.) and Hantzsch ester **34** (2.26 g, 8.918 mmol) under the catalysis of (*S*)-proline **3n** (51.33 mg, 5 mol%) in DCM (30.0 mL, 0.3 M) at 25 °C for 3.0 h followed by precipitation-filtration technique furnished the coupling product **35ba** in 91% (1.836 g) yield (Scheme 16).



(a) Visual appearance of the reaction mixture as soon as the reactants, catalyst and solvent were added.
(b) Visual appearance of the reaction mixture as soon as the reaction completed.
(c) Visual appearance of the precipitate formed as soon as the addition of cold 10% ethyl acetete in hexanes to the reaction mixture at 0 °C.
(d) Visual appearance of the pure product as precepitated after 2-3 washings of reaction mixture with 10% ethyl acetate in hexanes at 0 °C.

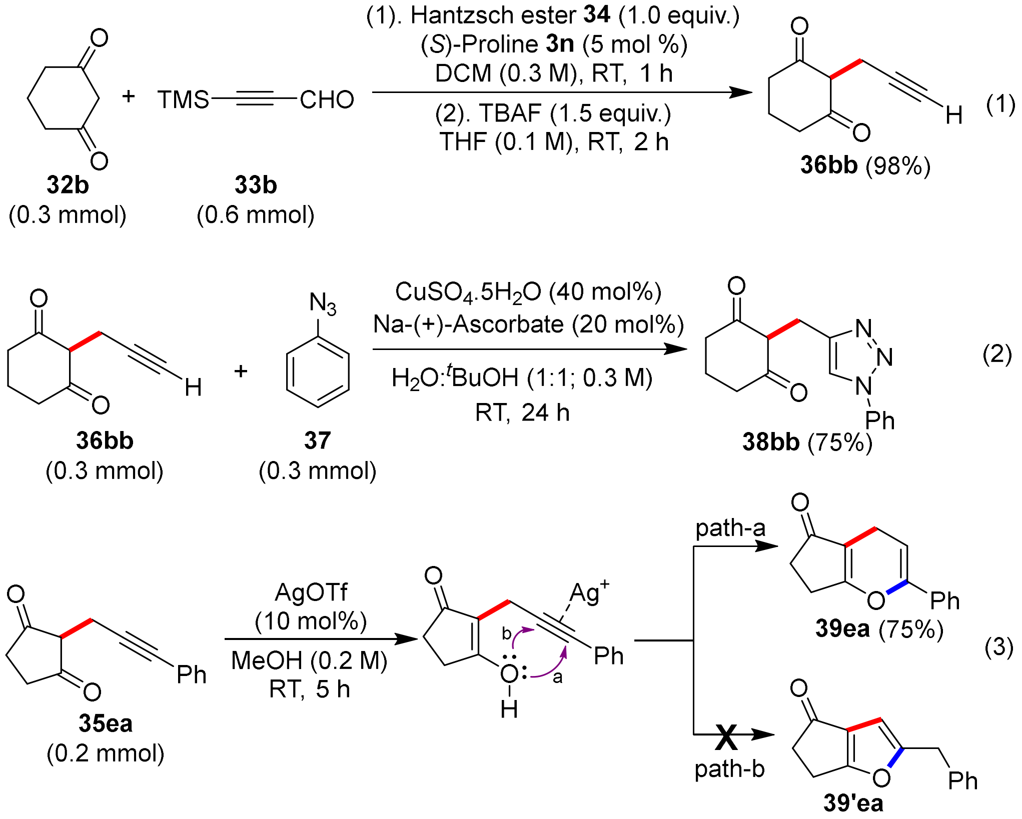
Scheme 16: Gram-Scale Synthesis of TCRP Products **35ba**/**35ea** and Pictorial representation of Gram-Scale reaction.

In a similar mode, reaction of cyclopentane-1,3-dione **32e** (1.0 g, 10.19 mmol) with **33a** (1.59 g, 12.22 mmol, 1.2 equiv.) and **34** (2.58 g, 10.19 mmol) under the catalysis of (*S*)-proline **3n** (58.66 mg, 5 mol%) in DCM (34.0 mL, 0.3 M) at 25 °C for 3.0 h followed by precipitation-filtration technique furnished the coupling product **35ea** in

87% (1.88 g) yield (Scheme 16). This clearly proves the simplicity and significance of the metal-free coupling reaction for industrial applications.

3.2.4 Synthetic applications of TCRP products:

As discussed earlier, there are plentiful potential applications for the propargylated coupling products **35** and few of them are demonstrated herein. Deprotection of the TMS group on the propargylated compound **35bb** with tetra-*n*-butylammonium fluoride (TBAF) was performed in sequential one-pot manner starting from **32b**, **33b**, **34** and **3n** in DCM followed by next reaction in THF furnished the 2-(prop-2-yn-1-yl)cyclohexane-1,3-dione **36bb** in 98% yield containing the terminal alkyne, which is a versatile unit that can be used in different type of organic reactions (Scheme 17, Eq. 1).[6d]



***Scheme 17*:** TMS-Deprotection, Click and Annulative Etherification Reactions on the Reductive Coupling Products **35**.

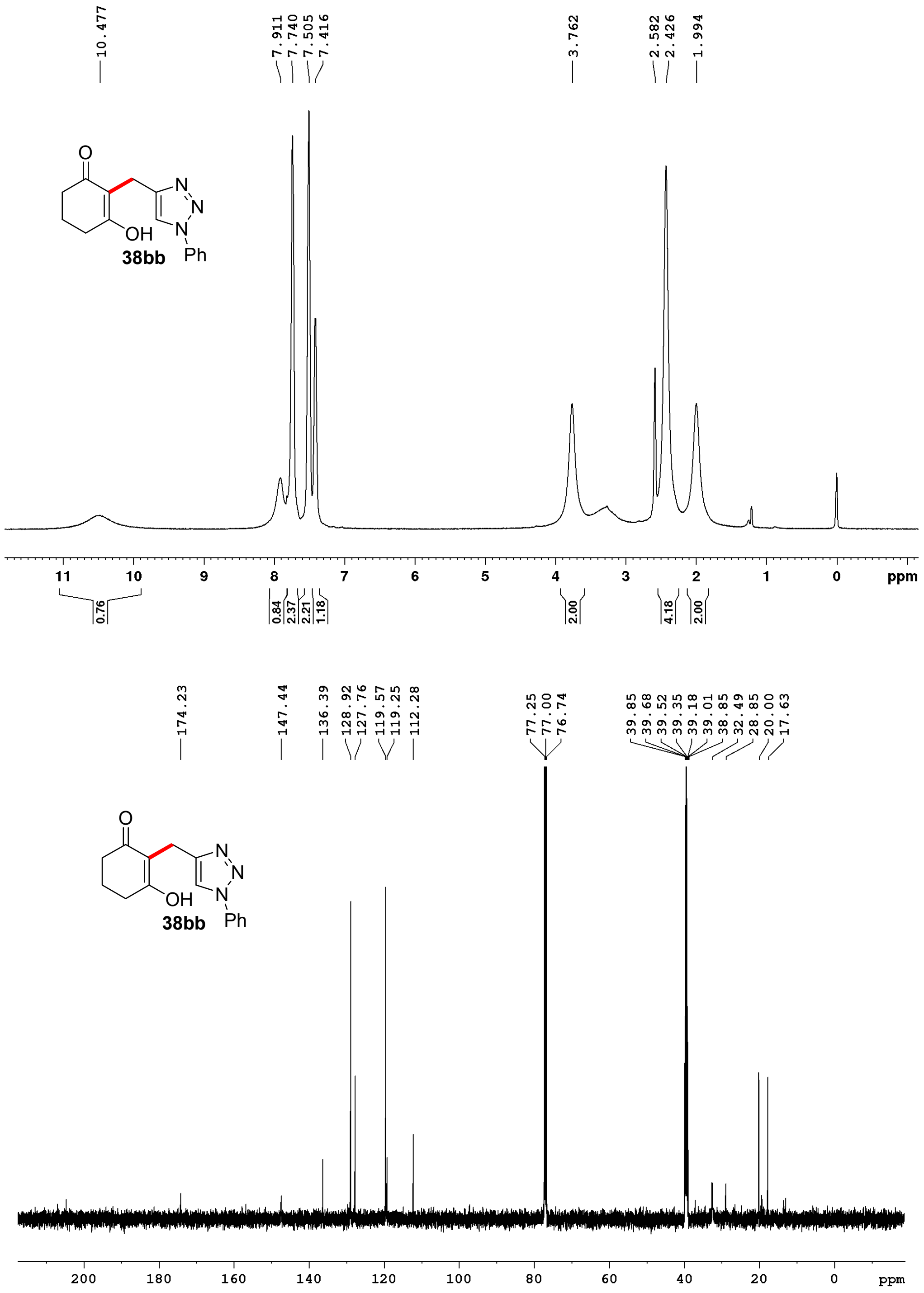
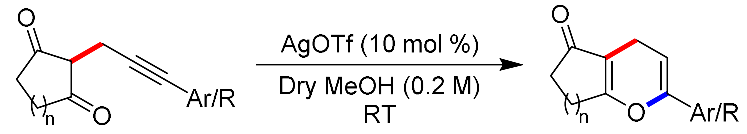


Figure 16: ^{1}H and ^{13}C spectra of the product **38bb**.

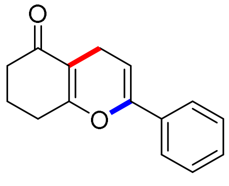
Copper-catalyzed azide–alkyne [3+2]-cycloaddition of **36bb** with PhN_3 **37** in water and *tert*-BuOH at 25 °C for 24 h furnished the click product **38bb** in 75% yield (Scheme 17, Eq. 2). It is a popular fact that 1,2,3-triazoles are biologically and medicinally important compounds and 1,2,3-triazoles containing cyclic-1,3-diketones will be interesting intermediates for medicinal to material chemistry.[10] Subsequently, we thought of executing an intramolecular cyclization of coupling products **35** under the Lewis acid-catalysis, as compounds **35** contain the requisite active functional groups.[11] First, we engineered the cyclization reaction of propargylated coupling compound **35ea** with 10 mol% of AgOTf in dry methanol at 25 °C for 5 h, which resulted in the annulative etherification product **39ea** in 75% yield with high selectivity (Scheme 17, Eq. 3).[11]

During the course of intramolecular cyclization, even though there is a chance for the formation of either substituted dihydrofuran or dihydropyran rings, but only substituted dihydropyran ring was formed exclusively. Observed high selectivity can be explained based on the stability of the carbocation formed during the course of reaction as shown in Scheme 17, Eq. 3. With annulative etherification protocol in hand, we further investigated the scope of this reaction by developing a library of functionally rich dihydropyrans **39** from the various coupling products **35** (Table 5).[12] Reaction of 2-(3-arylprop-2-yn-1-yl)cyclohexane-1,3-diones **35ba**-**bi** containing phenyl-, 4-bromophenyl, 4-cyanophenyl, 4-nitrophenyl, and 4-methylphenyl, under the catalysis of AgOTf in dry methanol at 25 °C for within 50 min. to 60 min. furnished the expected dihydropyrans **39ba**-**bi** in very good yields (85-76%) with high selectivity as shown in Table 5.

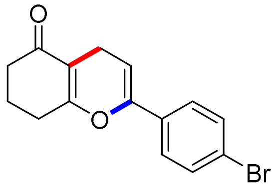
Table 5: Scope of Annulative Etherification Reaction.[a]



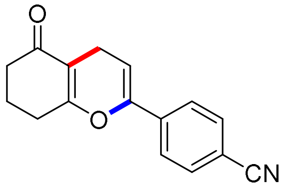
35 (n = 1,2) **39** (n = 1,2)



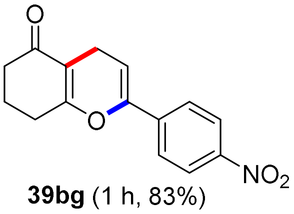
39ba (1 h, 85%)



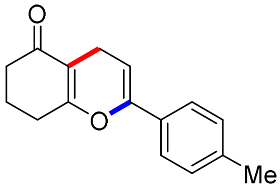
39be (50 min, 85%)



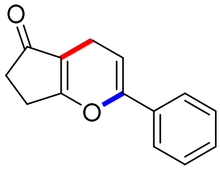
39bf (1 h, 82%)



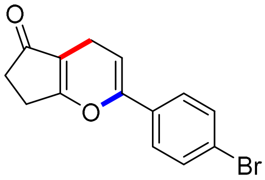
39bg (1 h, 83%)



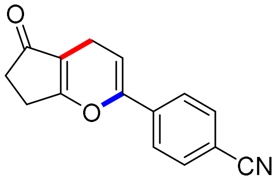
39bi (1 h, 76%)



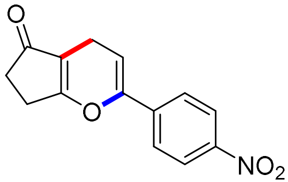
39ea (5 h, 75%)



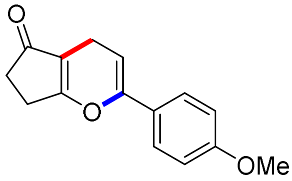
39ee (5 h, 84%)



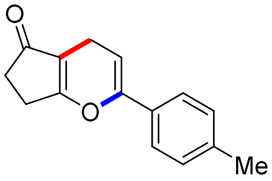
39ef (5 h, 72%)



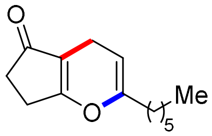
39eg (12 h, 69%)



39eh (5 h, 80%)



39ei (5 h, 81%)



39eq (5 h, 85%)

[a]Reactions were carried out in dry MeOH (1.0 mL) with 1.0 equiv of **35** (0.2 mmol) in the presence of 10 mol% of AgOTf and yield refers to the product obtained from column chromatography.

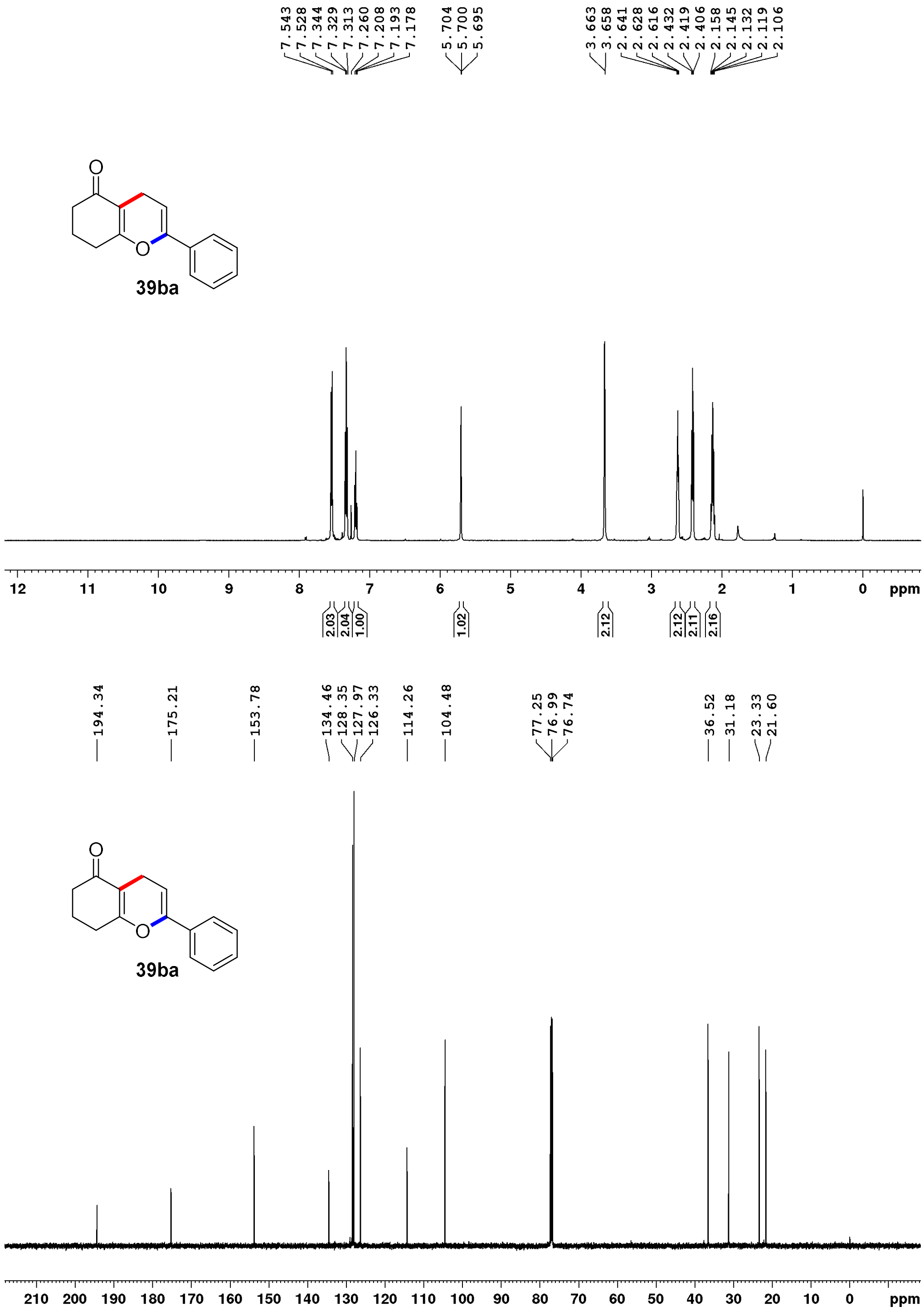


Figure 17: ^{1}H and ^{13}C spectra of the product **39ba**.

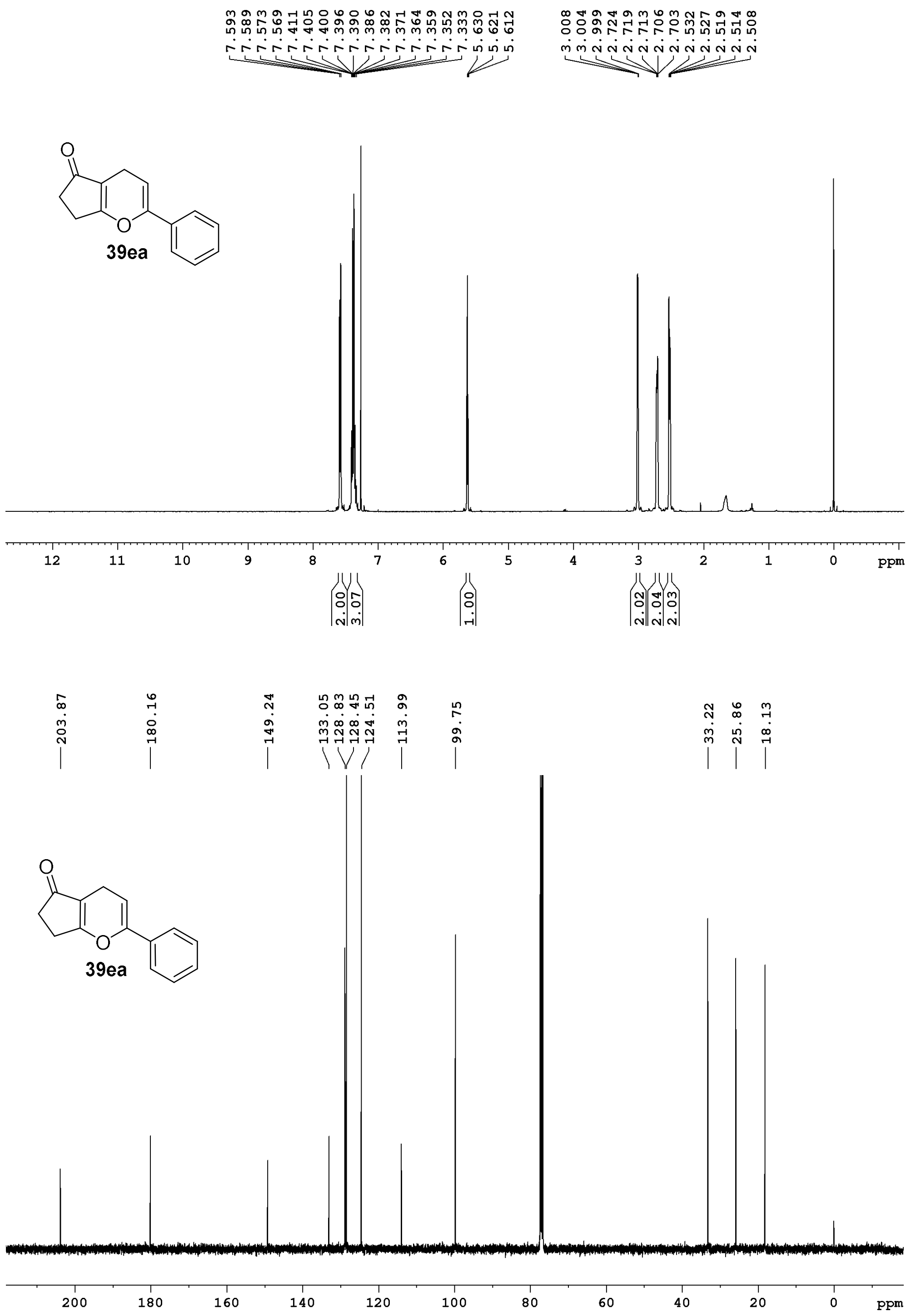
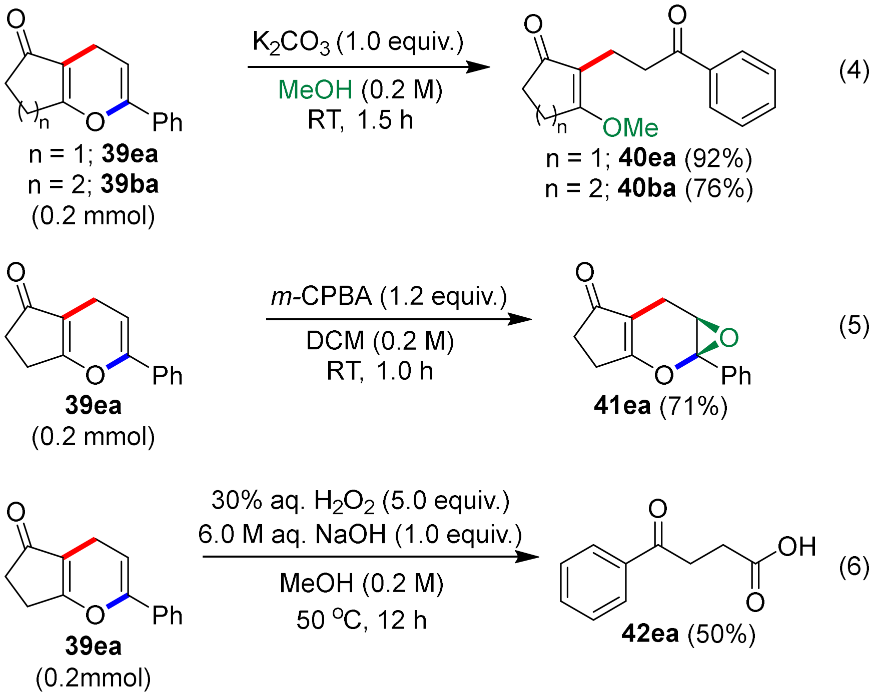


Figure 18: ^{1}H and ^{13}C spectra of the product **39ea**.

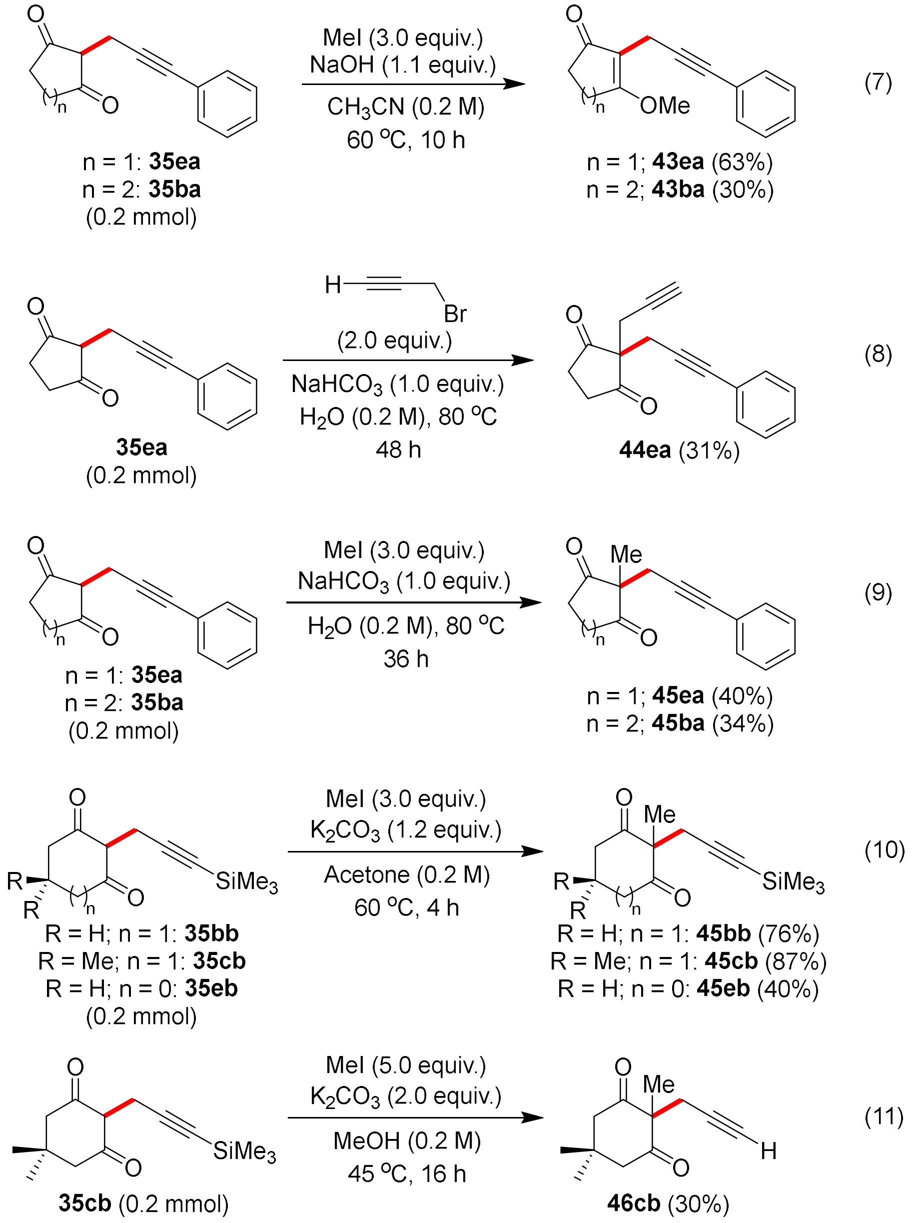
In a similar manner, cyclization reaction of 2-(3-aryl/alkylprop-2-yn-1-yl)cyclopentane-1,3-diones **35ea**-**eq** containing phenyl, 4-bromophenyl, 4-cyanophenyl, 4-nitrophenyl, 4-methoxyphenyl, 4-methylphenyl, and *n*-hexyl under the catalysis of 10 mol% AgOTf in dry methanol at 25 °C for longer reaction times (5 h to 12 h) furnished the expected dihydropyrans **39ea**-**eq** in good to excellent yields (85-69%) with high selectivity as shown in Table 5. Gratifyingly, the various substituents present on the propargylated products **35** seems not to have much effect on the Lewis acid-mediated annulative etherification reaction (Table 5).

In order to increase the versatility of the annulation reaction, we investigated few synthetic applications of annulation products **39**. Delightfully, treatment of dihydropyrans **39ea** or **39ba** with 1.0 equiv. of K_2CO_3 in dry methanol at room temperature for 1.5 h resulted in nucleophilic 1,4-addition of methanol followed by pyran ring opening to furnish the products **40ea** or **40ba** in excellent yields (92% and 76% respectively, Scheme 18, Eq. 4). On the other hand, epoxidation of **39ea** with 1.2 equiv. of m CPBA in DCM at 25 °C for 1 h furnished the selective epoxide product **41ea** in 71% yield (Scheme 18, Eq. 5). While oxidation of **39ea** with 5.0 equiv. of 30% aqueous H_2O_2 in the presence of 6.0 M aqueous NaOH in methanol at 50 °C for 12 h furnished the 4-oxo-4-phenylbutanoic acid **42ea** in 50% yield through a sequence of epoxidation/epoxide ring opening with hydroxide/Baeyer-Villiger oxidation reactions (Scheme 18, Eq. 6). These reactions not only for diversifying of dihydropyrans **39**, but gave strong support to the structural analysis of regioselective formation of **39** from Ag(I)-catalysis on **35** (see Table 5).



Scheme 18: Controlled Experiments on the Annulative Etherification Products **39**.

Further, we shown interest to synthesize the 2-methyl-2-(3-aryl/alkylprop-2-yn-1-yl)cyclopentane-1,3-diones and 2-methyl-2-(3-aryl/alkylprop-2-yn-1-yl)cyclohexane-1,3-diones from the corresponding coupling products **35** through *C*-methylation, as these compounds are prolific starting materials in various organic transformations (see Scheme 14).[7] Same time, base-mediated selective *C*-methylation of the propargylated coupling products **35** with methyl iodide is a challenging task as *O*-methylation will be a dominating side reaction. Firstly, reaction of **35ea** or **35ba** with 3 equiv. of MeI in the presence of 1.1 equiv. of NaOH in acetonitrile at 60 °C for 10 h, furnished only *O*-methylation products **43ea** or **43ba** in 63% and 30% yield, respectively and surprisingly didn’t find the *C*-methylation products (Scheme 19, Eq. 7). These results gave inspiration to study some more details about methylation reactions on **35** (Scheme 19). Reaction of **35ea** with 2.0 equiv. of propargyl bromide in the presence of 1.0 equiv. of sodium bicarbonate in water at 80 °C for 48 h, furnished only *C*-propargyl product **44ea** in 31% yield (Scheme 19, Eq. 8), which gave insight to install methyl group on C-2 position of **35**.



Scheme 19: Methylation Reactions on the Reductive Coupling Products **35**.

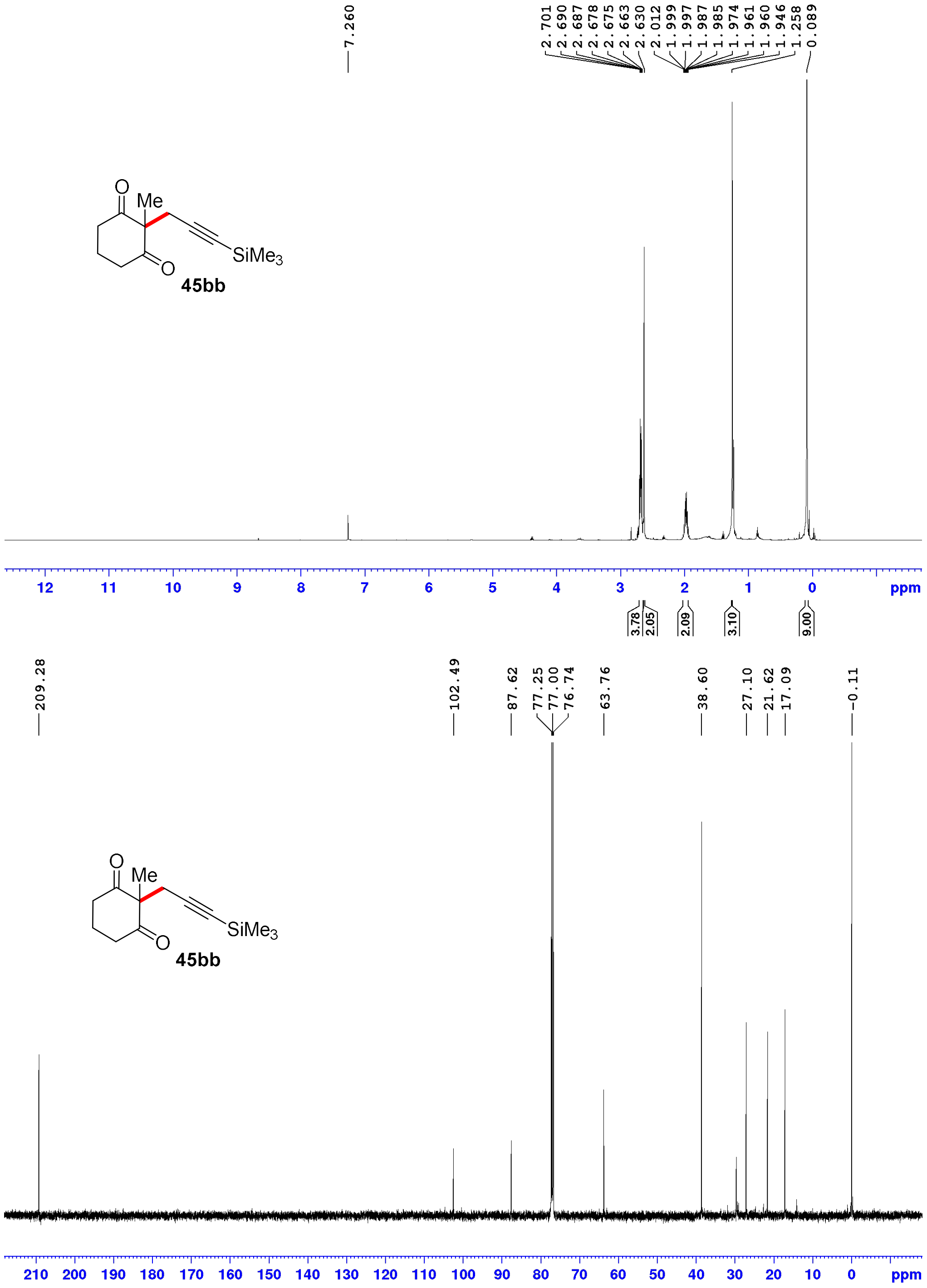


Figure 19: ^{1}H and ^{13}C spectra of the product **45bb**.

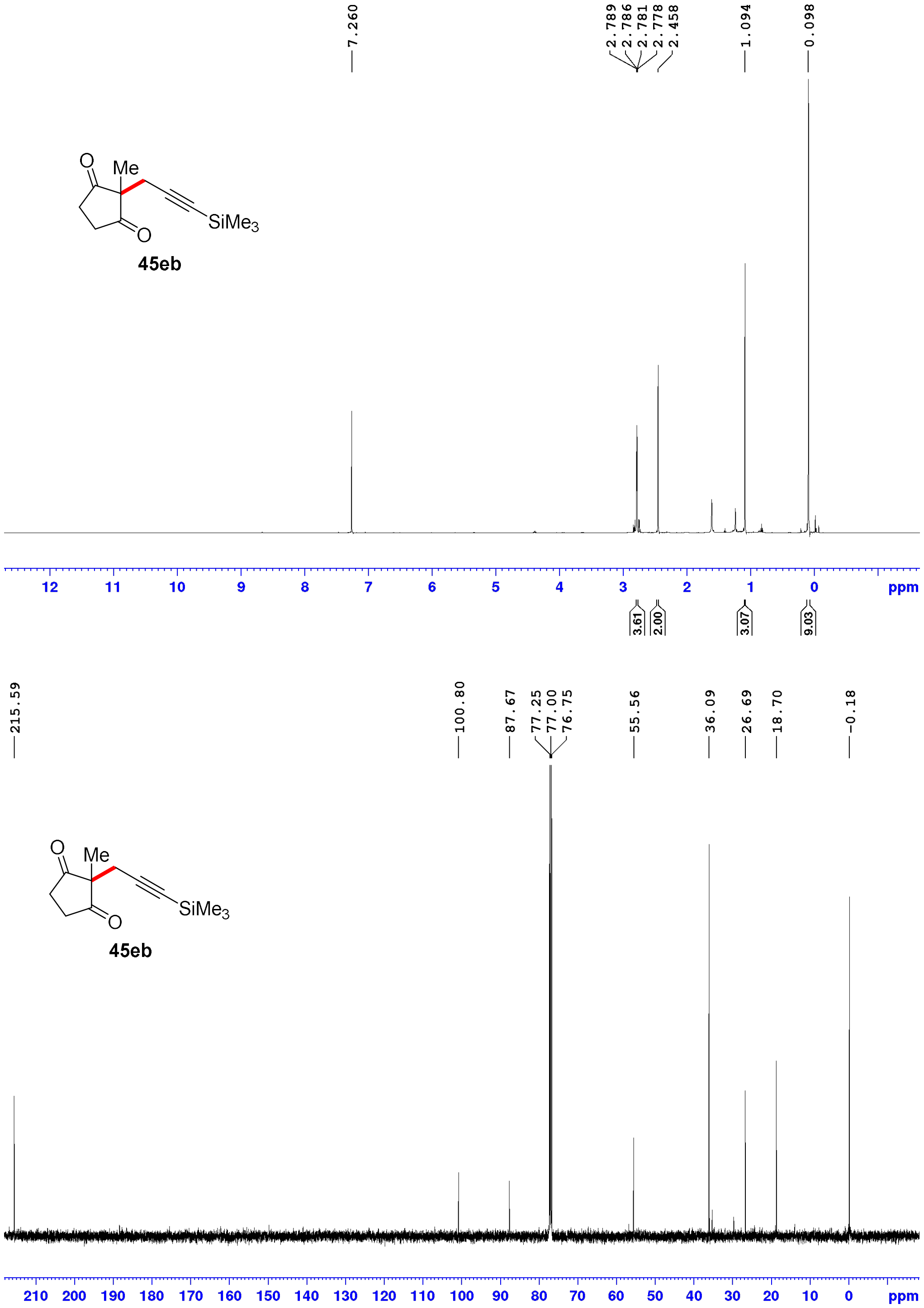
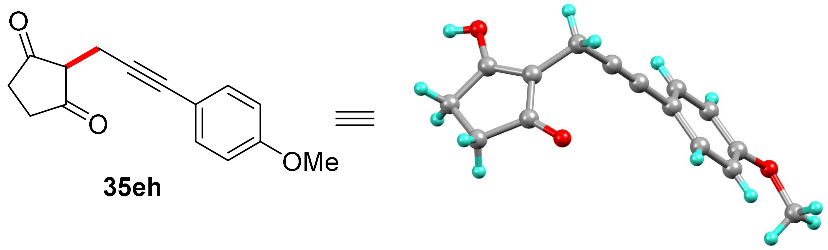


Figure 20: ^{1}H and ^{13}C spectra of the product **45eb**.

Strikingly, reaction of **35ea** or **35ba** with 3 equiv. of MeI in the presence of 1.0 equiv. of sodium bicarbonate in water at 80 °C for 36 h, furnished only *C*-methylation products **45ea** or **45ba** in moderate (40% and 34%) yields, respectively and we didn't find the *O*-methylation products (Scheme 19, Eq. 9). To improve yields and diversity of methylation reactions, we have tested next conditions on different substrates. Fortunately, reaction of 2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclohexane-1,3-diones **35bb**, **35cb** or 2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentane-1,3-dione **35eb** with 3 equiv. of MeI in the presence of 1.2 equiv. of potassium carbonate in acetone at 60 °C for 4 h, furnished *C*-methylation products **45bb** in 76%, **45cb** in 87% and **45eb** in 40% yields, respectively and in last case we observed the *O*-methylation product **43eb** in 60% yield (Scheme 19, Eq. 10). In a continuation, when we performed the methylation reaction of **35ba** with 3 equiv. of MeI in the presence of 2.0 equiv. of potassium carbonate in methanol at 45 °C for 16 h, furnished domino C-methylation/TMS-deprotection product **46ba** in 30% yield (Scheme 19, Eq. 11). Definitely these methylation reactions on reductive coupling products **35** will give inspiration for organic chemists to make useful library of **44-46** and use them as starting materials to investigate new annulation reactions.



35eh

Figure 21**:** X-ray crystal stucture of 2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)cyclopentane-1,3-dione **35eh**.

The structure and relative stereochemistry of the reductive coupling **35** and their application products **36**, and **38-46** were established by IR, NMR, and mass analysis and also finally confirmed by correlation with the X-ray crystal structure of **35eh** (Figure 21).[13]

3.3 Conclusions

In summary, we effectively established a new synthetic methodology named 'organocatalytic three-component reductive propargylation' for the selective coupling of propargyl aldehydes with CH-acids or active methylene compounds under the 5 mol% of (*S*)-proline in presence of Hantzsch ester as hydrogen source. The metal-free reductive coupling method has wide substrate tolerance in generating the mono-propargylated cyclic and acyclic products and which has lot more applications in total synthesis of natural products, drugs and designed materials. We have also shown applications of reductive coupling products **35** into synthesizing click 1,2,3-triazoles **38**, functionally rich dihydropyrans **39**, and methylation products **43-46**, which act as excellent building blocks for many natural products and pharmaceuticals. Further, more applications toward this 'organocatalytic three-component reductive propargylation' is currently underway.

4. Organocatalytic Asymmetric Formal [3+2] Cycloaddition as a Versatile Platform to Access Methanobenzo[7]annulenes

4.1 Introduction

Bicyclo[3.2.1]octane unit is widely present in both natural and synthetic compounds which possess various biological activities (Figure 22).[15] To date chiral bicyclo[3.2.1]octanes have been known to be prepared,[16] using organocatalytic Michael−aldol, Michael−Henry, Michael-isomerization-Michael, and Michael−elimination−Michael cascades from simple β-keto esters or ketones with α,β-unsaturated aldehydes or nitrostyrenes, respectively. Nevertheless, we still need newer high yielding catalytic methods for creating methanobenzo[7]annulenes containing multiple chiral centers, in a stereocontrolled fashion.[17]

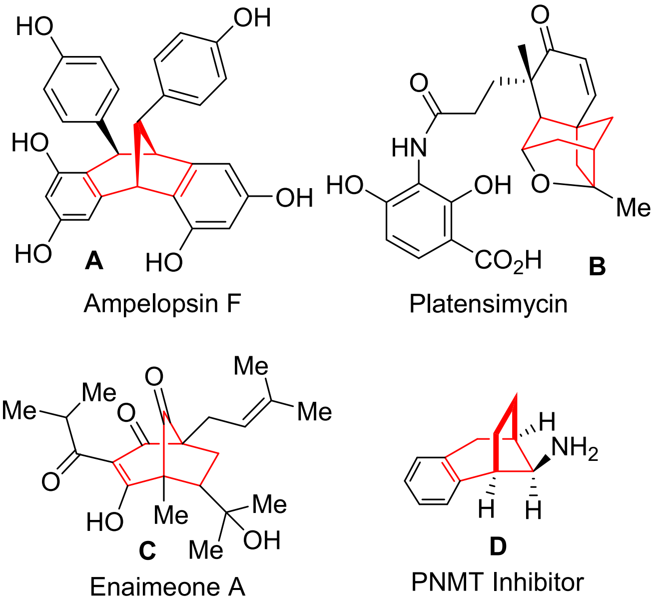
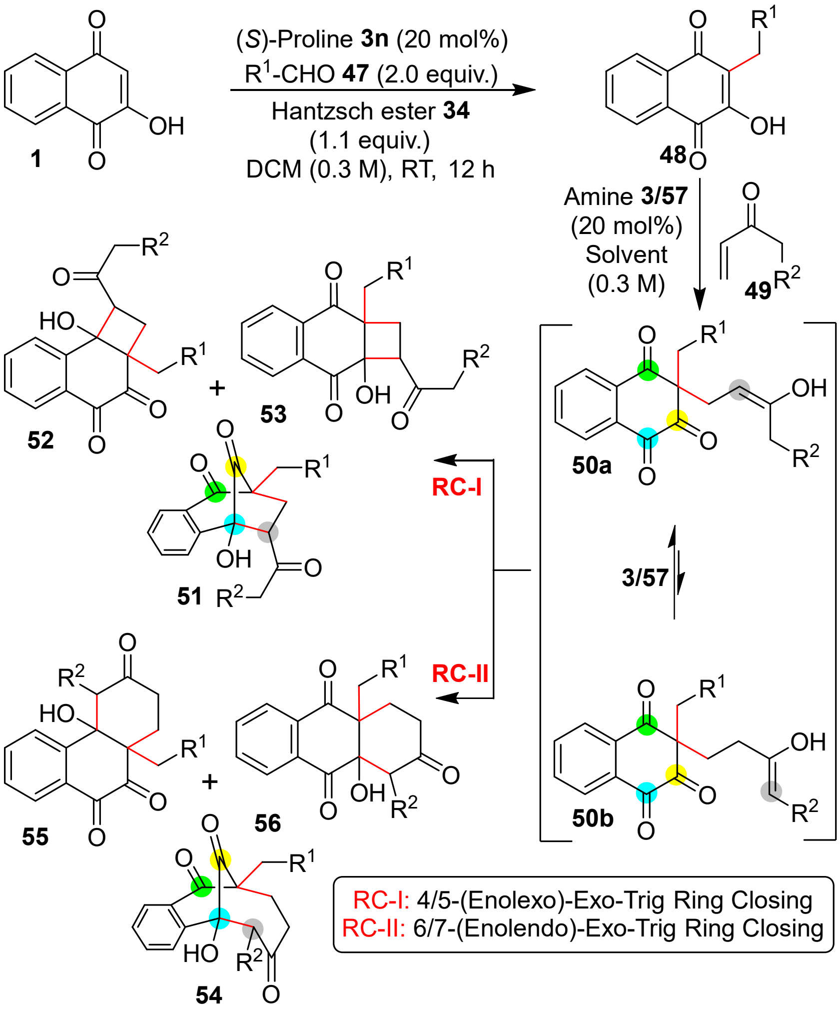


Figure 22: Medicinally important benzobicyclo[3.2.1]octanes.

We have developed here for the first time an economic metal-free approach for the high-yielding stereoselective synthesis of privileged bicyclo[3.2.1]octanes as substituted methanobenzo[7]annulenes in both achiral and chiral forms, through a novel organocatalytic formal [3+2]-cycloaddition [or] domino Michael/*5-(enolexo)-exo-trig* cyclization reactions of laboratory prepared 2-alkyl-3-hydroxynaphthalene-1,4-diones with commercially available alkyl vinyl ketones under catalytic and ambient conditions.



Scheme 20: Reaction layout for the methanobenzo[7]annulenes through domino Michael and 5-(*enolexo*)-*exo-trig* cyclizations or formal [3+2]-cycloadditions.

Hence, synthesis and investigation of synergistic nucleophilic and electrophilic nature of 2-alkyl-3-hydroxynaphthalene-1,4-diones **48** through organocatalysis presents an intriguing synthetic challenge to work on. Starting materials, 2-alkyl-3-hydroxynaphthalene-1,4-diones **48** could be prepared in good yields by using recently emerging organocatalytic three-component reductive alkylation (TCRA) or reductive coupling reaction.[8,18,19]

Surprisingly, there is no asymmetric transformation known utilizing 2-alkyl-3-hydroxynaphthalene-1,4-diones **48**[7] and herein, we used them as suitable starting materials along with alkyl vinyl ketones **49** for the designed asymmetric domino Michael and *5-(enolexo)-exo-trig* cyclizations or formal [3+2]-cycloadditions (Scheme 20).[20]

4.2 Results and Discussions

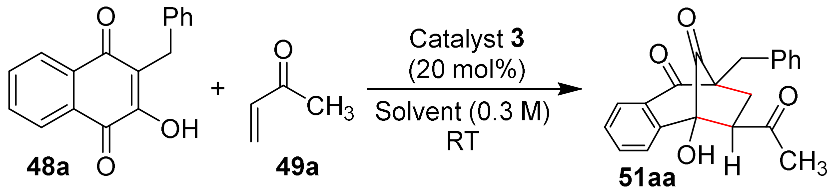
4.2.1 Reaction optimization:

Building on this backdrop and also due to the ease with which TCRA products could be made efficiently, we surmised to utilize (*S*)-proline **3n** would catalyze the TCRA reaction of Lawsone **1**, aldehydes **47** and Hantzsch ester **34** to furnish the alkylation products **48** in very good yields (Scheme 20). Organocatalytic domino Michael-aldol reactions between the resulting 2-alkyl-3-hydroxynaphthalene-1,4-diones **48** with alkyl vinyl ketones **49** would yield the unexpected methanobenzo[7]annulenes **51** in a highly stereoselective and product specific manner over competition with five other ring closing cyclizations (Scheme 20).

To understand the designed domino reaction rate, catalyst/solvent effect, selectivity, and product distribution over other possible ring closing cyclizations, first we investigated the organocatalytic racemic 5-(*enolexo*)-*exo-trig* cyclization through domino Michael-aldol reactions between hydroxy-dione **48a** and methyl vinyl ketone **49a** under the catalysis of achiral amines/base Et_3N (**3o**), DMAP (**3p**), TBD (**3q**), KO*t*Bu (**3r**), and DBU (**3s** (Table 6)). After thorough investigation, we found that

DMAP **3p** would catalyse the racemic domino reaction of **48a** with **49a** in toluene at 25 °C for 9 h to furnish the achiral methanobenzo[7]annulene **51aa** in 93% yield with 4:1 dr (Table 6).

Table 6: Investigation of the Proposed Racemic Reaction.[a]



Entry	Catalyst **3** [20 mol%]	Solvent [0.3 M]	Time [h]	Yield [%][b] **51aa**	dr [%][c] **51aa**
1	Et_3N **3o**	DMSO	14	75	2.8:1
2	Et_3N **3o**	DMF	18	78	2.9:1
3	Et_3N **3o**	THF	27	70	4.2:1
4	Et_3N **3o**	$CHCl_3$	16	78	5.3:1
5	Et_3N **3o**	CH_3CN	21	60	5.5:1
6	Et_3N **3o**	DCM	16	80	4.2:1
7	Et_3N **3o**	$C_6H_5CH_3$	15	90	5.3:1
8	DMAP **3p**	$C_6H_5CH_3$	9	93	4.0:1
9	TBD **3q**	$C_6H_5CH_3$	9	85	3.2:1
10	KO^{t}Bu **3r**	$C_6H_5CH_3$	10	80	1.4:1
11	DBU **3s**	$C_6H_5CH_3$	36	–	–
12	AcOH **3t**	$C_6H_5CH_3$	72	–	–

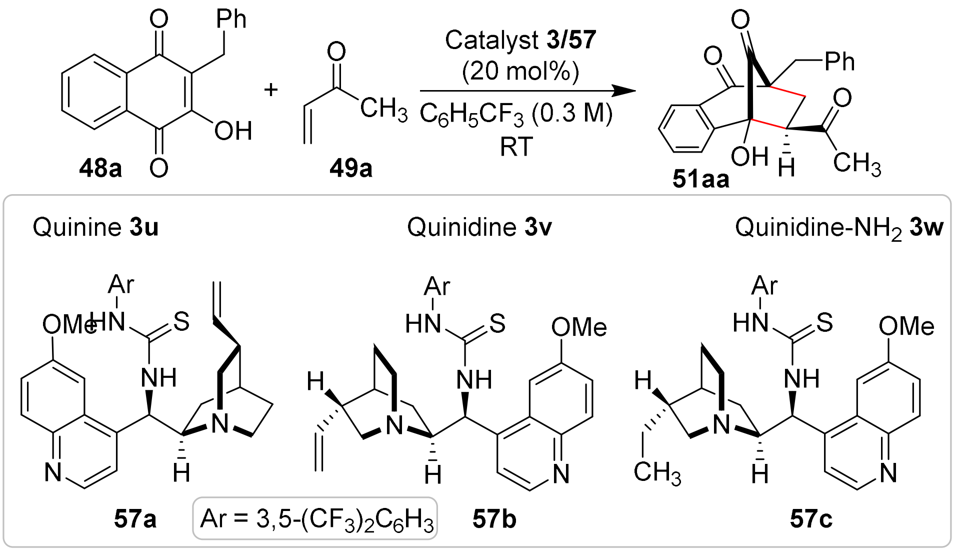
[a]Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **49a** relative to the **48a** (0.3 mmol) in the presence of 20 mol% of catalyst **3**. [b] Yield refers to the column-purified product. [c] dr determined by 1H NMR and CSP HPLC analysis.

Next, we focused to investigate the asymmetric induction in the designed domino reaction (Table 7). Stimulating investigative reports on the cinchona alkaloid catalysis,[21] by Deng and other research groups inspired us to utilize them in our present studies (Table 7). To start with, simple amino acid (*S*)-proline **3n** was tested as the catalyst for the chiral version of the domino reaction of **48a** with **49a** in toluene at 25 °C for 20 h (Table 7, entry 1). Though the reaction progressed well to furnish the desired product **51aa** in very good yield, the selectivity obtained was disappointingly poor. The same reaction with quinine **3u** as the catalyst at 25 °C for 36 h furnished the chiral product **51aa** in 90% yield with 34% *ee* and 5:1 dr (Table 7, entry 2). Quinidine **3v** catalysis also furnished the product **51aa** with little improvement (90% yield, 42% *ee* and 6:1 dr, entry 3). Surprisingly, the same reaction under the catalysis of *epi*-quinidine-NH_2 **3w** at 25 °C for 32 h furnished the product **51aa** in 80% yield with 0% *ee* and 2:1 dr (Table 7, entry 4).

After understanding the reactivity pattern of quinine/quinidine with **48a** and **49a**, we realized that the *tert*-amine of **3u-v** is acting as base to induce the nucleophilic nature of **48a** through hydrogen bonding, but the facial selectivity and electrophilicity of **49a** are not induced much under the reaction conditions. To perform the synergistic activation of both the functional groups of **48a** and **49a**, we thought of using the primary amine-thiourea **57a**, **57b** or **57c** as the catalyst to achieve high selectivity.

Interestingly, the domino reaction of **48a** and **49a** with 20 mol% of 9-*epi*-aminoquinidine-thiourea **57a** in toluene at 0-3 °C for 24 h furnished the chiral product (+)-**51aa** in 90% yield with 90% *ee* and 86:1 dr as expected (Table 7, entry 5). The same reaction in trifluorotoluene at 0-3 °C for longer time (72 h) furnished the chiral product (+)-**51aa** in reduced (75%) yield with increased (94%) *ee* and decreased (24:1) dr; but same reaction at 25 °C furnished (+)-**51aa** in 86% yield with 91% *ee* and 22:1 dr within 8 h (Table 7, entries 6-7). There is not much improvement in hexafluorobenzene as solvent compared to trifluorotoluene (entry 8). During subsequent optimization studies, we obtained the antipode (−)-**51aa** in 85-90% yield with high enantio- and diastereoselectivities (up to 97% *ee* and 99:1 dr) under the catalysis of 9-*epi*-aminoquinine-thiourea **57b** (15-30 mol%) in trifluorotoluene at 0-3 or 20 °C for 6-21 h (Table 7, entries 9-12).

***Table** 7*: Investigation of the Proposed Asymmetric Reaction.[a]



Entry	Catalyst [20 mol%]	Time [h]	Yield [%][*b*] **51aa**	dr [%][*c*] **51aa**	ee [%][*d*] **51aa**
1[e]	**3n**	20	90	1:1	7 [0]
2[e]	**3u**	36	90	5:1	34 [23]
3[e]	**3v**	36	90	6:1	42 [28]
4[e]	**3w**	32	80	2:1	0 [0]
5[e, f]	**57a**	24	90	86:1	90 [85]
6[f]	**57a**	72	75	24:1	94 [85]
7	**57a**	8	86	22:1	91 [86]
8[f,g]	**57a**	72	73	22:1	91 [94]
9[h]	**57b**	6	90	61:1	95 [99]
10[f]	**57c**	21	85	99:1	97 [99]
11[h,i]	**57b**	11	87	66:1	93 [99]
12[h,j]	**57b**	6	90	46:1	95 [99]
13[h]	**57c**	7	80	9:1	94 [99]

[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **49a** relative to the **48a** (0.3 mmol) in the presence of 20 mol% of catalyst **3**/**57**. [b] Yield refers to the column-purified product. [c] dr determined by ^{1}H NMR and CSP HPLC analysis. [d] *ee* determined by CSP HPLC analysis and values in paranthesis represent for minor diastereomer. [e] Toluene as the solvent. [f] T = 0-3 °C. [g] C_6F_6 as the solvent. [h] T = 20

°C. [i] 15 mol% of **57b** used. [j] 30 mol% of **57b** used. Note: Entries 5-8 represents the opposite enantiomers of compound **51aa** shown in Table.

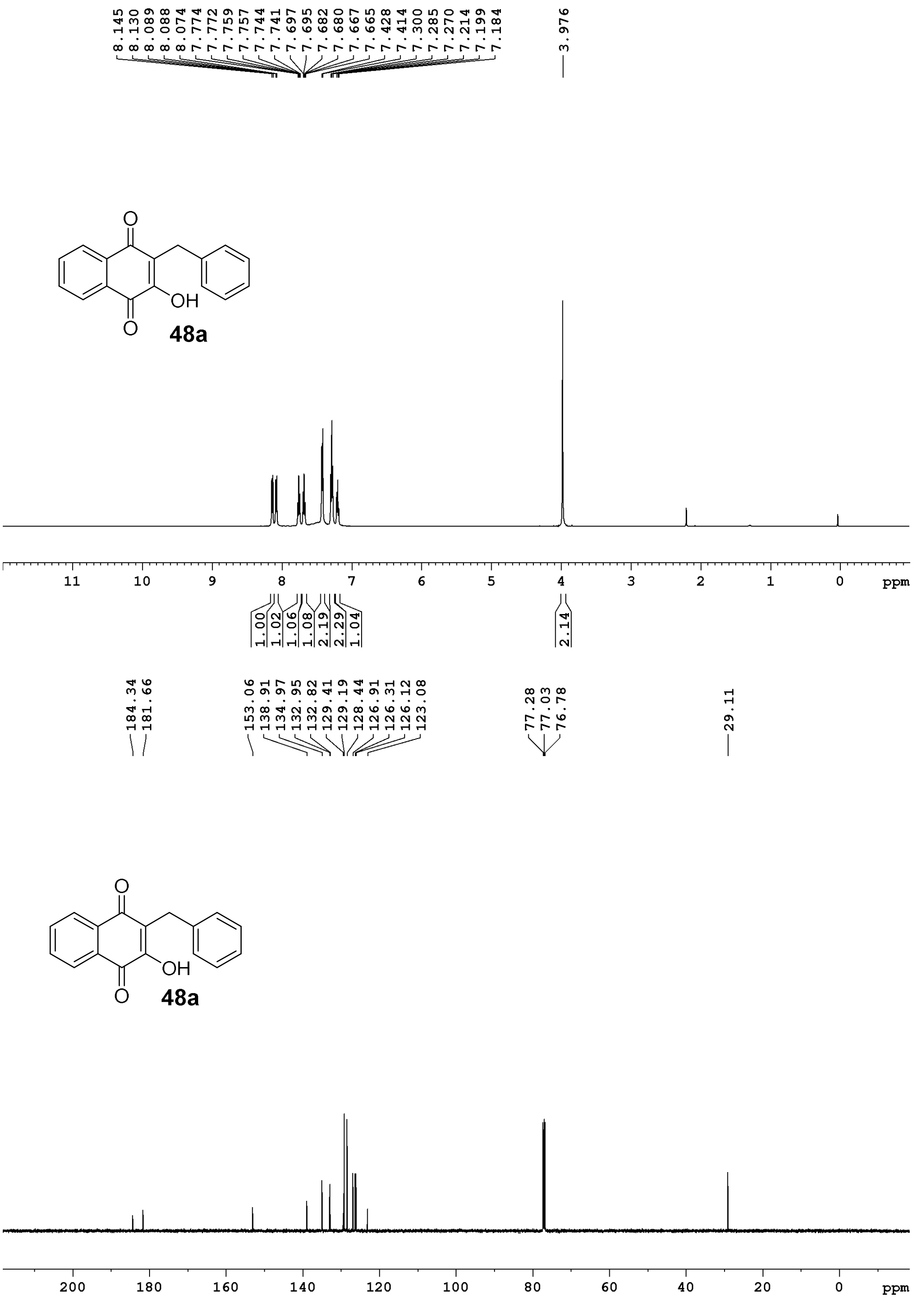


Figure 23: ^{1}H and ^{13}C spectra of the product **48a**.

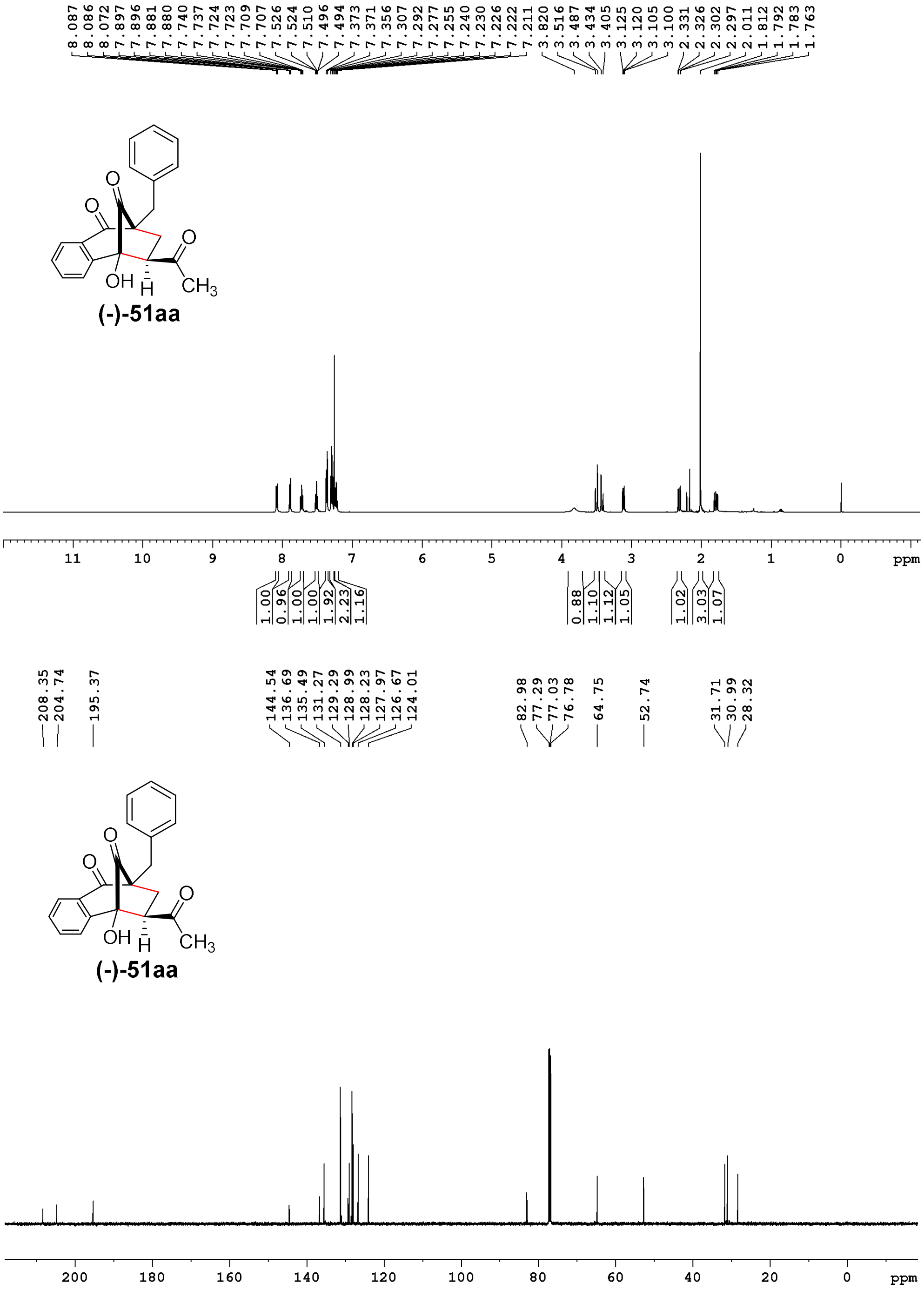
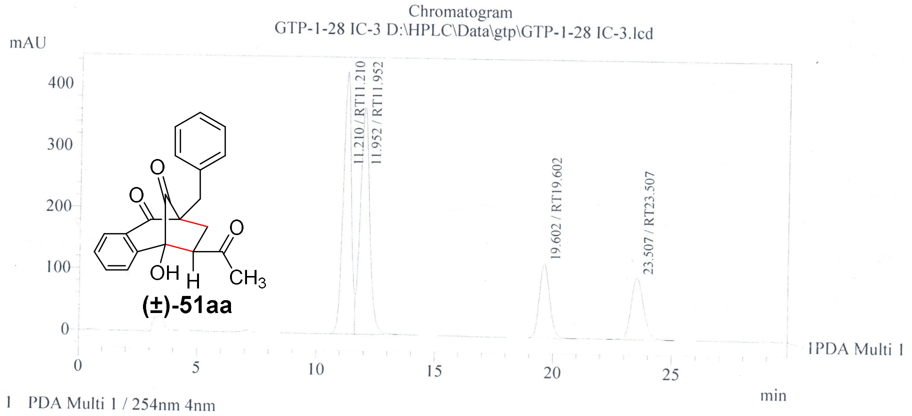


Figure 24: ^{1}H and ^{13}C spectra of the product **51aa**.

Racemic **(±)-51aa:**



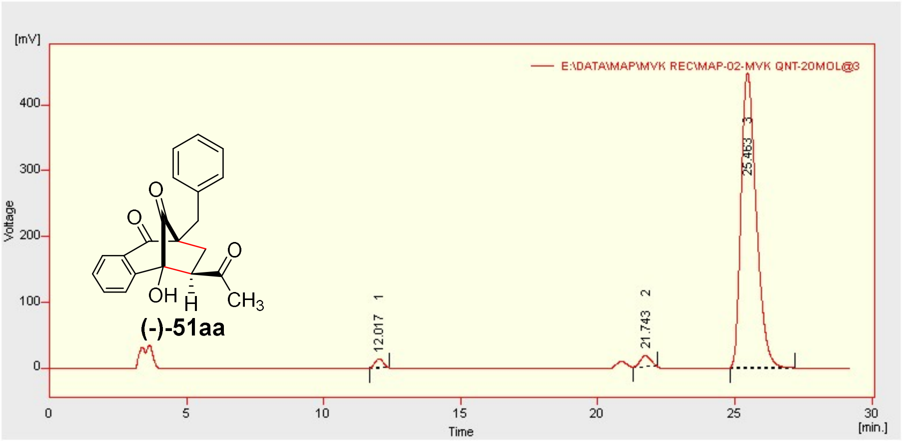
Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT11.210	11.210	10008122	425364	36.261	41.936
2	RT11.952	11.952	10298026	369456	37.312	36.425
3	RT19.602	19.602	3632593	119821	13.162	11.813
4	RT23.507	23.507	3661138	99664	13.265	9.826
Total			27599879	1014304	100.000	100.000

Chiral **(-)-51aa** (Major: 95% *ee*; Minor: >99% *ee*):



Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Result Table (Uncal - E:\DATA\MAP\MVK REC\MAP-02-MVK QNT-20MOL@3)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	12.017	293.544	13.634	1.6	2.9	0.36
2	21.743	439.534	16.351	2.4	3.4	0.45
3	25.463	17259.889	447.886	95.9	93.7	0.60
	Total	17992.966	477.872	100.0	100.0	

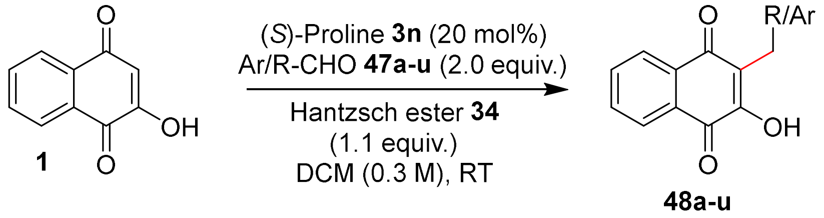
Figure 25: HPLC spectra of the chiral product **51aa**.

From these studies, the final optimized condition for the asymmetric domino Michael/*5-(enolexo)-exo-trig* cyclization between **48a** and **49a** was established to be **57b** catalysis in trifluorotoluene at 20 °C for 6 h and generated the chiral methanobenzo[7]annulene (−)-**51aa** in 90% yield with 95% *ee* and 61:1 dr (Table 7, entry 9). Not much improvement observed under the catalysis of 9-*epi*-aminodihydroquinine-thiourea **57c** compared to **57b** (Table 7, entry 13).

4.2.2 Scope of asymmetric domino reactions:

Further, the scope of the 9-*epi*-aminoquinine-thiourea **57b** catalysed domino Michael/*5-(enolexo)-exo-trig* cyclization was showcased by synthesising a library of functionalized chiral methanobenzo[7]annulenes **51ba-ua** from the reaction between various 2-alkyl-3-hydroxynaphthalene-1,4-diones **48b-u** and methyl vinyl ketone **49a** (Table 9). Various hydroxy-diones **48b-u** used in this reaction were synthesized in very good yields by using organocatalytic TCRA or reductive coupling of Lawsone **1**, aldehydes **47b-u** and Hantzsch ester **34** as shown in Table 8. The domino reaction was capable of generating the chiral methanobenzo[7]annulenes **51ba-ua** bearing a variety of functional groups such as neutral, electron-donating, electron-withdrawing, hetero-atom substituted and halogenated, with excellent *ee*'s (up to 99% *ee*) and dr's (up to 45:1 dr) in very good yields (Table 9). Thus for the first time, a variety of unchanged hydroxy-diones **48b-u** were used as source of in situ generated chiral enolates and utilized as mild nucleophiles in a domino reaction in order to furnish the functionalized drug-like methanobenzo[7]annulenes **51ba-ua**. Interestingly, the domino Michael/*5-(enolexo)-exo-trig* reaction of methyl vinyl ketone **49a** with 4-halobenzyl, 4-methylbenzyl, and 4-methoxybenzyl substituted hydroxy-diones **48b-f** under the catalysis of **57b** at 20 °C for 8-13 h furnished the chiral products (−)-**51ba** to (−)-**51fa** in 80-96% yields with 92-99% *ee* and 18:1-36:1 dr (Table 9, entries 1-5).

Table 8: Substrate scope of TCRA Reaction.[a]



Entry	Ar/R **47**	*t* [h]	Yield **48** [%][b]
1	**47a**: Ar = C_6H_5	12	90 (**48a**)
2	**47b**: Ar = 4-FC_6H_4	12	80 (**48b**)
3	**47c**: Ar = 4-ClC_6H_4	12	80 (**48c**)
4	**47d**: Ar = 4-BrC_6H_4	11	70 (**48d**)
5	**47e**: Ar = 4-$CH_3C_6H_4$	14	75 (**48e**)
6	**47f**: Ar = 4-$OMeC_6H_4$	13	50 (**48f**)
7	**47g**: Ar = 4-$CF_3C_6H_4$	12	70 (**48g**)
8	**47h**: Ar = 4-CNC_6H_4	12	80 (**48h**)
9	**47i**: Ar = 2-FC_6H_4	12	80 (**48i**)
10	**47j**: Ar = 2-BrC_6H_4	12	80 (**48j**)
11[c]	**47k**: Ar = 2-$CH_3C_6H_4$	17	60 (**48k**)
12	**47l**: Ar = 2-$N_3C_6H_4$	12	75 (**48l**)
13[c]	**47m**: Ar = 1-Naphthyl	15	50 (**48m**)
14	**47n**: Ar = 2-Furyl	12	80 (**48n**)
15	**47o**: Ar = 2-Thiophenyl	12	80 (**48o**)
16[c]	**47p**: Ar = *N*-Boc-indole-3-yl	12	60 (**48p**)
17	**47q**: R = CH_3	12	80 (**48q**)
18	**47r**: R = $CH_2CH_2CH_2CH_3$	13	85 (**48r**)
19	**47s**: R = CH_2CHMe_2	12	90 (**48s**)
20	**47t**: R = $CH_2[CH_2]_5CH_3$	12	90 (**48t**)
21	**47u**: R = CH_2CH_2Ph	16	82 (**48u**)

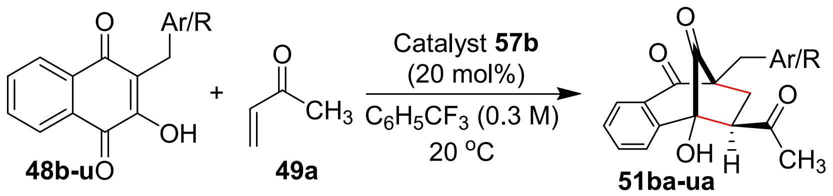
[a]Reactions were carried out in DCM (0.3 M) with 2.0 equiv. of **47** and 1.1 equiv. of **34** relative to the **1** (0.3 mmol) in the presence of 20-mol% of (*S*)-proline **3n**. [b] Yield refers to the column-purified product. [c] Reaction performed at 50 °C.

Likewise, the domino reaction of hydroxy-diones **48g-h** containing 4-(trifluoromethyl)benzyl and 4-cyanobenzyl with **49a** under the **57b** catalysis at 20 °C for 22 h furnished the expected chiral products (−)-**51ga** and (−)-**51ha** in good yields (70%, 65%) with high (93%, 95%) *ee* and moderate (11:1, 9:1) dr respectively (Table 9, entries 6-7). Further, the domino reaction of hydroxy-diones **48i-m** containing 2-fluorobenzyl, 2-bromobenzyl, 2-methylbenzyl, 2-azidobenzyl and naphthalen-1-ylmethyl with **49a** under the **57b** catalysis at 40 °C for 3-36 h furnished the chiral products (−)-**51ia** to (−)-**51ma** in good (70-75) yields and (82-90%) *ee*'s with moderate to poor (2.0:1 to 9:1) dr's. Notably, the same reactions didn't do well at 20 °C even for longer reaction times, except in the case of **48i**, may be due to the ortho-substitution effect (Table 9, entries 8-12).

Hetero-atom substituted hydroxy-diones **48n-p** too partook in the domino reaction with **49a** under the catalysis of **57b** at 20 °C for 5-9 h furnished the chiral products (−)-**51na** to (−)-**51pa** in 70-91% yields with 84-93% *ee* and 10:1-16:1 dr (Table 9, entries 13-15). Correspondingly, the hydroxy-diones **48q-u** containing five different alkyl groups also involved in the domino reaction with **49a** under the **57b** catalysis at 20 °C for 2-6 h to furnish the chiral products (−)-**51qa** to (−)-**51ua** in very good (90-99) yields and (90-96%) *ee*'s with good to excellent (12:1 to 45:1) dr's (Table 9, entries 16-20).

All these results put together point out conclusively that the strength of the hydrogen-bonding between the hydroxy-diones **48b-u** possessing 2-alkyl substitution and the catalyst 9-*epi*-aminoquinine-thiourea **57b** dictates the result of the reaction rate and selectivity. We established the structure of the domino products **51** by NMR analysis and absolute stereochemistry finally confirmed by X-ray structure analysis on (−)-**51da** and (−)-**51ea** (Figures 34).[22]

Table 9: 2-Alkyl-3-hydroxynaphthalene-1,4-dione scope.[a]



Entry	Ar/R **48**	*t* [h]	Yield **51** [%][*b*]	dr[c]	*ee* [%][*d*]
1	**48b**: Ar = 4-FC_6H_4	8	80 (**51ba**)	20:1	95 [99]
2	**48c**: Ar = 4-ClC_6H_4	10	90 (**51ca**)	18:1	95 [99]
3	**48d**: Ar = 4-BrC_6H_4	13	96 (**51da**)	36:1	96 [99]
4	**48e**: Ar = 4-$CH_3C_6H_4$	11	88 (**51ea**)	22:1	99 [84]
5	**48f**: Ar = 4-$OMeC_6H_4$	8	95 (**51fa**)	23:1	92 [99]
6	**48g**: Ar = 4-$CF_3C_6H_4$	22	70 (**51ga**)	11:1	93 [89]
7	**48h**: Ar = 4-CNC_6H_4	22	65 (**51ha**)	9:1	95 [95]
8	**48i**: Ar = 2-FC_6H_4	3	75 (**51ia**)	9:1	90 [88]
9[e]	**48j**: Ar = 2-BrC_6H_4	36	70 (**51ja**)	6:1	88 [98]
10[e]	**48k**: Ar = 2-$CH_3C_6H_4$	15	75 (**51ka**)	5:1	82 [81]
11[e]	**48l**: Ar = 2-$N_3C_6H_4$	16	75 (**51la**)	2.7:1	90 [88]
12[e]	**48m**: Ar = 1-Naphthyl	36	75 (**51ma**)	2.0:1	82 [86]
13	**48n**: Ar = 2-Furyl	9	78 (**51na**)	11:1	93 [86]
14	**48o**: Ar = 2-Thiophenyl	5	70 (**51oa**)	10:1	92 [81]
15	**48p**: Ar = *N*-Boc-indole-3-yl	8	91 (**51pa**)	16:1	84 [82]
16	**48q**: R = CH_3	2	90 (**51qa**)	28:1	96 [92]
17	**48r**: R = $CH_2CH_2CH_2CH_3$	6	95 (**51ra**)	22:1	94 [99]
18	**48s**: R = CH_2CHMe_2	6	99 (**51sa**)	24:1	94 [84]
19	**48t**: R = $CH_2[CH_2]_5CH_3$	6	95 (**51ta**)	12:1	95 [99]
20	**48u**: R = CH_2CH_2Ph	6	95 (**51ua**)	45:1	90 [99]

[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **49a** relative to the **48b-u** (0.3 mmol) in the presence of 20-mol% of catalyst **57b**. [b] Yield refers to the column-purified product. [c] dr determined by ^1H NMR and CSP HPLC analysis. [d] *ee*

determined by CSP HPLC analysis and values in parenthesis represent for minor diastereomer. [e] Reaction performed at 40 °C.

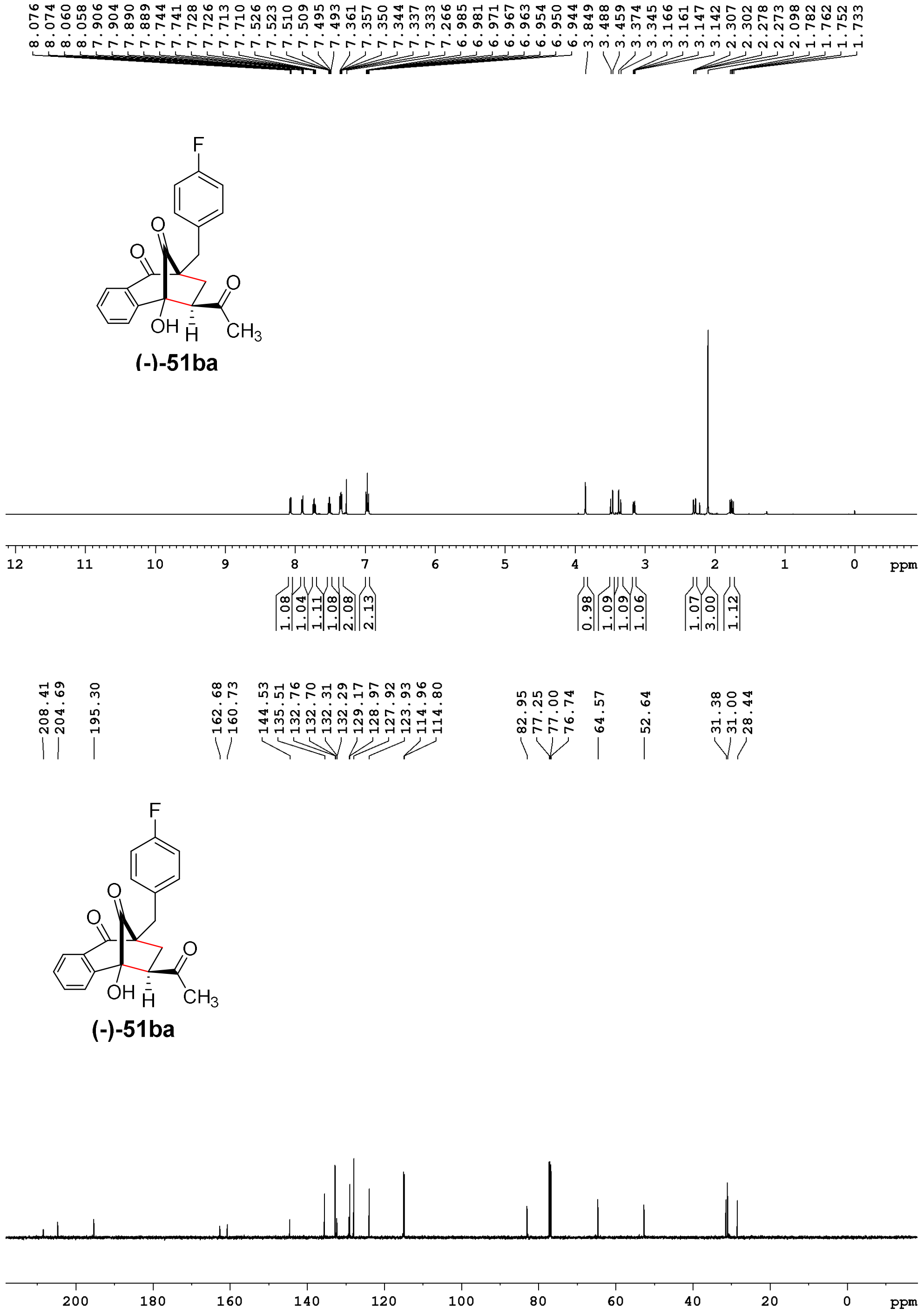
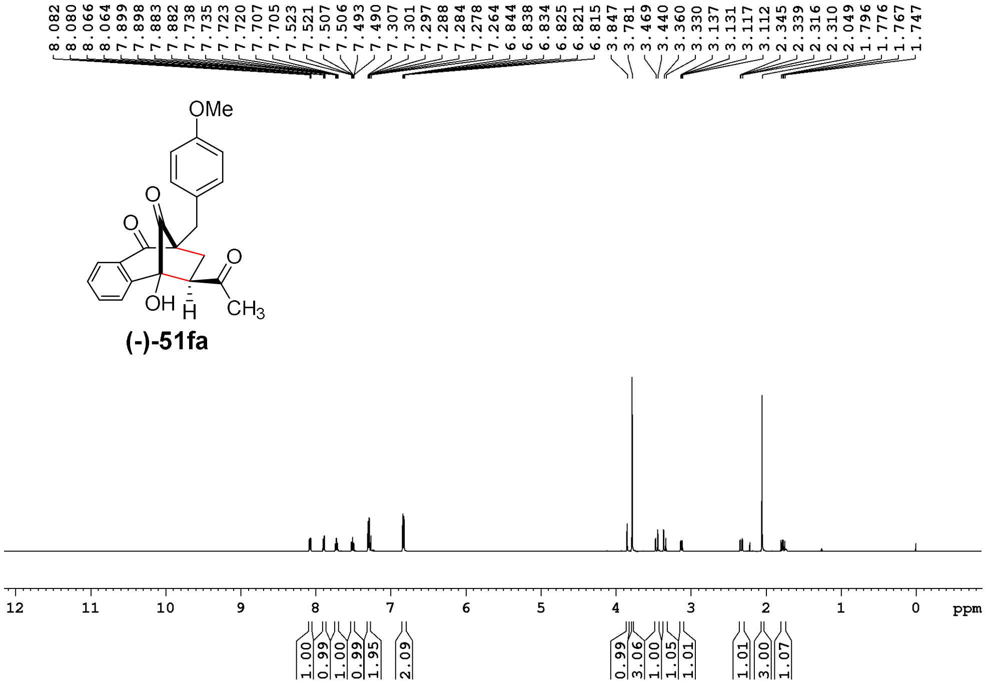


Figure 26: ^{1}H and ^{13}C spectra of the product **51ba**.



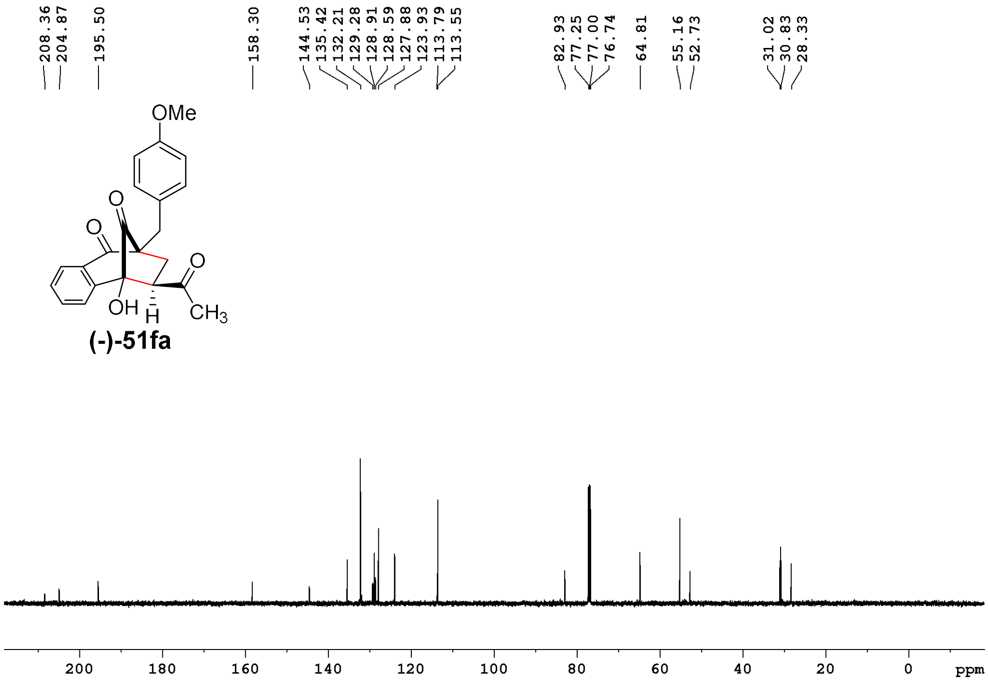


Figure 27: ^{1}H and ^{13}C spectra of the product **51fa**.

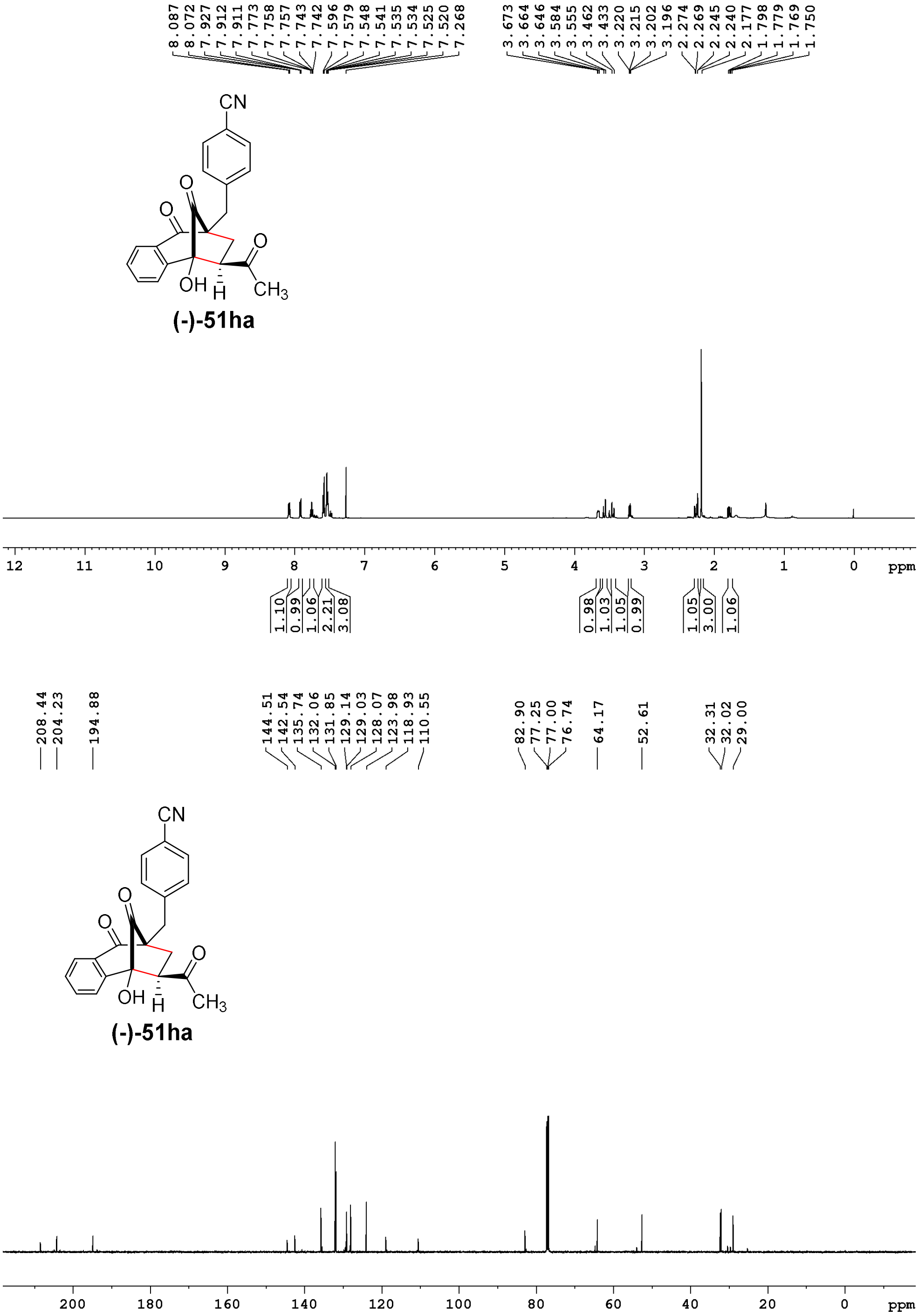


Figure 28: ^{1}H and ^{13}C spectra of the product **51ha**.

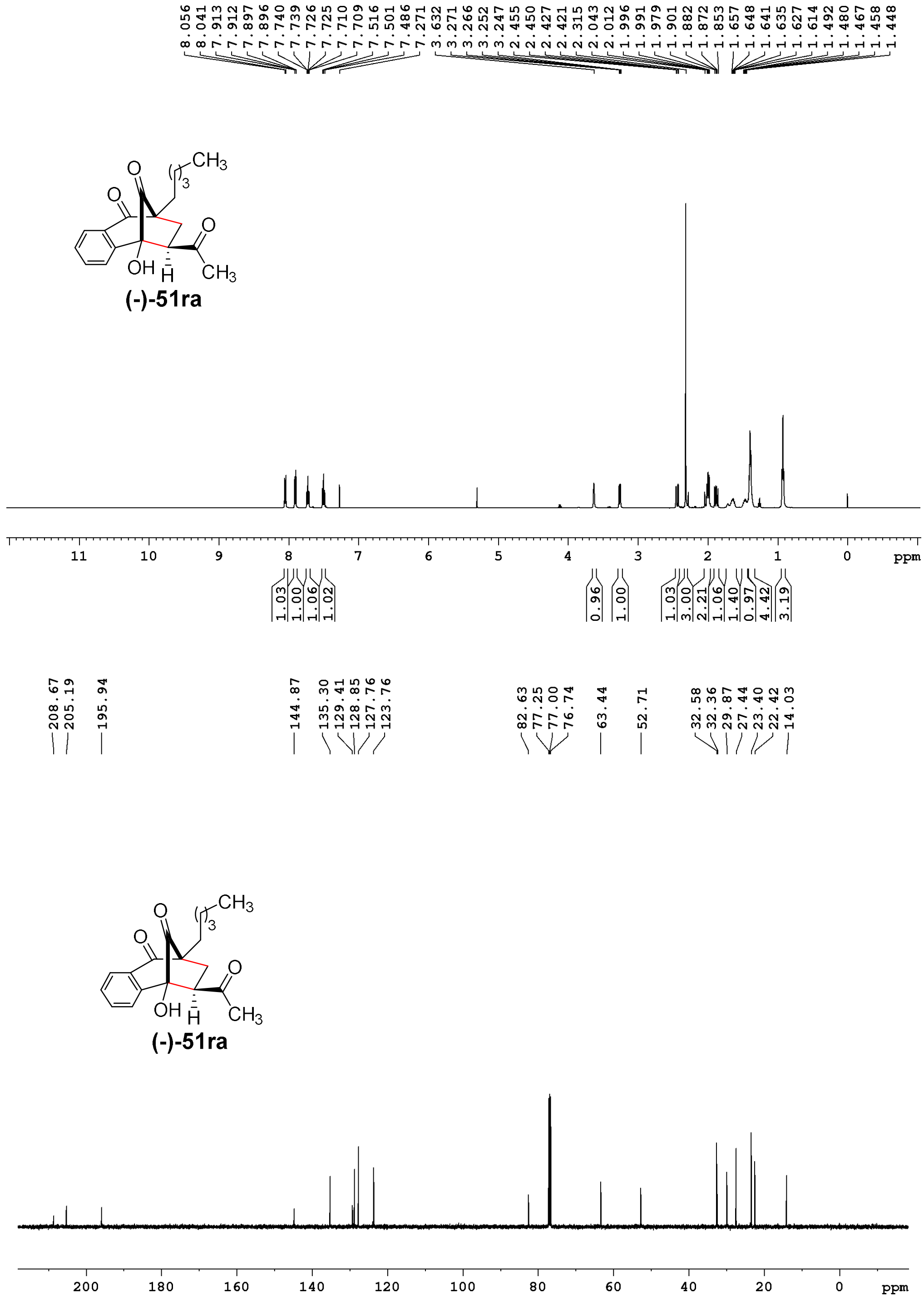
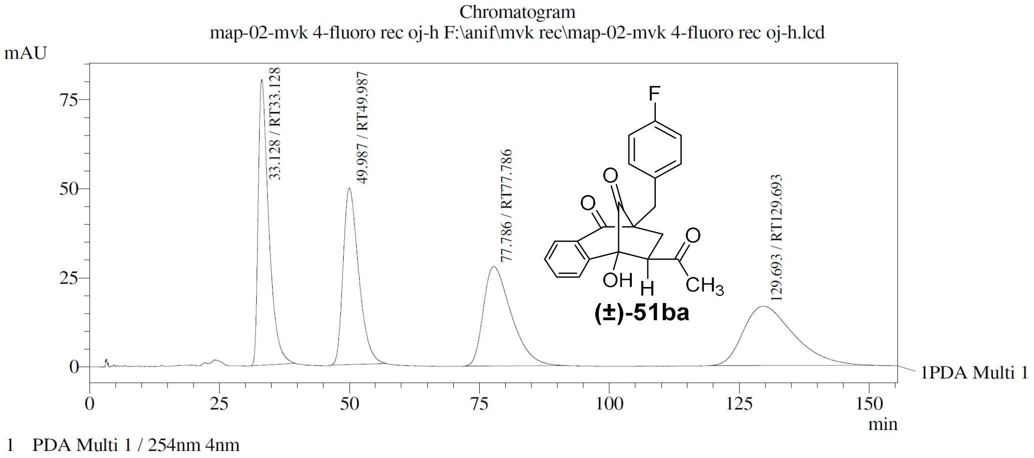


Figure 29: ^{1}H and ^{13}C spectra of the product **51ra**.

Racemic **(±)-51ba:**



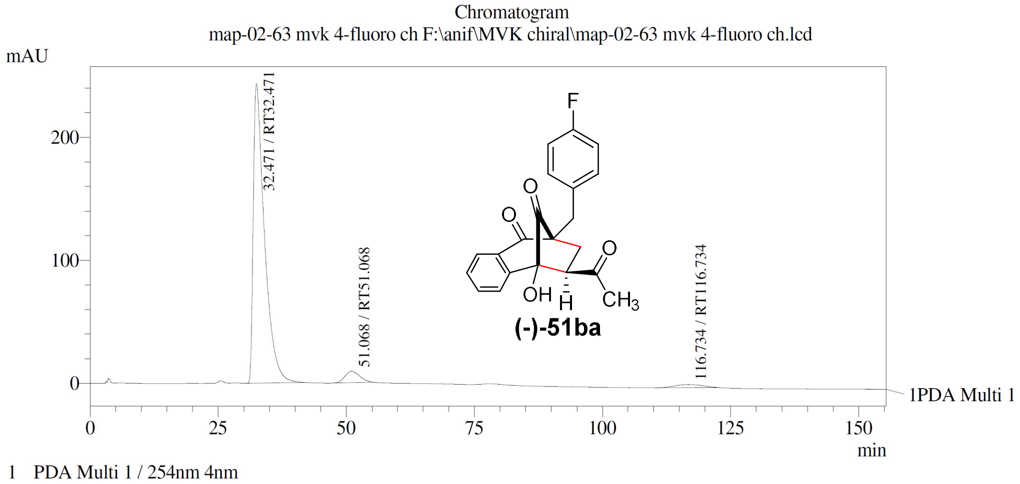
Chiralcel OJ-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT33.128	33.128	11327596	80251	26.104	45.992
2	RT49.987	49.987	10336220	49635	23.819	28.446
3	RT77.786	77.786	10437928	27934	24.054	16.009
4	RT129.693	129.693	11292494	16671	26.023	9.554
Total			43394237	174491	100.000	100.000

Chiral **(-)-51ba** (Major: 95% *ee*; Minor: >99% *ee*):



Chiralcel OJ-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

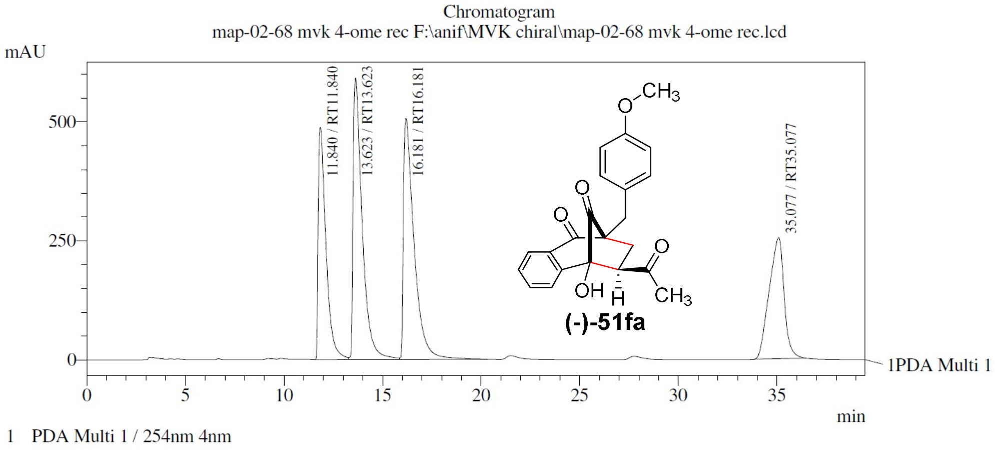
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT32.471	32.471	37099389	243176	92.777	95.321
2	RT51.068	51.068	1887870	9281	4.721	3.638
3	RT116.734	116.734	1000644	2656	2.502	1.041
Total			39987903	255112	100.000	100.000

Figure 30: HPLC spectra of the chiral product **51ba**.

Racemic **(±)-51fa:**



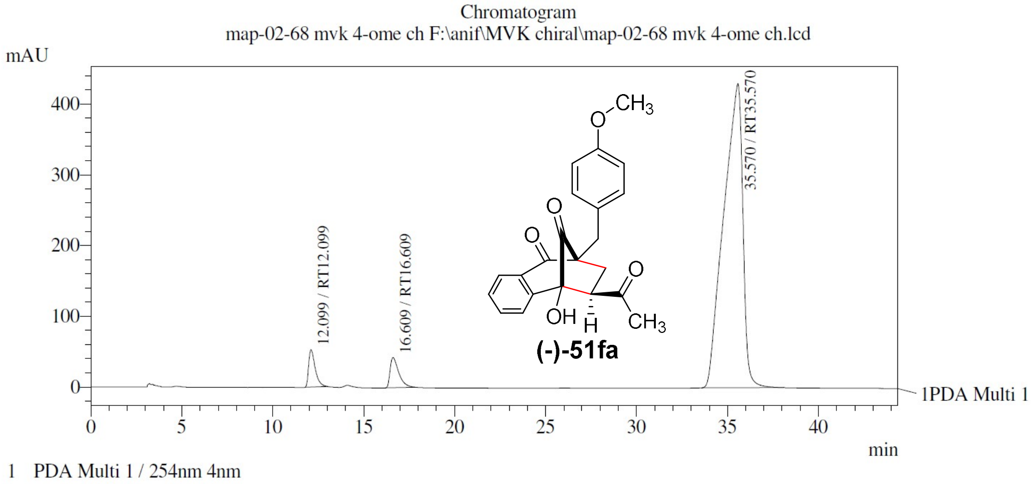
Chiralpak IB-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT11.840	11.840	13374312	488155	20.667	26.505
2	RT13.623	13.623	18917960	592001	29.234	32.143
3	RT16.181	16.181	19007039	506948	29.371	27.525
4	RT35.077	35.077	13413372	254642	20.728	13.826
Total			64712683	1841745	100.000	100.000

Chiral **(-)-51fa**: (Major: 92% *ee*; Minor: >99% *ee*):



Chiralpak IB-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

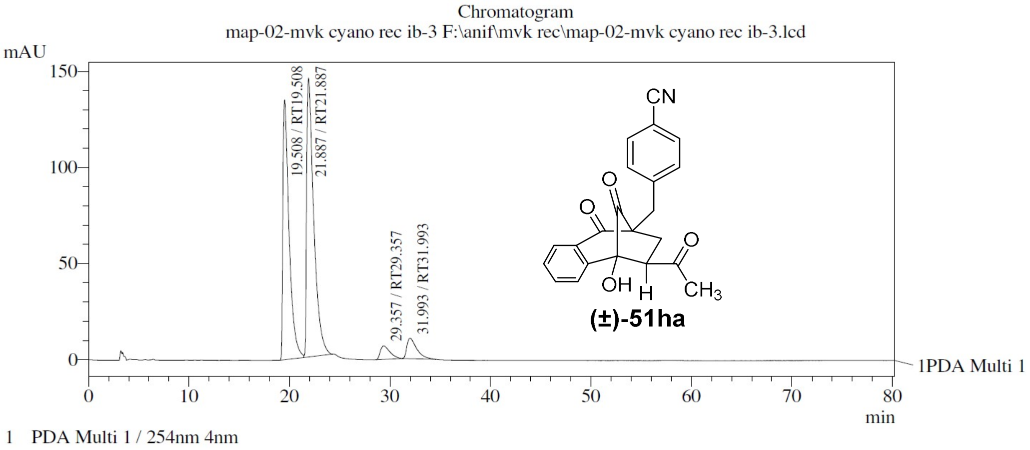
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT12.099	12.099	1330721	52967	3.904	10.079
2	RT16.609	16.609	1409689	42650	4.136	8.116
3	RT35.570	35.570	31343344	429912	91.960	81.806
Total			34083754	525529	100.000	100.000

Figure 31: HPLC spectra of the chiral product **51fa**.

Racemic **(±)-51ha:**



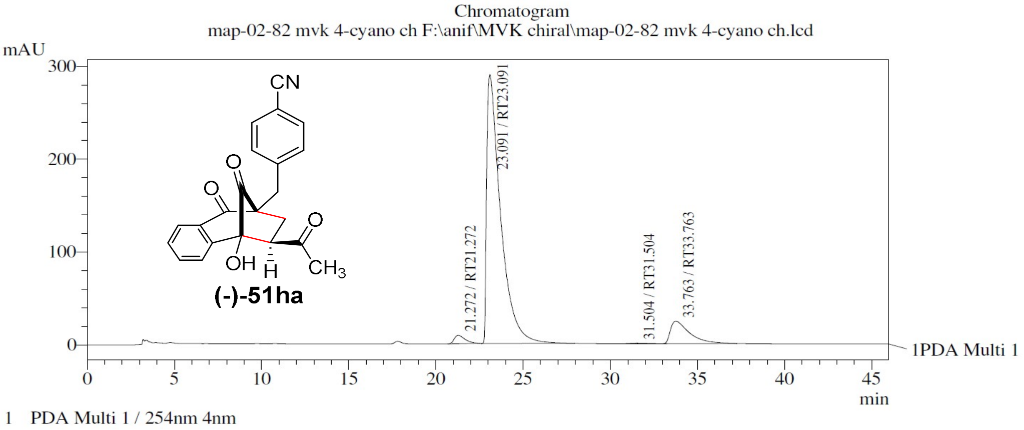
Chiralpak IB-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT19.508	19.508	5811137	135151	41.057	45.366
2	RT21.887	21.887	7149879	145082	50.515	48.700
3	RT29.357	29.357	468545	7064	3.310	2.371
4	RT31.993	31.993	724351	10616	5.118	3.563
Total			14153912	297913	100.000	100.000

Chiral **(-)-51ha**: (Major: 95% *ee*; Minor: 95% *ee*):



Chiralpak IB-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

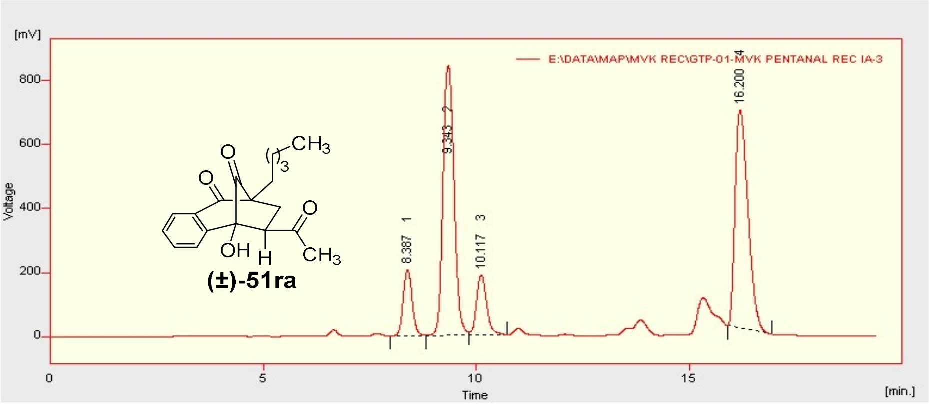
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT21.272	21.272	394492	9138	2.150	2.822
2	RT23.091	23.091	16063164	289814	87.533	89.495
3	RT31.504	31.504	41431	628	0.226	0.194
4	RT33.763	33.763	1851841	24254	10.091	7.490
Total			18350928	323834	100.000	100.000

Figure 32: HPLC spectra of the chiral product **51ha**.

Racemic **(±)-51ra:**

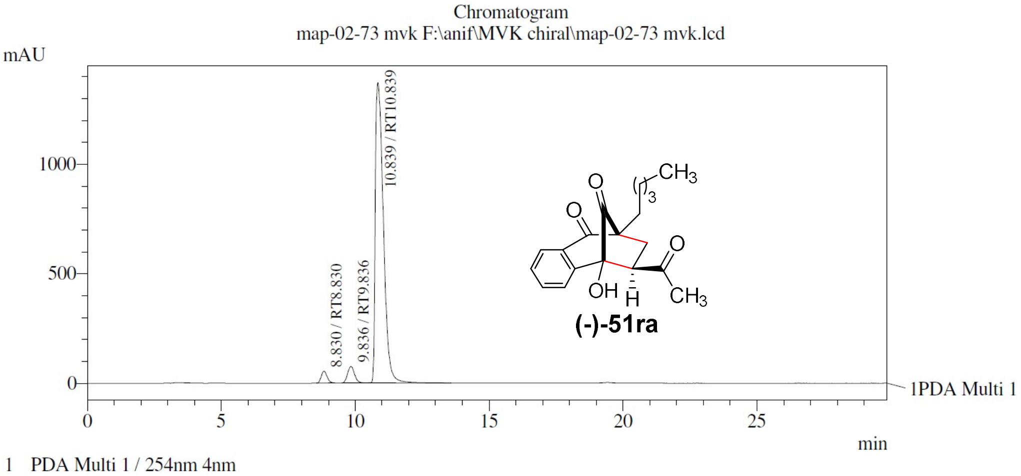


Chiralpak IA-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Result Table (Uncal - E:\DATA\MAP\MVK REC\GTP-01-MVK PENTANAL REC IA-3)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	8.387	3018.460	204.855	8.4	10.7	0.23
2	9.343	15313.539	843.188	42.7	43.9	0.29
3	10.117	3140.473	188.895	8.8	9.8	0.25
4	16.200	14407.330	682.067	40.2	35.5	0.34
	Total	35879.802	1919.005	100.0	100.0	

Chiral **(-)-51ra**: (Major: 94% *ee*; Minor: >99% *ee*):



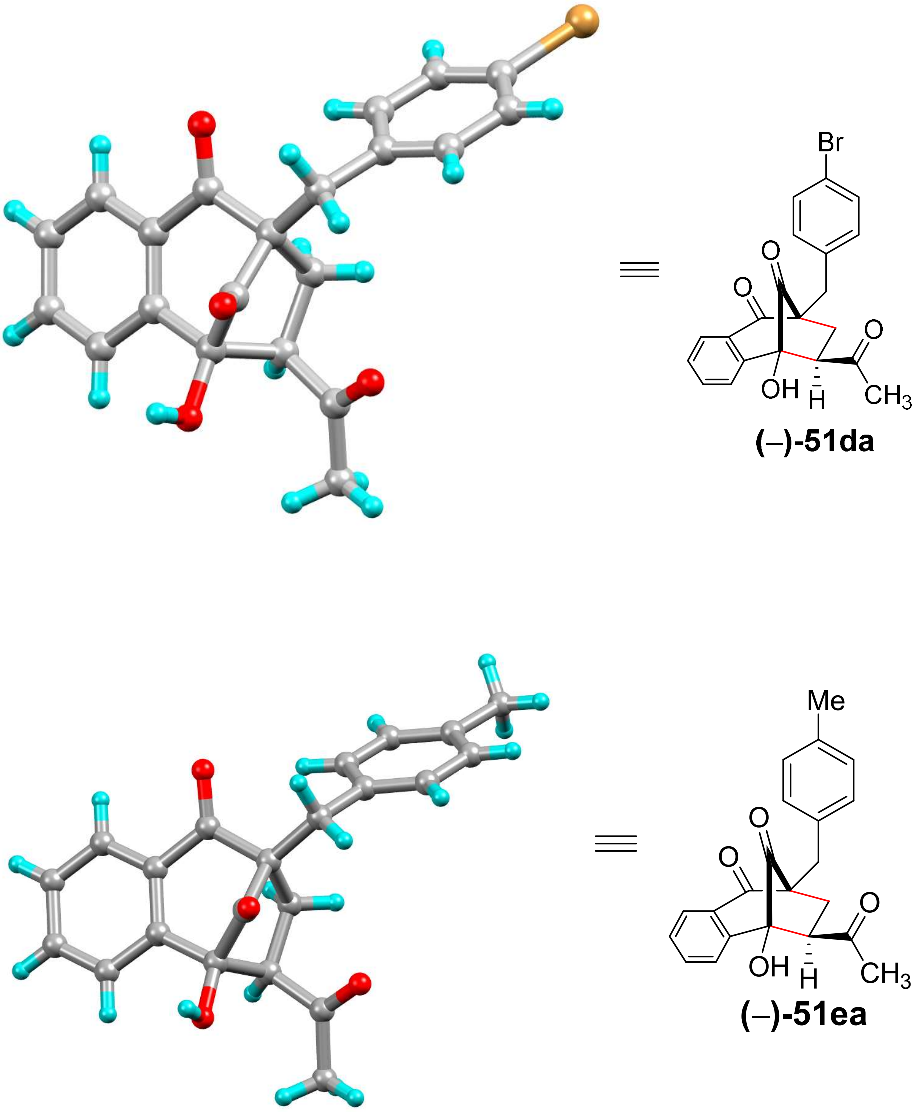
Chiralpak IA-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT8.830	8.830	822650	54317	2.659	3.621
2	RT9.836	9.836	1337347	75077	4.323	5.005
3	RT10.839	10.839	28777392	1370538	93.018	91.373
Total			30937389	1499932	100.000	100.000

Figure 33: HPLC spectra of the chiral product **51ra**.



(–)-51da

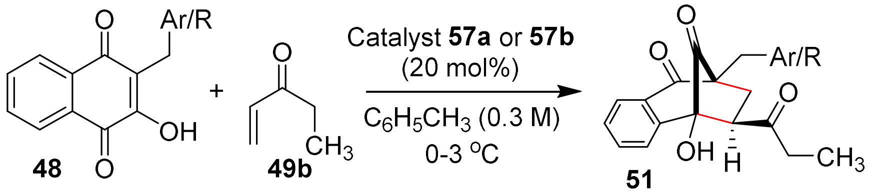
(–)-51ea

Figure 34: Crystal structure of (6*R*,8*R*)-6-acetyl-8-(4-bromobenzyl)-5-hydroxy-7,8-dihydro-5H-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (**51da**) and (6*R*,8*R*)-6-acetyl-5-hydroxy-8-(4-methylbenzyl)-7,8-dihydro-5H-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (**51ea**).

Moreover, the scope of **57a** or **57b** catalyzed domino reaction was extended further by developing a library of optically pure methanobenzo[7]annulenes **51ab-ae** through the reaction of various 2-alkyl-3-hydroxynaphthalene-1,4-diones **48a-u** with different alkyl vinyl ketones **49b-e** (Table 10). Notably, the domino reaction of ethyl vinyl ketone **49b** with hydroxy-dione **48a** under the catalysis of **57a** or **57b** in trifluorotoluene at 0-3 or 20 °C for 72 h furnished the chiral product **51ab** in very poor conversions; but the same reaction at 40 °C for 13 h furnished the chiral product (+)-**51ab** in 80% yield with 74% *ee* and 90:1 dr and (−)-**51ab** in 80% yield with 76% *ee* and 25:1 dr respectively (Table 10, entries 1-2). Also, the same reaction under **57a** catalysis in toluene at 0-3 °C for 48 h furnished the chiral product (+)-**51ab** in 85% yield with 81% ee and 53:1 dr and under the **57b** catalysis in toluene at 0-3 °C for 72 h furnished (−)-**51ab** in 85% yield with 83% *ee* and 14:1 dr respectively (Table 10, entries 3-4).

In a similar manner, domino reaction of hydroxy-diones **48b-u** containing 4-fluorobenzyl, 4-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, ethyl, *n*-octyl and 3-phenylpropyl with ethyl vinyl ketone **49b** under the **57a** catalysis in toluene at 0-3 °C for 24-72 h furnished the chiral products (+)-**51bb** to (+)-**51ub** in good to excellent (65-90) yields, (64-97%) *ee*'s and (11:1 to 90:1) dr's (Table 10, entries 5-11). Interestingly, the same reactions under the **57a** catalysis in toluene at 0-3 °C furnished the opposite enantiomers of (−)-**51cb** to (−)-**51ub** in improved yields (65-95) and *ee*'s (77-98%) but with reduced (7:1 to 97:1) dr's (Table 10, entries 12-18). Reaction of hydroxy-dione **48a** with *n*-propyl vinyl ketone **49c** under the **57b** catalysis at 40 °C for 12 h furnished the chiral product (−)-**51ac** in 80% yield and 79% *ee* with 76:1 dr (Table 10, entry 19). Reaction of **48a** with benzyl vinyl ketone **49d** under the **57b** catalysis at 20 °C for 22 h furnished the chiral product (−)-**51ad** in 80% yield with 76% *ee* and 28:1 dr (Table 10, entry 20).

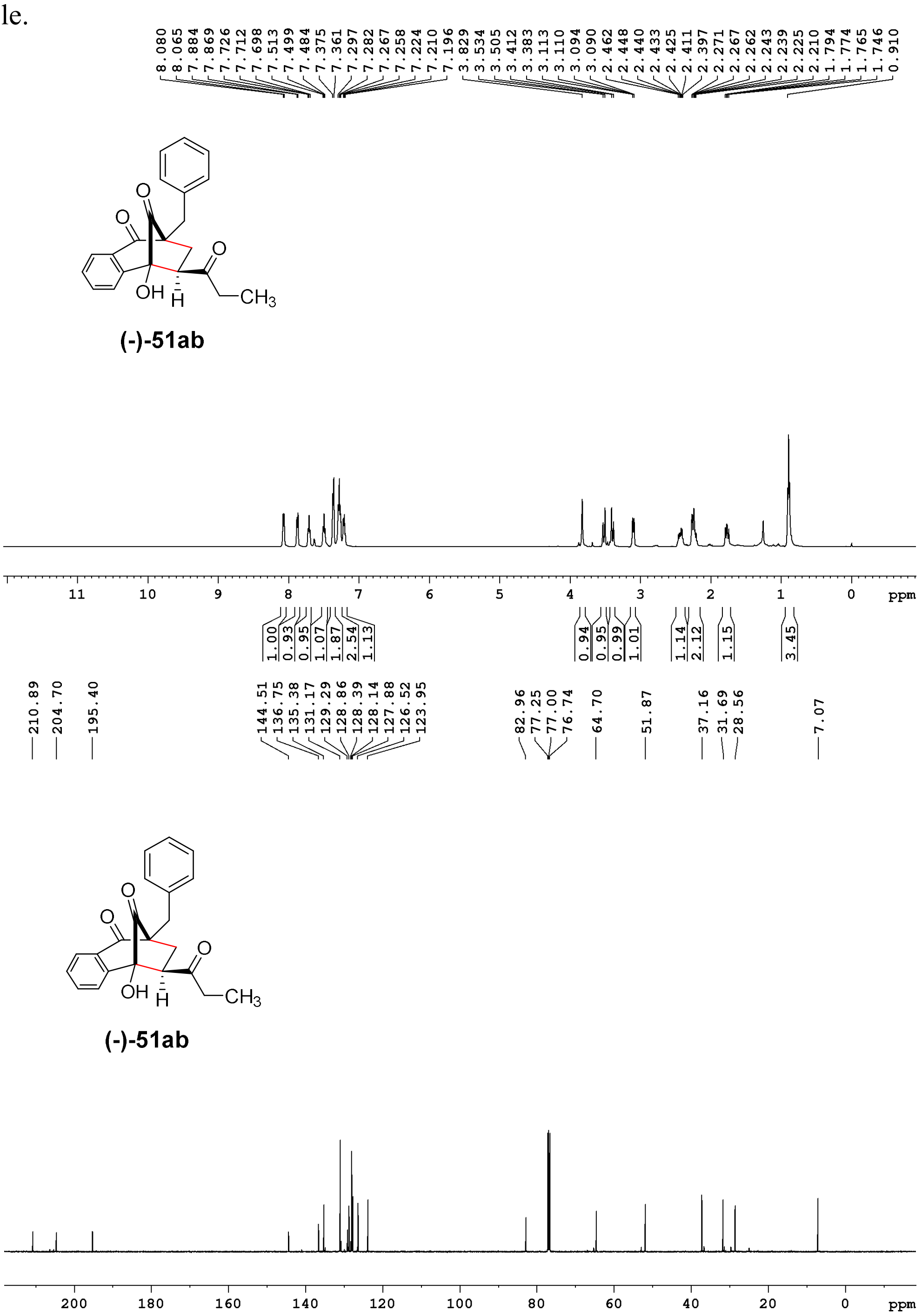
Table 10: Alkyl vinyl ketone scope.[a]



Entry	Ar/R **48**	Cat. **57**	*t* [h]	Yield **51** [%][*b*]	dr[c]	*ee* [%][*d*]
1[e]	**48a**: Ar = C_6H_5	**57a**	13	80 (**51ab**)	90:1	74 [–]
2[e]	**48a**: Ar = C_6H_5	**57b**	13	80 (**51ab**)	25:1	76 [99]
3	**48a**: Ar = C_6H_5	**57a**	48	85 (**51ab**)	53:1	81 [89]
4	**48a**: Ar = C_6H_5	**57b**	72	85 (**51ab**)	14:1	83 [99]
5	**48b**: Ar = 4-FC_6H_4	**57a**	48	65 (**51bb**)	90:1	97 [–]
6	**48c**: Ar = 4-ClC_6H_4	**57a**	48	75 (**51cb**)	90:1	73 [99]
7	**48e**: Ar = 4-$CH_3C_6H_4$	**57a**	72	65 (**51eb**)	16:1	74 [74]
8	**48f**: Ar = 4-$OMeC_6H_4$	**57a**	72	80 (**51fb**)	84:1	87 [38]
9	**48q**: R = CH_3	**57a**	24	90 (**51qb**)	11:1	74 [90]
10	**48t**: R = $CH_2[CH_2]_5CH_3$	**57a**	48	90 (**51tb**)	89:1	79 [61]
11	**48u**: R = CH_2CH_2Ph	**57a**	48	90 (**51ub**)	22:1	64 [79]
12	**48c**: Ar = 4-ClC_6H_4	**57b**	26	88 (**51cb**)	67:1	80 [99]
13	**48e**: Ar = 4-$CH_3C_6H_4$	**57b**	35	65 (**51eb**)	11:1	80 [87]
14	**48f**: Ar = 4-$OMeC_6H_4$	**57b**	48	87 (**51fb**)	62:1	98 [99]
15	**48n**: Ar = 2-Furyl	**57b**	72	75 (**51nb**)	97:1	84 [99]
16	**48q**: R = CH_3	**57b**	35	75 (**51qb**)	9:1	77 [74]
17	**48t**: R = $CH_2[CH_2]_5CH_3$	**57b**	24	95 **51tb**)	10:1	86 [86]
18	**48u**: R = CH_2CH_2Ph	**57b**	26	92 (**51ub**)	7:1	84 [85]
19[e,f]	**48a**: Ar = C_6H_5	**57b**	12	80 (**51ac**)	76:1	79 [96]
20[g]	**48a**: Ar = C_6H_5	**57b**	22	80 (**51ad**)	28:1	76 [87]
21[g]	**48a**: Ar = C_6H_5	**57b**	5.5	90 (**51ae**)	97:1	22 [99]

[a]Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **49b**/**c** relative to the **48** (0.3 mmol) in the presence of 20-mol% of catalyst **57a** or **57b**. [b] Yield refers to the column-purified product.[c] dr determined by ^{1}H NMR and CSP HPLC analysis. [d] ee determined by CSP HPLC analysis and values in paranthesis represent for minor

diastereomer. [e] Reaction performed in $C_6H_5CF_3$ at 40 °C. [f] *n*-Propylvinylketone **49c** used. [g] Benzyl vinyl ketone **49d** or phenyl vinyl ketone **49e** used in $C_6H_5CF_3$ at 20 °C. Note: Entries 1, 3, 5-11 represents the opposite enantiomers of compound **51** shown in Table.



(-)-51ab

(-)-51ab

Figure 35: ^{1}H and ^{13}C spectra of the product **51ab**.

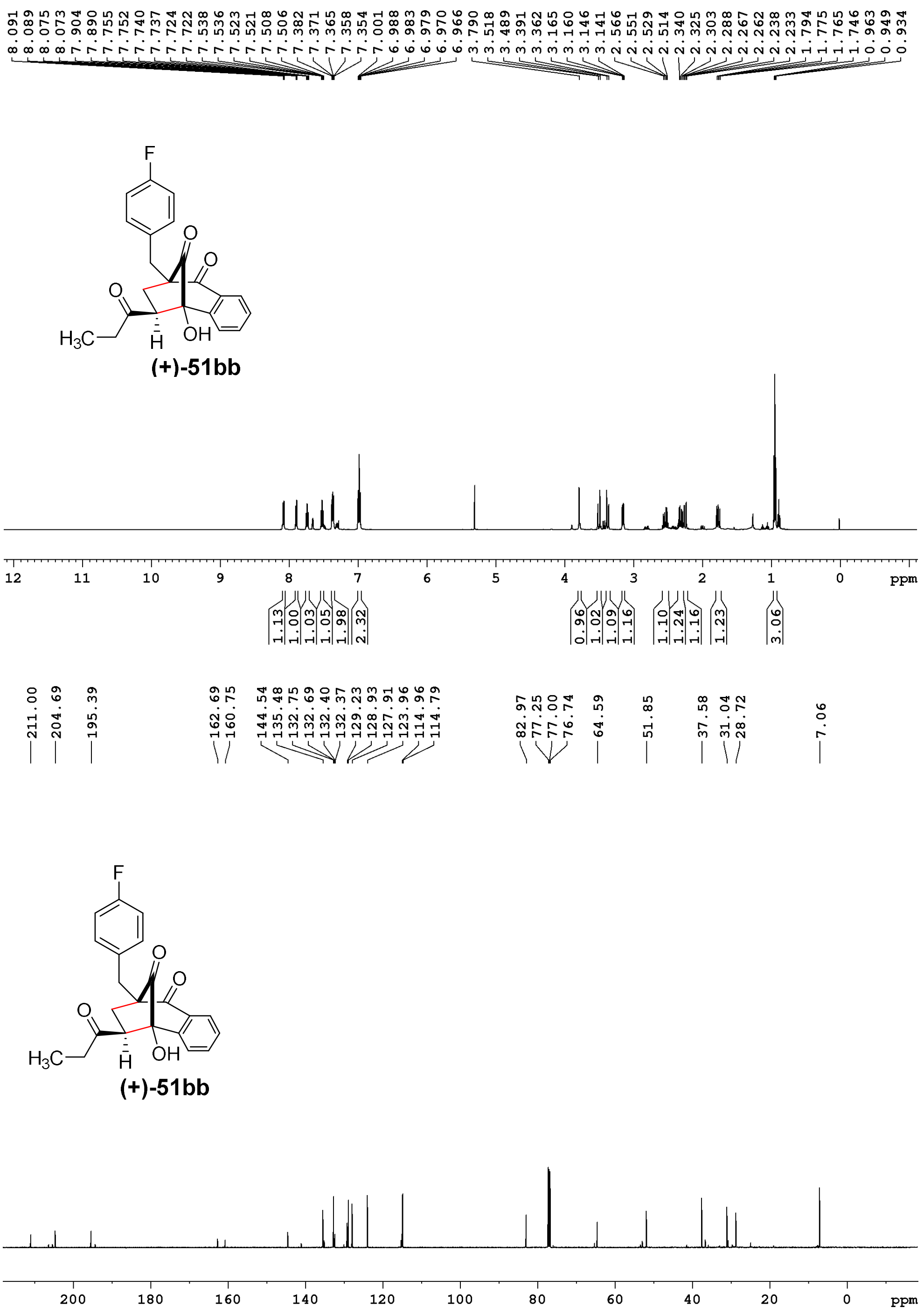
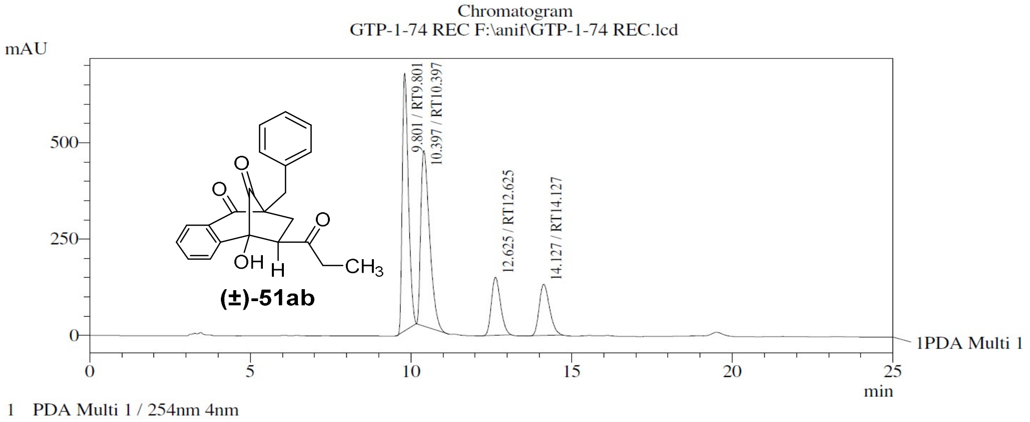


Figure 36: ^{1}H and ^{13}C spectra of the product **51bb**.

Racemic **(±)-51ab:**



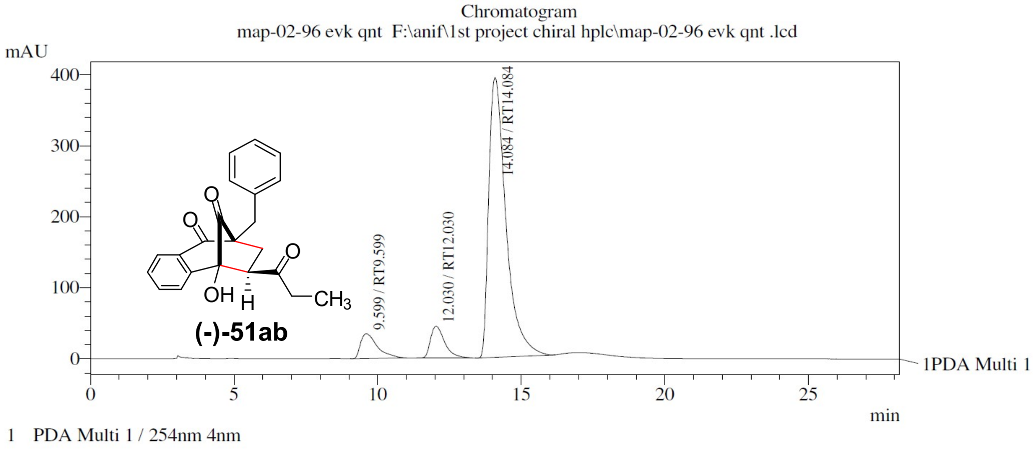
Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT9.801	9.801	8846198	668372	37.573	47.477
2	RT10.397	10.397	8741029	455834	37.126	32.380
3	RT12.625	12.625	2981955	150577	12.665	10.696
4	RT14.127	14.127	2974973	132985	12.636	9.447
Total			23544155	1407769	100.000	100.000

Chiral **(-)-51ab**: (Major: 83% *ee*; Minor: >99% *ee*):



Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

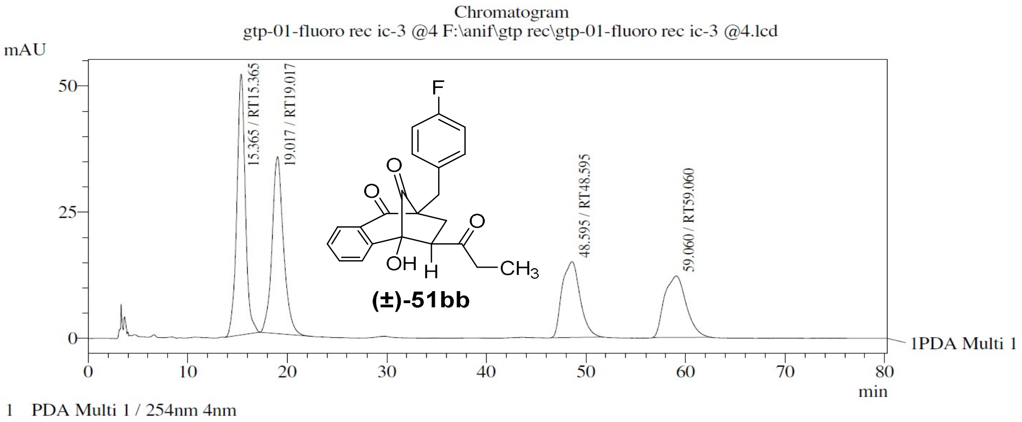
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT9.599	9.599	1429282	34954	7.383	7.383
2	RT12.030	12.030	1528240	44609	7.895	9.422
3	RT14.084	14.084	16400555	393880	84.722	83.195
Total			19358077	473442	100.000	100.000

Figure 37: HPLC spectra of the chiral product **51ab**.

Racemic **(±)-51bb**:



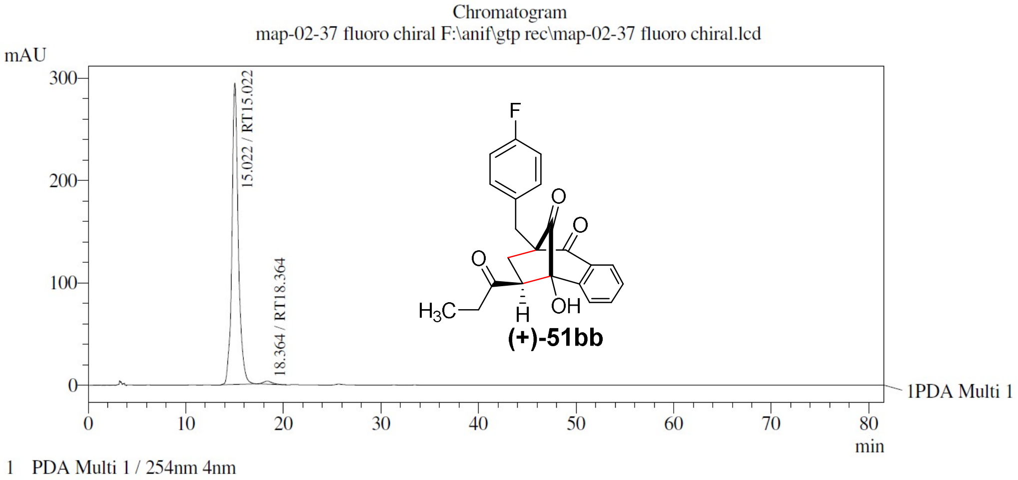
Chiralpak IC-3, Hexane/ *i*-PrOH = 95:05, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT15.365	15.365	3048375	51635	31.776	45.329
2	RT19.017	19.017	2809030	35068	29.281	30.785
3	RT48.595	48.595	1880500	15001	19.602	13.169
4	RT59.060	59.060	1855391	12208	19.340	10.717
Total			9593296	113911	100.000	100.000

Chiral **(+)-51bb**: (Major: 97% *ee*):



Chiralpak IC-3, Hexane/ *i*-PrOH = 95:05, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

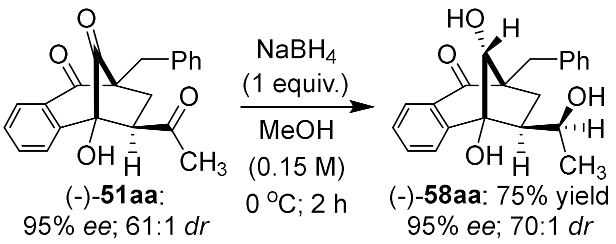
Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT15.022	15.022	13400594	294601	98.668	99.012
2	RT18.364	18.364	180972	2940	1.332	0.988
Total			13581566	297541	100.000	100.000

Figure 38: HPLC spectra of the chiral product **51bb**.

Surprisingly, domino reaction of **48a** with phenyl vinyl ketone **49e** under the **57b** catalysis in trifluorotoluene at 20 °C for 5.5 h furnished the expected product **51ae** in 90% yield with poor (22%) *ee* and high (97:1) dr (Table 10, entry 21). In similar conditions, we didn't observe the domino reaction between **48a** and 3-methylbut-3-en-2-one **49f** or ethyl acrylate **49g** for even for longer reaction times [results not shown in Table 10]. It is evident from the results that the size of the alkyl group on the enone **49** controls the reaction rate and selectivity.

4.2.3 Synthetic applications of methanobenzo[*f*]azulenes:

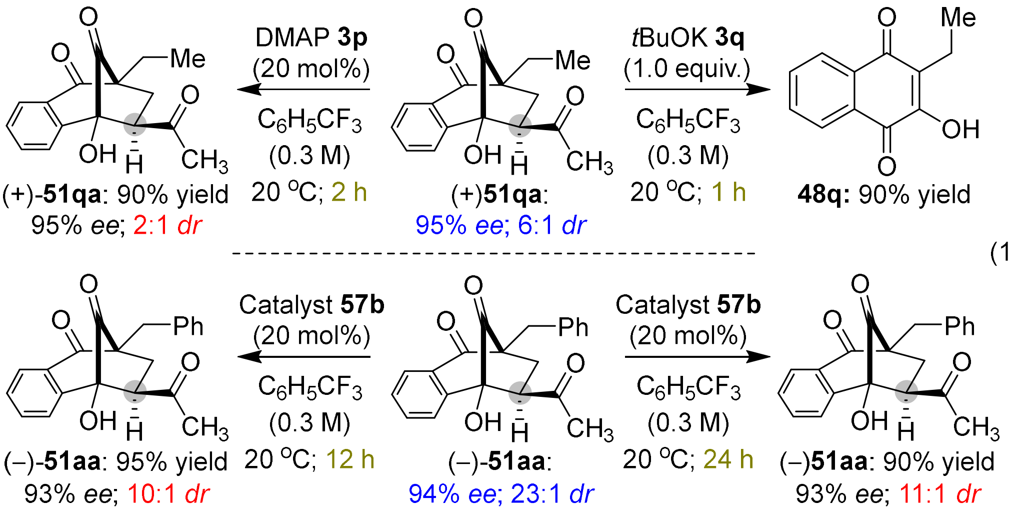
In line with synthetic applications, the generated triones **51** were utilized for the synthesis of hydroxy-rich chiral compounds **58** by simple reduction (Eq. 12). Straightforward $NaBH_4$ (1.0 equiv.) reduction of the chiral methanobenzo[7]annulene (−)-**51aa** in dry CH_3OH at 0 °C for 2 h produced the trihydroxy compound (−)-**58aa** in 75% yield with 95% *ee* and 70:1 dr (Eq. 12).



(12)

4.2.4 Controlled experiments

Basic nature of the catalyst **57** has strong influence on the stability and selectivity of the chiral products **51** (Eq. 13). Treatment of (+)-**51qa** with 20 mol% DMAP **3p** at 20 °C for 2 h resulted the product (+)-**51qa** with reduced dr and same *ee*; but treatment with one equivalent of KO*t*Bu **3r** at 20 °C for 1 h gave completely the starting materials **48q** and **49a** in 90% yield through retro-aldol/aldol and retro-aldol/retro-Michael reactions, respectively (Eq. 13). In a similar manner, reaction of (−)-**51aa** with 20 mol-% 9-*epi*-aminoquinine-thiourea **57b** at 20 °C for 12-24 h resulted the (−)-**51aa** with reduced dr and almost same *ee*; which is strong supportive of stepwise mechanism rather than concerted in the designed domino reactions (Eq. 13).



(13)

4.2.5 *Mechanistic insights:*

Despite the fact that further studies are necessary for elucidating the mechanism of the stereoselective domino Michael/*5-(enolexo)-exo-trig* cyclization through **57a** or **57b** catalysis, most probably, the reaction might be proceeding in a stepwise fashion between the in situ generated 3-alkyl-1,4-dioxo-1,4-dihydronaphthalen-2-olate and alkyl vinyl ketones **49** (Figure 40). The experiential high stereoselectivity could be explained on account of X-ray crystal structure studies, through an allowed *pre-*transition state, where the *Si*-face of alkyl vinyl ketone **49** approaches the *Re*-face of the in situ generated 3-alkyl-1,4-dioxo-1,4-dihydronaphthalen-2-olate owing to the strong hydrogen-bonding, electrostatic attraction and less steric hindrance between the catalyst **57b** and substrates **48**/**49** as shown in the **TS-1**. The model **TS-2** having weak hydrogen-bonding interactions between the catalyst **57b** and substrates **48**/**49** might explain the generation of the minor enantiomer (Figure 40)

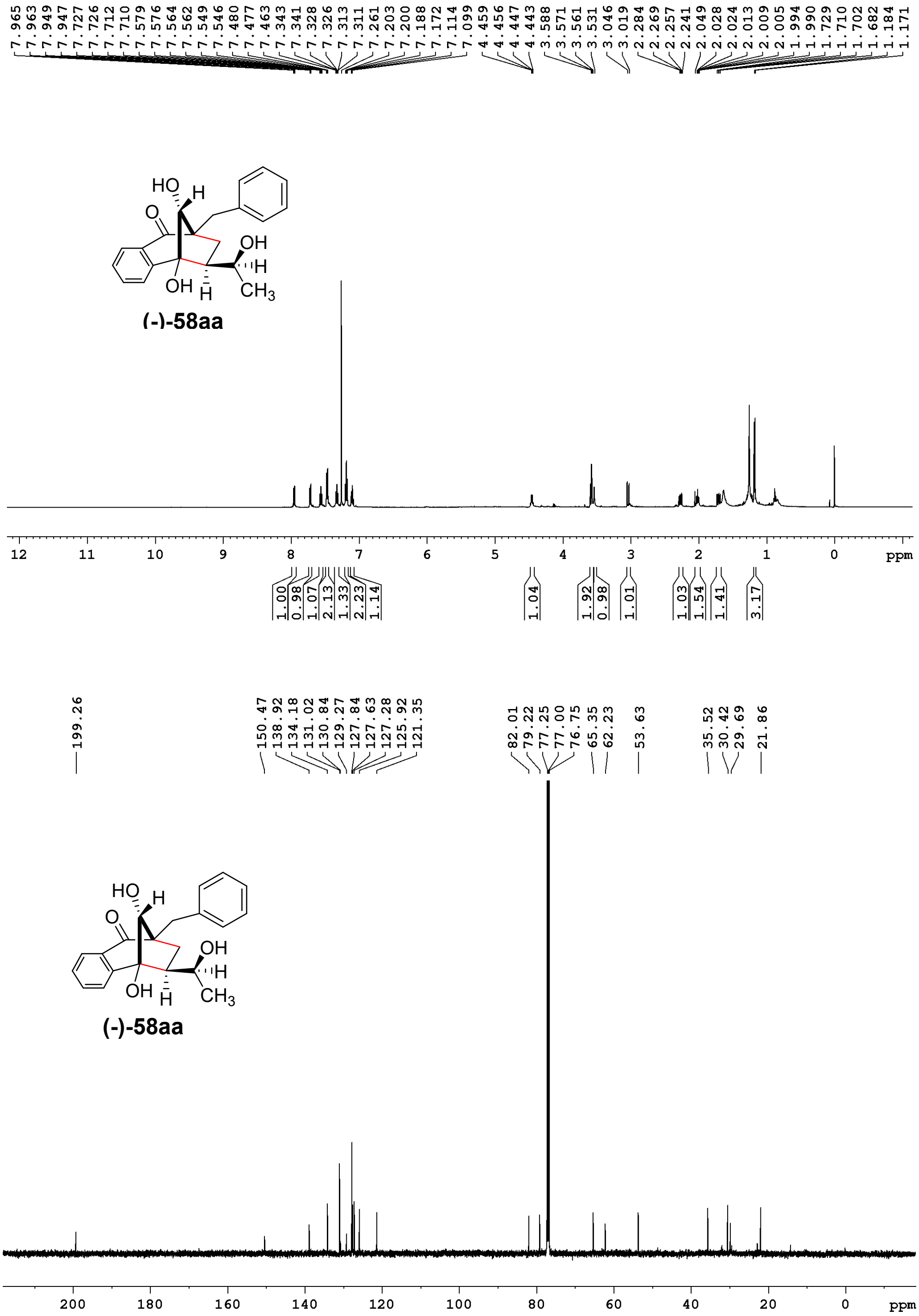
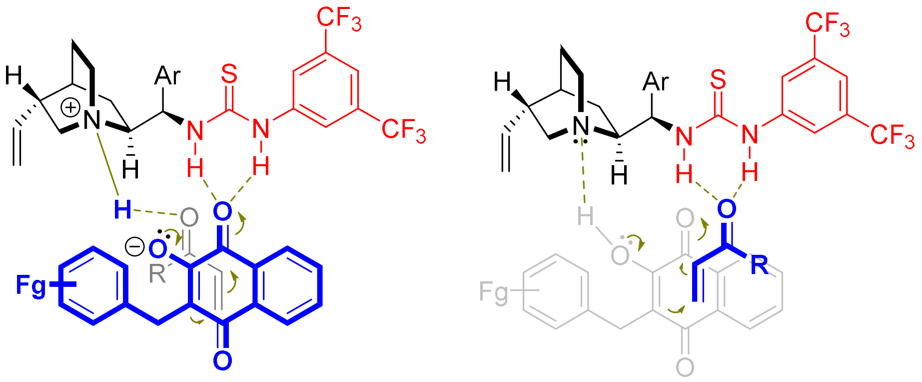


Figure 39: ^{1}H and ^{13}C spectra of the product **58aa**.



TS-1 [Favorable TS]
Synergistic activation in *Pre*-**TS**
[***Re-Si-face Approach***]

TS-2 [Unfavorable TS]
Non-synergistic activation in *Pre*-**TS**
[***Si-Si-face Approach***]

Figure 40: Proposed Reaction Mechanism.

We have also got strong support to our hypothesis of involving stable pre-transition state (*pre*-**TS-1**) through careful investigation of the domino reaction of **48g** with **49a** or **49b** under the **57b** catalysis using electrospray ionization with high resolution mass spectrometry (ESI-HRMS) technique, which enabled us to identify critical proposed *pre*-**TS-1** or Michael adduct-catalyst complex (Figure 41i&ii). The ESI-HRMS spectrum of an on-going reaction of **48g** with **49a** or **49b** (3 equiv.) in the presence of **57b** (20 mol-%) in the trifluorotoluene at 0-3 °C reveals the formation of the key catalytic intermediate *pre*-**TS-1**·Na+ (*m/z* 1019.2865) or *pre*-**TS-1**·Na+ (*m/z* 1033.3021) respectively. One of the important innovations in these reactions is that, out of the three carbonyls existed in the key Michael adduct intermediate (**50a**, Scheme 20), only C1-carbonyl group involved as the electrophile in the subsequent aldol reaction may be due to the consideration of length of the side chain *enolexo* and also structural/electronic nature of in situ generated naphthalene-1,2,4(*3H*)-trione. Even though, according to preliminary ab initio calculations, the charge on the C1 carbon is least (C4 = 0.397096; C2 = 0.406116; C1 = 0.349861).

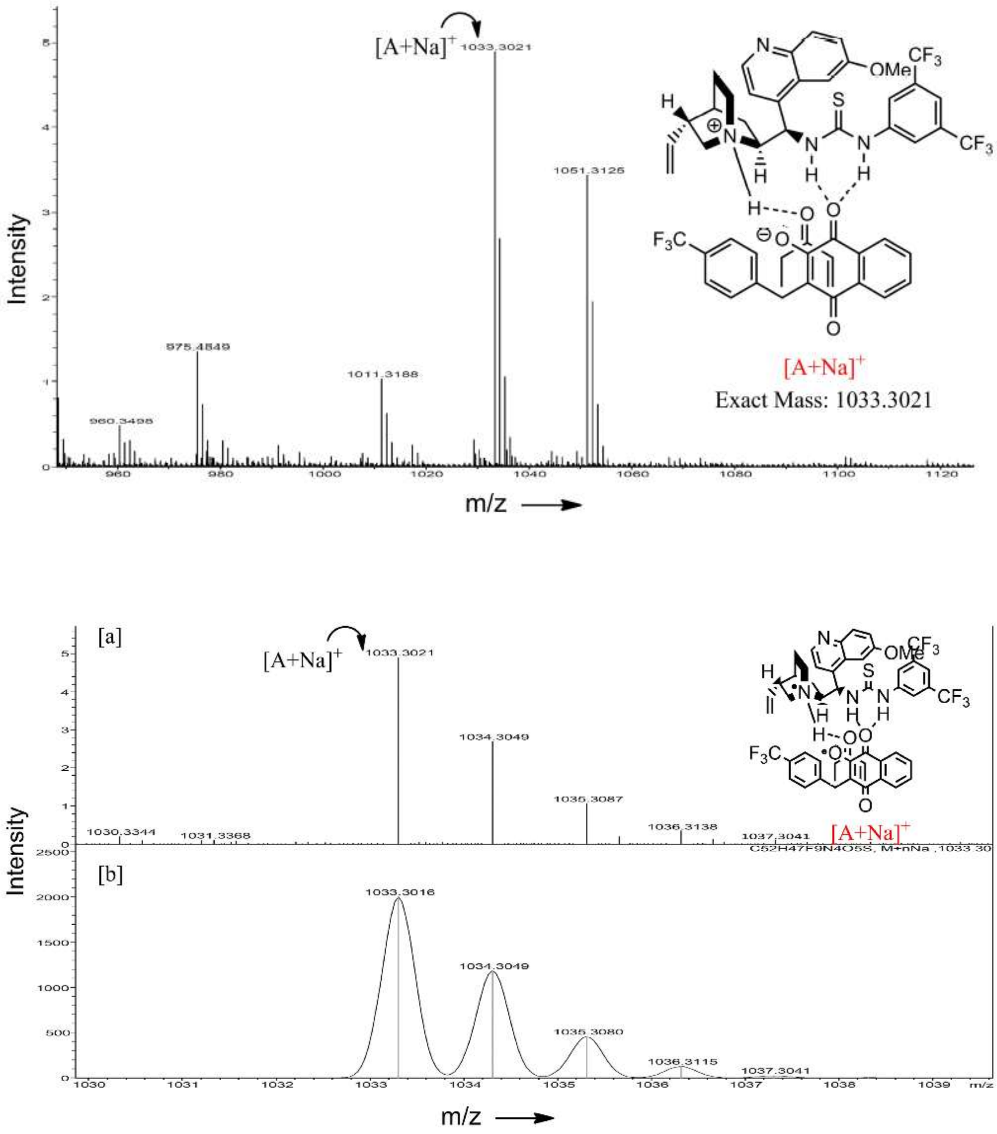


Figure 41i: The ESI-HRMS Spectrum and [a] observed [b] Stimulated isotopic pattern of an On-going Reaction of **48g** and **49b** (3 equiv.) in the Presence of **57b** (20 mol%).

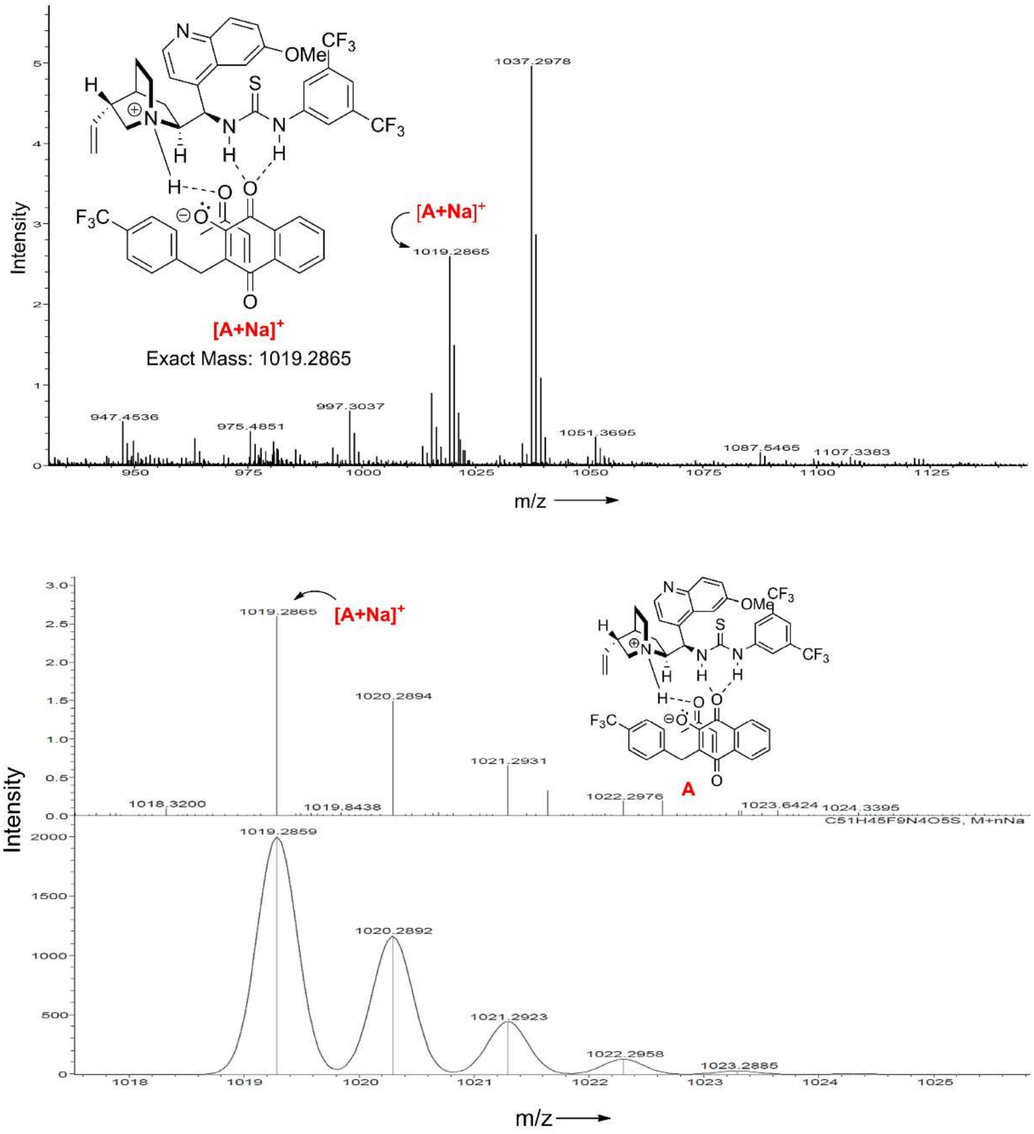


Figure 41ii: The ESI-HRMS Spectrum and [a] observed [b] Stimulated isotopic pattern of an On-going Reaction of **48g** and **49a** (3 equiv.) in the Presence of **57b** (20 mol%).

4.3 Conclusions

In conclusion, for the first time, we have utilized the in situ generated chiral enolates from lab-made 2-alkyl-3-hydroxynaphthalene-1,4-diones by 9-*epi*-aminoquinine-thiourea catalysis, as suitable dipolarophiles for formal [3+2]-cycloaddition with alkyl vinyl ketones to furnish the highly functionalized chiral methanobenzo[7]annulenes as a single compound out of six in very good yields with high *ee*'s/dr's. A library of methanobenzo[7]annulenes in both achiral and chiral forms were generated, which would be applicable in natural and pharmaceutical chemistry. Further work in this line of exploring the potential of novel modes available for the perfect pair of chiral amines with unmodified 2-alkyl-3-hydroxynaphthalene-1,4-diones is in progress.

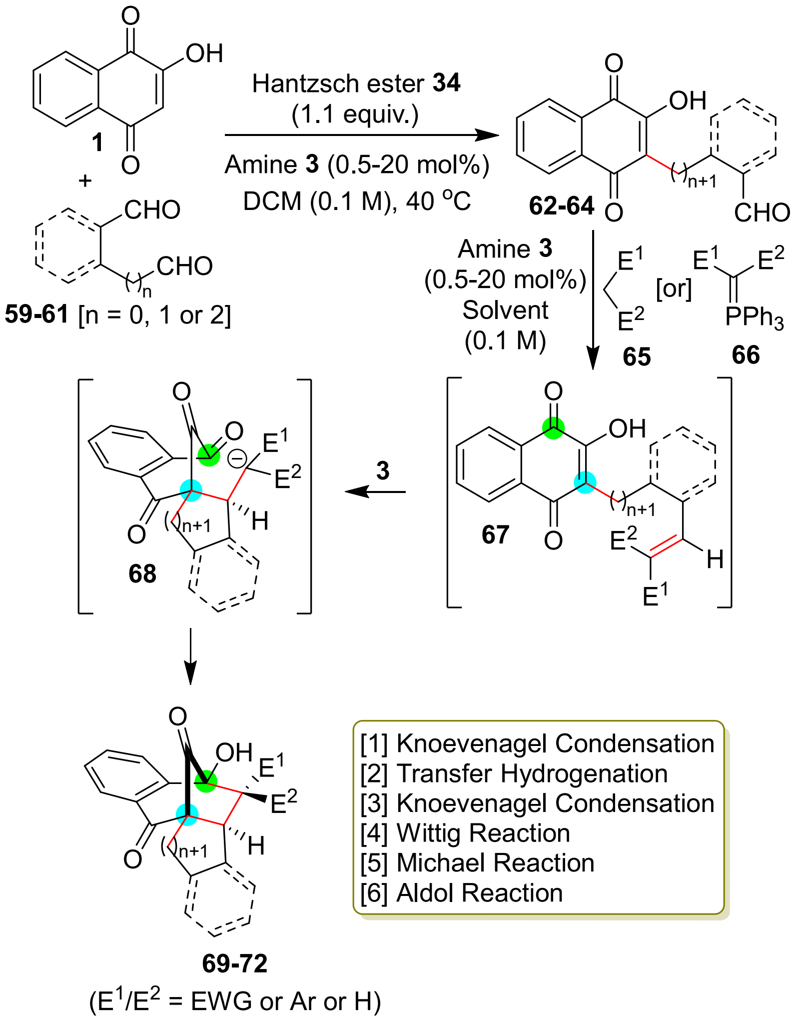
5. Organocatalytic Formal Intramolecular [3+2] Cycloaddition to Acquire Biologically Important Methanodibenzo[*a,f*]azulenes and Methanobenzo[*f*]azulenes

5.1 Introduction

Recently, lawsone and its cognates have become building blocks for cosmetic, organic, medicinal and material chemistry.[1] Due to the natural availability and the ambident nature, lawsone has become favorable starting material for organic chemists to design new chemical reactions to construct pharmaceutically important natural and unnatural molecules.[15] For the last few years, we have been investigating the ambident nature of lawsones with activated olefins through the intermolecular organocatalytic formal [3+2]-cycloaddition and [2+2]-cycloaddition followed by rearrangement to furnish the methanobenzo[7]annulenes and benzannulated bicyclo[3.3.0]octanes, respectively.[8a] In continuation of our scrutiny to explore the chemical reactivity/ambident nature of lawsones with olefins, herein, we outlined to study the domino formal intramolecular [3+2]-cycloaddition between functionalized lawsones and *in-situ* generated activated Knoevenagel or Wittig olefins (Scheme 21)**.**

In this unprecedented reaction, we are proposing that five domino reactions are sequentially going to be performed on lawsones **1** to make four C-C bonds, two C-H bonds and two rings in one- or two-pot manner (Scheme 21). First, organocatalytic chemoselective Knoevenagel condensation and transfer hydrogenation (reductive coupling) of lawsones **1** with di-aldehydes **59-61** and Hantzsch ester **34** generates the lawsone-aldehydes **62-64**. Further organocatalytic treatment of lawsone-aldehydes **62-64** with active methylenes or alkylidene phosphoranes **65**/**66** through Knoevenagel or Wittig reaction would generate the regioselective lawsone-olefins **67**, respectively.

Next, *in situ* reaction of lawsone-olefins **67** with organocatalyst **3** would generate the key intermediate **68** through diastereoselective intramolecular Michael reaction, which further undergoes chemoselective aldol reaction to furnish the functionalized, unique carbon skeleton of methanodibenzo[*a,f*]azulenes and methanobenzo[*f*]azulenes **69-72**, as a formal intramolecular [3+2]-cycloaddition product (Scheme 21).

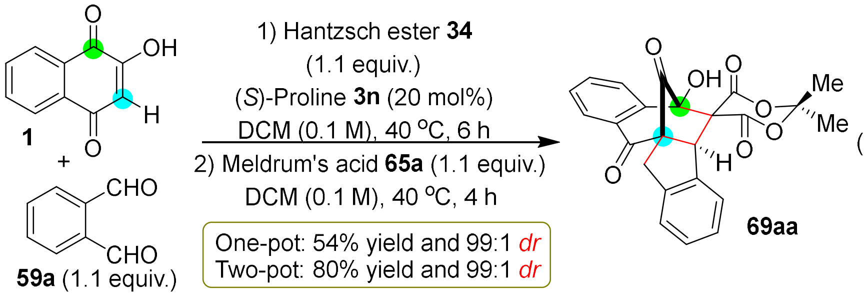


Scheme 21: Reaction design for acyclic/cyclic systems insertion into lawsones.

Organocatalytic *in situ* generated Knoevenagel condensation products, olefins from carbonyls and active methylenes are exceptionally reactive due to their self-activation.[23] For the last two decades, many chemists have investigated the unique organocatalytic generation of Knoevenagel olefins as intermediates to initiate domino reactions to synthesize complex molecules of diverse carbo- and heterocycles.[24] In particular, chemoselective synthesis of lawsone-olefins **67** through sequential domino Knoevenagel condensation-transfer hydrogenation-Knoevenagel condensation among lawsones **1**, di-aldehydes **59-61**, Hantzsch ester **34** and active methylenes **65**/**66** is highly challenging. Additionally, lawsone-olefins **67** has inspired us to further investigate the proposed intramolecular [3+2]-cyclizations through soft-catalysis (Scheme 21).

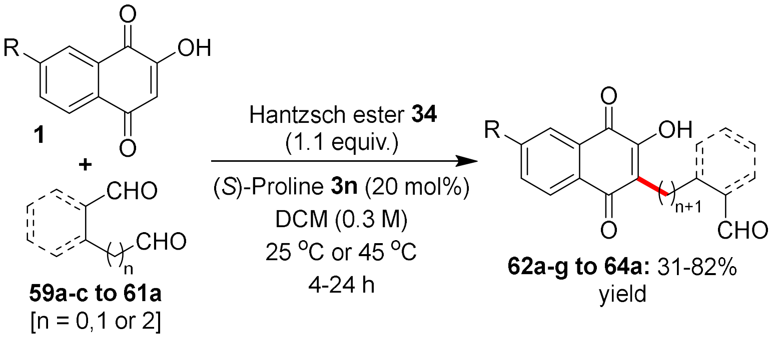
5.2 Results and Discussions

5.2.1 Reaction optimization:



One-pot: 54% yield and 99:1 *dr*
Two-pot: 80% yield and 99:1 *dr*

(14)

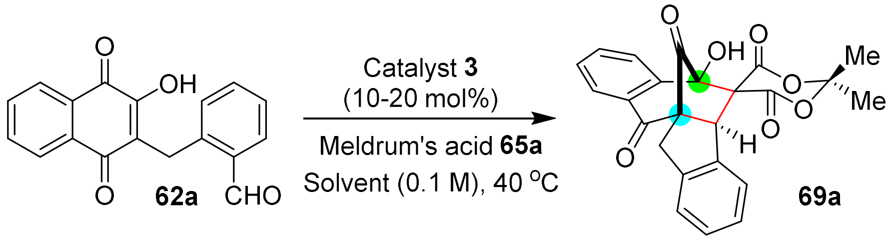


(15)

Preliminarily, to understand the designed domino reaction rate, catalyst/solvent effect, chemo-/diastereo-selectivity, and side reactions over the possible additions/cyclizations, first we investigated the proposed reaction among the simple substrates of lawsone **1**, phthalaldehyde **59a**, Hantzsch ester **34** and Meldrum's acid **65a** under the catalysis of (*S*)-proline **3n** in DCM at 40 °C for 10 h (Eq. 14). Surprisingly, the compound containing an unique carbon skeleton of methanodibenzo[*a,f*]azulene

(±)-**69aa** was obtained in 54% yield with 99:1 dr and 80% yield with 99:1 dr from sequential one-pot and two-pot manner, respectively (Eq. 14). Among these reaction sequences, **3n**-catalyzed chemoselective reductive coupling of **1**, **59a** and **34** in DCM at 40 °C for 4 h furnished the lawsone-aldehyde **62a** in 82% yield (Eq. 15).

Table 11: Investigationof the Proposed Domino Reaction.[a]



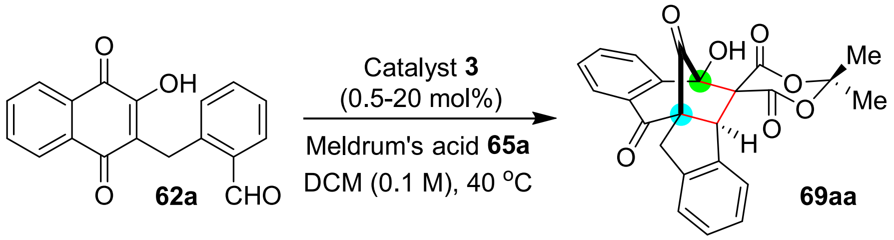
Entry	Solvent [0.1 M]	Catalyst **3** [mol%]	Time [h]	Yield [%][b] **69aa**	dr [%][c] **69aa**
1[d]	DCM	**3n** (20)	5.0	89	99:1
2[e]	DCM	**3n** (20)	6.0	84	99:1
3[f]	DCM	**3n** (20)	6.0	88	99:1
4	$CHCl_3$	**3n** (20)	5.0	95	99:1
5	CH_3CN	**3n** (20)	3.0	94	99:1
6	$CH_3C_6H_5$	**3n** (20)	5.0	26	99:1
7	EtOH	**3n** (20)	2.5	95	99:1
8	DMSO	**3n** (20)	0.5	88	99:1
9	H_2O	**3n** (20)	24	18	99:1
10[e,g]	DCM	**3z** (10)	0.41	97	99:1
11[e,h]	DCM	**3z**(10)	0.41	97	99:1

[a] Reactions were carried out in solvent (0.1 M) with 1.1 equiv. of **62a** relative to the **65a** (0.25 mmol) in the presence of catalyst **3**. [b] Yield refers to the column-purified product. [c] dr determined by ^{1}H NMR analysis of reaction mixture. [d] **62a** used in 1.05 equiv.[e] **62a** used in 1.0 equiv. [f] DCM used in 0.2 M. [g] T = 25 °C. [h] **65a** used in 1.1 equiv. with respect to **62a** (0.25 mmol, 1 equiv.). Note: **3z** = $PhCH_2NH_2$

Next, **3n** catalysed Knoevenagel-Michael-aldol reaction of **62a** with **65a** in DCM at 40 °C for 4 h furnished the domino product (±)-**69aa** in 98% yield with 99:1 dr (Table 11, entry 1). Based on our experience on reductive coupling,[8] we further initiated optimization on latter sequence of three reactions to improve the rate by investigating the catalyst structure, solvent nature and temperature (Table 11). The (*S*)-proline **3n**-catalyzed Knoevenagel condensation-intramolecular Michael and aldol (KC/IM/IA) reaction of **62a** with **65a** in DCM has shown that outcome of domino product (±)-**69aa** yield and reaction time is controlled by the catalyst loading and temperature (Table 12, entries 1-3 and Table 11). In a similar manner, with other catalysts such as glycine **3x**, $PhCO_2H$ **3y**, Et_3N **3o** and $BnNH_2$ **3z** too, the KC/IM/IA reaction proceeded to furnish the product **69aa** in poor to excellent yields, 3 to 97% yield with high selectivity of dr (99:1) in DCM at 40 °C under varying reaction times of 0.13 h to 96 h (Table 12, entries 4-7). This optimisation study clearly illustrated $BnNH_2$ **3z** as better catalyst.

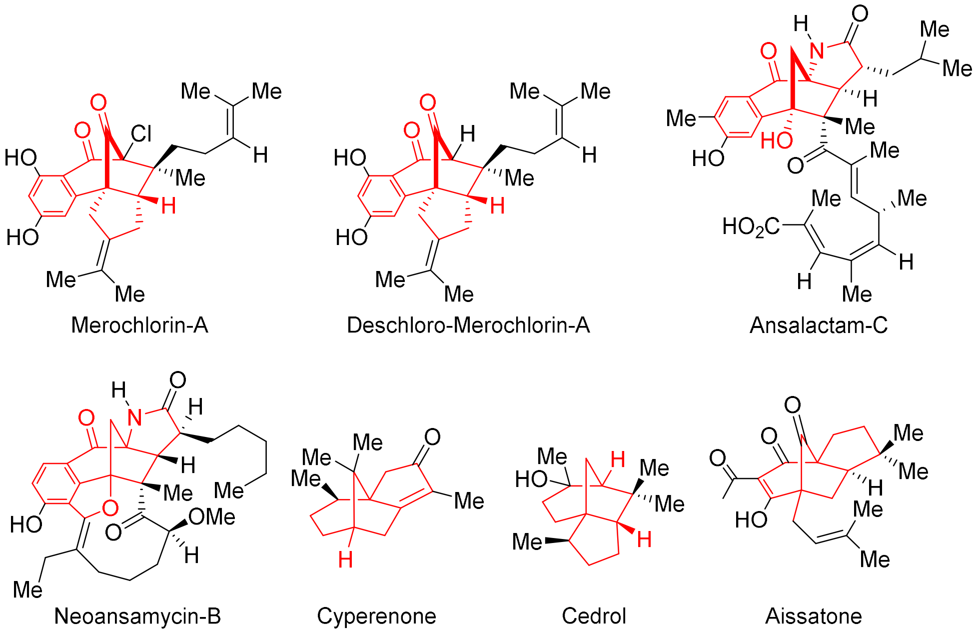
Further, we thoroughly investigated the catalyst **3z** loading (20 mol% to 0.5 mol%) of the domino reaction of **62a** and **65a** in DCM at 25 °C by looking at the outcome of the domino product **69aa** yield, selectivity and reaction time as shown in Table 12, entries 8-13. Surprisingly, we were able to obtain high yield and selectivity by compromising the reaction time at lower loading of the catalyst **3z** (Table 12 and Table 11). Finally, 10 mol% of **3z** in DCM (0.1 M) at 25 °C for 0.41 h was approved as the optimized condition for the domino KC/IM/IA reaction of **62a**and **65a** to furnish the methanodibenzo[*a,f*]azulene **69aa** in 98% yield with 99:1 dr (Table 12, entry 9).

Table 12: Investigation of the Proposed Domino Reaction.[a]



Entry	Catalyst **3** [mol%]	Time [h]	Yield [%][b] **69aa**	dr [%][c] **69aa**
1	(*S*)-Proline **3n** (20)	4.0	98	99:1
2	**3n** (10)	18	93	99:1
3[d]	**3n** (20)	6.0	88	99:1
4	Glycine **3x** (20)	24	<3	–
5	$PhCO_2H$ **3y** (20)	96	23	99:1
6	Et_3N **3o** (20)	3.0	93	99:1
7	$PhCH_2NH_2$ **3z** (20)	0.13	97	99:1
8[d]	**3z** (20)	0.16	98	99:1
9[d]	**3z** (10)	0.41	98	99:1
10[d]	**3z** (5.0)	1.0	98	99:1
11[d]	**3z** (2.5)	2.5	98	99:1
12[d]	**3z** (1.0)	12	98	99:1
13[d]	**3z** (0.5)	24	88	99:1
14	–	96	21	99:1

[a] Reactions were carried out in DCM (0.1 M) with 1.1 equiv. of **62a** relative to the **65a** (0.25 mmol) in the presence of catalyst **3**. [b] Yield refers to the column-purified product. [c] dr determined by ^{1}H NMR analysis of reaction mixture. [d] T = 25 °C.



Merochlorin-A

Deschloro-Merochlorin-A

Ansalactam-C

Neoansamycin-B

Cyperenone

Cedrol

Aissatone

Figure 42: Medicinally important products containing methanobenzo[*f*]azulenes and methanoazulenes.

Sequential domino reaction is not only fascinating but also product-wise interesting, as the methanoazulenes, methanodibenzo[*a*,*f*]azulenes, and methanobenzo[*f*]azulenes are the lead structural motifs found in the biologically active natural compounds (Figure 42).[15] Although very few methods have been developed for the synthesis of racemic methanobenzo[*f*]azulenes,[25] domino two-pot high-yielding methods for the construction of methanobenzo[*f*]azulenes with multiple functional groups and chiral centers are in high demand.[25] Thus, stereoselective sequential two-pot modular approach for the direct synthesis of methanodibenzo[*a*,*f*]azulenes, and methanobenzo[*f*]azulenes is further investigated.

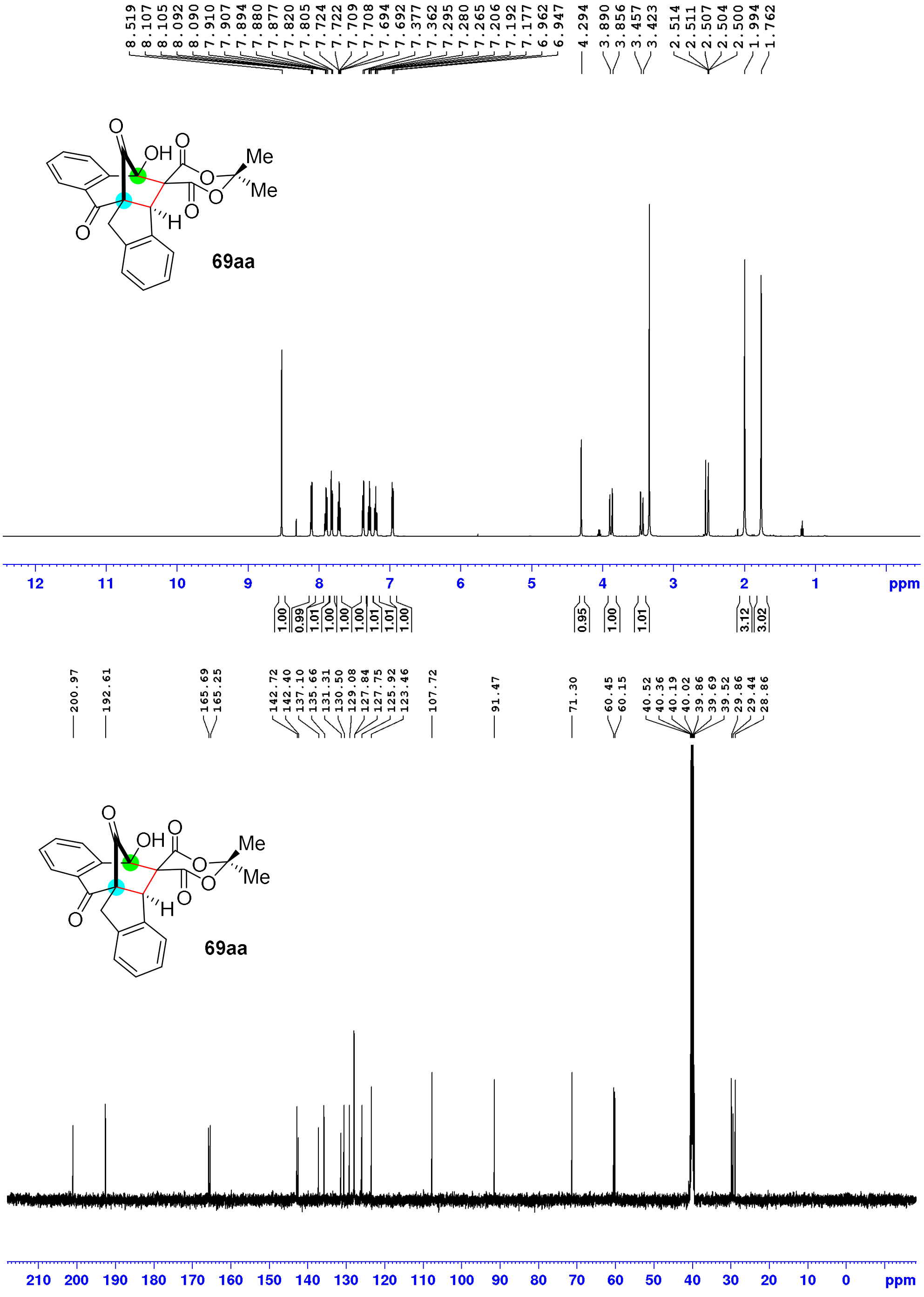


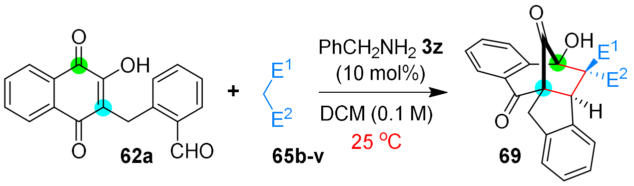
Figure 43: ^{1}H and ^{13}C spectra of the product **69aa**.

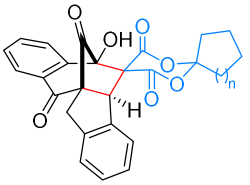
5.2.2 Scope of domino KC/IM/IA reactions:

Later we focused to investigate the **3n**-catalysed domino KC/IM/IA reaction by developing a library of structurally unique, functionally rich methanodibenzo[*a*,*f*]azulenes **69ab-69au**, benzo[*b*]indeno[1,2-*m*]xanthenetriones **69ak-69ao** and (epimethanetriyliminomethano)dibenzo[*a*,*f*]azulene-5-carbonitrile **69ap** through the domino reaction of various CH-acids or active methylenes **65b-v** with lawsone-aldehyde **62a** (Table 13). The reported methanodibenzo[*a*,*f*]azulenes **69ab-69af** were obtained in 88-97% yields with 99:1 dr's from the domino reaction of CH-acids containing spiro-Meldrum's acids **65b-c**, chiral spiro-Meldrum's acid **65d**, and Barbiturates **65e-f** with lawsone-aldehyde **62a** at 25 °C for 0.41 to 1.5 h (Table 13).

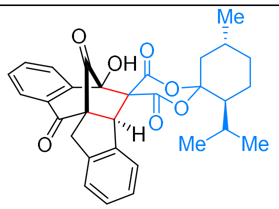
Strangely, the chiral domino product (-)-**69ad** was generated in 1:1 dr from **62a** and (-)-**65d** may be due to the poor facial selectivity. Structurally challenging indoline containing spiro[methanodibenzo[*a*,*f*]azulenes] **69ag-69ai** were furnished in 53-74% yields with 4:1 to 13:1 dr from the **3z**-catalysed domino reaction of **62a** with indolin-2-ones **65g-i** in EtOH or CH_3CN at 45-80 °C for 2.5-24 h (Table 13). The **3z**-catalysed domino product **69aj** was formed in 97% yield with 99:1 dr from the reaction between **62a** and 1,3-indandione **65j** within 0.41 h at 25 °C (Table 13). Peculiarly, the **3z**-catalysed domino reaction of lawsone-aldehyde **62a** with CH-acids of cyclopentane-1,3-dione **65k**, cyclohexane-1,3-dione **65l**, dimedone **65m**, lawsone **1**, and 4-hydroxy-6-methyl-2*H*-pyran-2-one **65o** at 25 °C in DCM for 0.75 to 90 h furnished the unexpected benzo[*b*]indeno[1,2-*m*]xanthenetriones **69ak-69ao** in excellent yields with 99:1 dr (Table 13). This unusual acetal formation over aldol reaction in the final domino reaction may be due to the more population of the enol tautomers than 1,3-diketones of the key intermediates **68ak-68ao** (Table 13 and see Scheme 21).

Table 13: CH-acids scope of the proposed design.[a]

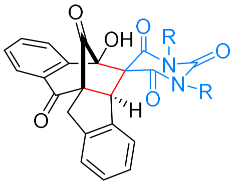




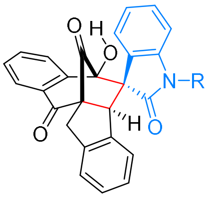
n = 1: **69ab**
[0.41 h, 89%, 99:1 *dr*]
n = 2: **69ac**
[0.41 h, 88%, 99:1 *dr*]



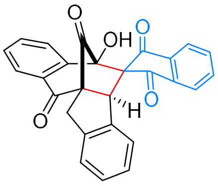
(-)-**69ad**
[0.41 h, 95%, 1:1 *dr*]



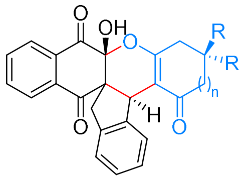
R = H: **69ae**
[1.5 h, 97%, 99:1 *dr*]
R = Me: **69af**
[0.41 h, 96%, 99:1 *dr*]



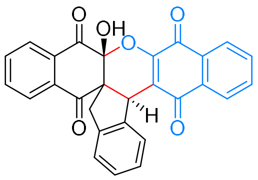
R = H: **69ag**[c]
[2.5 h, 56%, 13:1 *dr*]
R = Me: **69ah**[d]
[24 h, 53%, 10:1 *dr*]
R = Ac: **69ai**[d]
[2.5 h, 74%, 4:1 *dr*]



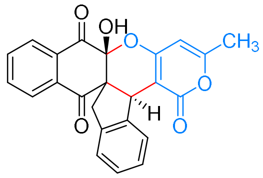
69aj
[0.41 h, 97%, 99:1 *dr*]



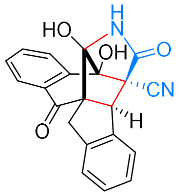
n = 0; R = H: **69ak**
[0.75 h, 98%, 99:1 *dr*]
n = 1; R = H: **69al**
[0.75 h, 98%, 99:1 *dr*]
n = 1; R = Me: **69am**
[0.75 h, 96%, 99:1 *dr*]



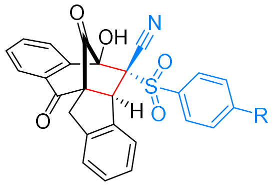
69an
[90 h, 95%, 99:1 *dr*]



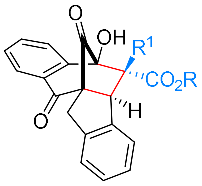
69ao
[2.5 h, 98%, 99:1 *dr*]



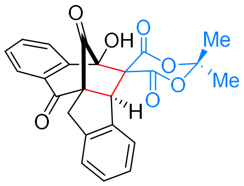
69ap from CH$_2$(CN)$_2$ **65p**
[0.75 h, 89%, 99:1 *dr*]
69ap from CNCH$_2$(CONH$_2$)
65q
[36 h, 85%, 99:1 *dr*][d]



R = H: **69aq**[e]
[6 h, 58%, 99:1 *dr*]
R = Me: **69ar**[e]
[24 h, 54%, 99:1 dr]



R = Et; R^1 = CN: **69as**[e-f]
[15 h, 78%, 14:1 *dr*]
R = Bn; R^1 = CN: **69at**[e-f]
[10 h, 75%, 7:1 *dr*]
R = Et; R^1 = NO$_2$: **69au**[e]
[10 h, 89%, 2:1 *dr*]



69aa [gm scale]
[3 mmol, 0.75 h]
[1.05 gm, 84%, 99:1 *dr*]

[a] Reactions were performed using **62a** (0.275 mmol, 1.1 equiv.), **65a-v** (0.25 mmol, 1 equiv.), and **3z** (10 mol%) in DCM (0.1 M) at 25 °C, and yield refers to the column-purified product. [b] dr was determined by ^{1}H NMR analysis of crude reaction mixture. [c] Reaction was performed in EtOH (0.1 M) at 80 °C. [d] Reaction was performed in CH_3CN (0.1 M) at 45 °C. [e] The reaction was performed at 50 °C in a sealed tube. [f] Reaction was carried out using **62a** (1.0 equiv.) and **6** (1.2 equiv.).

Strikingly, the domino reaction of lawsone-aldehyde **62a** with malononitrile **65p**, or 2-cyanoacetamide **65q** under the catalysis of $BnNH_2$ **3z** in DCM or CH_3CN at 25 °C or 45 °C for 0.75-36 h furnished the unexpected polycyclic domino product **69ap** as the single product in 85-89% yields with 99:1 dr through the formation of **69** followed by nitrile hydrolysis and aminal formation (Table 13). Surprisingly, the domino reaction of 2-(phenylsulfonyl)acetonitrile **65r**, and 2-tosylacetonitrile **65s** with **62a** under the catalysis of $BnNH_2$ **3z** in DCM at 50 °C in a sealed tube for longer reaction times (6 h and 24 h) furnished the expected domino products **69ak** and **69ar** in good yields (58%, 54%) with high (99:1) dr respectively (Table 13). In a similar manner, the domino reaction of ethyl 2-cyanoacetate **65t**, benzyl 2-cyanoacetate **65u**, and ethyl 2-nitroacetate **65v** with **62a** under the catalysis of $BnNH_2$ **3z** in DCM at 50 °C in a sealed tube for longer reaction times (10 to 15 h) furnished the domino products **69as** to **69au** in very good (78, 75, 89) yields with good to moderate (14:1 to 2:1) dr*'s,* respectively (Table 13). Gram scale domino reaction of **62a** and **65a** under the **3z** catalysis furnished the crystalline product **69aa** without compromising yield, rate and selectivity (Table 13). These results clearly suggest that the CH-acids **65a-v** containing various electron withdrawing groups have sufficient control over the outcome of the domino KC/IM/IA reaction product structure, rate, selectivity and yields through steric and electronic factors.

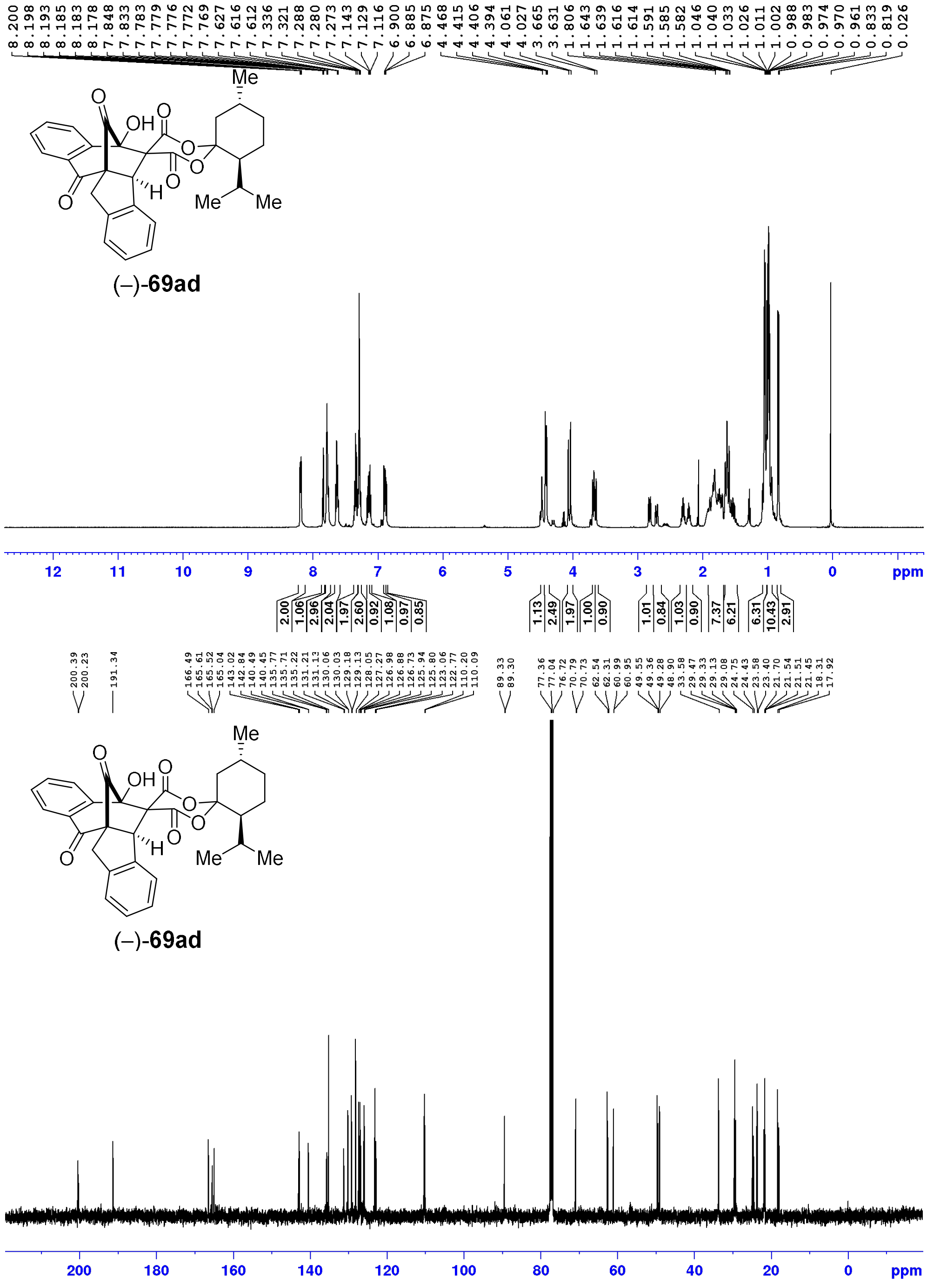


Figure 44: ^{1}H and ^{13}C spectra of the product **69ad**.

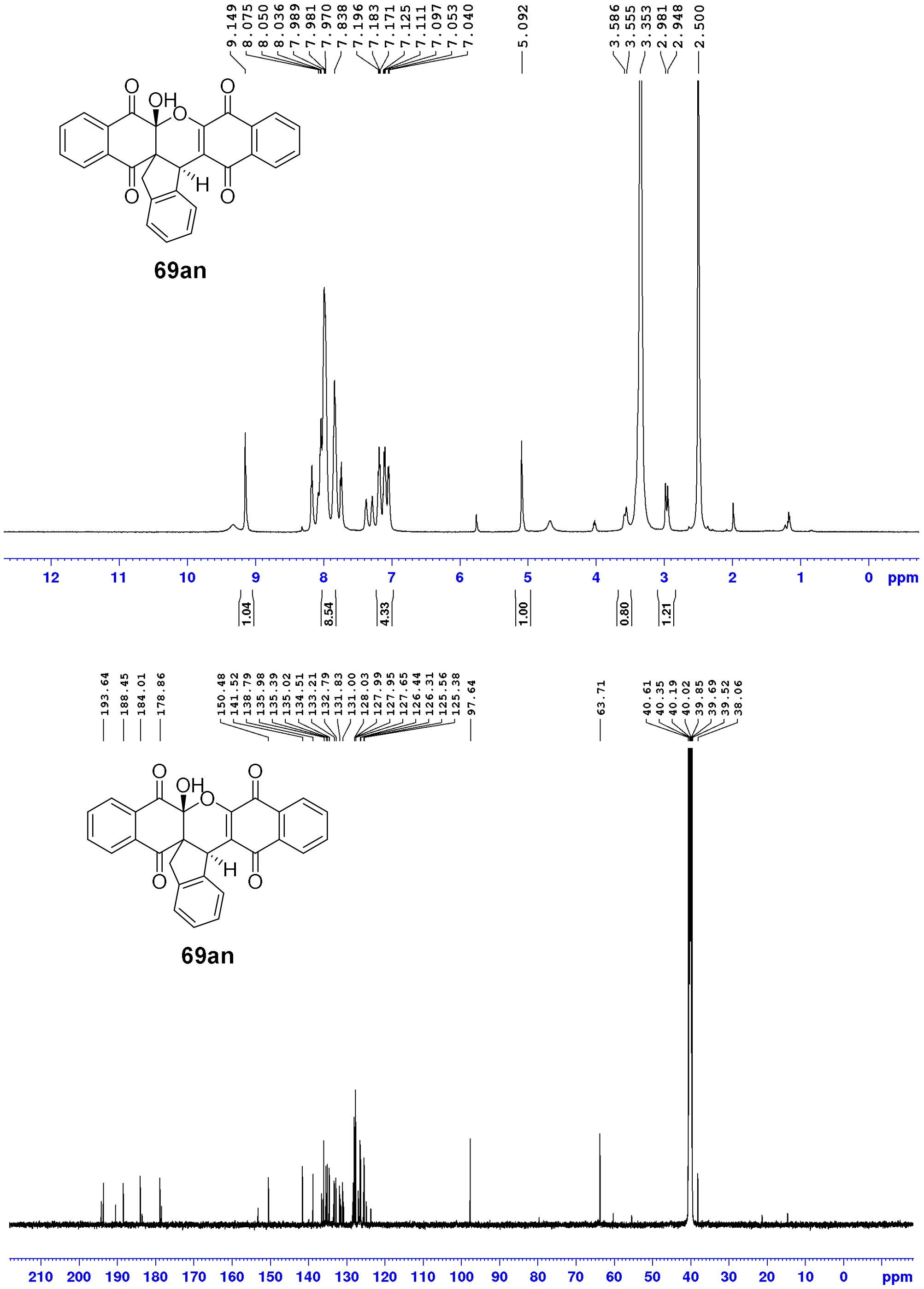


Figure 45: ^{1}H and ^{13}C spectra of the product **69an**.

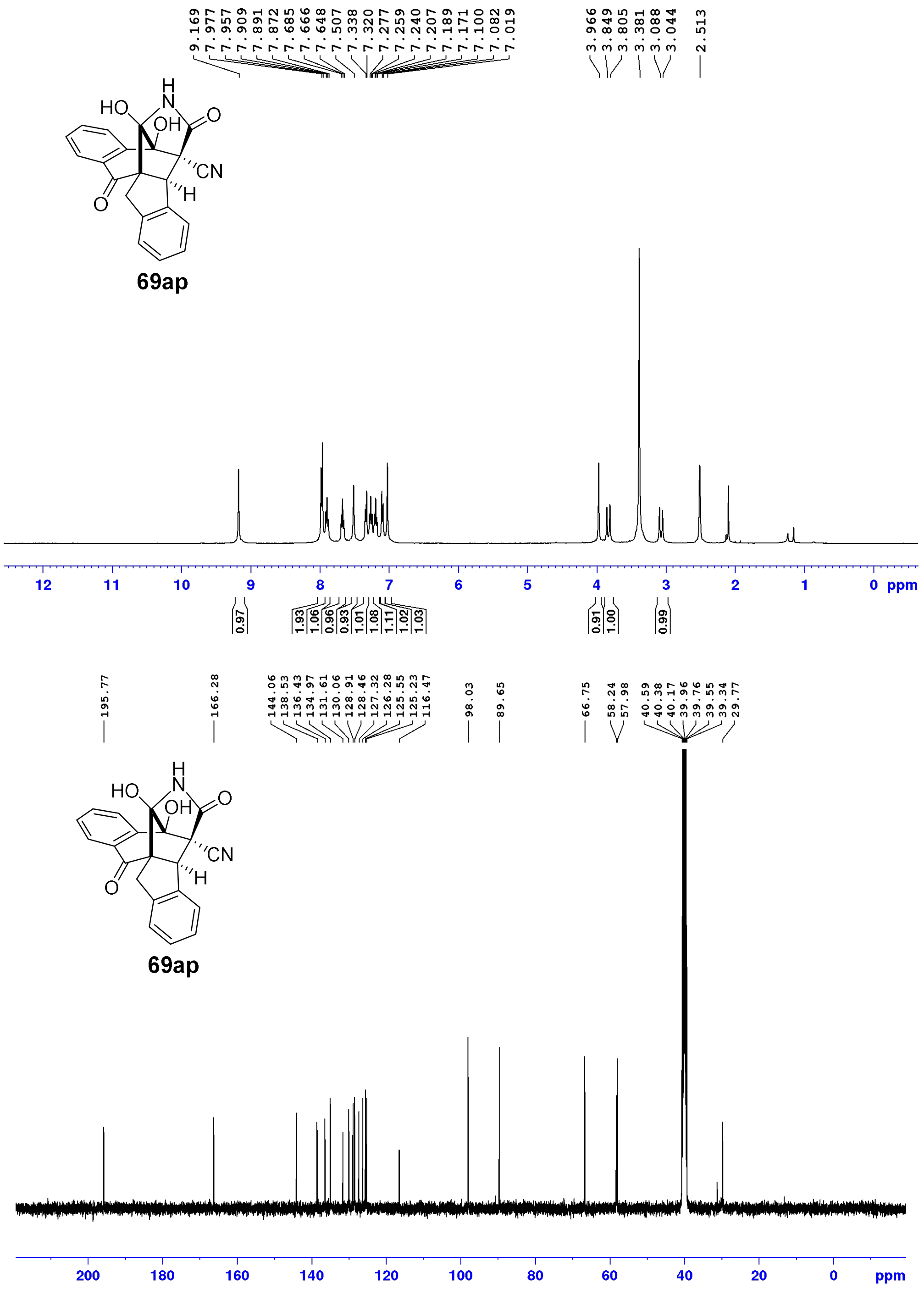
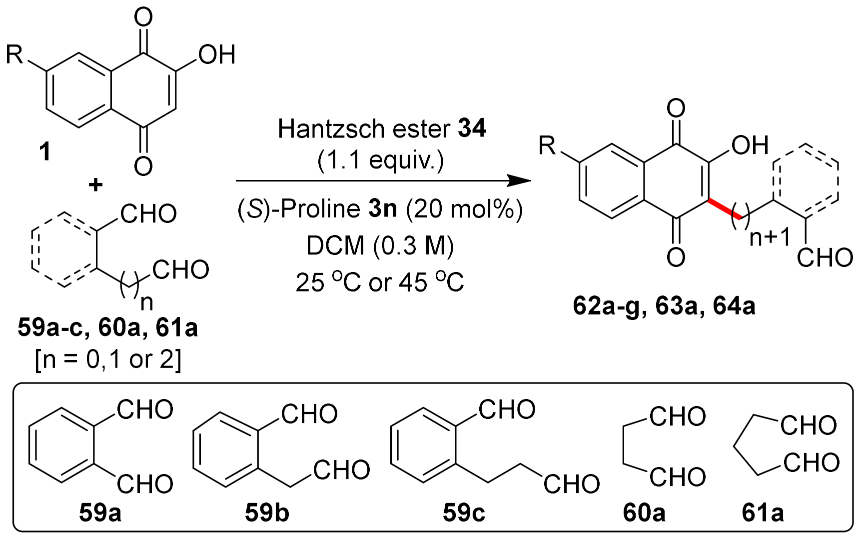


Figure 46: ^{1}H and ^{13}C spectra of the product **69ap**.

We further explored the scope of the **3z** catalysed domino KC/IM/IA reaction by developing a library of functionally rich methanodibenzo[*a*,*f*]azulenes **69ba-fa, 69bf-gf** through the reaction of various lawson-aldehydes **62b-g** with Meldrum's acid **65a** or Barbiturate **65f** (Table 15). Various lawsone aldehyde **62b-i**, **63a** and **64a** used in this reaction were synthesized in moderate to good yields by using organocatalytic TCRA or reductive coupling of Lawsone **1**, aldehydes **59-61** and Hantzsch ester **34** (Table 14). Notably, the domino reaction of **65a** with 6-methyl-lawsone-aldehyde **62b** under the **3z** catalysis in DCM at 25 °C for 0.5 h furnished the domino product **69ba** in 96% yield with 99:1 dr (Table 15). Similarly, the domino reaction of lawsone-aldehydes **62c-e** containing 6-methoxy, 6-chloro and 6-bromo groups with **65a** under the **3z** catalysis in DCM at 25 °C for 0.75 h furnished the domino products **69ca-ea** in 93%, 96% and 96% yields with 99:1 dr*'s*, respectively (Table 15).

To test the effect of length of the methylene side chain in lawsone-aldehydes **62** (n = 1 to 3) on the domino reaction, we performed the **3z** catalysed domino KC/IM/IA reaction of **65a** with two lawsone-aldehydes **62f-g** (n = 2-3) in DCM at 25 °C for 1.0 to 24.0 h (Table 15). Product **69fa** (n = 2) was furnished in 95% yield with 99:1 dr within 1.0 h; but there is no product formation of **69ga** (n = 3) even after longer reaction times and at higher temperatures and only the corresponding olefin **67** was observed. Same trend was observed while performing the domino reaction of lawsone-aldehydes **62b-g** with Barbiturate **65f** and the results of the domino products **69bf-gf** are presented in the Table 15. These results clearly highlight the importance of the domino KC/IM/IA reaction to construct functionally rich methanodibenzo[*a*,*f*]azulenes **69ba-gf**.

Table 14: Reaction Scope for Organocatalytic Chemoselective Reductive Coupling Reaction: Synthesis of Lawsone Derivatives.[a]

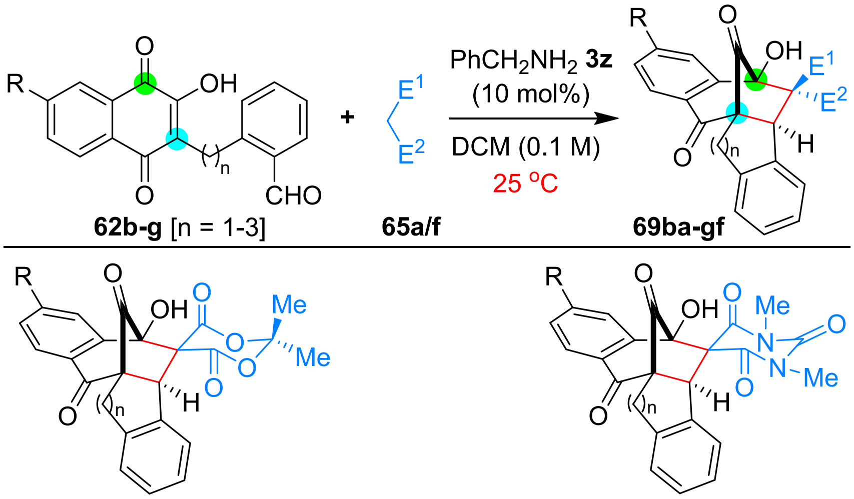


Entry	1	2	t [h]	Yield **5** [%][b]
1[c]	**1a**: R = H	**59a**	4.0	82 (**62a**)
2	**1b**: R = Me	**59a**	7.0	82 (**62b**)
3	**1c**: R = OMe	**59a**	7.0	69 (**62c**)
4[c]	**1d**: R = Cl	**59a**	24	57 (**62d**)
5[c]	**1e**: R = Br	**59a**	24	56 (**62e**)
6[d]	**1a**	**59b**	18	44 (**62f**)
7[c,d]	**1a**	**59c**	6.0	31 (**62g**)
8[e]	**1a**	**60a**	24	35 (**63a**)
9[f]	**1a**	**61a**	24	40 (**64a**)

[a]Reactions were carried out in DCM (0.3 M) with 1.1 equiv. of **59**-**61** and 1.1 equiv. of **34** relative to the **1** (0.3 mmol) in the presence of 20 mol% of (*S*)-proline **3n** at 25 °C. [b] Yield refers to the column-purified product. [c] Reaction performed at 40 to 45 °C. [d] The aldehyde **59** was added drop wise over 3-5 h using dropping funnel under N_2

atmosphere. [e] The aldehyde **60** was used in 3 equiv. with respect to **1**. [f] The aldehyde **61** was used in 4 equiv. with respect to **1**.

Table 15: Lawsone Derivatives Scope. [a]



n = 1; R = Me: **69ba** [0.5 h, 96%, 99:1 *dr*]	n = 1; R = Me: **69bf** [0.5 h, 97%, 99:1 *dr*]
n = 1; R = OMe: **69ca** [0.75 h, 93%, 99:1 *dr*]	n = 1; R = OMe: **69cf** [0.75 h, 92%, 99:1 *dr*]
n = 1; R = Cl: **69da** [0.75 h, 96%, 99:1 *dr*]	n = 1; R = Cl: **69df** [0.75 h, 96%, 99:1 *dr*]
n = 1; R = Br: **69ea** [0.75 h, 96%, 99:1 *dr*]	n = 1; R = Br: **69ef** [0.75 h, 97%, 99:1 *dr*]
n = 2; R = H:**69fa** [1.0 h, 95%, 99:1 *dr*]	n = 2; R = H: **69ff** [1.0 h, 98%, 99:1 *dr*]
n = 3; R = H: **69ga** [24 h, 0%]	n = 3; R = H: **69gf** [24 h, 0%]

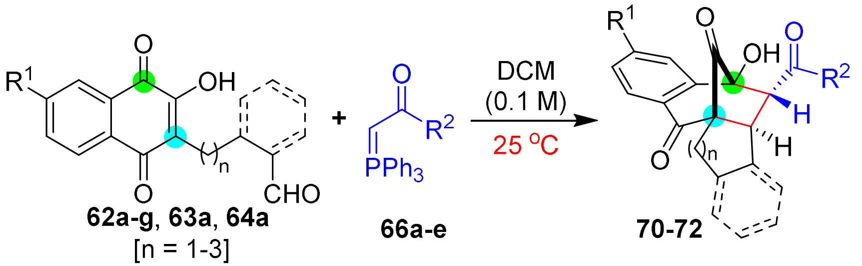
[a]Reactions were performed using **62a** (0.275 mmol, 1.1 equiv.), **65a/f** (0.25 mmol, 1 equiv.), and **3z** (10 mol%) in DCM (0.1 M) at 25 °C, and yield refers to the column-purified product. [b] dr was determined by ^1H NMR analysis of crude reaction mixture.

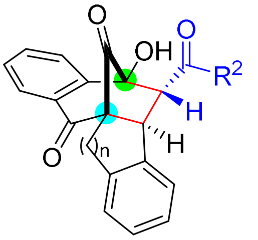
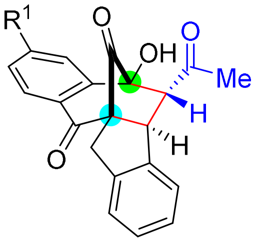
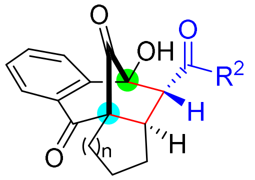
To investigate the outcome of rate and diastereoselectivity in the designed domino reaction by using disubstituted olefins **67**, we tested the domino W/IM/IA reaction of lawsone-aldehydes **62a-g**, **63a** and **64a** with various alkylidene phosphoranes **66a-e**

(Table 16). Surprisingly, the domino reaction of (triphenylphosphoranylidene)acetaldehyde **66a** with lawsone-aldehyde **62a** under the self-catalysis of Ph_3PO in DCM at 50 °C for 7 h furnished the domino product **70aa** in 92% yield with 99:1 dr (Table 16). Delightedly, the domino W/IM/IA reaction of (acetylmethylene)triphenylphosphorane **66b** and (benzoylmethylene)triphenylphosphorane **6d** with lawsone-aldehyde **62a** under the self-catalysis of Ph_3PO in DCM at 25 °C for 3 or 24 h furnished the domino product **70ab** in 95% yield with 99:1 *dr* and **70ad** in 98% yield with 99:1 dr, respectively (Table 16). The domino W/IM/IA reaction of ethyl (triphenylphosphoranylidene)acetate **66e** with lawsone-aldehyde **62a** under the catalysis of DMAP **3p** in toluene at 80 °C for 24 h furnished the domino product **70ae** in 81% yield with 12:1 dr; but there is no reaction at 25 °C and without **3p** (Table 16). We further performed the Ph_3PO-catalysed domino W/IM/IA reaction of **66d** with two more lawsone-aldehydes **62f-g** (n = 2-3) in DCM at 50 °C for 24 to 48 h (Table 16). Product **70fd** (n = 2) was furnished in 80% yield with 1.5:1 dr; but there is no product formation of **70gd** (n = 3) even after longer reaction times and at higher temperatures. Further, domino W/IM/IA reaction of **66b** with **62b-e** containing 6-methyl, 6-methoxy, 6-chloro and 6-bromo groups under the self-catalysis of Ph_3PO in DCM at 25 °C for 3 h furnished the products **70bb** to **70eb** in 95-97% yields with 99:1 dr (Table 16).

Next, we planned to construct the functionally rich and biologically active methanobenzo[*f*]azulenes in good yields as it is basic skeleton of many antibiotics (see Figure 38). The domino W/IM/IA reaction of **66a** with 4-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal **63a** under the self-catalysis of Ph_3PO in DCM at 25 °C for 2 h furnished the product **71aa** in 70% yield with 99:1 dr (Table 16).

Table 16: Lawsones and alkylidene-phosporanes Scope.[a]



		
n = 1; R^2 = H: **70aa**[c] [7 h, 92%, 99:1 *dr*]	R^1 = Me: **70bb** [3 h, 96%, 99:1 *dr*]	n = 1; R^2 = H: **71aa** [2 h, 70%, 99:1 *dr*]
n = 1; R^2 = Me: **70ab** [3 h, 95%, 99:1 *dr*]	R^1 = OMe: **70cb** [3 h, 95%, 99:1 *dr*]	n = 1; R^2 = Me: **71ab** [3 h, 85%, 99:1 *dr*]
n = 1; R^2 = Ph: **70ad** [24 h, 98%, 99:1 *dr*]	R^1 = Cl: **70db** [3 h, 95%, 99:1 *dr*]	n = 1; R^2 = Ph: **71ad** [1 h, 80%, 99:1 *dr*]
n = 1; R^2 = OEt: **70ae**[d] [24 h, 81%, 12:1 *dr*]	R^1 = Br: **70eb** [3 h, 97%, 99:1 *dr*]	n = 1; R^2 = OEt: **71ae**[f] [4 h, 67%, 13:1 *dr*]
n = 2; R^2 = Ph: **70fd**c] [24 h, 80%, 1.5:1 *dr*]		n = 2; R^2 = Me: **72ab**[g] [16 h, 65%, 2:1 *dr*]
n = 3; R^2 = Ph: **70gd**[e] [48 h, 0%]		n = 2; R^2 = Ph: **72ad**[g] [24 h, 67%, 7:1 *dr*]
		n = 2; R^2 = OEt: **72ae**[e] [48 h, 0%]

[a] Reactions were performed using **62a-e**, **63a** and **64a** (0.25 mmol, 1.0 equiv.), and **66a-e** (0.3 mmol, 1.2 equiv.) in DCM (0.1 M) at 25 °C, and yield refers to the column-purified product. [b] dr was determined by ^{1}H NMR analysis of crude reaction mixture. [c] T = 50 °C. [d] The reaction was performed in toluene (0.1 M) in the presence of DMAP (**3p**) (30 mol%) at 80 °C. [e] Corresponding Wittig product **67** was isolated in quantitative yields. [f] The reaction was performed in toluene (0.1 M) in the presence of

DMAP (30 mol%) at 150 ºC in a sealed tube. [g] The reaction was performed at 150 ºC in toluene (0.1 M) in a sealed tube.

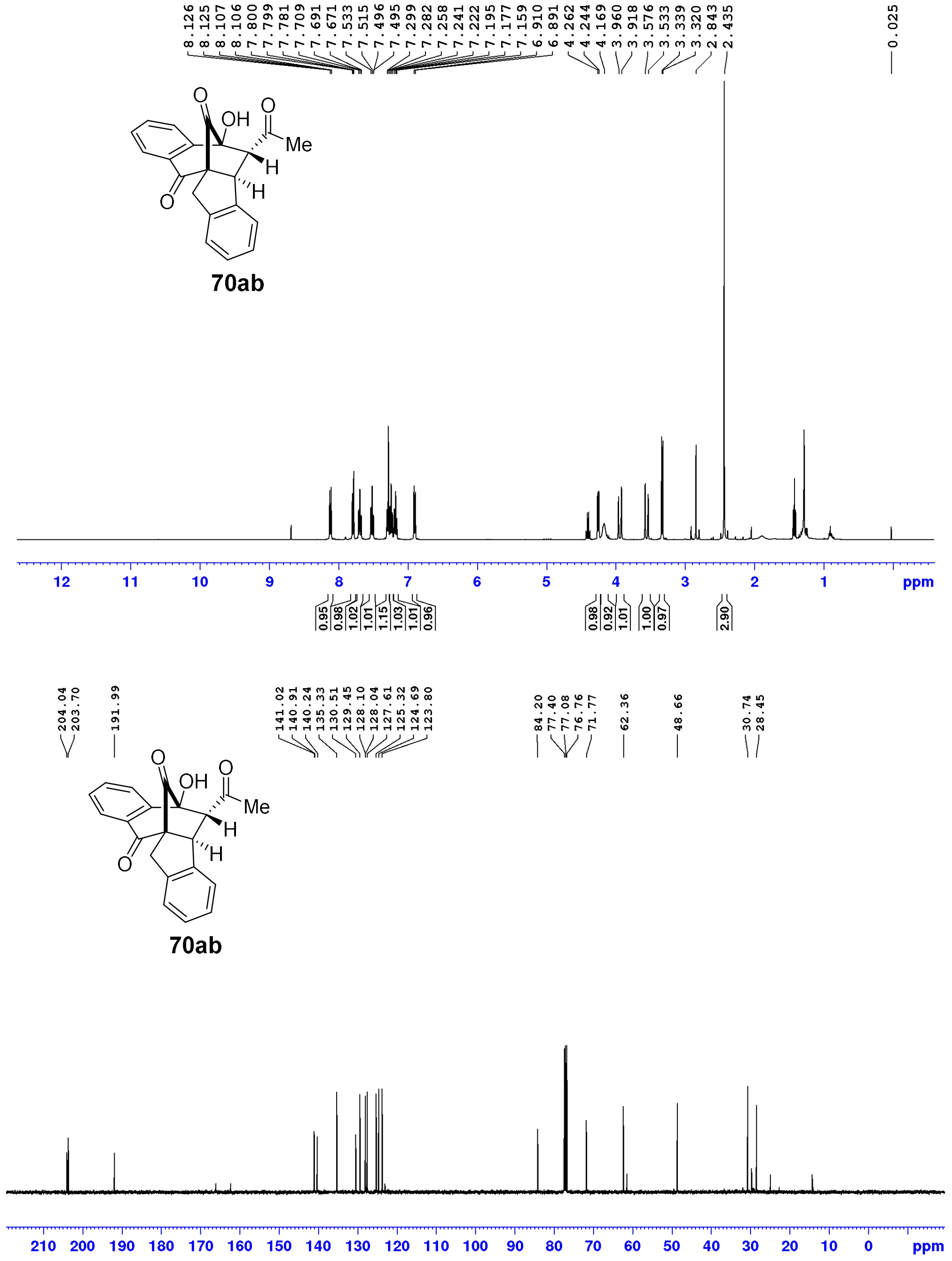


Figure 47: ^{1}H and ^{13}C spectra of the product **70ab**.

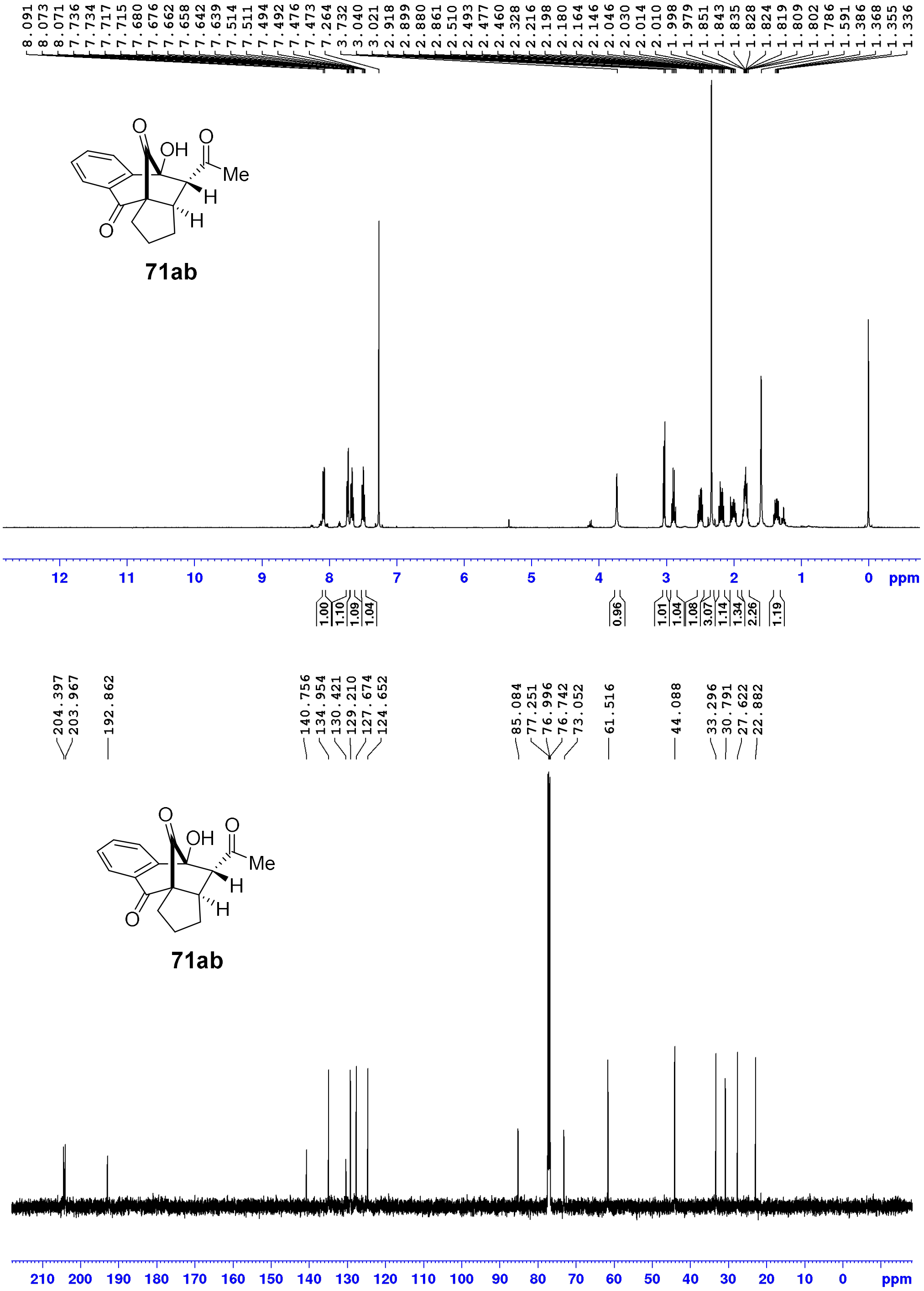


Figure 48: ^{1}H and ^{13}C spectra of the product **71ab**.

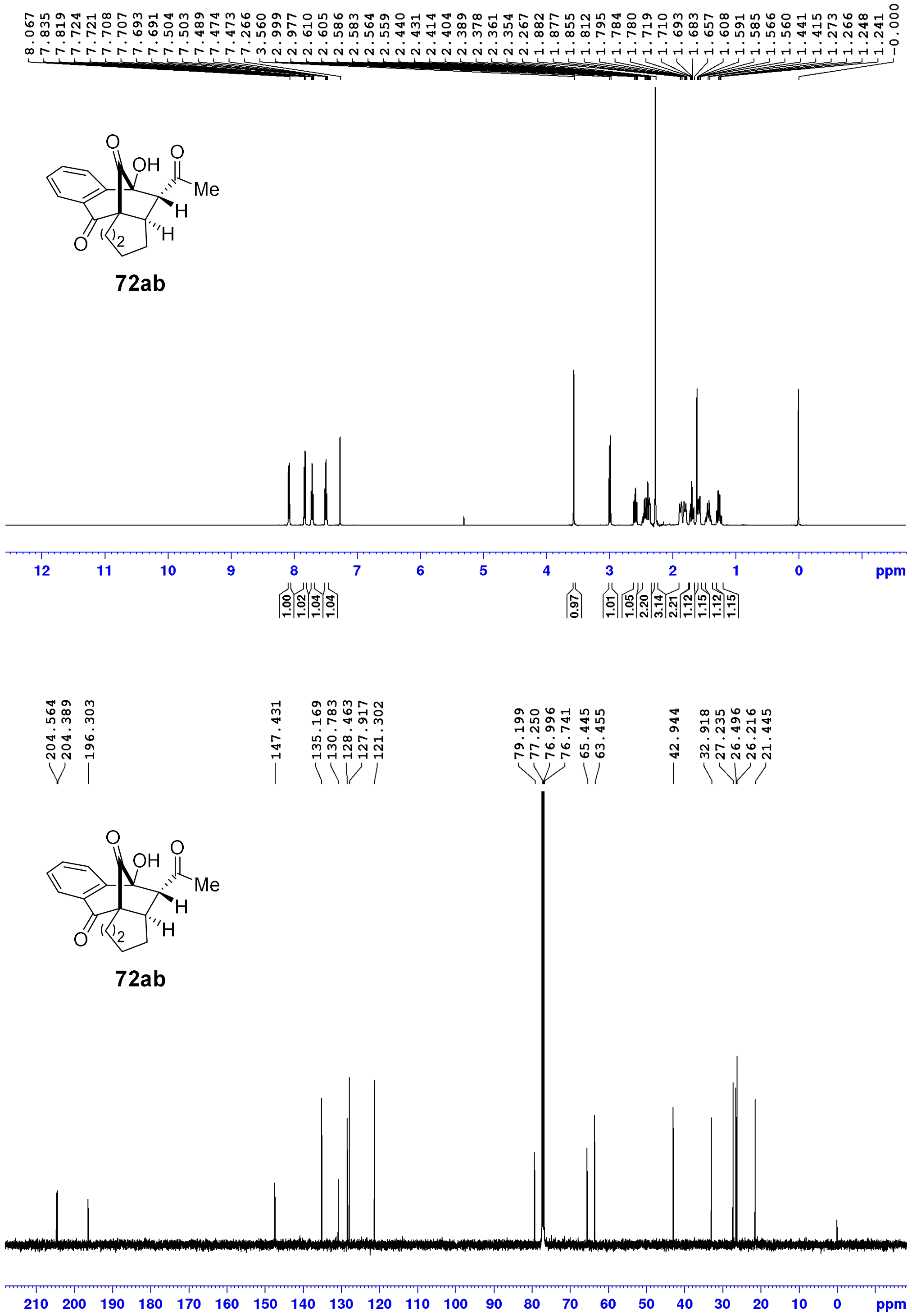


Figure 49: ^{1}H and ^{13}C spectra of the product **72ab**.

In a similar manner, domino self-catalysed reaction of **63a** with other Wittig reagents of **66b** or **66d** in DCM at 25 °C for 3 or 1 h; and with **66e** under the DMAP **3p** catalysis in toluene at 150 °C in a sealed tube for 4 h furnished the corresponding domino products **71ab**, **71ad** and **71ae** in 85%, 80% and 67% yields with 99:1, 99:1 and 13:1 dr, respectively (Table 16). To our surprise, we didn't see the product formation from the reaction between 5-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal **64a** and Wittig reagents **66a-e** in DCM at the ambient conditions. But, the domino W/IM/IA reaction of **64a** with **66b** or **66d** in toluene at 150 °C in a sealed tube for 16 or 24 h furnished the products **72ab** in 65% yield with 2:1 dr; and **72ad** in 67% yield with 7:1 dr, respectively (Table 16). There is no product formation of **72ae** after longer reaction times even at higher temperatures and only the corresponding olefin **67** was isolated. Some of the factors like, length of the side chain, nature/number of electron withdrawing groups, temperature and basic nature of catalyst **3p** have overall control on the outcome of the domino reaction rate/selectivity/yield as shown in Tables 15-16.

The structure and relative stereochemistry of the domino products **69-71** were established by IR, NMR, and mass analysis and also finally confirmed by correlation with the X-ray crystal structure of **69aa**, **69ai**, **69ar**, **69al**, **69ap** and **70ad** (Figures 50-55).[26] These functionally rich methanobenzo[*f*]azulenes **71-72** will be useful intermediates for the synthesis of antibiotics and their analogues (Figure 42).

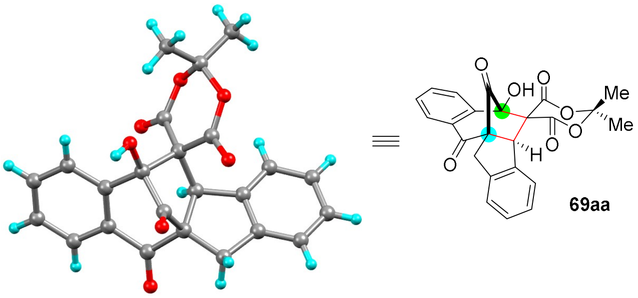
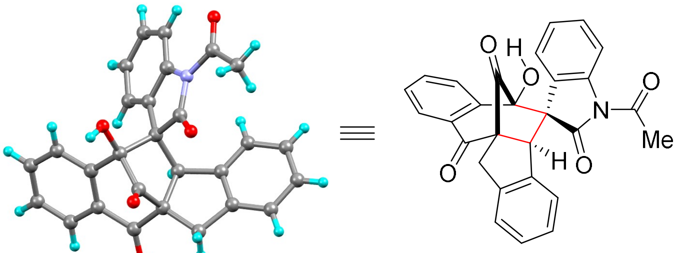
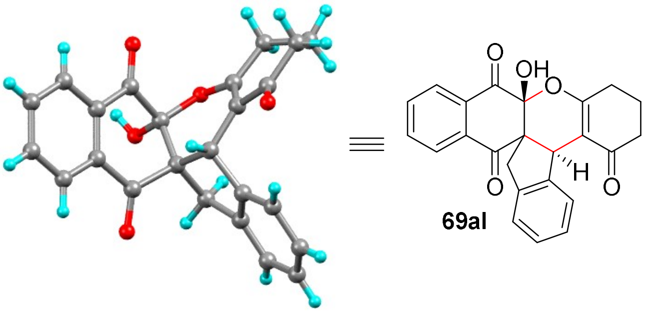


Figure 50: Crystal structure of (4b*S**,6*S**,11a*R**)-6-hydroxy-2',2'-dimethylspiro[6,11a-methanodibenzo[*a,f*]azulene-5,5'-[1,3]dioxane]-4',6',11,13(4b*H*,6*H*,12*H*)-tetraone (**69aa**).



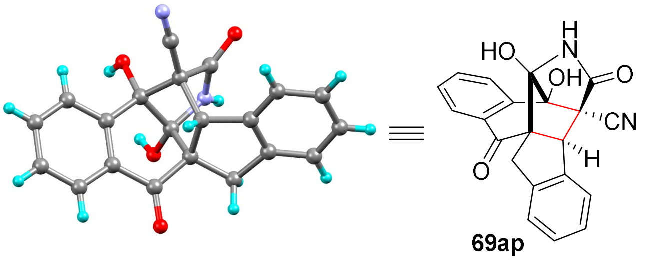
69ai (minor isomer)

Figure 51: Crystal structure of (3'*R**,4b*S**,6*S**,11a*R**)-1'-acetyl-6-hydroxyspiro[6,11a-methanodibenzo[*a,f*]azulene-5,3'-indoline]-2',11,13(4b*H*,6*H*,12*H*)-trione (**69ai**).



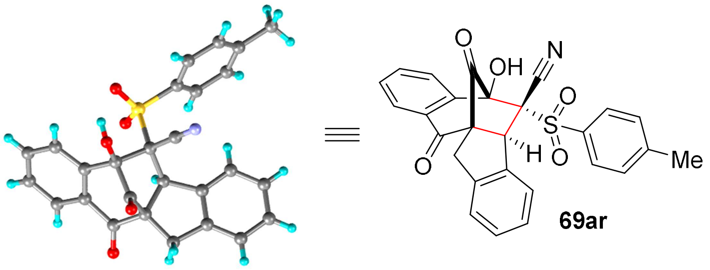
69al

Figure 52: Crystal structure of (4bR*,9aR*)-9a-hydroxy-7,8-dihydro-4bH-benzo[*b*]indeno[1,2-m]xanthene-5,10,15(6*H*,9a*H*,16*H*)-trione (**69al**).



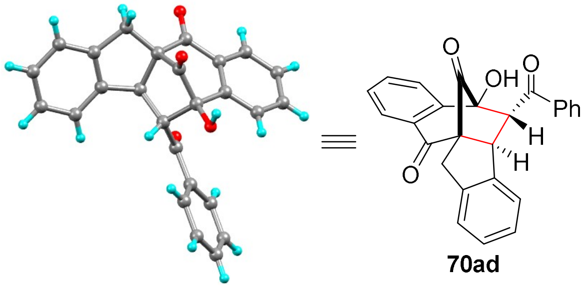
69ap

Figure 53**:** Crystal structure of (4b*S**,5*R**,6*S**,11a*S**)-6,13-dihydroxy-11,15-dioxo-5,6,11,12-tetrahydro-4bH-6,11a,5-(epimethanetriyliminomethano)dibenzo[*a,f*]azulene-5-carbonitrile (**69ap**).



69ar

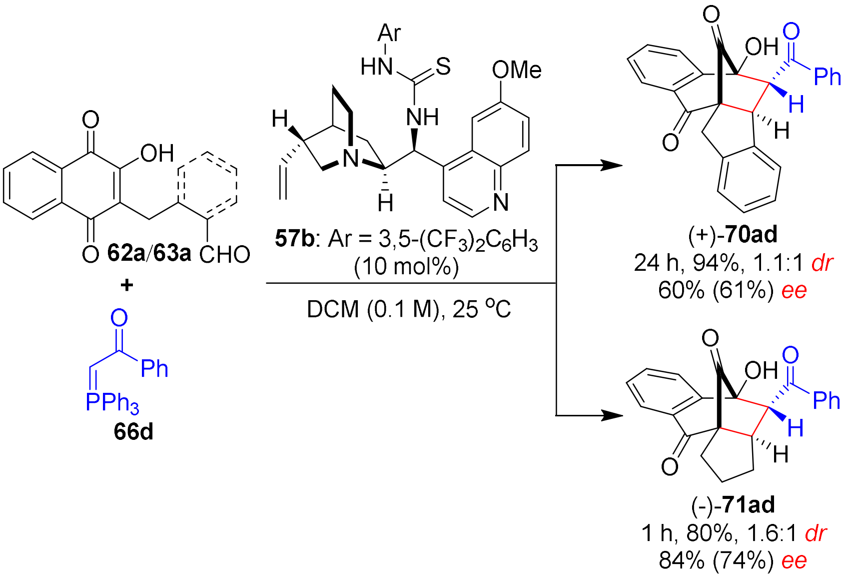
Figure 54: Crystal structure of (4b*S**,5*S**,6*R**,11a*R**)-6-hydroxy-11,13-dioxo-5-tosyl-5,6,11,12-tetrahydro-4bH-6,11a-methanodibenzo[*a,f*]azulene-5-carbonitrile (**69ar**).



70ad

Figure 55: Crystal structure of (4b*S**,5*R**,6*R**,11a*R**)-5-benzoyl-6-hydroxy-5,6-dihydro-4bH-6,11a-methanodibenzo[*a,f*]azulene-11,13(12*H*)-dione (**70ad**).

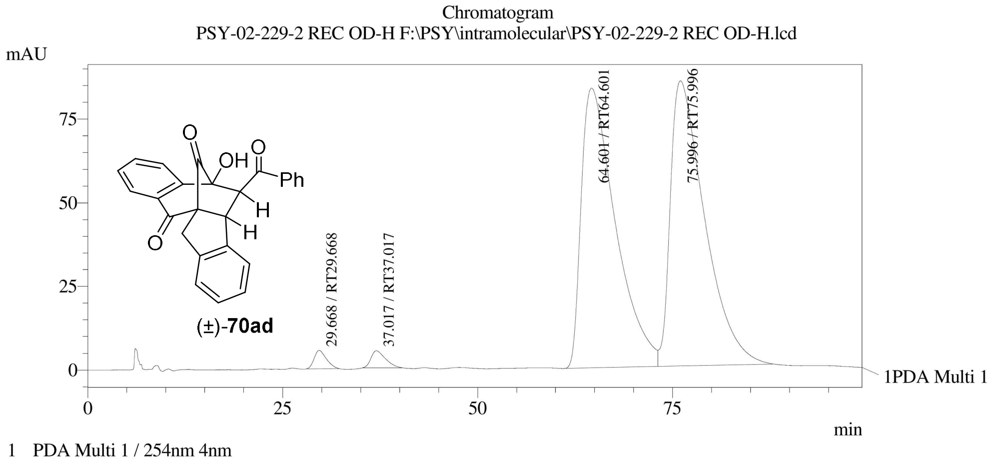
5.2.3 Investigation of asymmetric domino W/IM/IA reactions:



Scheme 22: Catalytic asymmetric synthesis of **70ad**, **71ad** [toluene used as solvent for (-)-**71ad** synthesis]

Further, we have shown interest to investigate the chiral induction of domino W/IM/IA in the presence of the chiral quinine thiourea catalyst **57b** (Scheme 22). Fashionably, domino reaction of **62a** and **66d** in the presence of 10 mol% of the quinine thiourea catalyst **57b** in DCM at 25 °C for 24 h furnished the product (+)-**70ad** in 94% yield with 1.1:1 dr and 60% (61%) *ee*. There is no improvement in dr/*ee*, when the same reaction performed in toluene might be due to the poor solubility of **62a**. The domino W/IM/IA reaction of **63a** and **66d** in the presence of 10 mol% of the quinine thiourea catalyst **57b** in toluene at 25 °C for 2.0 h furnished the product (-)-**71ad** in 80% yield with 1:1.5 dr and 87% (52%) *ee* (Scheme 22). In this reaction, **63a** has good solubility in toluene and these preliminary asymmetric results are inspiring to develop suitable organocatalysts to achieve high induction of *ee*/dr’s. In continuation, we have tested 10 mol% of (*S*)-**3n** effect on the asymmetric synthesis of **70ad** from the W/IM/IA reaction of **62a** and **66d** in DCM at 25 °C for 20 h.

Racemic **(±)-70ad** [Racemic product **70ad** obtained from DMAP **3p** mediated W/IM/IA reaction]**:**



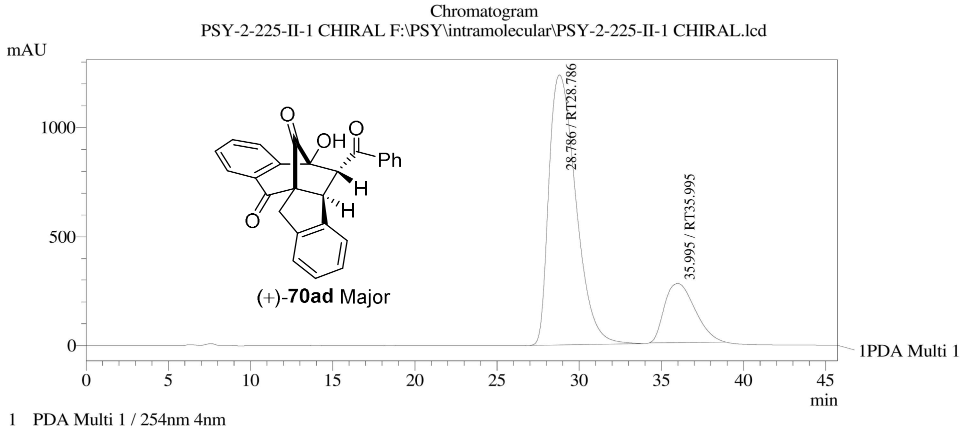
Chiralcel OD-H, Hexane/*i*-PrOH = 95:05, Flow Rate 0.5 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT29.668	29.668	601167	5502	1.136	3.068
2	RT37.017	37.017	658279	5114	1.244	2.852
3	RT64.601	64.601	25511095	83543	48.220	46.588
4	RT75.996	75.996	26135156	85164	49.400	47.492
Total			52905698	179323	100.000	100.000

Chiral **(+)-70ad** (Major: 60% *ee*):



Chiralcel OD-H, Hexane/*i*-PrOH = 95:05, Flow Rate 0.5 mL/Min, 254 nm

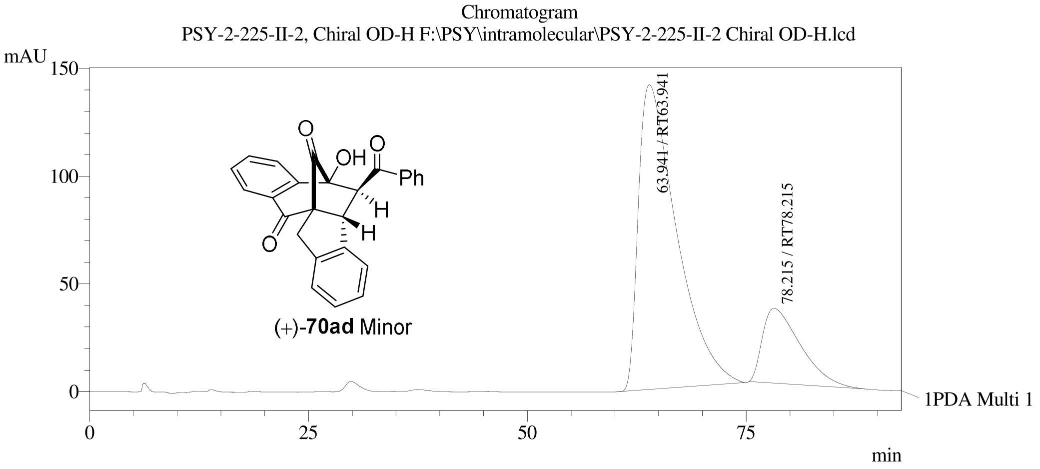
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT28.786	28.786	141426113	1237420	80.225	82.098
2	RT35.995	35.995	34860857	269831	19.775	17.902
Total			176286971	1507251	100.000	100.000

Figure 56: HPLC spectra of the chiral product **70ad**.

Chiral **(+)-70ad** (Minor: 61% *ee*):



1 PDA Multi 1 / 254nm 4nm

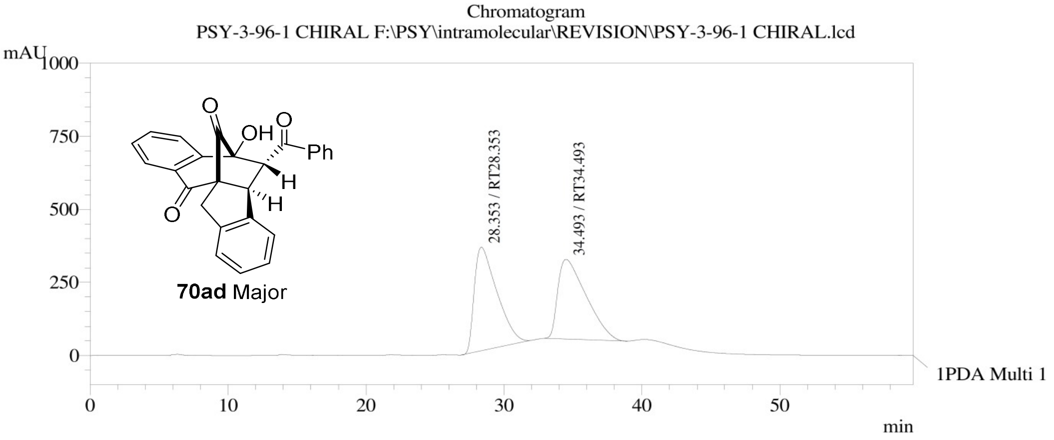
Chiralcel OD-H, Hexane/*i*-PrOH = 95:05, Flow Rate 0.5 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT63.941	63.941	43078354	141515	80.453	80.323
2	RT78.215	78.215	10466361	34667	19.547	19.677
Total			53544715	176182	100.000	100.000

Product-**70ad**[Major Isomer: 0% *ee* and 99:1 *dr* obtained from (*S*)-**3n** mediated W/IM/IA reaction]



Chiralcel OD-H, Hexane/*i*-PrOH = 95:05, Flow Rate 0.5 mL/Min, 254 nm

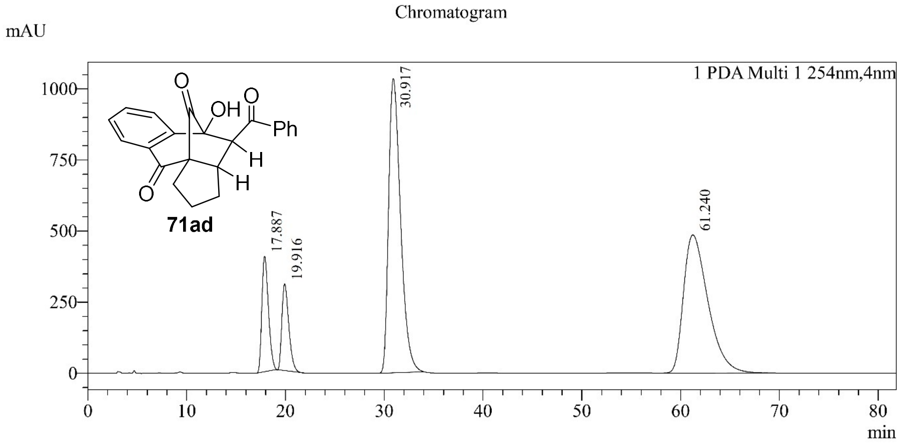
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT28.353	28.353	40356284	354165	50.852	56.505
2	RT34.493	34.493	39003457	272624	49.148	43.495
Total			79359741	626788	100.000	100.000

Figure 57: HPLC spectra of the chiral product **70ad**.

Racemic **(±)-71ad** [Obtained from the quinine-thiourea/quinidine-thiourea (1:1)-catalysed W/IM/IA reaction]:



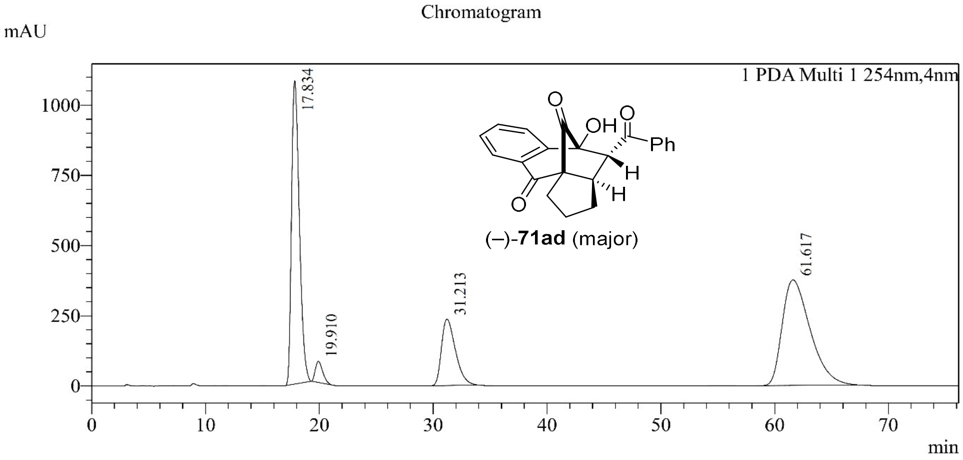
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:17.887	17.887	18719342	405813	9.166	18.193
2	RT:19.916	19.916	14883280	305244	7.288	13.684
3	RT:30.917	30.917	86976354	1034058	42.588	46.357
4	RT:61.240	61.240	83646637	485527	40.958	21.766
Total			204225613	2230643	100.000	100.000

Chiral **(-)-71ad** (Minor Isomer: 87% *ee* and Major Isomer: 52% *ee*; 1:1.5 *dr*):



Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

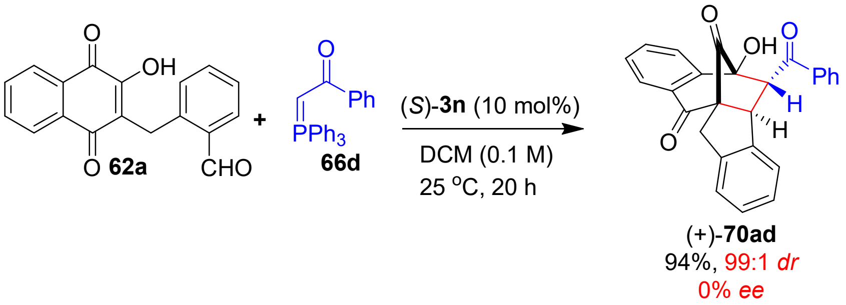
Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:17.834	17.834	51624065	1079443	37.075	61.103
2	RT:19.910	19.910	3402497	75449	2.444	4.271
3	RT:31.213	31.213	20097452	236300	14.433	13.376
4	RT:61.617	61.617	64119070	375415	46.048	21.251
Total			139243084	1766607	100.000	100.000

Figure 58: HPLC spectra of the chiral product **71ad**.

Surprisingly, we obtained product **70ad** in 89% yield with 99:1 dr and 0% *ee* (Scheme 23) and this observation might be similar for (*S*)-**3n** catalyzed KC/IM/IA reaction of **62a** and **65a** to furnish the racemic **69a** in high yields and dr (Table 12, entries 1-3).

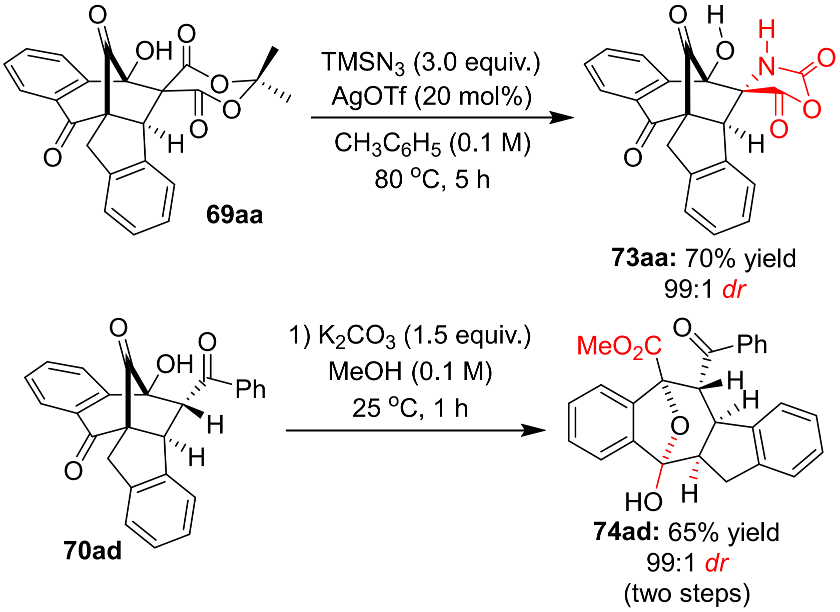


Scheme 23: Catalytic asymmetric synthesis of **70ad** under (*S*)-**3n** catalysis.

5.2.4 Synthetic applications of methanodibenzo[a,f]azulenes:

To test the reactivity pattern of **69-72** under simple conditions, we explored the utilization of **69aa** and **70ad** in the synthesis of bio-inspired compounds **73-74** *via* strategy of ring opening cyclisation (Scheme 24). Diastereoselective ring opening cyclisation of **69aa** with 3.0 equiv. of TMSN$_3$ under the catalysis of 20 mol% of AgOTf in toluene at 80 °C for 5 h furnished selectively oxazolidine inserted methanodibenzo[*a*,*f*]azulene **73aa** in 70% yield with 99:1 dr (Scheme 24 and Figure 59).[26]

Likewise, treatment of **70ad** with 1.5 equiv. of K$_2$CO$_3$ in dry methanol at 25 °C for 1 h followed by reaction with 5.0 equiv. of Me$_2$SO$_4$ in acetone under the presence of 5.0 equiv. of K$_2$CO$_3$ at 60 °C for 24 h furnished the functionalised epoxybenzo[7]annulen-5-ol **74ad** in 65% yield with 99:1 dr (Scheme 24 and Figures 60-61 for 2D NMR structural analysis)



Scheme 24: Applications of methanodibenzo[*a,f*]azulenes **69aa-70ad**.

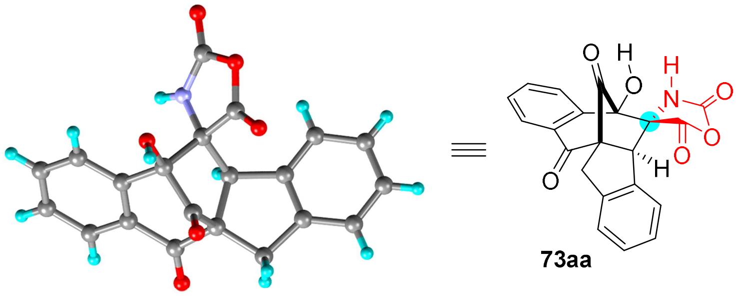


Figure 59: Crystal structure of (4b*S**,4'*R**,6*S**,11a*R**)-6-hydroxyspiro[6,11a-methanodibenzo[*a,f*]azulene-5,4'-oxazolidine]-2',5',11,13(4b*H*,6*H*,12*H*)-tetraone (**73aa**).

.

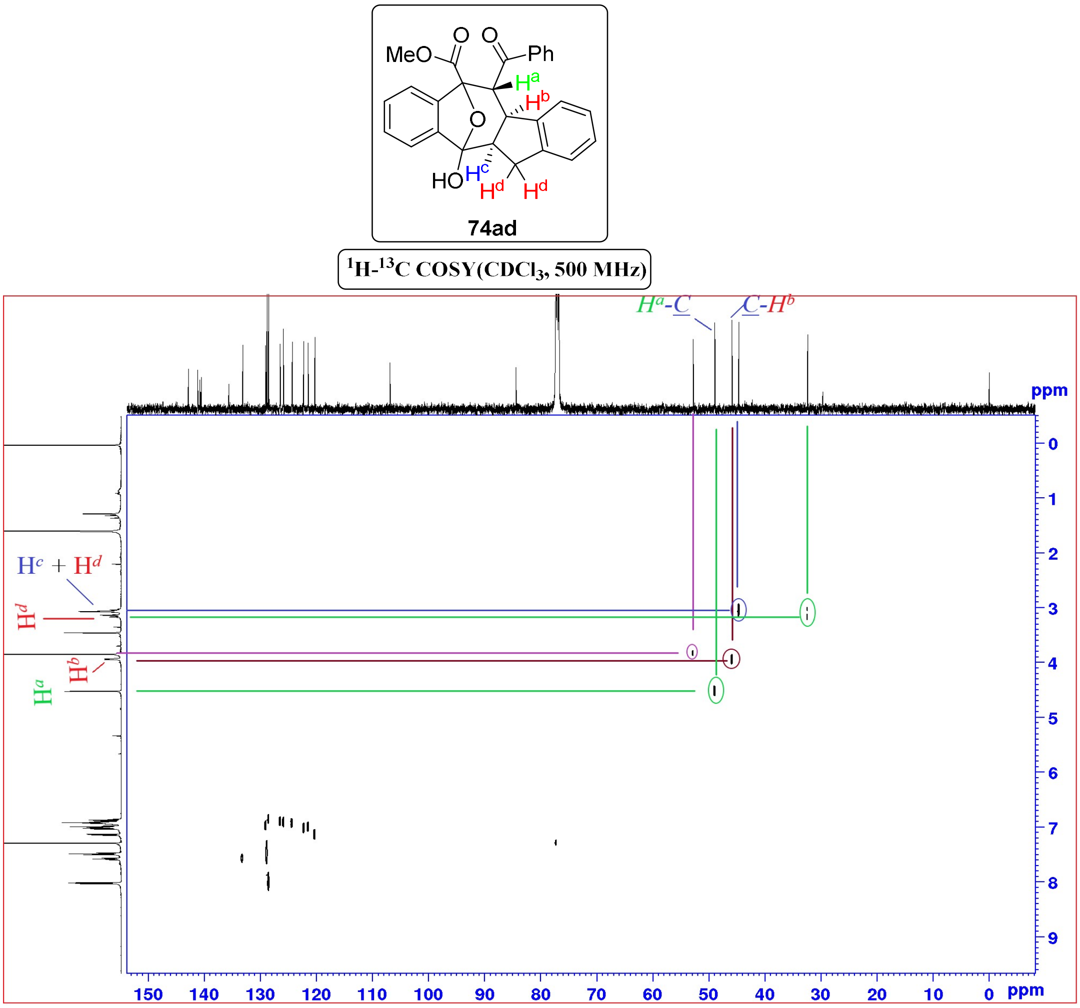


Figure 60: Hetero-COSY spectrum of compound **74ad** (500 MHz, $CDCl_3$ at 25 °C).

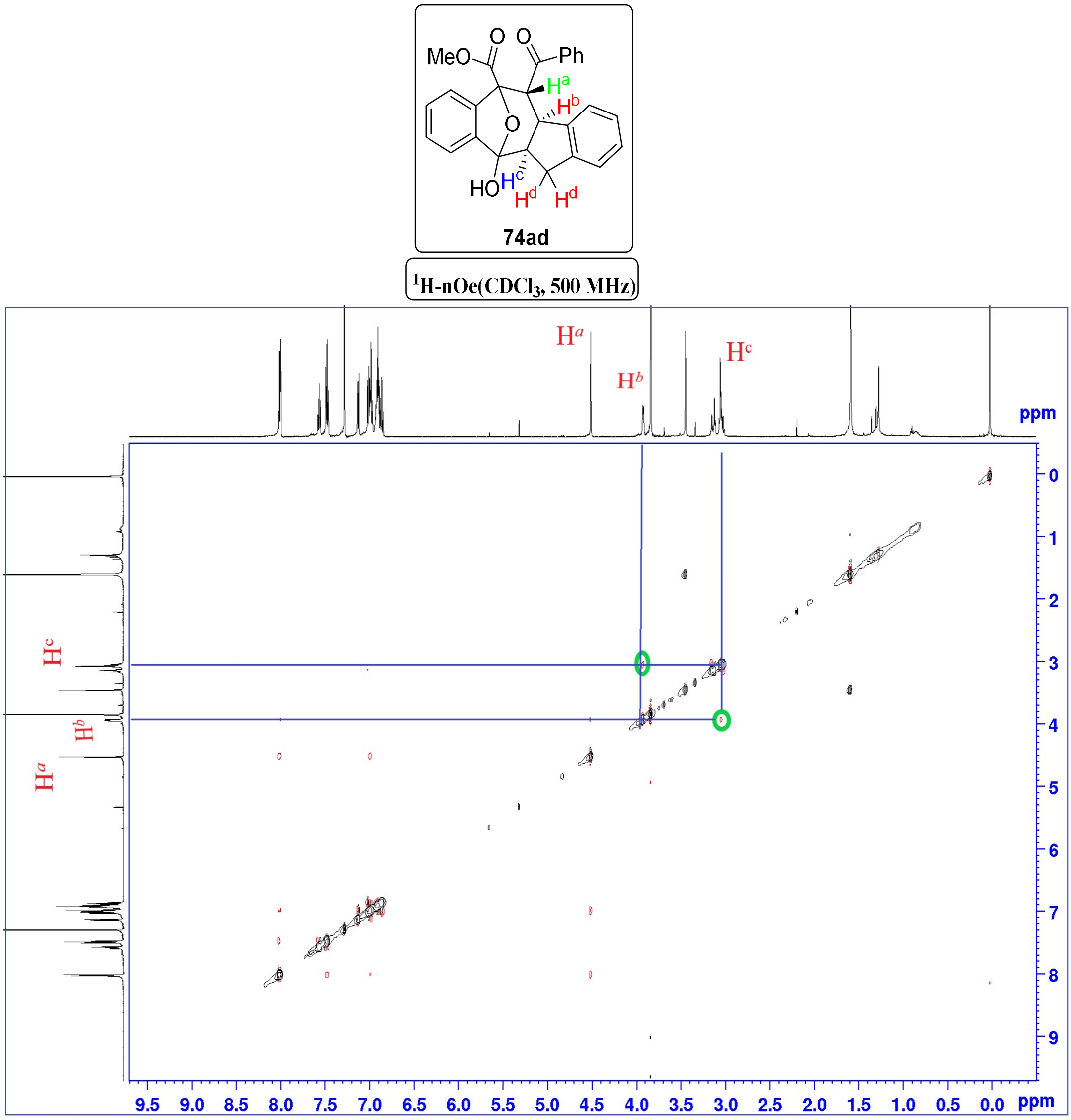
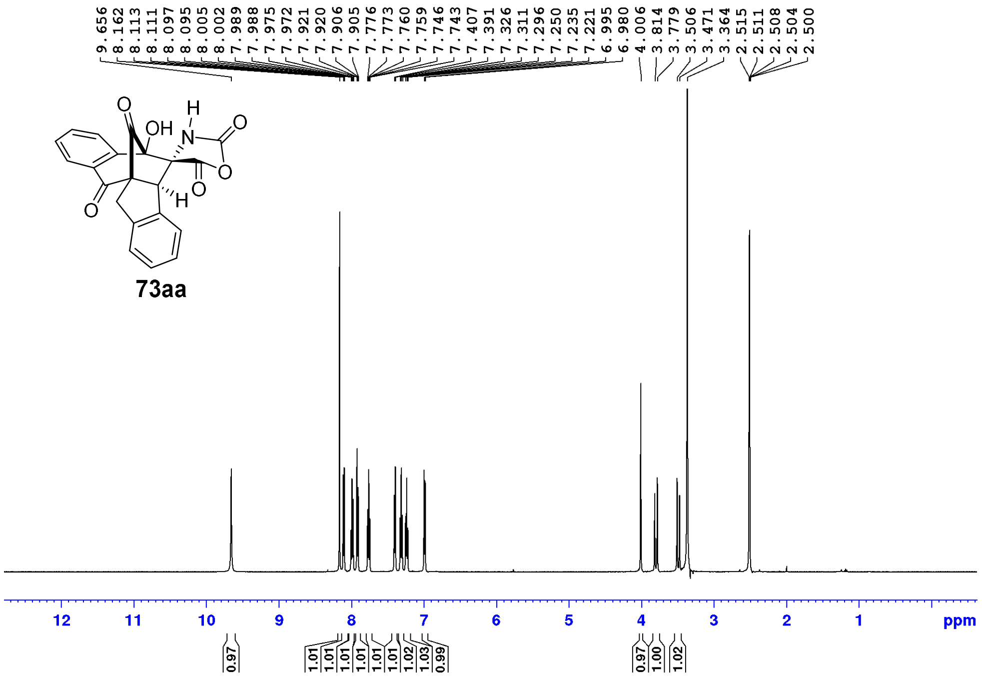


Figure 61**:** NOESY spectrum of compound **74ad** (500 MHz, $CDCl_3$ at 25 °C).

5.2.5 Controlled experiments and Mechanistic insights:

Herein, we explained diastereoselectivity by analysing each and every reaction of domino reaction sequence with controlled experiments (Scheme 25 and Scheme 26). (*S*)-**3n** Catalysed reductive coupling of lawsones **1** with di-aldehydes **59-61** and **34** at ambient conditions furnished lawsone-aldehydes **62-63** in a highly chemoselective manner may be due to the differences in steric and electronic nature of two aldehydes.[8]



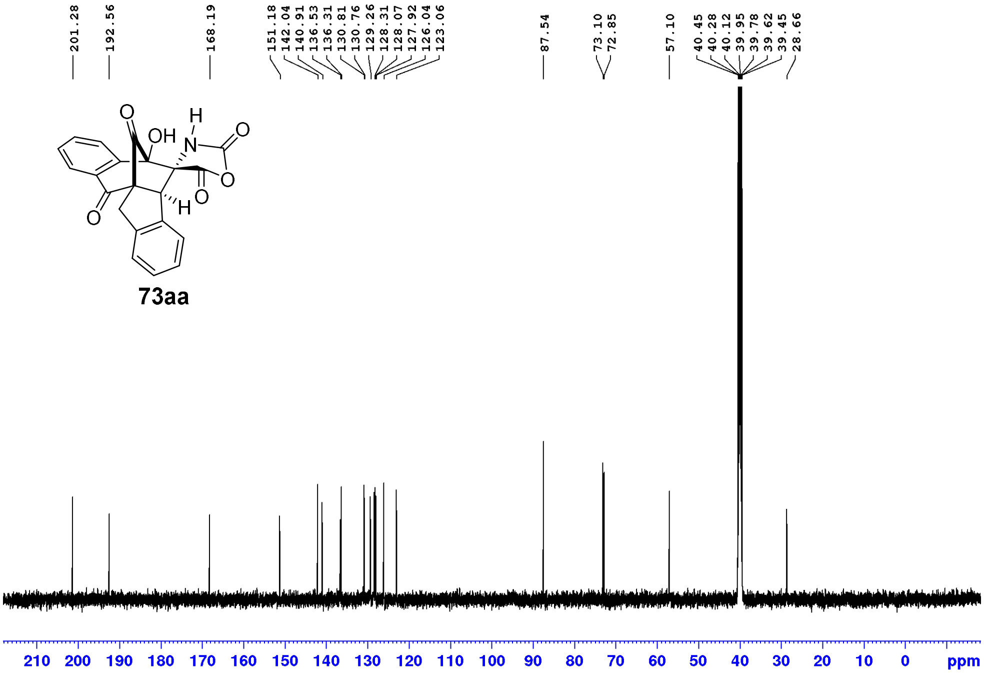


Figure 62: ^{1}H and ^{13}C spectra of the product **73aa**.

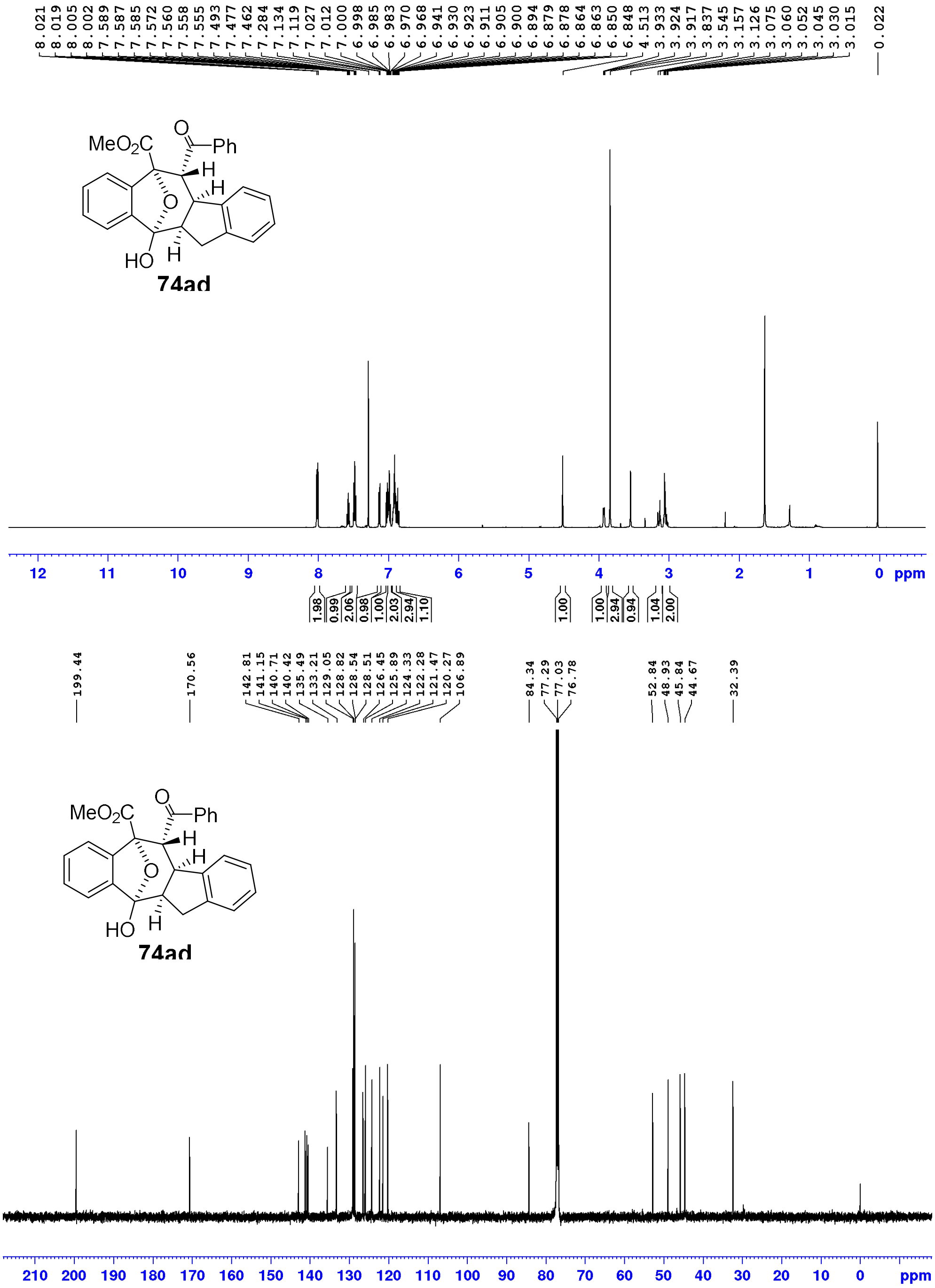
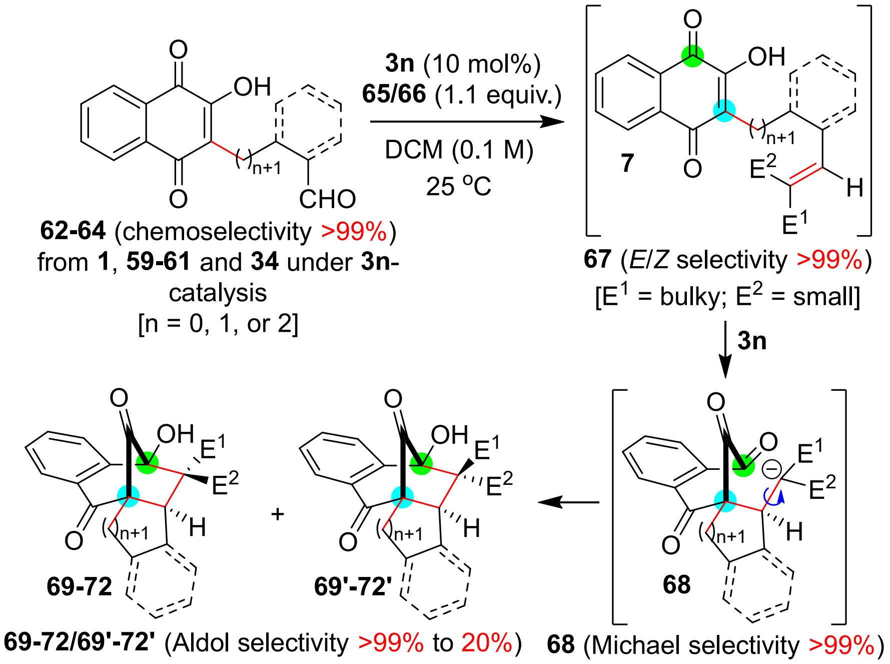
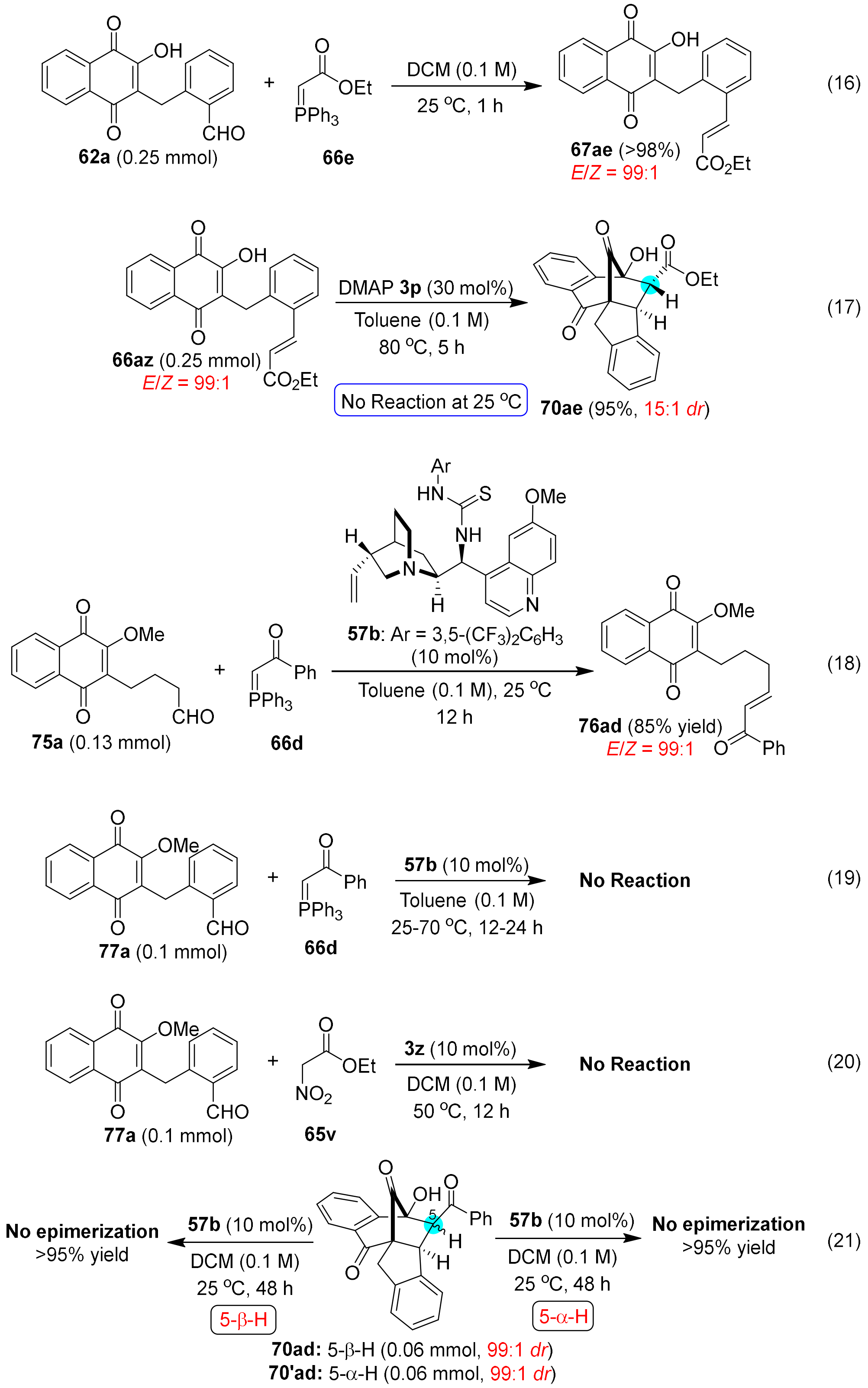


Figure 63: ^{1}H and ^{13}C spectra of the product **74ad**.

Further treatment of **62a** with **66e** under the thermodynamic soft-catalysis of **3n** or Ph3PO furnished the lawsone-olefins **67ae** in a highly regioselective manner and rate of aldehyde-olefination reaction is induced by intramolecular hydrogen bonding with OH group of lawsone-aldehydes **62a** (Scheme 26). Furthermore, intramolecular Michael/intramolecular aldol reactions are did not performed on lawosne olefine **67ae**, under **3p** catalysis at room temperature. Surprizingly, same reaction when performed at 80 °C for 5h furnished the **70ae** in good yield with 15:1 dr (Scheme 26, Eq. 16 and 17). Similarly, **75a** on treatment with **66d** under quinine thiourea catalysis in toulene solvent at 25 °C for 12 h furnished **76ad** in 85% yield with exclusively one diastereomer over other possible isomers (Scheme 26, Eq. 18). Moreover, we did not obseverd expected products when reactions performed on **77a** with **66d** and **65v** under the influence of **57b**, **3z** catalyst at 25-75 °C and 50 °C for 12-24 h repectively (Scheme 26, Eq. 19 and 20). Finally, we observed no epimerization of **70ad** and **70'ad** on treatment with quinine thiourea **57b** in DCM solvent at room temperature for 48 h (Scheme 26, Eq. 21).



Scheme 25: Reaction mechanism.



Scheme 26: Controlled experiments.

In a formal intramolecular [3+2]-cycloaddition, the first reaction step is organocatalytic Michael, which is generating two stereocenters in a highly selective manner. Next intramolecular aldol reaction is also generating two stereocenters with selectivity varying from >99% to 20% (Scheme 25). Aldol reaction selectivity depends on the C-C bond rotation of side chain, which is controlled by the nature/size of electron withdrawing groups, temperature, and catalysts hydrogen bonding ability with carbonyls (Scheme 22 and 25).

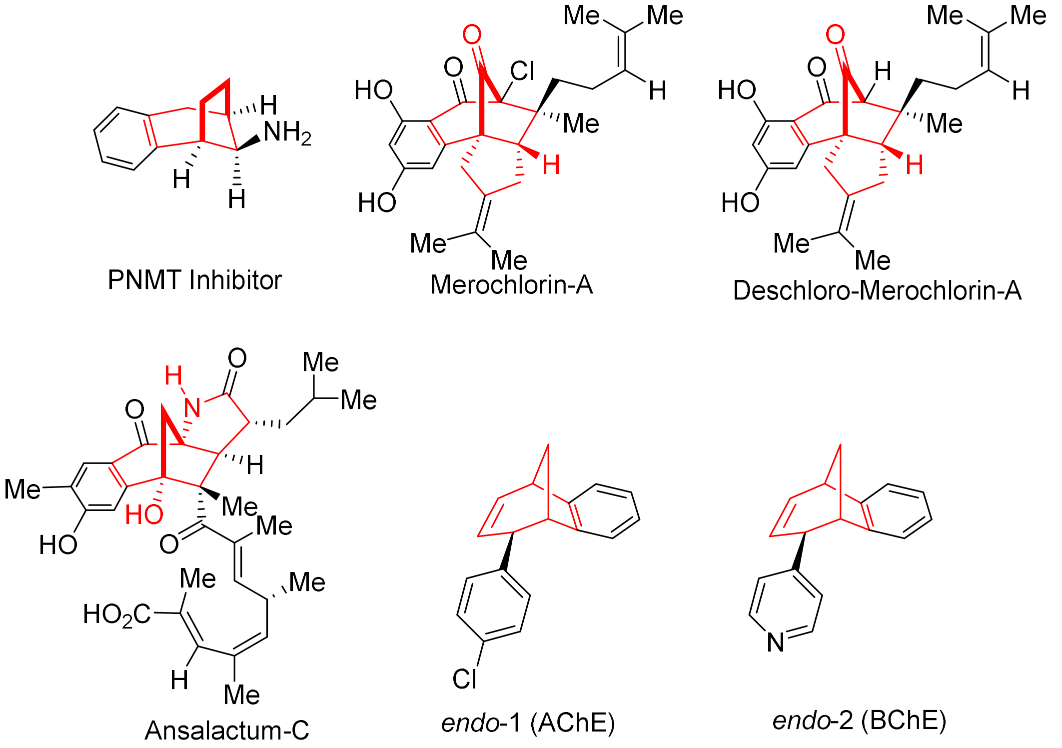
5.3 Conclusions

In summary, we have revealed an adaptable practical method for the two-pot domino achiral and chiral synthesis of an unique carbon skeleton of biologically important methanodibenzo[*a*,*f*]azulenes and methanobenzo[*f*]azulenes **69-72** from the readily available simple precursors through organocatalysis. The natural lawsones **1** were directly transformed into a library of highly functionalized methanodibenzo[*a*,*f*]azulenes and methanobenzo[*f*]azulenes **69-72** through an unprecedented organocatalytic path of domino sequential combination of KC/TH, KC/IM/IA and W/IM/IA with high selectivity and yields. We also demonstrated the synthetic application of these compounds **69-72** in medicinal chemistry by synthesizing functionally rich compounds **73-74**. We explained the observed high selectivity with controlled experiments in the reaction mechanism. Future investigations in our laboratory will continue to explore the scope of novel reactivity of lawsones

6. Direct Organocatalytic Asymmetric Synthesis of Biologically Important Methanobenzo[*f*]azulenes

6.1 Introduction

Undoubtedly, majority of pharmaceutically and biologically active natural products such as terpenes, lignans and alkaloids own bicyclo[3.2.1]octane scaffold as a key substructure in them. The bicyclo[3.2.1]octane acts as an inhibitor for the transport of dopamine and serotonin and also these are most frequently used in the synthesis of tricyclic sesquiterpenoids. Particularly benzobicyclo[3.2.1]oactanes, namely methanobenzo[7]annulenes and methanobenzo[*f*]azulenes are prominent medicinally active molecules like PNMT inhibitor, Merochlorin-A, Deschloro-Merochlorin-A and Ansalactum-C.[15]



PNMT Inhibitor

Merochlorin-A

Deschloro-Merochlorin-A

Ansalactum-C

endo-1 (AChE)

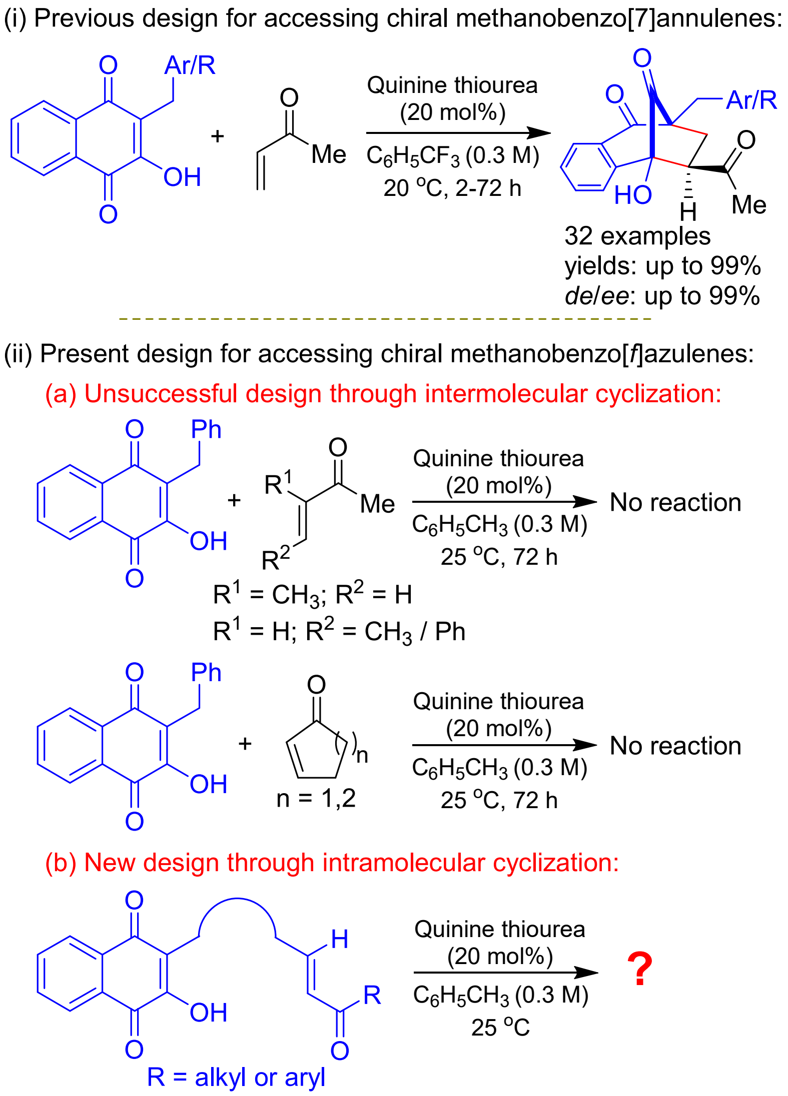
endo-2 (BChE)

Figure 64: Medicinally important benzobicyclo[3.2.1]octanes.

Similarly, in recent times *endo*-1 (AChE) and *endo*-2 (BChE) makes its way as potent cholinesterase inhibiter, as they control the acetyl/butyrylcholinesterase concentration in the synapsis. Due to this reason, these *endo*-1 (AChE) and *endo*-2 (BChE) are used as drug for treating neurodegenerative disorders (Figure 64).[15]

Over the decades the interest in the synthesis of benzobicyclo[3.2.1]octane is exponentially growing, due to their numerous applications in the biological, pharmaceutical arena and in the synthesis of functionally rich molecules which are greatly in need for the mankind. However, synthesis of functionalized methanobenzo[7]annulenes, methanobenzo[*f*]azulenes requires a tedious multi-step protocol under the influence of the metal/base catalyst at higher temperatures.[27] The synthesis of optically pure benzobicyclo[3.2.1]octanes and their analogues methanobenzo[7]annulenes, methanobenzo[*f*]azulenes is still underexplored.[28] Hence, the development of environmentally benign, single-step, one-pot stereoselective synthesis of methanobenzo[7]annulenes, methanobenzo[*f*]azulenes and their analogues is highly requisite.

Although, in 2017 our group reported environmentally benign, single-step one-pot protocol for the synthesis of optically pure benzobicyclo[3.2.1]octanes such as methanobenzo[7]annulenes in excellent yields with stereoselectivity, by treating 2-alkyl-3-hydroxynaphthalene-1,4-dione with α or β-unsubstituted alkyl vinyl ketones under quinine thiourea catalysis in benzotriflouride solvent at room temperature (Scheme 27, entry i). To further explore the unprecedented *5-(enolexo)-exo-trig* cyclization, we performed tandem inter-molecular Michael/intra-molecular aldol reactions by treating a variety of α or β-substituted vinyl ketones *viz*. 3-methylbut-3-en-2-one, (*E*)-pent-3-en-2-one, (*E*)-4-phenylbut-3-en-2-one, 2-cyclopentenone and 2-cyclohexenone with 2-benzyl-3-hydroxynaphthalene-1,4-dione in the presence of quinine thiourea catalyst. Unfortunately, none of these reactions performed well to furnish the expected multi-ring bicyclic products (Scheme 27, entry iia). We inspired by these captivating results and accepted the challenge for demonstrating the successful protocol for α or β-substituted alkyl vinyl ketones. To achieve our milestones, we assumed to perform the intra-molecular reaction by constructing a bridge between 2-alkyl lawsone and α or β-substituted alkyl vinyl ketone.



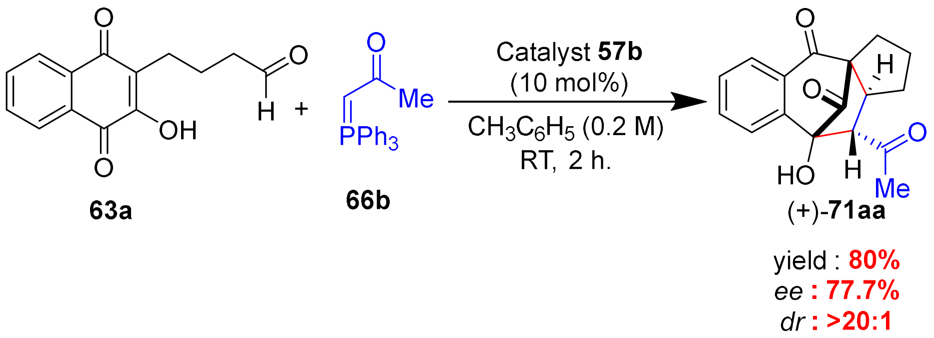
Scheme 27: Literature and present design for accessing chiral methanobenzo[*f*]azulenes.

Stimulated, from our very recent work, where the 2-alkyl naphthoquinones are bridged with either substituted or unsubstituted alkyl vinyl ketones by Knoevenagel condensation of active CH-acid with lawsone aldehyde or a Wittig reaction with lawsone aldehyde.[8] To our delight, it is intriguing to explore the asymmetric version of the tandem Wittig/intra-molecular Michael/intra-molecular aldol reactions with cinchona based chiral bifunctional thiourea catalysts[21] (Scheme 27, entry iib).

6.2 Results and Discussions

6.2.1 Reaction optimization:

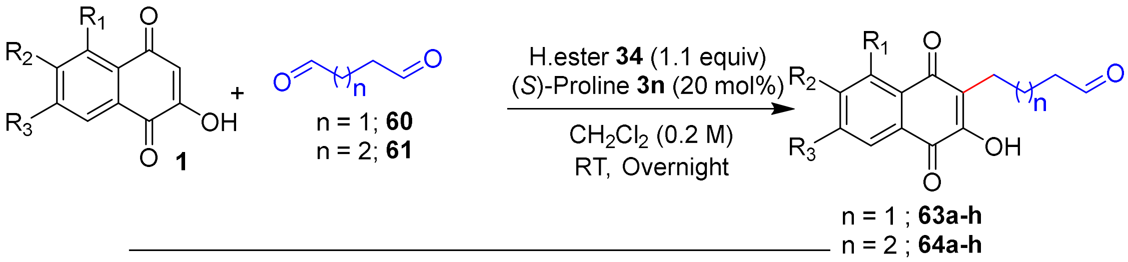
In this scenario, we first prepared the lawsone aldehyde by following standard procedure, where (*S*)-proline was chosen as a catalyst for TCRA reaction between lawsone, dialdehyde and the furnished Knoevenagel intermediate was reduced by Hantzsch ester to generate lawsone aldehyde products **63/64** in moderate yields (Table 17).[4]



Scheme 28: Preliminary investigation of the proposed design.

Preliminarily, to comprehend the reactivity pattern, we performed a reaction between lawsone aldehyde **63a** and acetyl Wittig reagent **66b** in toluene solvent, surprisingly, the reaction is completely converted into methanobenzo[*f*]azulenes **71ab** in 2.5 h at room temperature. Herein, the tandem Wittig/intra-molecular Michael/intra-molecular aldol reactions are the spontaneous reactions, which occurs immediately after the Wittig product was formed (Scheme 28).

Table 17: Synthesis of lawsone aldehydes.[a]



Entry	Product	R_1, R_2, R_3	Yield [%][b]
1	n = 1; **63b**	R_1= OMe	5
	n = 2; **64b**	R_2, R_3 = H	10
2	n = 1; **63c**	R_2= OMe	25
	n = 2; **64c**	R_1, R_3 = H	29
3	n = 1; **1d**	R_3= OMe	19
	n = 2; **8d**	R_1, R_2 = H	27
4	n = 1; **63e**	R_2, R_3 = OMe	10
	n = 2; **64e**	R_1 = H	30
5	n = 1; **63f**	R_3= Me	35
	n = 2; **64f**	R_1, R_2 = H	41
6	n = 1; **63g**	R_1, R_3 = Me	27
	n = 2; **64g**	R_2 = H	32
7	n = 1; **63h**	R_2= NH-Ac	11
	n = 2; **64h**	R_1, R_3 = H	18

[a] Reactions were carried out in solvent (0.2 M) with 2.0 equiv of **60-61** and 1.1 equiv of Hantzsch ester **34**, relative to lawsone **1** (0.2 mmol), in the presence of 20 mol% of the catalyst (*S*)-proline **3n**. [b]Yield refers to the column-purified product.

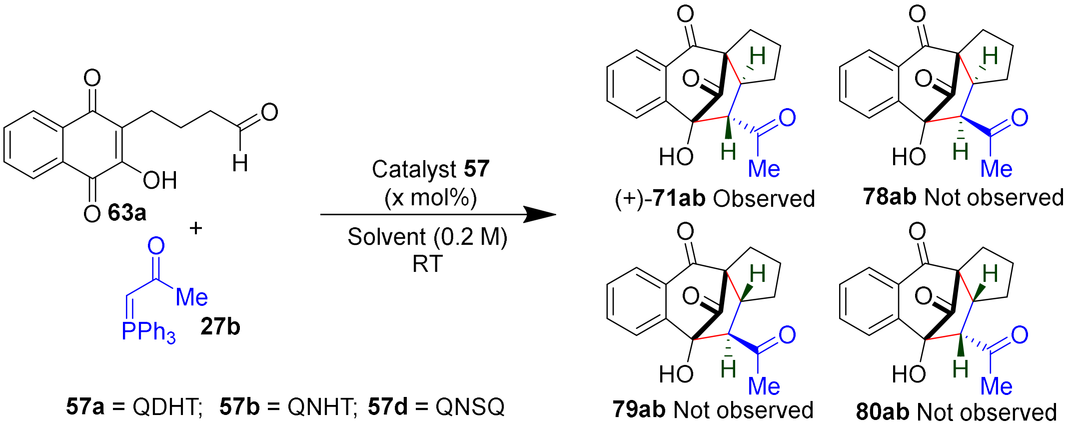
In order to accomplish the asymmetric induction in the designed tandem Wittig/intra-molecular Michael/intra-molecular aldol reactions, we treated lawsone aldehyde **63a** with acetyl Wittig **66b** under quinine thiourea **57b** catalysis for 2 h. Enlighteningly, the reaction performed well at room temperature and furnished (+)-**71ab** in 80% yield, 77.7% *ee* with at-most single diastereomer out of other possible three diastereomers (Scheme 28).

To perceive the solvent, catalyst, and temperature effects on asymmetric tandem reactions, we performed the reaction where lawsone aldehyde **63a** is treated with acetyl Wittig reagent **66b** under quinine thiourea **57b** catalysis in a variety of solvents like trifluoro toluene, benzene, dichloromethane and trichloroethane at room temperature for 1.5 to 2 h (Table 18, entries 2-5). In contrary to the preliminary results obtained, we found diminished enantioselectivity with almost sustained yields and dr ratios of (+)-**71ab**. Furthermore, lawsone aldehyde **63a** on treatment with acetyl Wittig reagent **66b** under a variety of thiourea and squaramide (**57a-f**) catalysis in toluene solvent at room temperature for 2 h resulted (+)-**71ab** in 70-87% yields, reduced *ee* (up to 60% *ee*) with single diastereomer (Table 18, entries 6-9). From these investigations, quinine thiourea catalyst **57b** was so far the best catalyst for tandem reactions.

Next, we performed the further optimization by fluctuating the catalyst loading *viz.* 5, 20, 25 and 30 mol% and the reactions completed in 180, 75, 45 and 45 min respectively. Interestingly, reactions furnished (+)-**71ab** in 80-85% yields, 64-90% *ee* with single diastereomer (Table 18, entries 10-13). Herein, the catalyst loading shows a visible effect on the asymmetric tandem reactions i.e., as of the catalyst loading increases the rate of the reaction was increased with improved facial selectivity. Similarly, we also performed the same reaction in the presence of quinidine thiourea **57a** catalyst in toluene solvent for 2.5 h. Unpredictably, the reaction furnished (-)-**71ab** in 79% yield, 66% *ee* with single diastereomer (Table 18, entry 14). During these investigations, we also performed the same reaction at 0-5 ºC for 5 h in toluene solvent, which furnishes the (+)-**71ab** in 86% yield, 90% *ee* with single diastereomer (Table 18, entry 15).

Moreover, the excessive catalyst loading for accomplishing better facial selectivity, forced us to recovery the catalyst and investigate the catalyst chiral activity. Initially, we performed the reaction by treating lawsone aldehyde **1a** with acetyl Wittig **2a** under the influence of 30 mol% quinine thiourea catalyst **3a** in toluene solvent for about 1.5 h at room temperature furnished the (+)-**4aa** in 84.5% yield, 90% *ee* with >20:1 dr (Eq. 22).

Table 18: Optimization of proposed reaction.[a]



57a = QDHT; **57b** = QNHT; **57d** = QNSQ
57e = QDSQ; **57f** = QDSQ-CH_2-Ar

Entry	Catalyst (x mol%)	Solvent	t [h]	Yield [%][b]	d r[c] **71**:**79**	*ee* [%][d] **71ab**
1	**57b** (10 mol%)	$CH_3C_6H_5$	2	80	>20:1	78
2	**57b** (10 mol%)	$CF_3C_6H_5$	1.5	77	>20:1	67
3	**57b** (10 mol%)	C_6H_6	1.5	73	>20:1	72
4	**57b** (10 mol%)	DCM	1.5	80	>20:1	67
5	**57b** (10 mol%)	TCE	1.5	78	>20:1	33
6	**57a** (10 mol%)	$CH_3C_6H_5$	2	70	>20:1	60
7	**57d** (20 mol%)	$CH_3C_6H_5$	2	86	>20:1	39
8	**57e** (20 mol%)	$CH_3C_6H_5$	2	84	>20:1	26
9	**57f** (20 mol%)	$CH_3C_6H_5$	2	87	>20:1	39
10	**57b** (5.0 mol%)	$CH_3C_6H_5$	2	80	>20:1	64
11	**57b** (20 mol%)	$CH_3C_6H_5$	1.25	82	>20:1	86
12	**57b** (25 mol%)	$CH_3C_6H_5$	0.75	82	>20:1	87
13	**57b** (30 mol%)	$CH_3C_6H_5$	0.75	84	>20:1	90
14	**57a** (30 mol%)	$CH_3C_6H_5$	2.5	81	>20:1	66
15[e]	**57b** (30 mol%)	$CH_3C_6H_5$	5	86	>20:1	90

[a]Reactions were carried out in solvent (0.2 M) with 1.1 equiv of **63a** relative to **66b** (0.2 mmol), in the presence of x mol% of the catalyst **57**. [b]Yield refers to the column-purified product. [c]Determined by CSP HPLC analysis. [d]Determined by CSP HPLC analysis. [e]T= 0-5 °C. **Note**: Data in entries 6-9 and 14 represent the antipode for the enantiomer of the structure **71ab**.

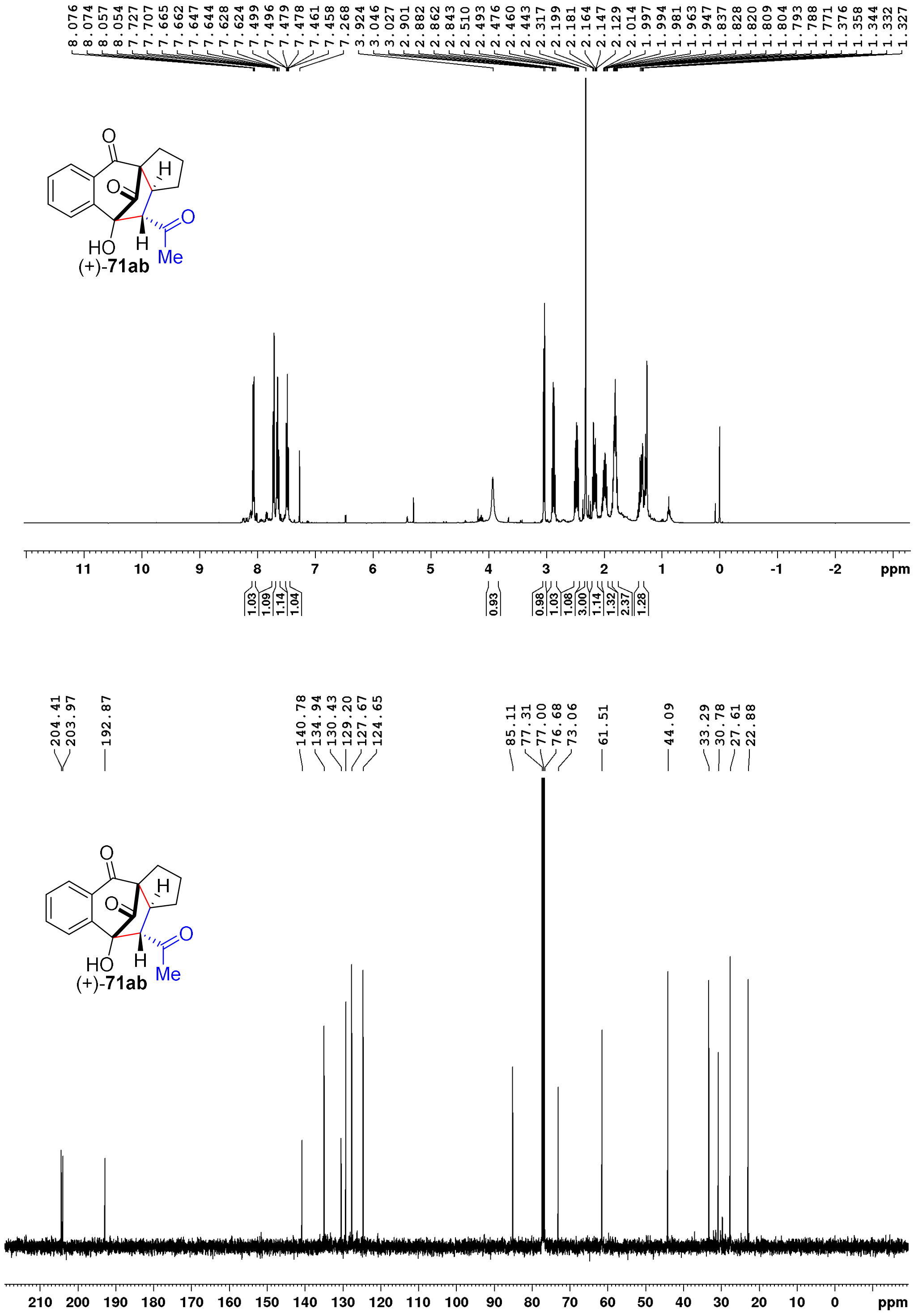
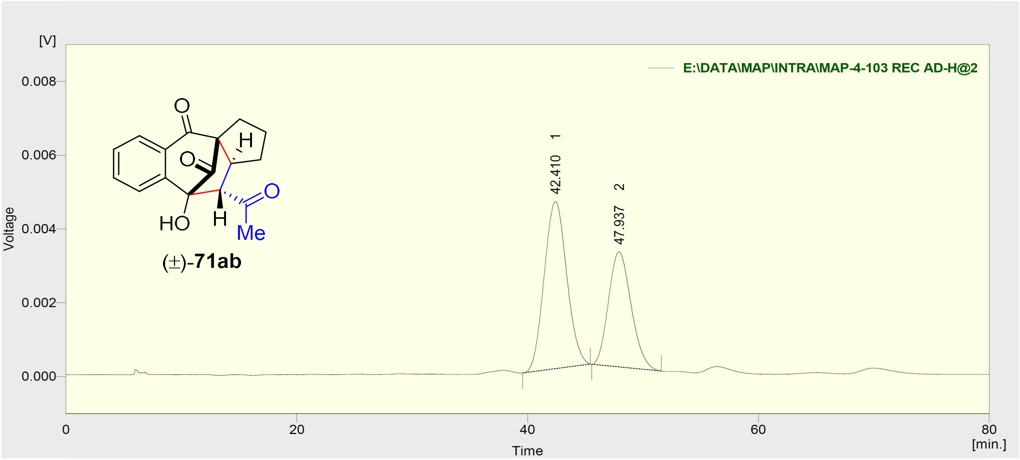


Figure 65: ^{1}H and ^{13}C spectra of the product **71ab**.

Racemic (±)-**71ab:**

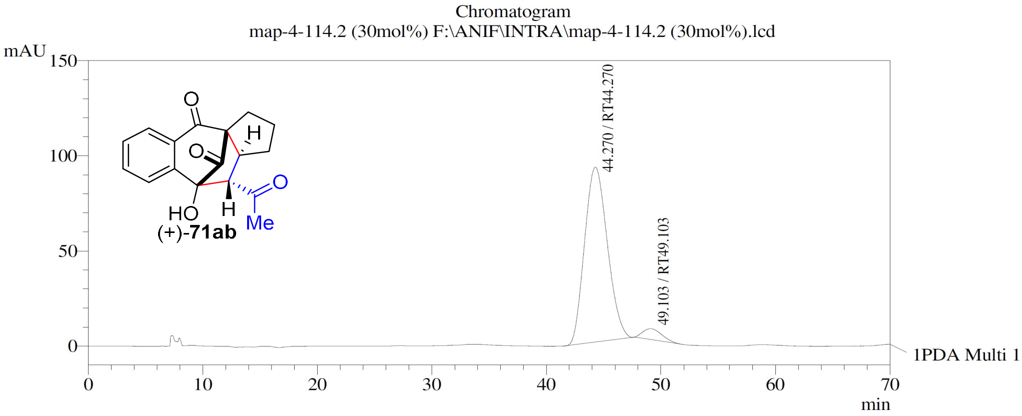


Chiralcel AD-H, Hexane/ i-PrOH = 95:5, Flow Rate 0.5 mL/Min, 254

Result Table (Uncal - E:\DATA\MAP\INTRA\MAP-4-103 REC AD-H@2)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	42.410	615.636	4.536	59.1	59.2	2.14
2	47.937	426.050	3.125	40.9	40.8	2.13
	Total	1041.686	7.661	100.0	100.0	

Chiral (+)-**71ab** (Major: 90.0% *ee*):



Chiralcel AD-H, Hexane/ i-PrOH = 95:5, Flow Rate 0.5 mL/Min, 254

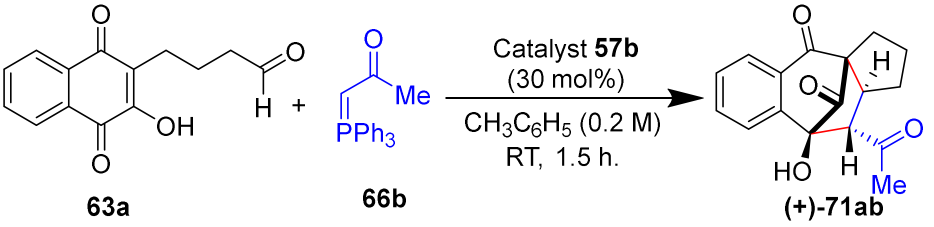
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT44.270	44.270	12737441	92015	95.017	94.131
2	RT49.103	49.103	668011	5737	4.983	5.869
Total			13405452	97752	100.000	100.000

Figure 66: HPLC spectra of the chiral product **71ab**.

After isolating the product (+)-**4aa** we then recovered the catalyst and which was utilized for the next circle of tandem reaction by adjusting reactants to 30 mol% isolated catalyst without adding a fresh catalyst. Which furnishes (+)-**4aa** in 1.5 h with 83.4% yield, 82.2% *ee* and >20:1 dr. Likewise, we again recovered the catalyst from the reaction mixture and utilized for next circle of tandem reaction, which furnishes the (+)-**4aa** in maintained yields and dr ratio with much diminished enantioselectivity (62.9% *ee* (Eq. 22)).



(22)

1st run yield : **84.5%** *ee* : **90%** *dr* : **>20:1**

2nd run yield : **83.4%** *ee* : **82.19%** *dr* : **>20:1**

3rd run yield : **84.3%** *ee* : **62.9%** *dr* : **>20:1**

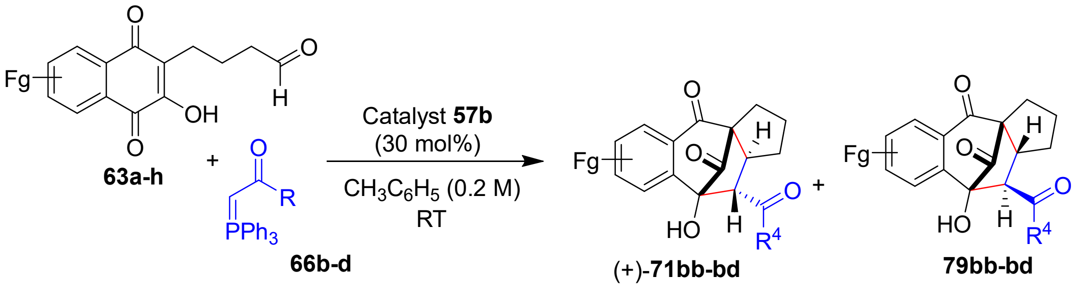
6.2.2 Scope of asymmetric tandem W/IM/IA reactions:

To study the substituent effect on the asymmetric tandem Wittig/intra-molecular Michael/intra-molecular aldol reactions, we synthesized a variety of methanobenzo[*f*]azulenes (+)-**71bb-bd** by reacting lawsone aldehydes **63b-h** with Wittig reagents **66b-d** under quinine thiourea **57b** catalysis in toluene solvent at room temperature for 1-6 h (Table 19). Notably, reactions with 6-methoxy, 7-methoxy and 6,7-dimethoxy lawsone aldehydes performed smoothly at room temperature and furnished methanobenzo[*f*]azulenes (+)-**71cb-eb** in 77-90% yields, 59-85.6% *ee* with single diastereomer (Table 19, entries 2 - 4). Although 8-methoxy and 6-*N*-acetyl lawsone aldehydes furnished products (+)-**71bb** and (+)-**71hb** in 74-80% yield, 95->99% *ee* with single diastereomer (Table 19, entries 1 and 7).

Similarly, 6-methyl lawsone aldehyde furnished (+)-**71fb** in 83% yield, 85% *ee* with single diastereomer, whereas 6,8-dimethyl lawsone aldehyde resulted (+)-**71gb** in 87% yield, 96% *ee* with single diastereomer (Table 19, entries 5 and 6). The substitution at

C-8 carbon makes better facial discrimination by sterically hindering one of the faces, subsequently, Michael addition takes place from the sterically unhindered side.

Table 19: Substrate scope of the proposed design.[a]



Entry	Fg **63**	R	t [h]	Yield [%][b]	d r[c] **71:79**	ee [%][d]
1	**63b** = 8-OMe	R= Me	1	74 ((+)-**71bb**)	>20:1	95(--)
2	**63c** = 7-OMe	R= Me	4	90 ((+)-**71cb**)	>20:1	80(--)
3	**63d** = 6-OMe	R= Me	2	77 ((+)-**71db**)	>20:1	85(--)
4	**63e** = 6,7-di OMe	R= Me	2.5	84 ((+)-**71eb**)	>20:1	59(--)
5	**63f** = 6-Me	R= Me	1.1	83 ((+)-**71fb**)	>20:1	85(--)
6	**63g** = 6,8-di Me	R= Me	1	87 ((+)-**71gb**)	>20:1	96(--)
7	**63h** = 7-NHAc	R= Me	1	62 ((+)-**71hb**)	>20:1	>99(--)
8	**63a** = H	R= Et	6	69 ((+)-**71ac**)	>20:1	84(--)
9	**63a** = H	R= Ph	2	81 ((-)-**71ad/79ad**)	1:1.6	94(30)

[a]Reactions were carried out in solvent (0.2 M) with 1.1 equiv of **66b-d** relative to **63a-h** (0.2 mmol), in the presence of 30 mol% of the catalyst **57b**. [b]Yield refers to the

column-purified product. [c]Determined by CSP HPLC analysis. [d]Determined by CSP HPLC analysis and values in parentheses represent those for the minor diastereomer.

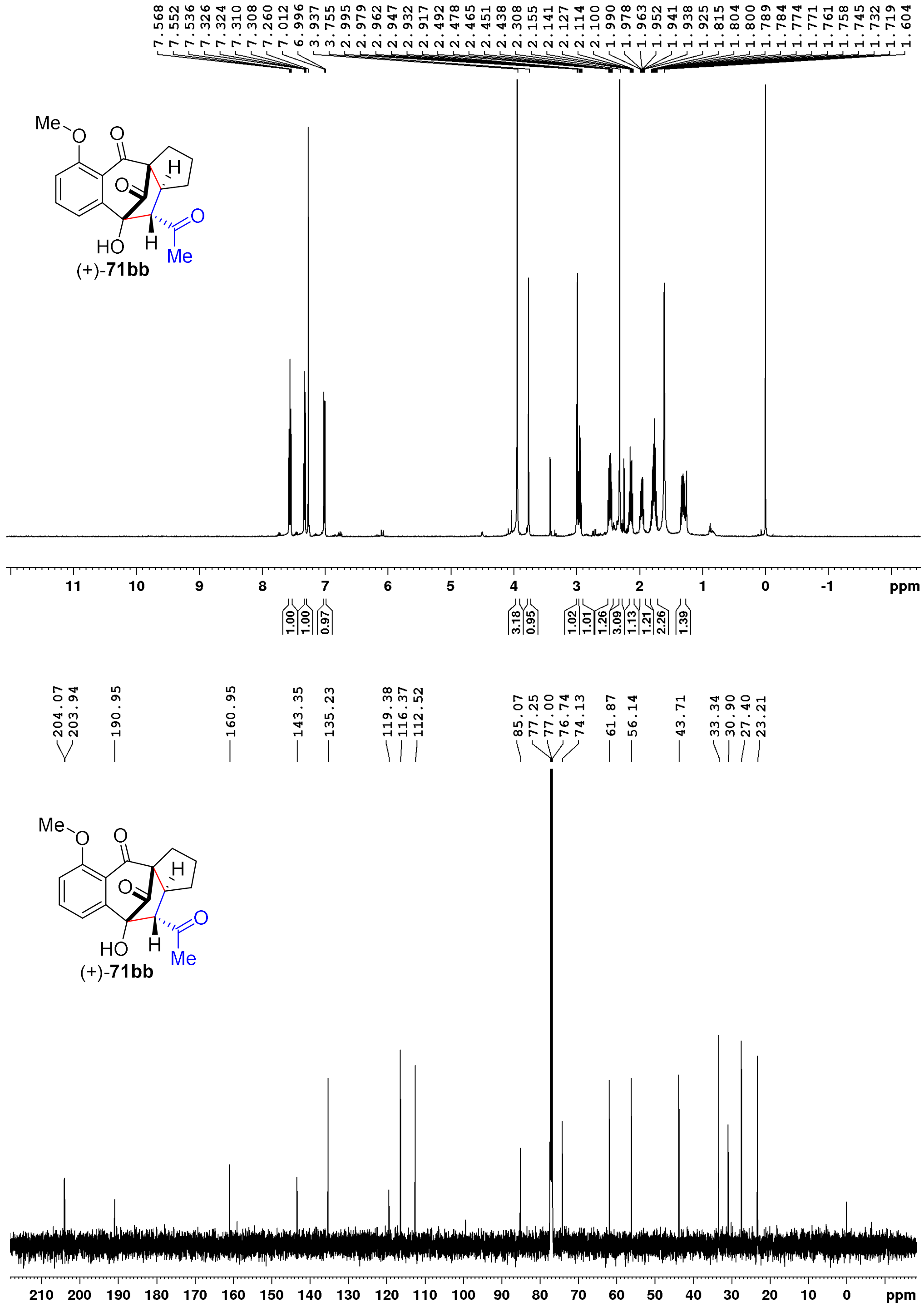


Figure 67: ^{1}H and ^{13}C spectra of the product **71bb**.

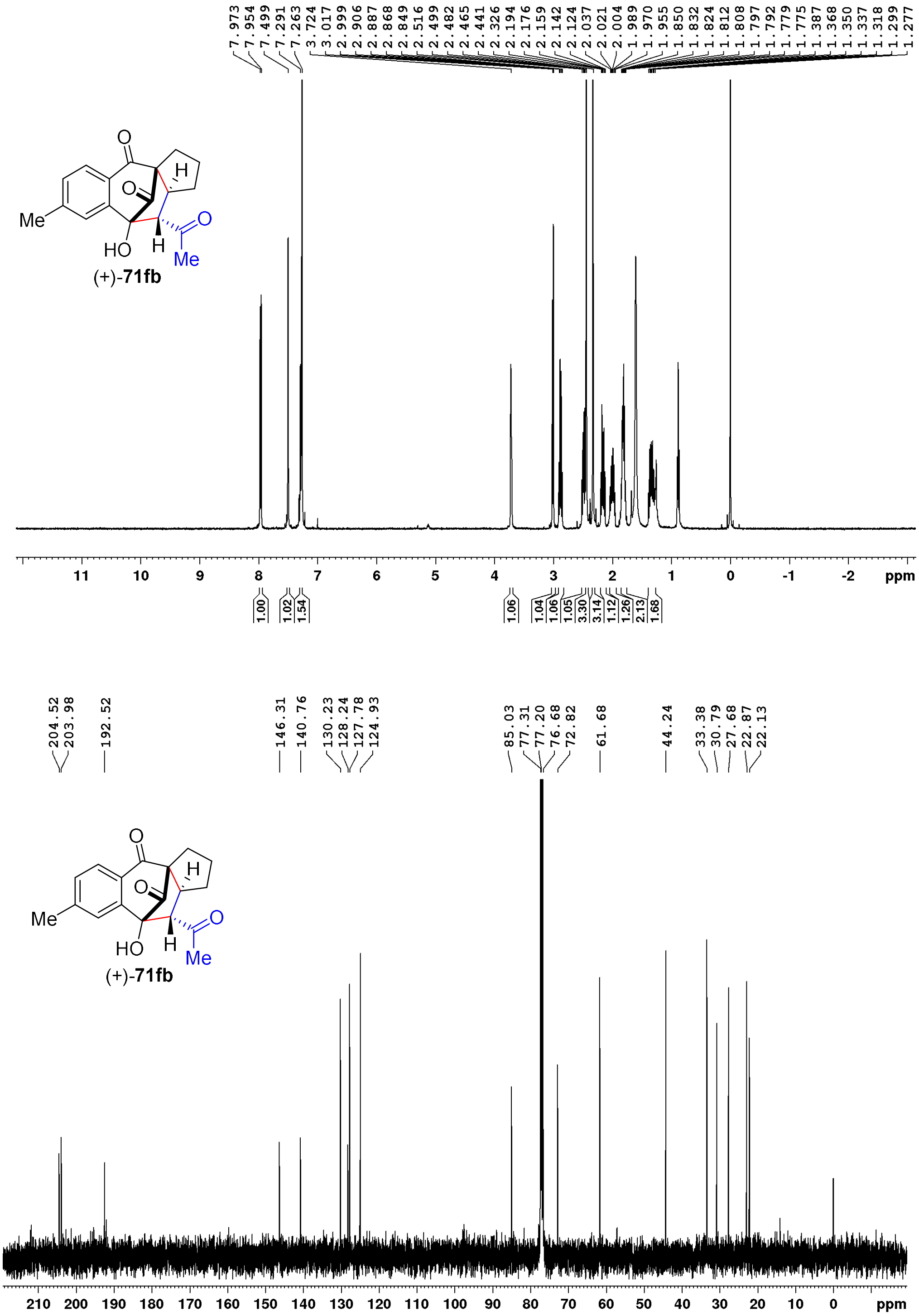


Figure 68: ^{1}H and ^{13}C spectra of the product **71fb**.

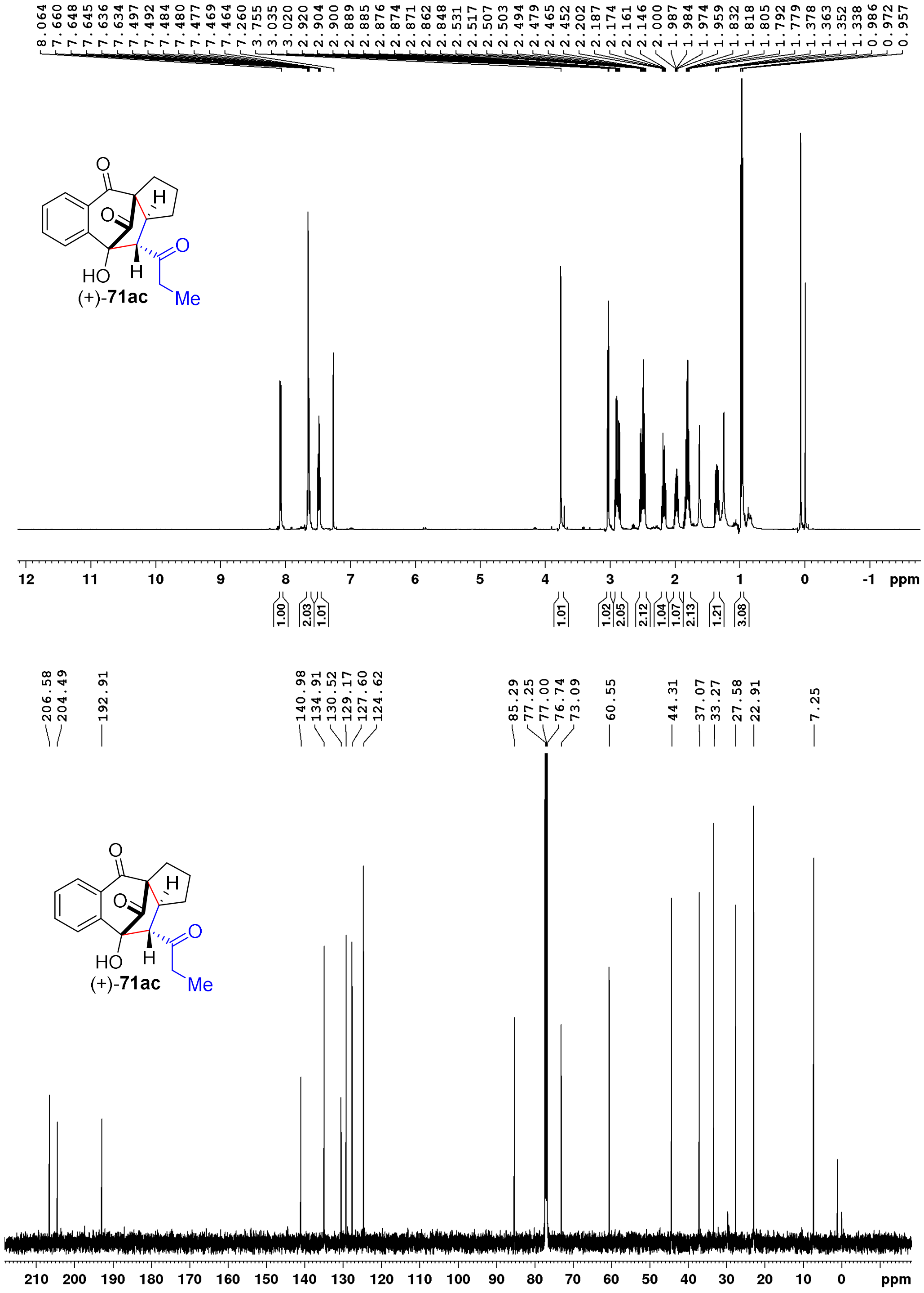


Figure 69: ^{1}H and ^{13}C spectra of the product **71ac**.

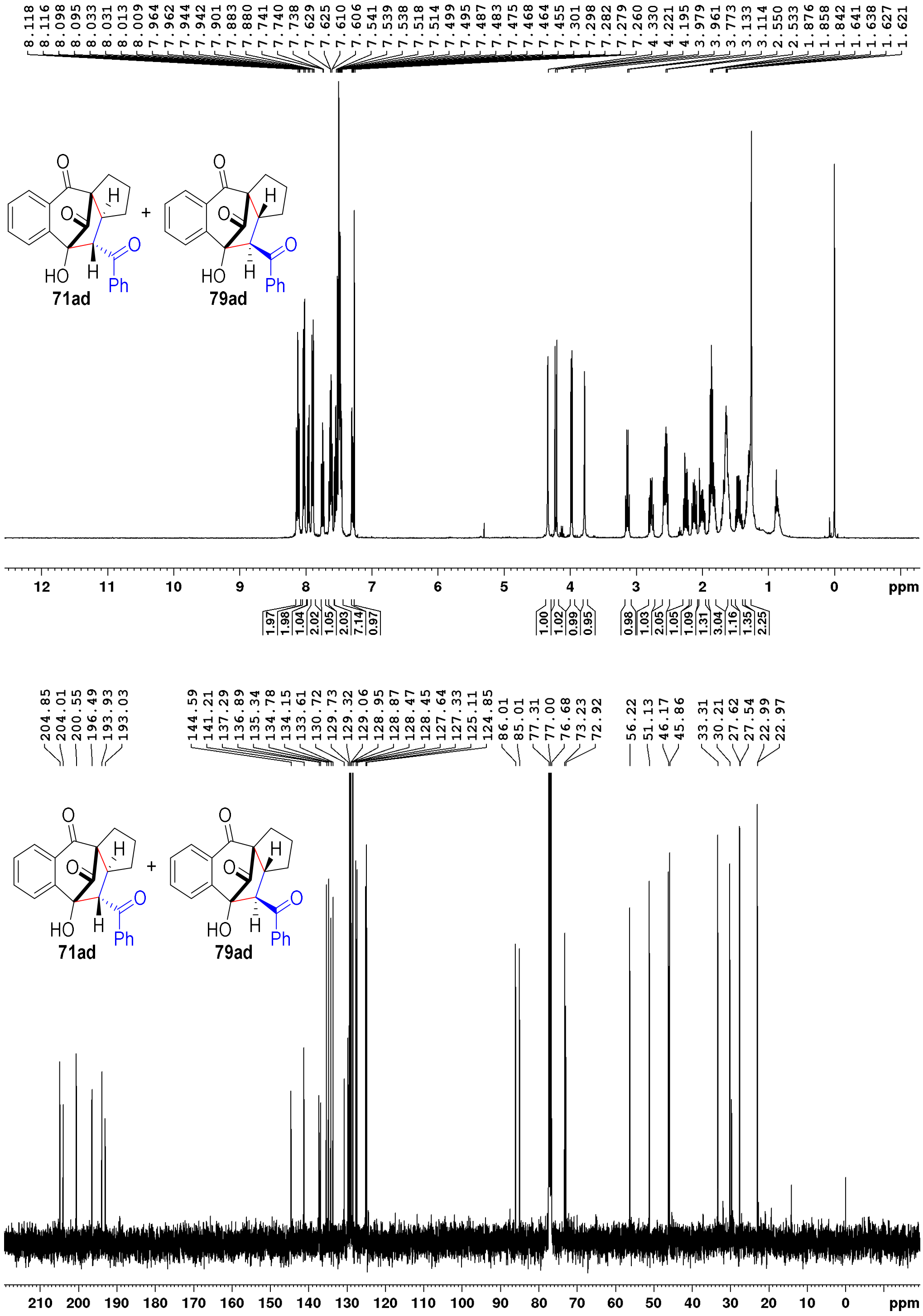
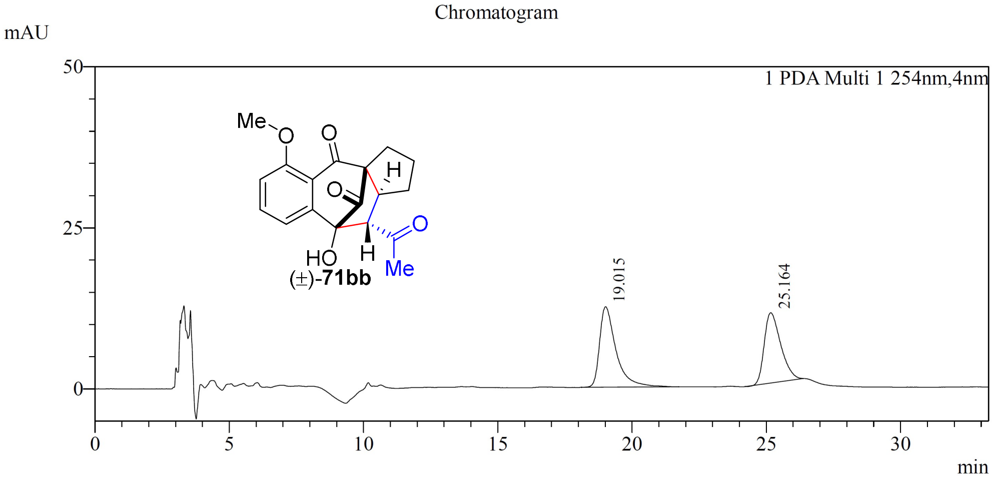


Figure 70: ^{1}H and ^{13}C spectra of the product **71ad** and **79ad**.

Racemic (±)-**71bb:**



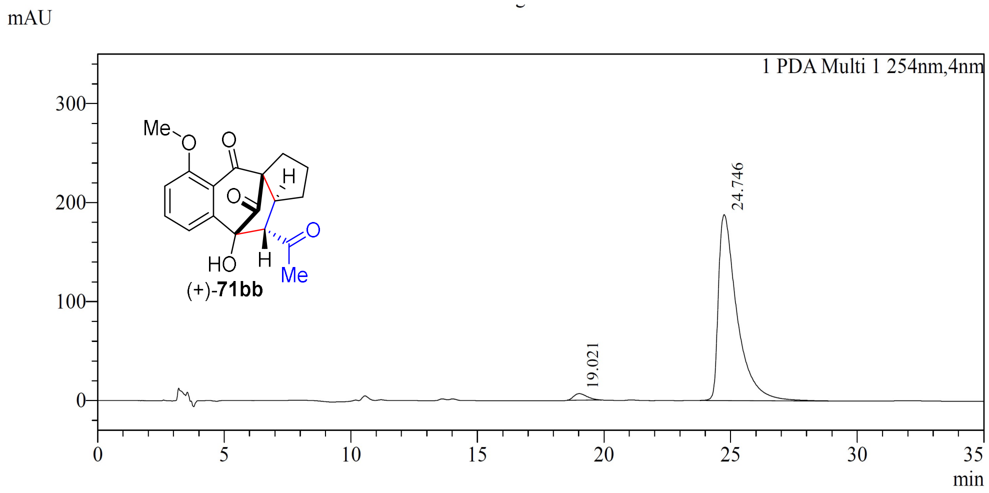
Chiralpak IB-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:19.015	19.015	532955	12486	53.367	53.355
2	RT:25.164	25.164	465704	10916	46.633	46.645
Total			998658	23402	100.000	100.000

Chiral (+)-**71bb:** (Major: 95.0% *ee*):



Chiralpak IB-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

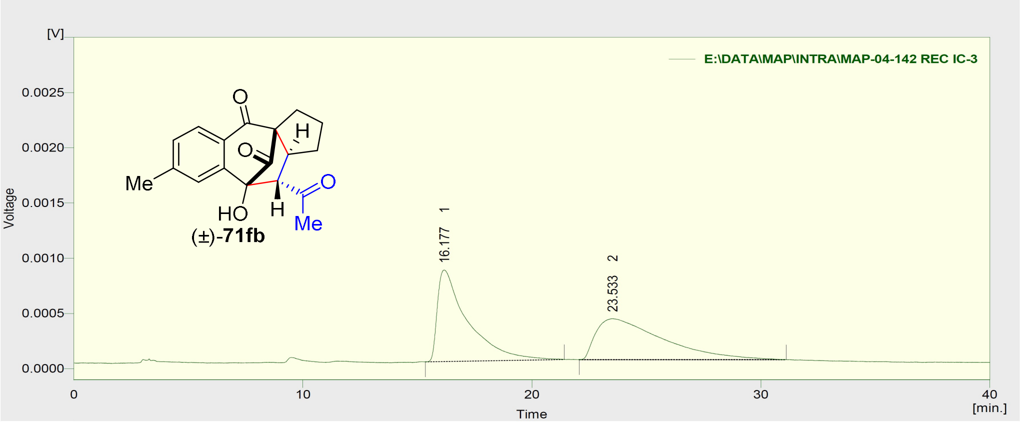
Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:19.021	19.021	243575	6655	2.472	3.422
2	RT:24.746	24.746	9611066	187842	97.528	96.578
Total			9854641	194497	100.000	100.000

Figure 71: HPLC spectra of the chiral product **71bb**.

Racemic (±)-**71fb:**

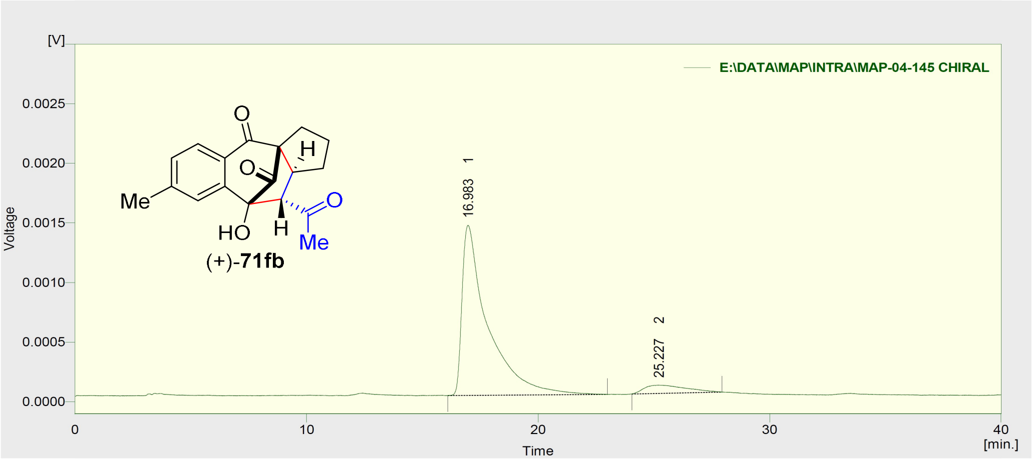


Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Result Table (Uncal - E:\DATA\MAP\INTRA\MAP-04-142 REC IC-3)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	16.177	76.315	0.830	50.2	69.0	1.20
2	23.533	75.812	0.373	49.8	31.0	3.07
	Total	152.128	1.204	100.0	100.0	

Chiral (+)-**71fb**: (Major: 85.2% *ee*):



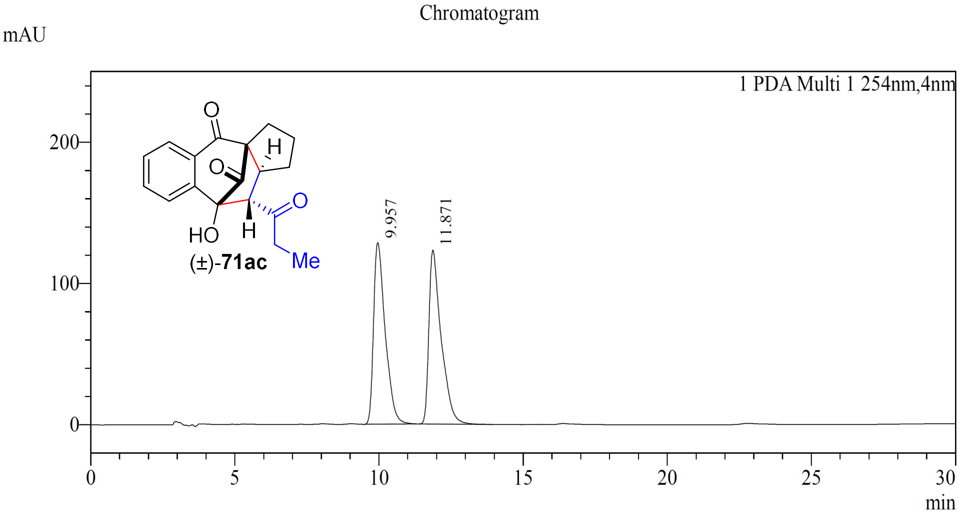
Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Result Table (Uncal - E:\DATA\MAP\INTRA\MAP-04-145 CHIRAL)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	16.983	110.784	1.429	92.6	95.2	0.92
2	25.227	8.896	0.072	7.4	4.8	2.24
	Total	119.680	1.501	100.0	100.0	

***Figure** 72*: HPLC spectra of the chiral product **71fb**.

Racemic (±)-**71ac:**



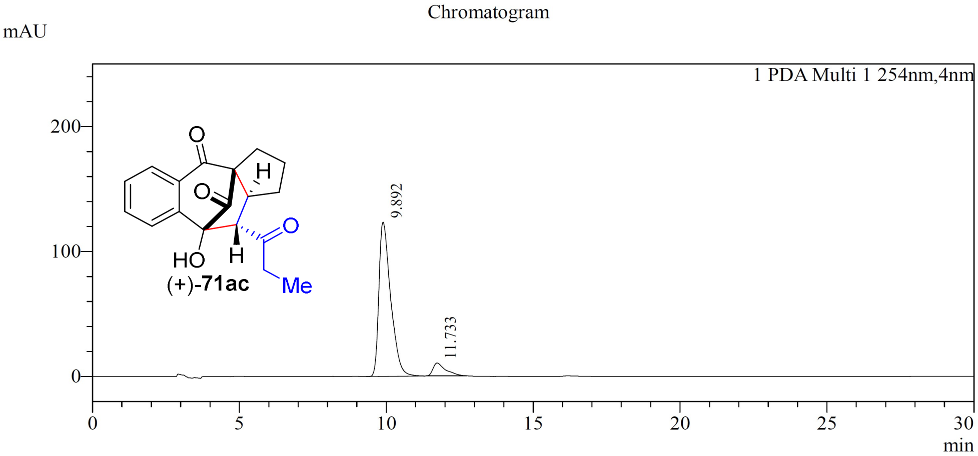
Chiralpak IA-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:9.957	9.957	3606642	128362	49.703	51.035
2	RT:11.871	11.871	3649760	123157	50.297	48.965
Total			7256401	251519	100.000	100.000

Chiral (+)-**71ac**: (Major: 83.7% *ee*):



Chiralpak IA-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

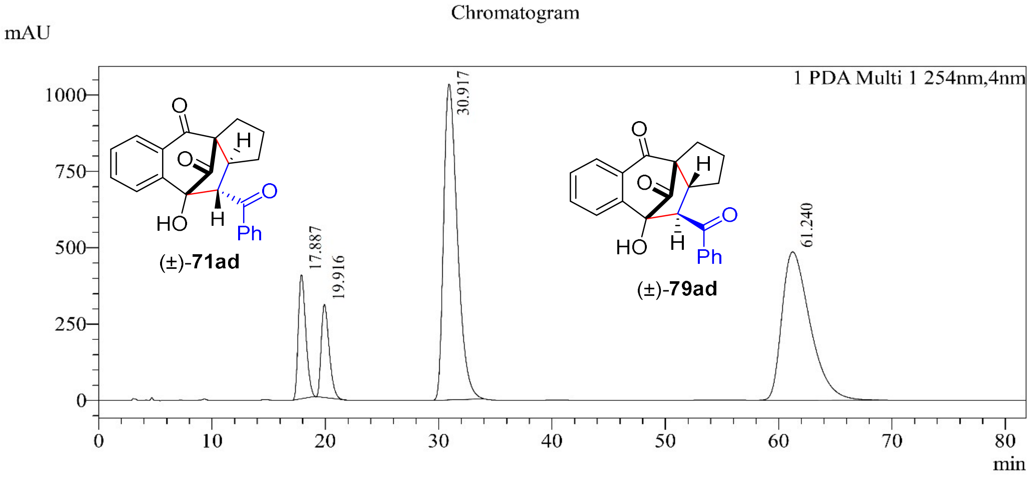
Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:9.892	9.892	3429733	123274	91.848	92.303
2	RT:11.733	11.733	304396	10279	8.152	7.697
Total			3734129	133553	100.000	100.000

Figure 73: HPLC spectra of the chiral product **71ac**.

Racemic (±)-**71ad** and (±)-**79ad:**



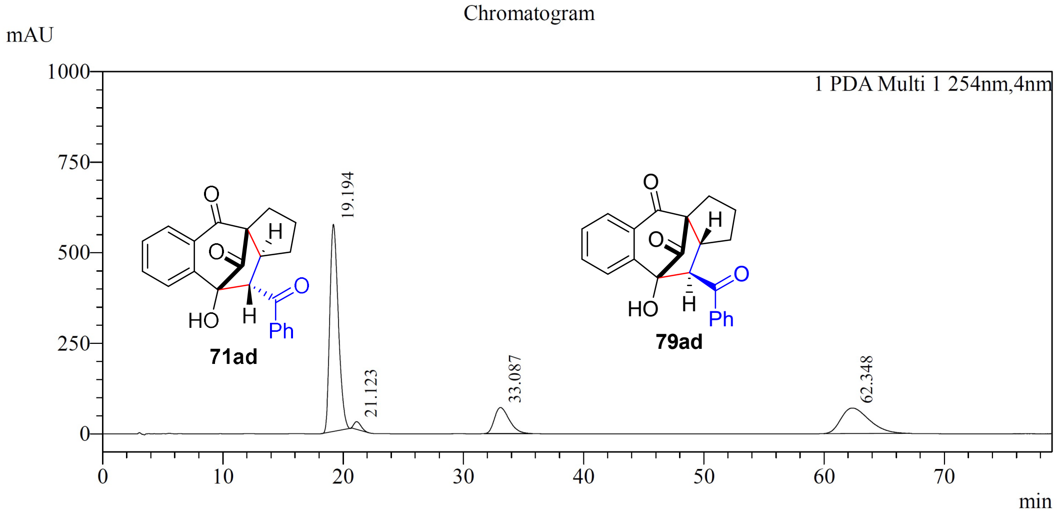
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:17.887	17.887	18719342	405813	9.166	18.193
2	RT:19.916	19.916	14883280	305244	7.288	13.684
3	RT:30.917	30.917	86976354	1034058	42.588	46.357
4	RT:61.240	61.240	83646637	485527	40.958	21.766
Total			204225613	2230643	100.000	100.000

Chiral **71ad** and **79ad**: (Major: 94.0% *ee*; Minor: 30.2% *ee*):



Chiralcel AD-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

PDA Ch1 254nm

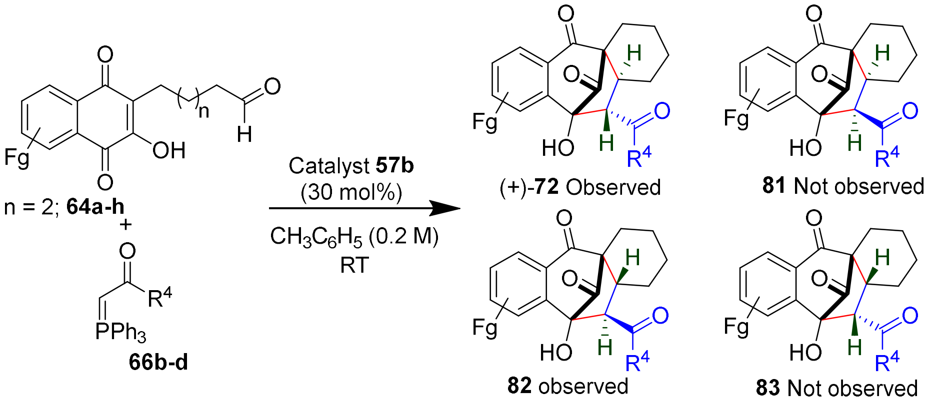
Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:19.194	19.194	28242613	571744	60.411	77.727
2	RT:21.123	21.123	869757	21337	1.860	2.901
3	RT:33.087	33.087	6155392	71988	13.166	9.786
4	RT:62.348	62.348	11482730	70514	24.562	9.586
Total			46750492	735582	100.000	100.000

Figure 74: HPLC spectra of the chiral product **71ad** and **79ad**.

To further extend the scope of this tandem reactions, we performed reaction by treating different Wittig reagents **66c-d** with 4-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal **63a** under quinine thiourea **57b** catalysis. Herein, the reaction with **66c** performed well at room temperature and furnished (+)-**71ac** in 69% yield, 84% *ee* with single diastereomer in 6 h (Table 19, entry 8). However, **66d** furnished (-)-**71ad** in 81% yield, 1:1 dr with 94% major *ee* and 30% minor *ee* (Table 19, entry 9). The unfavourable interaction between the phenyl group and the catalyst-lawsone aldehyde complex, can be cited as the reason for poor diastereoselectivity in (-)-**71ad** (Table 19).

Under the same limelight, we also made a chiral library of optically pure methanodibenzo[*f*]azulenes relating to 5-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal (**64a-h**). Herein, we treated **64a-h** with **66b-d** under 30 mol% of quinine thiourea **57b** catalysis in toluene solvent for 16-43 h (Table 20). Strikingly, all the reactions performed smoothly at room temperature, furnished (+)-**72ab-hb** in 68-91% yields, up to 99% *ee* for major isomer and other isomer almost racemic, with moderate to good dr ratios. Namely, 8-methoxy, 6-methoxy, 7-*N*-acetyl and 6,8-dimethyl substituents show significant enhancement in dr ratios *i.e.,* up to >20:1 (Table 20, entries 2, 4, 7, 8). Whereas **63a**, 7-methoxy, 6,7-dimethoxy and 6-methyl substituents gave moderate dr ratios (Table 20, entries 1, 3, 5, 6). The better dr ratios have resulted from better facial discrimination by substituents in the *pre*-transition state. To further extend the substrate scope of this asymmetric tandem Wittig/intra-molecular Michael/intra-molecular aldol reactions, we performed reaction between 5-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal **64a** and Wittig reagents like **66b-d** under 30 mol% **57b** in toluene solvent. Surprisingly, reaction with **2c** performed well at room temperature for 24 hr, furnished (+)-**74ac** in 70% yield, 1:1 dr with 98.5% major *ee* and 37.5% minor *ee* (Table 20, entry 9). Although **2d** reaction did not performed well at room temperature and performed at 80 ºC, furnished (-)-**74ad** in 81% yield, 74% *ee* for major isomer and almost racemic for minor isomer, with 3.5:1 dr ratio (Table 20, entry 10).

Table 20: Substrate scope of the proposed design.[a]



Entry	Fg **8**	R	t [h]	Yield [%][b]	d r[c] **72:82**	ee [%][d]
1	**64a** = H	R= Me	18	94 ((+)-**72ab/82ab**)	5:1	99(00)
2	**64b** = 8-OMe	R= Me	36	68 ((+)-**72bb/82bb**)	>20:1	99(--)
3	**64c** = 7-OMe	R= Me	20	92 ((+)-**72cb/82cb**)	5:1	99(00)
4	**64d** = 6-OMe	R= Me	16.7	88 ((+)-**72db/82db**)	9:1	99(00)
5	**64e** = 6,7-di OMe	R= Me	43	80 ((+)-**72eb/82eb**)	4:1	99(00)
6	**64f** = 6-Me	R= Me	18	77 ((+)-**72fb/82fb**)	6:1	99(00)
7	**64g** = 6,8-di Me	R= Me	22	89 ((+)-**72gb/82gb**)	8:1	98(15)
8	**64h** = 7-NHAc	R= Me	27	81 ((+)-**72hb/82hb**)	>20:1	96(24)
9	**64a** = H	R= Et	24	70 ((+)-**72ab/82ab**)	1:1	98(37)
10[e]	**64a** = H	R= Ph	6	79 ((-)-**72ab/82ab**)	3:1	74(00)
11[f]	**64a** = H	R= Me	24	87 ((-)-**72ab/82ab**)	3:1	99(00)

[a] Reactions were carried out in solvent (0.2 M) with 1.1 equiv of **66b-d** relative to **64a-h** (0.2 mmol), in the presence of 30 mol% of the catalyst **57b**. [b] Yield refers to the column-purified product. [c] Refers to the column-purified product weight.

[d]Determined by CSP HPLC analysis and values in parentheses represent those for the minor diastereomer. [e] T = 80 °C. [f]T = catalyst **57a** used as catalyst.

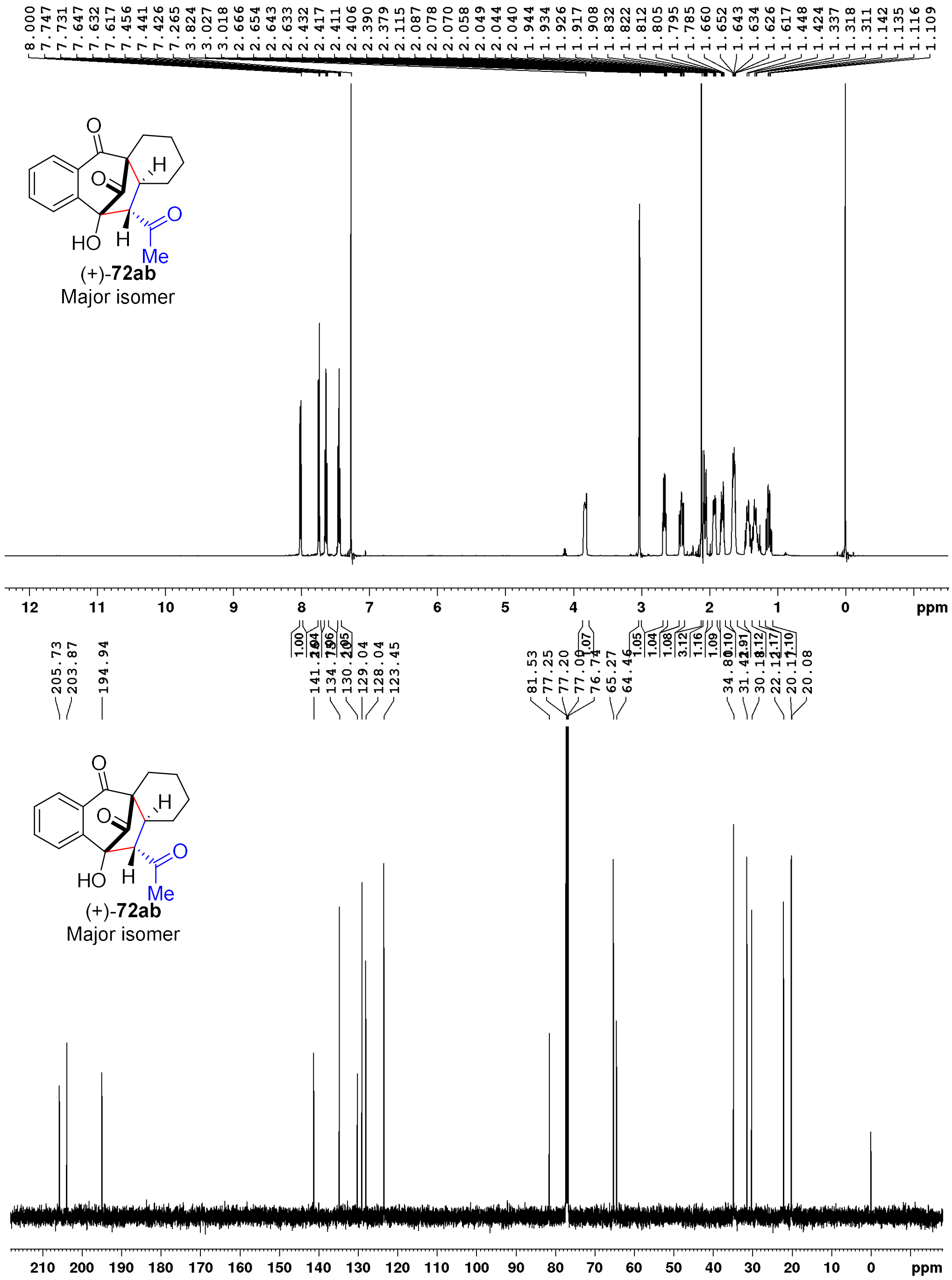


Figure 75: ^{1}H and ^{13}C spectra of the product **72ab**.

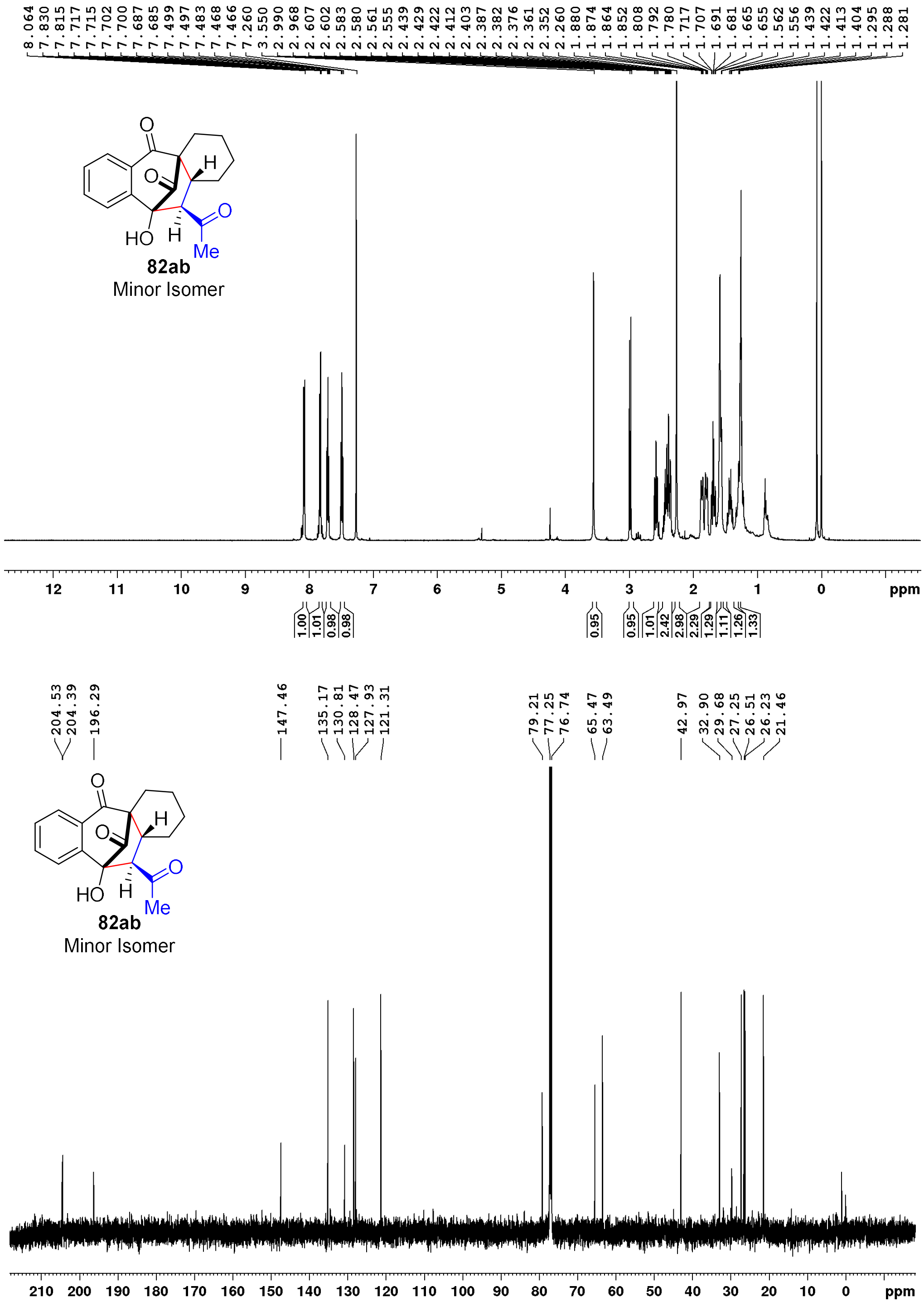


Figure 76: ^{1}H and ^{13}C spectra of the product **82ab**.

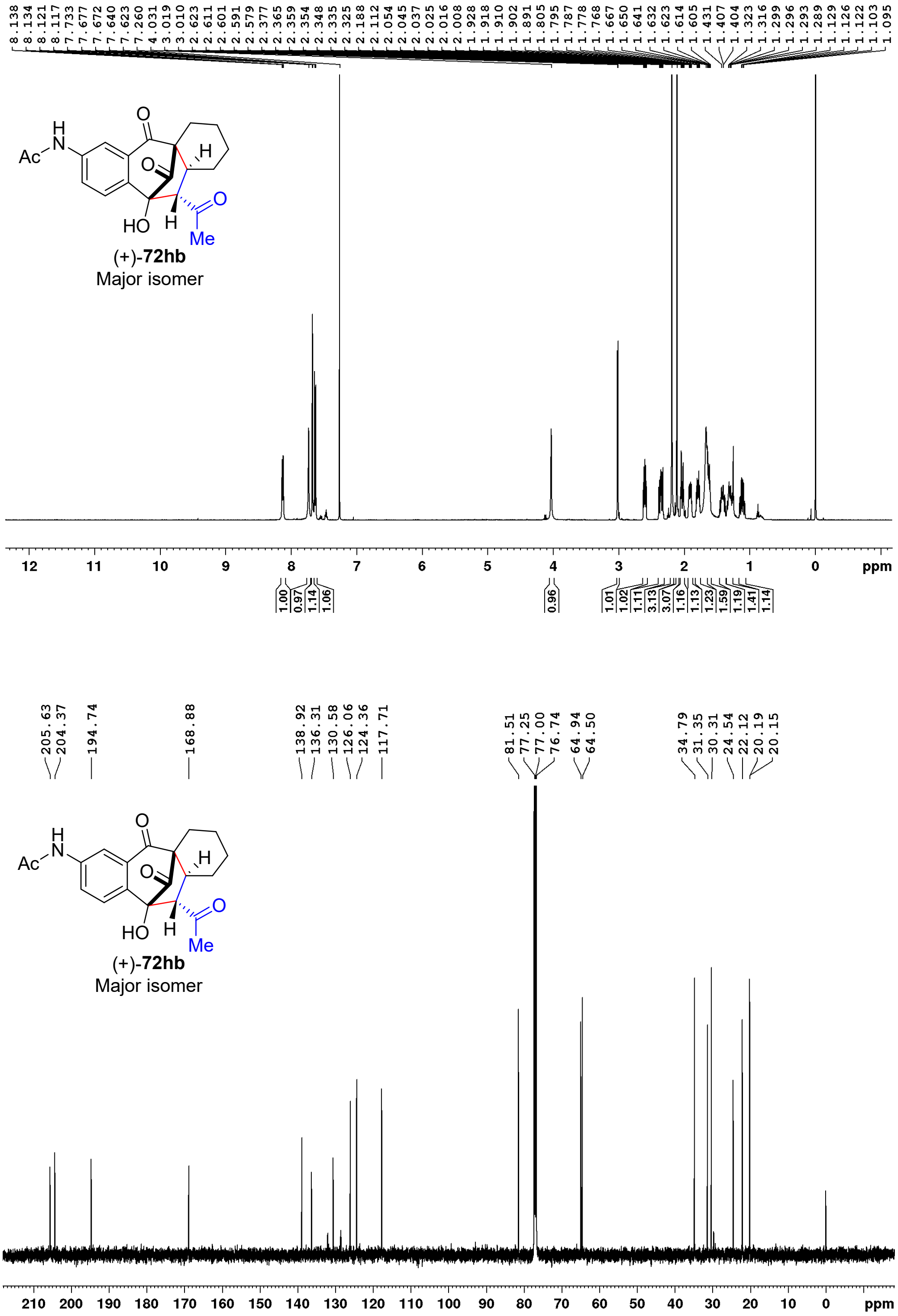


***Figure** 77*: ^{1}H and ^{13}C spectra of the product **72hb**.

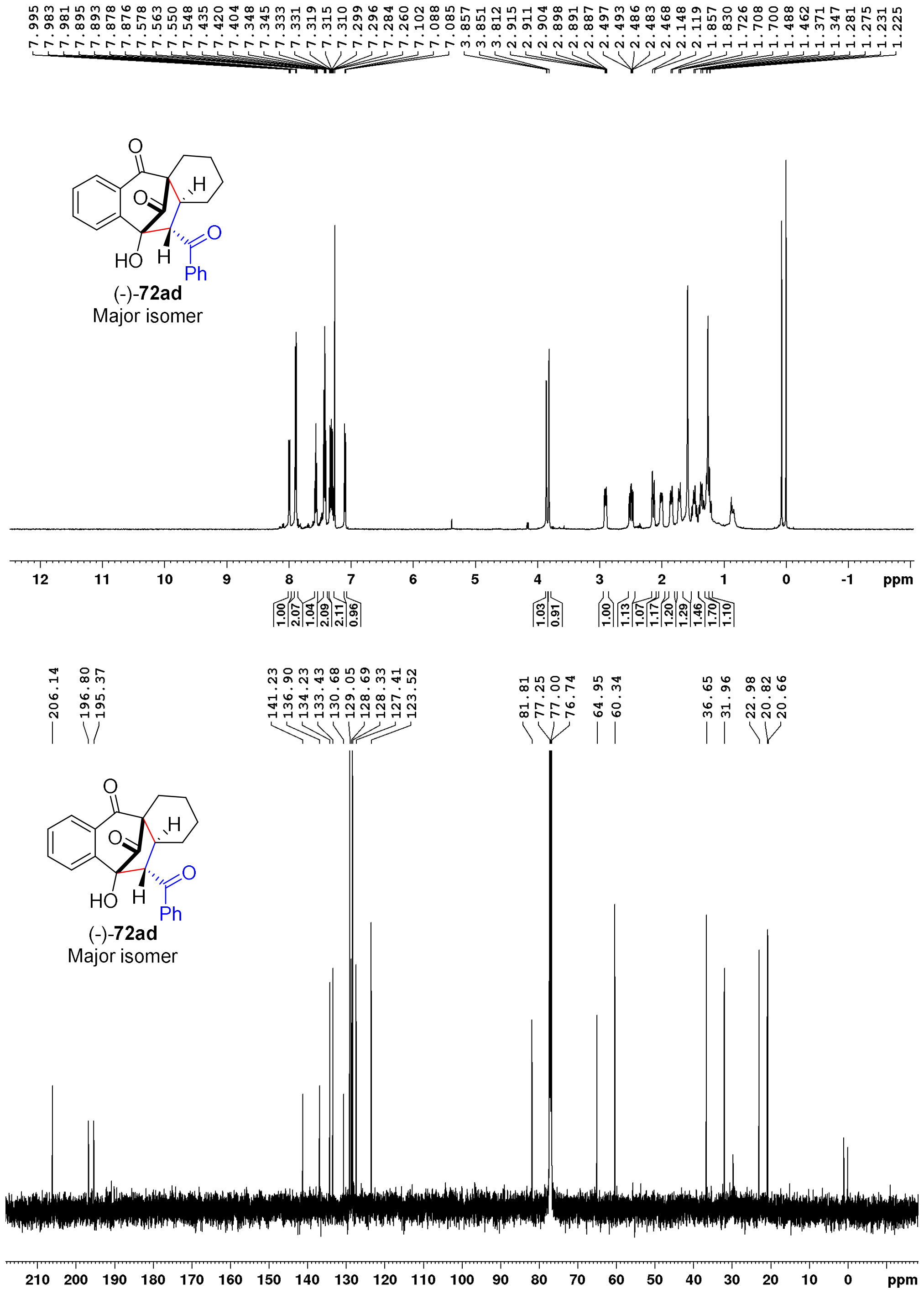


Figure 78: ^{1}H and ^{13}C spectra of the product **72ad**.

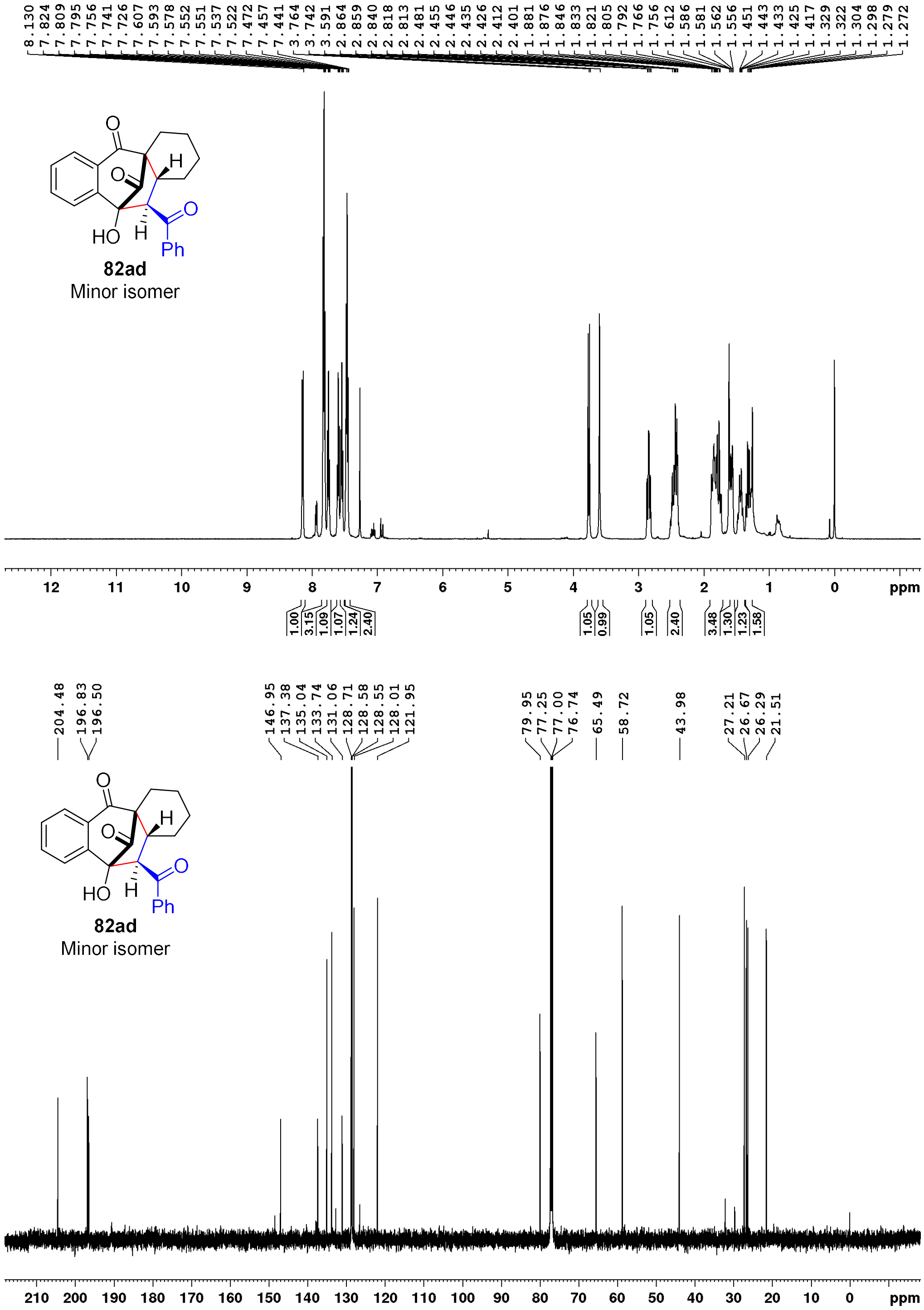
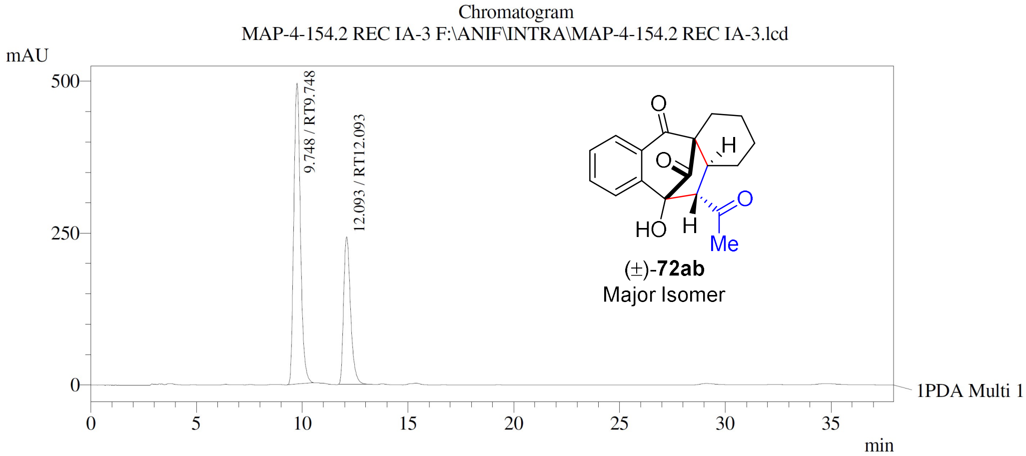


Figure 79: ^{1}H and ^{13}C spectra of the product **82ad**.

Racemic (±)-**72ab** Major**:**



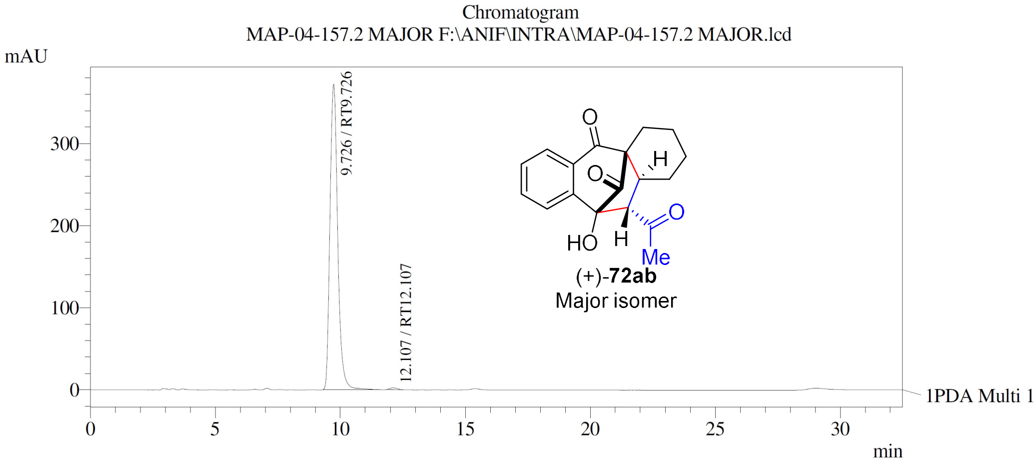
Chiralpak IA-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT9.748	9.748	10781195	495001	66.225	67.088
2	RT12.093	12.093	5498329	242837	33.775	32.912
Total			16279524	737838	100.000	100.000

Chiral (+)-**72ab**: (Major: 98.9% *ee*):



Chiralpak IA-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

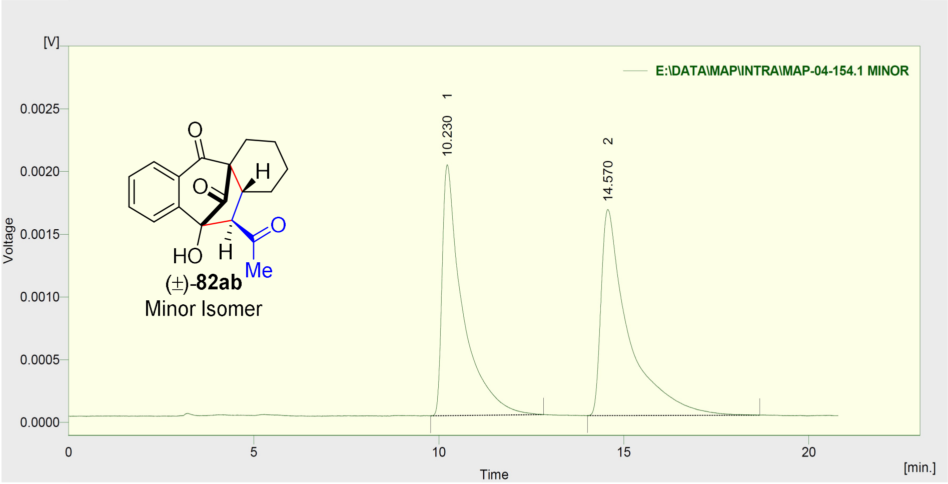
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT9.726	9.726	8043090	372032	99.465	99.404
2	RT12.107	12.107	43231	2232	0.535	0.596
Total			8086321	374264	100.000	100.000

Figure 80: HPLC spectra of the chiral product **72ab**.

Racemic (±)-**82ab** Minor**:**

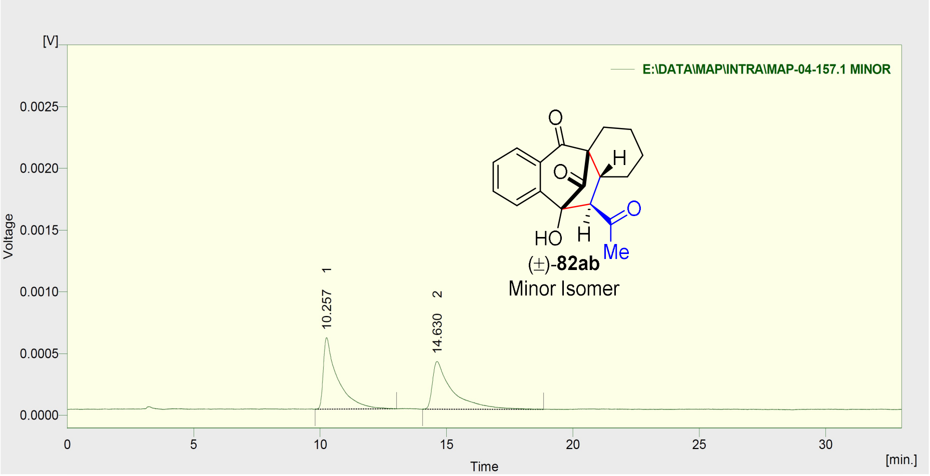


Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254

Result Table (Uncal - E:\DATA\MAP\INTRA\MAP-04-154.1 MINOR)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	10.230	76.981	2.000	47.5	54.9	0.49
2	14.570	85.036	1.644	52.5	45.1	0.63
	Total	162.018	3.644	100.0	100.0	

Chiral **82ab**: (Minor: 00.0% *ee*):



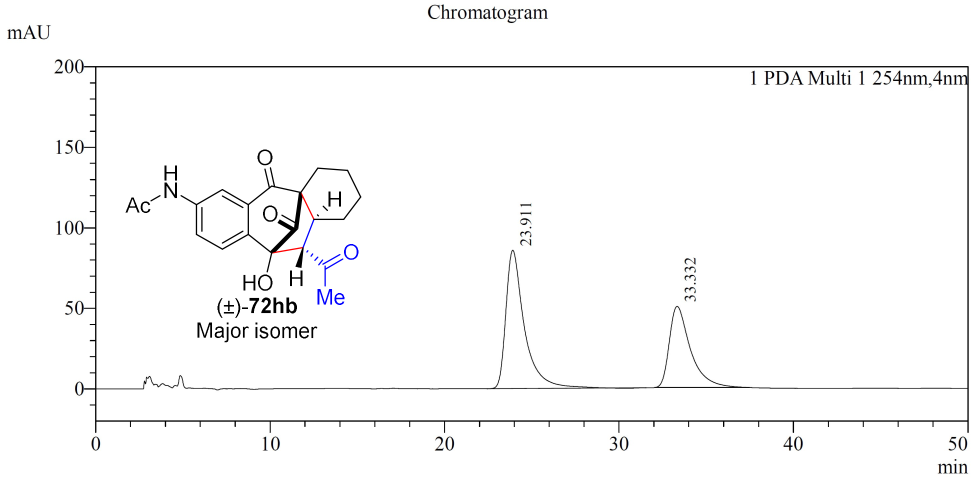
Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min,

Result Table (Uncal - E:\DATA\MAP\INTRA\MAP-04-157.1 MINOR)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	10.257	23.067	0.581	52.0	60.0	0.50
2	14.630	21.258	0.388	48.0	40.0	0.66
	Total	44.325	0.969	100.0	100.0	

Figure 81: HPLC spectra of the chiral product **82ab**.

Racemic (±)-**72hb** Major:



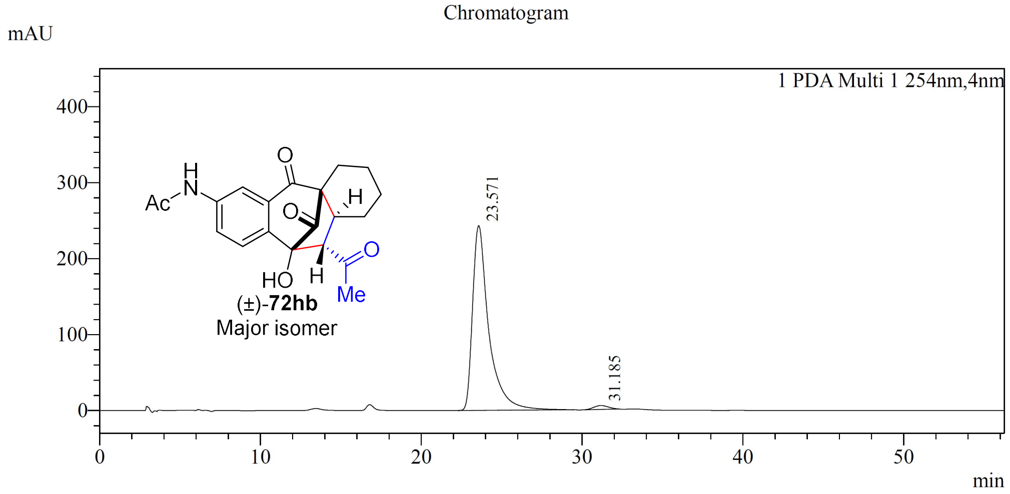
Chiralpak IA-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:23.911	23.911	6315439	85844	59.760	63.010
2	RT:33.332	33.332	4252586	50394	40.240	36.990
Total			10568025	136239	100.000	100.000

Chiral (+)-**72hb**: (Major: 96.4% *ee*):



Chiralpak IA-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

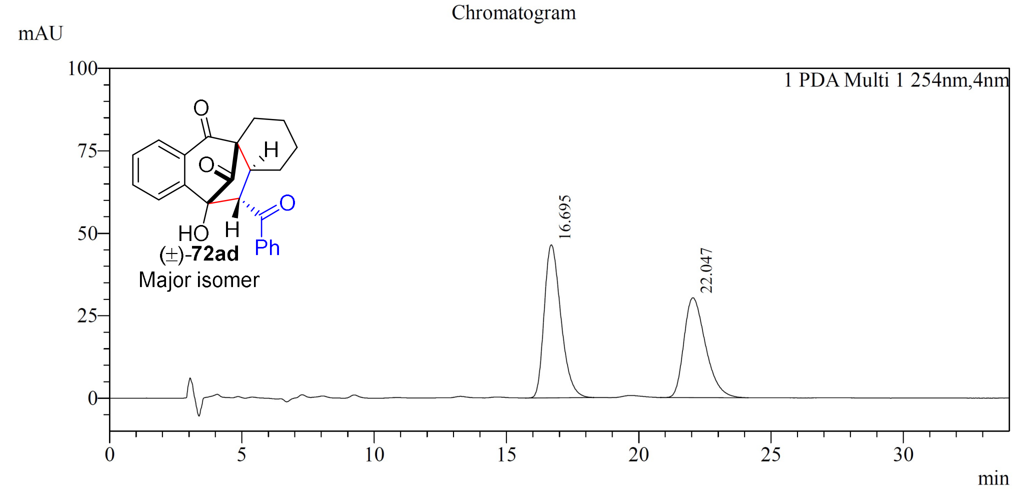
Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:23.570	23.571	17035321	243353	98.209	97.983
2	RT:31.185	31.185	310712	5010	1.791	2.017
Total			17346033	248364	100.000	100.000

Figure 82: HPLC spectra of the chiral product **72hb**.

Racemic (±)-**72ad** Major:



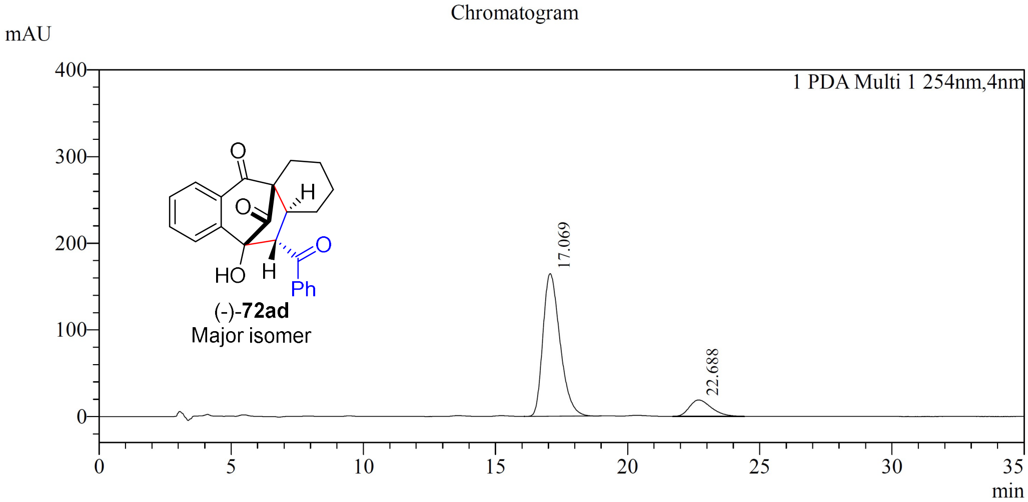
Chiralpak AD-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:16.695	16.695	2038313	46386	54.185	60.507
2	RT:22.047	22.047	1723464	30277	45.815	39.493
Total			3761778	76663	100.000	100.000

Chiral (-)-**72ad**: (Major: 74.1% *ee*):



Chiralpak AD-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

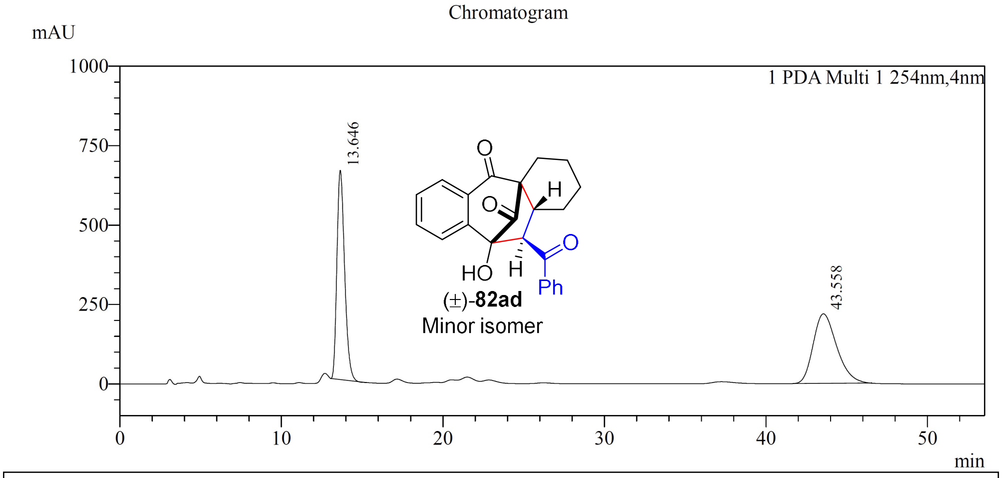
Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:17.069	17.069	7407323	164634	87.068	89.685
2	RT:22.688	22.688	1100191	18936	12.932	10.315
Total			8507514	183570	100.000	100.000

Figure 83: HPLC spectra of the chiral product **72ad**.

Racemic (±)-**82ad** Minor:



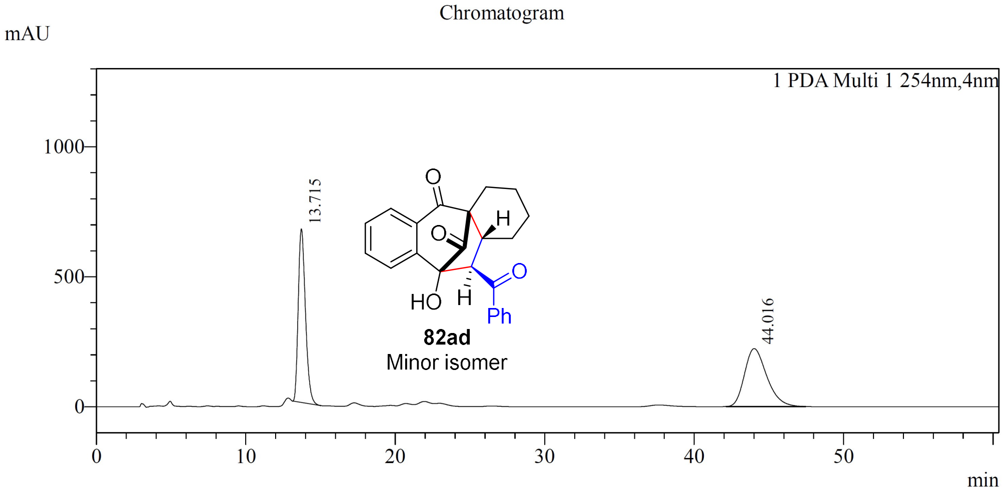
Chiralpak AD-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:13.646	13.646	21839821	658647	49.553	75.042
2	RT:43.558	43.558	22234053	219059	50.447	24.958
Total			44073873	877705	100.000	100.000

Chiral **82ad**: (Minor: 0.0% *ee*):



Chiralpak AD-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

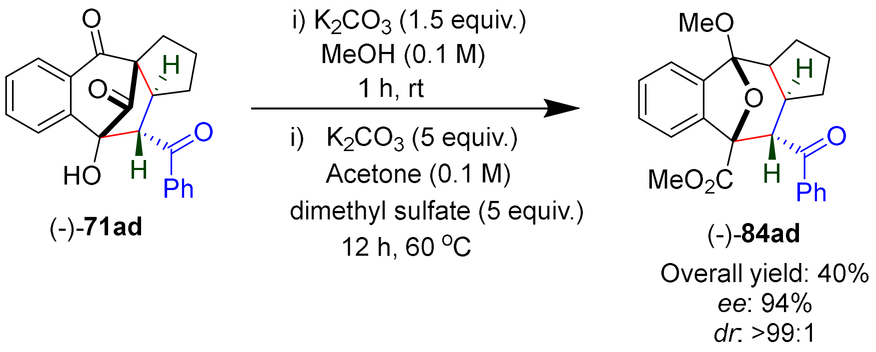
PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:13.715	13.715	22356120	668029	49.201	74.987
2	RT:44.016	44.016	23082586	222829	50.799	25.013
Total			45438706	890858	100.000	100.000

Figure 84: HPLC spectra of the chiral product **82ad**.

6.2.3 Synthetic applications of methanobenzo[f]azulenes:

Besides, the scope of tandem asymmetric Wittig/intra-molecular Michael/intra-molecular aldol reactions, we converted the chiral (-)-**71ad** into (-)-**84ad** by treating with 1.5 equivalents of K_2CO_3 in dry methanol at 25 °C for 1 h followed by the reaction with 5.0 equivalents of Me_2SO_4 in acetone in the presence of 5.0 equivalents of K_2CO_3 at 60 °C for 12 h gave the functionalized (-)-**84ad** in 40% yields, 94% *ee* with >99:1 dr (Scheme 29).



Scheme 29: Synthetic transformation of (-)-**71ad** into (-)-**84ad**.

6.2.4 Controlled experiments to study the poor dr ratios and their poor ee:

Herein, to explain the reasons for poor dr ratios and its *ee*, we conducted some controlled experiments. Initially, we treated chiral compounds (+)-**71ab** and (+)-**72eb** with chiral catalyst **57b** in toluene solvent at room temperature for 2, 24 h respectively. Undeniably, no change in the *ee* was observed, which confirms that dr is not generating from epimerization of major (+)-**71ab** and (+)-**72eb** isomers (Scheme 30, Eq. 23). Furthermore, we protected the *OH*-group by treating 5-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal **64a** with dimethyl sulfate, in the presence of K_2CO_3 in acetone for 4 h furnished in **85a**. We treated **85a** with 1.1 equiv of **66b** under quinine thiourea **57b** catalysis in toluene solvent for 3 h at room temperature resulted in only *trans*-**85ab** Wittig product in good yield (Scheme 30, Eq. 24).

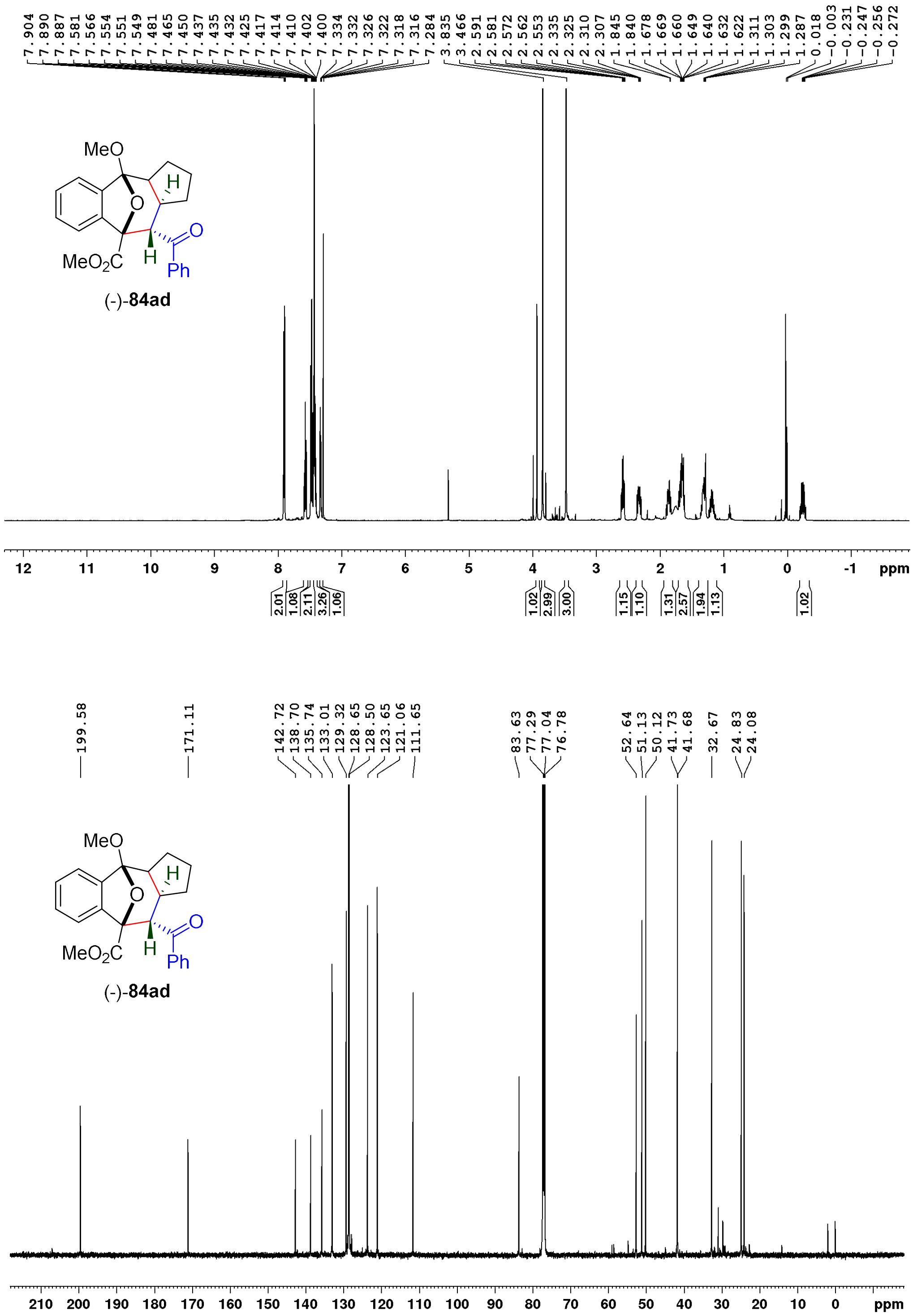
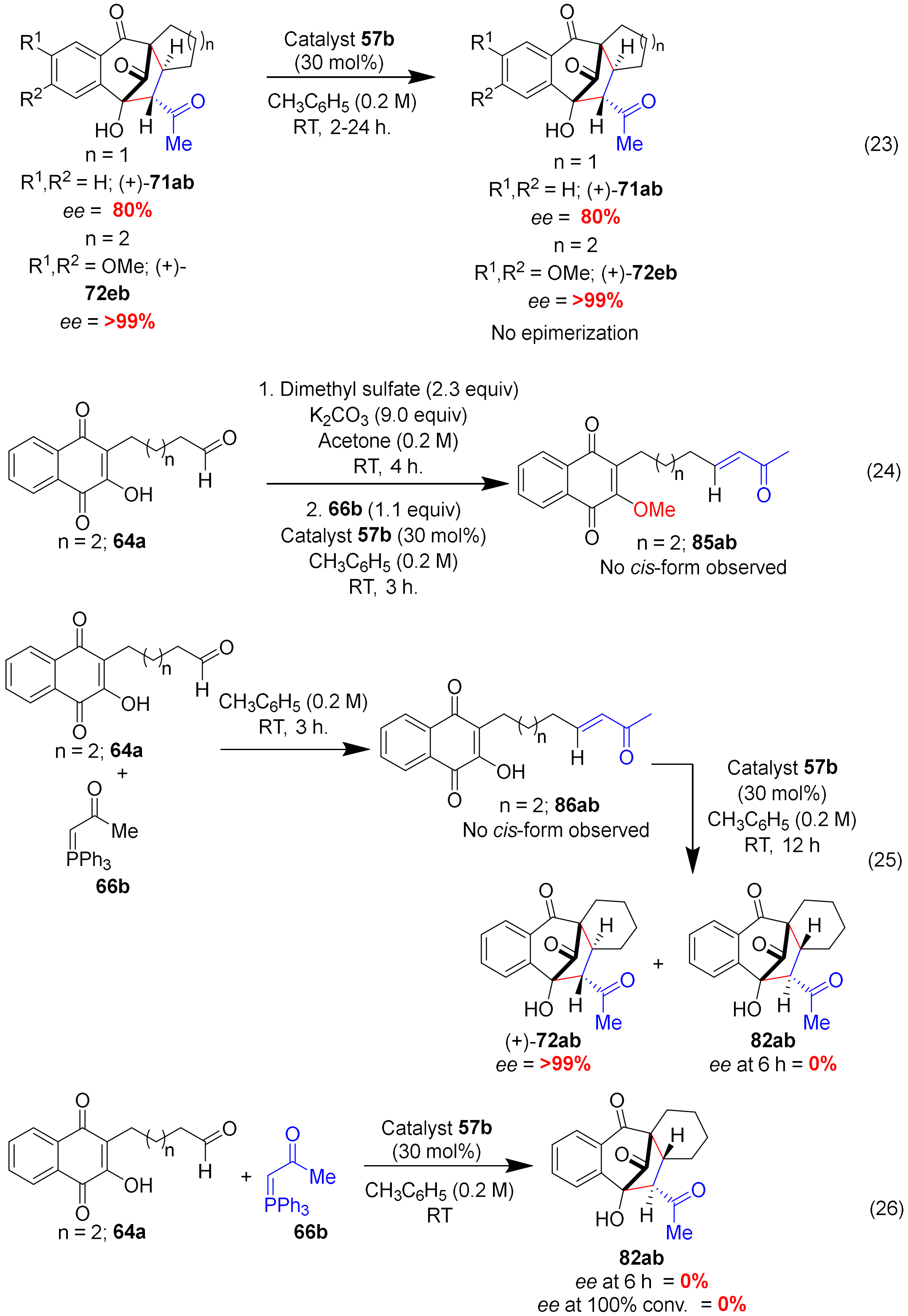


Figure 85: ^{1}H and ^{13}C spectra of the product **84ad**.

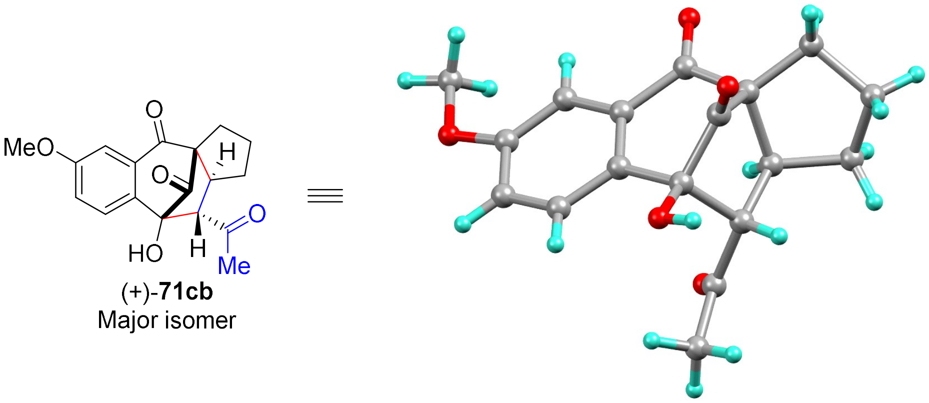


Scheme 30: Controlled experiments.

Plausibly, as the only *trans* Wittig product formed in the reaction, therefore the dr generating from *trans*-**85ab** isomer but not from the *cis*-isomer. Next, we performed reaction between 5-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal **64a** and **66b** in the absence of quinine thiourea **57b** catalyst in toluene solvent at room temperature, after 3 h of the reaction the only isomer formed in the reaction was isolated as *trans*-**86ab**, which upon treatment with quinine thiourea **57b** catalyst for 12 h resulted in (+)-**73ab** in >99% *ee* and **82ab** in the almost racemic form (Scheme 30, Eq. 25).

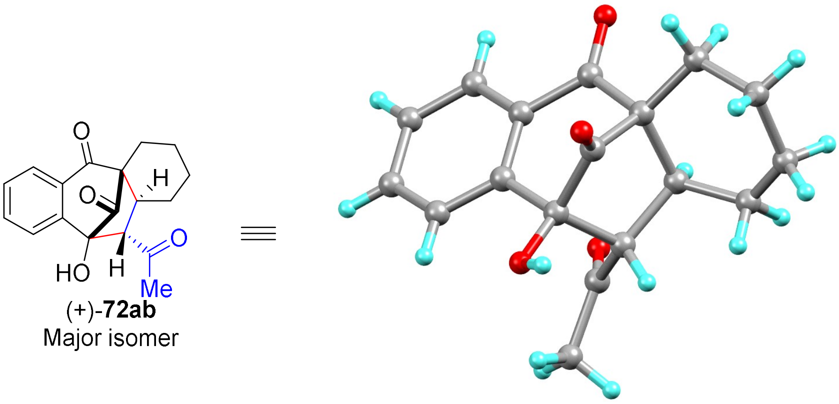
Furthermore, We then recorded the HPLC of minor isomer in two intervals (at 6 h and 100% conversion of reaction), by performing reaction between 5-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal **64a** and **66b** in the presence of quinine thiourea **57b** catalyst in toluene solvent at room temperature (Scheme 30, Eq. 26). Surprisingly, minor isomer shows the poor *ee* from the beginning of the reaction. From these investigations, the poor facial selectivity of the minor isomer is due to the no/fewer interactions between chiral thiourea and the *trans*-Wittig product (self-catalysed reaction). Herein, the self-catalysed reaction is also participating in the reaction along with the quinine thiourea catalysed reaction, which is comparably faster than the self-catalysed reaction. Therefore, the poor dr ratio is generating from the *trans*-isomer of the Wittig product with poor *ee* for the minor isomer.

We established the structure of the domino products by NMR analysis and absolute stereochemistry finally confirmed by X-ray structure analysis on (+)-**71cd**, (+)-**72ab** and **82ac** (Figures 86-88).[29]



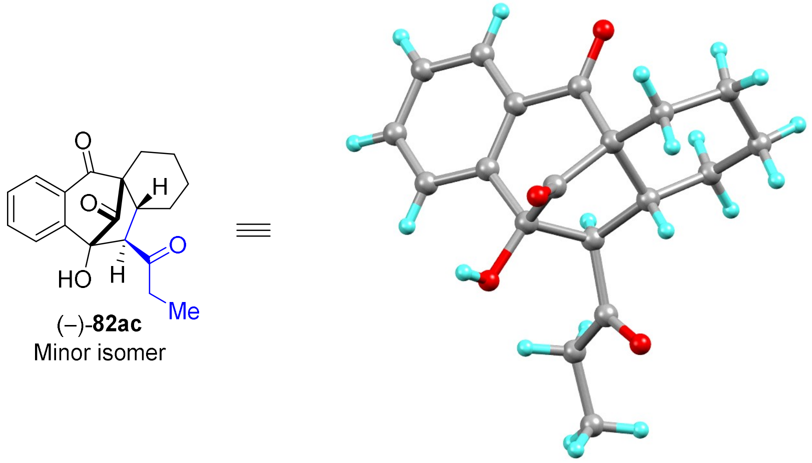
(+)-**71cb**
Major isomer

Figure 86: X-ray crystal structure of (3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-6-methoxy-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione **(71cb)**



(+)-**72ab**
Major isomer

Figure 87: X-ray crystal structure of (4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione **(72ab)**

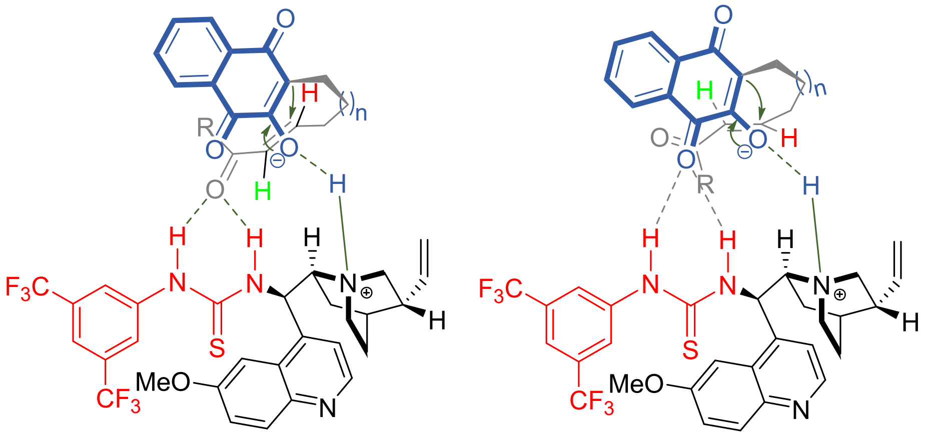


(−)-**82ac**
Minor isomer

Figure 88: X-ray crystal structure of (4a*S*,10*S*,11*R*,11a*R*)-10-hydroxy-11-propionyl-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione (**82ac**)

6.2.5 Mechanistic insights:

Furthermore, the plausible mechanism of tandem Wittig/intra-molecular Michael/intra-molecular aldol reactions was hypothesised by analysing the controlled experiments, crystal data of (−)-**71cd**, (-)-**72ab** and **82ac**. Herein, tertiary amine part of the catalyst interacts with the lawsone and the enone part interacts with the thiourea-*NH* through a double hydrogen bond. Finally, as depicted in the *pre*-**TS-1**, *Si,Si*-facial attack takes place to furnish the methanobenzo[*f*]azulenes in good yields with excellent enantio- and diastereoselectivity. Whereas the minor isomer with poor enantioselectivity generated from the no/fewer interactions of the catalyst with Wittig product in the *pre*-**TS-2** (Figure 89).



TS-1 [Favorable TS]
Synergistic activation in *pre*-**TS**
[*Si*-*Si*-*face* Approach]

TS-2 [Unfavorable TS]
Non-synergistic activation in *pre*-**TS**
[*Si*-*Re*-*face* Approach]

Figure 89: Reaction mechanism of the proposed design.

6.3 Conclusions

In conclusion, we developed a unique asymmetric tandem Wittig/intra-molecular Michael/intra-molecular aldol reactions protocol for the synthesis of pharmaceutically and biologically active methanobenzo[*f*]azulenes in excellent yields, good to excellent *ee* with moderate to excellent dr ratios. The lawsone aldehydes **63a-h**/**64a-h** are treated with different Wittig reagents **2a-c** under quinine thiourea **57b** catalysis furnishes into a huge library of functionalized methanobenzo[*f*]azulenes **71-82** through the asymmetric organocatalytic tandem reactions. The methanobenzo[*f*]azulenes are transformed into structurally important compound (-)-**84ad** in moderate yield with excellent facial selectivity. The uncertainty in the dr ratios and poor *ee* for minor isomer is explained with help of controlled experiments.

7. Experimental Section

General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS (δ = 0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses. The coupling constants J are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063-0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ = 0.71073 Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

Materials: All solvents and commercially available chemicals were used as received without further purification unless otherwise stated.

1. Organocatalytic Reductive Propargylation: Scope and Applications:

1a. (*S*)-Proline Catalysed Cascade Three-Component Reductive Propargylation (TCRP) Reactions:

For Table 1 and **2:** In an ordinary glass vial equipped with a magnetic stirring bar, to 2.0 equiv. of the 3-alkyl/arylpropiolaldehydes **33** (0.6 mmol), 1.0 equiv. of 1,3-diketones or active methylene compound **1/32** (0.3 mmol) and 1.0 equiv. of Hantzsch ester **34** (0.3 mmol, 76.0 mg) was added 1.0 mL of DCM (0.3 M), and then the catalyst (*S*)-proline **3n** (0.015 mmol, 1.73 mg, 5 mol%) was added, the resulting reaction mixture was stirred at 25 °C for the time indicated in Tables 1 and 2. The crude reaction mixture was directly loaded onto a silica gel column chromatography without aqueous workup, and pure coupling products **35** were obtained in 70–98% yield (eluent: mixture of hexanes/ethyl acetate). **For Table 3** and **4:** Reaction was performed as similar to above method and pure coupling products **35** were obtained through precipitation-filtration technique instead of column-chromatography. The crude reaction mixture was precipitated with cold 10% ethyl acetate in hexanes and washed with 10% cold ethyl acetate/hexanes (3 x 10 mL) and analytically pure coupling products **35** was obtained in 78-99% yield.

General Observations during the Recording of NMR Samples:

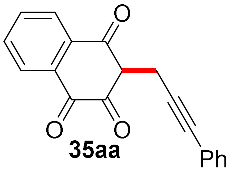
(1) Because of solubility problem of 2-propargyl-cycloalkane-1,3-diones **35** in $CDCl_3$, we have used few drops of CD_3OD or DMSO-d_6 for recording NMR spectra.

(2) Due to the keto-enol and enol-enol tautomerism of 2-propargyl-cycloalkane-1,3-diones **35**, ^{13}C NMR resulted in the poor resolution of few carbons (2 x CH_2 and

2 x C=O) even after more than 2000 scans in the solvent system of $CDCl_3$ + CD_3OD (few drops) or $CDCl_3$ + DMSO-d_6 (few drops).

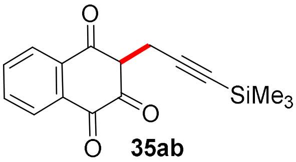
(3) In few compounds NMR spectra, even after addition of few drops of CD_3OD or DMSO-d_6 spectra has shown minor tautomeric mixture of keto-isomer along with major enol-isomer.

3-(3-Phenylprop-2-yn-1-yl)naphthalene-1,2,4(3*H*)-trione (35aa): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (1/9), and isolated as a yellow solid. Mp.: 170-172 °C. Yield: 98% (84.76 mg). IR (Neat): ν_{max} 3336, 2920, 1640, 1587, 1373, 1347, 1271, 1227, 1046, 1025, 752, 730, 686 and 579 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.17 (1H, dd, *J* = 7.6, 1.2 Hz), 8.10 (1H, td, *J* = 7.6, 1.2 Hz), 7.78 (1H, dt, *J* = 7.6, 1.2 Hz), 7.70 (1H, dt, *J* = 7.6, 1.2 Hz), 7.58 (1H, br s, OH), 7.39-7.37 (2H, m), 7.26-7.23 (3H, m), 3.75 (2H, s). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 183.3 (C, *C*=O), 181.4 (C, *C*=O), 153.3 (C, C=*C*–OH), 135.2 (CH), 133.1 (CH), 132.7 (C), 131.7 (2 x CH), 129.3 (C), 128.0 (2 x CH), 127.7 (CH), 127.0 (CH), 126.3 (CH), 123.5 (C), 118.7 (C, *C*=C–OH), 85.4 (C, acetylenic-*C*), 80.3 (C, acetylenic-*C*), 13.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{12}O_3H$ 289.0865; Found 289.0866.



35aa

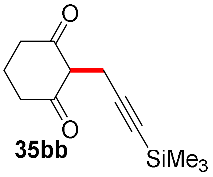
3-(3-(Trimethylsilyl)prop-2-yn-1-yl)naphthalene-1,2,4(3*H*)-trione (35ab): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (1/9), and isolated as a yellow solid. Mp.: 162-164 °C. Yield: 94% (80.19 mg). IR (Neat): ν_{max} 3365, 2957, 2176, 1644, 1588, 1372, 1343, 1272, 1225, 1047, 834, 761, 728, 672, 649



35ab

and 503 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.15 (1H, dd, *J* = 8.0, 1.0 Hz), 8.07 (1H, dd, *J* = 8.0, 1.0 Hz), 7.78 (1H, dt, *J* = 7.5, 1.5 Hz), 7.70 (1H, dt, *J* = 7.5, 1.5 Hz), 7.55 (1H, br s, OH), 3.55 (2H, s), 0.11 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 183.2 (C, *C*=O), 181.4 (C, *C*=O), 153.2 (C, C=*C*–OH), 135.1 (CH), 133.1 (CH), 132.7 (C), 129.3 (C), 127.0 (CH), 126.3 (CH), 118.4 (C, *C*=C–OH), 101.6 (C, acetylenic-*C*), 84.6 (C, acetylenic-*C*), 14.2 (CH$_2$), 0.01 (3 x CH$_3$, Si(*C*H$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{16}O_3SiNa$ 307.0766; Found 307.0766.

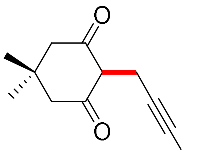
2-(3-(Trimethylsilyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as an off-white solid. Mp.: 130-132 °C. Yield: 93% (62.04 mg). IR (Neat): ν$_{max}$ 2958, 2642, 2172, 1661, 1631, 1556, 1411, 1383, 1266, 997, 841, 800, 759 and 642 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz, 12.8:1 ratio, major enol isomer): δ 8.53 (1H, s, O-*H*), 3.32 (2H, s), 2.48 (2H, t, *J* = 6.0 Hz), 2.36 (2H, t, *J* = 6.5 Hz), 1.95 (2H, quintet, *J* = 6.5 Hz), 0.17 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135, 6.25:1 ratio, major enol isomer): δ 197.0 (C, *C*=O), 173.5 (C, C=*C*-OH), 108.9 (C, *C*=C-OH), 104.5 (C, acetylenic-*C*), 103.7 (C, acetylenic-*C*), 36.4 (CH$_2$), 29.4 (CH$_2$), 20.4 (CH$_2$), 14.0 (CH$_2$), -0.3 (3 x CH$_3$, Si(*C*H$_3$)$_3$). ^{1}H NMR (CDCl$_3$, 500 MHz, 12.8:1 ratio, minor diketo isomer): δ 3.70 (1H, t, *J* = 6.0 Hz, C*H*), 2.74 (2H, d, *J* = 6.0 Hz), 2.72-2.69 (1H, m), 2.65-2.59 (2H, m), 2.22-2.17 (1H, m), 1.83-1.76 (2H, m), 0.10 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135, 6.25:1 ratio, minor diketo isomer): δ 202.4 (2 x C, *C*=O), 90.2 (C, acetylenic-*C*), 85.0 (C, acetylenic-*C*), 66.7 (CH), 39.9 (2 x CH$_2$), 18.0 (CH$_2$),



35bb

13.6 (CH_2), 0.02 (3 x CH_3, Si(*C*H_3)$_3$). ^{1}H NMR ($CDCl_3$+CD_3OD (three drops), 500 MHz, only major enol isomer): δ 3.25 (2H, br s), 2.39 (4H, t, *J* = 6.5 Hz), 1.92 (2H, quintet, *J* = 6.5 Hz), 0.12 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$+CD_3OD (three drops), DEPT-135, only major enol isomer): δ 109.6 (C, *C*=C–OH), 104.2 (C, acetylenic-*C*), 87.5 (C, acetylenic-*C*, broad peak), 33.2 (2 x CH_2, broad peak), 20.3 (CH_2), 13.5 (CH_2), -0.26 (3 x CH_3, Si(*C*H_3)$_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{18}O_2SiH$ 223.1154; Found 223.1157.

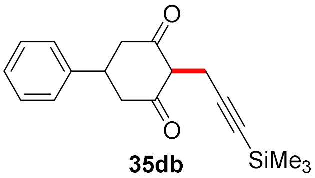
5,5-Dimethyl-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35cb):[14a]



35cb

The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 131-132 °C. Yield: 96% (72.11 mg). IR (Neat): ν_{max} 2957, 2922, 2854, 2178, 1551, 1332, 1306, 1249, 1201, 1149, 1042, 1015, 840, 757, 604 and 482 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-D_6 (three drops), 400 MHz): δ 2.95 (2H, br s), 2.03 (4H, br s), 0.79 (6H, s, 2 x C*H*$_3$), -0.15 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$+DMSO-D_6 (three drops), DEPT-135) δ 109.1 (C, *C*=C–OH), 105.4 (C, acetylenic-*C*), 81.7 (C, acetylenic-*C*), 31.31 (C), 27.6 (2 x CH_3), 12.2 (CH_2), -0.34 (3 x CH_3, Si(*C*H_3)$_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{22}O_2SiH$ 251.1467; Found 251.1467.

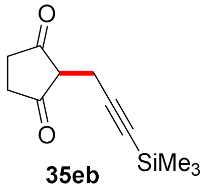
5-Phenyl-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35db): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (1/9), and isolated as a yellow solid. Mp.: 143-145 °C. Yield:



35db

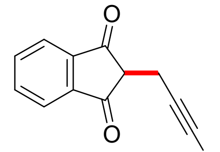
89% (79.90 mg). IR (Neat): ν_{max} 2953, 2895, 2175, 1564, 1385, 1343, 1248, 1214, 1039, 1007, 842, 753, 695, 561 and 474 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.53 (1H, s, O-*H*), 7.35 (2H, tt, *J* = 7.0, 1.5 Hz), 7.27 (1H, tt, *J* = 7.0, 1.5 Hz), 7.24 (2H, br d, *J* = 7.0 Hz), 3.45 (1H, dd, *J* = 20.0, 1.0 Hz), 3.37-3.32 (1H, m), 3.33 (1H, dd, *J* = 16.0, 1.0 Hz), 2.81-2.68 (3H, m), 2.67-2.57 (1H, m), 0.19 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 195.9 (C, *C*=O), 172.4 (C, C=*C*–OH), 142.5 (C), 128.8 (2 x CH), 127.0 (CH), 126.6 (2 x CH), 108.5 (C, *C*=C–OH), 103.4 (C, acetylenic-*C*), 90.8 (C, acetylenic-*C*), 43.4 (CH$_2$), 38.4 (CH), 36.9 (CH$_2$), 14.3 (CH$_2$), -0.3 (3 x CH$_3$, Si(*C*H$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{18}H_{22}O_2SiNa$ 321.1287; Found 321.1287.

2-(3-(Trimethylsilyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35eb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (4/6), and isolated as a white solid. Mp.: 154-156 °C. Yield: 93% (58.12 mg). IR (Neat): ν_{max} 2955, 2927, 2895, 2180, 1568, 1374, 1291, 1249, 1192, 1037, 1006, 993, 836, 755, 671 and 586 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.14 (2H, s), 2.49 (4H, br s), 0.18 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 110.3 (C, *C*=C–OH), 102.6 (C, acetylenic-*C*), 89.5 (C, acetylenic-*C*), 29.7 (2 x CH$_2$, broad peak), 13.9 (CH$_2$), -0.31 (3 x CH$_3$, Si(*C*H$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{11}H_{16}O_2SiH$ 209.0998; Found 209.0998.



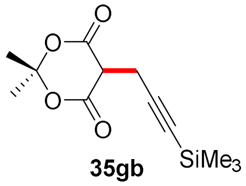
35eb

2-(3-(Trimethylsilyl)prop-2-yn-1-yl)-1*H*-indene-1,3(2*H*)-dione (35fb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (1/9), and isolated as a semi solid. Yield: 80% (61.53 mg). IR (Neat): ν_{max} 2960, 2178, 1747, 1710, 1600, 1348, 1329, 1249, 1027, 840, 757, 698 and 638 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (2H, dd, *J* = 6.0, 3.5 Hz), 7.86 (2H, dd, *J* = 6.0, 3.0 Hz), 3.09 (1H, t, *J* = 5.0 Hz), 2.94 (1H, d, *J* = 5.0 Hz), -0.18 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 199.2 (2 x C, *C*=O), 143.1 (2 x C), 135.7 (2 x CH), 123.1 (2 x CH), 101.0 (C, acetylenic-*C*), 88.0 (C, acetylenic-*C*), 51.7 (CH), 17.9 (CH_2), -0.5 (3 x CH_3, Si(*C*H$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{16}O_2SiH$ 257.0998; Found 257.0999.

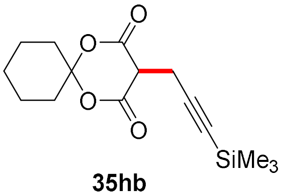


35fb

2,2-Dimethyl-5-(3-(trimethylsilyl)prop-2-yn-1-yl)-1,3-dioxane-4,6-dione (35gb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (1.4/8.6), and isolated as a white solid. Mp.: 72-74 °C. Yield: 95% (72.49 mg). IR (Neat): ν_{max} 2960, 2180, 1747, 1384, 1342, 1291, 1249, 1199, 1073, 1013, 942, 838, 757 and 637 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.65 (1H, t, *J* = 5.0 Hz), 3.06 (2H, d, *J* = 4.5 Hz), 1.80 (6H, s, 2 x C*H*$_3$), 0.13 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 164.2 (2 x C, O-*C*=O), 105.3 (C, O-*C*-O), 101.1 (C, acetylenic-*C*), 87.6 (C, acetylenic-*C*), 46.0 (CH), 28.7 (CH_3), 27.2 (CH_3), 18.1 (CH_2), -0.16 (3 x CH_3, Si(*C*H$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{18}O_4SiH$ 255.1053; Found 255.1055.

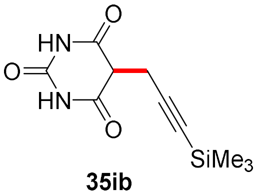


35gb



35hb

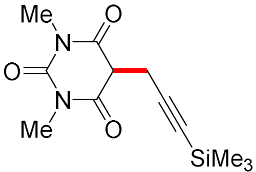
3-(3-(Trimethylsilyl)prop-2-yn-1-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (35hb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (0.7/9.3), and isolated as a semi solid; Yield: 94% (83.03 mg). IR (Neat): ν_{max} 2958, 2178, 1714, 1412, 1249, 1016, 840, 760, 700 and 640 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.66 (1H, t, J = 5.0 Hz), 3.04 (2H, d, J = 5.0 Hz), 1.98 (4H, t, J = 6.5 Hz), 1.77 (2H, quintet, J = 6.5 Hz), 1.70 (2H, quintet, J = 6.5 Hz), 1.50 (2H, quintet, J = 6.5 Hz), 0.11 (9H, s, Si(CH_3)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 164.3 (2 x C, O-*C*=O), 106.2 (C, O-*C*-O), 101.2 (C, acetylenic-*C*), 87.6 (C, acetylenic-*C*), 46.3 (CH), 37.3 (CH$_2$), 36.3 (CH$_2$), 24.0 (CH$_2$), 22.5 (CH$_2$), 21.8 (CH$_2$), 18.2 (CH$_2$), -0.15 (3 x CH$_3$, Si(CH$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{22}O_4SiH$ 295.1366; Found 295.1365.



35ib

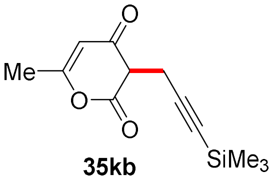
5-(3-(Trimethylsilyl)prop-2-yn-1-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (35ib): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (4/6), and isolated as an off-white solid. Mp.: 194-195 °C. Yield: 84% (60.05 mg). IR (Neat): ν_{max} 3224, 2958, 2184, 1736, 1699, 1681, 1441, 1358, 1301, 1222, 1203, 982, 838, 758, 638, 565, 509, 468 and 415 cm^{-1}. ^{1}H NMR (CDCl$_3$+CD$_3$OD, 500 MHz): δ 2.89 (2H, s), -0.023 (9H, s, Si(CH_3)$_3$). ^{13}C NMR (CDCl$_3$+CD$_3$OD, DEPT-135): δ 169.0 (2 x C, N–*C*=O), 150.3 (C, N–CO–N), 99.5 (C, acetylenic-*C*), 88.8 (C, acetylenic-*C*), 21.2 (CH$_2$), -0.76 (3 x CH$_3$, Si(CH$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{10}H_{14}N_2O_3SiH$ 239.0852; Found 239.0852.

1,3-Dimethyl-5-(3-(trimethylsilyl)prop-2-yn-1-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (35jb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (1.4/8.6), and isolated as a white semi solid. Yield: 87% (69.52 mg). IR (Neat): ν_{max} 2960, 2177, 1671, 1445, 1424, 1379, 1291, 1249, 1115, 1039, 838, 754, 701, 637, 559 and 462 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 3.55 (1H, t, *J* = 4.4 Hz), 3.33 (6H, s, 2 x N-C*H*$_3$), 3.03 (2H, d, *J* = 4.4 Hz), 0.07 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 167.7 (2 x C, N–*C*=O), 151.5 (C, N–CO–N), 99.0 (C, acetylenic-*C*), 89.8 (C, acetylenic-*C*), 48.1 (CH), 28.4 (2 x CH$_3$, 2 x N-*C*H$_3$), 24.0 (CH$_2$), -0.3 (3 x CH$_3$, Si(*C*H$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{18}N_2O_3SiH$ 267.1165; Found 267.1165.

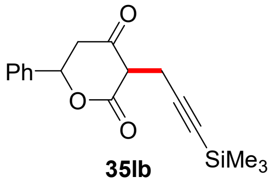


35jb

6-Methyl-3-(3-(trimethylsilyl)prop-2-yn-1-yl)-2*H*-pyran-2,4(3*H*)-dione (35kb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (3/7), and isolated as a yellow solid. Mp.: 166-167 °C. Yield: 70% (49.63 mg). IR (Neat): ν_{max} 2960, 2636, 2172, 1631, 1554, 1412, 1382, 1266, 1251, 1123, 994, 841, 798, 760, 642 and 450 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.81 (1H, s, olefinic-*H*), 3.48 (2H, s), 2.20 (3H, s, C*H*$_3$), 0.19 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.4 (C, C=O), 164.4 (C, O=*C*–O), 160.8 (C, C=*C*–O), 102.2 (C, *C*=C–OH), 101.0 (CH), 95.6 (C, acetylenic-*C*), 91.4 (C, acetylenic-*C*), 19.7 (CH$_3$), 15.9 (CH$_2$), -0.4 (3 x CH$_3$, Si(*C*H$_3$)$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{16}O_3SiH$ 237.0947; Found 237.0948.



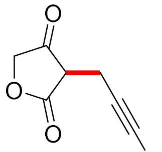
35kb



35lb

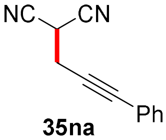
6-Phenyl-3-(3-(trimethylsilyl)prop-2-yn-1-yl)dihydro-2*H*-pyran-2,4(3*H*)-dione (35lb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (1.4/8.6), and isolated as a pale yellow semi solid; Yield: 80% (72.10 mg). IR (Neat): ν_{max} 2957, 2922, 2174, 1644, 1388, 1248, 1119, 1017, 840, 757 and 698 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz, 2:1, major enol isomer): δ 8.73 (1H, br s), 7.43-7.34 (5H, m), 5.42 (1H, dd, *J* = 12.8, 4.0 Hz), 3.51 (1H, dd, *J* = 19.2, 1.6 Hz), 3.32 (1H, dd, *J* = 20.0, 1.6 Hz), 2.88 (1H, dd, *J* = 17.6, 4.0 Hz), 2.61 (1H, dd, *J* = 17.6, 4.0 Hz), 0.20 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135, 2:1, major enol isomer): δ 167.2 (C, C=*C*-OH), 166.7 (C, O-*C*=O), 138.0 (C), 128.9 (CH), 128.7 (2 x CH), 126.0 (2 x CH), 103.0 (C, *C*=C-OH), 102.8 (C, acetylenic-*C*), 97.4 (C, acetylenic-*C*), 76.4 (CH), 35.5 (CH$_2$), 16.3 (CH$_2$), -0.37 (3 x CH$_3$, Si(*C*H$_3$)$_3$). ^{1}H NMR (CDCl$_3$, 400 MHz, 2:1, minor keto isomer): δ 7.43-734 (5H, m), 5.79 (1H, dd, *J* = 12.0, 2.8 Hz), 3.89 (1H, t, *J* = 5.6 Hz), 3.05-2.94 (2H, m), 2.91-2.77 (2H, m), 0.14 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135, 2:1, minor keto isomer): δ 198.4 (C, *C*=O), 166.8 (C, O-*C*=O), 136.2 (C), 129.3 (CH), 128.7 (2 x CH), 126.0 (2 x CH), 91.3 (C, acetylenic-*C*), 86.0 (C, acetylenic-*C*), 75.6 (CH), 56.6 (CH), 45.4 (CH$_2$), 14.9 (CH$_2$), -0.02 (3 x CH$_3$, Si(*C*H$_3$)$_3$). ^{1}H NMR (CDCl$_3$+CD$_3$OD (few drops), 500 MHz, major enol isomer): δ 7.42-7.33 (5H, m), 5.40 (1H, dd, *J* = 12.5, 4.0 Hz), 3.32 (2H, ABq, *J* = 18.0 Hz), 2.86 (1H, dd, *J* = 17.0, 12.0 Hz), 2.65 (1H, dd, *J* = 17.0, 3.5 Hz), 0.15 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR (CDCl$_3$+CD$_3$OD (few drops), DEPT-135, major enol isomer): δ 167.9 (C, C=*C*-OH), 166.5 (C, O-*C*=O), 138.2 (C), 128.5 (2 x CH), 128.4 (CH), 125.8 (2 x CH), 103.9 (C, *C*=C-OH), 98.9 (C, acetylenic-*C*), 85.2 (C, acetylenic-*C*), 76.2 (CH), 35.2 (CH_2), 14.7 (CH_2), -0.27 (3 x CH_3, Si(CH_3)$_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{20}O_3SiNa$ 323.1079; Found 323.1077.

3-(3-(Trimethylsilyl)prop-2-yn-1-yl)furan-2,4(3*H*,5*H*)-dione (35mb): The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a white semi solid. Yield: 95% (59.93 mg). IR (Neat): ν_{max} 2958, 2182, 1723, 1647, 1402, 1358, 1249, 1096, 1032, 1012, 838, 758, 701 and 644 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.61 (2H, t, *J* = 1.6 Hz), 3.22 (2H, t, *J* = 1.6 Hz), 0.21 (9H, s, Si(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 172.6 (C, O-*C*=O), 101.4 (C, *C*=C-OH), 94.9 (C, acetylenic-*C*), 77.0 (C, acetylenic-*C*), 66.9 (CH_2), 14.7 (CH_2), -0.36 (3 x CH_3, Si(CH_3)$_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{14}O_3SiH$ 211.0790; Found 211.0790.



35mb

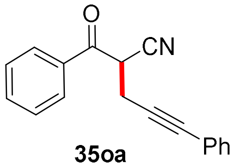
2-(3-Phenylprop-2-yn-1-yl)malononitrile (35na):[9,14b-c] The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (0.8/9.2), and isolated as a pale yellow semi solid. Yield: 97% (52.44 mg). IR (Neat): ν_{max} 3035, 2918, 2260, 2242, 1598, 1490, 1442, 1337, 1070, 1032, 919, 755, 690 and 529 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.45 (2H, m), 7.36-7.31 (3H, m), 3.99 (1H, t, *J* = 7.0 Hz), 3.18 (2H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 131.9 (2 x CH), 129.1 (CH), 128.4 (2 x CH), 121.5 (C), 111.5 (2 x C, *C*≡N), 86.5 (C, acetylenic-*C*), 80.0 (C, acetylenic-*C*), 23.2



35na

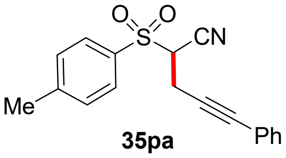
(CH), 22.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_8N_2H$ 181.0766; Found 181.0767.

2-Benzoyl-5-phenylpent-4-ynenitrile (35oa):[9] The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (0.5/9.5), and isolated as a pale yellow semi solid; Yield: 80% (62.23 mg). IR (Neat): ν_{max} 3061, 2924, 2853, 2245, 1695, 1596, 1490, 1336, 1268, 1222, 953, 757, 691 and 529 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.04 (2H, td, *J* = 8.0, 1.6 Hz), 7.68 (1H, tt, *J* = 7.2, 1.2 Hz), 7.55 (2H, tt, *J* = 8.0, 1.6 Hz), 7.37 (2H, td, *J* = 6.5, 2.0 Hz), 7.31-7.26 (3H, m), 4.60 (1H, t, *J* = 7.2 Hz), 3.15 (2H, d, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 188.8 (C, *C*=O), 134.8 (CH), 133.9 (C), 131.7 (2 x CH), 129.1 (2 x CH), 128.9 (2 x CH), 128.4 (CH), 128.2 (2 x CH), 122.4 (C), 116.3 (C, *C*≡N), 84.4 (C, acetylenic-*C*), 83.4 (C, acetylenic-*C*), 39.0 (CH), 20.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}NOH$ 260.1075; Found 260.1075.



35oa

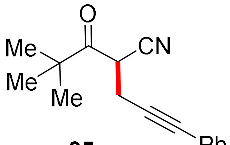
5-Phenyl-2-tosylpent-4-ynenitrile (35pa):[9] The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (0.4/9.6), and isolated as a pale yellow semi solid. Yield: 73% (67.75 mg). IR (Neat): ν_{max} 3055, 2918, 2850, 2253, 1596, 1490, 1335, 1154, 1139, 1085, 906, 814, 727, 690, 659 and 587 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.92 (2H, td, *J* = 8.5, 1.5 Hz), 7.40 (2H, td, *J* = 8.0, 1.5 Hz), 7.33 (2H, td, *J* = 6.5, 1.5 Hz), 7.30-7.25 (3H, m), 4.20 (1H, dd, *J* = 9.5, 5.0 Hz), 3.29 (1H, dd, *J* = 17.0, 5.0 Hz), 3.09 (1H, dd, *J* = 17.0, 9.5 Hz), 2.43 (3H, s,



35pa

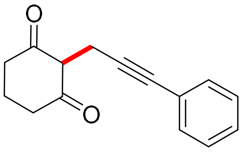
Ar-C*H*$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 147.1 (C), 131.9 (C), 131.7 (2 x CH), 130.3 (2 x CH), 129.8 (2 x CH), 128.6 (CH), 128.2 (2 x CH), 121.6 (C), 113.2 (C, *C*≡N), 85.2 (C, acetylenic-*C*), 80.6 (C, acetylenic-*C*), 56.4 (CH), 21.7 (CH$_3$), 19.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{15}NO_2SH$ 310.0902; Found 310.0905.

5-Phenyl-2-pivaloylpent-4-ynenitrile (35qa):[9] The title compound was prepared following procedure **1a**, purified by column chromatography using EtOAc/hexanes (0.2/9.8), and isolated as a pale yellow semi solid; Yield: 75% (53.84 mg). IR (Neat): ν$_{max}$ 2970, 2920, 2850, 2247, 2189, 1721, 1661, 1597, 1475, 1369, 1065, 907, 757, 729 and 690 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.37 (2H, dd, *J* = 8.0, 2.5 Hz), 7.31-7.26 (3H, m), 4.11 (1H, t, *J* = 7.5 Hz), 3.01 (2H, dABq, *J* = 17.0, 8.0 Hz), 1.28 (9H, s, 3 x C*H*$_3$). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 203.7 (C, *C*=O), 131.6 (2 x CH), 128.4 (CH), 128.3 (2 x CH), 122.4 (C), 116.1 (C, *C*≡N), 83.8 (C, acetylenic-*C*), 83.78 (C, acetylenic-*C*), 45.5 (C), 36.3 (CH), 25.9 (3 x CH$_3$), 20.8 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{17}NONa$ 262.1208; Found 262.1208.



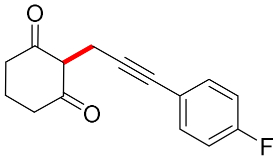
35qa

2-(3-Phenylprop-2-yn-1-yl)cyclohexane-1,3-dione (35ba): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a white solid. Mp.: 163-165 °C. Yield: 85% (57.70 mg). IR (Neat): ν$_{max}$ 2954, 2890, 1565, 1357, 1267, 1187, 1140, 1067, 1007, 907, 856, 748, 687, 544 and 491 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-*d*$_6$, 400 MHz): δ 7.29 (2H, br s), 7.16 (3H, br s), 3.34 (2H, s), 2.37-2.36 (4H, m), 1.89-1.88 (2H, m). ^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$, DEPT-135): δ 131.4 (2 x



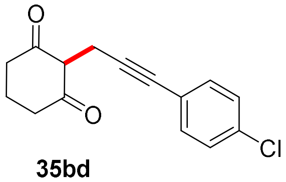
35ba

CH), 127.9 (2 x CH), 127.3 (CH), 123.7 (C), 111.3 (C, *C*=C–OH), 88.2 (C, acetylenic-*C*), 79.2 (C, acetylenic-*C*), 20.4 (CH_2), 12.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{14}O_2Na$ 249.0891; Found 249.0891.



35bc

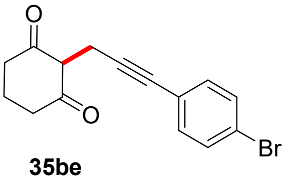
2-(3-(4-Fluorophenyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bc): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a yellow solid. Mp.: 176-178 °C. Yield: 85% (62.28 mg). IR (Neat): ν_{max} 2958, 2904, 1561, 1504, 1384, 1353, 1271, 1215, 1187, 1140, 1070, 1008, 922, 832, 814, 545 and 491 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-D_6, 400 MHz): δ 7.34 (2H, dd, *J* = 8.4, 5.2 Hz), 6.95 (2H, dd, *J* = 8.4, 5.2 Hz), 3.35 (4H, m), 2.47 (2H, m), 2.00 (2H, quintet, *J* = 6.4 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.5 (C, d, *J* = 246.0 Hz, *C*-F), 132.8 (2 x CH, d, *J* = 8.0 Hz), 119.9 (C, d, *J* = 4.0 Hz), 114.5 (2 x CH, d, *J* = 22.0 Hz), 111.1 (C, *C*=C–OH), 87.8 (C, acetylenic-*C*), 77.2 (C, acetylenic-*C*), 20.0 (CH_2), 11.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{13}FO_2H$ 245.0978; Found 245.0979.



35bd

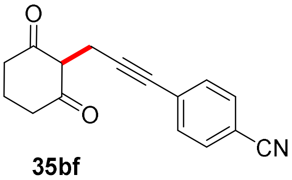
2-(3-(4-Chlorophenyl)prop-2-yn-1-yl)cyclohexane-1,3-dionee (35bd): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 184-186 °C. Yield: 95% (74.30 mg). IR (Neat): ν_{max} 3020, 2958, 2356, 1563, 1488, 1382, 1355, 1272, 1215, 1188, 1070, 1007, 751, 547 and 488 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz): δ 7.29 (2H, dd, *J* = 10.4, 2.0 Hz), 7.18 (2H, dd, *J* = 8.4, 1.6 Hz), 3.36 (2H, s), 2.42 (4H, t, *J* = 6.0 Hz), 1.95 (2H, quintet, *J* = 6.4 Hz). ^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$, DEPT-135) δ 133.1 (C), 132.7 (2 x CH), 128.1 (2 x CH), 122.4 (C), 111.2 (C, *C*=C–OH), 89.5 (C, acetylenic-*C*), 77.3 (C, acetylenic-*C*), 20.4 (CH$_2$), 12.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{13}ClO_2H$ 261.0682; Found 261.0681.

2-(3-(4-Bromophenyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35be): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 166-168 °C. Yield: 90% (82.39 mg). IR (Neat): ν$_{max}$ 2951, 1563, 1354, 1272, 1217, 1187, 1101, 1007, 817, 546 and 483 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-*d*$_6$, 500 MHz): δ 7.33 (2H, td, *J* = 6.5, 2.0 Hz), 7.19 (2H, td, *J* = 8.5, 1.5 Hz), 3.36 (2H, s), 2.46 (2H, br s), 2.35 (2H, br s), 1.95 (2H, quintet, *J* = 6.5 Hz). ^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$, DEPT-135): δ 131.7 (2 x CH), 129.9 (2 x CH), 122.0 (C), 119.7 (C), 109.4 (C, *C*=C-OH), 90.0 (C, acetylenic-*C*), 75.4 (C, acetylenic-*C*), 19.3 (CH$_2$), 10.9 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{15}H_{13}BrO_2Na$ 326.9997; Found 326.9997.



35be

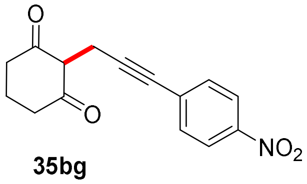
4-(3-(2,6-Dioxocyclohexyl)prop-1-yn-1-yl)benzonitrile (35bf): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 179-181 °C. Yield: 95% (71.61 mg). IR (Neat): ν$_{max}$ 3432, 2362, 2341, 1716, 1599, 1509, 1462, 1286, 1220, 1095, 998 and 771 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-*d*$_6$, 500 MHz): δ 10.70 (1H, br s, O-*H*), 7.60 (2H, br d, *J* = 7.5 Hz), 7.45 (2H, br d, *J* = 7.5 Hz), 3.35 (2H, s), 2.53 (2H, br s), 2.31 (2H, br



35bf

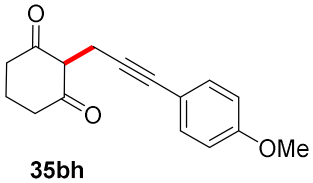
s), 1.94 (2H, quintet, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 196.0 (C, *C*=O, br s), 172.7 (C, C=*C*-OH, br s), 131.6 (2 x CH), 131.4 (2 x CH), 128.8 (C), 117.9 (C), 109.83 (C, *C*=C-OH), 109.78 (C, *C*≡N), 94.8 (C, acetylenic-*C*), 76.3 (C, acetylenic-*C*), 35.8 (CH_2, br s), 28.8 (CH_2, br s), 20.1 (CH_2), 11.9 (CH_2). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{13}NO_2H$ 252.1025; Found 252.1025.

2-(3-(4-Nitrophenyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bg): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 170-172 °C. Yield: 78% (63.47 mg). IR (Neat): ν_{max} 3019, 1557, 1515, 1344, 1275, 1214, 1010, 858, 748, 668 and 486 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 8.13 (2H, br d, *J* = 8.0 Hz), 7.52 (2H, br d, *J* = 8.0 Hz), 3.36 (2H, s), 2.42 (4H, br s), 1.94 (2H, br quintet, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 144.6 (C), 130.6 (2 x CH), 129.6 (C), 121.8 (2 x CH), 108.4 (C, *C*=C–OH), 94.8 (C, acetylenic-*C*), 75.0 (C, acetylenic-*C*), 18.9 (CH_2), 10.8 (CH_2). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{13}NO_4H$ 272.0923; Found 272.0923.



35bg

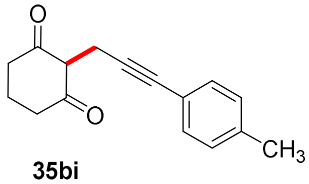
2-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bh): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 142-144 °C. Yield: 90% (69.20 mg). IR (Neat): ν_{max} 2950, 2634, 2360, 1604, 1562, 1358, 1268, 1244, 1188, 1027, 837, 558 and 501 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 7.27 (2H, br d, *J* = 8.8 Hz),



35bh

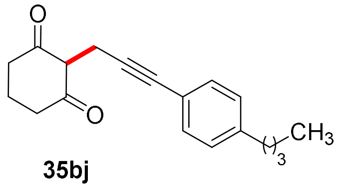
6.77 (2H, br d, J = 8.4 Hz), 3.78 (3H, s, OCH_3), 3.35 (2H, s), 2.43 (4H, br s), 1.95 (2H, quintet, J = 6.4 Hz). ^{13}C NMR (CDCl$_3$+DMSO-d_6, DEPT-135): δ 157.6 (C, *C*–OMe), 131.6 (2 x CH), 115.2 (C), 112.6 (2 x CH), 110.2 (C, *C*=C-OH), 86.9 (C, acetylenic-*C*), 77.3 (C, acetylenic-*C*), 54.0 (CH$_3$, O*C*H$_3$), 19.5 (CH$_2$), 11.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{16}O_3Na$ 279.0997; Found 279.0997.

2-(3-(*p*-Tolyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bi): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 176-178 °C. Yield: 90% (64.88 mg). IR (Neat): ν_{max} 3019, 1565, 1358, 1269, 1214, 1189, 1007, 815, 746, 668 and 489 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-d_6, 500 MHz): δ 10.31 (1H, br s, OH), 7.22 (2H, br d, J = 7.0 Hz), 7.04 (2H, br d, J = 7.0 Hz), 3.35 (2H, s), 2.44 (4H, br s), 2.30 (3H, s, Ar-CH_3), 1.96 (2H, br s). ^{13}C NMR (CDCl$_3$+DMSO-d_6, DEPT-135): δ 136.3 (C), 130.6 (2 x CH), 128.0 (2 x CH), 120.4 (C), 110.6 (C, *C*=C-OH), 88.0 (C, acetylenic-*C*), 77.0 (C, acetylenic-*C*), 20.5 (CH$_3$), 19.8 (CH$_2$), 11.5 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{16}O_2H$ 241.1229; Found 241.1229.



35bi

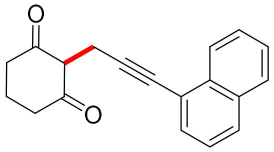
2-(3-(4-Butylphenyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bj): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 134-136 °C. Yield: 85% (72.0 mg). IR (Neat): ν_{max} 2952, 2929, 1567, 1365, 1267, 1189, 1067, 1009, 900, 822, 757, 596, 545 and 476 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-d_6, 500 MHz): δ 7.10 (1H, d, J



35bj

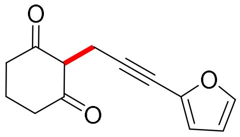
= 8.0 Hz), 7.07 (1H, d, *J* = 8.0 Hz), 6.89 (1H, d, *J* = 8.0 Hz), 6.86 (1H, d, *J* = 8.0 Hz), 3.24 (2H, s), 2.39 (2H, quintet, *J* = 7.5 Hz), 2.27 (4H, br s), 1.79 (2H, m), 1.43-1.34 (2H, m), 1.16 (2H, m), 0.74 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135) δ 141.8 (C), 131.1 (2 x CH), 127.7 (2 x CH), 120.9 (C), 111.1 (C, *C*=C–OH), 88.1 (C, acetylenic-*C*), 78.2 (C, acetylenic-*C*), 35.0 (CH_2), 33.0 (CH_2), 21.8 (CH_2), 20.2 (CH_2), 13.5 (CH_3), 12.0 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{22}O_2H$ 283.1698; Found 283.1697.

2-(3-(Naphthalen-1-yl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bk): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 176-178 °C. Yield: 95% (78.75 mg). IR (Neat): ν_{max} 3046, 2953, 2676, 1567, 1363, 1263, 1188, 1068, 1008, 794, 767, 561, 544 and 481 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 10.22 (1H, s, OH), 8.33 (1H, dd, *J* = 8.4, 2.8 Hz), 7.79 (1H, dd, *J* = 8.0, 2.0 Hz), 7.73 (1H, dd, *J* = 8.0, 2.4 Hz), 7.56 (1H, dd, *J* = 6.8, 3.2 Hz), 7.54-7.42 (2H, m), 7.36 (1H, dt, *J* = 8.4, 4.0 Hz), 3.56 (2H, s), 2.57 (2H, br s), 2.39 (2H, br s), 1.98 (2H, m). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135) δ 196.8 (C, *C*=O), 172.6 (C, C=*C*-OH), 133.1 (C), 132.6 (C), 129.3 (CH), 127.6 (CH), 127.2 (CH), 126.1 (CH), 125.9 (CH), 125.7 (CH), 124.7 (CH), 121.5 (C), 111.1 (C, *C*=C-OH), 94.4 (C, acetylenic-*C*), 75.9 (C, acetylenic-*C*), 36.0 (CH_2), 29.2 (CH_2), 20.3 (CH_2), 12.2 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}O_2H$ 277.1229; Found 277.1228.

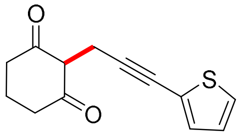


35bk

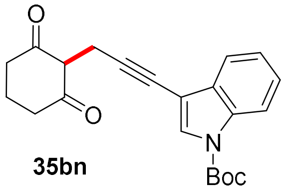
2-(3-(Furan-2-yl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bl): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 156-158 °C. Yield: 90% (58.38 mg). IR (Neat): ν_{max} 2949, 2367, 2330, 1570, 1362, 1267, 1187, 1066, 1007, 901, 733, 597, 545, 482 and 443 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-d_6, 500 MHz): δ 10.34 (1H, br s, OH), 7.26 (1H, s), 6.40 (1H, d, J = 3.5 Hz), 6.29 (1H, d, J = 2.0 Hz), 3.37 (2H, s), 2.49 (2H, br s), 2.32 (2H, m), 1.92 (2H, quintet, J = 6.0 Hz). ^{13}C NMR (CDCl$_3$+DMSO-d_6, DEPT-135): δ 196.4 (C, *C*=O), 172.7 (C, C=*C*-OH), 141.7 (CH), 137.1 (C), 112.9 (CH), 110.0 (CH), 109.99 (C, *C*=C–OH), 93.3 (C, acetylenic-*C*), 67.9 (C, acetylenic-*C*), 35.7 (CH$_2$), 28.9 (CH$_2$), 19.9 (CH$_2$), 11.7 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{13}$H$_{12}$O$_3$H 217.0865; Found 217.0865.


35bl

2-(3-(Thiophen-2-yl)prop-2-yn-1-yl)cyclohexane-1,3-dione (35bm): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 146-148 °C. Yield: 88% (61.32 mg). IR (Neat): ν_{max} 2949, 2660, 1567, 1363, 1266, 1186, 1140, 1066, 1008, 753, 698, 544 and 482 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-d_6, 500 MHz): δ 10.22 (1H, br s, OH), 7.13 (1H, dd, J = 5.5, 1.0 Hz), 7.07 (1H, dd, J = 3.5, 0.5 Hz), 6.90 (1H, dd, J = 5.0, 3.5 Hz), 3.41 (2H, s), 2.44 (4H, br s), 1.96 (2H, quintet, J = 6.5 Hz). ^{13}C NMR (CDCl$_3$+DMSO-d_6, DEPT-135): δ 130.4 (CH), 126.2 (CH), 125.1 (CH), 124.0 (C), 110.6 (C, *C*=C–OH), 93.2 (C,


35bm

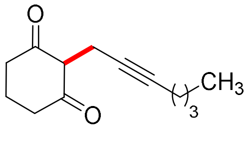
acetylenic-*C*), 70.9 (C, acetylenic-*C*), 20.2 (CH_2), 12.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{12}O_2SH$ 233.0636; Found 233.0632.



35bn

***tert*-Butyl 3-(3-(2,6-dioxocyclohexyl)prop-1-yn-1-yl)-1*H*-indole-1-carboxylate (35bn)**: The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a semi-solid. Yield: 86% (94.28 mg). IR (Neat): ν_{max} 2978, 1736, 1584, 1452, 1371, 1273, 1232, 1154, 1101, 1009 and 750 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 9.99 (1H, br s, OH), 8.08 (1H, d, *J* = 7.0 Hz), 7.64 (2H, m), 7.31 (1H, dt, *J* = 7.0, 1.0 Hz), 7.24 (1H, dt, *J* = 7.5, 1.0 Hz), 3.49 (2H, s), 2.46 (4H, br s), 1.97 (2H, quintet, *J* = 6.5 Hz), 1.65 (9H, s, OC(CH_3)$_3$). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135) δ 148.8 (C, O–C=O), 134.2 (C), 130.7 (C), 127.7 (CH), 124.6 (CH), 122.6 (CH), 119.9 (CH), 114.7 (CH), 111.2 (C), 104.0 (C, *C*=C–OH), 92.4 (C, acetylenic-*C*), 83.7 (C, acetylenic-*C*), 69.9 (C), 27.9 (3 x CH_3), 20.4 (CH_2), 12.4 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{23}NO_4Na$ 388.1525; Found 388.1528.

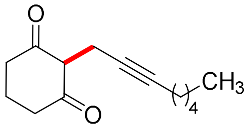
2-(Hept-2-yn-1-yl)cyclohexane-1,3-dione (35bo): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a pale yellow semi solid. Yield: 85% (52.60 mg). IR (Neat): ν_{max} 2958, 2932, 1709, 1455, 1403, 1238, 1190 and 757 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 9.48 (1H, s, OH), 3.00 (2H, br s), 2.33 (2H, br s), 2.18 (2H, br s), 1.97-1.93 (2H, m), 1.77 (2H, m), 1.30-1.25 (2H, m), 1.23-1.17 (2H, m), 0.73 (3H, t, *J* = 4.5 Hz). ^{13}C NMR ($CDCl_3$+DMSO-



35bo

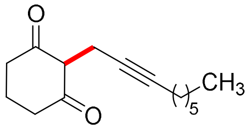
d$_6$, DEPT-135) δ 196.9 (C, *C*=O), 172.2 (C, C=*C*-OH), 111.4 (C, *C*=C-OH), 79.2 (C, acetylenic-*C*), 78.0 (C, acetylenic-*C*), 36.1 (CH$_2$), 30.7 (CH$_2$), 29.1 (CH$_2$), 21.5 (CH$_2$), 20.3 (CH$_2$), 18.2 (CH$_2$), 13.2 (CH$_3$), 11.5 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{13}H_{18}O_2H$ 207.1385; Found 207.1384.

2-(Oct-2-yn-1-yl)cyclohexane-1,3-dione (35bp): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a pale yellow solid. Mp.: 105-107 °C. Yield: 92% (60.80 mg). IR (Neat): ν_{max} 2928, 2855, 2609, 1570, 1365, 1268, 1191, 1070, 1010, 919, 546 and 483 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-*d*$_6$, 400 MHz): δ 9.79 (1H, br s, OH), 3.14 (2H, br s), 2.49 (2H, t, *J* = 4.8 Hz), 2.33 (2H, t, *J* = 4.8 Hz), 2.10 (2H, tt, *J* = 5.6, 2.0 Hz), 1.93 (2H, quintet, *J* = 5.2 Hz), 1.45 (2H, quintet, *J* = 5.6 Hz), 1.33-1.25 (4H, m), 0.88 (3H, t, *J* = 5.6 Hz). ^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$, DEPT-135) δ 111.2 (C, *C*=C–OH), 78.0 (C, acetylenic-*C*), 77.2 (C, acetylenic-*C*), 32.1 (CH$_2$), 30.2 (CH$_2$), 28.6 (CH$_2$), 27.9 (CH$_2$), 21.3 (CH$_2$), 19.8 (CH$_2$), 18.0 (CH$_2$), 13.2 (CH$_3$), 10.8 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{14}H_{20}O_2Na$ 243.1361; Found 243.1368.



35bp

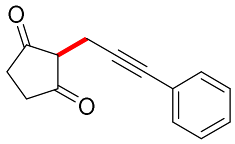
2-(Non-2-yn-1-yl)cyclohexane-1,3-dione (35bq): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a pale yellow semi solid. Mp.: 102-104 °C. Yield: 92% (64.67 mg). IR (Neat): ν_{max} 2948, 2930, 2851, 1568, 1364, 1267, 1221, 1190, 1146, 1070, 1009, 910, 597, 545 and 484 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-*d*$_6$, 500 MHz): δ 9.55 (1H, s, OH), 2.95 (2H, m), 2.30 (2H, br s),



35bq

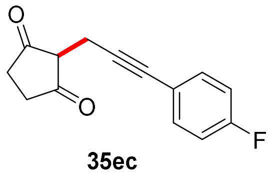
2.13 (2H, br s), 1.90 (2H, m), 1.74 (2H, m), 1.25 (2H, m), 1.15-1.05 (6H, m), 0.68 (3H, t, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 197.0 (C, *C*=O), 172.0 (C, C=*C*-OH), 111.4 (C, *C*=C-OH), 78.8 (C, acetylenic-*C*), 78.0 (C, acetylenic-*C*), 36.0 (CH_2), 30.8 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 28.0 (CH_2), 22.0 (CH_2), 20.2 (CH_2), 18.4 (CH_2), 13.6 (CH_3), 11.3 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}O_2H$ 235.1698; Found 235.1697.

2-(3-Phenylprop-2-yn-1-yl)cyclopentane-1,3-dione (35ea): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a yellow solid. Mp.: 159-160 °C. Yield: 95% (60.49 mg). IR (Neat): ν_{max} 2920, 2851, 2609, 1571, 1383, 1260, 1199, 1036, 757, 691, 664, 583 and 529 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 11.09 (1H, br s, OH), 7.37 (2H, m), 7.25 (3H, m), 3.28 (2H, d, *J* = 5.5 Hz), 2.51 (4H, br s). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 130.9 (2 x CH), 127.5 (2 x CH), 126.9 (CH), 123.2 (C), 112.0 (C, *C*=C–OH), 87.1 (C, acetylenic-*C*), 78.3 (C, acetylenic-*C*), 10.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{12}O_2H$ 213.0916; Found 213.0915.



35ea

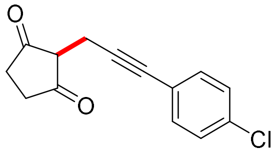
2-(3-(4-Fluorophenyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35ec): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 191-192 °C. Yield: 95% (65.61 mg). IR (Neat): ν_{max} 2928, 2553, 2334, 1567, 1505, 1358, 1262, 1215, 1191, 1036, 833, 656, 577 and 412 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 7.34-7.30 (2H, m), 6.93-6.89



35ec

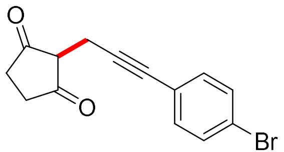
(2H, m), 3.21 (2H, br s), 2.47 (4H, br s). ^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$, DEPT-135): δ 162.2 (C, d, *J* = 246.2 Hz, *C*-F), 133.4 (2 x CH, d, *J* = 7.5 Hz), 119.2 (C, d, *J* = 3.75 Hz), 115.3 (2 x CH, d, *J* = 22.5 Hz), 112.4 (C, *C*=C–OH), 85.8 (C, acetylenic-*C*), 79.6 (C, acetylenic-*C*), 30.0 (2 x CH$_2$, broad peak), 11.8 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{11}FO_2H$ 231.0821; Found 231.0821.

2-(3-(4-Chlorophenyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35ed): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 195-197 °C. Yield: 95% (70.30 mg). IR (Neat): ν_{max} 2361, 2337, 1561, 1488, 1371, 1302, 1264, 1193, 1086, 1035, 826, 670, 584, 547 and 525 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-*d*$_6$, 400 MHz): δ 7.29 (2H, td, *J* = 6.8, 2.0 Hz), 7.21 (2H, td, *J* = 6.8, 2.0 Hz), 3.25 (2H, s), 2.49 (4H, s). ^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$, DEPT-135): δ 133.8 (C), 132.8 (2 x CH), 128.4 (2 x CH), 121.7 (C), 112.3 (C, *C*=C–OH), 87.3 (C, acetylenic-*C*), 79.6 (C, acetylenic-*C*), 11.8 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{11}ClO_2H$ 247.0526; Found 247.0527.



35ed

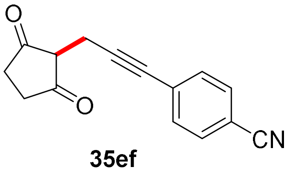
2-(3-(4-Bromophenyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35ee): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 170-172 °C. Yield: 93% (81.22 mg). IR (Neat): ν_{max} 2361, 1600, 1553, 1412, 1371, 1262, 1195, 1069, 1033, 1009, 823, 669, 628 and 557 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-*d*$_6$, 500 MHz): δ 7.43 (2H, d, *J* = 8.5 Hz), 7.26 (2H, d, *J* = 8.0 Hz), 3.22 (2H, s), 2.50 (4H, s). ^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$,



35ee

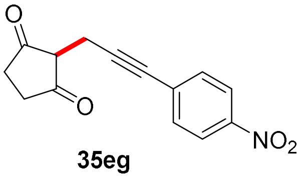
DEPT-135): δ 132.6 (2 x CH), 130.8 (2 x CH), 122.5 (C), 120.8 (C), 111.5 (C, *C*=C–OH), 88.9 (C, acetylenic-*C*), 77.5 (C, acetylenic-*C*), 10.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{11}BrO_2H$ 291.0021; Found 291.0021.

4-(3-(2,5-Dioxocyclopentyl)prop-1-yn-1-yl)benzonitrile (35ef): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 189-191 °C. Yield: 95% (67.61 mg). IR (Neat): ν_{max} 2881, 2596, 2225, 1577, 1385, 1265, 1197, 1036, 842, 773, 675, 601 and 557 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 11.81 (1H, br s, OH), 7.67-7.63 (2H, m), 7.52-7.49 (2H, m), 3.27 (2H, d, *J* = 8.0 Hz), 2.50 (4H, s). ^{13}C NMR ($CDCl_3$+DMSO-D_6, DEPT-135): δ 131.7 (2 x CH), 131.5 (2 x CH), 128.8 (C), 118.0 (C), 111.0 (C, *C*≡N), 110.1 (C, *C*=C–OH), 92.7 (C, acetylenic-*C*), 77.2 (C, acetylenic-*C*), 11.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}NO_2H$ 238.0868; Found 238.0867.



35ef

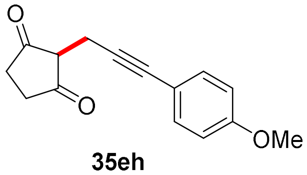
2-(3-(4-Nitrophenyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35eg): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 188-190 °C. Yield: 90% (69.45 mg). IR (Neat): ν_{max} 2602, 2360, 1577, 1513, 1379, 1340, 1264, 1195, 1035, 857, 823, 749, 669 and 588 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 11.78 (1H, br s, OH), 8.13 (2H, td, *J* = 9.0, 2.0 Hz), 7.54 (2H, td, *J* = 9.0, 2.0 Hz), 3.26 (2H, s), 2.48 (4H, br s). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 145.1 (C), 131.0 (2 x CH), 129.6 (C),



35eg

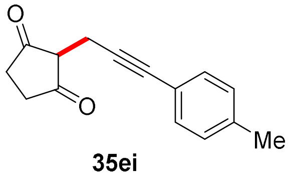
122.0 (2 x CH), 110.1 (C, *C*=C–OH), 92.9 (C, acetylenic-*C*), 76.1 (C, acetylenic-*C*), 10.3 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{11}NO_4H$ 258.0766; Found 258.0760.

2-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35eh): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 145-147 °C. Yield: 88% (63.96 mg). IR (Neat): ν_{max} 2926, 1605, 1566, 1509, 1369, 1289, 1246, 1195, 1173, 1033, 834, 756 and 577 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 7.30 (2H, d, *J* = 7.0 Hz), 6.80 (2H, d, *J* = 7.0 Hz), 3.78 (3H, s, OCH_3), 3.24 (2H, s), 2.48 (4H, s). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 158.2 (C), 132.1 (2 x CH), 115.3 (C), 113.0 (2 x CH), 112.0 (C, *C*=C–OH), 85.3 (C, acetylenic-*C*), 78.0 (C, acetylenic-*C*), 54.5 (CH_3, OCH_3), 10.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}O_3H$ 243.1021; Found 243.1024.



35eh

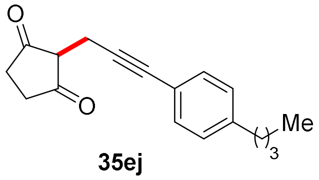
2-(3-(*p*-Tolyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35ei): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 172-174 °C. Yield: 95% (64.48 mg). IR (Neat): ν_{max} 2922, 2664, 1572, 1509, 1382, 1263, 1195, 1036 and 817 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 7.15 (2H, d, *J* = 7.5 Hz), 6.98 (2H, d, *J* = 8.0 Hz), 3.13 (2H, s), 2.40 (4H, s), 2.23 (3H, s, Ar-CH_3). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 136.4 (C), 130.4 (2 x CH), 127.9 (2 x CH), 119.9 (C), 111.6 (C, *C*=C–OH), 86.0 (C,



35ei

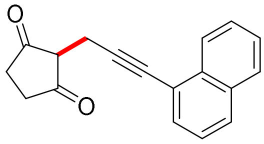
acetylenic-*C*), 77.9 (C, acetylenic-*C*), 20.3 (CH_3, Ar-CH_3), 10.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}O_2H$ 227.1072; Found 227.1073.

2-(3-(4-Butylphenyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35ej): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 153-154 °C. Yield: 96% (77.28 mg). IR (Neat): ν_{max} 2958, 2923, 2856, 1571, 1420, 1384, 1259, 1198, 1037, 819, 659, 582 and 539 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 7.35-7.27 (2H, m), 7.11-7.05 (2H, m), 3.28 (2H, s), 2.65-2.50 (2H, m), 2.49 (4H, br s), 1.65-1.50 (2H, m), 1.40-1.20 (2H, m), 0.89 (3H, t, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 142.5 (C), 131.3 (2 x CH), 128.1 (2 x CH), 120.5 (C), 112.5 (C, *C*=C–OH), 86.0 (C, acetylenic-*C*), 80.2 (C, acetylenic-*C*), 35.3 (CH_2), 33.2 (CH_2), 30.2 (2 x CH_2, broad peak), 22.1 (CH_2), 13.7 (CH_3), 11.8 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{20}O_2H$ 269.1542; Found 269.1542.



35ej

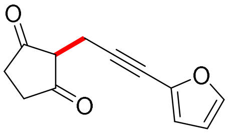
2-(3-(Naphthalen-1-yl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35ek): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a yellow solid. Mp.: 138-139 °C. Yield: 95% (74.75 mg). IR (Neat): ν_{max} 3052, 2921, 2359, 2339, 1547, 1428, 1365, 1292, 1263, 1195, 1028, 797, 771, 654, 631, 564, 483 and 433 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 11.47 (1H, br s, OH), 8.35 (1H, br d, *J* = 8.0 Hz), 7.80 (1H, br d, *J* = 8.0 Hz), 7.75 (1H, br d, *J* = 8.0 Hz), 7.58 (1H, br dd, *J* = 7.0, 1.0 Hz), 7.53 (1H, dt, *J* = 7.0, 1.0 Hz), 7.49-7.46



35ek

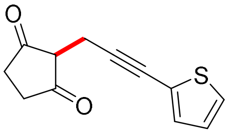
(1H, m), 7.36 (1H, dd, J = 8.0, 7.0 Hz), 3.43 (2H, s), 2.52 (4H, br s). ^{13}C NMR (CDCl$_3$+DMSO-d_6, DEPT-135): δ 133.0 (C), 132.5 (C), 129.4 (CH), 127.6 (CH), 127.4 (CH), 126.0 (CH), 125.9 (CH), 125.7 (CH), 124.7 (CH), 121.1 (C), 112.2 (C, *C*=C–OH), 92.3 (C, acetylenic-*C*), 76.7 (C, acetylenic-*C*), 11.4 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{14}O_2H$ 263.1072; Found 263.1072.

2-(3-(Furan-2-yl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35el): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a yellow solid. Mp.: 119-120 °C. Yield: 95% (57.63 mg). IR (Neat): ν_{max} 2925, 2553, 2107, 1544, 1448, 1358, 1259, 1195, 1035, 974, 818, 741, 662, 586 and 452 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-d_6, 500 MHz): δ 11.51 (1H, br s, OH), 7.31 (1H, d, J = 1.0 Hz), 6.45 (1H, d, J = 3.0 Hz), 6.34 (1H, dd, J = 3.0, 2.0 Hz), 3.28 (2H, s), 2.49 (4H, br s). ^{13}C NMR (CDCl$_3$+DMSO-d_6, DEPT-135): δ 142.3 (CH), 137.3 (C), 113.7 (CH), 111.8 (C, *C*=C–OH), 110.4 (CH), 91.7 (C, acetylenic-*C*), 69.4 (C, acetylenic-*C*), 11.4 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{10}O_3H$ 203.0708; Found 203.0708.



35el

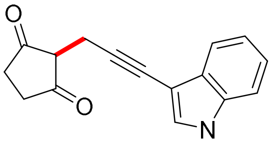
2-(3-(Thiophen-2-yl)prop-2-yn-1-yl)cyclopentane-1,3-dione (35em): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as a yellow solid. Mp.: 170-172 °C. Yield: 92% (60.24 mg). IR (Neat): ν_{max} 1571, 1421, 1395, 1368, 1292, 1196, 1032, 904, 716, 698 and 584 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-d_6, 500 MHz): δ 7.15 (1H, d, J = 5.0 Hz), 7.07 (1H, d, J = 3.5 Hz), 6.90



35em

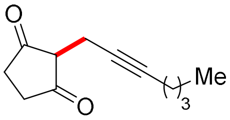
(1H, dd, J = 5.5, 4.0 Hz), 3.26 (2H, s), 2.47 (4H, s). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 130.5 (CH), 126.1 (CH), 125.3 (CH), 123.5 (C), 111.6 (C, *C*=C–OH), 91.3 (C, acetylenic-*C*), 71.6 (C, acetylenic-*C*), 11.2 (CH_2). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{10}O_2SH$ 219.0480; Found 219.0482.

***tert*-Butyl 3-(3-(2,5-dioxocyclopentyl)prop-1-yn-1-yl)-1*H*-indole-1-carboxylate (35en)**: The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off white semi-solid. Yield: 85% (89.60 mg). IR (Neat): ν_{max} 2924, 1733, 1573, 1451, 1366, 1258, 1230, 1150, 1098, 1029, 746, 665 and 578 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 11.36 (1H, br s, OH), 8.08 (1H, br d, J = 7.5 Hz), 7.65 (2H, dd, J = 6.0, 3.5 Hz), 7.32 (1H, tt, J = 8.0, 2.5 Hz), 7.25 (1H, tt, J = 7.5, 2.0 Hz), 3.34 (2H, s), 2.51 (4H, br s), 1.66 (9H, s, OC(CH_3)$_3$). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 148.5 (C, O–C=O), 134.0 (C), 130.3 (C), 127.6 (CH), 124.4 (CH), 122.5 (CH), 119.7 (CH), 114.5 (CH), 112.2 (C, *C*=C–OH), 103.5 (C), 90.6 (C, acetylenic-*C*), 83.6 (C, O-*C*(CH_3)$_3$), 70.2 (C, acetylenic-*C*), 27.6 (3 x CH_3, OC(*C*H_3)$_3$), 11.4 (CH_2). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{21}NO_4H$ 352.1549; Found 352.1548.



35en

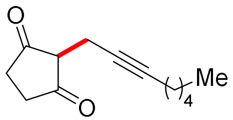
2-(Hept-2-yn-1-yl)cyclopentane-1,3-dione (35eo): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 112-114 °C. Yield: 80% (46.14 mg). IR (Neat): ν_{max} 2961, 2929, 2859, 2349, 1534, 1351, 1299, 1259, 1198, 1033, 825, 658, 631, 564 and 470 cm^{-1}. ^{1}H NMR



35eo

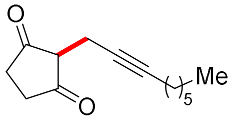
(CDCl$_3$+DMSO-d_6, 500 MHz): δ 10.65 (1H, br s, OH), 2.85 (2H, br s), 2.37 (2H, br s), 2.23 (2H, br s), 1.98-1.94 (2H, m), 1.28 (2H, m), 1.20 (2H, m), 0.72 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (CDCl$_3$+DMSO-d_6, DEPT-135): δ 204.0 (C, *C*=O, br s), 184.3 (C, C=*C*-OH, br s), 112.9 (C, *C*=C-OH), 79.3 (C, acetylenic-*C*), 76.5 (C, acetylenic-*C*), 32.7 (CH$_2$, br s), 30.6 (CH$_2$), 27.1 (CH$_2$, br s), 21.5 (CH$_2$), 18.1 (CH$_2$), 13.2 (CH$_3$), 10.7 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{12}$H$_{16}$O$_2$H 193.1229; Found 193.1229.

2-(Oct-2-yn-1-yl)cyclopentane-1,3-dione (35ep): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 100-102 °C. Yield: 90% (55.69 mg). IR (Neat): ν$_{max}$ 2931, 2869, 2416, 1532, 1443, 1353, 1031, 1261, 1200, 1140, 827, 660 and 475 cm^{-1}. ^{1}H NMR (CDCl$_3$+DMSO-d_6, 400 MHz): δ 10.81 (1H, br s, OH), 3.02 (2H, s), 2.53 (2H, br s), 2.40 (2H, br s), 2.12 (2H, tt, *J* = 7.2, 2.4 Hz), 1.47 (2H, quintet, *J* = 7.2 Hz), 1.34-1.27 (4H, m), 0.88 (3H, t, *J* = 7.6 Hz). ^{13}C NMR (CDCl$_3$+DMSO-d_6, DEPT-135): δ 113.2 (C, *C*=C–OH), 79.8 (C, acetylenic-*C*), 76.8 (C, acetylenic-*C*), 31.0 (CH$_2$), 28.5 (CH$_2$), 22.1 (CH$_2$), 18.7 (CH$_2$), 13.9 (CH$_3$), 11.0 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for C$_{13}$H$_{18}$O$_2$Na 229.1204; Found 229.1208.



35ep

2-(Non-2-yn-1-yl)cyclopentane-1,3-dione (35eq): The title compound was prepared following procedure **1a**, purified by precipitating with cold EtOAc/hexanes (1/9), and isolated as an off-white solid. Mp.: 114-115 °C. Yield: 95% (62.78 mg). IR (Neat): ν$_{max}$ 2958, 2929, 2852, 1542, 1431, 1351, 1301, 1260, 1198, 1035, 827, 658, 564 and 476 cm^{-1}. ^{1}H NMR

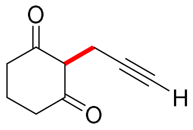


35eq

($CDCl_3$+DMSO-d_6, 500 MHz): δ 10.84 (1H, br s, OH), 2.71 (2H, s), 2.17 (4H, br s), 1.82 (2H, tt, *J* = 7.0, 2.4 Hz), 1.17 (2H, quintet, *J* = 7.0 Hz), 1.07-0.95 (6H, m), 0.60 (3H, t, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135): δ 112.7 (C, *C*=C–OH), 78.5 (C, acetylenic-*C*), 76.4 (C, acetylenic-*C*), 30.6 (CH_2), 28.2 (CH_2), 27.8 (CH_2), 21.8 (CH_2), 18.1 (CH_2), 13.4 (CH_3), 10.2 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{20}O_2H$ 221.1542; Found 221.1544.

1b. **General Procedure for the Trimethylsilyl Deprotection of Coupling Products 35:** In an ordinary glass vial equipped with a magnetic stirring bar, to 1.5 equiv. of TBAF (0.45 mmol, 117.66 mg) and 1.0 equiv. of coupling product **35bb** (0.3 mmol, 66.71 mg) was added 1.0 mL of THF (0.3 M) and the reaction mixture was stirred at room temperature for 2 h. The crude reaction was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product **36bb** (98%, 44.15 mg) were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

2-(Prop-2-yn-1-yl)cyclohexane-1,3-dione (36bb):[6d] The title compound was prepared following procedure **1b**, purified by column chromatography using EtOAc/hexanes (1.5/8.5), and isolated as a pale yellow solid. Yield: 98% (44.14 mg). IR (Neat): ν_{max} 3303, 2956, 2923, 2853, 2629, 2115, 1568, 1365, 1267, 1218, 1188, 1139, 1066, 1010, 919, 749, 647, 611 and 557 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 10.84 (1H, br s, O-*H*), 2.96 (2H, d, *J* = 2.5 Hz), 2.45 (1H, t, *J* = 2.5 Hz), 2.33 (4H, br s), 1.82 (2H, quintet, *J* = 6.5 Hz). ^{13}C

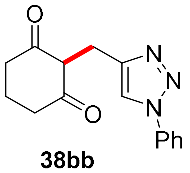


36bb

NMR (DMSO-d_6, DEPT-135) δ 110.1 (C, *C*=C–OH), 83.7 (C, acetylenic-*C*), 68.2 (CH, acetylenic-*CH*), 20.4 (CH_2), 11.0 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{10}O_2H$ 151.0759; Found 151.0759.

1c. General Procedure for the Click Reaction of 2-(Prop-2-yn-1-yl)cyclohexane-1,3-dione 36bb: In an ordinary glass vial equipped with a magnetic stirring bar, 1.0 equiv. of 2-(prop-2-yn-1-yl)cyclohexane-1,3-dione **36bb** (0.3 mmol, 45.05 mg) and 1.0 equiv. of phenyl azide **37** (0.3 mmol, 35.74 mg) was added to 0.2 equiv. of 1.0 M aqueous sodium ascorbate (0.06 mmol, 11.89 mg, 60.01 µL), 0.4 equiv. of copper sulfate pentahydrate (0.12 mmol, 29.96 mg) in 1.0 mL of water and *tertiary*-butanol solvent (1:1 mixture, 0.3 M), then the reaction mixture was stirred at room temperature for 24 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure click product **38bb** (75%, 60.59 mg) were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

3-Hydroxy-2-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)cyclohex-2-enone (38bb): The title compound was prepared following procedure **1c**, purified by column chromatography using EtOAc/hexanes (3/7), and isolated as a semi-solid. Yield: 75% (60.59 mg). IR (Neat): ν_{max} 3404, 3138, 2949, 2089, 1604, 1500, 1385, 1363, 1275, 1227, 1184, 1138, 1062, 1016, 990, 805, 757, 684, 583 and 513 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6, 500 MHz): δ 10.48 (1H, br s, O-*H*), 7.91 (1H, br s), 7.74 (2H, br s), 7.50 (2H, br s), 7.41 (1H, br s), 3.76 (2H, br s),

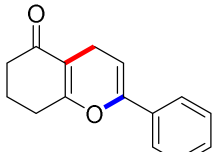


38bb

2.43 (4H, br s), 1.99 (2H, br s). ^{13}C NMR ($CDCl_3$+DMSO-d_6, DEPT-135) δ 174.2 (C, C=*C*-OH), 147.4 (C), 136.4 (C), 128.9 (2 x CH), 127.8 (CH), 119.6 (2 x CH), 119.2 (CH), 112.3 (C, *C*=C–OH), 32.5 (2 x CH_2), 20.0 (CH_2), 17.6 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}N_3O_2H$ 270.1243; Found 270.1243.

1d. General Procedure for the Annulative Etherification of 2-(3-Arylprop-2-yn-1-yl)cyclic-1,3-diones 35: In an ordinary glass vial equipped with a magnetic stirring bar, 0.1 equiv. of silver triflate (0.02 mmol, 5.14 mg, 10 mol%) was added to 1.0 equiv. of propargyl cyclic-1,3-diones **35** (0.2 mmol) in 1.0 mL of dry methanol (0.2 M) solvent and the reaction mixture was stirred at room temperature for 1-12 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **39** were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

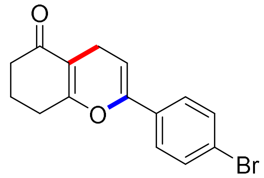
2-Phenyl-4,6,7,8-tetrahydro-5*H*-chromen-5-one (39ba): The title compound was prepared following procedure **1d**, purified by column chromatography using



39ba

EtOAc/hexanes (2/8), and isolated as a semi-solid. Yield: 85% (38.46 mg). IR (Neat): ν_{max} 2952, 1718, 1678, 1646, 1523, 1455, 1320, 1214, 1124, 1006, 967, 900, 752, 722 and 701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53 (2H, br d, *J* = 7.5 Hz), 7.33 (2H, br t, *J* = 7.5 Hz), 7.19 (1H, br t, *J* = 7.5 Hz), 5.70 (1H, t, *J* = 2.5 Hz), 3.66 (2H, d, *J* = 2.5 Hz), 2.63 (2H, tt, *J* = 8.5, 2.0 Hz), 2.42 (2H, t, *J* = 7.0 Hz), 2.13 (2H, quintet, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 194.3 (C, *C*=O), 175.2 (C, C=*C*–O), 153.8 (C, C=*C*–O), 134.5 (C), 128.3

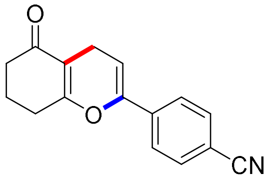
(2 x CH), 128.0 (2 x CH), 126.3 (CH), 114.3 (C, *C*=C–O), 104.5 (CH), 36.5 (CH$_2$), 31.2 (CH$_2$), 23.3 (CH$_2$), 21.6 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M-H]$^+$ Calcd for $C_{15}H_{13}O_2$ 225.0915; Found 225.0915.



39be

2-(4-Bromophenyl)-4,6,7,8-tetrahydro-5*H*-chromen-5-one (39be): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as an off-white semi-solid. Yield: 85% (51.88 mg). IR (Neat): ν_{max} 3274, 2948, 1645, 1487, 1401, 1224, 1179, 1071, 992, 897, 857 and 586 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.44 (2H, br td, *J* = 9.0, 2.0 Hz), 7.40 (2H, br td, *J* = 8.8, 2.0 Hz), 5.64 (1H, t, *J* = 2.5 Hz), 3.64 (2H, br dd, *J* = 4.4, 2.5 Hz), 2.64 (2H, tt, *J* = 6.5, 2.5 Hz), 2.43 (2H, t, *J* = 7.0 Hz), 2.15 (2H, quintet, *J* = 6.5 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 194.4 (C, *C*=O), 175.0 (C, C=*C*–O), 154.4 (C, C=*C*–O), 133.4 (C), 131.4 (2 x CH), 129.5 (2 x CH), 120.0 (C), 114.3 (C, *C*=C–O), 103.4 (CH), 36.5 (CH$_2$), 31.3 (CH$_2$), 23.3 (CH$_2$), 21.6 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{15}H_{13}BrO_2Na$ 326.9997; Found 326.9997.

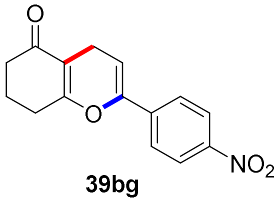
4-(5-Oxo-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)benzonitrile (39bf): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a white semi-solid. Yield: 82% (41.21 mg). IR (Neat): ν_{max} 3428, 2922, 2851, 2229, 1714, 1651, 1522, 1457, 1408, 1264, 1216, 1124, 1005, 731 and 703 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.63-7.58 (4H, m), 5.73 (1H, t, *J* = 2.8 Hz), 3.71 (2H, td, *J* = 2.4, 2.4 Hz), 2.67 (2H, tt, *J* = 8.8, 2.4 Hz), 2.45 (2H, t, *J* = 6.8 Hz),



39bf

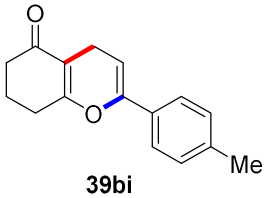
2.17 (2H, quintet, *J* = 6.4 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 194.3 (C, *C*=O), 174.7 (C, C=*C*–O), 157.0 (C, C=*C*–O), 139.1 (C), 132.2 (2 x CH), 128.3 (2 x CH), 119.2 (C), 114.5 (C, *C*=C–O), 109.2 (C, *C*≡N), 103.8 (CH), 36.5 (CH$_2$), 31.8 (CH$_2$), 23.3 (CH$_2$), 21.6 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{13}NO_2H$ 252.1026; Found 252.1026.

2-(4-Nitrophenyl)-4,6,7,8-tetrahydro-5*H*-chromen-5-one (39bg): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a yellow semi-solid. Yield: 83% (45.03 mg). IR (Neat): ν$_{max}$ 2955, 1686, 1642, 1590, 1503, 1398, 1329, 1212, 1106, 1050, 987, 896, 867, 845, 775, 691 and 582 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.17 (2H, br d, *J* = 9.0 Hz), 7.66 (2H, br d, *J* = 9.0 Hz), 5.79 (1H, t, *J* = 2.5 Hz), 3.72 (2H, br d, *J* = 2.0 Hz), 2.69 (2H, tt, *J* = 6.5, 2.0 Hz), 2.45 (2H, t, *J* = 7.0 Hz), 2.17 (2H, quintet, *J* = 6.5 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 194.2 (C, *C*=O), 174.6 (C, C=*C*–O), 157.7 (C, C=*C*–O), 145.5 (C), 141.2 (C), 128.2 (2 x CH), 123.8 (2 x CH), 114.6 (C, *C*=C–O), 102.8 (CH), 36.5 (CH$_2$), 31.9 (CH$_2$), 23.3 (CH$_2$), 21.6 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{15}H_{13}NO_4Na$ 294.0742; Found 294.0746.



39bg

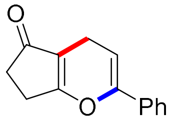
2-(*p*-Tolyl)-4,6,7,8-tetrahydro-5*H*-chromen-5-one (39bi): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as an off-white semi-solid. Yield: 76% (36.52 mg). IR (Neat): ν$_{max}$ 3250, 2947, 1631, 1512, 1453, 1403, 1229, 1179, 1086, 991,



39bi

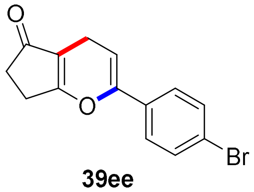
897, 860, 728 and 601 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.43 (2H, br d, *J* = 8.4 Hz), 7.14 (2H, br d, *J* = 8.0 Hz), 5.68 (1H, t, *J* = 2.4 Hz), 3.65 (2H, br d, *J* = 2.0 Hz), 2.64 (2H, tt, *J* = 6.4, 2.4 Hz), 2.42 (2H, t, *J* = 7.2 Hz), 2.34 (3H, s, Ar-C*H*$_3$), 2.14 (2H, quintet, *J* = 6.8 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 194.4 (C, *C*=O), 175.3 (C, C=*C*–O), 153.1 (C, C=*C*–O), 136.1 (C), 131.6 (C), 129.1 (2 x CH), 127.9 (2 x CH), 114.3 (C, *C*=C–O), 104.4 (CH), 36.5 (CH$_2$), 31.1 (CH$_2$), 23.4 (CH$_2$), 21.6 (CH$_2$), 21.2 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{16}O_2Na$ 263.1048; Found 263.1048.

2-Phenyl-6,7-dihydrocyclopenta[*b*]pyran-5(4*H*)-one (39ea): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a white semi-solid. Yield: 75% (31.83 mg). IR (Neat): ν$_{max}$ 3073, 2917, 2845, 1705, 1672, 1627, 1495, 1436, 1339, 1298, 1276, 1230, 1111, 1019, 994, 951, 810, 756, 700, 688, 645 and 623 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.58 (2H, dd, *J* = 8.0, 1.6 Hz), 7.41-7.35 (3H, m), 5.62 (1H, t, *J* = 3.6 Hz), 3.00-2.99 (2H, m), 2.72-2.70 (2H, m), 2.53-2.51 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 203.9 (C, *C*=O), 180.2 (C, C=*C*–O), 149.2 (C, C=*C*–O), 133.0 (C), 128.8 (CH), 128.4 (2 x CH), 124.5 (2 x CH), 114.0 (C, *C*=C–O), 99.7 (CH), 33.2 (CH$_2$), 25.9 (CH$_2$), 18.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{12}O_2H$ 213.0916; Found 213.0915.



39ea

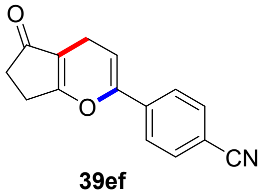
2-(4-Bromophenyl)-6,7-dihydrocyclopenta[*b*]pyran-5(4*H*)-one (39ee): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (1.5/8.5), and isolated as a white semi-solid. Yield: 84% (48.91 mg). IR (Neat):



39ee

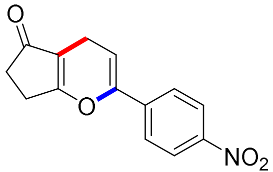
ν_{max} 2843, 1702, 1671, 1629, 1586, 1389, 1286, 1263, 1233, 1108, 994, 847, 828, 787 and 661 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.51 (2H, br d, *J* = 8.4 Hz), 7.44 (2H, br d, *J* = 8.8 Hz), 5.63 (1H, t, *J* = 3.6 Hz), 2.98 (2H, d, *J* = 2.0 Hz), 2.71-2.70 (2H, m), 2.53-2.51 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 203.7 (C, *C*=O), 179.9 (C, C=*C*–O), 148.4 (C, C=*C*–O), 131.9 (C), 131.6 (2 x CH), 126.0 (2 x CH), 122.9 (C), 114.0 (C, *C*=C–O), 100.3 (CH), 33.2 (CH$_2$), 25.8 (CH$_2$), 18.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{11}BrO_2H$ 291.0021; Found 291.0021.

4-(5-Oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-2-yl)benzonitrile (39ef): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a white semi-solid. Yield: 72% (34.16 mg). IR (Neat): ν_{max} 2922, 2852, 2360, 2340, 2225, 1704, 1675, 1630, 1443, 1399, 1309, 1274, 1239, 1113, 1003, 846, 798, 677 and 625 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.69-7.68 (4H, m), 5.80 (1H, t, *J* = 3.5 Hz), 3.05-3.04 (2H, m), 2.74-2.72 (2H, m), 2.55-2.53 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 203.6 (C, *C*=O), 179.5 (C, C=*C*–O), 147.7 (C, C=*C*–O), 137.0 (C), 132.3 (2 x CH), 124.9 (2 x CH), 118.5 (C), 113.9 (C, *C*=C–O), 112.3 (C, *C*≡N), 103.2 (CH), 33.3 (CH$_2$), 25.8 (CH$_2$), 18.3 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{11}NO_2H$ 238.0868; Found 238.0868.



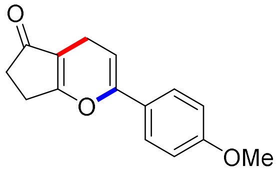
39ef

2-(4-Nitrophenyl)-6,7-dihydrocyclopenta[*b*]pyran-5(4*H*)-one (39eg): The title compound was prepared following procedure **1d,** purified by column chromatography using EtOAc/hexanes (1.5/4), and isolated as a white semi-solid. Yield: 69% (35.50 mg). IR (Neat): ν_{max} 2838, 1701, 1672, 1512, 1398, 1341, 1239, 1109, 1002, 862, 848, 751, 708 and 691 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.25 (2H, br d, *J* = 9.0 Hz), 7.75 (2H, br d, *J* = 9.0 Hz), 5.86 (1H, t, *J* = 4.0 Hz), 3.06-3.058 (2H, m), 2.76-2.74 (2H, m), 2.56-2.54 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 203.4 (C, *C*=O), 179.4 (C, C=*C*–O), 147.8 (C, C=*C*–O), 147.6 (C), 138.8 (C), 125.1 (2 x CH), 123.8 (2 x CH), 113.9 (C, *C*=C–O), 104.0 (CH), 33.3 (CH$_2$), 25.8 (CH$_2$), 18.4 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{11}NO_4H$ 258.0766; Found 258.0766.



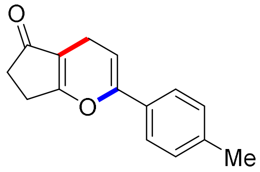
39eg

2-(4-Methoxyphenyl)-6,7-dihydrocyclopenta[*b*]pyran-5(4*H*)-one (39eh): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a white semi-solid. Yield: 80% (38.76 mg). IR (Neat): ν_{max} 2839, 2360, 1704, 1671, 1608, 1513, 1399, 1242, 1178, 1114, 1027, 997, 837 and 685 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.51 (2H, br d, *J* = 8.8 Hz), 6.91 (2H, br d, *J* = 8.8 Hz), 5.48 (1H, t, *J* = 3.6 Hz), 3.83 (3H, s, OC*H*$_3$), 2.98 (2H, br s), 2.70-2.69 (2H, m), 2.52-2.50 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 203.9 (C, *C*=O), 180.2 (C, C=*C*–O), 160.0 (C, C=*C*–O), 149.0 (C), 125.9 (2 x CH), 125.7 (C), 114.0 (C, *C*=C–O), 113.8 (2 x CH), 97.8 (CH), 55.3 (CH$_3$), 33.2 (CH$_2$), 25.9 (CH$_2$), 18.0 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{14}O_3H$ 243.1021; Found 243.1019.



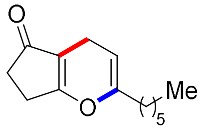
39eh

2-(*p*-Tolyl)-6,7-dihydrocyclopenta[*b*]pyran-5(4*H*)-one (39ei): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (1.5/8), and isolated as a white semi-solid. Yield: 81% (36.65 mg). IR (Neat): ν_{max} 2923, 1726, 1667, 1441, 1400, 1270, 1240, 1113, 1068, 1000, 954 and 812 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (2H, br d, *J* = 8.0 Hz), 7.19 (2H, br d, *J* = 8.0 Hz), 5.56 (1H, t, *J* = 4.0 Hz), 2.99-2.98 (2H, m), 2.71-2.69 (2H, m), 2.52-2.50 (2H, m), 2.37 (3H, s, Ar-C*H*$_3$). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 204.0 (C, *C*=O), 180.3 (C, C=*C*–O), 149.2 (C, C=*C*–O), 138.8 (C), 130.2 (C), 129.1 (2 x CH), 124.4 (2 x CH), 114.0 (C, *C*=C–O), 98.8 (CH), 33.2 (CH_2), 25.9 (CH_2), 21.2 (CH_3, O*C*H_3), 18.0 (CH_2). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{14}O_2H$ 227.1072; Found 227.1073.



39ei

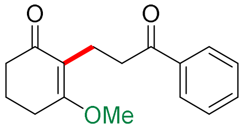
2-Hexyl-6,7-dihydrocyclopenta[*b*]pyran-5(4*H*)-one (39eq): The title compound was prepared following procedure **1d**, purified by column chromatography using EtOAc/hexanes (1/9), and isolated as a white semi-solid. Yield: 85% (37.45 mg). IR (Neat): ν_{max} 2926, 2854, 1729, 1691, 1636, 1400, 1276, 1167, 985, 966, 874, 702 and 651 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.80 (1H, t, *J* = 3.5 Hz), 2.77 (2H, br s), 2.58-2.56 (2H, m), 2.45-2.43 (2H, m), 2.12 (2H, t, *J* = 7.5 Hz), 1.49 (2H, quintet, *J* = 6.8 Hz), 1.35-1.25 (6H, m), 0.88 (3H, t, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 204.2 (C, *C*=O), 180.6 (C, C=*C*–O), 151.8 (C, C=*C*–O), 114.0 (C, *C*=C–O), 98.2 (CH), 33.1 (CH_2), 32.7 (CH_2), 31.5 (CH_2), 28.6 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 22.5 (CH_2), 17.6 (CH_2), 14.0 (CH_3). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{20}O_2H$ 221.1541; Found 221.1543.



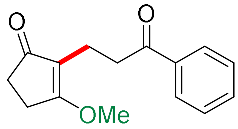
39eq

1e. General Procedure for the Ring Opening of 4*H*-Pyran Derivatives 39: In an ordinary glass vial equipped with a magnetic stirring bar, 1.0 equiv. of potassium carbonate (0.2 mmol, 27.64 mg) was added to 1.0 equiv. of 4*H*-pyran derivative **39** (0.2 mmol) in 1.0 mL of dry methanol (0.2 M) solvent and the reaction mixture was stirred at room temperature for 1.5 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **40** were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

3-Methoxy-2-(3-oxo-3-phenylpropyl)cyclohex-2-en-1-one (40ba): The title compound was prepared following procedure **1e**, purified by column chromatography using EtOAc/hexanes (3/7), and isolated as a semi-solid. Yield: 76% (39.26 mg). IR (Neat): ν_{max} 2948, 1713, 1606, 1455, 1366, 1243, 1166, 1116, 1080, 1038, 969, 735 and 700 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.31-7.28 (2H, m), 7.23-7.20 (3H, m), 3.71 (2H, s), 3.66 (3H, s, OC*H*$_3$), 3.39 (2H, s), 2.52 (2H, t, *J* = 6.5 Hz), 2.35 (2H, t, *J* = 6.5 Hz), 1.99 (2H, quintet, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 206.1 (C, *C*=O), 197.3 (C, *C*=O), 173.7 (C, C=*C*–O), 134.7 (C), 129.4 (2 x CH), 128.3 (2 x CH), 126.6 (CH), 113.2 (C, *C*=C–O), 55.2 (CH_3), 49.3 (CH_2), 36.0 (CH_2), 35.7 (CH_2), 24.5 (CH_2), 20.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{18}O_3Na$ 281.1154; Found 281.1154.



40ba

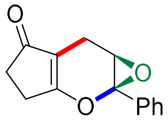


40ea

3-Methoxy-2-(3-oxo-3-phenylpropyl)cyclopent-2-en-1-one (40ea): The title compound was prepared following procedure **1e**, purified by column chromatography using EtOAc/hexanes (3/7), and isolated as a semi-solid. Yield: 92% (44.94 mg). IR (Neat): ν_{max} 2950, 1680, 1621, 1449, 1410, 1361, 1271, 1205, 1177, 1092, 997, 743, 692 and 635 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.93 (2H, br d, J = 7.5 Hz), 7.51 (1H, br t, J = 7.5 Hz), 7.42 (2H, br t, J = 7.5 Hz), 3.90 (3H, s, $\mathrm{OC}H_3$), 3.12 (2H, t, J = 8.0 Hz), 2.64-2.62 (2H, m), 2.54 (2H, t, J = 7.5 Hz), 2.43-2.41 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 204.7 (C, *C*=O), 199.8 (C, *C*=O), 184.9 (C, C=*C*–O), 136.9 (C), 132.8 (CH), 128.4 (2 x CH), 128.0 (2 x CH), 119.0 (C, *C*=C–O), 56.4 (CH$_3$), 36.2 (CH$_2$), 33.4 (CH$_2$), 24.5 (CH$_2$), 16.4 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{15}H_{16}O_3Na$ 267.0997; Found 267.0996.

1f. General Procedure for the Epoxidation of 4*H*-Pyran Derivative 39ea: In an ordinary glass vial equipped with a magnetic stirring bar, 1.2 equiv. of *m*-CPBA (0.24 mmol, 41.42 mg) was added to 1.0 equiv. of 4*H*-pyran derivative **39ea** (0.2 mmol, 42.45 mg) in 1.0 mL of dry DCM (0.2 M) solvent and the reaction mixture was stirred at room temperature for 1.0 h. The crude reaction mixture was quenched with aqueous NH$_4$Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. Pure product **41ea** (71%, 32.41 mg) were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

1a-Phenyl-3,4,6,6a-tetrahydrocyclopenta[*b*]oxireno[2,3-*e*]pyran-5(1a*H*)-one (41ea): The title compound was prepared following procedure **1f**, purified by column chromatography using EtOAc/hexanes (1.5/8.5), and isolated as a white semi-solid.

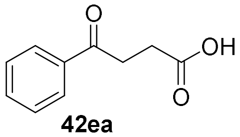


41ea

Yield: 71% (32.41 mg). IR (Neat): ν_{max} 2924, 1703, 1647, 1427, 1397, 1279, 1232, 1198, 1111, 1039, 1022, 978, 936, 908, 757, 699, 647 and 610 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.55-7.52 (2H, m), 7.45-7.43 (3H, m), 3.49 (1H, dd, *J* = 2.8, 1.2 Hz), 2.95 (1H, br d, *J* = 18.4 Hz), 2.78-2.68 (2H, m), 2.65-2.63 (1H, m), 2.52-2.49 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 203.7 (C, *C*=O), 179.0 (C, C=*C*–O), 133.9 (C), 129.6 (CH), 128.6 (2 x CH), 125.8 (2 x CH), 111.9 (C, *C*=C–O), 85.3 (C, O–*C*–O), 59.9 (CH), 33.5 (CH$_2$), 26.1 (CH$_2$), 19.9 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{12}O_3H$ 229.0865; Found 229.0865.

1g. General Procedure for the Fragmentation of 4*H*-Pyran Derivative 39ea: In an ordinary glass vial equipped with a magnetic stirring bar, 5.0 equiv. of 30% aqueous H_2O_2 (1.0 mmol, 34.01 mg, 30.64 μL) and 1.0 equiv. of 6.0 M aqueous NaOH (0.2 mmol, 8.0 mg, 33.33 μL) were added to 1.0 equiv. of 4*H*-pyran derivative **39ea** (0.2 mmol, 42.45 mg) in 1.0 mL of methanol (0.2 M) solvent and the reaction mixture was stirred at 50 °C (oil bath) for 12 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product **42ea** (50%, 17.82 mg) were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

4-Oxo-4-phenylbutanoic acid (42ea):[14d] The title compound was prepared following procedure **1g**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a semi-solid. Yield: 50% (17.82 mg). IR (Neat): ν_{max} 3028, 2923, 2680, 1712, 1679, 1595, 1433, 1400, 1299, 1260, 1236, 1172, 990, 963, 945, 762 and 689 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.98 (2H, d, *J* = 7.5 Hz), 7.58 (1H, t, *J* = 7.5 Hz), 7.47 (2H, t, *J* = 7.5 Hz), 3.32 (2H, t, *J* = 6.5 Hz), 2.82 (2H, t, *J* = 6.5 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 197.8 (C, *C*=O), 178.3 (C, HO–*C*=O), 136.4 (C), 133.3 (CH), 128.6 (2 x CH), 128.0 (2 x CH), 33.1 (CH$_2$), 27.9 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{10}H_{10}O_3H$ 179.0708; Found 179.0708.



42ea

1h. General Procedure for the *O*-Methylation of TCRP Products 35: In an ordinary glass vial equipped with a magnetic stirring bar, 1.1 equiv. of NaOH (0.22 mmol, 8.8 mg), 3.0 equiv. of methyl iodide (0.6 mmol, 37.35 µL) were added to 1.0 equiv. of 1,3-cyclic diketone propragyl derivative **35** (0.2 mmol) in 1.0 mL of CH_3CN (0.2 M) solvent and the reaction mixture was stirred at 60 °C (oil bath) for 10 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **43** were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

1i. General Procedure for the *C*-Alkylation Reaction of TCRP Products 45:

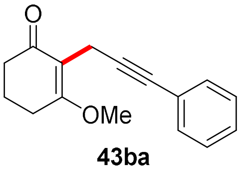
Method 1: In an ordinary glass vial equipped with a magnetic stirring bar, 1.0 equiv. of $NaHCO_3$ (0.2 mmol, 16.8 mg), 2.0 equiv. of propargyl bromide (80 wt.% in toluene, 0.4

mmol, 35.64 μL) were added to 1.0 equiv. of 1,3-cyclic diketone propragyl derivative **35** (0.2 mmol) in 1.0 mL of water (0.2 M) and the reaction mixture was stirred at 80 °C (oil bath) for 48 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **44** were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

Method 2: In an ordinary glass vial equipped with a magnetic stirring bar, 1.0 equiv. of $NaHCO_3$ (0.2 mmol, 16.8 mg), 3.0 equiv. of methyl iodide (0.6 mmol, 37.35 μL) were added to 1.0 equiv. of 1,3-cyclic diketone propragyl derivative **35** (0.2 mmol) in 1.0 mL of water (0.2 M) and the reaction mixture was stirred at 80 °C (oil bath) for 36 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **45** were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

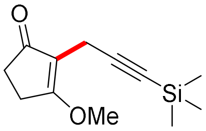
Method 3: In an ordinary glass vial equipped with a magnetic stirring bar, 1.2 equiv. of K_2CO_3 (0.24 mmol, 33.17 mg), 3.0 equiv. of methyl iodide (0.6 mmol, 37.35 μL) were added to 1.0 equiv. of 1,3-cyclic diketone propragyl derivative **35** (0.2 mmol) in 1.0 mL of acetone (0.2 M) solvent and the reaction mixture was stirred at 60 °C (oil bath) for 4 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **45** were obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

3-Methoxy-2-(3-phenylprop-2-yn-1-yl)cyclohex-2-en-1-one (43ba): The title compound was prepared following procedure **1h**, purified by column chromatography using EtOAc/hexanes (3/7), and isolated as a white semi solid. Yield: 30% (14.42 mg). IR (Neat): ν_{max} 2924, 2852, 1720, 1645, 1612, 1489, 1459, 1421, 1367, 1243, 1189, 1167, 1105, 1081, 1040, 960, 918, 758 and 693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.36 (2H, m), 7.23-7.22 (3H, m), 3.89 (3H, s, OC*H*$_3$), 3.40 (2H, s), 2.62 (2H, t, *J* = 6.0 Hz), 2.41 (2H, t, *J* = 6.5 Hz), 2.03 (2H, quintet, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 196.6 (C, *C*=O), 172.8 (C, C=*C*–OMe), 131.7 (2 x CH), 128.0 (2 x CH), 127.2 (CH), 124.4 (C), 115.3 (C, *C*=C–O), 89.0 (C, acetylenic-*C*), 78.2 (C, acetylenic-*C*), 55.4 (CH_3), 36.1 (CH_2), 25.0 (CH_2), 20.6 (CH_2), 12.5 (CH_2). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{16}O_2H$ 241.1228; Found 241.1229.



43ba

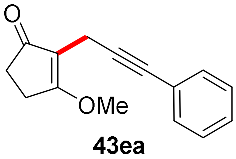
3-Methoxy-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopent-2-enone (43eb): The title compound was prepared following procedure **1i** (Method-3), purified by column chromatography using EtOAc/hexanes (3/7), and isolated as a yellow liquid. Yield: 60% (26.67 mg). IR (Neat): ν_{max} 2925, 2173, 1691, 1622, 1461, 1356, 1250, 1209, 1091, 1052, 1002, 960, 839, 759, 644, 616 and 593 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.01 (3H, s, OC*H*$_3$), 3.08 (2H, s), 2.67-2.65 (2H, m), 2.45 (2H, m), 0.11 (9H, s). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 203.1 (C, *C*=O), 185.2 (C, C=*C*–O), 115.1 (C, *C*=C–O), 103.4 (C, acetylenic-*C*), 83.4 (C,



43eb

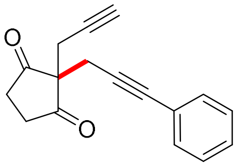
acetylenic-*C*), 56.8 (CH_3, O*C*H_3), 33.2 (CH_2), 24.9 (CH_2), 12.3 (CH_2), 0.04 (3 x CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{18}O_2SiH$ 223.1154; Found 223.1156.

3-Methoxy-2-(3-phenylprop-2-yn-1-yl)cyclopent-2-en-1-one (43ea): The title compound was prepared following procedure **1h**, purified by column chromatography using EtOAc/hexanes (3/7), and isolated as a white semi solid. Yield: 63% (28.51 mg). IR (Neat): ν_{max} 2922, 2854, 1689, 1628, 1489, 1461, 1412, 1361, 1262, 1087, 962, 759, 694 and 611 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.37 (2H, m), 7.25-7.23 (3H, m), 4.04 (3H, s, OC*H*$_3$), 3.28 (2H, s), 2.69-2.68 (2H, m), 2.50-2.48 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 203.3 (C, *C*=O), 185.3 (C, C=*C*–O), 131.6 (2 x CH), 128.0 (2 x CH), 127.5 (CH), 123.9 (C), 115.5 (C, *C*=C–O), 86.8 (C, acetylenic-*C*), 79.4 (C, acetylenic-*C*), 56.8 (CH_3), 33.3 (CH_2), 24.9 (CH_2), 11.8 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}O_2H$ 227.1072; Found 227.1076.



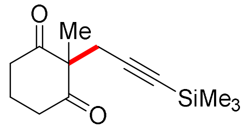
43ea

2-(3-Phenylprop-2-yn-1-yl)-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (44ea): The title compound was prepared following procedure **1i** (Method-1), purified by column chromatography using EtOAc/hexanes (1/9), and isolated as a white semi solid. Yield: 31% (15.52 mg). IR (Neat): ν_{max} 3287, 2922, 1728, 1490, 1423, 1344, 1196, 1030, 991, 758, 691 and 652 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.31 (2H, m), 7.30-7.26 (3H, m), 2.86 (4H, dABq, *J* = 17.6, 4.0 Hz), 2.68 (2H, s), 2.52 (2H, d, *J* = 2.8 Hz), 2.01 (1H, t, *J* = 2.8 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 214.3 (2 x C, *C*=O), 131.6 (2 x CH), 128.5 (CH), 128.3 (2 x CH), 122.2 (C), 83.3 (C, acetylenic-*C*), 82.9 (C, acetylenic-*C*), 78.1 (C,



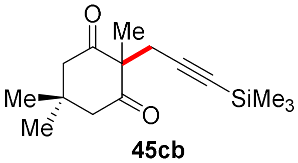
44ea

acetylenic-*C*), 71.2 (CH, acetylenic-*C*H), 58.2 (C), 37.1 (2 x CH_2), 24.9 (CH_2), 23.2 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{14}O_2Na$ 273.0891; Found 273.0892.



45bb

2-Methyl-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (45bb): The title compound was prepared following procedure **1i** (Method-3), purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a pale-yellow liquid. Yield: 76% (35.93 mg). IR (Neat): ν_{max} 2958, 2924, 2176, 1729, 1698, 1455, 1414, 1371, 1317, 1249, 1030, 841, 760, 699, 643 and 582 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.75-2.65 (4H, m), 2.63 (2H, s), 2.01-1.95 (2H, m), 1.26 (3H, s, CH_3), 0.01 (9H, s). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 209.3 (2 x C, *C*=O), 102.5 (C, acetylenic-*C*), 87.6 (C, acetylenic-*C*), 63.8 (C), 38.6 (2 x CH_2), 27.1 (CH_2), 21.6 (CH_3), 17.1 (CH_2), -0.11 (3 x CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{20}O_2SiH$ 237.1311; Found 237.1312.

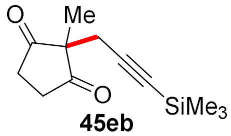


45cb

2,5,5-Trimethyl-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclohexane-1,3-dione (45cb): The title compound was prepared following procedure **1i** (Method-3), purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a pale-yellow liquid. Yield: 87% (46.01 mg). IR (Neat): ν_{max} 2956, 2176, 1727, 1696, 1456, 1408, 1373, 1327, 1249, 1052, 842, 760 and 656 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.64 (4H, br s), 2.61 (2H, s), 1.28 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.02 (3H, s, CH_3), 0.09 (9H, s, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.8 (2 x C, *C*=O), 102.7 (C, acetylenic-*C*), 87.9 (C, acetylenic-*C*), 62.9 (C), 52.1 (2 x CH_2), 30.4 (C), 29.3 (CH_3), 28.1 (CH_3), 26.7 (CH_2), 22.1 (CH_3), -0.14 (3 x

CH_3, $Si(CH_3)_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{24}O_2SiNa$ 287.1443; Found 287.1443.

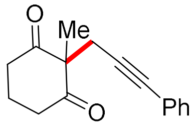
2-Methyl-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (45eb):[5b]



45eb

The title compound was prepared following procedure **1i** (Method-3), purified by column chromatography using EtOAc/hexanes (3/7), and isolated as a pale yellow liquid. Yield: 40% (17.79 mg). IR (Neat): ν_{max} 2959, 2176, 1728, 1452, 1417, 1372, 1315, 1250, 1073, 1044, 1021, 843, 761 and 643 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.78 (4H, m), 2.44 (2H, br s), 1.10 (3H, s), 0.01 (9H, s). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 215.6 (2 x C, *C*=O), 100.8 (C, acetylenic-*C*), 87.7 (C, acetylenic-*C*), 55.6 (C), 36.1 (2 x CH_2), 26.7 (CH_2), 18.7 (CH_3), -0.2 (3 x CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{18}O_2SiH$ 223.1154; Found 223.1153.

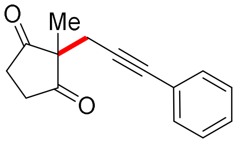
2-Methyl-2-(3-phenylprop-2-yn-1-yl)cyclohexane-1,3-dione (45ba):[5a] The title compound was prepared following procedure **1i** (Method-2), purified by column chromatography using EtOAc/hexanes (1.5/8.5), and isolated as a white semi solid.



45ba

Yield: 34% (16.34 mg). IR (Neat): ν_{max} 2923, 2853, 1728, 1696, 1597, 1489, 1455, 1416, 1371, 1317, 1216, 1130, 1024, 913, 757 and 692 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.32 (2H, m), 7.27-7.25 (3H, m), 2.86 (2H, s), 2.73 (4H, dt, J = 6.5, 2.5 Hz), 2.0 (2H, quintet, J = 6.5 Hz), 1.35 (3H, s). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 209.2 (2 x C, *C*=O), 131.6 (2 x CH), 128.2 (2 x CH), 128.0 (CH), 123.1 (C), 85.6 (C, acetylenic-*C*), 83.0 (C, acetylenic-*C*), 64.0 (C), 38.5 (2 x CH_2), 26.5 (CH_2), 21.7 (CH_3), 17.3 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}O_2H$ 241.1229; Found 241.1232.

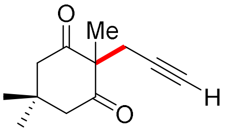
2-Methyl-2-(3-phenylprop-2-yn-1-yl)cyclopentane-1,3-dione (45ea):[5a] The title compound was prepared following procedure **1i** (Method-2), purified by column chromatography using EtOAc/hexanes (1/9), and isolated as a white semi solid. Yield: 40% (18.10 mg). IR (Neat): ν_{max} 2926, 1725, 1490, 1450, 1416, 1372, 1318, 1227, 1070, 991, 758 and 692 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.31 (2H, m), 7.30-7.26 (3H, m), 2.84 (4H, s), 2.70 (2H, s), 1.18 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 215.5 (2 x C, *C*=O), 131.6 (2 x CH), 128.3 (2 x CH), 128.3 (CH), 122.5 (C), 84.0 (C, acetylenic-*C*), 82.9 (C, acetylenic-*C*), 55.4 (C), 35.9 (2 x CH_2), 25.9 (CH_2), 18.9 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{14}O_2Na$ 249.0891; Found 249.0892.



45ea

1j. General Procedure for the Domino *C*-Methylation Followed by Trimethylsilyl Deprotection of TCRP Product 35cb: In an ordinary glass vial equipped with a magnetic stirring bar, 2.0 equiv. of K_2CO_3 (0.4 mmol, 55.28 mg), 5.0 equiv. of methyl iodide (1.0 mmol, 141.94 mg, 62.25 µL) were added to 1.0 equiv. of TCRP compound **35cb** (0.2 mmol, 50.08 mg) in 1.0 mL of methanol (0.2 M) solvent and the reaction mixture was stirred at 45 °C (oil bath) for 16 h. The crude reaction mixture was quenched with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure domino product **46cb** (30%, 11.53 mg) was obtained by column chromatography (silica gel, mixture of hexanes/ethyl acetate).

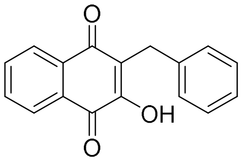
2,5,5-Trimethyl-2-(prop-2-yn-1-yl)cyclohexane-1,3-dione (46cb):[7a] The title compound was prepared following procedure **1i**, purified by column chromatography using EtOAc/hexanes (2/8), and isolated as a pale yellow liquid. Yield: 30% (11.53 mg). IR (Neat): ν_{max} 3280, 2955, 2360, 1728, 1695, 1455, 1373, 1326, 1094, 1058, 958 and 634 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.71 (2H, d, J = 14.8 Hz), 2.63 (2H, d, J = 2.4 Hz), 2.55 (2H, d, J = 14.8 Hz), 1.97 (1H, t, J = 2.4 Hz), 1.34 (3H, s, CH_3), 1.07 (3H, s, CH_3), 0.99 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (2 x C, *C*=O), 80.5 (C, acetylenic-*C*), 70.8 (CH, acetylenic-*C*H), 63.2 (C), 51.4 (2 x CH_2), 30.6 (C), 29.6 (CH_3), 27.4 (CH_3), 23.9 (CH_2), 22.7 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{16}O_2Na$ 215.1048; Found 215.1048.



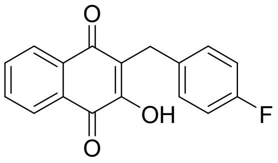
46cb (30%)

2.Organocatalytic Asymmetric Formal [3+2]-Cycloaddition as a Versatile Platform to Methanobenzo[7]annulenes:

2a. ʟ-Proline Catalyzed Cascade Three-Component Reductive Alkylation (TCRA) Reactions with 2-Hydroxy-1,4-naphthoquinone: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the aldehyde **47**, 0.3 mmol of 2-hydroxy-1,4-naphthoquinone **1** and 0.33 mmol of Hantzsch ester **34** was added 1.0 mL of DCM, and then the catalyst ʟ-proline **3n** (0.06 mmol) was added, and the reaction mixture was stirred at room temparature for 12-17 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products **48a–u** were obtained in 50-90% yield (silica gel, mixture of hexane/ethyl acetate).


48a

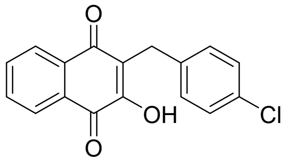
2-Benzyl-3-hydroxy-[1,4]naphthoquinone (48a): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 90%; Mp.: 174-175 °C; IR (Neat): ν_{max} 3344, 1639, 1587, 1453, 1376, 1278, 1216, 1076, 1024, 942, 761, 730 and 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (1H, d, *J* = 7.5 Hz), 8.07 (1H, d, *J* = 7.5 Hz), 7.75 (1H, dt, *J* = 7.5, 1.0 Hz), 7.68 (1H, dt, *J* = 7.5, 1.0 Hz), 7.42 (2H, d, *J* = 7.0 Hz), 7.28 (2H, t, *J* = 7.5 Hz), 7.20 (1H, t, *J* = 7.5 Hz), 3.97 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.3 (C, C=O), 181.6 (C, C=O), 153.0 (C), 138.9 (C), 134.9 (CH), 132.9 (CH), 132.8 (C), 129.4 (C), 129.2 (2 x CH), 128.4 (2 x CH), 126.9 (CH), 126.3 (CH), 126.1 (CH), 123.0 (C), 29.1 (CH$_2$); HRMS m/z 287.0686 (M + Na$^+$), calcd for $C_{17}H_{12}O_3Na$ 287.0684.


48b

2-(4-Fluorobenzyl)-3-hydroxynaphthalene-1,4-dione (48b): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 80%; Mp.: 176-178 °C; IR (Neat): ν_{max} 3328, 1660, 1634, 1593, 1371, 1350, 1278, 1221, 823 and 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, dd, *J* = 7.5, 1.0 Hz), 8.07 (1H, dd, *J* = 7.5, 1.0 Hz), 7.75 (1H, dt, *J* = 7.5, 1.5 Hz), 7.68 (1H, dt, *J* = 7.5 1.0 Hz), 7.42 (1H, s), 7.35 (2H, m), 6.94 (2H, tt, *J* = 9.5, 3.0 Hz), 3.90 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.3 (C, C=O), 181.6 (C, C=O), 161.5 (C, d, *J* = 242.5 Hz, *C*-F), 152.9 (C), 135.0 (CH), 134.5 (C, d, *J* = 3.75 Hz), 133.0 (CH), 132.7 (C), 130.6 (2 x CH, d, *J* = 7.5 Hz), 129.3 (C), 126.9 (CH), 126.1

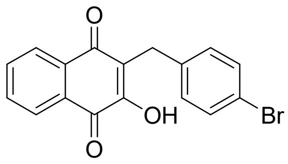
(CH), 122.8 (C), 115.1 (2 x CH, d, *J* = 20.0 Hz), 28.3 (CH_2); HRMS m/z 305.0586 (M + Na^+), calcd for $C_{17}H_{11}FO_3Na$ 305.0590.

2-(4-Chlorobenzyl)-3-hydroxynaphthalene-1,4-dione (48c): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 80%; Mp.: 163-165 °C; IR (KBr): ν_{max} 3380, 2357, 2331, 1665, 1634, 1587, 1494, 1365, 1272, 1226, 1092, 1040, 792, 653 and 560 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.10 (1H, dd, *J* = 8.0, 1.0 Hz), 8.05 (1H, dd, *J* = 7.5, 1.0 Hz), 7.74 (1H, dt, *J* = 7.5, 1.5 Hz), 7.66 (1H, dt, *J* = 7.5 1.0 Hz), 7.31 (2H, td, *J* = 8.5, 1.5 Hz), 7.20 (2H, td, *J* = 8.5, 1.5 Hz), 3.89 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.2 (C, C=O), 181.5 (C, C=O), 153.0 (C), 137.3 (C), 135.0 (CH), 133.0 (CH), 132.6 (C), 132.1 (C), 130.5 (2 x CH), 129.3 (C), 128.4 (2 x CH), 126.9 (CH), 126.2 (CH), 122.5 (C), 28.4 (CH_2); HRMS m/z 321.0294 (M + Na^+), calcd for $C_{17}H_{11}ClO_3Na$ 321.0294.



48c

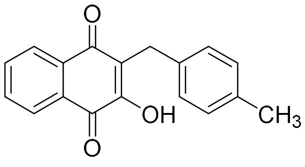
2-(4-Bromobenzyl)-3-hydroxynaphthalene-1,4-dione (48d): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 70%; Mp.: 166-168 °C; IR (Neat): ν_{max} 3375, 2356, 2339, 1671, 1632, 1594, 1484, 1369, 1271, 1227 and 783 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, dd, *J* = 7.5, 1.0 Hz), 8.07 (1H, dd, *J* = 7.5, 1.0 Hz), 7.75 (1H, dt, *J* = 7.5, 1.0 Hz), 7.68 (1H, dt, *J* = 7.5, 1.0 Hz), 7.37 (2H, br d, *J* = 8.5 Hz), 7.27 (2H, br d, *J* = 8.5 Hz),



48d

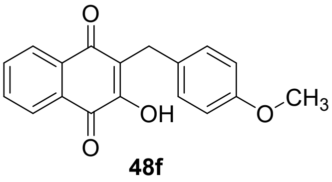
3.88 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.2 (C, C=O), 181.5 (C, C=O), 153.1 (C), 137.9 (C), 135.1 (CH), 133.1 (CH), 132.7 (C), 131.4 (2 x CH), 130.9 (2 x CH), 129.3 (C), 126.9 (CH), 126.2 (CH), 122.4 (C), 120.2 (C), 28.5 (CH_2); HRMS m/z 364.9786 (M + Na^+), calcd for $C_{17}H_{11}BrO_3Na$ 364.9789.

2-Hydroxy-3-(4-methylbenzyl)naphthalene-1,4-dione (48e): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 75%; Mp.: 162-164 °C; IR (Neat): ν_{max} 3359, 2925, 1655, 1587, 1505, 1458, 1355, 1210, 1035, 952, 808, 756, 725 and 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (1H, dd, *J* = 8.0, 1.5 Hz), 8.04 (1H, dd, *J* = 8.0, 1.5 Hz), 7.73 (1H, dt, *J* = 7.5, 1.0 Hz), 7.65 (1H, dt, *J* = 7.5, 1.5 Hz), 7.43 (1H, s), 7.27 (2H, br d, *J* = 8.0 Hz), 7.06 (2H, br d, *J* = 8.0 Hz), 3.90 (2H, s), 2.28 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.4 (C, C=O), 181.7 (C, C=O), 152.9 (C), 135.8 (2 x C), 134.9 (CH), 132.9 (CH), 132.8 (C), 129.4 (C), 129.1 (2 x CH), 129.0 (2 x CH), 126.9 (CH), 126.0 (CH), 123.3 (C), 28.6 (CH_2), 20.9 (CH_3); HRMS m/z 301.0838 (M + Na^+), calcd for $C_{18}H_{14}O_3Na$ 301.0841.



48e

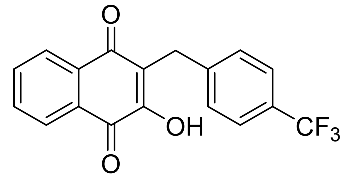
2-Hydroxy-3-(4-methoxybenzyl)naphthalene-1,4-dione (48f): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 50%; Mp.: 145-147 °C; IR (Neat): ν_{max} 3344, 2930, 1660, 1644, 1593, 1510, 1458, 1371, 1350, 1278, 1216, 1107, 1030, 947, 813 and 725



48f

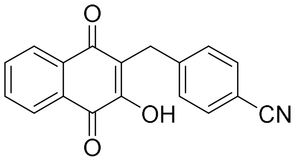
cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.10 (1H, dd, *J* = 7.5, 1.0 Hz), 8.04 (1H, dd, *J* = 7.5, 1.0 Hz), 7.72 (1H, dt, *J* = 7.5, 1.0 Hz), 7.65 (1H, dt, *J* = 7.5, 1.0 Hz), 7.31 (2H, br d, *J* = 8.5 Hz), 6.79 (2H, td, *J* = 9.5, 2.0 Hz), 3.88 (2H, s), 3.74 (3H, s); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 184.4 (C, C=O), 181.7 (C, C=O), 158.1 (C), 152.8 (C), 134.9 (CH), 132.9 (CH), 132.7 (C), 130.9 (C), 130.1 (2 x CH), 129.4 (C), 126.8 (CH), 126.0 (CH), 123.3 (C), 113.8 (2 x CH), 55.2 (CH$_3$), 28.1 (CH$_2$); HRMS m/z 317.0791 (M + Na$^+$), calcd for $C_{18}H_{14}O_4Na$ 317.0790.

2-Hydroxy-3-(4-(trifluoromethyl)benzyl)naphthalene-1,4-dione (48g): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 70%; Mp.: 188-190 °C; IR (Neat): ν_{max} 3364, 1676, 1627, 1589, 1369, 1331, 1282, 1227, 1156, 1106, 1063, 1002 and 942 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.12 (1H, dd, *J* = 7.5, 1.0 Hz), 8.08 (1H, dd, *J* = 7.5, 1.0 Hz), 7.76 (1H, dt, *J* = 7.5, 1.5 Hz), 7.69 (1H, dt, *J* = 7.5, 1.5 Hz), 7.50 (4H, m), 3.99 (2H, s); ^{13}C NMR (CDCl$_3$, 100 Mz, DEPT-135) δ 184.2 (C, C=O), 181.4 (C, C=O), 153.2 (C), 142.9 (C), 135.1 (CH), 133.1 (CH), 132.7 (C), 129.4 (2 x CH), 129.3 (C), 128.6 (C, q, *J* = 32.0 Hz), 126.9 (CH), 126.2 (CH), 125.3 (2 x CH, q, *J* = 4.0 Hz), 124.2 (C, q, *J* = 270.0 Hz, *C*F$_3$), 122.0 (C), 29.0 (CH$_2$); HRMS m/z 355.0556 (M + Na$^+$), calcd for $C_{18}H_{11}F_3O_3Na$ 355.0558.



48g

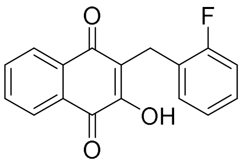
4-((3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)benzonitrile (48h):



48h

Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 80%; Mp.: 185-186 °C; IR (KBr): ν_{max} 3349, 2915, 2223, 1639, 1587, 1371, 1350, 1272, 1221, 1019, 926, 725 and 668 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.12 (1H, dd, *J* = 7.5, 1.0 Hz), 8.09 (1H, dd, *J* = 7.5, 1.0 Hz), 7.77 (1H, dt, *J* = 7.5, 1.0 Hz), 7.70 (1H, dt, *J* = 7.5, 1.5 Hz), 7.55 (2H, br d, *J* = 6.5 Hz), 7.49 (2H, br d, *J* = 8.5 Hz), 3.99 (2H, s); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 184.1 (C, C=O), 181.3 (C, C=O), 153.3 (C), 144.4 (C), 135.2 (CH), 133.2 (CH), 132.5 (C), 132.2 (2 x CH), 129.9 (2 x CH), 129.3 (C), 126.9 (CH), 126.3 (CH), 121.4 (C), 118.9 (C), 110.2 (C), 29.3 (CH$_2$); HRMS m/z 312.0637 (M + Na$^+$), calcd for $C_{18}H_{11}NO_3Na$ 312.0637.

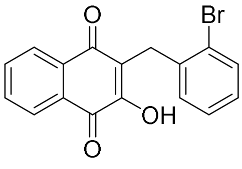
2-(2-Fluorobenzyl)-3-hydroxynaphthalene-1,4-dione (48i): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 80%; Mp.: 158-160 °C; IR (KBr): ν_{max} 3380, 1639, 1582, 1448, 1355, 1278, 1221, 1019, 725 and 653 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.14 (1H, dd, *J* = 7.6, 0.8 Hz), 8.10 (1H, dd, *J* = 7.6, 1.2 Hz), 7.78 (1H, dt, *J* = 7.6, 1.6 Hz), 7.70 (1H, dt, *J* = 7.6, 1.6 Hz), 7.50 (1H, s), 7.32-7.28 (1H, m), 7.21-7.15 (1H, m), 7.05-7.01 (2H, m), 4.02 (2H, s); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 184.2 (C, C=O), 181.5 (C, C=O), 160.9 (C, d, *J* = 244.0 Hz, *C*-F), 153.6 (C), 135.1 (CH), 133.0 (CH), 132.8 (C), 130.8 (CH, d, *J* = 5.0 Hz), 129.3 (C), 128.0 (CH, d, *J* = 8.0 Hz), 127.0 (CH), 126.2 (CH), 125.4 (C, d, *J* =



48i

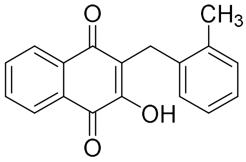
16.0 Hz), 123.9 (CH, d, *J* = 3.0 Hz), 121.5 (C), 115.3 (CH, d, *J* = 22.0 Hz), 22.1 (CH_2, d, *J* = 4.0 Hz); HRMS m/z 305.0585 ($M + Na^+$), calcd for $C_{17}H_{11}FO_3Na$ 305.0590.

2-(2-Bromobenzyl)-3-hydroxynaphthalene-1,4-dione (48j): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 80%; Mp.: 162-164 °C; IR (KBr): ν_{max} 3380, 1639, 1577, 1360, 1272, 1221, 1019, 823 and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.14-8.11 (2H, m), 7.78 (1H, dt, *J* = 7.5, 1.5 Hz), 7.71 (1H, dt, *J* = 7.6, 1.5 Hz), 7.56 (1H, dd, *J* = 8.0, 1.0 Hz), 7.46 (1H, s), 7.17 (1H, dt, *J* = 7.5, 2.0 Hz), 7.14 (1H, dt, *J* = 7.5, 2.0 Hz), 7.05 (1H, dt, *J* = 7.0, 2.0 Hz), 4.09 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.2 (C, C=O), 181.4 (C, C=O), 153.9 (C), 137.8 (C), 135.1 (CH), 133.0 (CH), 132.8 (C), 132.8 (CH), 129.6 (CH), 129.4 (C), 127.8 (CH), 127.3 (CH), 127.1 (CH), 126.2 (CH), 124.6 (C), 121.4 (C), 29.6 (CH_2); HRMS m/z 364.9789 ($M+Na^+$), calcd for $C_{17}H_{11}BrO_3Na$ 364.9789.



48j

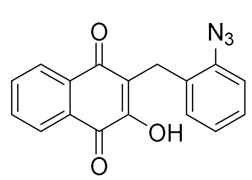
2-Hydroxy-3-(2-methylbenzyl)naphthalene-1,4-dione (48k): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 60%; Mp.: 168-170 °C; IR (Neat): ν_{max} 3369, 1639, 1587, 1371, 1350, 1272, 1231, 1040, 957 and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, dd, *J* = 7.5, 1.0 Hz), 8.09 (1H, dd, *J* = 7.5, 1.0 Hz), 7.75 (1H, dt, *J* = 7.5, 1.5 Hz), 7.68 (1H, dt, *J* = 7.5, 1.5 Hz), 7.17-7.14 (2H, m), 7.12-7.04 (2H, m), 3.94 (2H, s), 2.47 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.4 (C, C=O), 181.5 (C, C=O), 153.6



48k

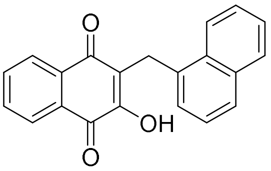
(C), 136.8 (C), 136.4 (C), 135.0 (CH), 132.9 (CH), 132.9 (C), 130.2 (CH), 129.4 (C), 128.6 (CH), 126.9 (CH), 126.3 (CH), 126.1 (CH), 125.8 (CH), 122.7 (C), 26.2 (CH_2), 19.9 (CH_3); HRMS m/z 279.1022 ($M + H^+$), calcd for $C_{18}H_{15}O_3$ 279.1022.

2-(2-Azidobenzyl)-3-hydroxynaphthalene-1,4-dione (48l): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 75%; Mp.: 142-144 °C; IR (KBr): ν_{max} 3333, 2104, 1634, 1582, 1484, 1376, 1267, 1221, 1040, 761 and 735 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.13 (1H, dd, *J* = 7.5, 1.0 Hz), 8.12 (1H, dd, *J* = 7.5, 1.0 Hz), 7.78 (1H, dt, *J* = 7.5, 1.5 Hz), 7.71 (1H, dt, *J* = 7.5, 1.5 Hz), 7.49 (1H, s), 7.26 (1H, dt, *J* = 7.5, 1.0 Hz), 7.20-7.15 (2H, m), 7.03 (1H, dt, *J* = 7.5, 1.0 Hz), 3.94 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.2 (C, C=O), 181.4 (C, C=O), 153.8 (C), 138.1 (C), 135.0 (CH), 133.0 (CH), 132.8 (C), 130.1 (CH), 129.9 (C), 129.4 (C), 127.7 (CH), 127.0 (CH), 126.2 (CH), 124.7 (CH), 122.0 (C), 118.1 (CH), 24.2 (CH_2); HRMS m/z 328.0698 ($M+Na^+$), calcd for $C_{17}H_{11}N_3O_3Na$ 328.0698.



48l

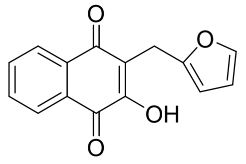
2-Hydroxy-3-(naphthalen-1-ylmethyl)naphthalene-1,4-dione (48m): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 50%; Mp.: 167-170 °C; IR (Neat): ν_{max} 3359, 3049, 1665, 1644, 1587, 1365, 1340, 1267, 1226, 1045, 1014, 947, 787 and 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.32 (1H, d, *J* = 8.4 Hz), 8.09 (1H, dd, *J* = 7.6, 0.8 Hz),



48m

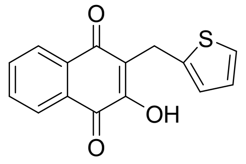
8.03 (1H, d, *J* = 7.2 Hz), 7.81 (1H, d, *J* = 8.0 Hz), 7.72-7.68 (2H, m), 7.62 (1H, br t, *J* = 7.6 Hz), 7.52 (1H, dt, *J* = 6.8, 1.2 Hz), 7.46-7.43 (2H, m), 7.34 (1H, t, *J* = 8.0 Hz), 4.39 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.4 (C, C=O), 181.4 (C, C=O), 153.9 (C), 134.9 (CH), 134.4 (C), 133.8 (C), 132.9 (C), 132.9 (CH), 132.1 (C), 129.4 (C), 128.6 (CH), 127.0 (CH), 126.9 (CH), 126.7 (CH), 126.1 (CH), 125.9 (CH), 125.4 (CH), 125.4 (CH), 124.0 (CH), 122.3 (C), 26.2 (CH_2); HRMS m/z 337.0891 (M + Na^+), calcd for $C_{21}H_{14}O_3Na$ 337.0841.

2-(Furan-2-ylmethyl)-3-hydroxynaphthalene-1,4-dione (48n): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 80%; Mp.: 151-153 °C; IR (Neat): ν_{max} 3333, 1639, 1587, 1371, 1350, 1272, 1210, 1071, 942, 808 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (1H, dd, *J* = 8.0, 1.2 Hz), 8.08 (1H, dd, *J* = 8.0, 1.2 Hz), 7.76 (1H, dt, *J* = 7.6, 1.2 Hz), 7.69 (1H, dt, *J* = 7.6 1.2 Hz), 7.28 (1H, dd, *J* = 2.0, 0.8 Hz), 6.27 (1H, dd, *J* = 3.2, 2.5 Hz), 6.12 (1H, dd, *J* = 3.2, 0.8 Hz), 3.99 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.9 (C, C=O), 181.5 (C, C=O), 153.4 (C), 151.6 (C), 141.3 (CH), 135.1 (CH), 133.0 (CH), 132.7 (C), 129.3 (C), 126.9 (CH), 126.2 (CH), 119.6 (C), 110.3 (CH), 106.4 (CH), 21.9 (CH_2); HRMS m/z 277.0477 (M + Na^+), calcd for $C_{15}H_{10}O_4Na$ 277.0477.



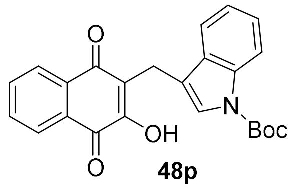
48n

2-Hydroxy-3-(thiophen-2-ylmethyl)naphthalene-1,4-dione (48o): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 80%; Mp.: 154-156 °C; IR (Neat): ν_{max} 3333, 2357, 1639, 1598, 1371, 1340, 1272, 1257, 1216, 1112, 1045, 931 and 730 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.13 (1H, dd, J = 8.0, 1.0 Hz), 8.06 (1H, dd, J = 7.5, 1.0 Hz), 7.75 (1H, dt, J = 7.5, 1.0 Hz), 7.67 (1H, dt, J = 7.5 1.5 Hz), 7.51 (1H, s), 7.10 (1H, dd, J = 5.5, 1.5 Hz), 6.97 (1H, dd, J = 3.5, 1.0 Hz), 6.88 (1H, dd, J = 5.5, 3.5 Hz), 4.13 (2H, s); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 183.9 (C, C=O), 181.6 (C, C=O), 152.8 (C), 140.4 (C), 135.0 (CH), 133.0 (CH), 132.7 (C), 129.4 (C), 126.9 (CH), 126.7 (CH), 126.1 (CH), 125.9 (CH), 124.0 (CH), 121.9 (C), 23.2 (CH$_2$); HRMS m/z 293.0248 (M + Na$^+$), calcd for $C_{15}H_{10}O_3SNa$ 293.0248.



48o

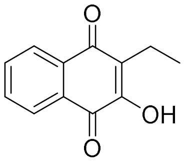
***tert*-Butyl 3-((3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-1*H*-indole-1-carboxylate (48p)**: Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 60%; Mp.: 101-102 °C; IR (Neat): ν_{max} 3375, 2977, 2920, 1727, 1660, 1587, 1448, 1360, 1303, 1272, 1221, 1159, 1076, 1019, 942, 854 and 725 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.11 (1H, dd, J = 7.6, 0.8 Hz), 8.04 (1H, dd, J = 7.6, 0.8 Hz), 8.10-8.00 (1H, m), 7.77 (1H, br d, J = 7.6 Hz), 7.72 (1H, dt, J = 7.6, 1.2 Hz), 7.64 (1H, dt, J = 7.6, 1.2 Hz), 7.52 (1H, s), 7.29-7.20 (2H, m), 3.99 (2H, s), 1.64 (9H, s); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 184.2 (C, C=O), 181.4 (C, C=O), 153.0 (C), 149.8 (C),



48p

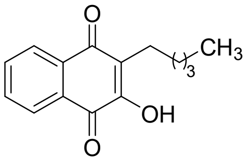
135.2 (C), 134.9 (CH), 132.9 (CH), 132.7 (C), 130.3 (C), 129.3 (C), 126.9 (CH), 126.1 (CH), 124.3 (CH), 124.2 (CH), 122.4 (CH), 121.8 (C), 119.4 (CH), 117.3 (C), 115.0 (CH), 83.4 (C), 28.1 (3 x CH_3), 18.6 (CH_2); HRMS m/z 426.1315 (M + Na^+), calcd for $C_{24}H_{21}NO_5Na$ 426.1317.

2-Ethyl-3-hydroxynaphthalene-1,4-dione (48q): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 80%; Mp.: 138-139 °C; IR (KBr): ν_{max} 3354, 2972, 2920, 2858, 1639, 1587, 1448, 1376, 1350, 1247, 1097, 968, 864 and 725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, br d, J = 8.0 Hz), 8.06 (1H, br d, J = 8.0 Hz), 7.74 (1H, dt, J = 7.5, 1.0 Hz), 7.67 (1H, dt, J = 8.0, 1.0 Hz), 7.41 (1H, s), 2.62 (2H, q, J = 7.5 Hz), 1.15 (3H, t, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.5 (C, C=O), 181.5 (C, C=O), 152.7 (C), 134.7 (CH), 132.9 (C), 132.8 (CH), 129.4 (C), 126.7 (CH), 126.0 (CH), 125.9 (C), 16.7 (CH_2), 12.6 (CH_3); HRMS m/z 203.0700 (M + H^+), calcd for $C_{12}H_{11}O_3$ 203.0708.



48q

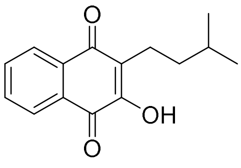
2-Hydroxy-3-pentylnaphthalene-1,4-dione (48r): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 85%; Mp.: 98-99 °C; IR (KBr): ν_{max} 3416, 3344, 2951, 2920, 2853, 1655, 1644, 1593, 1463, 1381, 1210, 1112, 1014, 937, 864, 797, 735, 689 and 575 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, d, J = 6.7 Hz), 8.06 (1H, d, J = 7.5 Hz), 7.74 (1H, dt, J = 8.0, 1.0 Hz), 7.67 (1H, dt, J = 7.5, 1.0 Hz), 7.39 (1H, s), 2.59 (2H, t, J



485r

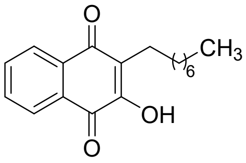
= 7.5 Hz), 1.57-1.51 (2H, m), 1.39-1.31 (4H, m), 0.90 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.6 (C, C=O), 181.4 (C, C=O), 153.0 (C), 134.7 (CH), 132.9 (C), 132.8 (CH), 129.4 (C), 126.7 (CH), 126.0 (CH), 124.8 (C), 31.8 (CH_2), 27.9 (CH_2), 23.3 (CH_2), 22.4 (CH_2), 13.9 (CH_3); HRMS m/z 267.0995 (M + Na^+), calcd for $C_{15}H_{16}O_3Na$ 267.0997.

2-Hydroxy-3-isopentylnaphthalene-1,4-dione (48s): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 90%; Mp.: 101-102 °C; IR (Neat): ν_{max} 3359, 2951, 1639, 1593, 1453, 1376, 1350, 1278, 1221, 1112, 725 and 658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (1H, dd, *J* = 7.6, 0.4 Hz), 8.07 (1H, dd, *J* = 7.6, 0.4 Hz), 7.74 (1H, dt, *J* = 7.6, 1.2 Hz), 7.67 (1H, dt, *J* = 7.6, 1.2 Hz), 7.34 (1H, d, *J* = 1.6 Hz), 2.62-2.58 (2H, m), 1.62 (1H, septet, *J* = 6.8 Hz), 1.44-1.38 (2H, m), 0.97 (6H, d, *J* = 6.8 Hz, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.6 (C, C=O), 181.4 (C, C=O), 152.9 (C), 134.8 (CH), 132.9 (C), 132.8 (CH), 129.4 (C), 126.7 (CH), 126.0 (CH), 125.1 (C), 37.2 (CH_2), 28.3 (CH), 22.4 (2 x CH_3), 21.4 (CH_2); HRMS m/z 267.0993 (M + Na^+), calcd for $C_{15}H_{16}O_3Na$ 267.0997.



48s

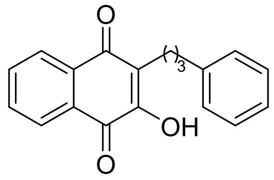
2-Hydroxy-3-octylnaphthalene-1,4-dione (48t): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 90%; Mp.: 87-88 °C; IR (KBr): ν_{max} 3349, 2956, 2920, 2848, 1665, 1639, 1587, 1458, 1345, 1272, 1252, 1221, 1102, 1024, 999, 937 and 720 cm^{-1}; ^{1}H



48t

NMR ($CDCl_3$, 400 MHz): δ 8.11 (1H, d, *J* = 7.6 Hz), 8.07 (1H, d, *J* = 7.6 Hz), 7.75 (1H, t, *J* = 7.6 Hz), 7.67 (1H, t, *J* = 7.6 Hz), 7.34 (1H, br s), 2.59 (2H, t, *J* = 8.0 Hz), 1.53 (2H, quintet, *J* = 8.0 Hz), 1.37-1.26 (10H, m), 0.86 (3H, t, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.7 (C, C=O), 181.4 (C, C=O), 153.0 (C), 134.8 (CH), 132.9 (C), 132.8 (CH), 129.4 (C), 126.7 (CH), 126.0 (CH), 124.8 (C), 31.8 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.3 (CH_2), 23.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS m/z 309.1467 (M + Na^+), calcd for $C_{18}H_{22}O_3Na$ 309.1467.

2-Hydroxy-3-(3-phenylpropyl)naphthalene-1,4-dione (48u): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid; Yield: 82%; Mp.: 127-128°C; IR (Neat): ν_{max} 3354, 1639, 1582, 1371, 1340, 1262, 1221, 1050, 973, and 720 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, dd, *J* = 7.5, 1.0 Hz), 8.06 (1H, dd, *J* = 7.5, 1.0 Hz), 7.74 (1H, dt, *J* = 7.5, 1.0 Hz), 7.66 (1H, dt, *J* = 7.5, 1.5 Hz), 7.35 (1H, s), 7.26-7.23 (2H, m), 7.21-7.14 (2H, m), 7.15-7.12 (1H, m), 2.71 (2H, t, *J* = 8.0 Hz), 2.67 (2H, t, *J* = 8.0 Hz), 1.89 (2H, quintet, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.6 (C, C=O), 181.3 (C, C=O), 153.1 (C), 142.1 (C), 134.8 (CH), 132.9 (C), 132.8 (CH), 129.4 (C), 128.3 (2 x CH), 128.2 (2 x CH), 126.8 (CH), 126.0 (CH), 125.7 (CH), 124.2 (C), 36.0 (CH_2), 29.6 (CH_2), 23.3 (CH_2); HRMS m/z 293.1178 (M + H^+), calcd for $C_{19}H_{17}O_3$ 293.1178.



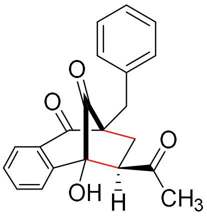
48u

2b. Preparation of Racemic Methanobenzo[7]annulenes 51 under the 4-Dimethylaminopyridine catalysis: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-hydroxy-1,4-naphthoquinone derivative **48** and 0.9 mmol of alkyl vinyl ketone **47** with a catalytic amount of 4-dimethylaminopyridine **3p** in 1.0 mL of toluene solvent and the reaction mixture was stirred at room temparature for 9-12 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **51** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2c. Preparation of Racemic Methanobenzo[7]annulenes 51 under the 1:1 mixture of 57a and 57b: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-hydroxy-1,4-naphthoquinone derivative **48** and 0.9 mmol of alkyl vinyl ketone **49** with a catalytic amount of 1:1 mixture of **57a** and **57b** in 1.0 mL of toluene solvent and the reaction mixture was stirred at room temparature for 6-12 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **51** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2d. Preparation of Asymmetric Methanobenzo[7]annulenes 51aa-51ua under the Chiral Quinine Thiourea 57b catalysis: In an ordinary glass vial equipped with a magnetic stirring bar, to Q-NH-thiourea **57b** (0.06 mmol) and $C_6H_5CF_3$ (1.0 mL) was added and stirred at 20 °C for 5 minutes then 0.3 mmol of 2-hydroxy-1,4-naphthoquinone derivative **48a-u** and 0.9 mmol of methyl vinyl ketone **49a** was added, and the reaction mixture was stirred at 20 °C for 2-36 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure chiral products **51aa-51ua** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

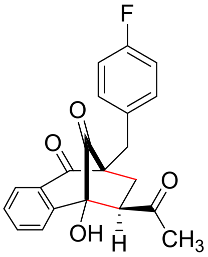
(5*S*,6*R*,8*R*)-6-Acetyl-8-benzyl-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51aa): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 90%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 25.46 min (major), t_R = 21.74 min (minor) [For major isomer]; t_R = 12.01 min (major), t_R = 11.2 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -4.9° [*c* = 0.76, $CHCl_3$, 95% *ee* and 61:1 *dr*]; IR (Neat): ν_{max} 3447, 3028, 2915, 2853, 1768, 1691, 1598, 1453, 1355, 1278, 1169, 1055, 942 and 709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer): δ 8.08 (1H, dd, *J* = 8.0, 0.5 Hz), 7.88 (1H, dd, *J* = 8.0, 0.5 Hz), 7.72 (1H, dt, *J* = 8.0, 1.0 Hz), 7.51 (1H, dt, *J* = 8.0, 1.0 Hz), 7.36 (2H, br d, *J* = 7.5 Hz), 7.29 (2H, br t, *J* = 7.5 Hz), 7.22 (1H, tt, *J* = 7.5, 2.0 Hz), 3.82 (1H, s), 3.50 (1H, d, *J* = 14.5 Hz), 3.41 (1H, d, *J* = 14.5 Hz), 3.11 (1H, dd, *J* = 10.0, 2.5 Hz), 2.31 (1H, dd, *J* = 14.5, 2.5 Hz), 2.01 (3H, s), 1.78 (1H, dd, *J* = 14.5, 10.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer): δ 208.3 (C, *C*=O), 204.7 (C, *C*=O), 195.4 (C, *C*=O), 144.5 (C), 136.7 (C), 135.5 (CH), 131.3 (2 x CH), 129.3 (C), 129.0 (CH), 128.2 (2 x CH), 127.9 (CH), 126.7 (CH), 124.0 (CH), 83.0 (C), 64.7 (C), 52.7 (CH), 31.7



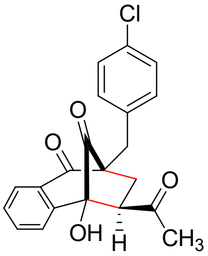
(-)-51aa

(CH_2), 31.0 (CH_3), 28.3 (CH_2); HRMS m/z 357.1104 (M + Na^+), calcd for $C_{21}H_{18}O_4Na$ 357.1103.

(5*S*,6*R*,8*R*)-6-Acetyl-8-(4-fluorobenzyl)-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ba): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 80%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 32.47 min (major), t_R = 116.73 min (minor) [For major isomer], t_R = 51.06 min (major), t_R = 77.78 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -14.6° (*c* = 0.92, $CHCl_3$, 95% *ee* and 20:1 *dr*); IR (Neat): ν_{max} 3458, 3069, 3006, 2928, 1771, 1689, 1599, 1510, 1360, 1331, 1280, 1223, 1162, 931, 849, 783, 736, 669 and 589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.07 (1H, dd, *J* = 8.0, 1.0 Hz), 7.90 (1H, dd, *J* = 8.0, 1.0 Hz), 7.73 (1H, dt, *J* = 8.0, 1.5 Hz), 7.50 (1H, dt, *J* = 8.0, 1.5 Hz), 7.36-7.33 (2H, m), 6.97 (2H, tt, *J* = 9.5, 2.0 Hz), 3.85 (1H, s), 3.47 (1H, d, *J* = 14.5 Hz), 3.35 (1H, d, *J* = 14.5 Hz), 3.15 (1H, dd, *J* = 9.5, 2.5 Hz), 2.29 (1H, dd, *J* = 14.5, 2.5 Hz), 2.10 (3H, s), 1.76 (1H, dd, *J* = 15.0, 10.0 Hz), ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.4 (C, *C*=O), 204.7 (C, *C*=O), 195.3 (C, *C*=O), 161.7 (C, d, *J* = 243.7 Hz, *C*-F), 144.5 (C), 135.5 (CH), 132.7 (2 x CH, d, *J* = 7.5 Hz), 132.3 (C, d, *J* = 2.5 Hz), 129.2 (C), 129.0 (CH), 127.9 (CH), 123.9 (CH), 114.9 (2 x CH, d, *J* = 20.0 Hz), 82.9 (C), 64.6 (C), 52.6 (CH), 31.4 (CH_3), 31.0 (CH_2), 28.4 (CH_2), HRMS m/z 375.1011 (M + Na^+), calcd for $C_{21}H_{17}FO_4Na$ 375.1009.



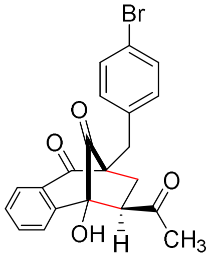
(-)-51ba



(-)-51ca

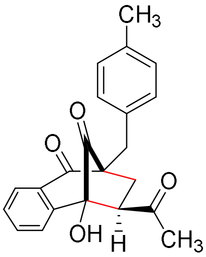
(5*S*,6*R*,8*R*)-6-Acetyl-8-(4-chlorobenzyl)-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ca): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as oily liquid; Yield: 90%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 28.07 min (major), t_R = 27.01 min (minor) [For major isomer], t_R = 23.31 min (major), t_R = 52.9 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -5.6° (*c* = 1.25, $CHCl_3$, 95% *ee* and 18:1 *dr*); IR (Neat): ν_{max} 3459, 3068, 2926, 1770, 1690, 1597, 1491, 1453, 1359, 1330, 1280, 1168, 1090 , 1069, 977, 932, 845, 779 and 734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer): δ 8.08 (1H, br d, *J* = 8.0 Hz), 7.90 (1H, br d, *J* = 7.5 Hz), 7.74 (1H, br t, *J* = 7.5 Hz), 7.52 (1H, br t, *J* = 7.5 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 7.26 (2H, m), 3.72 (1H, s), 3.50 (1H, d, *J* = 14.5 Hz), 3.36 (1H, d, *J* = 14.5 Hz), 3.16 (1H, dd, *J* = 9.5, 2.5 Hz), 2.28 (1H, dd, *J* = 14.5, 2.5 Hz), 2.12 (3H, s), 1.76 (1H, dd, *J* = 14.5, 10.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer): δ 208.4 (C, *C*=O), 204.5 (C, *C*=O), 195.2 (C, *C*=O), 144.5 (C), 135.6 (CH), 135.2 (C), 132.6 (2 x CH), 132.5 (C), 129.2 (C), 129.0 (CH), 128.3 (2 x CH), 128.0 (CH), 123.9 (CH), 82.9 (C), 64.4 (C), 52.6 (CH), 31.6 (CH_3), 31.3 (CH_2), 28.6 (CH_2); HRMS m/z 391.0713 (M + Na^+), calcd for $C_{21}H_{17}ClO_4Na$ 391.0713.

(5*S*,6*R*,8*R*)-6-Acetyl-8-(4-bromobenzyl)-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51da): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily; Yield: 96%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 25.1 min (major), t_R = 90.96 min (minor) [For major isomer], t_R = 29.56 min (major), t_R = 58.85 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -4.2° (*c* = 1.51, $CHCl_3$, 96% *ee* and 36:1 *dr*); IR (Neat): ν_{max} 3396, 3070, 1769, 1690, 1596, 1486, 1450, 1359, 1068, 854, 779 and 728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.06 (1H, dd, *J* = 8.0, 1.0 Hz), 7.90 (1H, dd, *J* = 8.0, 0.5 Hz), 7.73 (1H, dt, *J* = 8.0, 1.5 Hz), 7.50 (1H, dt, *J* = 8.0, 1.5 Hz), 7.38 (2H, td, *J* = 8.0, 1.5 Hz), 7.26 (2H, td, *J* = 9.5, 2.5 Hz), 3.88 (1H, s), 3.46 (1H, d, *J* = 14.5 Hz), 3.31 (1H, d, *J* = 15.0 Hz), 3.16 (1H, dd, *J* = 9.5, 2.5 Hz), 2.27 (1H, dd, *J* = 14.5, 2.5 Hz), 2.12 (3H, s), 1.74 (1H, dd, *J* = 14.5, 9.5 Hz), ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.5 (C, *C*=O), 204.5 (C, *C*=O), 195.2 (C, *C*=O), 144.5 (C), 135.7 (C), 135.5 (CH), 132.9 (2 x CH), 131.1 (2 x CH), 129.1 (C), 129.0 (CH), 128.0 (CH), 124.0 (CH), 120.6 (C), 82.9 (C), 64.3 (C), 52.6 (CH), 31.5 (CH_3), 31.3 (CH_2), 28.6 (CH_2); HRMS m/z 435.0208 (M + Na^+), calcd for $C_{21}H_{17}BrO_4Na$ 435.0208.



(-)-51da

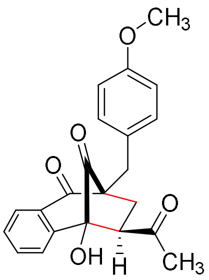
(5*S*,6*R*,8*R*)-6-Acetyl-5-hydroxy-8-(4-methylbenzyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ea):



(-)-51ea

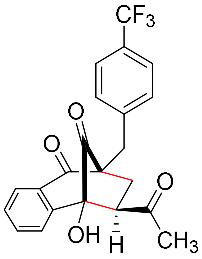
Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 88%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 34.74 min (major), t_R = 15.66 min (minor) [For major isomer], t_R = 22.61 min (major), t_R = 18.99 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -4.5° (*c* = 1.15, $CHCl_3$, 99% *ee* and 22:1 *dr*); IR (Neat): ν_{max} 3457, 3059, 3006, 2956, 2922, 1769, 1691, 1597, 1514, 1453, 1359, 1329, 1168, 1069, 931, 781 and 734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.08 (1H, dd, *J* = 8.0, 1.0 Hz), 7.89 (1H, br d, *J* = 7.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.5 Hz), 7.51 (1H, dt, *J* = 7.5, 1.0 Hz), 7.26 (2H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 3.82 (1H, br d, *J* = 1.5 Hz), 3.47 (1H, d, *J* = 14.5 Hz), 3.37 (1H, d, *J* = 14.5 Hz), 3.11 (1H, dd, *J* = 10.0, 2.5 Hz), 2.33 (1H, dd, *J* = 14.5, 2.5 Hz), 2.31 (3H, s), 2.03 (3H, s), 1.78 (1H, dd, *J* = 14.5, 10.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.3 (C, *C*=O), 204.8 (C, *C*=O), 195.4 (C, *C*=O), 144.5 (C), 136.1 (C), 135.4 (CH), 133.5 (C), 131.1 (2 x CH), 129.3 (C), 128.9 (CH), 128.9 (2 x CH), 127.9 (CH), 123.9 (CH), 82.9 (C), 64.7 (C), 52.7 (CH), 31.3 (CH_2), 30.9 (CH_3), 28.3 (CH_2), 21.0 (CH_3); HRMS m/z 371.1259 (M + Na^+), calcd for $C_{22}H_{20}O_4Na$ 371.1259.

(5*S*,6*R*,8*R*)-6-Acetyl-5-hydroxy-8-(4-methoxybenzyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene- 9,10(6*H*)-dione ((-)-51fa): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 95%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 35.57 min (major), t_R = 12.09 min (minor) [For major isomer], t_R = 16.60 min (major), t_R = 13.62 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -3.3° (*c* = 1.38, $CHCl_3$, 92% *ee* and 23:1 *dr*); IR (Neat): ν_{max} 3445, 3070, 3002, 2952, 2837, 1769, 1691, 1598, 1512, 1454, 1359, 1250, 1178, 1069, 1034, 932, 844, 782 and 733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.07 (1H, dd, *J* = 8.0, 1.0 Hz), 7.89 (1H, dd, *J* = 8.0, 0.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.5 Hz), 7.50 (1H, dt, *J* = 8.0, 1.5 Hz), 7.29 (2H, td, *J* = 9.5, 3.0 Hz), 6.83 (2H, td, *J* = 9.5, 2.0 Hz), 3.85 (1H, s), 3.78 (3H, s), 3.45 (1H, d, *J* = 14.5 Hz), 3.34 (1H, d, *J* = 15.0 Hz), 3.12 (1H, dd, *J* = 10.0, 3.0 Hz), 2.33 (1H, dd, *J* = 14.5, 3.0 Hz), 2.05 (3H, s), 1.77 (1H, dd, *J* = 14.5, 10.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.3 (C, *C*=O), 204.9 (C, *C*=O), 195.5 (C, *C*=O), 158.3 (C), 144.5 (C), 135.4 (CH), 132.2 (2 x CH), 129.2 (C), 128.9 (CH), 128.6 (C), 127.8 (CH), 123.9 (CH), 113.5 (2 x CH), 82.9 (C), 64.8 (C), 55.1 (CH), 52.7 (CH_3), 31.0 (CH_3), 30.8 (CH_2), 28.3 (CH_2); HRMS m/z 387.1211 (M + Na^+), calcd for $C_{22}H_{20}O_5Na$ 387.1208.



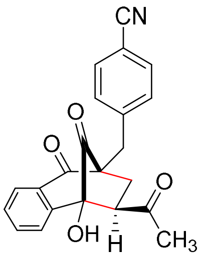
(-)-51fa

(5*S*,6*R*,8*R*)-6-Acetyl-5-hydroxy-8-(4-(trifluoromethyl)benzyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ga): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 70%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.30 min (major), t_R = 12.37 min (minor) [For major isomer], t_R = 10.78 min (major), t_R = 21.06 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -5.4° (*c* = 0.98, $CHCl_3$, 93% *ee* and 11:1 *dr*); IR (Neat): ν_{max} 3450, 2930, 1770, 1692, 1598, 1420, 1360, 1326, 1281, 1165, 1117, 1067, 1020, 979, 934, 854 and 723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.08 (1H, br d, *J* = 8.0 Hz), 7.91 (1H, br dd, *J* = 8.0, 1.0 Hz), 7.74 (1H, dt, *J* = 8.0, 1.0 Hz), 7.56-7.51 (5H, m), 3.73 (1H, br d, *J* = 3.0 Hz), 3.59 (1H, d, *J* = 14.0 Hz), 3.44 (1H, d, *J* = 14.0 Hz), 3.18 (1H, dd, *J* = 9.5, 2.5 Hz), 2.26 (1H, dd, *J* = 14.5, 2.5 Hz), 2.13 (3H, s), 1.77 (1H, dd, *J* = 16.0, 9.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.4 (C, *C*=O), 204.4 (C, *C*=O), 195.1 (C, *C*=O), 144.5 (C), 141.0 (C), 135.6 (CH), 131.6 (2 x CH), 129.1 (C), 129.1 (CH), 128.9 (C, q, *J* = 32.5 Hz), 128.0 (CH), 125.0 (2 x CH, q, *J* = 3.75 Hz), 124.3 (C, q, *J* = 271.25 Hz, CF_3), 124.0 (CH), 82.9 (C), 64.3 (C), 52.6 (CH), 31.8 (CH_2), 31.7 (CH_3), 28.9 (CH_2), HRMS m/z 425.0981 (M + Na^+), calcd for $C_{22}H_{17}F_3O_4Na$ 425.0977.



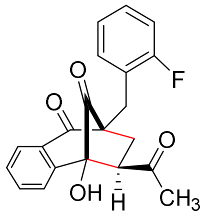
(-)-51ga

4-(((5*S*,6*R*,8*R*)-6-Acetyl-5-hydroxy-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-8-yl)methyl)benzonitrile ((-)-51ha): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as pale yellow oily liquid; Yield: 65%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 23.09 min (major), t_R = 21.27 min (minor) [For major isomer], t_R = 33.76 min (major), t_R = 31.50 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -3.5° (*c* = 0.87, $CHCl_3$, 95% *ee* and 9:1 *dr*); IR (Neat): ν_{max} 3441, 3066, 2926, 2853, 2228, 1770, 1691, 1599, 1505, 1453, 1360, 1330, 1280, 1169, 1069, 933, 853 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.08 (1H, br d, *J* = 7.5 Hz), 7.92 (1H, br d, *J* = 7.5 Hz), 7.76 (1H, br t, *J* = 7.5 Hz), 7.58 (2H, br d, *J* = 7.5 Hz), 7.56-7.50 (3H, m), 3.67-3.64 (1H, m), 3.56 (1H, d, *J* = 14.5 Hz), 3.44 (1H, d, *J* = 14.5 Hz), 3.20 (1H, dd, *J* = 9.5, 3.0 Hz), 2.25 (1H, dd, *J* = 14.5, 2.5 Hz), 2.17 (3H, s), 1.77 (1H, dd, *J* = 14.5, 9.5 Hz), ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.4 (C, *C*=O), 204.2 (C, *C*=O), 194.9 (C, *C*=O), 144.5 (C), 142.5 (C), 135.7 (CH), 132.0 (2 x CH), 131.8 (2 x CH), 129.1 (CH), 129.0 (C), 128.1 (CH), 124.0 (CH), 118.9 (C), 110.5 (C), 82.9 (C), 64.2 (C), 52.6 (CH), 32.3 (CH_2), 32.0 (CH_3), 29.0 (CH_2); HRMS m/z 382.1058 (M + Na$^+$), calcd for $C_{22}H_{17}NO_4Na$ 382.1055.

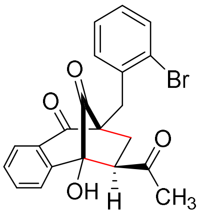


(-)-51ha

(5*S*,6*R*,8*R*)-6-Acetyl-8-(2-fluorobenzyl)-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ia): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as oil; Yield: 75%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 30.11 min (major), t_R = 14.69 min (minor) [For major isomer], t_R = 17.63 min (major), t_R = 16.26 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -8.9° (*c* = 0.97, $CHCl_3$, 90% *ee* and 9:1 *dr*); IR (Neat): ν_{max} 3450, 3067, 2929, 2853, 1770, 1691, 1597, 1492, 1454, 1360, 1329, 1280, 1232, 1171, 1066, 929, 761, and 734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.09 (1H, br d, *J* = 8.0 Hz), 7.89 (1H, br d, *J* = 8.0 Hz), 7.73 (1H, br t, *J* = 8.0 Hz), 7.52 (2H, br t, *J* = 8.0 Hz), 7.24-7.22 (1H, m), 7.11 (1H, br t, *J* = 7.5 Hz), 7.02 (1H, br t, *J* = 9.0 Hz), 3.75 (1H, br s), 3.68 (1H, br d, *J* = 14.5 Hz), 3.35 (1H, br d, *J* = 15.0 Hz), 3.13 (1H, dd, *J* = 10.0, 3.0 Hz), 2.30 (1H, dd, *J* = 14.5, 2.5 Hz), 2.05 (3H, s), 1.92 (1H, br dd, *J* = 15.5, 10 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.1 (C, *C*=O), 204.5 (C, *C*=O), 194.8 (C, *C*=O), 161.5 (C, d, *J* = 242.5 Hz, *C*-F), 144.6 (C), 135.5 (CH), 133.7 (CH, d, *J* = 3.75 Hz), 129.1 (C), 128.9 (CH), 128.6 (CH, d, *J* = 8.75 Hz), 128.0 (CH), 124.0 (CH, d, *J* = 3.75 Hz), 123.9 (CH), 123.5 (C, d, *J* = 13.75 Hz), 114.9 (CH, d, *J* = 22.5 Hz), 82.8 (C), 64.5 (C), 52.7 (CH), 31.0 (CH_3), 28.4 (CH_2), 24.2 (CH_2, d, *J* = 3.75 Hz), HRMS m/z 375.1010 (M + Na^+), calcd for $C_{21}H_{17}FO_4Na$ 375.1009.



(-)-51ia

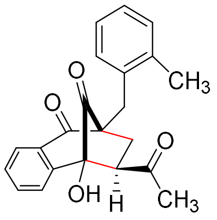


(-)-51ja

(5*S*,6*R*,8*R*)-6-Acetyl-8-(2-bromobenzyl)-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ja): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 70%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 20.18 min (major), t_R = 17.60 min (minor) [For major isomer], t_R = 8.64 min (major), t_R = 17.12 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -23.8° (*c* = 0.82, $CHCl_3$, 88% *ee* and 6:1 *dr*); IR (Neat): ν_{max} 3463, 3066, 2926, 2854, 1769, 1692, 1597, 1470, 1360, 1279, 1203, 1169, 1062, 1024, 975, 929, 760 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.10 (1H, dd, *J* = 8.0, 1.0 Hz), 7.89 (1H, dd, *J* = 7.5, 0.5 Hz), 7.75-7.70 (1H, m), 7.56-7.47 (3H, m), 7.28 (1H, dt, *J* = 7.5, 1.5 Hz), 7.11 (1H, dt, *J* = 7.5, 1.5 Hz), 3.94 (1H, d, *J* = 14.5 Hz), 3.86 (1H, s), 3.53 (1H, d, *J* = 15.0 Hz), 3.11 (1H, dd, *J* = 10.0, 2.5 Hz), 2.23-2.20 (1H, m), 2.01 (3H, s), 2.00-1.95 (1H, m); minor isomer: δ 8.10 (1H, dd, *J* = 8.0, 1.0 Hz), 7.75-7.70 (1H, m), 7.66 (1H, dt, *J* = 7.5, 1.5 Hz), 7.56-7.47 (3H, m), 7.30-7.23 (1H, m), 7.10 (1H, dt, *J* = 7.5, 1.5 Hz), 3.94 (1H, d, *J* = 14.5 Hz), 3.86 (1H, s), 3.53 (1H, d, *J* = 15.0 Hz), 3.17 (1H, dd, *J* = 10.0, 8.0 Hz), 2.34 (1H, dd, *J* = 10.0, 8.0 Hz), 2.21 (3H, s), 1.91-1.86 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.1 (C, *C*=O), 204.6 (C, *C*=O), 194.4 (C, *C*=O), 144.5 (C), 136.5 (C), 135.5 (CH), 133.4 (CH), 132.5 (CH), 129.2 (C), 128.9 (CH), 128.5 (CH), 128.1 (CH), 127.5 (CH), 126.4 (C), 123.9 (CH), 82.6 (C), 64.8 (C), 52.6 (CH), 30.9 (CH_3), 30.5 (CH_2), 27.9 (CH_2); minor isomer: δ

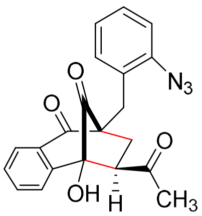
205.0 (C, *C*=O), 203.7 (C, *C*=O), 193.6 (C, *C*=O), 140.8 (C), 136.9 (C), 135.2 (CH), 132.8 (CH), 132.5 (CH), 129.9 (C), 128.9 (CH), 128.4 (CH), 128.2 (CH), 127.7 (CH), 126.7 (C), 124.0 (CH), 82.7 (C), 65.0 (C), 54.0 (CH), 30.4 (CH_3), 30.3 (CH_2), 24.9 (CH_2); HRMS m/z 435.0209 (M + Na^+), calcd for $C_{21}H_{17}BrO_4Na$ 435.0208.

(5*S*,6*R*,8*R*)-6-Acetyl-5-hydroxy-8-(2-methylbenzyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((+)-51ka): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 75%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 22.67 min (major), t_R = 14.23 min (minor) [For major isomer], t_R = 7.79 min (major), t_R = 9.94 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +8.1° (*c* = 0.49, $CHCl_3$, 82% *ee* and 5:1 *dr*); IR (Neat): ν_{max} 3459, 3067, 2923, 1768, 1690, 1597, 1454, 1361, 1279, 1234, 1167, 1056, 931, 765 and 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.11 (1H, br d, *J* = 8.0, Hz), 7.90 (1H, br d, *J* = 7.5 Hz), 7.75-7.70 (1H, m), 7.51 (1H, br t, *J* = 7.5 Hz), 7.34-7.33 (1H, m), 7.18-7.11 (3H, m), 3.82 (1H, br s), 3.73 (1H, d, *J* = 15.0 Hz), 3.43 (1H, d, *J* = 15.5 Hz), 3.13-3.09 (1H, m), 2.32 (3H, s), 2.20 (3H, s), 2.09 (1H, dd, *J* = 14.5, 3.0 Hz), 1.85-1.76 (1H, m), minor isomer: 8.11 (1H, br d, *J* = 8.0 Hz), 7.75-7.70 (1H, m), 7.66 (1H, br t, *J* = 8.0 Hz), 7.51 (1H, t, *J* = 7.5 Hz), 7.27-7.25 (1H, m), 7.18-7.11 (3H, m), 3.80 (1H, m), 3.72 (1H, d, *J* = 15.0 Hz), 3.43 (1H, d, *J* = 15.5 Hz), 3.13-3.09 (1H, m), 2.36 (3H, s), 2.30-2.27 (1H, m), 2.01 (3H, s), 1.85-1.76 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, major



(+)-51ka

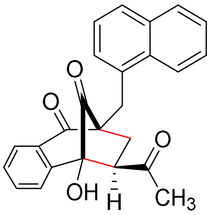
isomer) δ 208.2 (C, *C*=O), 204.8 (C, *C*=O), 195.2 (C, *C*=O), 140.9 (C), 137.6 (C), 135.6 (C), 135.5 (CH), 131.4 (CH), 130.4 (CH), 129.9 (C), 129.3 (CH), 128.2 (CH), 126.8 (CH), 126.3 (CH), 124.0 (CH), 82.7 (C), 65.4 (C), 54.2 (CH), 31.0 (CH_3), 28.3 (CH_2), 26.6 (CH_2), 20.2 (CH_3); minor isomer: δ 205.4 (C, *C*=O), 203.8 (C, *C*=O), 194.1 (C, *C*=O), 144.6 (C), 137.4 (C), 135.5 (C), 135.2 (CH), 130.7 (CH), 130.1 (CH), 129.1 (C), 128.9 (CH), 128.1 (CH), 126.7 (CH), 126.1 (CH), 123.9 (CH), 82.6 (C), 64.7 (C), 52.7 (CH), 30.4 (CH_3), 26.9 (CH_2), 24.5 (CH_2), 20.2 (CH_3); HRMS m/z 371.1258 (M + Na^+), calcd for $C_{22}H_{20}O_4Na$ 371.1259.



(+)-51la

(5*S*,6*R*,8*R*)-6-Acetyl-8-(2-azidobenzyl)-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((+)-51la): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 75%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.61 min (major), t_R = 13.12 min (minor) [For major isomer], t_R = 9.68 min (major), t_R = 24.17 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +3.5° (*c* = 0.72, $CHCl_3$, 90% *ee* and 2.7:1 *dr*); IR (Neat): ν_{max} 3465, 3065, 2924, 2123, 1769, 1691, 1597, 1491, 1452, 1360, 1282, 1168, 1058, 930 and 753 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.08 (1H, br d, *J* = 8.0 Hz), 7.88 (1H, br d, *J* = 8.0 Hz), 7.72 (1H, br t, *J* = 8.0 Hz), 7.53-7.45 (2H, m), 7.32-7.27 (1H, m), 7.15-7.06 (2H, m), 3.80 (1H, s), 3.69 (1H, d, *J* = 14.5 Hz), 3.29 (1H, d, *J* = 15.5 Hz), 3.18-3.10 (1H, m), 2.25-2.20 (1H, m), 2.04 (3H, s), 1.92-1.87 (1H, m); minor isomer: δ

8.08 (1H, br d, *J* = 8.0 Hz), 7.74-7.69 (1H, m), 7.65 (1H, dt, *J* = 7.5, 1.0 Hz), 7.53-7.45 (2H, m), 7.32-7.27 (1H, m), 7.15-7.06 (2H, m), 3.90 (1H, s), 3.69 (1H, d, *J* = 14.5 Hz), 3.27 (1H, d, *J* = 15.5 Hz), 3.18-3.10 (1H, m), 2.34-2.29 (1H, m), 2.22 (3H, s), 1.92-1.87 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.0 (C, *C*=O), 204.7 (C, *C*=O), 194.8 (C, *C*=O), 144.7 (C), 139.3 (C), 135.5 (CH), 133.4 (CH), 129.0 (C), 128.9 (CH), 128.3 (CH), 128.2 (C), 128.0 (CH), 124.8 (CH), 123.8 (CH), 117.7 (CH), 82.7 (C), 64.7 (C), 52.8 (CH), 31.0 (CH_3), 28.2 (CH_2), 25.4 (CH_2); minor isomer: δ 205.2 (C, *C*=O), 203.8 (C, *C*=O), 194.0 (C, *C*=O), 140.8 (C), 139.1 (C), 135.1 (CH), 132.8 (CH), 129.9 (C), 129.2 (CH), 128.4 (C), 128.3 (CH), 128.1 (CH), 124.8 (CH), 123.9 (CH), 117.9 (CH), 82.68 (C), 65.0 (C), 54.0 (CH), 30.4 (CH_3), 25.7 (CH_2), 24.9 (CH_2); HRMS m/z 398.1118 (M + Na^+), calcd for $C_{21}H_{17}N_3O_4Na$ 398.1117.

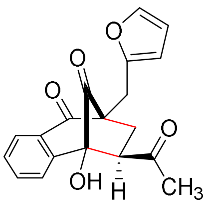


(-)-51ma

(5*S*,6*R*,8*R*)-6-acetyl-5-hydroxy-8-(naphthalen-1-ylmethyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7] annulene-9,10(6*H*)-dione ((-)-51ma): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 75%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 88.22 min (major), t_R = 31.46 min (minor) [For major isomer], t_R = 14.52 min (major), t_R = 16.66 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -25.3° (*c* = 0.52, $CHCl_3$, 82% *ee* and 2.0:1 *dr*); IR (Neat): ν_{max} 3450, 3059, 2927, 2853, 1767, 1690, 1597, 1508, 1453, 1361, 1279, 1168, 1062, 926, 781, 734 and 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.18-

8.12 (2H, m), 7.90-7.84 (2H, m), 7.78-7.64 (3H, m), 7.57-7.41 (4H, m), 4.30 (1H, d, J = 15.5 Hz), 3.83 (1H, d, J = 15.0 Hz), 3.02-2.97 (1H, m), 1.98 (1H, dd, J = 15.0, 3.0 Hz), 1.83 (3H, s), 1.75 (1H, dd, J = 14.5, 10.0 Hz); minor isomer: δ 8.18-8.12 (1H, m), 8.08 (1H, d, J = 8.5 Hz), 7.90-7.84 (1H, m), 7.78-7.64 (3H, m), 7.57-7.41 (5H, m), 4.33 (1H, d, J = 15.5 Hz), 3.77 (1H, d, J = 15.0 Hz), 3.02-2.97 (1H, m), 2.25 (1H, dd, J = 15.0, 8.0 Hz), 2.12 (3H, s), 1.67 (1H, dd, J = 14.5, 10.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.0 (C, *C*=O), 204.8 (C, *C*=O), 195.2 (C, *C*=O), 144.6 (C), 135.5 (CH), 133.6 (C), 133.3 (C), 133.0 (C), 129.6 (CH), 129.0 (C), 128.9 (CH), 128.8 (CH), 128.1 (CH), 127.4 (CH), 126.1 (CH), 125.6 (CH), 125.4 (CH), 124.1 (CH), 123.9 (CH), 82.7 (C), 64.9 (C), 52.6 (CH), 30.8 (CH_3), 28.5 (CH_2), 25.9 (CH_2); minor isomer: δ 205.4 (C, *C*=O), 203.7 (C, *C*=O), 194.2 (C, *C*=O), 140.9 (C), 135.2 (CH), 133.7 (C), 133.3 (C), 133.3 (C), 129.9 (C), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 126.4 (CH), 125.6 (CH), 125.5 (CH), 124.0 (CH), 123.9 (CH), 82.6 (C), 65.5 (C), 54.2 (CH), 30.3 (CH_3), 26.2 (CH_2), 25.1 (CH_2); HRMS m/z 407.1262 (M + Na^+), calcd for $C_{25}H_{20}O_4Na$ 407.1259.

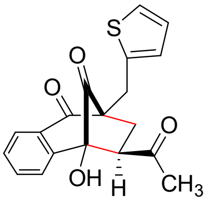
(5*S*,6*R*,8*R*)-6-Acetyl-8-(furan-2-ylmethyl)-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((+)-51na): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as pale yellowish oily liquid; Yield: 78%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.66 min (major), t_R = 15.76 min (minor) [For major



(+)-51na

isomer], t_R = 12.09 min (major), t_R = 28.59 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +32.9° (*c* = 0.89, $CHCl_3$, 93% *ee* and 11:1 *dr*); IR (Neat): ν_{max} 3455, 3069, 2927, 1770, 1692, 1597, 1504, 1453, 1421, 1360, 1332, 1281, 1170, 1072, 937, 783 and 736 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.07 (1H, dd, *J* = 8.0, 1.0 Hz), 7.91 (1H, br d, *J* = 8.0 Hz), 7.73 (1H, dt, *J* = 7.5, 1.0 Hz), 7.51 (1H, dt, *J* = 7.5, 1.0 Hz), 7.33 (1H, d, *J* = 1.0 Hz), 6.33 (1H, dd, *J* = 3.5, 2.0 Hz), 6.25 (1H, d, *J* = 3.0 Hz), 3.81 (1H, s), 3.50 (1H, d, *J* = 16.0 Hz), 3.39 (1H, d, *J* = 15.5 Hz), 3.16 (1H, dd, *J* = 10.0, 3.0 Hz), 2.44 (1H, dd, *J* = 15.0, 3.0 Hz), 2.16 (3H, s), 1.95 (1H, dd, *J* = 14.5, 10.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.2 (C, *C*=O), 203.7 (C, *C*=O), 194.6 (C, *C*=O), 151.0 (C), 144.6 (C), 141.5 (CH), 135.5 (CH), 129.1 (C), 129.0 (CH), 127.9 (CH), 124.0 (CH), 110.5 (CH), 109.1 (CH), 82.7 (C), 63.6 (C), 52.6 (CH), 31.2 (CH_3), 29.0 (CH_2), 25.0 (CH_2); HRMS m/z 347.0901 (M + Na^+), calcd for $C_{19}H_{16}O_5Na$ 347.0895.

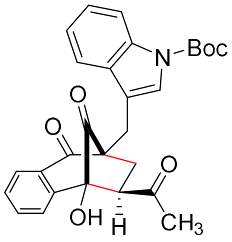
(5*S*,6*R*,8*R*)-6-Acetyl-5-hydroxy-8-(thiophen-2-ylmethyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7] annulene-9,10(6*H*)-dione ((+)-51oa): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as pale yellowish oily liquid; Yield: 70%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 18.71 min (major), t_R = 17.05 min (minor) [For major isomer], t_R = 12.30 min (major), t_R = 60.67 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +1.7° (*c* = 0.82, $CHCl_3$, 92% *ee* and 10:1 *dr*); IR (Neat): ν_{max} 3462, 3106, 3068, 2947, 2915, 1771, 1693, 1597, 1452, 1424, 1360, 1330,



(+)-51oa

1281, 1173, 1073, 936, 782, 733, 699 and 529 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz, major isomer) δ 8.08 (1H, br d, *J* = 7.5 Hz), 7.91 (1H, br d, *J* = 7.5 Hz), 7.74 (1H, br t, *J* = 7.5 Hz), 7.52 (1H, br t, *J* = 7.5 Hz), 7.17 (1H, br d, *J* = 5.5 Hz), 6.98 (1H, br d, *J* = 3.0 Hz), 6.94 (1H, m), 3.86 (1H, br s), 3.69 (1H, d, *J* = 15.5 Hz), 3.53 (1H, dd, *J* = 15.5, 1.5 Hz), 3.16 (1H, dd, *J* = 9.5, 2.5 Hz), 2.41 (1H, dd, *J* = 14.5, 2.5 Hz), 2.15 (3H, s), 1.83 (1H, br dd, *J* = 14.5, 10.0 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, major isomer) δ 208.5 (C, *C*=O), 204.1 (C, *C*=O), 195.1 (C, *C*=O), 144.6 (C), 138.2 (C), 135.5 (CH), 129.2 (C), 129.0 (CH), 128.5 (CH), 127.9 (CH), 126.7 (CH), 125.0 (CH), 124.0 (CH), 82.9 (C), 64.4 (C), 52.6 (CH), 31.3 (CH$_3$), 28.6 (CH$_2$), 26.6 (CH$_2$); HRMS m/z 363.0667 (M + Na$^+$), calcd for $C_{19}H_{16}O_4SNa$ 363.0667.

***tert*-Butyl 3-(((5*S*,6*R*,8*R*)-6-Acetyl-5-hydroxy-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-8-yl)methyl)-1*H*-indole-1-carboxylate ((-)-51pa):**

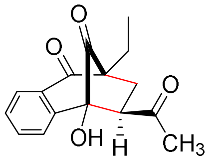


(-)-51pa

Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 91%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 53.61 min (major), t_R = 21.06 min (minor) [For major isomer], t_R = 12.12 min (major), t_R = 10.73 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -26.9° (*c* = 0.92, CHCl$_3$, 84% *ee* and 16:1 *dr*); IR (Neat): ν_{max} 3451, 3066, 2979, 2933, 1770, 1727, 1692, 1598, 1453, 1369, 1310, 1257, 1157, 1087, 1016, 936, 856 and 745 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz, major isomer) δ 8.09 (1H, dd, *J* = 8.0, 1.0 Hz), 7.90

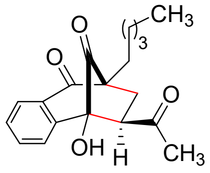
(1H, dd, J = 8.0, 1.0 Hz), 7.72 (1H, dt, J = 7.5, 1.5 Hz), 7.68 (1H, br dd, J = 6.5, 1.5 Hz), 7.64 (1H, br s), 7.50 (1H, dt, J = 8.0, 1.0 Hz), 7.31-7.24 (3H, m), 3.84 (1H, s), 3.59 (1H, dd, J = 15.5, 0.5 Hz), 3.38 (1H, br d, J = 15.0 Hz), 3.13 (1H, dd, J = 9.5, 2.5 Hz), 2.36 (1H, dd, J = 14.5, 2.5 Hz), 2.10 (3H, s), 1.81 (1H, dd, J = 15.0, 10.0 Hz), 1.67 (9H, s); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.5 (C, *C*=O), 204.6 (C, *C*=O), 195.2 (C, *C*=O), 149.7 (C, O-*C*=O), 144.4 (C), 135.4 (CH), 134.9 (C), 131.8 (C), 129.3 (C), 128.9 (CH), 127.9 (CH), 126.1 (CH), 124.1 (CH), 123.9 (CH), 122.5 (CH), 119.1 (CH), 115.1 (C), 115.1 (CH), 83.5 (C), 82.9 (C), 64.3 (C), 52.5 (CH), 31.5 (CH_3), 29.2 (CH_2), 28.2 (3 x CH_3), 20.7 (CH_2); HRMS m/z 496.1736 (M + Na$^+$), calcd for $C_{28}H_{27}NO_6Na$ 496.1736.

(5*S*,6*R*,8*S*)-6-Acetyl-8-ethyl-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((+)-51qa): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 90%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.22 min (major), t_R = 9.68 min (minor) [For major isomer], t_R = 10.28 min (major), t_R = 14.59 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +2.6° (c = 0.31, $CHCl_3$, 96% *ee* and 28:1 *dr*); IR (Neat): ν_{max} 3458, 3067, 2971, 2942, 1763, 1689, 1597, 1456, 1360, 1332, 1258, 1176, 1060, 966, 917, 889, 786 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.05 (1H, dd, J = 7.5, 1.0 Hz), 7.90 (1H, br d, J = 7.5 Hz), 7.72 (1H, dt, J = 7.5, 1.0 Hz), 7.50 (1H, dt, J = 7.5, 1.0 Hz), 3.64



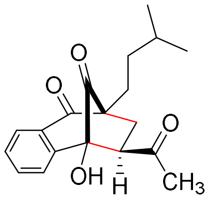
(+)-51qa

(1H, s), 3.26 (1H, dd, *J* = 9.5, 2.5 Hz), 2.43 (1H, dd, *J* = 14.5, 3.0 Hz), 2.31 (3H, s), 2.07 (2H, q, *J* = 7.5 Hz), 1.84 (1H, dd, *J* = 15.0, 9.5 Hz), 1.13 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.7 (C, *C*=O), 205.1 (C, *C*=O), 195.9 (C, *C*=O), 144.9 (C), 135.3 (CH), 129.4 (C), 128.8 (CH), 127.7 (CH), 123.8 (CH), 82.7 (C), 63.7 (C), 52.6 (CH), 32.3 (CH_3), 29.4 (CH_2), 20.3 (CH_2), 8.4 (CH_3); HRMS m/z 295.0946 ($M + Na^+$), calcd for $C_{16}H_{16}O_4Na$ 295.0946.



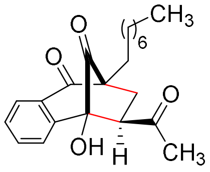
(-)-51ra

(5*S*,6*R*,8*S*)-6-Acetyl-5-hydroxy-8-pentyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ra): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 95%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.83 min (major), t_R = 08.83 min (minor) [For major isomer], t_R = 9.83 min (major), t_R = x.xx min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -3.3° (*c* = 0.86, $CHCl_3$, 94% *ee* and 22:1 *dr*); IR (Neat): ν_{max} 3457, 2955, 2869, 1766, 1692, 1598, 1454, 1359, 1331, 1280, 1257, 1201, 1175, 1063, 957, 913, 782, 723 and 581 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.04 (1H, br d, *J* = 7.5 Hz), 7.90 (1H, dd, *J* = 8.0, 0.5 Hz), 7.72 (1H, dt, *J* = 8.0, 0.5 Hz), 7.50 (1H, br t, *J* = 7.5 Hz), 3.63 (1H, br s), 3.26 (1H, dd, *J* = 9.5, 2.5 Hz), 2.43 (1H, dd, *J* = 14.5, 3.0 Hz), 2.31 (3H, s), 2.04-1.98 (2H, m), 1.93 (1H, dd, *J* = 14.5, 9.5 Hz), 1.66-1.61 (1H, m), 1.49-1.44 (1H, m), 1.41-1.38 (4H, m), 0.92 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.7 (C, *C*=O), 205.2 (C, *C*=O), 195.9 (C, *C*=O), 144.9 (C), 135.3 (CH), 129.4 (C), 128.8 (CH), 127.7 (CH), 123.7 (CH), 82.6 (C), 63.4 (C), 52.7 (CH), 32.5 (CH_2), 32.3 (CH_3), 29.9 (CH_2), 27.4 (CH_2), 23.4 (CH_2), 22.4 (CH_2), 14.1 (CH_3); HRMS m/z 337.1418 (M + Na^+), calcd for $C_{19}H_{22}O_4Na$ 337.1416.



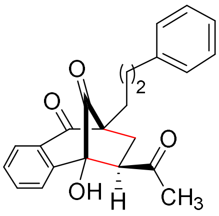
(-)-51sa

(5*S*,6*R*,8*S*)-6-Acetyl-5-hydroxy-8-isopentyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51sa): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 99%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.61 min (major), t_R = 8.153 min (minor) [For major isomer], t_R = 8.92 min (major), t_R = 16.39 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -1.7° (*c* = 1.33, $CHCl_3$, 94% *ee* and 24:1 *dr*); IR (Neat): ν_{max} 3434, 3069, 2953, 2868, 1761, 1706, 1597, 1453, 1362, 1329, 1258, 1199, 1066, 943, 783 and 723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.04 (1H, dd, *J* = 7.5, 1.0 Hz), 7.90 (1H, br d, *J* = 7.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.0 Hz), 7.45 (1H, dt, *J* = 7.5, 1.0 Hz), 3.67 (1H, s), 3.26 (1H, dd, *J* = 9.5, 2.5 Hz), 2.42 (1H, dd, *J* = 14.5, 3.0 Hz), 2.31 (3H, s), 2.01 (2H, quintet, *J* = 6.0 Hz), 1.87 (1H, dd, *J* = 14.5, 9.5 Hz), 1.64 (1H, quintet, *J* = 7.0 Hz), 1.56-1.50 (1H, m), 1.40-1.32 (1H, m), 0.97 (6H, d, *J* = 6.5 Hz, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.7 (C, *C*=O), 205.2 (C, *C*=O), 196.0 (C, *C*=O), 144.8 (C), 135.3 (CH), 129.4 (C), 128.8 (CH), 127.7 (CH), 123.7 (CH), 82.6 (C), 63.4 (C), 52.7 (CH), 32.5 (CH_2), 32.3 (CH_3), 29.8 (CH_2), 28.8 (CH), 25.4 (CH_2), 22.5 (CH_3), 22.4 (CH_3); HRMS m/z 337.1416 (M + Na^+), calcd for $C_{19}H_{22}O_4Na$ 337.1416.



(-)-51ta

(5*S*,6*R*,8*S*)-6-Acetyl-5-hydroxy-8-octyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ta): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 95%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.80 min (major), t_R = 8.39 min (minor) [For major isomer], t_R = 10.85 min (major), t_R = 22.33 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -4.4° (*c* = 1.0, $CHCl_3$, 95% *ee* and 12:1 *dr*); IR (Neat): ν_{max} 3438, 2946, 2924, 2854, 1767, 1691, 1597, 1454, 1359, 1331, 1279, 1253, 1173, 1081, 926, 781, 722 and 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.04 (1H, br d, *J* = 8.0 Hz), 7.90 (1H, br d, *J* = 8.0 Hz), 7.72 (1H, br t, *J* = 7.5 Hz), 7.49 (1H, br t, *J* = 7.5 Hz), 3.61 (1H, br s), 3.25 (1H, dd, *J* = 9.0, 2.5 Hz), 2.44 (1H, dd, *J* = 15.0, 2.5 Hz), 2.31 (3H, s), 2.03-1.98 (2H, m), 1.87 (1H, dd, *J* = 14.5, 9.5 Hz), 1.70-1.60 (1H, m), 1.50-1.29 (11H, m), 0.89 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.6 (C, *C*=O), 205.2 (C, *C*=O), 195.9 (C, *C*=O), 144.9 (C), 135.3 (CH), 129.4 (C), 128.9 (CH), 127.7 (CH), 123.7 (CH), 82.6 (C), 63.4 (C), 52.7 (CH), 32.3 (CH_3), 31.9 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 23.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS m/z 379.1888 (M + Na^+), calcd for $C_{22}H_{28}O_4Na$ 379.1885.



(-)-51ua

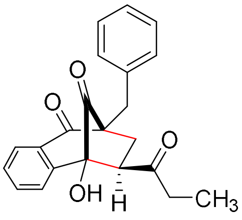
(5*S*,6*R*,8*S*)-6-acetyl-5-hydroxy-8-(3-phenylpropyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ua): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 95%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.21 min (major), t_R = 21.07 min (minor) [For major isomer], t_R = 15.23 min (major), t_R = 13.78 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -3.2° (*c* = 1.04, $CHCl_3$, 90% *ee* and 45:1 *dr*); IR (Neat): ν_{max} 3453, 3064, 3025, 2950, 2855, 1768, 1689, 1598, 1453, 1359, 1331, 1258, 1203, 1173, 1081, 964, 920, 732, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.05 (1H, dd, *J* = 8.0, 2.0 Hz), 7.91 (1H, br d, *J* = 8.0 Hz), 7.73 (1H, dt, *J* = 7.5, 1.5 Hz), 7.51 (1H, dt, *J* = 7.5, 1.0 Hz), 7.32-7.27 (4H, m), 7.21-7.18 (1H, m), 3.66 (1H, br s), 3.26 (1H, dd, *J* = 9.5, 2.5 Hz), 2.77 (2H, m), 2.42 (1H, dd, *J* = 14.5, 3.0 Hz), 2.32 (3H, s), 2.10-2.00 (3H, m), 1.90-1.84 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 208.7 (C, *C*=O), 205.0 (C, *C*=O), 195.7 (C, *C*=O), 144.8 (C), 142.1 (C), 135.3 (CH), 129.3 (C), 128.8 (CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.7 (CH), 125.6 (CH), 123.7 (CH), 82.6 (C), 63.3 (C), 52.6 (CH), 36.5 (CH_2), 32.4 (CH_3), 29.9 (CH_2), 27.3 (CH_2), 25.4 (CH_2); HRMS m/z 385.1415 (M + Na^+), calcd for $C_{23}H_{22}O_4Na$ 385.1416.

2e. Preparation of Asymmetric Methanobenzo[7]annulenes 8ab-8ub under the Chiral Quinidine Thiourea 57a or Chiral Quinine Thiourea 57b catalysis: In an ordinary glass vial equipped with a magnetic stirring bar, to QD-NH-thiourea **57a** or Q-

NH-thiourea **57b** (0.06 mmol) and $C_6H_5CH_3$ (1.0 mL) was added and stirred at 0-3 °C for 5 minutes then 0.3 mmol of 2-hydroxy-1,4-naphthoquinone derivative **48a-u** and 0.9 mmol of ethyl vinyl ketone **49b** was added, and the reaction mixture was stirred at 0-3 °C for 24-72 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure chiral products **51ab-51ub** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

8-Benzyl-5-hydroxy-6-propionyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione:

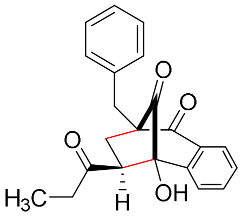
(-)-51ab: Prepared by following the procedure **2e** (**57b**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 85%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.08 min (major), t_R = 12.03 min (minor) [For major isomer]; t_R = 9.59 min (major), t_R = 10.39 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -9.9° [c = 0.52, $CHCl_3$, 83% *ee* and 14:1 *dr*];



(5S,6R,8R)
(-)-51ab

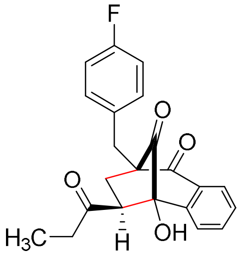
(+)-51ab: Prepared by following the procedure **2e** (**57a**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 85%; The enantiomeric excess (*ee*) was determined by chiral stationary phase

HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.53 min (major), t_R = 14.17 min (minor) [For major isomer]; t_R = 10.58 min (major), t_R = 9.91 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +3.0° [*c* = 0.4, $CHCl_3$, 81% *ee* and 53:1 *dr*]; IR (Neat): ν_{max} 3462, 3059, 3023, 2977, 2936, 1768, 1691, 1603, 1494, 1453, 1355, 1278, 1236, 1112, 1071, 1035, 926 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.07 (1H, d, *J* = 7.5 Hz), 7.87 (1H, d, *J* = 7.5 Hz), 7.71 (1H, t, *J* = 7.0 Hz), 7.50 (1H, t, *J* = 7.0 Hz), 7.36 (2H, d, *J* = 7.0 Hz), 7.28 (2H, t, *J* = 7.0 Hz), 7.21 (1H, t, *J* = 7.0 Hz), 3.83 (1H, s), 3.52 (1H, d, *J* = 14.5 Hz), 3.39 (1H, d, *J* = 14.5 Hz), 3.10 (1H, dd, *J* = 10.0, 2.0 Hz), 2.46-2.39 (1H, m), 2.27-2.21 (2H, m), 1.77 (1H, dd, *J* = 14.5, 10.0 Hz), 0.89 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 210.9 (C, *C*=O), 204.7 (C, *C*=O), 195.4 (C, *C*=O), 144.5 (C), 136.7 (C), 135.4 (CH), 131.2 (2 x CH), 129.3 (C), 128.8 (CH), 128.1 (2 x CH), 127.8 (CH), 126.5 (CH), 123.9 (CH), 82.9 (C), 64.7 (C), 51.9 (CH), 37.1 (CH_2), 31.7 (CH_2), 28.5 (CH_2), 7.1 (CH_3); HRMS m/z 371.1259 (M + Na^+), calcd for $C_{22}H_{20}O_4Na$ 371.1259.



(5*R*,6*S*,8*S*)
(+)-51ab

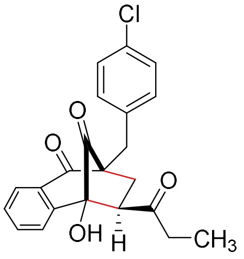
(5*S*,6*R*,8*R*)-8-(4-Fluorobenzyl)-5-hydroxy-6-propionyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (51bb): Prepared by following the procedure **2e** (**57a**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 65%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel



(+)-51bb

Chiralpak IC-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 15.02 min (major), t_R = 18.36 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +8.0° (*c* = 0.64, $CHCl_3$, 97% *ee* and 90:1 *dr*); IR (Neat): ν_{max} 3426, 3075, 2977, 2930, 1763, 1691, 1598, 1510, 1458, 1221, 1164, 1112, 1081, 931, 854 and 720 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major) δ 8.08 (1H, dd, *J* = 8.0, 1.0 Hz), 7.89 (1H, br d, *J* = 7.0 Hz), 7.73 (1H, dt, *J* = 7.5, 1.5 Hz), 7.52 (1H, dt, *J* = 7.5, 1.0 Hz), 7.38-7.35 (2H, m), 7.00-6.96 (2H, m), 3.79 (1H, s), 3.50 (1H, br d, *J* = 14.5 Hz), 3.37 (1H, br d, *J* = 14.5 Hz), 3.15 (1H, dd, *J* = 9.5, 2.5 Hz), 2.54 (1H, qd, *J* = 18.5, 7.5 Hz), 2.31 (1H, qd, *J* = 18.5, 7.5 Hz), 2.25 (1H, dd, *J* = 14.5, 2.5 Hz), 1.77 (1H, dd, *J* = 14.5, 9.5 Hz), 0.95 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major) δ 211.0 (C, *C*=O), 204.7 (C, *C*=O), 195.4 (C, *C*=O), 161.7 (C, d, *J* = 242.5 Hz, *C*-F), 144.5 (C), 135.4 (CH), 132.7 (2 x CH, d, *J* = 7.5 Hz), 132.3 (C, d, *J* = 3.75 Hz), 129.2 (C), 128.9 (CH), 127.9 (CH), 123.9 (CH), 114.8 (2 x CH, d, *J* = 21.2 Hz), 82.97 (C), 64.6 (C), 51.8 (CH), 37.6 (CH_2), 31.0 (CH_2), 28.7 (CH_2), 7.0 (CH_3); HRMS m/z 389.1165 (M + Na^+), calcd for $C_{22}H_{19}FO_4Na$ 389.1165.

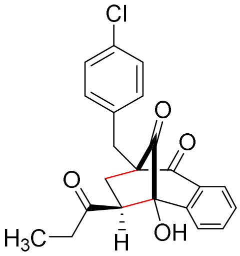
8-(4-Chlorobenzyl)-5-hydroxy-6-propionyl-7,8-dihydro-5*H*-5,8-methanobenzo[7] annulene-9,10(6*H*)-dione: (-)-51cb: Prepared by following the procedure **2e** (**57a**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 88%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 24.40 min (major), t_R = 20.57 min (minor) [For major isomer]; t_R = 31.73 min



(5S,6R,8R)
(-)-51cb

(major), t_R = 28.97 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -10.3° [*c* = 1.3, $CHCl_3$, 80% *ee* and 67:1 *dr*];

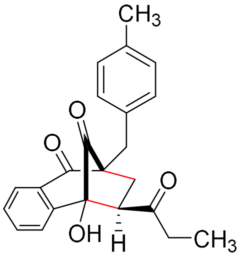
(+)-51cb: Prepared by following the procedure **2e** (**2j**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 75%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 20.15 min (major), t_R = 24.13 min (minor) [For major isomer]; t_R = 29.17 min (major), t_R = 31.47 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +7.0° [*c* = 0.33, $CHCl_3$, 73% *ee* and 90:1 *dr*]; IR (Neat): ν_{max} 3457, 3070, 2924, 2853, 1770, 1691, 1597, 1491, 1455, 1359, 1281, 1112, 1090 , 1035, 930, 854, 787 and 718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major) δ 8.06 (1H, dd, *J* = 7.5, 0.5 Hz), 7.88 (1H, d, *J* = 7.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.0 Hz), 7.51 (1H, dt, *J* = 7.5, 1.0 Hz), 7.33 (2H, td, *J* = 8.5, 1.0 Hz), 7.25 (2H, td, *J* = 8.5, 1.0 Hz), 3.49 (1H, d, *J* = 14.5 Hz), 3.34 (1H, d, *J* = 14.5 Hz), 3.14 (1H, dd, *J* = 9.5, 2.5 Hz), 2.54 (1H, qd, *J* = 18.5, 7.5 Hz), 2.30 (1H, qd, *J* = 18.5, 7.5 Hz), 2.22 (1H, dd, *J* = 14.5, 2.5 Hz), 1.75 (1H, dd, *J* = 14.5, 9.5 Hz), 0.95 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major) δ 211.0 (C, *C*=O), 204.5 (C, *C*=O), 195.3 (C, *C*=O), 144.5 (C), 135.5 (CH), 135.3 (C), 132.6 (2 x CH), 132.5 (C), 129.2 (C), 128.9 (CH), 128.2 (2 x CH), 127.9 (CH), 123.9 (CH), 82.9 (C), 64.4 (C), 51.8 (CH), 37.7 (CH_2), 31.3 (CH_2), 28.9 (CH_2), 7.0 (CH_3); HRMS m/z 405.0871 (M + Na^+), calcd for $C_{22}H_{19}ClO_4Na$ 405.0870.



(5*R*,6*S*,8*S*)

(+)-51cb

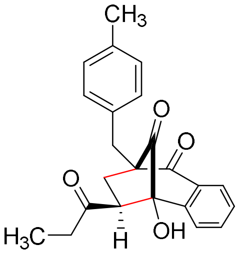
5-Hydroxy-8-(4-methylbenzyl)-6-propionyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*) -dione: (-)-51eb: Prepared by following the procedure **2e** (**57b**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 65%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 28.94 min (major), t_R = 25.16 min (minor), [For major isomer], t_R = 18.21 min (major), t_R = 20.69 min (minor), [For minor isomer]; $[\alpha]_D^{25}$ = -3.7° (*c* = 0.74, $CHCl_3$, 80% *ee* and 11:1 *dr*)



(5S,6R,8R)

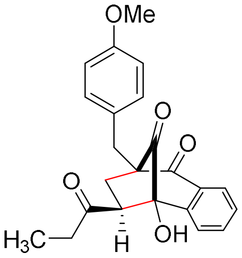
(-)-51eb

(+)-51eb: Prepare d by following the procedure **2e** (**57a**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 65%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 23.83 min (major), t_R = 28.57 min (minor) [For major isomer]; t_R = 20.53 min (major), t_R = 18.19 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +6.6° (*c* = 0.78, $CHCl_3$, 74% *ee* and 16:1 *dr*);IR (Neat): ν_{max} 3465, 3065, 2977, 2924, 1769, 1690, 1597, 1514, 1454, 1359, 1321, 1281, 1233, 1154, 1113, 1038, 928, 779, 737 and 717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major) δ 8.06 (1H, br d, *J* = 7.5 Hz), 7.87 (1H, br d, *J* = 8.0 Hz), 7.70 (1H, br t, *J* = 8.0 Hz), 7.49 (1H, br t, *J* = 7.5 Hz), 7.25 (2H, d, *J* = 8.0 Hz), 7.08 (1H, d, *J* = 8.0 Hz), 3.82 (1H, s),



(5*R*,6*S*,8*S*)

(+)-51eb



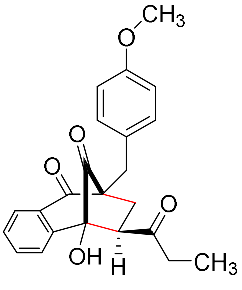
(5R,6S,8S)
(+)-51fb

3.47 (1H, d, J = 14.5 Hz), 3.35 (1H, d, J = 14.5 Hz), 3.09 (1H, dd, J = 9.5, 2.0 Hz), 2.46-2.38 (1H, m), 2.30 (3H, s), 2.28-2.21 (2H, m), 1.76 (1H, dd, J = 14.5, 10.0 Hz), 0.90 (3H, t, J = 7.5 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, major) δ 210.9 (C, *C*=O), 204.8 (C, *C*=O), 195.5 (C, *C*=O), 144.5 (C), 136.0 (C), 135.3 (CH), 133.6 (C), 131.0 (2 x CH), 129.3 (C), 128.8 (2 x CH), 128.8 (CH), 127.8 (CH), 123.9 (CH), 82.97 (C), 64.7 (C), 51.9 (CH), 37.1 (CH$_2$), 31.2 (CH$_2$), 28.6 (CH$_2$), 20.9 (CH$_3$), 7.0 (CH$_3$); HRMS m/z 385.1420 (M + Na$^+$), calcd for $C_{23}H_{22}O_4Na$ 385.1416.

5-Hydroxy-8-(4-methoxybenzyl)-6-propionyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10 (6*H*)-dione: (-)-51fb: Prepared by following the procedure **2e** (**57b**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourles oily liquid; Yield: 87%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.14 min (major), t_R = 8.06 min (minor) [For major isomer], t_R = 11.76 min (major), [For minor isomer]; $[\alpha]_D^{25}$ = -2.6° (*c* = 1.43, CHCl$_3$, 98% *ee* and 62:1 *dr*);

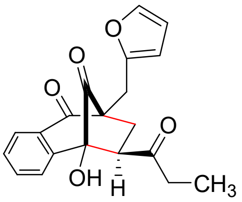
(+)-51fb: Prepared by following the procedure **2e** (**57a**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourles oily liquid; Yield: 80%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.89 min (major), t_R = 10.39 min (minor) [For major isomer];

t_R = 9.84 min (major), t_R = 11.67 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +4.5° (c = 0.38, CHCl$_3$, 87% *ee* and 84:1 *dr*);IR (KBr): ν_{max} 3446, 2936, 1769, 1690, 1598, 1512, 1454, 1359, 1251, 1180, 1113, 1035, 932, 800, 740 and 714 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, major) δ 8.08 (1H, dd, J = 8.0, 1.2 Hz), 7.88 (1H, br d, J = 8.0, Hz), 7.72 (1H, dt, J = 7.6, 1.2 Hz), 7.51 (1H, dt, J = 7.6, 1.2 Hz), 7.30 (2H, br td, J = 8.4, 1.2 Hz), 6.82 (2H, br td, J = 8.4, 1.2 Hz), 3.78 (3H, s), 3.72 (1H, s), 3.47 (1H, d, J = 14.8 Hz), 3.36 (1H, d, J = 14.8 Hz), 3.11 (1H, dd, J = 10.0, 2.8 Hz), 2.45 (1H, qd, J = 18.5, 7.5 Hz), 2.31-2.21 (2H, m), 1.77 (1H, dd, J = 14.8, 10.0 Hz), 0.92 (3H, t, J = 7.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, major) δ 211.0 (C, *C*=O), 204.8 (C, *C*=O), 195.6 (C, *C*=O), 158.3 (C), 144.5 (C), 135.4 (CH), 132.2 (2 x CH), 129.3 (C), 128.9 (CH), 128.7 (C), 127.9 (CH), 124.0 (CH), 113.5 (2 x CH), 82.9 (C), 64.8 (C), 55.2 (CH), 51.9 (CH$_3$), 37.2 (CH$_2$), 30.8 (CH$_2$), 28.6 (CH$_2$), 7.10 (CH$_3$); HRMS m/z 401.1365 (M + Na$^+$), calcd for C$_{23}$H$_{22}$O$_5$Na 401.1365.



(5S,6R,8R)
(-)-51fb

(5*S*,6*R*,8*R*)-8-(Furan-2-ylmethyl)-5-hydroxy-6-propionyl-7,8-dihydro-5*H*-5,8-methanobenzo[7] annulene-9,10(6*H*)-dione ((-)-51nb): Prepared by following the procedure **2e** (**57b**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as pale yellowish oily liquid; Yield: 75%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 29.97 min (major), t_R = 74.15 min (minor) [For major isomer], t_R = 23.07

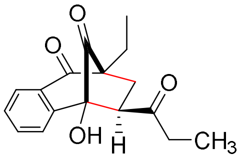


(-)-51nb

min (major), t_R = 54.23 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -5.6° (*c* = 0.13, $CHCl_3$, 84% *ee* and 97:1 *dr*); IR (Neat): ν_{max} 3468, 2977, 2930, 2853, 1768, 1686, 1603, 1453, 1360, 1283, 1117, 1076, 1009, 937 and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, major) δ 8.07 (1H, d, *J* = 7.5 Hz), 7.89 (1H, d, *J* = 8.0, Hz), 7.73 (1H, t, *J* = 8.0 Hz), 7.51 (1H, t, *J* = 7.5 Hz), 7.32 (1H, d, *J* = 1.0 Hz), 6.32 (1H, t, *J* = 2.5 Hz), 6.25 (1H, d, *J* = 3.0 Hz), 3.75 (1H, s), 3.52 (1H, d, *J* = 16.0 Hz), 3.37 (1H, d, *J* = 16.0 Hz), 3.15 (1H, dd, *J* = 9.5, 2.5 Hz), 2.56 (1H, qd, *J* = 18.5, 7.5 Hz), 2.41-2.38 (1H, m), 2.37-2.32 (1H, m), 1.94 (1H, dd, *J* = 15.0, 10.0 Hz), 1.00 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major) δ 210.97 (C, *C*=O), 203.8 (C, *C*=O), 194.7 (C, *C*=O), 151.1 (C), 144.6 (C), 141.5 (CH), 135.5 (CH), 129.2 (C), 128.9 (CH), 127.9 (CH), 124.0 (CH), 110.5 (CH), 109.0 (CH), 82.8 (C), 63.7 (C), 51.8 (CH), 37.5 (CH_2), 29.7 (CH_2), 25.1 (CH_2), 7.2 (CH_3); HRMS m/z 361.1052 (M + Na$^+$), calcd for $C_{20}H_{18}O_5Na$ 361.1052.

6-Acetyl-8-ethyl-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione:

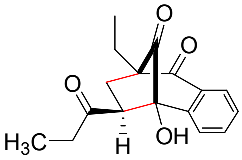
(-)-51qb: Prepared by following the procedure **2e** (**57b**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 75%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 32.53 min (major), t_R = 26.84 min (minor) [For major



(5S,6R,8S)
(-)-51qb

isomer], t_R = 35.01 min (major), t_R = 54.62 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -1.3° (*c* = 0.49, CHCl$_3$, 77% *ee* and 9:1 *dr*);

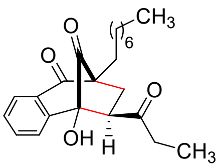
(+)-51qb: Prepared by following the procedure **2e** (**57a**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 90%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 25.14 min (major), t_R = 31.23 min (minor) [For major isomer], t_R = 48.91 min (major), t_R = 33.06 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +4.6° (*c* = 0.99, CHCl$_3$, 74% *ee* and 11:1 *dr*);



(5R,6S,8R)
(+)-51qb

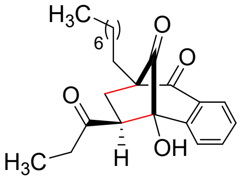
IR (Neat): ν_{max} 3442, 3065, 2974, 2940, 2879, 1764, 1688, 1598, 1456, 1360, 1247, 1201, 1113, 1031, 939, 917, 892, 784 and 717 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, major) δ 8.00 (1H, dd, *J* = 7.6, 0.8 Hz), 7.86 (1H, br d, *J* = 7.2 Hz), 7.68 (1H, dt, *J* = 7.2, 1.2 Hz), 7.46 (1H, dt, *J* = 7.2, 1.2 Hz), 3.68 (1H, s), 3.21 (1H, dd, *J* = 9.6, 2.8 Hz), 2.74 (1H, qd, *J* = 18.5, 7.5 Hz), 2.45 (1H, qd, *J* = 18.5, 7.5 Hz), 2.38 (1H, dd, *J* = 14.4, 2.8 Hz), 2.03 (2H, q, *J* = 7.2 Hz), 1.82 (1H, dd, *J* = 14.4, 9.6 Hz), 1.11 (3H, t, *J* = 7.6 Hz), 1.04 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, major) δ 211.7 (C, *C*=O), 205.2 (C, *C*=O), 196.0 (C, *C*=O), 144.9 (C), 135.2 (CH), 129.3 (C), 128.7 (CH), 127.6 (CH), 123.7 (CH), 82.8 (C), 63.7 (C), 51.7 (CH), 38.5 (CH$_2$), 29.4 (CH$_2$), 20.2 (CH$_2$), 8.4 (CH$_3$), 7.0 (CH$_3$); HRMS m/z 309.1103 (M + Na$^+$), calcd for $C_{17}H_{18}O_4Na$ 309.1103.

5-Hydroxy-8-octyl-6-propionyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione:



(5S,6R,8S)
(-)-51tb

(–)-51tb: Prepared by following the procedure **2e** (**2k**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 95%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.63 min (major), t_R = 10.56 min (minor) [For major isomer], t_R = 13.67 min (major), t_R = 25.35 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -7.9° (*c* = 1.43, $CHCl_3$, 86% *ee* and 10:1 *dr*);



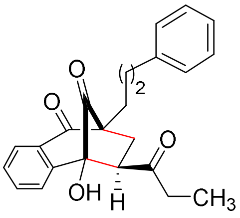
(5R,6S,8R)
(+)-51tb

(+)-51tb: Prepared by following the procedure **2e** (**57a**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 90%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.23 min (major), t_R = 11.49 min (minor) [For major isomer]; t_R = 24.83 min (major), t_R = 13.62 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -13.3° (*c* = 1.48, $CHCl_3$, 79% *ee* and 89:1 *dr*); IR (Neat): ν_{max} 3462, 2925, 2848, 1763, 1686, 1603, 1453, 1355, 1200, 1112, 1081, 1040, 911, 782 and 725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major) δ 8.04 (1H, d, *J* = 8.0 Hz), 7.89 (1H, d, *J* = 8.0 Hz), 7.71 (1H, t, *J* = 7.5 Hz), 7.49 (1H, t, *J* = 7.5 Hz), 3.61 (1H, s), 3.24 (1H, dd, *J* = 9.5, 2.5

Hz), 2.76 (1H, qd, *J* = 18.5, 7.5 Hz), 2.47 (1H, qd, *J* = 18.5, 7.5 Hz), 2.42 (1H, dd, *J* = 14.5, 2.5 Hz), 2.01-1.99 (2H, m), 1.87 (1H, dd, *J* = 14.0, 9.5 Hz), 1.70-1.60 (1H, m), 1.50-1.26 (11H, m), 1.08 (3H, t, *J* = 7.0 Hz), 0.89 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major) δ 211.4 (C, *C*=O), 205.2 (C, *C*=O), 196.0 (C, *C*=O), 144.9 (C), 135.2 (CH), 129.4 (C), 128.8 (CH), 127.7 (CH), 123.7 (CH), 82.7 (C), 63.5 (C), 51.9 (CH), 38.5 (CH_2), 31.8 (CH_2), 30.4 (CH_2), 30.0 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 23.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 7.1 (CH_3); HRMS m/z 393.2042 (M + Na^+), calcd for $C_{23}H_{30}O_4Na$ 393.2042.

5-Hydroxy-8-(3-phenylpropyl)-6-propionyl-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione

(-)-51ub: Prepared by following the procedure **2e** (**57b**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; yield: 92%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 13.36 min (major), t_R = 12.26 min (minor), [For major isomer], t_R = 18.00 min (major), t_R = 28.91 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -5.17° (*c* = 1.18, $CHCl_3$, 84% *ee* and *dr* = 7:1);

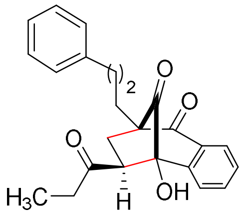


(5S,6R,8S)

(-)-51ub

(+)-51ub: Prepared by following the procedure **2e** (**57a**-catalysis) and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; yield: 90%; The enantiomeric excess (*ee*) was determined by chiral stationary phase

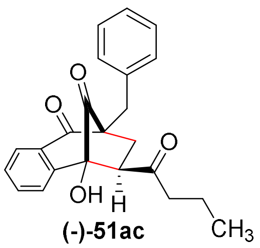
HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.43 min (major), t_R = 12.69 min (minor) [For major isomer], t_R = 24.72 min (major), t_R = 15.90 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +7.11° (*c* = 1.38, $CHCl_3$, 64% *ee* and *dr* = 22:1); IR (Neat): ν_{max} 3437, 2936, 1763, 1686, 1598, 1453, 1355, 1288, 1200, 1112, 1081, 1019, 921 and 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major) δ 8.00 (1H, dd, *J* = 8.0, 1.2 Hz), 7.86 (1H, br d, *J* = 8.0 Hz), 7.67 (1H, dt, *J* = 7.6, 1.2 Hz), 7.46 (1H, dt, *J* = 7.6, 1.2 Hz), 7.29-7.23 (4H, m), 7.18-7.14 (1H, m), 3.68 (1H, s), 3.19 (1H, dd, *J* = 9.2, 2.8 Hz), 2.77-2.69 (3H, m), 2.43 (1H, qd, *J* = 18.5, 7.5 Hz), 2.35 (1H, dd, *J* = 14.5, 2.5 Hz), 2.07-1.98 (3H, m), 1.85-1.78 (2H, m), 1.05 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major) δ 211.6 (C, *C*=O), 205.2 (C, *C*=O), 195.7 (C, *C*=O), 144.8 (C), 142.0 (C), 135.3 (CH), 129.2 (C), 128.8 (CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.6 (CH), 125.6 (CH), 123.7 (CH), 82.8 (C), 63.3 (C), 51.7 (CH), 38.5 (CH_2), 36.5 (CH_2), 30.1 (CH_2), 27.2 (CH_2), 25.3 (CH_2), 7.0 (CH_3); HRMS m/z 399.1572 (M + Na^+), calcd for $C_{24}H_{24}O_4Na$ 399.1572.



(5R,6S,8R)

(+)-51ub

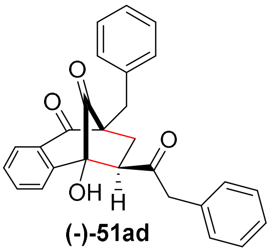
(5*S*,6*R*,8*R*)-8-benzyl-6-butyryl-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ac): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 80%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 41.53 min (major),



(-)-51ac

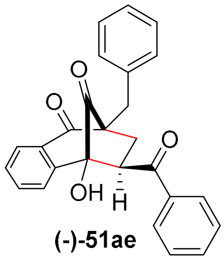
t_R = 37.05 min (minor) [For major isomer]; *t_R* = 23.62 min (major), *t_R* = 28.51 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -11.4° [*c* = 0.79, $CHCl_3$, 79% *ee* and 76:1 *dr*]; IR (Neat): ν_{max} 3431, 3065, 3028, 2961, 2930, 1763, 1691, 1598, 1494, 1458, 1376, 1329, 1278, 1086, 1040, 983, 931, 766 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major) δ 8.08 (1H, dd, *J* = 8.0, 1.5 Hz), 7.88 (1H, dd, *J* = 7.5, 0.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.0 Hz), 7.50 (1H, dt, *J* = 8.0, 1.0 Hz), 7.37-7.36 (2H, m), 7.31-7.27 (2H, m), 7.23-7.19 (1H, m), 3.81 (1H, s), 3.52 (1H, d, *J* = 14.5 Hz), 3.41 (1H, d, *J* = 14.5 Hz), 3.08 (1H, dd, *J* = 10.0, 2.5 Hz), 2.40-2.34 (1H, m), 2.25-2.15 (2H, m), 1.78 (1H, dd, *J* = 15.0, 10.0 Hz), 1.49-1.35 (2H, m), 0.78 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major) δ 210.4 (C, *C*=O), 204.7 (C, *C*=O), 195.4 (C, *C*=O), 144.5 (C), 136.7 (C), 135.4 (CH), 131.2 (2 x CH), 129.2 (C), 128.9 (CH), 128.2 (2 x CH), 127.9 (CH), 126.6 (CH), 124.0 (CH), 83.0 (C), 64.7 (C), 51.9 (CH), 45.7 (CH_2), 31.7 (CH_2), 28.5 (CH_2), 16.3 (CH_2), 13.4 (CH_3); HRMS m/z 385.1416 (M + Na^+), calcd for $C_{23}H_{22}O_4Na$ 385.1416.

(5*S*,6*R*,8*R*)-8-Benzyl-5-hydroxy-6-(2-phenylacetyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7] annulene-9,10(6*H*)-dione ((-)-51ad): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 80%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), *t_R* = 18.06 min (major), *t_R* = 15.13 min (minor) [For major isomer]; *t_R* = 8.88 min (major), *t_R* = 12.59 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = -2.2° [*c* = 1.4, $CHCl_3$, 76% *ee* and *dr* = 28:1]; IR (KBr):



(-)-51ad

ν_{max} 3434, 2922, 2849, 1769, 1690, 1597, 1454, 1281, 1157, 1088, 933, 758 and 701 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz, major isomer) δ 8.07 (1H, dd, *J* = 8.0, 1.0 Hz), 7.88 (1H, dd, *J* = 8.0, 0.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.0 Hz), 7.51 (1H, dt, *J* = 7.5, 1.0 Hz), 7.36 (2H, br d, *J* = 7.5 Hz), 7.31-7.27 (4H, m), 7.25-7.23 (2H, m), 7.00 (2H, br d, *J* = 6.5 Hz), 3.71 (1H, br s), 3.69 (1H, d, *J* = 16.0 Hz), 3.60 (1H, d, *J* = 16.0 Hz), 3.51 (1H, d, *J* = 14.5 Hz), 3.40 (1H, d, *J* = 14.5 Hz), 3.20 (1H, dd, *J* = 10.0, 2.5 Hz), 2.24 (1H, dd, *J* = 15.0, 3.0 Hz), 1.66 (1H, dd, *J* = 14.5, 9.5 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, major isomer) δ 207.7 (C, *C*=O), 204.5 (C, *C*=O), 195.3 (C, *C*=O), 144.4 (C), 136.7 (C), 135.4 (CH), 132.7 (C), 131.2 (2 x CH), 129.6 (2 x CH), 129.3 (C), 128.9 (CH), 128.7 (2 x CH), 128.2 (2 x CH), 127.9 (CH), 127.2 (CH), 126.6 (CH), 124.0 (CH), 83.0 (C), 64.7 (C), 51.13 (CH), 51.03 (CH$_2$), 31.7 (CH$_2$), 28.7 (CH$_2$); HRMS m/z 433.1416 (M + Na$^+$), calcd for $C_{27}H_{22}O_4Na$ 433.1416.

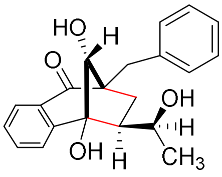


(-)-51ae

(5*S*,6*R*,8*R*)-6-Benzoyl-8-benzyl-5-hydroxy-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione ((-)-51ae): Prepared by following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 90%; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 95:05, flow rate 1.0 mL/min, λ = 254 nm), t_R = 53.12 min (major), t_R = 28.86 min (minor) [For major isomer]; t_R = 24.79 min (major), t_R = 106.66 min (minor) [For minor isomer]; 22.5% *ee* and *dr* = 97:1; IR (KBr): ν_{max} 3425, 2964, 2923, 2852, 1786, 1663, 1597, 1461, 1383, 1344, 1243, 1168, 1041, 929, 750, 706 and 597 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz, major isomer) δ 8.14 (1H, d, *J* = 8.0 Hz), 7.98 (1H, d, *J* = 8.0 Hz), 7.77 (1H, dt, *J* = 8.0, 1.0 Hz), 7.72 (2H, d, *J* = 7.5 Hz), 7.57 (1H, t, *J* = 6.5 Hz), 7.55 (1H, t, *J* = 6.5 Hz), 7.42 (2H, t, *J* = 8.0 Hz), 7.36 (2H, d, *J* = 7.5 Hz), 7.24 (2H, t, *J* = 7.5 Hz), 7.19 (1H, t, *J* = 7.5 Hz), 4.12 (1H, s), 3.95 (1H, dd, *J* = 10.0, 2.5 Hz), 3.53 (1H, d, *J* = 14.5 Hz), 3.48 (1H, d, *J* = 14.5 Hz), 2.36 (1H, dd, *J* = 15.0, 2.5 Hz), 1.97 (1H, dd, *J* = 15.0, 10.5 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135, major isomer) δ 204.5 (C, *C*=O), 200.1 (C, *C*=O), 195.3 (C, *C*=O), 144.2 (C), 136.5 (C), 135.7 (C), 135.4 (CH), 133.7 (CH), 131.0 (2 x CH), 129.4 (C), 128.8 (CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 127.8 (CH), 126.3 (CH), 124.2 (CH), 83.2 (C), 64.8 (C), 47.6 (CH), 31.7 (CH$_2$), 29.5 (CH$_2$); HRMS m/z 419.1259 (M + Na$^+$), calcd for $C_{26}H_{21}O_4Na$ 419.1259.

2f. General Procedure for the Reduction of Methanobenzo[7]annulenes 51: In a 10 mL round-bottom flask equipped with a magnetic stirring bar, compound **(−)-51aa** (0.15 mmol) was dissolved in dry MeOH (1.0 mL) and then cooled to ice temperature, followed by addition of NaBH$_4$ (5.67 mg, 0.15 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 2.0 h. The crude reaction mixture was worked up with aqueous NH$_4$Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. Pure product **(-)-58aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(6*S*,8*S*,10*R*)-8-benzyl-5,10-dihydroxy-6-((*S*)-1-hydroxyethyl)-7,8-dihydro-5*H*-5,8-methanobenzo [7]annulen-9(6*H*)-one ((-)-58aa): Prepared by following the procedure **2f** and purified by column chromatography using EtOAc/hexane and isolated as colourless oily liquid; Yield: 75%; $[\alpha]_D^{25}$ = -33.8° [*c* = 0.28, $CHCl_3$, 95% *ee* and 70:1 *dr*]; IR (Neat): ν_{max} 3380, 2961, 2915, 2848, 1680, 1598, 1453, 1283, 1226, 1081, 916 and 859 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major) δ 7.95 (1H, dd, *J* = 8.0, 1.0 Hz), 7.72 (1H, dd, *J* = 8.0, 1.0 Hz), 7.56 (1H, dt, *J* = 7.5, 1.5 Hz), 7.47 (2H, dd, *J* = 7.5, 1.5 Hz), 7.32 (1H, dt, *J* = 7.5, 1.0 Hz), 7.19 (2H, tt, *J* = 7.5, 1.5 Hz), 7.10 (1H, tt, *J* = 7.5, 1.5 Hz), 4.45 (1H, dq, *J* = 6.5, 2.0 Hz), 3.58-3.53 (2H, m), 3.03 (1H, d, *J* = 13.5 Hz), 2.26 (1H, dd, *J* = 14.0, 8.0 Hz), 2.01 (1H, m), 1.70 (1H, dd, *J* = 14.0, 10.0 Hz), 1.17 (3H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major) δ 199.2 (C, *C*=O), 150.5 (C), 138.9 (C), 134.2 (CH), 131.0 (2 x CH), 129.3 (C), 127.8 (2 x CH), 127.6 (CH), 127.3 (CH), 125.9 (CH), 121.3 (CH), 82.0 (C), 79.2 (CH), 65.3 (CH), 62.2 (C), 53.6 (CH), 35.5 (CH_2), 30.4 (CH_2), 21.8 (CH_3); HRMS m/z 361.1414 (M + Na^+), calcd for $C_{21}H_{22}O_4Na$ 361.1416.



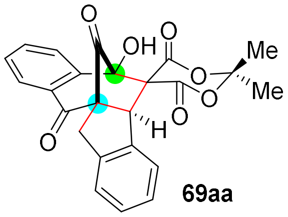
(-)-58aa

2g: General Procedure for the Reaction of Methanobenzo[7]annulene 8qa with Potassium *tert*-butoxide: In a 10 mL round-bottom flask equipped with a magnetic stirring bar, compound **(+)-51qa** (0.28 mmol) was dissolved in $C_6H_5CF_3$ (0.93 mL) and then cooled to 20 °C, followed by addition of potassium *tert*-butoxide (31.41 mg, 0.28 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 1.0 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product **48q** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

3. Organocatalytic Formal Intramolecular [3+2]-Cycloaddition to Acquire Biologically Important Methanodibenzo[*a*,*f*]azulenes and Methanobenzo[*f*]azulenes

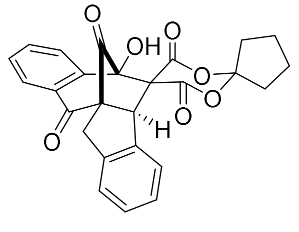
3a. Sequential One-pot Synthesis of 69 from Phthalaldehyde (59), 2-Hydroxy-1,4-naphthoquinone (1) and Meldrum's acid (65): To a 25 mL of round bottom flask equipped with a magnetic stirring bar were added 0.1 mmol of catalyst **3n**, 0.55 mmol of phthalaldehyde **59** and 5.0 mL of anhydrous DCM. Then, 0.55 mmol of Hantzsch ester **34** and 0.5 mmol of 2-hydroxy-1,4-naphthoquinone **1** were added sequentially to a well stirred solution and the resulting mixture was allowed to stir for 6 h at 40 °C. Next, 0.55 mmol of Meldrum's acid **65** was added to the above mixture and the stirring was further continued for 4 h at same temperature. The pure domino product **69** was obtained in 54% yield after the purification.

3b. Procedure for the Gram Scale Synthesis of 69aa: To a 100 mL round bottom flask equipped with a magnetic stirring bar were added 3.0 mmol of **62a**, 3.15 mmol of **65a** and 30 mL of anhydrous DCM. Then, 0.3 mmol of freshly distilled benzyl amine **3z** was added and the resulting mixture was allowed to stir at 25 ºC for 45 min. Next, the crude reaction mixture was directly loaded onto a silica gel packed column without aqueous workup to give pure **69aa** after column chromatography using 100% $CHCl_3$ to 5% ethyl acetate in $CHCl_3$ as an eluent.



69aa

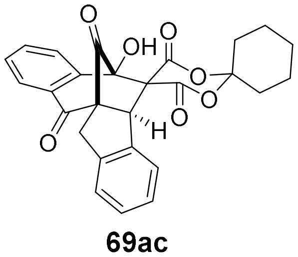
(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-2,2-dimethyl-4b',12'-dihydrospiro[[1,3]dioxane-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-4,6,11',13'(6'*H*)-tetraone (69aa):** The compound was prepared following procedure **3a,** purified by column chromatography using EtOAc/$CHCl_3$ (0:10 to 0.2:9.8), and isolated as a white solid. Yield: 98% (102.5 mg). Mp: 230-232 °C. $[\alpha]_D^{25} = 0.0^o$ (*c* = 0.068, acetone, 99:1 *dr*). IR (Neat): ν_{max} 3373, 2926, 2850, 2504, 1781, 1756, 1694, 1598, 1454, 1395, 1338, 1293, 1245, 1198, 1117, 1065, 1023, 954, 923, 906, 889, 752, and 737 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 8.52 (1H, s, O*H*), 8.10 (1H, dd, *J* = 7.5, 1.0 Hz), 7.89 (1H, dt, *J* = 8.0, 1.5 Hz), 7.81 (1H, br d, *J* = 7.5 Hz), 7.71 (1H, dt, *J* = 7.5, 1.0 Hz), 7.37 (1H, br d, *J* = 7.5 Hz), 7.28 (1H, br t, *J* = 7.5 Hz), 7.19 (1H, br t, *J* = 7.5 Hz), 6.95 (1H, br d, *J* = 7.5 Hz), 4.29 (1H, s), 3.87 (1H, d, *J* = 17.0 Hz), 3.44 (1H, d, *J* = 17.0 Hz), 1.99 (3H, s), 1.76 (3H, s). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 201.0 (C, *C*=O), 192.6 (C, *C*=O), 165.7 (C, O-*C*=O), 165.2 (C, O-*C*=O), 142.7 (C), 142.4 (C), 137.1 (C), 135.7 (CH), 131.3 (C), 130.5 (CH), 129.1 (CH), 127.8 (2 x CH), 127.7 (CH), 125.9 (CH), 123.5 (CH), 107.7 (C, O-*C*-O), 91.5 (C, *C*-OH), 71.3 (C), 60.4 (C), 60.1 (CH), 29.9 (CH_3), 29.4 (CH_2), 28.9 (CH_3). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{18}O_7Na$ 441.0950; Found 441.0951.



69ab

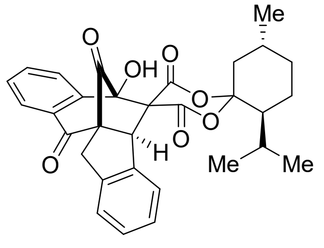
(4b''*S,6''*S**,11a''*R**)-6''-Hydroxy-4b'',12''-dihydrodispiro[cyclopentane-1,2'-[1,3]dioxane-5',5''-[6,11a]methanodibenzo[*a,f*]azulene]-4',6',11'',13''(6''*H*)-tetraone (69ab):** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/CHCl$_3$ (0:10 to 0.2:9.8), and isolated as a white solid. Yield: 89% (98.9 mg). Mp: 250-252 °C. IR (Neat): $\nu_{\max}$ 3293, 1780, 1726, 1704, 1600, 1453, 1343, 1293, 1248, 1154, 1111, 1076, 1046, 1023, 993, 972, 926, 847, 779, and 751 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.16 (1H, d, J = 8.0 Hz), 7.79 (1H, d, J = 7.5 Hz), 7.74 (1H, t, J = 7.5 Hz), 7.60 (1H, t, J = 8.0 Hz), 7.31 (1H, d, J = 7.5 Hz), 7.25 (1H, t, J = 7.5 Hz), 7.14 (1H, t, J = 7.5 Hz), 6.84 (1H, d, J = 7.5 Hz), 4.39 (1H, s), 4.33 (1H, br s, O*H*), 4.02 (1H, d, J = 17.0 Hz), 3.62 (1H, d, J = 17.0 Hz), 2.45 (1H, quint, J = 7.5 Hz), 2.36 (1H, quint, J = 7.0 Hz), 2.21 (2H, m), 1.96-1.90 (2H, m), 1.86 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 200.3 (C, *C*=O), 191.3 (C, *C*=O), 166.0 (C, O-*C*=O), 165.2 (C, O-*C*=O), 142.7 (C), 140.3 (C), 136.0 (C), 135.3 (CH), 131.2 (C), 130.1 (CH), 129.0 (CH), 128.1 (CH), 127.4 (CH), 126.6 (CH), 125.8 (CH), 122.6 (CH), 116.1 (C, O-*C*-O), 89.8 (C, *C*-OH), 70.9 (C), 61.6 (CH), 61.1 (C), 40.9 (CH$_2$), 39.3 (CH$_2$), 29.0 (CH$_2$), 23.8 (CH$_2$), 22.3 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{26}H_{20}O_7H$ 445.1287; Found 445.1287.

(4b''*S,6''*S**,11a''*R**)-6''-Hydroxy-4b'',12''-dihydrodispiro[cyclohexane-1,2'-[1,3]dioxane-5',5''-[6,11a]methanodibenzo[*a,f*]azulene]-4',6',11'',13''(6''*H*)-tetraone (69ac):** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/CHCl$_3$ (0:10 to 0.2:9.8), and isolated as a white solid. Yield: 88% (100.9 mg). Mp: 252-254 °C. IR (Neat): ν_{max} 3362, 2940, 1778, 1726, 1689, 1597, 1455, 1367, 1326, 1293, 1263, 1209, 1152, 1109, 1081, 1065, 1043, 1020, 986, 952, 924, 911, 846, 774, and 756 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.51 (1H, s, O*H*), 8.09 (1H, dd, *J* = 7.6, 0.8 Hz), 7.90 (1H, dt, *J* = 7.2, 1.2 Hz), 7.79 (1H, br d, *J* = 7.6 Hz), 7.71 (1H, dt, *J* = 7.6, 0.8 Hz), 7.37 (1H, br d, *J* = 7.6 Hz), 7.28 (1H, br t, *J* = 7.6 Hz), 7.19 (1H, br t, *J* = 7.2 Hz), 6.95 (1H, br d, *J* = 7.6 Hz), 4.29 (1H, s), 3.86 (1H, d, *J* = 17.2 Hz), 3.43 (1H, d, *J* = 17.2 Hz), 2.28 (2H, br s), 1.99-1.90 (2H, m), 1.63 (4H, br s), 1.45 (2H, br s). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 201.0 (C, *C*=O), 192.6 (C, *C*=O), 165.7 (C, O-*C*=O), 165.2 (C, O-*C*=O), 142.7 (C), 142.4 (C), 137.1 (C), 135.7 (CH), 131.3 (C), 130.5 (CH), 129.1 (CH), 127.8 (2 x CH), 127.8 (CH), 125.9 (CH), 123.5 (CH), 107.8 (C, O-*C*-O), 91.3 (C, *C*-OH), 71.3 (C), 60.9 (C), 60.2 (CH), 38.7 (CH$_2$), 37.1 (CH$_2$), 29.4 (CH$_2$), 23.7 (CH$_2$), 22.5 (CH$_2$), 22.2 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{27}H_{22}O_7Na$ 481.1263; Found 481.1259.



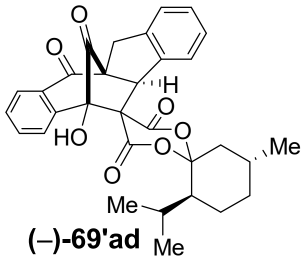
69ac

(1*S,2*S**,4b''*S**,5*R**,5'*S**,6''*S**,11a''*R**)-6''-Hydroxy-2-isopropyl-5-methyl-4b'',12''-dihydrodispiro[cyclohexane-1,2'-[1,3]dioxane-5',5''-[6,11a]methanodibenzo[*a,f*]azulene]-4',6',11'',13''(6''*H*)-tetraone [(−)-69ad and (−)-69'ad]:** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/CHCl$_3$ (0:10 to 0.2:9.8), and isolated as a white solid. Yield: 95% (122.2 mg). Mp: 158-160 °C. $[\alpha]_D^{25} = -45.94$□ (*c* = 0.10, CHCl$_3$, 1:1 *dr*). IR (Neat): ν_{max} 3345, 2952, 1779, 1759, 1718, 1696, 1597, 1455, 1371, 1290, 1251, 1210, 1170, 1146, 1108, 1078, 1017, 971, 949, 925, 912, 887, 848, 797, and 757 cm^{-1}.



(–)-**69ad**

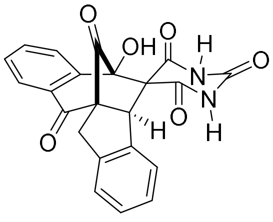
+



(–)-69'ad

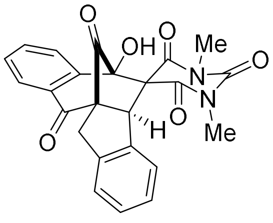
^{1}H NMR ($CDCl_3$, 500 MHz, 1:1 *dr*): δ 8.19 (2H, dd, *J* = 7.5, 3.0 Hz), 7.84 (1H, d, *J* = 7.5 Hz), 7.78-7.77 (3H, m), 7.64-7.60 (2H, m), 7.35 (2H, t, *J* = 7.0 Hz), 7.30-7.26 (2H, m), 7.14 (1H, t, *J* = 7.5 Hz), 7.12 (1H, t, *J* = 7.5 Hz), 6.89 (1H, d, *J* = 7.5 Hz), 6.87 (1H, d, *J* = 7.5 Hz), 4.47 (1H, br s, O*H*), 4.41 (1H, s), 4.40 (1H, br s, O*H*), 4.39 (1H, s), 4.04 (2H, br d, *J* = 18.0 Hz), 3.67 (1H, d, *J* = 17.0 Hz), 3.65 (1H, d, *J* = 17.0 Hz), 2.81 (1H, br d, *J* = 13.0 Hz), 2.70 (1H, br d, *J* = 13.5 Hz), 2.29 (1H, m), 2.21 (1H, m), 1.91-1.67 (7H, m), 1.64-1.50 (7H, m), 1.06-1.03 (6H, m), 1.01-0.96 (9H, m), 0.83 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 *dr*) δ 200.4 (C, *C*=O), 200.2 (C, *C*=O), 191.3 (2 x C, *C*=O), 166.5 (C, O-*C*=O), 165.6 (C, O-*C*=O), 165.5 (C, O-*C*=O), 165.0 (C, O-*C*=O), 143.0 (C), 142.8 (C), 140.5 (C), 140.4 (C), 135.8 (C), 135.7 (C), 135.2 (2 x CH), 131.2 (C), 131.1 (C), 130.06 (CH), 130.03 (CH), 129.2 (CH), 129.1 (CH), 128.0 (2 x CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 126.7 (CH), 125.9 (CH), 125.8 (CH), 123.1 (CH), 122.8 (CH), 110.2 (C, O-*C*-O), 110.1 (C, O-*C*-O), 89.3 (C, *C*-OH), 89.3 (C, *C*-OH), 70.8 (C), 70.7 (C), 62.5 (CH), 62.3 (CH), 60.99 (C), 60.95 (C), 49.5 (CH), 49.4 (CH), 49.3 (CH_2), 48.9 (CH_2), 33.6 (2 x CH_2), 29.5 (CH), 29.3 (CH), 29.1 (CH_2), 29.08 (CH_2), 24.7 (CH), 24.4 (CH), 23.6 (CH_3), 23.4 (CH_3), 21.7 (CH_3), 21.54 (CH_2), 21.51 (CH_3), 21.4 (CH_2), 18.3 (CH_3), 17.9 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{31}H_{30}O_7Na$ 537.1889; Found 537.1882.

(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-4b',12'-dihydro-2*H*-spiro[pyrimidine-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-2,4,6,11',13'(1*H*,3*H*,6'*H*)-pentaone (69ae):**



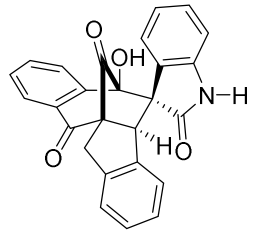
69ae

The compound was prepared following procedure **3a**, purified by column chromatography using DCM, and isolated as a white solid. Yield: 97% (97.6 mg). Mp: 231-233 °C. IR (Neat): ν_{max} 3628, 3523, 3409, 3196, 3094, 2853, 1778, 1727, 1694, 1455, 1419, 1351, 1294, 1244, 1197, 1075, 972, 920, 859, 815, 785, 762, 714, and 683 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.81 (1H, s, N*H*), 11.63 (1H, s, N*H*), 8.16 (1H, s, O*H*), 8.07 (1H, d, *J* = 7.5 Hz), 7.84 (1H, t, *J* = 7.5 Hz), 7.72 (1H, d, *J* = 7.5 Hz), 7.67 (1H, t, *J* = 7.5 Hz), 7.34 (1H, d, *J* = 7.5 Hz), 7.22 (1H, t, *J* = 7.5 Hz), 7.12 (1H, t, *J* = 7.5 Hz), 6.94 (1H, d, *J* = 7.5 Hz), 4.27 (1H, br s), 3.86 (1H, d, *J* = 17.0 Hz), 3.33 (1H, d, *J* = 17.0 Hz). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 201.6 (C, *C*=O), 193.2 (C, *C*=O), 169.1 (C, O=*C*-NH), 168.3 (C, O=*C*-NH), 150.4 (C, O=*C*-NH), 142.9 (C), 142.7 (C), 138.0 (C), 135.4 (CH), 131.4 (C), 130.2 (CH), 128.4 (CH), 127.6 (3 x CH), 125.6 (CH), 123.3 (CH), 92.5 (C, *C*-OH), 71.4 (C), 61.6 (C), 55.9 (CH), 29.4 (CH_2). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{22}H_{14}N_2O_6Na$ 425.0750; Found 425.0751.



69af

(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-1,3-dimethyl-4b',12'-dihydro-2*H*-spiro[pyrimidine-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-2,4,6,11',13'(1*H*,3*H*,6'*H*)-pentaone (69af):** The compound was prepared following procedure **3a**, purified by column chromatography using $CHCl_3$, and isolated as a white solid. Yield: 96% (103.3 mg). Mp: 227-229 °C. IR (Neat): ν_{max} 3355, 1769, 1678, 1530, 1434, 1417, 1375, 1329, 1295, 1250, 1223, 1202, 1178, 1130, 1065, 1047, 1015, 981, 958, 936, 907, 751, 717, 683, and 649 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.24 (1H, s, O*H*), 8.09 (1H, br d, J = 8.0 Hz), 7.85 (1H, br t, J = 7.6 Hz), 7.68 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.6 Hz), 7.34 (1H, d, J = 7.6 Hz), 7.22 (1H, br t, J = 7.6 Hz), 7.13-7.06 (2H, m), 4.43 (1H, s), 3.90 (1H, d, J = 17.2 Hz), 3.47 (1H, d, J = 17.2 Hz), 3.20 (3H, s), 3.00 (3H, s). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 201.6 (C, *C*=O), 193.0 (C, *C*=O), 167.3 (C, O=*C*-N), 166.7 (C, O=*C*-N), 151.4 (C, O=*C*-N), 142.6 (C), 142.3 (C), 138.0 (C), 135.8 (CH), 131.4 (C), 130.4 (CH), 128.4 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 125.4 (CH), 123.9 (CH), 92.8 (C, *C*-OH), 71.2 (C), 62.7 (C), 55.7 (CH), 29.7 (CH$_3$), 29.2 (CH$_2$), 28.5 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{18}N_2O_6Na$ 453.1063; Found 453.1063.

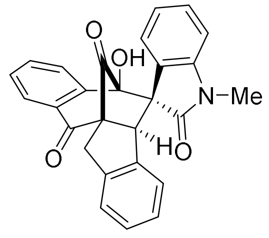


69ag

(3'*S,4b*S**,6*S**,11a*R**)-6-Hydroxyspiro[6,11a-methanodibenzo[*a,f*]azulene-5,3'-indoline]-2',11,13(4b*H*,6*H*,12*H*)-trione (69ag):** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/hexanes (3:7 to 4:6), and isolated as a white solid. Yield: 56% (57 mg). Mp: 250-252°C. IR (Neat): $\nu_{\max}$ 3338, 3221, 3066, 1767, 1691, 1619, 1594, 1487, 1471, 1438, 1341, 1298, 1250, 1229, 1181, 1154, 1117, 1101, 1083, 1064, 1005, 962, 926, 909, 868, 746, 691, and 674 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz, 13:1 *dr*, major isomer): δ 10.64 (1H, s, N*H*), 8.09 (1H, d, J = 7.6 Hz), 7.84 (1H, t, J = 7.6 Hz), 7.77 (1H, d, J = 7.2 Hz), 7.66 (1H, t, J = 7.6 Hz), 7.34 (1H, d, J = 7.6 Hz), 7.11 (1H, t, J = 7.6 Hz), 7.07 (1H, s, O*H*), 7.07 (1H, t, J = 7.6 Hz), 6.84 (1H, d, J = 8.0 Hz), 6.83 (1H, t, J = 7.6 Hz), 6.56 (1H, t, J

= 7.6 Hz), 6.21 (1H, d, *J* = 7.6 Hz), 5.98 (1H, d, *J* = 7.2 Hz), 4.04 (1H, s), 3.94 (1H, d, *J* = 17.2 Hz), 3.59 (1H, d, *J* = 17.2 Hz). ^{13}C NMR (DMSO-d_6, DEPT-135, 13:1 *dr*, major isomer) δ 205.1 (C, *C*=O), 193.0 (C, *C*=O), 176.2 (C, O=*C*-N), 143.9 (C), 142.8 (C), 141.4 (C), 137.9 (C), 135.1 (CH), 130.9 (C), 129.5 (CH), 128.5 (CH), 128.4 (2 x CH), 127.3 (CH), 127.1 (CH), 126.6 (C), 125.5 (CH), 124.7 (CH), 124.6 (CH), 121.3 (CH), 109.9 (CH), 89.2 (C, *C*-OH), 71.2 (C), 57.9 (C), 57.8 (CH), 28.6 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{26}H_{17}NO_4H$ 408.1236; Found 408.1235.

(3'*S,4b*S**,6*S**,11a*R**)-6-Hydroxy-1'-methylspiro[6,11a-methanodibenzo[*a,f*]azulene-5,3'-indoline]-2',11,13(4b*H*,6*H*,12*H*)-trione (69ah):**

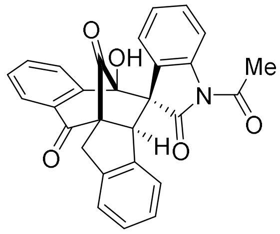


69ah

The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/hexanes (2:8 to 3:7), and isolated as a white solid. Yield: 53% (55.8 mg). Mp: 256-258 °C. IR (Neat): ν_{max} 3330, 2920, 2850, 1766, 1684, 1609, 1597, 1494, 1468, 1374, 1352, 1300, 1266, 1251, 1233, 1199, 1097, 1054, 1001, 960, 941, 909, 745, and 685 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz, 10:1 *dr*, major isomer): δ 8.11 (1H, dd, *J* = 7.6, 0.8 Hz), 7.85 (1H, dt, *J* = 7.6, 1.2 Hz), 7.73 (1H, d, *J* = 7.6 Hz), 7.67 (1H, dt, *J* = 8.0, 0.8 Hz), 7.34 (1H, d, *J* = 7.6 Hz), 7.16 (1H, dt, *J* = 7.6, 0.8 Hz), 7.12 (1H, br s, O*H*), 7.10 (1H, t, *J* = 7.6 Hz), 7.02 (1H, d, *J* = 8.0 Hz), 6.80 (1H, t, *J* = 7.6 Hz), 6.64 (1H, dt, *J* = 7.6, 0.4 Hz), 6.18 (1H, d, *J* = 7.6 Hz), 6.03 (1H, d, *J* = 7.6 Hz), 4.06 (1H, s), 3.94 (1H, d, *J* = 17.2 Hz), 3.60 (1H, d, *J* = 17.2 Hz), 3.20 (3H, s). ^{13}C NMR (DMSO-d_6, DEPT-135, 10:1 *dr*, major isomer) δ205.0 (C, *C*=O), 192.9 (C, *C*=O), 174.4 (C, N-*C*=O), 144.3 (C), 143.9 (C), 141.4 (C), 137.7 (C), 135.1 (CH), 130.9 (C), 129.6

(CH), 128.6 (CH), 128.4 (2 x CH), 127.2 (CH), 127.1 (CH), 125.9 (C), 125.4 (CH), 124.9 (CH), 124.3 (CH), 121.9 (CH), 108.9 (CH), 89.1 (C, *C*-OH), 71.3 (C), 58.0 (CH), 57.6 (C), 28.6 (CH_2), 27.1 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{27}H_{19}NO_4NH_4$ 439.1658; Found 439.1659.

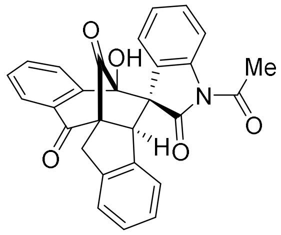
(3'*S,4b*S**,6*S**,11a*R**)-1'-Acetyl-6-hydroxyspiro[6,11a-methanodibenzo[*a,f*]azulene-5,3'-indoline]-2',11,13(4b*H*,6*H*,12*H*)-trione (69ai-major diastereomer):** The compound was prepared following procedure **3a**, purified by column chromatography using $CHCl_3$/hexanes (8:2 to 10:0), and isolated as a white solid. Yield: 59.2% (66.5 mg). Mp: 216-218 °C; IR (Neat): ν_{max} 3493, 1761, 1704, 1685, 1599, 1459, 1414, 1368, 1339, 1309, 1283, 1256, 1193, 1168, 1119, 1100, 1073, 1054, 1038, 1005, 967, 924, 910, 896, 871, 847, 809, 782, 755, 728, 701, 677, and 638 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 4:1 *dr*, major isomer): δ 8.30 (1H, d, *J* = 8.5 Hz), 8.27 (1H, d, *J* = 8.0 Hz), 7.81-7.77 (2H, m), 7.67 (1H, dt, *J* = 7.5, 1.5 Hz), 7.33 (1H, d, *J* = 8.0 Hz), 7.26 (1H, d, *J* = 8.0 Hz), 7.16 (1H, t, *J* = 7.5 Hz), 6.84 (1H, t, *J* = 7.0 Hz), 6.82 (1H, t, *J* = 7.0 Hz), 6.16 (1H, d, *J* = 7.5 Hz), 6.04 (1H, d, *J* = 7.5 Hz), 4.39 (1H, s), 4.16 (1H, d, *J* = 17.0 Hz), 3.76 (1H, d, *J* = 17.0 Hz), 3.30 (1H, s, O*H*), 2.62 (3H, s). ^{13}C NMR ($CDCl_3$, DEPT-135, 4:1 *dr*, major isomer) δ 203.7 (C, *C*=O), 191.3 (C, *C*=O), 175.8 (C, O=*C*-N), 170.4 (C, O=*C*-N), 141.6 (C), 140.8 (C), 140.3 (C), 136.2 (C), 135.2 (CH), 130.9 (C), 129.7 (CH), 129.4 (CH), 128.5 (CH), 127.8 (CH), 126.9 (CH), 126.4 (CH), 125.3 (CH), 125.2 (CH), 124.7 (CH), 124.1 (CH), 123.7 (C), 116.6 (CH), 88.7 (C, *C*-OH), 70.6 (C), 58.9 (C), 58.0 (CH), 28.3 (CH_2), 26.7 (CH_3).



69ai-major

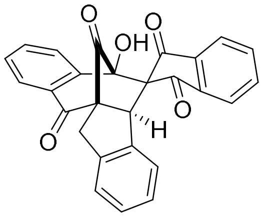
HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{28}H_{19}NO_5NH_4$ 467.1607; Found 467.1607.

(3'*R,4b*S**,6*S**,11a*R**)-1'-Acetyl-6-hydroxyspiro[6,11a-methanodibenzo[*a,f*]azulene-5,3'-indoline]-2',11,13(4b*H*,6*H*,12*H*)-trione (69ai-minor diastereomer):**


69ai-minor

The compound was prepared following procedure **3a**, purified by column chromatography using $CHCl_3$/hexanes (8:2 to 10:0), and isolated as a white solid. Yield: 14.8% (16.6 mg). Mp: 198-200 °C. IR (Neat): ν_{max} 3460, 2980, 1772, 1751, 1718, 1678, 1646, 1459, 1366, 1340, 1300, 1269, 1213, 1170, 1039, 1015, 956, 914, 752, 724, 694, 670, 640, and 596 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 4:1 *dr*, minor isomer): δ 8.34 (1H, d, J = 8.0 Hz), 8.31 (1H, dd, J = 8.0, 1.5 Hz), 7.78 (1H, dt, J = 7.5, 1.5 Hz), 7.72 (1H, dt, J = 7.5, 1.0 Hz), 7.64 (1H, dd, J = 7.5, 1.5 Hz), 7.41 (1H, dt, J = 8.0, 1.0 Hz), 7.37 (1H, d, J = 7.5 Hz), 7.25 (1H, t, J = 7.5 Hz), 7.03 (1H, dt, J = 8.0, 1.0 Hz), 7.02 (1H, dt, J = 7.5, 1.0 Hz), 6.40 (1H, d, J = 7.5 Hz), 5.83 (1H, dd, J = 7.5, 1.0 Hz), 4.79 (1H, d, J = 17.5 Hz), 4.03 (1H, s), 3.83 (1H, br s, O*H*), 3.76 (1H, d, J = 17.5 Hz), 2.34 (3H, s). ^{13}C NMR ($CDCl_3$, DEPT-135, 4:1 *dr*, minor isomer) δ 202.6 (C, *C*=O), 192.1 (C, *C*=O), 175.7 (C, N-*C*=O), 170.4 (C, N-*C*=O), 142.5 (C), 141.3 (C), 140.6 (C), 136.7 (C), 135.0 (CH), 130.9 (C), 130.1 (CH), 129.8 (CH), 128.8 (CH), 128.1 (CH), 127.9 (CH), 127.3 (CH), 125.9 (C), 125.8 (CH), 125.0 (CH), 124.1 (CH), 122.4 (CH), 116.7 (CH), 88.4 (C, *C*-OH), 72.0 (C), 61.0 (CH), 60.0 (C), 28.8 (CH_2), 26.4 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{19}NO_5Na$ 472.1161; Found 472.1156.

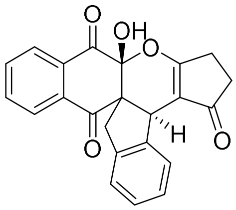
(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-4b',12'-dihydrospiro[indene-2,5'-[6,11a]methanodibenzo[*a,f*]azulene]-1,3,11',13'(6'*H*)-tetraone (69aj):** The compound was prepared following procedure **3a**, purified by column chromatography using $CHCl_3$/hexanes (8:2 to 10:0), and isolated as a white solid. Yield: 97% (101.9 mg). Mp: 246-248 °C. IR (Neat): ν_{max} 3422, 2919, 1780, 1700, 1686, 1593, 1453, 1302, 1257, 1230, 1204, 1179, 1156, 1075, 1006, 977, 946, 773, 751, 726, 685, and 638 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.23 (1H, d, *J* = 8.0 Hz), 8.05 (1H, d, *J* = 7.5 Hz), 7.92 (1H, dt, *J* = 7.0, 1.0 Hz), 7.89 (1H, t, *J* = 7.0 Hz), 7.85 (1H, d, *J* = 7.0 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 7.71 (1H, d, *J* = 7.0 Hz), 7.64 (1H, t, *J* = 7.5 Hz), 7.34 (1H, d, *J* = 7.5 Hz), 7.20 (1H, t, *J* = 7.5 Hz), 6.90 (1H, t, *J* = 7.5 Hz), 6.27 (1H, d, *J* = 7.5 Hz), 4.19 (1H, s), 4.07 (1H, d, *J* = 17.0 Hz), 3.84 (1H, br s, O*H*), 3.74 (1H, d, *J* = 17.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 201.6 (C, *C*=O), 197.7 (C, *C*=O), 197.5 (C, *C=O*), 191.8 (C, *C=O*), 143.0 (C), 142.9 (C), 142.3 (C), 140.7 (C), 136.4 (CH), 136.2 (C), 136.1 (CH), 135.0 (CH), 130.9 (C), 129.7 (CH), 128.5 (CH), 127.9 (CH), 127.0 (CH), 126.8 (CH), 125.8 (CH), 123.6 (CH), 123.4 (CH), 123.0 (CH), 88.6 (C, *C*-OH), 71.2 (C), 62.5 (C), 56.5 (CH), 28.6 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{27}H_{16}O_5NH_4$ 438.1341; Found 438.1341.



69aj

(4b*R,8a*R**)-8a-Hydroxy-4b,6,7,15-tetrahydro-5*H*,14*H*-benzo[g]cyclopenta[b]indeno[1,2-d]chromene-5,9,14(8a*H*)-trione (69ak):** The compound was prepared following procedure **3a**, purified by column chromatography using MeOH/$CHCl_3$ (0:10 to 0.2:9.8), and isolated as a white solid. Yield: 98% (91.2

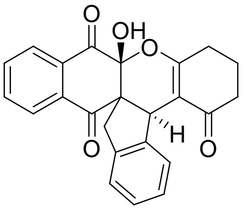
mg). Mp: 224-226 °C. IR (Neat): ν_{max} 2961, 2924, 2850, 1697, 1670, 1603, 1439, 1378, 1258, 1194, 1097, 1057, 1014, 988, 958, 943, 883, 792, 757, 737, 705, and 683 cm^{-1}.



69ak

^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.29 (1H, dd, J = 7.5, 1.0 Hz), 8.24 (1H, dd, J = 7.5, 1.0 Hz), 7.95 (1H, dt, J = 7.5, 1.5 Hz), 7.91 (1H, dt, J = 7.5, 1.0 Hz), 7.69 (1H, d, J = 7.5 Hz), 7.24 (1H, br t, J = 7.5 Hz), 7.19 (1H, br t, J = 7.5 Hz), 7.06 (1H, br d, J = 7.5 Hz), 5.27 (1H, br s, OH), 5.21 (1H, s), 3.27 (1H, d, J = 16.0 Hz), 3.10 (1H, d, J = 16.0 Hz), 2.56-2.50 (4H, m). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 203.7 (C, C=O), 193.5 (C, C=O), 190.3 (C, C=O), 180.6 (C, C=C-O), 141.9 (C), 138.1 (C), 136.4 (CH), 135.0 (CH), 134.7 (C), 130.5 (C), 128.4 (CH), 128.0 (CH), 127.6 (CH), 127.3 (CH), 124.8 (CH), 123.2 (CH), 117.5 (C), 98.1 (C, O-C-OH), 61.5 (C), 40.4 (CH), 33.6 (CH$_2$), 29.7 (CH$_2$), 26.8 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{23}H_{16}O_5H$ 373.1076; Found 373.1077.

(4b*R,9a*R**)-9a-Hydroxy-4b,7,8,16-tetrahydro-15*H*-benzo[b]indeno[1,2-m]xanthene-5,10, 15(6*H*,9a*H*)-trione (69al):** The compound was prepared following

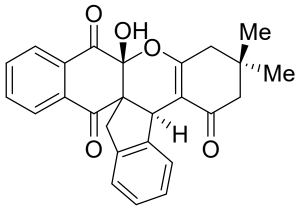


69al

procedure **3a**, purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 4:6), and isolated as a white solid. Yield: 98% (94.7 mg). Mp: 126-128 °C. IR (Neat): ν_{max} 3028, 2799, 1702, 1622, 1586, 1425, 1372, 1255, 1207, 1184, 1102, 1083, 1024, 1002, 964, 886, 860, 787, 768, 757, 739, and 690 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.24 (1H, dd, J = 7.2, 1.6 Hz), 8.19 (1H, dd, J = 7.2, 1.6 Hz), 7.89 (1H, dt, J = 7.2, 1.6 Hz), 7.85 (1H, dt, J = 7.2, 1.6 Hz), 7.36-7.34 (1H, m), 7.18-7.13 (2H, m), 7.05-7.03 (1H, m), 5.25 (1H, s), 5.07 (1H, br s, OH), 3.28 (1H, d, J = 16.0 Hz), 3.06

(1H, d, J = 16.0 Hz), 2.56-2.45 (2H, m), 2.43-2.27 (2H, m), 2.03-1.93 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 198.1 (C, *C*=O), 193.7 (C, *C*=O), 190.9 (C, *C*=*O*), 168.1 (C, C=*C*-O), 142.8 (C), 138.6 (C), 136.1 (CH), 134.8 (CH), 134.6 (C), 130.6 (C), 128.2 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 124.9 (CH), 123.0 (CH), 114.0 (C), 95.9 (C, O-*C*-OH), 61.1 (C), 40.4 (CH), 39.8 (CH$_2$), 37.1 (CH$_2$), 28.4 (CH$_2$), 20.4 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{18}O_5H$ 387.1232; Found 387.1236.

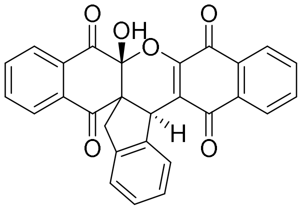
(4b*R,9a*R**)-9a-Hydroxy-7,7-dimethyl-4b,7,8,16-tetrahydro-15*H*-benzo[b]indeno[1,2-m]xanthene-5,10,15(6*H*,9a*H*)-trione (69am):** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 4:6), and isolated as a white solid. Yield: 96% (99.5 mg). Mp: 232-236 °C. IR (Neat): $\nu_{\max}$ 3225, 2951, 2926, 1709, 1696, 1613, 1475, 1370, 1263, 1214, 1147, 1094, 1078, 1062, 1011, 975, 954, 897, 883, 790, 777, 735, 705, and 631 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.24 (1H, dd, J = 7.2, 1.6 Hz), 8.19 (1H, dd, J = 7.2, 1.6 Hz), 7.90 (1H, dt, J = 7.2, 1.6 Hz), 7.86 (1H, dt, J = 7.2, 1.6 Hz), 7.34-7.33 (1H, m), 7.19-7.13 (2H, m), 7.04-7.02 (1H, m), 5.30 (1H, s), 4.97 (1H, br s, O*H*), 3.25 (1H, d, J = 15.6 Hz), 3.03 (1H, d, J = 15.6 Hz), 2.46 (1H, d, J = 15.6 Hz), 2.32 (2H, br d, J = 17.2 Hz), 2.11 (1H, td, J = 17.6, 1.6 Hz), 1.06 (3H, s), 0.99 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 198.0 (C, *C*=O), 193.6 (C, *C*=O), 190.9 (C, *C*=*O*), 166.4 (C, C=*C*-O), 142.9 (C), 138.4 (C), 136.2 (CH), 134.8 (C), 134.7 (CH), 130.5 (C), 128.2 (CH), 127.8 (CH), 127.3 (CH), 126.9 (CH), 124.8 (CH), 123.0 (CH), 112.8 (C), 95.9 (C, O-*C*-OH), 61.1 (C), 51.2 (CH$_2$), 42.2 (CH$_2$), 39.9 (CH$_2$), 32.4 (C), 29.1 (CH$_3$),



69am

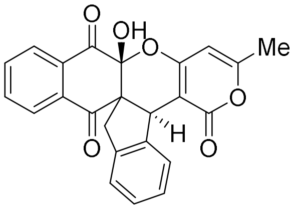
27.1 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{22}O_5H$ 415.1545; Found 415.1547.

(11a*R,18b*R**)-11a-Hydroxy-5,18b-dihydro-6*H*-dibenzo[b,i]indeno[2,1-l]xanthene-6,11,13,18(11a*H*)-tetraone (69an):** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/$CHCl_3$ (0.1:9.9 to 0.4:9.6), and isolated as a white solid. Yield: 95% (106.5 mg). Mp: 248-250 °C. IR (Neat): ν_{max} 3439, 1706, 1677, 1655, 1623, 1586, 1480, 1366, 1331, 1302, 1277, 1257, 1236, 1187, 1148, 1126, 1085, 1070, 1013, 968, 907, 798, 783, 745, 721, 698, 666, 648, 619, 606, and 552 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 9.15 (1H, s, O*H*), 8.18-7.74 (8H, m), 7.20-7.04 (4H, m), 5.09 (1H, s), 3.57 (1H, d, J = 16.0 Hz), 2.96 (1H, d, J = 16.0 Hz). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 193.6 (C, *C*=O), 188.4 (C, *C*=*O*), 184.0 (C, *C*=*O*), 178.9 (C, *C*=*O*), 150.5 (C, C=*C*-O), 141.5 (C), 138.8 (C), 136.0 (CH), 135.4 (CH), 135.0 (CH), 134.5 (CH), 133.2 (C), 132.8 (C), 131.8 (C), 131.0 (C), 128.0 (CH), 127.99 (CH), 127.95 (CH), 127.6 (2 x CH), 126.4 (CH), 126.3 (CH), 125.6 (C), 125.4 (CH), 97.6 (C, *C*-OH), 63.7 (C), 40.0 (CH), 38.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{16}O_6H$ 449.1025; Found 449.1025.



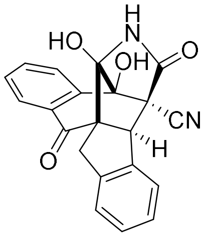
69an

(4b*S,9a*R**)-9a-Hydroxy-7-methyl-4b,16-dihydro-5*H*,15*H*-benzo[g]indeno[1,2-d]pyrano[4,3-b]chromene-5,10,15(9a*H*)-trione (69ao):**


69ao

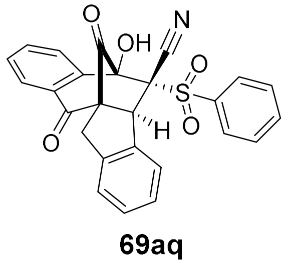
The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/hexanes (3:7 to 4:6), and isolated as a white solid. Yield: 98% (98 mg). Mp: 208-212 °C. IR (Neat): ν_{max} 3339, 3061, 1697, 1654, 1636, 1590, 1480, 1435, 1385, 1339, 1265, 1226, 1148, 1099, 1077, 1028, 995, 960, 925, 887, 808, 790, 740, 703, 677, 636, and 613 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.16 (1H, s, O*H*), 8.15 (1H, dd, *J* = 6.5, 2.0 Hz), 7.99-7.95 (2H, m), 7.85 (1H, d, *J* = 7.5 Hz), 7.21-7.06 (3H, m), 7.03 (1H, d, *J* = 7.5 Hz), 6.28 (1H, s), 4.75 (1H, s), 3.24 (1H, d, *J* = 17.0 Hz), 2.93 (1H, d, *J* = 17.0 Hz), 2.17 (3H, s). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 193.5 (C, *C*=O), 188.5 (C, *C*=O), 162.8 (C, O-*C*=*O*), 162.0 (C, C=*C*-O), 160.4 (C, C=*C*-O), 142.6 (C), 138.0 (C), 136.0 (CH), 135.3 (CH), 133.2 (C), 132.6 (C), 128.2 (CH), 127.99 (CH), 127.88 (CH), 127.3 (CH), 126.7 (CH), 125.1 (CH), 102.6 (C), 100.7 (CH), 97.4 (C, O-*C*-OH), 63.5 (C), 39.2 (CH), 38.0 (CH$_2$), 19.6 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{16}O_6H$ 401.1025; Found 401.1025.

(4b*S,5*R**,6*S**,11a*S**)-6,13-Dihydroxy-11,15-dioxo-4b,6,11,12-tetrahydro-5*H*-6,11a,5-(epimethanetriyliminomethano)dibenzo[*a,f*]azulene-5-carbonitrile (69ap):**


69ap

The compound was prepared following procedure **3a**, purified by column chromatography using MeOH/CHCl$_3$ (0:10 to 0.5:9.5), and isolated as a white solid. Yield: 89% (79.7 mg, from **65p**), and 85% (76 mg, from **65q**). Mp: 184-186 °C. IR (Neat): ν_{max} 3357, 3260, 2926, 2261, 1723, 1687, 1599, 1456, 1394, 1350, 1300, 1257, 1238, 1176, 1145, 1102, 1078, 1017, 953, 935, 911, 835, 800, 761, 747, 719, 689, 666, and 605 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.17 (1H, s, O*H*), 7.97 (2H, d, J = 8.0 Hz), 7.89 (1H, t, J = 7.6 Hz), 7.67 (1H, t, J = 7.6 Hz), 7.51 (1H, s, O*H*), 7.33 (1H, d, J = 7.2 Hz), 7.26 (1H, t, J = 7.2 Hz), 7.19 (1H, t, J = 7.2 Hz), 7.09 (1H, d, J = 7.2 Hz), 7.02 (1H, s, N*H*), 3.97 (1H, s), 3.83 (1H, d, J = 17.6 Hz), 3.07 (1H, d, J = 17.6 Hz). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 195.8 (C, *C*=O), 166.3 (C, HN-*C*=O), 144.1 (C), 138.5 (C), 136.4 (C), 135.0 (CH), 131.6 (C), 130.1 (CH), 128.9 (CH), 128.5 (CH), 127.3 (CH), 126.3 (CH), 125.5 (CH), 125.2 (CH), 116.5 (C), 98.0 (C, HN-*C*-OH), 89.6 (C, *C*-OH), 66.7 (C), 58.2 (CH), 58.0 (C), 29.8 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{14}N_2O_4H$ 359.1032; Found 359.1032.

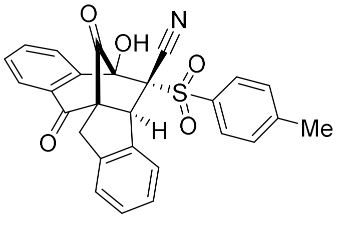
(4b*S,5*S**,6*R**,11a*R**)-6-Hydroxy-11,13-dioxo-5-(phenylsulfonyl)-4b,6,11,12-tetrahydro-5*H*-6,11a-methanodibenzo[*a,f*]azulene-5-carbonitrile (69aq):** The compound was prepared following procedure **3a**, purified by column chromatography using CHCl$_3$/hexanes (8:2 to 10:0), and isolated as a white solid. Yield: 58% (66 mg). Mp: 199-201 °C. IR (Neat): ν_{max} 3361, 2923, 2852, 2252, 2256, 1775, 1695, 1599, 1456, 1438, 1333, 1310, 1293, 1252, 1208, 1149, 1078, 1054, 1028, 997, 974, 927, 909, 847, 812, 773, 752, 715, 685, 666, 610, and 584 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.38 (1H, s, O*H*), 8.13 (1H, dd, J = 7.5, 0.5 Hz), 8.04 (2H, d, J = 8.5 Hz), 8.00 (2H, br t, J = 8.0 Hz), 7.93 (1H, d, J = 8.0 Hz), 7.83 (2H, t, J = 8.0 Hz), 7.77 (1H, dt, J = 7.5, 0.5 Hz), 7.42 (1H, d, J = 8.0 Hz), 7.34 (1H, t, J = 7.5 Hz), 7.18 (1H, t,



69aq

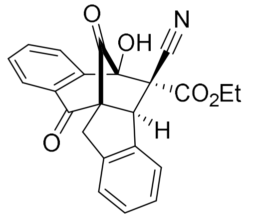
J = 7.5 Hz), 6.66 (1H, d, J = 8.0 Hz), 4.76 (1H, s), 3.87 (1H, d, J = 17.5 Hz), 3.51 (1H, d, J = 17.5 Hz). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 199.5 (C, *C*=O), 190.6 (C, *C*=O), 141.8 (C), 139.0 (C), 136.7 (CH), 136.1 (CH), 135.6 (C), 135.4 (C), 131.3 (2 x CH), 131.05 (CH), 131.03 (C), 130.3 (2 x CH), 129.7 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 126.8 (CH), 125.8 (CH), 113.5 (C), 88.0 (C, *C*-OH), 73.7 (C), 70.7 (C), 53.5 (CH), 28.8 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{17}NO_5SH$ 456.0906; Found 456.0905.

(4b*S,5*S**,6*R**,11a*R**)-6-Hydroxy-11,13-dioxo-5-tosyl-4b,6,11,12-tetrahydro-5*H*-6,11a-methanodibenzo[*a,f*]azulene-5-carbonitrile (69ar):** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7), and isolated as a white solid. Yield: 54% (63.4 mg). Mp: 188-190 °C. IR (Neat): ν_{max} 3474, 2961, 1778, 1695, 1592, 1454, 1325, 1290, 1256, 1225, 1146, 1079, 1012, 960, 932, 909, 878, 844, 801, 763, 739, 702, 661, 648, and 573 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (1H, dd, J = 7.5, 1.0 Hz), 7.96 (1H, dd, J = 8.0, 0.5 Hz), 7.94 (2H, d, J = 8.5 Hz), 7.89 (1H, dt, J = 7.5, 1.0 Hz), 7.71 (1H, dt, J = 7.5, 1.0 Hz), 7.51 (2H, d, J = 8.0 Hz), 7.34 (2H, d, J = 4.0 Hz), 7.19 (1H, m), 6.85 (1H, d, J = 8.0 Hz), 4.59 (1H, s), 4.18 (1H, br s, O*H*), 4.06 (1H, d, J = 17.0 Hz), 3.66 (1H, d, J = 17.0 Hz), 2.57 (3H, s). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.2 (C, *C*=O), 189.8 (C, *C*=O), 147.5 (C), 141.5 (C), 137.3 (C), 135.6 (CH), 134.1 (C), 132.6 (C), 131.1 (2 x CH), 130.8 (C), 130.7 (CH), 130.1 (2 x CH), 129.6 (CH), 128.2 (CH), 127.8 (2 x CH), 126.6 (CH), 125.4 (CH), 112.7 (C), 86.5 (C, *C*-OH), 74.0



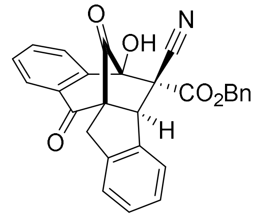
69ar

(C), 70.3 (C), 54.4 (CH), 28.5 (CH_2), 21.9 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{19}NO_5SH$ 470.1062; Found 470.1063.


69as

Ethyl (4b*S,5*S**,6*S**,11a*R**)-5-cyano-6-hydroxy-11,13-dioxo-5,6,11,12-tetrahydro-4b*H*-6,11a-methanodibenzo[*a,f*]azulene-5-carboxylate (69as):** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/$CHCl_3$ (0:10 to 0.2:9.8), and isolated as a white solid. Yield: 78% (75.5 mg). Mp: 194-196 °C. IR (Neat): ν_{max} 3382, 1787, 1738, 1701, 1595, 1464, 1371, 1330, 1292, 1233, 1182, 1131, 1101, 1084, 1064, 1042, 1018, 983, 948, 926, 876, 852, 783, 765, 756, 711, 676, and 645 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz, 14:1 *dr*, major isomer): δ 8.29 (1H, s, O*H*), 8.09 (1H, d, $J = 7.5$ Hz), 8.05 (1H, d, $J = 8.0$ Hz), 8.00 (1H, t, $J = 7.5$ Hz), 7.77 (1H, t, $J = 7.5$ Hz), 7.39 (1H, d, $J = 7.5$ Hz), 7.31 (1H, t, $J = 7.5$ Hz), 7.23 (1H, t, $J = 7.5$ Hz), 7.03 (1H, d, $J = 7.5$ Hz), 4.53 (1H, s), 3.85 (1H, d, $J = 17.5$ Hz), 3.83-3.65 (2H, br m, OCH_2CH_3), 3.40 (1H, d, $J = 17.5$ Hz), 0.75 (3H, br s, OCH_2CH_3). ^{13}C NMR (DMSO-d_6, DEPT-135, 14:1 *dr*, major isomer) δ 200.5 (C, *C*=O), 192.1 (C, *C*=O), 164.5 (C, O-*C*=O), 142.4 (C), 142.0 (C), 136.8 (C), 136.0 (CH), 131.0 (C), 130.97 (CH), 129.2 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 125.8 (CH), 123.9 (CH), 117.0 (C, *C*N), 89.3 (C, *C*-OH), 71.8 (2 x C), 63.4 (CH_2, OCH_2CH_3), 56.8 (CH), 29.5 (CH_2), 13.4 (CH_3, OCH_2CH_3). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{23}H_{17}NO_5NH_4$ 405.1450 Found 405.1450.

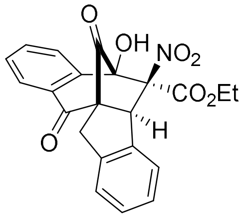
Benzyl (4b*S,5*S**,6*S**,11a*R**)-5-cyano-6-hydroxy-11,13-dioxo-5,6,11,12-tetrahydro-4b*H*-6,11a-methanodibenzo[*a,f*]azulene-5-carboxylate (69at):** The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/CHCl$_3$ (0:10 to 0.5:9.5), and isolated as a white solid. Yield: 75% (84.3 mg). Mp: 182-184 °C. IR (Neat): ν_{max} 3408, 3065, 2927, 1779, 1727, 1701, 1599, 1483, 1456, 1433, 1371, 1325, 1292, 1245, 1205, 1158, 1124, 1085, 1064, 1044, 1014, 986, 917, 903, 883, 829, 789, 752, 712, 697, 675, 643, and 591 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz, 7:1 *dr*, major isomer): δ 8.37 (1H, s, O*H*), 8.09 (1H, d, *J* = 8.0 Hz), 8.05 (1H, d, *J* = 8.0 Hz), 8.00 (1H, t, *J* = 8.0 Hz), 7.77 (1H, t, *J* = 7.2 Hz), 7.46-7.39 (1H, m), 7.35 (3H, br s), 7.29-7.26 (2H, m), 7.19-7.15 (1H, m), 7.09 (1H, br s), 6.99 (1H, d, *J* = 7.2 Hz), 4.85 (1H, d, *J* = 12.0 Hz), 4.55 (1H, s), 3.79 (1H, d, *J* = 17.6 Hz), 3.34 (1H, d, *J* = 12.0 Hz), 3.26 (1H, d, *J* = 17.6 Hz). ^{13}C NMR (CDCl$_3$ + Acetone-d_6, DEPT-135, 7:1 *dr*, major isomer) δ 198.9 (C, *C*=O), 191.2 (C, *C*=O), 163.8 (C, O-*C*=O), 142.1 (C), 141.1 (C), 135.22 (CH), 135.20 (C), 133.3 (C), 130.3 (C), 130.0 (CH), 128.7 (CH), 128.25 (2 x CH), 128.22 (CH), 128.0 (2 x CH), 127.5 (CH), 126.9 (CH), 126.8 (CH), 125.9 (CH), 123.1 (CH), 116.0 (C, *C*N), 88.4 (C, *C*-OH), 71.1 (C), 68.4 (CH$_2$), 57.9 (CH), 56.9 (C), 28.6 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{28}H_{19}NO_5Na$ 472.1161; Found 472.1158.



69at

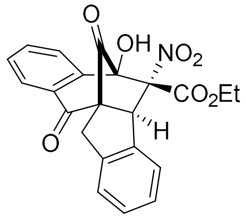
Ethyl (4b*S,5*S**,6*S**,11a*R**)-6-hydroxy-5-nitro-11,13-dioxo-5,6,11,12-tetrahydro-4b*H*-6,11a-methanodibenzo[*a,f*]azulene-5-carboxylate (69au) and Ethyl (4b*S**,5*R**,6*S**,11a*R**)-6-hydroxy-5-nitro-11,13-dioxo-5,6,11,12-tetrahydro-4b*H*-**

6,11a-methanodibenzo[*a,f*]azulene-5-carboxylate (69'au): The compound was prepared following procedure **3a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2:8), and isolated as a white solid. Yield: 89% (90.6 mg). Mp: 202-205 °C. IR (Neat): $\nu_{\max}$ 3448, 2953, 2553, 1779, 1755, 1702, 1596, 1558, 1487, 1455, 1438, 1391, 1349, 1312, 1286, 1232, 1208, 1165, 1094, 1004, 967, 924, 889, 856, 820, 786, 750, 715, 691, 641, 582, and 552 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz, 2:1 *dr*): δ 8.21 (1H, s, O*H*), 8.11 (1H, s, O*H*), 8.06 (2H, d, *J* = 7.5 Hz), 7.99 (2H, br d, *J* = 7.0 Hz), 7.94 (1H, d, *J* = 8.5 Hz), 7.91 (1H, d, *J* = 7.5 Hz), 7.73 (1H, d, *J* = 7.5 Hz), 7.70 (1H, d, *J* = 7.5 Hz), 7.41 (2H, t, *J* = 7.5 Hz), 7.35 (1H, d, *J* = 7.5 Hz), 7.32 (1H, d, *J* = 8.5 Hz), 7.26 (1H, t, *J* = 7.5 Hz), 7.21 (1H, t, *J* = 7.5 Hz), 7.15 (1H, d, *J* = 7.5 Hz), 7.08 (1H, d, *J* = 7.5 Hz), 4.90 (1H, s), 4.76 (1H, s), 4.28 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.89 (2H, d, *J* = 17.5 Hz), 3.82-3.77 (1H, m, OCH_2CH_3), 3.62 (1H, br s, OCH_2CH_3), 3.50 (1H, d, *J* = 17.0 Hz), 3.49 (1H, d, *J* = 17.5 Hz), 1.27 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.64 (3H, br s, OCH_2CH_3). ^{13}C NMR (DMSO-d_6, DEPT-135, 2:1 *dr)* δ 201.1 (C, *C*=O), 199.5 (C, *C*=O), 191.7 (C, *C*=O), 191.6 (C, *C*=O), 163.1 (C, O-*C*=O), 163.0 (C, O-*C*=O), 142.5 (C), 142.4 (C), 140.4 (C), 139.6 (C), 136.6 (C), 136.2 (C), 135.8 (CH), 135.7 (CH), 131.1 (CH), 130.9 (2 x CH), 129.6 (CH), 129.3 (CH), 128.8 (CH), 128.6 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 125.9 (CH), 125.8 (CH), 124.4 (CH), 124.1 (CH), 100.7 (C), 99.4 (C), 89.1 (C, *C*-OH), 89.0 (C, *C*-OH), 73.1 (C), 71.3 (C), 63.9 (CH_2), 63.7 (CH_2), 56.1 (CH), 55.9 (CH), 28.4 (CH_2), 29.2 (CH_2), 14.0 (CH_3),



69au

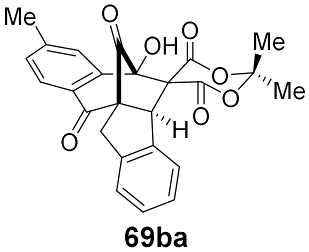
+



69'au

13.1 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + NH$_4$]$^+$ Calcd for $C_{22}H_{17}NO_7NH_4$ 425.1349; Found 425.1348.

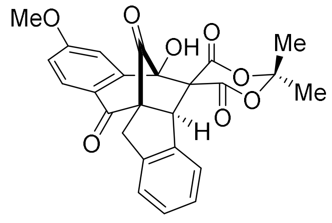
3c. General Procedures for the Synthesis of Products 69: To an ordinary glass vial equipped with a magnetic stirring bar were added 0.25 mmol of **65**, 0.275 mmol of **62** and 2.5 mL of anhydrous DCM. Then, 0.025 mmol of freshly distilled benzyl amine **3z** was added and the resulting mixture was allowed to stir at 25 °C or higher temperatures, until complete consumption of **65** (monitored by TLC). Next, the crude reaction mixture was directly loaded onto a silica gel packed column without aqueous workup to give pure products **69** after column chromatography (eluent: DCM or CHCl$_3$ or mixture of hexanes/ethyl acetate or hexanes/CHCl$_3$, hexanes/DCM, or MeOH/CHCl$_3$ or ethyl acetate/CHCl$_3$).



69ba

(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-2,2,8'-trimethyl-4b',12'-dihydrospiro[[1,3]dioxane-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-4,6,11',13'(6'*H*)-tetraone (69ba):** The compound was prepared following procedure **3c**, purified by column chromatography using DCM/hexanes (5:5 to 10:0), and isolated as a white solid. Yield: 96% (103.8 mg). Mp: 260-262 °C. IR (Neat): ν_{max} 3388, 2926, 1779, 1762, 1718, 1688, 1605, 1444, 1385, 1338, 1288, 1238,1200, 1146, 1118, 1059, 1024, 978, 944, 916, 853, 807, 764, 739, 719, 678, and 622 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.49 (1H, s, O*H*), 7.99 (1H, d, J = 7.6 Hz), 7.60 (1H, s), 7.52 (1H, dd, J = 7.6, 0.8 Hz), 7.36 (1H, d, J = 7.6 Hz), 7.27 (1H, t, J

= 7.6 Hz), 7.19 (1H, t, *J* = 7.2 Hz), 6.95 (1H, d, *J* = 7.6 Hz), 4.26 (1H, s), 3.85 (1H, d, *J* = 17.2 Hz), 3.46 (1H, d, *J* = 17.2 Hz), 2.49 (3H, s), 1.99 (3H, s), 1.76 (3H, s). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 201.0 (C, *C*=O), 192.2 (C, *C*=O), 165.7 (C, O-*C*=O), 165.3 (C, O-*C*=O), 146.5 (C), 142.7 (C), 142.5 (C), 137.1 (C), 131.3 (CH), 129.14 (C), 129.07 (CH), 127.9 (CH), 127.8 (2 x CH), 125.9 (CH), 123.4 (CH), 107.7 (C, O-*C*-O), 91.4 (C, *C*-OH), 71.0 (C), 60.4 (CH), 60.3 (C), 29.9 (CH$_3$), 29.4 (CH$_2$), 28.8 (CH$_3$), 22.2 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{25}H_{20}O_7Na$ 455.1107; Found 455.1108.

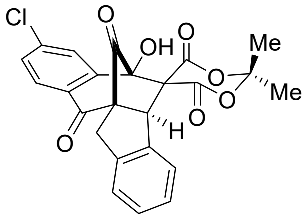


69ca

(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-8'-methoxy-2,2-dimethyl-4b',12'-dihydrospiro[[1,3]dioxane-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-4,6,11',13'(6'*H*)-tetraone (69ca):** The compound was prepared following procedure **3c**, purified by column chromatography using CHCl$_3$, and isolated as a white solid. Yield: 93% (104.2 mg). Mp: 175-177 °C. IR (Neat): $\nu_{\max}$ 3398, 2923, 2852, 1785, 1765, 1731, 1684, 1599, 1482, 1456, 1461, 1386, 1331, 1289, 1249, 1220, 1201, 1115, 1064, 1023, 984, 962, 935, 910, 873, 852, 831, 810, 773, 759, 733, 716, 688, 656, 637, 604, and 561 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.72 (1H, d, *J* = 9.0 Hz), 7.64 (1H, d, *J* = 2.5 Hz), 7.35 (1H, d, *J* = 8.0 Hz), 7.31 (1H, dd, *J* = 9.0, 3.0 Hz), 7.29 (1H, t, *J* = 7.5 Hz), 7.18 (1H, t, *J* = 7.5 Hz), 6.88 (1H, d, *J* = 7.5 Hz), 4.37 (1H, s), 4.25 (1H, s, O*H*), 4.06 (1H, d, *J* = 17.0 Hz), 3.93 (1H, s), 3.66 (1H, d, *J* = 17.0 Hz), 2.03 (3H, s), 1.80 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 199.9 (C, *C*=O), 191.2 (C, *C*=O), 165.7 (C, O-*C*=O), 165.0 (C, O-*C*=O), 160.9 (C), 142.8 (C), 136.0 (C), 132.6 (C), 132.4 (C), 129.1 (CH), 128.0 (CH), 127.3 (CH), 125.9 (CH), 123.1

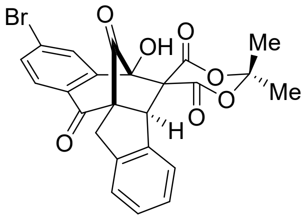
(CH), 122.6 (CH), 110.4 (CH), 107.1 (C, O-*C*-O), 89.6 (C, *C*-OH), 70.7 (C), 61.9 (CH), 60.5 (C), 55.8 (CH_3), 30.0 (CH_3), 29.1 (CH_2), 28.9 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{25}H_{20}O_8NH_4$ 466.1502; Found 466.1502.

(4b'*S,6'*S**,11a'*R**)-8'-Chloro-6'-hydroxy-2,2-dimethyl-4b',12'-dihydrospiro[[1,3]dioxane-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-4,6,11',13'(6'*H*)-tetraone (69da):** The compound was prepared following procedure **3c**, purified by column chromatography using EtOAc/hexanes (2:8), and isolated as a white solid. Yield: 96% (108.7 mg). Mp: 167-169 °C. IR (Neat): ν_{max} 3371, 2929, 1783, 1759, 1717, 1690, 1590, 1446, 1398, 1381, 1341, 1289, 1246, 1226, 1199, 1162, 1104, 1063, 1023, 978, 942, 912, 854, 837, 805, 763, 738, 673, and 631 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.12 (1H, d, J = 8.0 Hz), 7.78 (1H, d, J = 1.5 Hz), 7.58 (1H, dd, J = 8.5, 2.0 Hz), 7.33 (1H, d, J = 7.5 Hz), 7.28 (1H, t, J = 7.5 Hz), 7.17 (1H, t, J = 7.5 Hz), 6.87 (1H, d, J = 7.5 Hz), 4.36 (1H, s), 4.28 (1H, br s, O*H*), 4.03 (1H, d, J = 17.0 Hz), 3.65 (1H, d, J = 17.0 Hz), 2.02 (3H, s), 1.80 (3H, s). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 199.4 (C, *C*=O), 190.0 (C, *C*=O), 165.7 (C, O-*C*=O), 164.7 (C, O-*C*=O), 142.7 (C), 142.1 (C), 142.0, (C), 135.6 (C), 130.6 (CH), 129.6 (C), 129.4 (CH), 129.2 (CH), 127.4 (CH), 127.0 (CH), 125.9 (CH), 122.6 (CH), 107.2 (C, O-*C*-O), 89.0 (C, *C*-OH), 70.8 (C), 61.9 (CH), 60.6 (C), 30.1 (CH_3), 29.1 (CH_2), 28.8 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{17}ClO_7Na$ 475.0561; Found 475.0562.



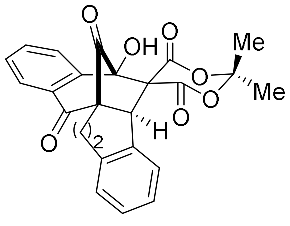
69da

(4b'*S,6'*S**,11a'*R**)-8'-Bromo-6'-hydroxy-2,2-dimethyl-4b',12'-dihydrospiro[[1,3]dioxane-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-4,6,11',13'(6'*H*)-tetraone (69ea):** The compound was prepared following procedure **3c**, purified by column chromatography using DCM/hexanes (5:5 to 10:0), and isolated as a white solid. Yield: 96% (119.3 mg). Mp: 250-252 °C. IR (Neat): ν_{max} 2998, 2850, 1781, 1730, 1696, 1582, 1484, 1458, 1398, 1324, 1290, 1248, 1204,1158, 1119, 1099, 1058, 1042, 1020, 986, 648, 928, 912, 852, 824, 802, 768, 739, 715, 672, and 633 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ 8.73 (1H, s, O*H*), 8.00 (1H, d, *J* = 8.0 Hz), 7.93 (1H, dd, *J* = 8.0, 2.0 Hz), 7.89 (1H, d, *J* = 2.0 Hz), 7.36 (1H, d, *J* = 7.5 Hz), 7.28 (1H, t, *J* = 7.5 Hz), 7.19 (1H, t, *J* = 7.5 Hz), 6.96 (1H, d, *J* = 7.5 Hz), 4.33 (1H, s), 3.84 (1H, d, *J* = 17.5 Hz), 3.41 (1H, d, *J* = 17.5 Hz), 1.98 (3H, s), 1.76 (3H, s). ^{13}C NMR (DMSO-*d*$_6$, DEPT-135) δ 200.3 (C, *C*=O), 191.5 (C, *C*=O), 165.8 (C, O-*C*=O), 165.1 (C, O-*C*=O), 144.3 (C), 142.6 (C), 136.9 (C), 133.8 (CH), 130.5 (C), 130.4 (CH), 129.8 (CH), 129.7 (C), 129.2 (CH), 127.9 (CH), 125.9 (CH), 123.6 (CH), 107.9 (C, O-*C*-O), 90.9 (C, *C*-OH), 71.4 (C), 60.3 (C), 60.2 (CH), 30.0 (CH$_3$), 29.4 (CH$_2$), 28.6 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{17}BrO_7Na$ 519.0055; Found 519.0055.

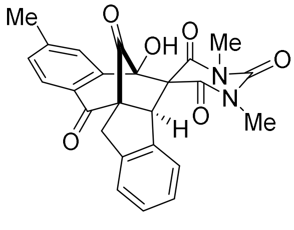


69ea

(6a'*S,12'*S**,13a'*S**)-12'-Hydroxy-2,2-dimethyl-5',13a'-dihydro-6'*H*-spiro[[1,3]dioxane-5,13'-[6a,12]methanobenzo[4,5]cyclohepta[1,2-a]naphthalene]-4,6,7',14'(12'*H*)-tetraone (69fa):** The compound was prepared following procedure **3c**, purified by column chromatography using DCM/hexanes (5:5 to 10:0), and isolated as a white solid. Yield: 95% (102.7 mg). Mp: 254-256 °C. IR (Neat): ν_{max} 3499, 2937, 1768, 1729, 1696, 1597, 1496, 1455, 1386, 1327, 1283, 1196, 1120, 1080, 1048, 1027, 1000, 980, 945, 923, 903, 833, 774, 746, 703, 671, 651, and 628 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.19 (1H, d, *J* = 7.5 Hz), 7.81-7.76 (2H, m), 7.63 (1H, dt, *J* = 7.5, 2.0 Hz), 7.19 (2H, d, *J* = 4.0 Hz), 7.11-7.08 (1H, m), 6.84 (1H, d, *J* = 7.5 Hz), 4.25 (1H, br s, O*H*), 4.25 (1H, s), 3.10 (1H, dt, *J* = 14.5, 4.0 Hz), 2.76 (1H, td, *J* = 15.0, 4.0 Hz), 2.65 (1H, td, *J* = 14.0, 4.0 Hz), 2.46 (1H, dt, *J* = 14.0, 4.5 Hz), 1.95 (3H, s), 1.61 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 201.2 (C, *C*=O), 193.1 (C, *C*=O), 166.1 (C, O-*C*=O), 165.1 (C, O-*C*=O), 140.3 (C), 139.7 (C), 135.4 (CH), 130.8 (C), 130.4 (C), 130.0 (CH), 129.6 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 126.4 (CH), 125.9 (CH), 106.9 (C, O-*C*-O), 87.7 (C, *C*-OH), 63.7 (C), 63.2 (C), 50.7 (CH), 29.8 (CH$_3$), 28.9 (CH$_3$), 25.6 (CH$_2$), 20.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{25}H_{20}O_7Na$ 455.1107; Found 455.1108.



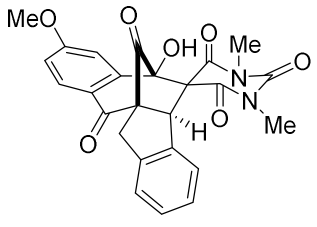
69fa



69bf

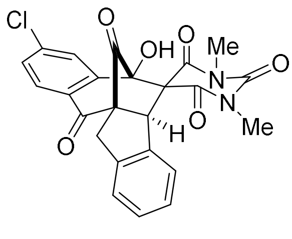
(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-1,3,8'-trimethyl-4b',12'-dihydro-2*H*-spiro[pyrimidine-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-2,4,6,11',13'(1*H*,3*H*,6'*H*)-pentaone (69bf):** The compound was prepared following procedure **3c**, purified by column chromatography using DCM/hexanes (5:5 to 10:0), and isolated as a white solid. Yield: 97% (107.8 mg). Mp: 246-248 °C. IR (Neat): $\nu_{\max}$ 3412, 2921, 2852, 1778, 1747, 1685, 1660, 1600, 1449, 1423, 1373, 1293, 1253, 1199, 1169, 1126, 1062, 1042, 989, 944, 912, 863, 843, 426, 747, 715, 671, and 619 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.08 (1H, d, *J* = 8.0 Hz), 7.67 (1H, s), 7.41 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 7.6 Hz), 7.25 (1H, t, *J* = 7.6 Hz), 7.09 (1H, t, *J* = 7.6 Hz), 6.69 (1H, d, *J* = 7.6 Hz), 4.52 (1H, s), 4.16 (1H, br s, O*H*), 4.07 (1H, d, *J* = 17.2 Hz), 3.65 (1H, d, *J* = 17.2 Hz), 3.38 (3H, s), 3.10 (3H, s), 2.51 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 200.9 (C, *C*=O), 191.2 (C, *C*=O), 167.2 (C, N-*C*=O), 166.7 (C, N-*C*=O), 150.8 (C, N-*C*=O), 146.6 (C), 143.1 (C), 140.3 (C), 136.7 (C), 131.0 (CH), 129.2 (C), 128.6 (CH), 128.1 (CH), 127.0 (CH), 126.5 (CH), 125.8 (CH), 122.2 (CH), 91.3 (C, *C*-OH), 70.9 (C), 62.9 (C), 58.2 (CH), 29.7 (CH$_2$), 29.5 (CH$_3$), 28.4 (CH$_3$), 22.2 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for C$_{25}$H$_{20}$N$_2$O$_6$Na 467.1219; Found 467.1218.

(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-8'-methoxy-1,3-dimethyl-4b',12'-dihydro-2*H*-spiro[pyrimidine-5,5'-[6,11a]methanodibenzo[*a,f*]azulene]-2,4,6,11',13'(1*H*,3*H*,6'*H*)-pentaone (69cf):** The compound was prepared following procedure **3c**, purified by column chromatography using $CHCl_3$, and isolated as a white solid. Yield: 92% (105.9 mg). Mp: 250-252 °C. IR (Neat): ν_{max} 3451, 2922, 2851, 1770, 1748, 1667, 1601, 1486, 1422, 1377, 1330, 1280, 1250, 1213, 1129, 1101, 1065, 1044, 1020, 986, 951, 932, 875, 849, 830, 818, 798, 778, 752, 651, 636, and 608 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.63 (1H, d, J = 2.5 Hz), 7.56 (1H, d, J = 9.0 Hz), 7.35 (1H, d, J = 7.5 Hz), 7.28 (1H, dd, J = 8.5, 2.5 Hz), 7.26 (1H, t, J = 7.5 Hz), 7.09 (1H, t, J = 7.5 Hz), 6.69 (1H, d, J = 7.5 Hz), 4.50 (1H, s), 4.08 (1H, d, J = 17.0 Hz), 3.97 (1H, s), 3.92 (3H, s), 3.67 (1H, d, J = 17.0 Hz), 3.38 (3H, s), 3.11 (3H, s). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 200.4 (C, *C*=O), 191.4 (C, *C*=O), 167.3 (C, N-*C*=O), 166.7 (C, N-*C*=O), 160.9 (C, N-*C*=O), 150.8 (C), 143.0 (C), 136.6 (C), 132.9 (C), 132.3 (C), 128.6 (CH), 127.5 (CH), 127.1 (CH), 125.8 (CH), 123.0 (CH), 122.2 (CH), 110.3 (CH), 91.3 (C, *C-OH*), 71.0 (C), 62.7 (C), 58.3 (CH), 55.7 (CH_3), 29.5 (CH_3), 29.2 (CH_2), 28.4 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{20}N_2O_7H$ 461.1349; Found 461.1349.



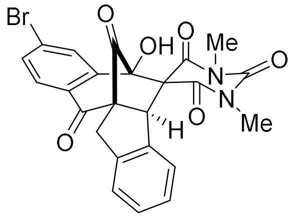
69cf

(4b'*S,6'*S**,11a'*R**)-8'-Chloro-6'-hydroxy-1,3-dimethyl-4b',12'-dihydro-2*H*-spiro[pyrimidine-5,5'-[6,11a]methanodibenzo[*a*,*f*]azulene]-2,4,6,11',13'(1*H*,3*H*,6'*H*)-pentaone (69df):** The compound was prepared following procedure **3c**, purified by column chromatography using DCM, and isolated as a white solid. Yield: 96% (111.6 mg). Mp: 204-208 °C. IR (Neat): $\nu_{\max}$ 3414, 2925, 1777, 1748, 1673, 1588, 1426, 1422, 1375, 1290, 1277, 1159, 1131, 1102, 1066, 1041, 991, 941, 915, 873, 844, 807, 751, and 656 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.12 (1H, d, J = 8.5 Hz), 7.66 (1H, d, J = 2.0 Hz), 7.57 (1H, dd, J = 8.5, 2.0 Hz), 7.33 (1H, d, J = 7.5 Hz), 7.25 (1H, t, J = 7.5 Hz), 7.09 (1H, t, J = 7.5 Hz), 6.67 (1H, d, J = 7.5 Hz), 4.48 (1H, s), 4.15 (1H, br s, O*H*), 4.05 (1H, d, J = 17.0 Hz), 3.65 (1H, d, J = 17.0 Hz), 3.38 (3H, s), 3.08 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 200.0 (C, *C*=O), 190.3 (C, *C*=O), 167.1 (C, N-*C*=O), 166.6 (C, N-*C*=O), 150.5 (C, N-*C*=O), 142.9 (C), 142.2 (C), 141.9 (C), 136.3 (C), 130.5 (CH), 129.8 (C), 129.4 (CH), 128.8 (CH), 127.2 (CH), 126.6 (CH), 125.9 (CH), 122.2 (CH), 90.8 (C, *C*-OH), 71.1 (C), 62.7 (C), 58.4 (CH), 29.6 (CH$_3$), 29.1 (CH$_2$), 28.5 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{17}ClN_2O_6Na$ 487.0673; Found 487.0673.



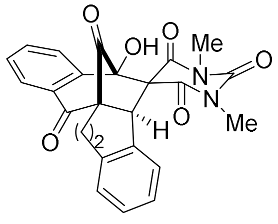
69df

(4b'*S,6'*S**,11a'*R**)-8'-Bromo-6'-hydroxy-1,3-dimethyl-4b',12'-dihydro-2*H*-spiro[pyrimidine-5,5'-[6,11a]methanodibenzo[*a*,*f*]azulene]-2,4,6,11',13'(1*H*,3*H*,6'*H*)-pentaone (69ef):** The compound was prepared following procedure **3c**, purified by column chromatography using DCM/hexanes (5:5 to 10:0), and isolated as a white solid. Yield: 97% (123.5 mg). Mp: 228-230 °C. IR (Neat): $\nu_{\max}$ 3382, 3026, 2919, 2850, 1781, 1748, 1675, 1581, 1421, 1374, 1290, 1234, 1160, 1130, 1096, 1066, 1039, 1018, 977, 951, 915, 841, 793, 749, 673, and 654 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.06 (1H, d, J = 8.0 Hz), 7.86 (1H, d, J = 2.0 Hz), 7.76 (1H, dd, J = 8.0, 2.0 Hz), 7.36 (1H, d, J = 7.5 Hz), 7.27 (1H, t, J = 7.5 Hz), 7.11 (1H, t, J = 7.5 Hz), 6.69 (1H, d, J = 7.5 Hz), 4.50 (1H, s), 4.07 (1H, d, J = 17.0 Hz), 4.05 (1H, br s, O*H*), 3.68 (1H, d, J = 17.0 Hz), 3.41 (3H, s), 3.11 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 200.0 (C, *C*=O), 190.5 (C, *C*=O), 167.1 (C, N-*C*=O), 166.6 (C, N-*C*=O), 150.5 (C, N-*C*=O), 142.9 (C), 142.1 (C), 136.3 (C), 133.4 (CH), 130.5 (C), 130.2 (C), 129.6 (CH), 129.3 (CH), 128.8 (CH), 127.2 (CH), 125.8 (CH), 122.2 (CH), 90.8 (C, *C*-O*H*), 71.1 (C), 62.7 (C), 58.3 (CH), 29.6 (CH$_3$), 29.1 (CH$_2$), 28.5 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{17}BrN_2O_6Na$ 531.0168; Found 531.0169.



69ef

(6a'*S,12'*S**,13a'*S**)-12'-Hydroxy-1,3-dimethyl-5',13a'-dihydro-2*H*,6'*H*-spiro[pyrimidine-5,13'-[6a,12]methanobenzo[4,5]cyclohepta[1,2-a]naphthalene]-2,4,6,7', 14'(1*H*,3*H*,12'*H*)-pentaone (69ff):** The compound was prepared following procedure **3c**, purified by column chromatography using EtOAc/hexanes (2:8), and isolated as a white solid. Yield: 98% (108.9 mg). Mp: 234-238 °C. IR (Neat): $\nu_{\max}$ 3396, 1776, 1747, 1670, 1595, 1443, 1420, 1373, 1292, 1258, 1206, 1160, 1124, 1079, 1034, 987, 949, 898, 839, 800, 764, 746, 698, 663, 643, 603, and 569 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.15 (1H, dd, J = 8.0, 1.0 Hz), 7.72 (1H, dt, J = 8.0, 1.5



69ff

Hz), 7.63 (1H, br d, *J* = 7.5 Hz), 7.59 (1H, dt, *J* = 7.5, 1.0 Hz), 7.14 (1H, t, *J* = 7.0 Hz), 7.11 (1H, d, *J* = 7.0 Hz), 6.99 (1H, t, *J* = 7.5 Hz), 6.55 (1H, d, *J* = 7.5 Hz), 4.28 (1H, s), 4.19 (1H, br s, O*H*), 3.31 (3H, s), 3.12 (1H, dt, *J* = 14.0, 4.0 Hz), 2.95 (3H, s), 2.76 (1H, td, *J* = 15.5, 4.5 Hz), 2.56 (1H, td, *J* = 14.0, 4.0 Hz), 2.48 (1H, dt, *J* = 13.0, 4.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 201.8 (C, *C*=O), 193.5 (C, *C*=O), 167.6 (C, N-*C*=O), 167.3 (C, N-*C*=O), 150.4 (C, N-*C*=O), 140.4 (C), 139.6 (C), 135.2 (CH), 131.7 (C), 130.7 (C), 129.9 (CH), 129.3 (CH), 128.1 (CH), 127.4 (CH), 126.6 (CH), 125.9 (CH), 125.5 (CH), 89.0 (C, *C*-OH), 65.3 (C), 63.7 (C), 47.1 (CH), 29.5 (CH_3), 28.3 (CH_3), 25.9 (CH_2), 20.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{20}N_2O_6Na$ 467.1219; Found 467.1219.

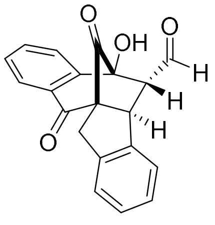
3d. General Procedures for the Synthesis of Products 67 and 70-72:

Method 1: To an ordinary glass vial equipped with a magnetic stirring bar were added 0.25 mmol of **62-64** and 2.5 mL of anhydrous DCM. Then, 0.3 mmol of **66** was added and the resulting mixture was allowed to stir at 25 ºC or higher temperatures, until complete consumption of **62-64** (monitored by TLC). Next, the crude reaction mixture was directly loaded onto a silica gel packed column without aqueous workup to give pure products **67, 70aa-eb, 71aa-ad** and **72ab-ad** after column chromatography (eluent: DCM or $CHCl_3$ or mixture of hexanes/ethyl acetate or hexanes/$CHCl_3$).

Method 2: To a 15 mL of sealed tube equipped with a magnetic stirring bar were added 0.25 mmol of **62-64** and 2.5 mL of anhydrous toluene. Then, 0.3 mmol of **66e** and 0.075 mmol of DMAP **3p** were added sequentially and the resulting mixture was allowed to stir at 80 °C or 150 °C, until complete consumption of **62-64** (monitored by TLC). Next, the crude reaction mixture was directly loaded onto a silica gel packed column without aqueous workup to give pure products **70ae** and **72ae** after column chromatography (eluent: $CHCl_3$ or mixture of ethyl acetate/$CHCl_3$).

<u>Method 3:</u> To an ordinary glass vial equipped with a magnetic stirring bar were added 0.025 mmol of quinine-thiourea **57b**, 0.3 mmol of **66d** and anhydrous DCM (0.1 M) or toluene (0.3 M). Then, 0.25 mmol of **62a** or **63a** was added and the resulting mixture was allowed to stir at RT until complete consumption of **62-63** (monitored by TLC). Next, the crude reaction mixture was directly loaded onto a silica gel packed column without aqueous workup to give pure products (+)-**70ad** and (-)-**71ad** after column chromatography (eluent: $CHCl_3$ or mixture of $CHCl_3$/hexanes or mixture of ethyl acetate/hexanes).

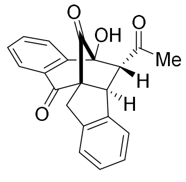
(4b*S,5*R**,6*R**,11a*R**)-6-Hydroxy-11,13-dioxo-4b,6,11,12-tetrahydro-5*H*-6,11a-methanodi benzo[*a,f*]azulene-5-carbaldehyde (70aa):** The compound was prepared



70aa

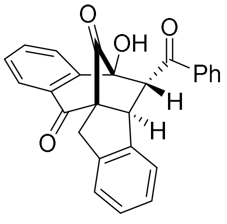
following procedure **3d**, purified by column chromatography using $CHCl_3$, and isolated as a semi-solid. Yield: 92% (73.2 mg). IR (Neat): ν_{max} 3422, 3068, 2924, 1769, 1718, 1685, 1596, 1482, 1455, 1435, 1306, 1249, 1183, 1154, 1086, 1060, 1008, 974, 907, 781, 728, and 648 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 9.90 (1H, s, C*H*O), 8.12 (1H, br d, J = 8.0 Hz), 7.91 (1H, br d, J = 8.0 Hz), 7.72 (1H, br t, J = 7.5 Hz), 7.53 (1H, br t, J = 7.5 Hz), 7.29 (1H, br d, J = 8.0 Hz), 7.25 (1H, br t, J = 7.5 Hz), 7.20 (1H, br t, J = 7.5 Hz), 7.01 (1H, br d, J = 7.5 Hz), 4.25 (1H, br s, O*H*), 4.07 (1H, d, J = 7.0 Hz), 3.92

(1H, d, J = 17.0 Hz), 3.54 (1H, d, J = 17.0 Hz), 3.23 (1H, d, J = 7.0 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 203.0 (C, *C*=O), 198.4 (CH, H-*C*=O), 191.9 (C, *C*=O), 141.0 (C), 140.9 (C), 139.7 (C), 135.5 (CH), 130.3 (C), 129.7 (CH), 128.31 (CH), 128.28 (CH), 127.8 (CH), 125.3 (CH), 125.1 (CH), 124.1 (CH), 83.7 (C, *C*-OH), 72.2 (C), 61.3 (CH), 48.1 (CH), 28.4 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{14}O_4H$ 319.0970; Found 319.0970.


70ab

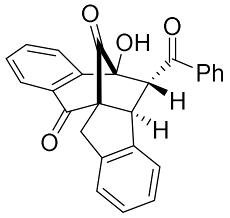
(4b*S,5*R**,6*R**,11a*R**)-5-Acetyl-6-hydroxy-4b,5,6,12-tetrahydro-11*H*-6,11a-methanodi benzo[*a,f*]azulene-11,13-dione (70ab):** The compound was prepared following procedure **3d**, purified by column chromatography using CHCl$_3$, and isolated as a semi-solid. Yield: 95% (78.9 mg). IR (Neat): ν_{max} 3483, 3307, 3070, 2921, 1764, 1693, 1676, 1596, 1480, 1455, 1431, 1358, 1296, 1249, 1226, 1209, 1177, 1087, 1054, 1009, 982, 964, 916, 797, 769, 752, 729, 710, 686, and 652 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.12 (1H, dd, J = 7.6, 0.4 Hz), 7.79 (1H, br d, J = 7.6 Hz), 7.69 (1H, br t, J = 7.6 Hz), 7.51 (1H, br t, J = 7.6 Hz), 7.29 (1H, d, J = 7.2 Hz), 7.24 (1H, t, J = 7.2 Hz), 7.18 (1H, t, J = 7.2 Hz), 6.90 (1H, d, J = 7.2 Hz), 4.25 (1H, d, J = 7.2 Hz), 4.17 (1H, br s, O*H*), 3.94 (1H, d, J = 16.8 Hz), 3.55 (1H, d, J = 16.8 Hz), 3.33 (1H, d, J = 7.2 Hz), 2.43 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 204.0 (C, *C*=O), 203.7 (C, *C*=O), 192.0 (C, *C*=O), 141.0 (C), 140.9 (C), 140.2 (C), 135.3 (CH), 130.5 (C), 129.4 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 125.3 (CH), 124.7 (CH), 123.8 (CH), 84.2 (C, *C*-OH), 71.8 (C), 62.4 (CH), 48.7 (CH), 30.7 (CH$_3$), 28.4(CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{21}H_{16}O_4Na$ 355.0946; Found 355.0946.

(4b*S,5*R**,6*R**,11a*R**)-5-Benzoyl-6-hydroxy-4b,5,6,12-tetrahydro-11*H*-6,11a-methanodi benzo[*a,f*]azulene-11,13-dione (70ad):** The compound was prepared following procedure **3d**, purified by column chromatography using $CHCl_3$/hexanes (8:2), and isolated as a white solid. Yield: 98% (96.6 mg). Mp: 218-220 °C. IR (Neat): ν_{max} 3506, 2926, 1762, 1673, 1596, 1477, 1452, 1425, 1310, 1252, 1216, 1149, 1085, 1050, 998, 977, 914, 895, 804,786, 767, 754, 716, 687, 663, 638, and 620 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.17 (1H, dd, J = 7.5, 1.0 Hz), 8.08 (2H, dd, J = 7.5, 1.0 Hz), 7.68 (1H, t, J = 7.5 Hz), 7.58-7.50 (4H, m), 7.35-7.32 (2H, m), 7.28 (1H, t, J = 7.5 Hz), 7.15 (1H, t, J = 7.5 Hz), 6.86 (1H, d, J = 7.5 Hz), 4.51 (1H, d, J = 7.0 Hz), 4.32 (1H, d, J = 7.0 Hz), 4.03 (1H, d, J = 17.0 Hz), 3.93 (1H, br s, O*H*), 3.64 (1H, d, J = 17.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.2 (C, *C*=O), 196.5 (C, *C*=O), 192.1 (C, *C*=O), 141.3 (C), 141.1 (C), 140.4 (C), 137.1 (C), 135.2 (CH), 133.9 (CH), 130.7 (C), 129.6 (2 x CH), 129.3 (CH), 128.6 (2 x CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 125.4 (CH), 125.1 (CH), 123.8 (CH), 85.2 (C, *C*-OH), 72.0 (C), 57.0 (CH), 50.5 (CH), 28.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{18}O_4H$ 395.1283; Found 395.1283.



70ad

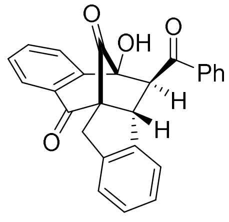
(4b*S*,5*R*,6*R*,11a*R*)-5-Benzoyl-6-hydroxy-4b,5,6,12-tetrahydro-11*H*-6,11a-methanodibenzo [*a,f*]azulene-11,13-dione [(+)-70ad major diastereomer]: The compound was prepared following procedure **3d**, purified by column chromatography using $CHCl_3$/hexanes (8:2 to 10:0), and isolated as a white solid. Yield: 49% (48.3 mg). Mp: 151-153 °C. The enantiomeric excess (*ee*) was determined by



(+)-**70ad**
major diastereomer

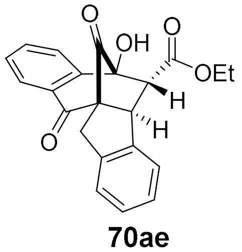
chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 28.786 min (major), t_R = 35.99 min (minor). $[\alpha]_D^{25}$ = +28.92° (*c* = 0.08, $CHCl_3$, 60% *ee*). IR (Neat): ν_{max} 3506, 2926, 1762, 1673, 1596, 1477, 1452, 1425, 1310, 1252, 1216, 1149, 1085, 1050, 998, 977, 914, 895, 804,786, 767, 754, 716, 687, 663, 638, and 620 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.15 (1H, dd, *J* = 7.5, 1.0 Hz), 8.06 (2H, dd, *J* = 8.5, 1.0 Hz), 7.66 (1H, t, *J* = 7.5 Hz), 7.57-7.48 (4H, m), 7.33-7.30 (2H, m), 7.24 (1H, t, *J* = 7.5 Hz), 7.13 (1H, t, *J* = 7.5 Hz), 6.83 (1H, d, *J* = 7.0 Hz), 4.50 (1H, d, *J* = 6.5 Hz), 4.29 (1H, d, *J* = 6.5 Hz), 4.01 (1H, d, *J* = 17.0 Hz), 3.79 (1H, br s, *OH*), 3.63 (1H, d, *J* = 17.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.1 (C, *C*=O), 196.4 (C, *C*=O), 192.1 (C, *C*=O), 141.3 (C), 141.1 (C), 140.4 (C), 137.1 (C), 135.2 (CH), 133.9 (CH), 130.7 (C), 129.5 (2 x CH), 129.3 (CH), 128.6 (2 x CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 125.4 (CH), 125.1 (CH), 123.8 (CH), 85.1 (C, *C*-OH), 72.0 (C), 57.1 (CH), 50.5 (CH), 28.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{18}O_4H$ 395.1283; Found 395.1283.

(4b*R*,5*S*,6*R*,11a*R*)-5-Benzoyl-6-hydroxy-4b,5,6,12-tetrahydro-11*H*-6,11a-methanodibenzo [*a,f*]azulene-11,13-dione [(+)-70’ad minor diastereomer]: The compound was prepared following procedure **3d**, purified by column chromatography using $CHCl_3$/hexanes (8:2 to 10:0), and isolated as a white solid. Yield: 45% (44.4 mg), Mp: 189-191 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 63.94 min (major), t_R = 78.21 min



(+)-**70'ad**
minor diastereomer

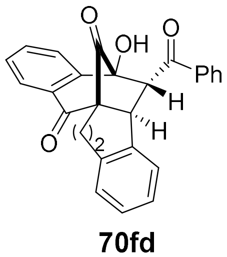
(minor). [□]$_D^{25}$ = □64.95□ (*c* = 0.097, $CHCl_3$, 61% *ee*). IR (Neat): ν_{max} 3481, 3064, 2925, 1764, 1688, 1663, 1596, 1482, 1450, 1432, 1360, 1302, 1272, 1228, 1100, 1082, 1063, 1044, 1009, 957, 894, 850, 795, 755, 727, 714, 685, 640, 627, 609, and 592 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.16 (1H, d, *J* = 7.5 Hz), 8.08 (1H, d, *J* = 8.0 Hz), 7.84 (2H, d, *J* = 7.5 Hz), 7.81 (1H, t, *J* = 7.5 Hz), 7.63 (1H, t, *J* = 7.5 Hz), 7.56 (1H, t, *J* = 7.5 Hz), 7.50 (2H, t, *J* = 8.0 Hz), 7.31 (1H, d, *J* = 7.5 Hz), 7.16 (1H, t, *J* = 7.5 Hz), 6.86 (1H, t, *J* = 7.5 Hz), 6.50 (1H, d, *J* = 8.0 Hz), 4.73 (1H, d, *J* = 9.0 Hz), 4.11 (1H, d, *J* = 9.0 Hz), 4.02 (1H, d, *J* = 17.0 Hz), 3.70 (1H, d, *J* = 17.0 Hz) 3.69 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.5 (C, *C*=O), 199.9 (C, *C*=O), 192.8 (C, *C*=O), 144.3 (C), 142.7 (C), 138.5 (C), 137.4 (C), 135.4 (CH), 133.8 (CH), 130.4 (C), 129.2 (CH), 128.9 (2 x CH), 128.4 (2 x CH), 128.1 (CH), 127.8 (CH), 126.5 (CH), 125.7 (CH), 125.4 (CH), 123.8 (CH), 86.3 (C, *C*-OH), 71.4 (C), 53.4 (CH), 51.6 (CH), 28.8 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{18}O_4H$ 395.1283; Found 395.1283.



70ae

Ethyl (4b*S,5*R**,6*R**,11a*R**)-6-hydroxy-11,13-dioxo-4b,6,11,12-tetrahydro-5*H*-6,11a-metha nodibenzo[*a,f*]azulene-5-carboxylate (70ae):** The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/$CHCl_3$ (0:10 to 0.2:9.8), and isolated as a white solid. Yield: 81% (73.4 mg). Mp: 132-134 °C. IR (Neat): ν_{max} 3472, 2925, 2850, 1761, 1722, 1693, 1598, 1485, 1454, 1429, 1372, 1355, 1303, 1252, 1192, 1089, 1066, 1054, 1003, 965, 924, 900, 852, 799, 783, 751, 728, 687, and 659 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 12:1 *dr*, major isomer): δ 8.12 (1H, d, *J* = 7.5 Hz), 7.87 (1H, d, *J* = 7.5 Hz), 7.71 (1H, dt, *J* = 7.5, 1.0

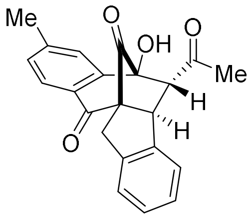
Hz), 7.53 (1H, dt, *J* = 7.5, 1.0 Hz), 7.29 (1H, d, *J* = 7.5 Hz), 7.25 (1H, t, *J* = 7.5 Hz), 7.20 (1H, t, *J* = 7.5 Hz), 7.12 (1H, d, *J* = 7.5 Hz), 4.20-4.13 (2H, m), 4.12 (1H, d, *J* = 7.5 Hz), 3.94 (1H, d, *J* = 17.0 Hz), 3.81 (1H, br s, O*H*), 3.57 (1H, d, *J* = 17.0 Hz), 3.25 (1H, d, *J* = 7.5 Hz), 1.23 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135, 12:1 *dr*, major isomer) δ 203.2 (C, *C*=O), 192.2 (C, *C*=O), 169.9 (C, O-*C*=O), 141.6 (C), 141.1 (C), 140.0 (C), 135.0 (CH), 130.4 (C), 129.4 (CH), 128.3 (CH), 127.75 (CH), 127.68 (CH), 126.0 (CH), 125.3 (CH), 124.1 (CH), 83.8 (C, *C*-OH), 72.1 (C), 61.9 (CH$_2$), 55.4 (CH), 50.8 (CH), 28.5 (CH$_2$), 14.3 (CH$_3$). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{22}H_{18}O_5NH_4$ 380.1498; Found 380.1498.



70fd

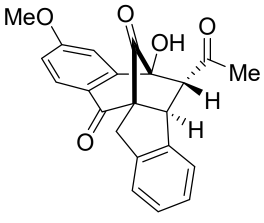
(6a*S,12*R**,13*R**,13a*S**)-13-Benzoyl-12-hydroxy-5,12,13,13a-tetrahydro-6a,12-methanobenzo[4,5]cyclohepta[1,2-a]naphthalene-7,14(6*H*)-dione (70fd):** The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (2:8 to 3:7), and isolated as a white solid. Yield: 80% (81.7 mg). Mp: 228-230 °C. IR (Neat): ν_{max} 3463, 2918, 2849, 1765, 1677, 1595, 1491, 1449, 1352, 1296, 1250, 1215, 1084, 1002, 975, 938, 909, 894, 747, 687, 659, 622, and 564 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz, 1.5:1 *dr*, major isomer): δ 8.17 (1H, dd, *J* = 7.5, 1.0 Hz), 8.01 (2H, dd, *J* = 8.5, 1.0 Hz), 7.64 (1H, tt, *J* = 7.5, 1.0 Hz), 7.59 (1H, dt, *J* = 7.5, 1.5 Hz), 7.54-7.49 (3H, m), 7.33 (1H, dd, *J* = 7.5, 1.0 Hz), 7.18 (1H, d, *J* = 7.0 Hz), 7.12 (1H, t, *J* = 7.5 Hz), 7.01 (1H, t, *J* = 7.5 Hz), 6.50 (1H, d, *J* = 7.5 Hz), 4.30 (1H, d, *J* = 8.5 Hz), 4.18 (1H, d, *J* = 8.5 Hz), 3.71 (1H, s, O*H*), 2.91-2.81 (2H, m), 2.54 (1H, td, *J* = 13.5, 4.0 Hz), 2.48-2.42 (1H, m). ^{13}C NMR (CDCl$_3$, DEPT-135, 1.5:1 *dr*, major isomer) δ 205.6 (C, *C*=O), 196.9 (C, *C*=O), 194.2 (C, *C*=O), 141.2 (C), 137.3 (C), 136.6 (C), 135.7 (C), 135.2 (CH), 133.8 (CH), 130.3 (C), 129.5 (2 x CH), 129.3 (CH), 129.0 (CH), 128.5 (2 x CH), 127.8 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 124.9 (CH), 84.0 (C, *C*-OH), 64.6 (C), 59.2 (CH), 40.0 (CH), 26.4 (CH_2), 20.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{20}O_4H$ 409.1440; Found 409.1440.

(4b*S,5*R**,6*R**,11a*R**)-5-Acetyl-6-hydroxy-8-methyl-4b,5,6,12-tetrahydro-11*H*-6,11a-methanodibenzo[*a,f*]azulene-11,13-dione (70bb):** The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (2:8), and isolated as a white solid. Yield: 96% (83.1 mg). Mp: 178-180 °C. IR (Neat): ν_{max} 3483, 2924, 1759, 1704, 1685, 1601, 1482, 1458, 1433, 1357, 1311, 1252, 1212, 1181, 1165, 1140, 1103, 1052, 994, 918, 892, 838, 785, 762, 750, 727, 711, 666, and 576 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, d, J = 8.0 Hz), 7.58 (1H, s), 7.32 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 9.2 Hz), 7.24 (1H, t, J = 7.6 Hz), 7.18 (1H, t, J = 7.6 Hz), 6.91 (1H, d, J = 7.6 Hz), 4.26 (1H, d, J = 7.2 Hz), 3.95 (1H, d, J = 17.2 Hz), 3.90 (1H, br s, O*H*), 3.55 (1H, d, J = 17.2 Hz), 3.32 (1H, d, J = 7.2 Hz), 2.48 (3H, s), 2.45 (3H, s). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.9 (C, *C*=O), 203.8 (C, *C*=O), 191.5 (C, *C*=O), 146.7 (C), 141.1 (C), 140.8 (C), 140.3 (C), 130.4 (CH), 128.2 (C), 128.1 (CH), 128.0 (CH), 127.5 (CH), 125.3 (CH), 124.9 (CH), 123.7 (CH), 84.0 (C, *C*-OH), 71.4 (C), 62.4 (CH), 48.7 (CH), 30.7 (CH_3), 28.4 (CH_2), 22.2 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{18}O_4H$ 347.1283; Found 347.1286.



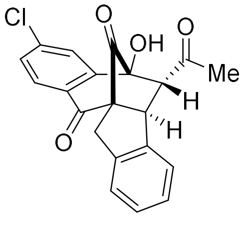
70bb

(4b*S,5*R**,6*R**,11a*R**)-5-Acetyl-6-hydroxy-8-methoxy-4b,5,6,12-tetrahydro-11*H*-6,11a-methanodibenzo[*a,f*]azulene-11,13-dione (70cb):** The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (2:8), and isolated as a white solid. Yield: 95% (86 mg). Mp: 184-186 °C. IR (Neat): ν_{max} 3487, 2922, 2850, 1762, 1684, 1598, 1570, 1483, 1458, 1430, 1360, 1323, 1276, 1252, 1165, 1100, 1052, 1002, 892, 864, 832, 813, 790, 751, 729, and 662 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.69 (1H, d, *J* = 8.8 Hz), 7.58 (1H, d, *J* = 2.8 Hz), 7.30 (1H, d, *J* = 7.6 Hz), 7.27-7.23 (2H, m), 7.19 (1H, t, *J* = 7.2 Hz), 6.91 (1H, d, *J* = 7.2 Hz), 4.26 (1H, d, *J* = 7.2 Hz), 3.96 (1H, d, *J* = 17.2 Hz), 3.89 (3H, s), 3.84 (1H, br s, O*H*), 3.57 (1H, d, *J* = 17.2 Hz), 3.30 (1H, d, *J* = 6.8 Hz), 2.44 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 204.1 (C, *C*=O), 203.5 (C, *C*=O), 191.8 (C, *C*=O), 160.4 (C), 141.1 (C), 140.3 (C), 133.1 (C), 131.9 (C), 128.1 (CH), 127.6 (CH), 126.0 (CH), 125.3 (CH), 123.8 (CH), 123.3 (CH), 110.3 (CH), 83.9 (C, *C*-OH), 71.6 (C), 62.3 (CH), 55.7 (CH$_3$), 48.9 (CH), 30.7 (CH$_3$), 28.5 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{22}H_{18}O_5H$ 363.1232; Found 363.1233.



70cb

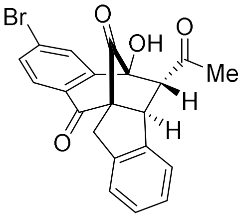
(4b*S,5*R**,6*R**,11a*R**)-5-Acetyl-8-chloro-6-hydroxy-4b,5,6,12-tetrahydro-11*H*-6,11a-methanodibenzo[*a,f*]azulene-11,13-dione (70db):** The compound was prepared following procedure **3d**, purified by column chromatography using CHCl$_3$, and isolated as a white solid. Yield: 95% (87 mg). Mp: 154-158 °C. IR (Neat): ν_{max} 3446, 3015, 2922, 2852, 1767, 1690, 1587, 1481, 1458, 1435, 1402, 1361, 1308, 1290,



70db

1252, 1155, 1100, 1048, 994, 974, 909, 890, 851, 809, 789, 752, 712, and 661 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.05 (1H, d, J = 8.5 Hz), 7.75 (1H, d, J = 2.0 Hz), 7.48 (1H, dd, J = 8.5, 2.0 Hz), 7.28 (1H, d, J = 7.5 Hz), 7.23 (1H, t, J = 7.5 Hz), 7.17 (1H, t, J = 7.5 Hz), 6.89 (1H, d, J = 7.5 Hz), 4.25 (1H, d, J = 7.5 Hz), 3.92 (1H, d, J = 17.0 Hz), 3.90 (1H, br s, O*H*), 3.55 (1H, d, J = 17.0 Hz), 3.32 (1H, d, J = 7.5 Hz), 2.44 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 203.7 (C, *C*=O), 202.9 (C, *C*=O), 190.6 (C, *C*=O), 142.5 (C), 142.1 (C), 140.9 (C), 139.9 (C), 130.0 (CH), 129.5 (CH), 128.9 (C), 128.2 (CH), 127.7 (CH), 125.4 (CH), 125.0 (CH), 123.7 (CH), 83.9 (C, *C*-OH), 71.7 (C), 62.4 (CH), 48.7 (CH), 30.9 (CH$_3$), 28.4 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + NH$_4$]$^+$ Calcd for $C_{21}H_{15}ClO_4NH_4$ 384.1003; Found 384.1001.

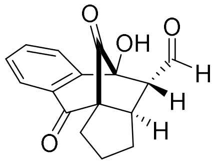
(4b*S,5*R**,6*R**,11a*R**)-5-Acetyl-8-bromo-6-hydroxy-4b,5,6,12-tetrahydro-11*H*-6,11a-methanodibenzo[*a,f*]azulene-11,13-dione (70eb):** The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (2:8), and isolated as a white solid. Yield: 97% (99.7 mg). Mp: 160-162 °C. IR (Neat): ν_{max} 3431, 2918, 2849, 1756, 1713, 1693, 1581, 1485, 1459, 1437, 1359, 1300, 1277, 1246, 1212, 1197, 1155, 1097, 1072, 1047, 1004, 979, 919, 887, 864, 842, 802, 788, 751, 711, 680, 657, and 635 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.98 (1H, d, J = 8.5 Hz), 7.93 (1H, d, J = 1.5 Hz), 7.66 (1H, dd, J = 8.0, 2.0 Hz), 7.29 (1H, d, J = 7.5 Hz), 7.24 (1H, t, J = 7.5 Hz), 7.18 (1H, t, J = 7.5 Hz), 6.89 (1H, d, J = 7.5 Hz), 4.27 (1H, d, J = 7.0 Hz), 3.93 (1H, d, J = 17.0 Hz), 3.81 (1H, s, O*H*), 3.56 (1H, d, J = 17.0 Hz), 3.32 (1H, d, J = 7.0 Hz), 2.45 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 203.6 (C,



70eb

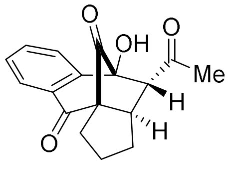
C=O), 202.9 (C, *C*=O), 190.8 (C, *C*=O), 142.4 (C), 140.9 (C), 139.9 (C), 133.0 (CH), 130.9 (C), 129.4 (CH), 129.3 (C), 128.2 (CH), 128.0 (CH), 127.7 (CH), 125.4 (CH), 123.8 (CH), 83.8 (C, *C*-OH), 71.7 (C), 62.4 (CH), 48.7 (CH), 30.8 (CH_3), 28.4 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{15}BrO_4H$ 411.0232; Found 411.0233.

(3a*R,9*R**,10*R**,10a*R**)-9-Hydroxy-4,11-dioxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,9-methanobenzo[*f*]azulene-10-carbaldehyde (71aa):** The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 70% (47.3 mg). IR (Neat): ν_{max} 3433, 2957, 2868, 1769, 1722, 1688, 1598, 1453, 1384, 1299, 1259, 1184,1047, 1016, 961, 909, 773, 731, and 681 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.70 (1H, d, *J* = 0.8 Hz, C*H*O), 8.10 (1H, dd, *J* = 8.0, 0.8 Hz), 7.84 (1H, dd, *J* = 8.0, 0.8 Hz), 7.70 (1H, dt, *J* = 7.6, 1.2 Hz), 7.52 (1H, dt, *J* = 7.6, 1.2 Hz), 3.74 (1H, br s, O*H*), 2.95 (1H, dd, *J* = 7.6, 0.8 Hz), 2.74 (1H, q, *J* = 7.6 Hz), 2.50 (1H, td, *J* = 13.6, 6.8 Hz), 2.20 (1H, td, *J* = 13.6, 7.2 Hz), 2.11-2.02 (1H, m), 1.89-1.81 (2H, m), 1.50-1.40 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.6 (C, *C*=O), 198.4 (CH, *C*HO), 192.7 (C, *C*=O), 140.7 (C), 135.2 (CH), 130.3 (C), 129.5 (CH), 128.0 (CH), 125.2 (CH), 84.7 (C, *C*-OH), 73.5 (C), 60.6 (CH), 43.5 (CH), 33.4 (CH_2), 27.6 (CH_2), 22.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}O_4H$ 271.0970; Found 271.0970.



71aa

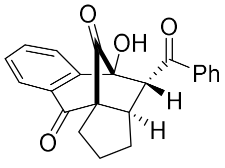
(3a*R,9*R**,10*R**,10a*R**)-10-Acetyl-9-hydroxy-1,2,3,9,10,10a-hexahydro-4*H*-3a,9-methano benzo[*f*]azulene-4,11-dione (71ab):** The compound was prepared following



71ab

procedure **3d**, purified by column chromatography using EtOAc/hexanes (1:9 to 1.5:8.5), and isolated as a semi-solid. Yield: 85% (60.4 mg). IR (Neat): ν_{max} 3428, 2968, 2921, 2851, 1762, 1692, 1619, 1595, 1450, 1363, 1336, 1299, 1269, 1188, 1161, 1117, 1075, 1042, 1019, 1001, 974, 953, 901, 885, 850, 798,776, 724, 680, 648, 631, 604, 580, and 560 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.08 (1H, dd, J = 10.0, 1.0 Hz), 7.72 (1H, dd, J = 9.5, 1.0 Hz), 7.66 (1H, dt, J = 9.0, 2.0 Hz), 7.49 (1H, dt, J = 9.5, 1.5 Hz), 3.73 (1H, s, O*H*), 3.03 (1H, d, J = 9.5 Hz), 2.89 (1H, q, J = 9.5 Hz), 2.49 (1H, td, J = 16.5, 8.5 Hz), 2.33 (3H, s), 2.18 (1H, td, J = 17.0, 9.0 Hz), 2.04-1.96 (1H, m), 1.86-1.79 (2H, m), 1.40-1.32 (1H, m). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 204.4 (C, *C*=O), 204.0 (C, *C*=O), 192.9 (C, *C*=O), 140.8 (C), 134.9 (CH), 130.4 (C), 129.2 (CH), 127.7 (CH), 124.6 (CH), 85.1 (C, *C*-OH), 73.0 (C), 61.5 (CH), 44.1 (CH), 33.3 (CH$_2$), 30.8 (CH$_3$), 27.6 (CH$_2$), 22.9 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M - H]$^-$ Calcd for $C_{17}H_{15}O_4$ 283.0970; Found 283.0973.

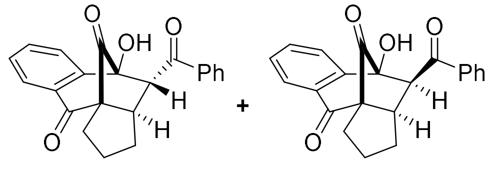
(3a*R,9*R**,10*R**,10a*R**)-10-Benzoyl-9-hydroxy-2,3,10,10a-tetrahydro-1*H*-3a,9-methanobenzo[*f*]azulene-4,11(9*H*)-dione (71ad):** The compound was prepared



71ad

following procedure **3d**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 80% (69.3 mg). IR (Neat): ν_{max} 3413, 3067, 2959, 2871, 2846, 1762, 1687, 1666, 1595, 1445, 1367, 1301, 1270, 1218, 1182, 1151, 1085, 1042, 1017, 989, 962, 910, 887, 845, 796, 765, 732, 684, and 620 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz):

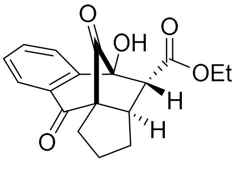
δ 8.10 (1H, dd, J = 7.5, 1.0 Hz), 8.02 (2H, d, J = 7.5 Hz), 7.62 (1H, t, J = 7.5 Hz), 7.53-7.45 (4H, m), 7.28 (1H, dd, J = 8.0, 1.0 Hz), 3.97 (1H, d, J = 7.5 Hz), 3.83 (1H, s, O*H*), 3.12 (1H, q, J = 7.5 Hz), 2.54 (1H, td, J = 13.5, 7.0 Hz), 2.23 (1H, td, J = 14.0, 7.0 Hz), 2.03-1.96 (1H, m), 1.85 (2H, quint, J = 6.5 Hz), 1.47-1.41 (1H, m). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 204.9 (C, *C*=O), 196.5 (C, *C*=O), 193.0 (C, *C*=O), 141.2 (C), 137.3 (C), 134.8 (CH), 133.6 (CH), 130.7 (C), 129.3 (2 x CH), 129.1 (CH), 128.5 (2 x CH), 127.3 (CH), 125.1 (CH), 86.0 (C, *C*-OH), 73.2 (C), 56.1 (CH), 45.8 (CH), 33.3 (CH$_2$), 27.5 (CH$_2$), 23.0 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{22}H_{18}O_4Na$ 369.1103; Found 369.1103.



(–)-**71ad**
(Minor)

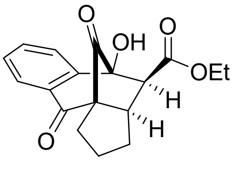
(–)-**71'ad**
(Major)

(3a*R*,9*R*,10*R*,10a*R*)-10-Benzoyl-9-hydroxy-2,3,10,10a-tetrahydro-1*H*-3a,9-methanobenzo[*f*]azulene-4,11(9*H*)-dione [(-)-71ad] and (3a*R*,9*R*,10*S*,10a*S*)-10-Benzoyl-9-hydroxy-2,3,10,10a-tetrahydro-1*H*-3a,9-methanobenzo[*f*]azulene-4,11(9*H*)-dione [(-)-71'ad]: The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 80% (69.3 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.887 min (major), t_R = 19.916 min (minor) [For minor isomer (-)-**71ad**], t_R = 30.917 min (minor), t_R = 61.24 min (major) [For major isomer (-)-**71'ad**]. $[\alpha]_D^{25}$ = –39.02° (c = 0.264, CHCl$_3$, 87% *ee*; 52% *ee* and 1:1.5 *dr*). IR (Neat): ν_{max} 3413, 3067, 2959, 2871, 2846, 1762, 1687, 1666, 1595, 1445, 1367, 1301, 1270, 1218, 1182, 1151, 1085, 1042, 1017, 989, 962, 910, 887, 845, 796, 765, 732, 684, and 620 cm^{-1}. For major isomer (**71'ad**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.14 (1H, dd, *J* = 8.0, 1.5 Hz), 7.97 (1H, dd, *J* = 7.5, 0.5 Hz), 7.91 (2H, dd, *J* = 8.0, 1.0 Hz), 7.76 (1H, dt, *J* = 7.5, 1.5 Hz), 7.63 (1H, tt, *J* = 7.5, 1.5 Hz), 7.56 (1H, dt, *J* = 7.5, 1.0 Hz), 7.51-7.45 (2H, m), 4.37 (1H, s), 4.23 (1H, d, *J* = 10.5 Hz), 2.79 (1H, br q, *J* = 8.5 Hz), 2.60-2.53 (1H, m), 2.16-2.01 (1H, m), 1.90-1.83 (1H, m), 1.71-1.60 (2H, m), 1.34-1.27 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 204.0 (C, *C*=O), 200.6 (C, *C*=O), 193.9 (C, *C*=O), 144.5 (C), 136.7 (C), 135.3 (CH), 134.2 (CH), 129.6 (C), 128.9 (2 x CH), 128.8 (CH), 128.4 (2 x CH), 127.6 (CH), 124.8 (CH), 85.0 (C, *C*-OH), 72.8 (C), 51.0 (CH), 46.1 (CH), 30.2 (CH_2), 27.6 (CH_2), 22.9 (CH_2). For minor isomer (**71ad**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12 (1H, dd, *J* = 8.0, 1.5 Hz), 8.04 (2H, dd, *J* = 8.0, 1.0 Hz), 7.63 (1H, tt, *J* = 7.5, 1.5 Hz), 7.53-7.46 (4H, m), 7.31 (1H, dd, *J* = 7.5, 1.0 Hz), 4.00 (1H, d, *J* = 7.0 Hz), 3.91 (1H, s), 3.14 (1H, q, *J* = 7.5 Hz), 2.60-2.53 (1H, m), 2.26 (1H, td, *J* = 13.5, 7.0 Hz), 2.03-1.98 (1H, m), 1.90-1.80 (2H, m), 1.50-1.43 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 204.8 (C, *C*=O), 196.5 (C, *C*=O), 193.1 (C, *C*=O), 141.2 (C), 137.2 (C), 134.8 (CH), 133.6 (CH), 130.7 (C), 129.3 (2 x CH), 129.0 (CH), 128.4 (2 x CH), 127.3 (CH), 125.1 (CH), 86.0 (C, *C*-OH), 73.2 (C), 56.1 (CH), 45.8 (CH), 33.2 (CH_2), 27.5 (CH_2), 22.9 (CH_2). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{22}H_{18}O_4Na$ 369.1103; Found 369.1103.



71ae
major diastereomer

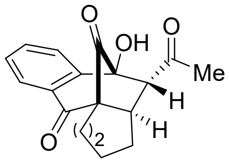
Ethyl (3a*R,9*R**,10*R**,10a*R**)-9-hydroxy-4,11-dioxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,9-methanobenzo[*f*]azulene-10-carboxylate (71ae major diastereomer):** The compound was prepared following procedure **3d,** purified by column chromatography using EtOAc/hexanes (1:9 to 1.5:8.5), and isolated as a semi-solid. Yield: 62.2% (49 mg). IR (Neat): ν_{max} 3447, 2958, 2869, 1975, 1769, 1730, 1688, 1598, 1453, 1374, 1259, 1206, 1090, 1045, 1022, 992, 942, 889, 794, and 728 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.09 (1H, dd, J = 8.0, 1.0 Hz), 7.80 (1H, d, J = 8.0 Hz), 7.67 (1H, dt, J = 7.5, 1.0 Hz), 7.51 (1H, dt, J = 7.5, 1.0 Hz), 4.08-4.02 (2H, m), 3.70 (1H, s, O*H*), 2.93 (1H, d, J = 7.5 Hz), 2.76 (1H, q, J = 7.5 Hz), 2.50 (1H, td, J = 13.5, 7.0 Hz), 2.19 (1H, td, J = 13.5, 7.0 Hz), 2.12-2.04 (1H, m), 1.86-1.80 (2H, m), 1.52-1.45 (1H, m), 1.17 (3H, t, J = 7.0 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 203.9 (C, *C*=O), 193.1 (C, *C*=O), 169.8 (C, *C*=O), 141.4 (C), 134.7 (CH), 130.5 (C), 129.1 (CH), 127.4 (CH), 125.7 (CH), 84.8 (C, *C*-OH), 73.3 (C), 61.5 (CH$_2$), 54.8 (CH), 46.4 (CH), 33.5 (CH$_2$), 27.4 (CH$_2$), 23.0 (CH$_2$), 14.2 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{18}O_5H$ 315.1232; Found 315.1232.



71'ae
minor diastereomer

Ethyl (3a*R,9*R**,10*S**,10a*S**)-9-hydroxy-4,11-dioxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,9-methanobenzo[*f*]azulene-10-carboxylate (71'ae minor diastereomer):** The compound was prepared following procedure **3d,** purified by column chromatography using EtOAc/hexanes (1:9 to 1.5:8.5), and isolated as a semi-solid. Yield: 4.8% (3.8 mg). IR (Neat): ν_{max} 3447, 2958, 2869, 1975, 1769, 1730, 1688, 1598, 1453, 1374, 1259, 1206, 1090, 1045, 1022, 992, 942, 889, 794, and 728 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.07 (1H, dd, J = 8.0, 1.2 Hz), 7.93 (1H, dd, J = 8.0, 0.4 Hz), 7.72 (1H, dt, J = 7.6, 1.6 Hz), 7.51 (1H, dt, J = 8.0, 1.2 Hz), 4.29-4.16 (2H, m), 3.98 (1H, s, O*H*), 3.21 (1H, d, J = 10.4 Hz), 2.65-2.50 (2H, m), 2.17-2.09 (1H, m), 1.92-1.85 (2H, m), 1.80-1.71 (1H, m), 1.49-1.39 (1H, m), 1.30 (3H, t, J = 7.2 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 204.0 (C, *C*=O), 193.8 (C, *C*=O), 171.2 (C, O-*C*=O), 144.0 (C), 135.3 (CH), 129.8 (C), 129.0 (CH), 127.5 (CH), 124.9 (CH), 84.6 (C, *C*-OH), 72.4 (C), 61.4 (CH$_2$), 51.2 (CH), 45.5 (CH), 29.8 (CH$_2$), 27.6 (CH$_2$), 23.4 (CH$_2$), 14.2 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{18}O_5H$ 315.1232; Found 315.1233.

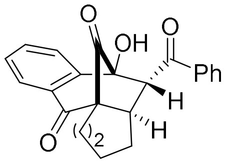
(4aS*,10R*,11R*,11aR*)-11-Acetyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methano dibenzo[*a,d*][7]annulene-5,12(2*H*)-dione (72ab): The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 65% (48.48 mg). IR (Neat): ν_{max} 3451, 2931, 2858, 1765, 1713, 1680, 1597, 1454, 1357, 1329, 1301, 1277, 1231, 1172, 1085, 1038, 971, 915, 781, and 735 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.07 (1H, d, J = 7.5 Hz), 7.83 (1H, d, J = 8.0 Hz), 7.70 (1H, dt, J = 8.0, 1.0 Hz), 7.49 (1H, dt, J = 8.0, 0.5 Hz), 3.56 (1H, s, O*H*), 2.99 (1H, d, J = 11.0 Hz), 2.58 (1H, dt, J = 12.0, 2.5 Hz), 2.48-2.35 (2H, m), 2.27 (3H, s), 1.88-1.78 (2H, m), 1.69 (1H, dt, J = 13.5, 5.5 Hz), 1.57 (1H, dd, J = 12.5, 3.0 Hz), 1.48-1.38 (1H, m), 1.26 (1H, dq, J = 12.5, 3.5 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 204.6 (C, *C*=O), 204.4 (C, *C*=O), 196.3 (C, *C*=O), 147.4 (C), 135.2 (CH), 130.8 (C), 128.5 (CH), 127.9 (CH), 121.3 (CH), 79.2 (C, *C*-OH), 65.4 (C), 63.4 (CH),



72ab

42.9 (CH), 32.9 (CH_3), 27.2 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 21.4 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{18}O_4Na$ 321.1103; Found 321.1103.

(4a*S,10*R**,11*R**,11a*R**)-11-Benzoyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione**

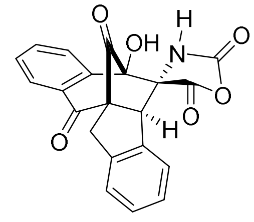


72ad

(72ad): The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 67% (60.4 mg). IR (Neat): ν_{max} 3443, 3067, 2925, 2855, 1763, 1683, 1597, 1449, 1379, 1283, 1235, 1203, 1002, 767, 732, 690, 636, and 580 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.99 (1H, dd, *J* = 8.0, 2.0 Hz), 7.89 (2H, dd, *J* = 8.0, 1.0 Hz), 7.56 (1H, tt, *J* = 7.5, 1.0 Hz), 7.42 (2H, t, *J* = 7.5 Hz), 7.33 (1H, dd, *J* = 8.0, 1.5 Hz), 7.29 (1H, dd, *J* = 8.0, 1.0 Hz), 7.09 (1H, dd, *J* = 7.0, 1.5 Hz), 3.86 (1H, s), 3.85 (1H, s), 2.92-2.88 (1H, m), 2.52-2.45 (1H, m), 2.13 (1H, td, *J* = 14.5, 3.5 Hz), 2.02-1.98 (1H, m), 1.84 (1H, td, *J* = 13.5, 4.0 Hz), 1.71 (1H, td, *J* = 13.0, 4.0 Hz), 1.51-1.41(1H, m), 1.40-1.31 (1H, m), 1.27-1.20 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.1 (C, *C*=O), 196.8 (C, *C*=O), 195.3 (C, *C*=O), 141.2 (C), 136.9 (C), 134.2 (CH), 133.4 (CH), 130.7 (C), 129.0 (2 x CH), 128.7 (CH), 128.3 (2 x CH), 127.4 (CH), 123.5 (CH), 81.8 (C, *C*-OH), 64.9 (C), 60.3 (CH), 36.6 (CH), 31.9 (CH_2), 22.9 (CH_2), 20.8 (CH_2), 20.6 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{20}O_4H$ 361.1440; Found 361.1440.

3e. General Procedures for Synthetic Transformation of Products 69aa: To an ordinary glass vial equipped with a magnetic stirring bar were added 0.2 mmol of 6**9aa**

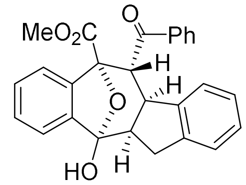
and 2 mL of toluene. Then, 0.6 mmol of trimethylsilyl azide ($TMSN_3$) and 0.04 mmol of silver trifluoromethanesulfonate (AgOTf) were added and the resulting mixture was allowed to stir at 80 °C. After complete consumption of **69aa**, as monitored by TLC, the reaction was quenched with water, extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and dried. The resulting solid components were dissolved in $CHCl_3$ and filtered through a filter paper to get pure **73aa** as a white solid.



73aa

(4b'*S,6'*S**,11a'*R**)-6'-Hydroxy-4b',12'-dihydrospiro[oxazolidine-4,5'-[6,11a]methanodi benzo[*a,f*]azulene]-2,5,11',13'(6'*H*)-tetraone (73aa):** The compound was prepared following procedure **3e** and obtained as a white solid. Yield: 70% (52.5 mg). Mp: 250-252 °C. IR (Neat): ν_{max} 3326, 2924, 2851, 2360, 2340, 1849, 1774, 1697, 1594, 1482, 1455, 1441, 1339, 1286, 1240, 1222, 1201, 1160, 1087, 1046, 997, 933, 814, 770, 750, 728, 698, 650, and 560 cm^{-1}. ^1H NMR (DMSO-D_6, 500 MHz): δ 9.65 (1H, s, N*H*), 8.16 (1H, s, O*H*), 8.10 (1H, dd, *J* = 8.0, 1.0 Hz), 7.99 (1H, dt, *J* = 8.0, 1.5 Hz), 7.91 (1H, dd, *J* = 7.5, 0.5 Hz), 7.76 (1H, dt, *J* = 8.0, 1.5 Hz), 7.40 (1H, d, *J* = 8.0 Hz), 7.31 (1H, t, *J* = 7.5 Hz), 7.23 (1H, t, *J* = 7.5 Hz), 6.99 (1H, d, *J* = 7.5 Hz), 4.01 (1H, s), 3.80 (1H, d, *J* = 17.5 Hz), 3.49 (1H, d, *J* = 17.5 Hz). ^{13}C NMR (DMSO-D_6, DEPT-135) δ 201.3 (C, *C*=O), 192.6 (C, *C*=O), 168.2 (C, O-*C*=O), 151.2 (C, HN-*C*=O), 142.0 (C), 140.9 (C), 136.5 (C), 136.3 (CH), 130.81 (C), 130.76 (CH), 129.3 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 126.0 (CH), 123.1 (CH), 87.5 (C, *C*-OH), 73.1 (C), 72.8 (C), 57.1 (CH), 28.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{17}NO_5H$ 364.1185; Found 364.1185.; and $[M + Na]^+$ Calcd for $C_{21}H_{17}NO_5Na$ 386.1004; Found 386.1002. [M = M-CO_2 + MeOH].

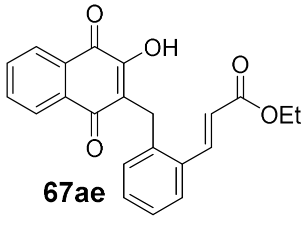
3f. General Procedures for Synthetic Transformation of Products 70ad: To a 25 mL of round bottom flask equipped with a magnetic stirring bar were added 0.2 mmol of **70ad** and 2 mL of methanol. Then, 0.4 mmol of K_2CO_3 was added in two portions with 0.5 h time intervals and the resulting mixture was allowed to stir at RT. After complete consumption of **70ad**, as monitored by TLC, methanol was removed by rotary evaporation. To this crude reaction mixture was added acetone (0.1 M), dimethyl sulfate (5 equiv.) and K_2CO_3 (5 equiv.) and the resulting mixture was allowed to stir at 60 ºC for 24 h. Next, the reaction mixture was allowed to cool to RT and then the solvent was removed by rotary evaporation. The resulting product mixture was partitioned between aqueous and ethyl acetate layers and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product **74ad** was obtained after column chromatography purification using ethyl acetate/hexanes as an eluent system.



74ad

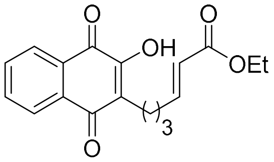
Methyl (4b*S,5*R**,6*R**,11*S**,11a*S**)-5-benzoyl-11-hydroxy-4b,11,11a,12-tetrahydro-6,11-epoxydibenzo[a,f]azulene-6(5*H*)-carboxylate (74ad):** The compound was prepared following procedure **3f**, purified by column chromatography using EtOAc/hexanes (3:7 to 4:6), and isolated as a white solid. Yield: 65% (55.4 mg). Mp: 174-176 °C. IR (Neat): ν_{max} 3451, 2927, 2843, 2360, 1731, 1687, 1596, 1438, 1361, 1311, 1274, 1219, 1201, 1172, 1153, 1122, 1079, 1033, 964, 931, 905, 879, 852, 832, 809, 791, 753, 723, 687, 645, 617, and 572 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.01 (2H, dd, *J* = 8.5, 1.5 Hz), 7.57 (1H, tt, *J* = 7.5, 1.0 Hz), 7.48 (2H, t, *J* = 7.5 Hz), 7.13 (1H, d, *J* = 7.5 Hz), 7.02 (1H, d, *J* = 7.5 Hz), 6.98 (2H, dt, *J* = 7.5, 1.0 Hz), 6.94-6.89 (3H, m), 6.86 (1H, dt, *J* = 7.5, 0.5 Hz), 4.51 (1H, s), 3.92 (1H, m), 3.84 (3H, s), 3.54 (1H, s, O*H*), 3.14 (1H, br d, *J* = 15.5 Hz), 3.07-3.01 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 199.4 (C, *C*=O), 170.6 (C, O-*C*=O), 142.8 (C), 141.1 (C), 140.7 (C), 140.4 (C), 135.5 (C), 133.2 (CH), 129.0 (CH), 128.8 (2 x CH), 128.54 (CH), 128.51 (2 x CH), 126.4 (CH), 125.9 (CH), 124.3 (CH), 122.3 (CH), 121.5 (CH), 120.3 (CH), 106.9 (C, O-*C*-OH), 84.3 (C, *C*-O), 52.8 (CH$_3$), 48.9 (CH), 45.8 (CH), 44.7 (CH), 32.4 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{27}H_{22}O_5Na$ 449.1365; Found 449.1368.

Ethyl (*E*)-3-(2-((3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)phenyl)acrylate (67ae): The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (1:9 to 2:8), and isolated as a yellow solid. Yield: 95% (86 mg). Mp: 120-123 °C. IR (Neat): ν_{max} 3341, 3067, 2917, 2849, 1772, 1708, 1638, 1588, 1482, 1459, 1427, 1355, 1309, 1276, 1262, 1235, 1155, 1090, 1048, 1029, 977, 957, 856, 838, 798, 760, 727, 669, and 605 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.39 (1H, d, *J* = 16.0 Hz), 8.08 (2H, dt, *J* = 9.0, 1.0 Hz), 7.83 (1H, br s, O*H*), 7.73 (1H, dt, *J* = 7.5, 1.0 Hz), 7.66 (1H, dt, *J* = 7.5, 1.5 Hz), 7.54 (1H, d, *J* = 7.0 Hz), 7.37 (1H, d, *J* = 7.0 Hz), 7.27 (1H, dt, *J* = 7.5, 1.0 Hz), 7.21 (1H, t, *J* = 7.0 Hz), 6.35 (1H, d, *J* = 16.0 Hz), 4.28 (2H, q, *J* = 7.0 Hz), 4.09 (2H, s), 1.36 (3H,


67ae

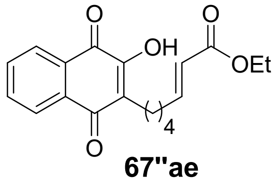
t, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.2 (C, *C*=O), 181.3 (C, *C*=O), 167.0 (C, O-*C*=O), 153.5 (C, *C*-OH), 142.9 (CH), 138.1 (C), 135.0 (CH), 133.7 (C), 133.0 (CH), 132.8 (C), 130.3 (CH), 129.9 (CH), 129.4 (C), 126.9 (CH), 126.8 (CH), 126.7 (CH), 126.2 (CH), 122.1 (C), 119.9 (CH), 60.5 (CH_2), 26.5 (CH_2), 14.3 (CH_3). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{22}H_{18}O_5Na$ 385.1052; Found 385.1057.

Ethyl (*E*)-6-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)hex-2-enoate (67'ae): The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 2:8), and isolated as a yellow solid. Yield: 70% (67 mg). Mp: 73-75 °C. IR (Neat): ν_{max} 3267, 2933, 1713, 1650, 1591, 1525, 1474, 1369, 1275, 1216, 1177, 1135, 1037 and 726 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (1H, d, *J* = 7.6 Hz), 8.06 (1H, d, *J* = 7.6 Hz), 7.74 (1H, tt, *J* = 7.6, 1.2 Hz), 7.66 (1H, tt, *J* = 7.6 Hz), 7.43 (1H, br s, O*H*), 6.97 (1H, td, *J* = 13.6, 6.8 Hz), 5.83 (1H, td, *J* = 13.6, 0.8 Hz), 4.15 (2H, q, *J* = 6.8 Hz), 2.63 (2H, t, *J* = 7.6 Hz), 2.27 (2H, q, *J* = 8.0 Hz), 1.72 (2H, quint, *J* = 7.6 Hz), 1.26 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.5 (C, *C*=O), 181.3 (C, *C*=O), 166.6 (C, O-*C*=O), 153.2 (C, *C*-OH), 148.5 (CH), 134.9 (CH), 132.91 (CH), 132.8 (C), 129.4 (C), 126.8 (CH), 126.1 (CH), 123.7 (C), 121.6 (CH), 60.1 (CH_2), 32.1 (CH_2), 26.4 (CH_2), 22.8 (CH_2), 14.2 (CH_3). HRMS (ESI-TOF) *m/z*: [M - H]$^-$ Calcd for $C_{18}H_{17}O_5$ 313.1076; Found 313.1074.



67'ae

Ethyl (E)-7-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)hept-2-enoate



67"ae

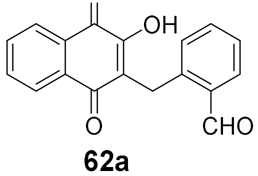
(67''ae): The compound was prepared following procedure **3d**, purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 2:8), and isolated as a yellow solid. Yield: 82% (67 mg). Mp: 78-80 °C. IR (Neat): ν_{max} 3336, 2927, 2855, 1701, 1642, 1589, 1460, 1369, 1347, 1323, 1265, 1208, 1185, 1132, 1099, 1074, 1036, 976, 943, 841, 796, 728, 689, and 574 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.12 (1H, d, J = 7.6 Hz), 8.09 (1H, d, J = 7.6 Hz), 7.76 (1H, t, J = 7.6 Hz), 7.69 (1H, t, J = 7.6 Hz), 7.45 (1H, br s, O*H*), 6.96 (1H, td, J = 15.6, 7.2 Hz), 5.82 (1H, d, J = 15.6 Hz), 4.18 (2H, q, J = 7.2 Hz), 2.62 (2H, t, J = 6.4 Hz), 2.25 (2H, q, J = 6.4 Hz), 1.63-1.55 (4H, m), 1.28 (3H, t, J = 7.2 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 184.7 (C, *C*=O), 181.4 (C, *C*=O), 166.7 (C, O-*C*=O), 153.2 (C, *C*-OH), 149.0 (CH), 134.9 (CH), 132.91 (CH), 132.88 (C), 129.4 (C), 126.8 (CH), 126.1 (CH), 124.1 (C), 121.4 (CH), 60.1 (CH$_2$), 32.0 (CH$_2$), 28.0 (CH$_2$), 27.7 (CH$_2$), 23.0 (CH$_2$), 14.3 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for C$_{19}$H$_{20}$O$_5$Na 351.1208; Found 351.1203.

3g. Organocatalytic Reductive Coupling of Dialdehydes 59-61 with 2-Hydroxy-1,4-naphthoquinone Derivatives 1:

Method 1: To a 10 mL of round bottom flask equipped with a magnetic stirring bar were added 0.06 mmol of catalyst **3n**, 0.33 mmol of dialdehydes **59-61** and 1.0 mL of anhydrous DCM. Then, 0.33 mmol of Hantzsch ester **34** and 0.3 mmol of 2-hydroxy-1,4-naphthoquinone derivatives **1** were added sequentially to a well stirred solution and the resulting mixture was allowed to stir for few hours. The solvent was removed under reduced pressure, the solid reaction mixture was dissolved in hexanes and the solvent was decanted and dried. Then, the solid product mixture was redissolved in 5-10% $CHCl_3$/hexanes mixtures and the solvent was decanted and dried. This process was repeated for 3-4 times to give the products **62-64** with >80% purity. Further purification was carried out by passing the compound through short silica gel column using $CHCl_3$ as an eluent. The pure coupling products **62a-e** and **63a-64a** were obtained in 35-82% yields.

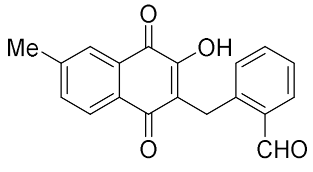
Method 2: To a 10 mL of round bottom flask equipped with a magnetic stirring bar were added 0.06 mmol of catalyst **3n**, 0.33 mmol of Hantzsch ester **34**, 0.3 mmol of 2-hydroxy-1,4-naphthoquinone **1** and 0.5 mL of anhydrous DCM. The resulting mixture was stirred for some time, then the dialdehyde **59b** or **59c** (dissolved in 0.5 mL of DCM) was added dropwise over 3-4 hours at constant speed from dropping funnel under N_2 atmosphere, and stirring was continued for few more hours. The pure coupling products **62f** and **62g** were obtained in 44% and 31% yields.

2-((3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)benzaldehyde (62a):



62a

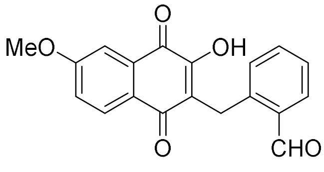
The compound was prepared following procedure **3g**, and obtained as a pale yellow solid. Mp: 176-178 °C. Yield: 82% (72.0 mg). IR (Neat): ν_{max} 3100, 2161, 1978, 1673, 1642, 1594, 1455, 1411, 1361, 1342, 1303, 1270, 1212, 1181, 1154, 1090, 1048, 1037, 1016, 968, 952, 930, 855, 825, 791, 765, 736, 723, 693, 637, and 604 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.54 (1H, s, C*H*O), 7.99 (1H, dd, $J = 7.2, 1.2$ Hz), 7.94 (1H, dd, $J = 7.2$, 1.2 Hz), 7.82 (1H, d, *J* = 6.8 Hz), 7.80-7.75 (2H, m), 7.51 (1H, dt, *J* = 7.6, 1.6 Hz), 7.38 (1H, t, *J* = 7.6 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 2.51 (2H, s). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 193.7 (H*C*, H-*C*=O), 184.5 (C, C=O), 181.6 (C, C=O), 157.6 (C, *C*-OH), 142.4 (C), 134.9 (CH), 134.3 (CH), 134.0 (C), 133.5 (CH), 132.5 (C), 130.7 (C), 130.5 (CH), 130.3 (CH), 126.9 (CH), 126.23 (CH), 126.16 (CH), 121.7 (C), 25.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{12}O_4H$ 293.0814; Found 293.0812.



62b

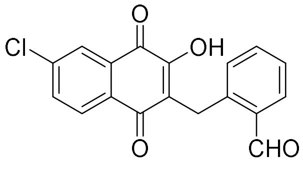
2-((3-Hydroxy-6-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)benzaldehyde (62b): The compound was prepared following procedure **3g** and obtained as a yellow solid. Mp: 196-198 °C. Yield: 82% (75.3 mg). IR (Neat): ν_{max} 3342, 1688, 1638, 1596, 1450, 1347, 1312, 1274, 1228, 1209, 1163, 1089, 1048, 995, 946, 873, 854, 820, 799, 758, 744, 676, and 631 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400MHz): δ 10.60 (1H, s, C*H*O), 8.01 (1H, d, *J* = 7.6 Hz), 7.89 (1H, br s), 7.87 (1H, dd, *J* = 7.6, 1.6 Hz), 7.62 (1H, s, O*H*), 7.56 (1H, qd, *J* = 8.0, 0.8 Hz), 7.48 (1H, dt, *J* = 7.6, 1.6 Hz), 7.42 (1H, d, *J* = 6.8 Hz), 7.37 (1H, dt, *J* = 7.6, 1.2 Hz), 4.41 (2H, s), 2.49 (3H, s). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 192.9 (*HC*, H-C=O), 184.3 (C, C=O), 181.6 (C, C=O), 153.5 (C, *C*-OH), 144.2 (C), 141.1 (C), 135.8 (CH), 134.0 (C), 133.8 (CH), 130.8 (CH), 130.7 (CH), 130.4 (C), 129.3 (C), 127.2 (CH), 126.9 (CH), 126.7 (CH), 121.7 (C), 24.9 (CH$_2$), 21.6 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{14}O_4H$ 307.0970; Found 307.0966.

2-((3-Hydroxy-6-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)benzaldehyde (62c): The compound was prepared following procedure **3g**, and obtained as a yellow solid. Mp: 157-159 °C. Yield: 69% (66.7 mg). IR (Neat): $\nu_{\max}$ 3321, 2918, 2849, 1688, 1638, 1576, 1492, 1448, 1433, 1376, 1338, 1288, 1242, 1198, 1102, 1047, 1020, 972, 913, 865, 848, 828, 790, 749, 726, 691, and 615 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500MHz): δ 11.37 (1H, s, O*H*), 10.53 (1H, s, C*H*O), 7.94 (1H, d, *J* = 8.5 Hz), 7.82 (1H, dd, *J* = 7.5, 1.5 Hz), 7.51 (1H, dt, *J* = 7.5, 1.5 Hz), 7.38 (1H, t, *J* = 7.5 Hz), 7.36 (1H, d, *J* = 2.5 Hz), 7.31 (1H, d, *J* = 7.5 Hz), 7.26 (1H, dd, *J* = 8.5, 2.5 Hz), 4.24 (2H, s), 3.90 (3H, s). ^{13}C NMR (DMSO-d_6, DEPT-135): δ 193.6 (H*C*, H-C=O), 184.5 (C, C=O), 180.1 (C, C=O), 164.7 (C), 157.0 (C, *C*-OH), 142.3 (C), 134.7 (C), 134.3 (CH), 134.0 (C), 130.5 (CH), 130.3 (CH), 129.0 (CH), 127.0 (CH), 123.7 (C), 121.5 (C), 119.2 (CH), 110.7 (CH), 56.4 (CH$_3$), 25.0 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{14}O_5Na$ 345.0739; Found 345.0739.



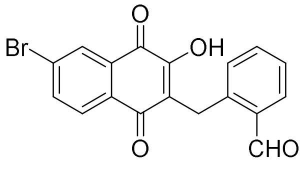
62c

2-((6-Chloro-3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)benzaldehyde (62d): The compound was prepared following procedure **3g** and obtained as a yellowish orange solid. Mp: 195-197 °C. Yield: 57% (55.9 mg). IR (Neat): $\nu_{\max}$ 2977, 2929, 1714, 1590, 1546, 1440, 1366, 1284, 1253, 1220, 1103, 1042, 1022, 982, 866, 770, and 697 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.59 (1H, br s, O*H*), 10.50 (1H, s, C*H*O), 7.92 (1H, d, *J* = 8.0 Hz), 7.91 (1H, s), 7.84 (1H, dd, *J* = 8.0, 2.5 Hz), 7.82 (1H, dd, *J* = 8.0, 1.5 Hz), 7.50 (1H, dt, *J* = 7.5, 1.0 Hz), 7.38 (1H, t, *J*



62d

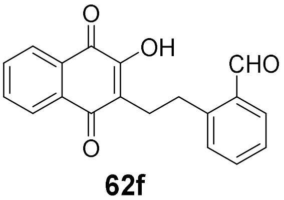
= 7.5 Hz), 7.32 (1H, d, *J* = 7.5 Hz), 4.25 (2H, s). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 193.6 (H*C*, H-C=O), 183.9 (C, C=O), 180.3 (C, C=O), 157.0 (C, *C*-OH), 141.9 (C), 138.7 (C), 134.5 (CH), 134.3 (CH), 134.0 (C), 132.3 (C), 130.9 (C), 130.7 (CH), 130.3 (CH), 128.4 (CH), 127.0 (CH), 125.6 (CH), 122.1 (C), 25.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{18}H_{11}ClO_4Na$ 349.0244; Found 349.0244.



62e

2-((6-Bromo-3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)benzaldehyde (62e): The compound was prepared following procedure **3g** and obtained as a brown solid. Mp: 186-188 °C. Yield: 56% (62.3 mg). IR (Neat): ν_{max} 2921, 1673, 1634, 1594, 1578, 1450, 1409, 1342, 1296, 1247, 1202, 1153, 1090, 1065, 1045, 1031, 952, 938, 906, 864, 828, 794, 759, 745, 684, 657, and 635 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.61 (1H, br s, O*H*), 10.50 (1H, s, C*H*O), 8.07 (1H, d, *J* = 2.0 Hz), 8.01 (1H, dd, *J* = 8.4, 2.0 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 7.83 (1H, dd, *J* = 7.6, 0.8 Hz), 7.51 (1H, dt, *J* = 7.6, 1.2 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 7.32 (1H, d, *J* = 7.6 Hz), 4.26 (2H, s). ^{13}C NMR (DMSO-d_6, DEPT-135) δ 193.7 (H*C*, H-C=O), 184.1 (C, C=O), 180.3 (C, C=O), 157.0 (C, *C*-OH), 141.9 (C), 137.5 (CH), 134.3 (CH), 134.0 (C), 132.3 (C), 131.2 (C), 130.8 (CH), 130.3 (CH), 128.5 (2 x CH), 127.5 (C), 127.0 (CH), 122.0 (C), 25.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{18}H_{11}BrO_4Na$ 392.9738; Found 392.9733.

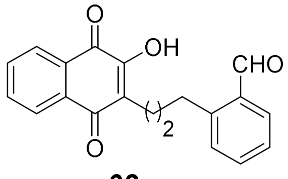
2-(2-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)benzaldehyde



62f

(62f): The compound was prepared following **procedure 3g**, and obtained as a yellow solid. Mp: 152-154 °C. Yield: 44% (40.4 mg). IR (Neat): ν_{max} 3228, 2922, 2852, 1691, 1665, 1633, 1592, 1461, 1358, 1273, 1258, 1215, 1183, 1091, 1052, 860, 752, and 694 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 10.45 (1H, s, C*H*O), 8.15 (1H, dd, *J* = 7.5, 1.0 Hz), 8.11 (1H, dd, *J* = 7.5, 1.0 Hz), 7.88 (1H, dd, *J* = 7.5, 1.0 Hz), 7.79 (1H, dt, *J* = 7.5, 1.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.5 Hz), 7.52 (1H, dt, *J* = 7.5, 1.5 Hz), 7.42 (1H, s), 7.40 (1H, dt, *J* = 7.5, 1.0 Hz), 7.36 (1H, d, *J* = 7.5 Hz), 3.31-3.28 (2H, m), 2.98-2.95 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 192.5 (H*C*, H-*C*=O), 184.5 (C, C=O), 181.2 (C, C=O), 153.5 (C, *C*-OH), 144.1 (C), 135.0 (CH), 133.93 (CH), 133.90 (C), 133.0 (CH), 132.8 (C), 131.2 (CH), 131.1 (CH), 129.4 (C), 126.9 (CH), 126.8 (CH), 126.2 (CH), 122.8 (C), 30.7 (CH$_2$), 25.8 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{14}O_4Na$ 329.0790; Found 329.0790.

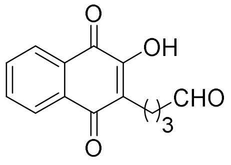
2-(3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)propyl)benzaldehyde



62g

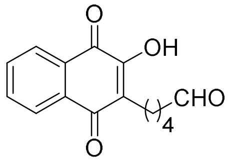
(62g): The compound was prepared following **procedure 3g**, and obtained as a yellow solid. Mp: 94-98 °C. Yield: 31% (29.8 mg). IR (Neat): ν_{max} 3351, 2923, 2854, 1691, 1642, 1594, 1458, 1368, 1345, 1272, 1210, 1158, 1097, 1059, 1000, 946, 908, 794, 755, 723, and 649 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 10.27 (1H, s, C*H*O), 8.11 (1H, d, *J* = 7.2 Hz), 8.07 (1H, d, *J* = 7.6 Hz), 7.81 (1H, d, *J* = 7.6 Hz), 7.75 (1H, dt, *J* = 7.2, 0.8 Hz), 7.68 (1H, dt, *J* = 7.2, 0.8 Hz), 7.55 (1H, br s, O*H*), 7.49 (1H, dt, *J* = 7.6, 1.2 Hz), 7.34 (1H, t, *J* = 7.6 Hz), 7.32 (1H, d, *J* = 7.6 Hz), 3.14 (2H, t, *J* = 7.6 Hz), 2.73 (2H, t, *J* = 7.6 Hz), 1.90 (2H, quint, *J* = 7.6 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 192.4 (H*C*, H-*C*=O), 184.6 (C, C=O), 181.3 (C, C=O), 153.2 (C, *C*-OH), 144.9 (C), 134.9 (CH), 133.8 (CH), 133.6 (C), 132.9 (CH), 132.9 (C), 131.8 (CH), 130.9 (CH), 129.4 (C), 126.8 (CH), 126.6 (CH), 126.1 (CH), 123.8 (C), 32.5 (CH$_2$), 30.3 (CH$_2$), 23.3 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{16}O_4H$ 321.1127; Found 321.1127.

4-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal (63a): The compound was prepared following **procedure 3g**, purified by the column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as a yellow solid. Mp: 183-190 °C. Yield: 35% (25.6 mg). IR (Neat): ν_{max} 3110, 2958, 2862, 1726, 1671, 1644, 1590, 1363, 1344, 1262, 1210, 1187, 1088, 1012, 949, 788, 720, 689, 665, and 566 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.79 (1H, t, *J* = 1.5 Hz), 8.12 (1H, dd, *J* = 7.5, 1.0 Hz), 8.09 (1H, dd, *J* = 7.5, 1.0 Hz), 7.77 (1H, dt, *J* = 7.5, 1.0 Hz), 7.70 (1H, dt, *J* = 7.5, 1.0 Hz), 7.42 (1H, s), 2.67 (2H, t, *J* = 8.0 Hz), 2.52 (2H, dt, *J* = 7.5, 1.5 Hz), 1.92 (2H, quint, *J* = 7.5 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 202.1 (H*C*, H-*C*=O), 184.5 (C, C=O), 181.2 (C, C=O), 153.4 (C, *C*-OH), 135.0 (CH), 133.0 (CH), 132.8 (C), 129.4 (C), 126.8 (CH), 126.2 (CH), 123.2 (C), 43.4 (CH$_2$), 22.5 (CH$_2$), 20.6 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{12}O_4H$ 245.0814; Found 245.0815.



63a

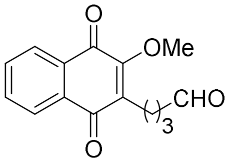
5-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal (63a): The compound was prepared following **procedure 3g**, purified by column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as a yellow solid. Mp: 190-192 °C. Yield: 40% (31 mg). IR (Neat): ν_{max} 3073, 2934, 2853, 2755, 1701, 1671, 1641, 1590, 1364, 1342, 1275, 1245, 1206, 1182, 1094, 997, 942, 898, 794, 723, 691, and 563 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.76 (1H, t, J = 2.0 Hz), 8.09 (1H, dd, J = 7.5, 1.5 Hz), 8.06 (1H, dd, J = 7.5, 1.5 Hz), 7.74 (1H, dt, J = 7.5, 1.5 Hz), 7.67 (1H, dt, J = 7.5, 1.0 Hz), 7.41 (1H, s, O*H*), 2.62 (2H, t, J = 7.5 Hz), 2.48 (2H, dt, J = 7.0, 1.5 Hz), 1.71 (2H, quint, J = 7.0 Hz), 1.59 (2H, quint, J = 7.0 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135) δ 202.5 (H*C*, H-*C*=O), 184.6 (C, C=O), 181.3 (C, C=O), 153.2 (C, *C*-OH), 134.9 (CH), 132.9 (CH), 132.9 (C), 129.4 (C), 126.8 (CH), 126.1 (CH), 123.8 (C), 43.6 (CH$_2$), 27.6 (CH$_2$), 22.9 (CH$_2$), 21.9 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{14}O_4H$ 259.0970; Found 259.0970.



63a

3h. General Procedures for Synthetic Transformation of 62-63: To a 10 mL round bottom flask equipped with a magnetic stirring bar were added 1.0 mmol of **62-63**, 5.0 mmol of CH_3I and 2 mL of acetone. Then, 2.0 mmol of K_2CO_3 was added and the resulting mixture was allowed to stir at 60 °C for 24 h. Next, the crude reaction mixture was directly loaded onto a dry silica gel packed column without aqueous workup to give pure **75-77** in good yields after column chromatography using ethyl acetate/hexane as an eluent.

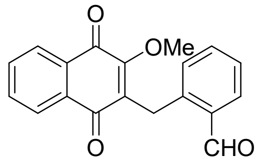
4-(3-Methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal (75a): The compound



75a

was prepared following procedure **3h**, purified by the column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as a yellow liquid. Yield: 76% (196.3 mg). IR (Neat): ν_{max} 2919, 2849, 1721, 1669, 1651, 1595, 1449, 1391, 1336, 1305, 1263, 1216, 1170, 1088, 1042, 964, 917, 797, 726, and 469 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.79 (1H, t, J = 1.6 Hz, C*H*O), 8.08-8.02 (2H, m), 7.73-7.67 (2H, m), 4.16 (3H, s, OCH_3), 2.64 (2H, t, J = 7.6 Hz), 2.50 (2H, dt, J = 7.2, 1.6 Hz), 1.85 (2H, quint, J = 7.6 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 202.1 (H*C*, H-*C*=O), 185.2 (C, C=O), 181.4 (C, C=O), 158.0 (C, *C*-OMe), 134.0 (C), 133.8 (CH), 133.3 (CH), 131.9 (C), 131.5 (C), 126.2 (CH), 126.1 (CH), 61.3 (CH$_3$), 43.4 (CH$_2$), 22.9 (CH$_2$), 21.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + K]$^+$ Calcd for $C_{15}H_{14}O_4K$ 297.0529; Found 297.0524.

2-((3-Methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)benzaldehyde

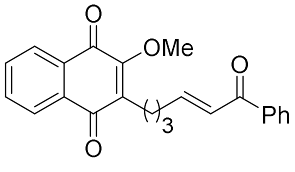


77a

(77a): The compound was prepared following procedure **3h**, purified by the column chromatoghraphy using EtOAc/hexane (1.5:8.5 to 2.0:8.0), and obtained as a yellow solid. Mp: 98-100 °C. Yield: 82% (251 mg). IR (Neat): ν_{max} 2955, 1674, 1634, 1592, 1572, 1480, 1450, 1402, 1331, 1261, 1222, 1169, 1086, 1062, 999, 980, 951, 914, 842, 824, 810, 787, 762, 745, 719, 694, 658, 637, and 599 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 10.52 (1H, s, C*H*O), 8.08-8.03 (2H, m), 7.86 (1H, dd, J = 7.6, 1.6 Hz), 7.73-7.68 (2H, m), 7.46 (1H, dt, J = 7.6, 1.6 Hz), 7.35 (1H, br t, J = 7.6 Hz), 7.30 (1H, br d, J = 7.6 Hz), 4.41 (2H, s), 4.07 (3H, s, OCH_3). ^{13}C NMR (CDCl$_3$, DEPT-135): δ 192.5 (H*C*, H-*C*=O), 184.9 (C, C=O), 181.5 (C, C=O), 158.0 (C, *C*-OMe), 141.3 (C), 134.0 (CH), 133.9 (C), 133.7 (CH), 133.4 (CH), 132.3 (C), 131.7 (C), 131.5 (C), 131.0 (CH), 130.3 (CH), 126.8 (CH), 126.4 (CH), 126.2 (CH), 61.2 (CH_3), 25.2 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{14}O_4H$ 307.0970; Found 307.0972.

3i. General Procedures for Synthetic Transformation of Products 75ad: To an ordinary glass vial equipped with a magnetic stirring bar were added 0.025 mmol of quinine-thiourea **57b**, 0.3 mmol of **66d** and anhydrous toluene (0.1 M). Then, 0.25 mmol of **75a** was added and the resulting mixture was allowed to stir at RT for 12 h. Next, the crude reaction mixture was directly loaded onto a dry silica gel packed column without aqueous workup to give **76ad** in 85% yield after column chromatography (eluent: ethyl acetate/hexane).

(*E*)-2-Methoxy-3-(6-oxo-6-phenylhex-4-en-1-yl)naphthalene-1,4-dione (76ad): The compound was prepared following procedure **3i**, purified by the column chromatography using EtOAc/hexane (1:9), and isolated as a yellow semi-solid. Yield: 85% (76.5 mg).



76ad

IR (Neat): ν_{max} 2933, 2852, 1668, 1649, 1614, 1447, 1335, 1298, 1262, 1215, 967, 917, 725 and 694 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.07-8.04 (2H, m), 7.94-7.93 (2H, m), 7.70-7.68 (2H, m), 7.55 (1H, tt, *J* = 7.5, 1.5 Hz), 7.46 (2H, tt, *J* = 8.0, 1.5 Hz), 7.08 (1H, td, *J* = 15.5, 6.5 Hz, olefinic-*H*), 6.94 (1H, td, *J* = 15.5, 1.5 Hz, olefinic-*H*), 4.15 (3H, s, OCH_3), 2.67 (2H, t, *J* = 8.0 Hz), 2.43-2.38 (2H, m), 1.75 (2H, quint, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135): δ 190.8 (C, C=O), 185.3 (C, C=O), 181.4 (C, C=O), 157.9 (C, *C*-OMe), 149.0 (CH), 137.9 (C), 134.6 (C), 133.8 (CH), 133.2 (CH), 132.6 (CH), 131.9 (C), 131.6 (C), 128.54 (2 x CH), 128.47 (2 x CH), 126.2 (2 x CH), 126.1 (CH), 61.2 (CH_3), 32.7 (CH_2), 27.1 (CH_2), 23.3 (CH_2). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{23}H_{20}O_4H$ 361.1440; Found 361.1437.

4. Direct Organocatalytic Asymmetric Synthesis of Biologically Important Methanobenzo[*f*]azulenes

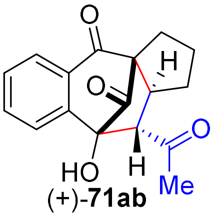
4a. General Procedures for Asymmetric Synthesis of (+)-4aa-ac /(+)-9aa-ac:

To an ordinary glass vial equipped with a magnetic stirring bar were added 0.06 mmol of quinine-thiourea **57b**, 0.2 mmol of **63a-h** or **64a-h** and anhydrous Toluene (0.2 M). Then, 0.22 mmol of **66b-d** was added and the resulting mixture was allowed to stir at RT until complete consumption of **63/64** (monitored by TLC). Next, the crude reaction mixture was directly loaded onto a dry silica gel packed column without aqueous workup to give pure products **(+)-4aa-ac** and (+)-**9aa-ac** after column chromatography (eluent: mixture of ethyl acetate/hexanes).

4b. General Procedures for Racemic Synthesis of 71aa-ac/72aa-ac:

Methode 1: To an ordinary glass vial equipped with a magnetic stirring bar were added 0.2 mmol of **63a-h** and anhydrous toluene (0.2 M). Then, 0.22 mmol of **66b-d** was added and the resulting mixture was allowed to stir at RT until complete consumption of **63a-h** (monitored by TLC). Next, the crude reaction mixture was directly loaded onto a silica gel packed column without aqueous workup to give pure products (±)-**71aa-ac** after column chromatography (eluent: mixture of ethyl acetate/hexanes).

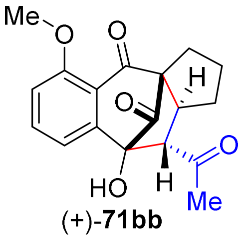
Methode 2: To an ordinary glass vial equipped with a magnetic stirring bar were added 0.01 mmol of 1:1 ratio of quinine thiourea and quinidine thiourea, 0.2 mmol of **64a-h** and anhydrous Toluene (0.2 M). Then, 0.22 mmol of **66b-d** was added and the resulting mixture was allowed to stir at RT until complete consumption of **64a-h** (monitored by TLC). Next, the crude reaction mixture was directly loaded onto a silica gel packed column without aqueous workup to give pure products (±)-**72aa-ac** after column chromatography (eluent: mixture of ethyl acetate/hexanes).



(+)-**71ab**

(3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-1,2,3,9,10,10a-hexahydro-4*H*-3a,9-methanobenzo[*f*]azulene-4,11-dione ((+)-71ab): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 1.5:8.5), and isolated as a semi-solid. Yield: 84% (47.7mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 44.27 min (major), t_R = 49.10 min (minor). $[\alpha]_D^{25}$ = +116.5° (c = 0.27, $CHCl_3$, 90.0% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3428, 2968, 2921, 2851, 1762, 1692, 1619, 1595, 1450, 1363, 1336, 1299, 1269, 1188, 1161, 1117, 1075, 1042, 1019, 1001, 974, 953, 901, 885, 850, 798,776, 724, 680, 648, 631, 604, 580, and 560 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.06 (1H, dd, J = 7.6, 0.8 Hz), 7.72 (1H, d, J = 8.0 Hz), 7.64 (1H, dt, J = 9.0, 1.2 Hz), 7.48 (1H, dt, J = 8.0, 1.2 Hz), 3.92 (1H, s, O*H*), 3.03 (1H, d, J = 7.6 Hz), 2.87 (1H, q, J

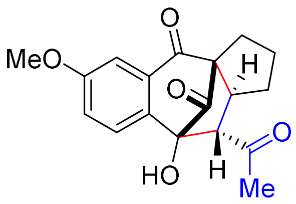
= 7.6 Hz), 2.47 (1H, quintate, *J* = 6.8 Hz), 2.32 (3H, s), 2.20-2.13 (1H, m), 2.01-1.95 (1H, m), 1.84-1.77 (2H, m), 1.37-1.33 (1H, m). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 204.4 (C, *C*=O), 203.9 (C, *C*=O), 192.9 (C, *C*=O), 140.8 (C), 134.9 (CH), 130.4 (C), 129.2 (CH), 127.7 (CH), 124.6 (CH), 85.1 (C, *C*-OH), 73.0 (C), 61.5 (CH), 44.1 (CH), 33.3 (CH_2), 30.8 (CH_3), 27.6 (CH_2), 22.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}O_3H$ 271.1334; Found 271.1335.



(+)-**71bb**

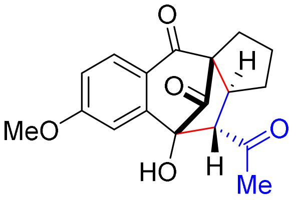
(3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-5-methoxy-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione ((+)-71bb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2:8), and isolated as a semi-solid. Yield: 73.8% (46.4 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IB-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 24.74 min (major), t_R = 19.02 min (minor). $[\alpha]_D^{26} = +34.9^\circ$ (*c* = 0.04, $CHCl_3$, 95.0% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3409, 3018, 2939, 2872, 1768, 1712, 1684, 1589, 1468, 1437, 1278, 1249, 1214, 1177, 1058, 1025, 751, 725, 696 and 542 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.55 (1H, t, *J* = 8.0 Hz), 7.32 (1H, dd, *J* = 8.0, 1.0 Hz), 7.00 (1H, d, *J* = 8.0 Hz), 3.94 (3H, s), 3.75 (1H, s, O*H*), 2.99 (1H, d, *J* = 8.0 Hz), 2.94 (1H, q, *J* = 7.5 Hz), 2.46 (1H, td, *J* = 13.5, 7.0 Hz), 2.31 (3H, s), 2.13 (1H, td, *J* = 14.0, 7.0 Hz), 1.99-1.92 (1H, m), 1.81-1.72 (2H, m), 1.31 (1H, sextet, *J* = 7.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 204.1 (C, *C*=O), 203.9 (C, *C*=O), 190.9 (C, *C*=O), 160.9 (C), 143.3 (C), 135.2 (CH), 119.4 (C), 116.4 (CH), 112.5 (CH), 85.1 (C, *C*-OH), 74.1 (C), 61.9 (CH), 56.1 (CH_3), 43.7 (CH), 33.3 (CH_2), 30.9 (CH_3), 27.4 (CH_2), 23.2 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{18}O_5H$ 315.1232; Found 315.1234.

(3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-6-methoxy-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione ((+)-71cb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2:8), and isolated as a semi-solid. Yield: 90.6% (57.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 66.83 min (major), t_R = 58.07 min (minor). $[\alpha]_D^{28}$ = +16.7° (*c* = 0.03, $CHCl_3$, 80.2% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3440, 2956, 2868, 1766, 1687, 1604, 1486, 1329, 1279, 1239, 1195, 1165, 1026, 954, 827, 731 and 571 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.61 (1H, d, *J* = 8.5 Hz), 7.52 (1H, d, *J* = 3.0 Hz), 7.19 (1H, dd, *J* = 8.5, 2.5 Hz), 3.85 (3H, s), 3.71 (1H, s, O*H*), 2.99 (1H, d, *J* = 7.5 Hz), 2.86 (1H, q, *J* = 7.5 Hz), 2.48 (1H, quintet, *J* = 6.5 Hz), 2.32 (3H, s), 2.17 (1H, td, *J* = 13.5, 7.0 Hz), 1.99 (1H, sextet, *J* = 6.0 Hz), 1.81 (2H, sextet, *J* = 6.0 Hz), 1.35 (1H, sextet, *J* = 7.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 204.2 (C, *C*=O), 204.1 (C, *C*=O), 192.8 (C, *C*=O), 160.2 (C), 133.0 (C), 131.8 (C), 125.9 (CH), 122.8 (CH), 110.0 (CH), 84.9 (C, *C*-OH), 72.9 (C), 61.4 (CH), 55.6 (CH_3), 44.3 (CH), 33.2 (CH_2), 30.7 (CH_3), 27.6 (CH_2), 22.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{18}O_5H$ 315.1232; Found 315.1232.



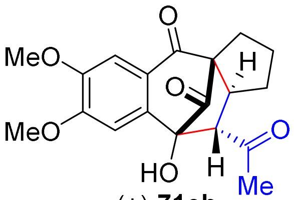
(+)-**71cb**

(3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-7-methoxy-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione ((+)-71db): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2.0:8.0), and isolated as a semi-solid. Yield: 76.7% (48.2 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 28.16 min (major), t_R = 33.55 min (minor). $[\alpha]_D^{28}$ = +64.0° (c = 0.06, $CHCl_3$, 85.6% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3418, 3021, 2939, 2867, 1765, 1709, 1679, 1597, 1488, 1442, 1321, 1262, 1229, 1024, 889, 753 and 667 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.02 (1H, d, J = 8.5 Hz), 7.15 (1H, d, J = 2.0 Hz), 6.96 (1H, dd, J = 8.5, 2.5 Hz), 3.88 (3H, s), 3.77 (1H, s, O*H*), 3.01 (1H, d, J = 7.5 Hz), 2.88 (1H, q, J = 8.0 Hz), 2.48 (1H, td, J = 13.5, 7.0 Hz), 2.32 (3H, s), 2.14 (1H, td, J = 14.0, 7.0 Hz), 1.99 (1H, sextet, J = 6.5 Hz), 1.83-1.78 (2H, m), 1.32 (1H, sextet, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 204.3 (C, *C*=O), 203.8 (C, *C*=O), 191.4 (C, *C*=O), 164.9 (C), 143.3 (C), 130.1 (CH), 123.8 (C), 115.1 (CH), 109.3 (CH), 85.1 (C, *C*-OH), 72.5 (C), 61.8 (CH), 55.7 (CH_3), 44.4 (CH), 33.5 (CH_2), 30.7 (CH_3), 27.7 (CH_2), 22.8 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{18}O_5H$ 315.1232; Found 315.1235.



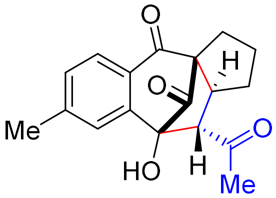
(+)-**71db**

(3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-6,7-dimethoxy-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione ((+)-71eb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2.0:8.0), and isolated as a semi-solid. Yield: 84.2% (58.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 99.04 min (major), t_R = 87.15 min (minor). $[\alpha]_D^{28}$ = +37.5° (*c* = 0.03, $CHCl_3$, 59.0% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3418, 3019, 2957, 1765, 1708, 1677, 1595, 1507, 1360, 1279, 1215, 1024, 883, 751 and 672 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.48 (1H, s), 7.11 (1H, s), 3.95 (3H, s), 3.92 (3H, s), 3.83 (1H, s, O*H*), 2.99 (1H, d, *J* = 7.0 Hz), 2.83 (1H, q, *J* = 7.5 Hz), 2.48 (1H, quintet, *J* = 6.5 Hz), 2.32 (3H, s), 2.14 (1H, td, *J* = 14.5, 7.5 Hz), 2.03-1.96 (1H, m), 1.83-1.78 (2H, m), 1.33 (1H, sextet, *J* = 7.5 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 203.9 (C, *C*=O), 203.7 (C, *C*=O), 191.7 (C, *C*=O), 154.7 (C), 149.7 (C), 135.4 (C), 123.9 (C), 108.6 (CH), 106.1 (CH), 84.9 (C, *C*-OH), 72.5 (C), 61.6 (CH), 56.3 (CH_3), 56.1 (CH_3), 44.7 (CH), 33.3 (CH_2), 30.7 (CH_3), 27.7 (CH_2), 22.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}O_6H$ 345.1338; Found 345.1334.



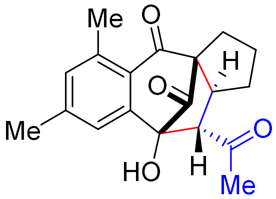
(+)-**71eb**

(3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-7-methyl-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione ((+)-71fb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2.0:8.0), and isolated as a semi-solid. Yield: 83.2% (49.6 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.98 min (major), t_R = 25.22 min (minor). $[\alpha]_D^{28}$ = +71.6° (*c* = 0.07, $CHCl_3$, 85.2% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3428, 2924, 2853, 1764, 1715, 1685, 1604, 1447, 1365, 1275, 1260, 1204, 1038, 908, 749 and 542 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (1H, d, *J* = 7.6 Hz), 7.50 (1H, s), 7.28 (1H, d, *J* = 7.6 Hz), 3.72 (1H, s, O*H*), 3.01 (1H, d, *J* = 7.2 Hz), 2.88 (1H, q, *J* = 7.6 Hz), 2.48 (1H, quintet, *J* = 6.8 Hz), 2.44 (3H, s), 2.32 (3H, s), 2.16 (1H, td, *J* = 13.6, 7.2 Hz), 1.99 (1H, sextet, *J* = 6.4 Hz), 1.85-1.77 (2H, m), 1.39-1.28 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, DEPT-135): δ 204.5 (C, *C*=O), 203.9 (C, *C*=O), 192.5 (C, *C*=O), 146.3 (C), 140.7 (C), 130.2 (CH), 128.2 (C), 127.8 (CH), 124.9 (CH), 85.0 (C, *C*-OH), 72.8 (C), 61.7 (CH), 44.2 (CH), 33.4 (CH_2), 30.8 (CH_3), 27.7 (CH_2), 22.9 (CH_2), 22.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{18}O_4Na$ 321.1103; Found 321.1104.



(+)-**71fb**

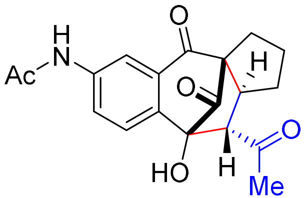
(3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-5,7-dimethyl-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione ((+)-71gb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2.0:8.0), and isolated as a semi-solid. Yield: 87.2% (54.5 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.11 min (major), t_R = 7.98 min (minor). $[\alpha]_D^{26}$ = +52.9° (*c* = 0.05, $CHCl_3$, 96.6%



(+)-**71gb**

ee and >20:1 *dr*). IR (Neat): ν_{max} 3424, 2961, 2925, 2866, 1765, 1712, 1680, 1602, 1445, 1362, 1305, 1258, 1240, 1191, 1037, 869 and 771 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.39 (1H, s), 7.07 (1H, s), 3.71 (1H, s, O*H*), 2.98 (1H, d, *J* = 8.0 Hz), 2.88 (1H, q, *J* = 7.5 Hz), 2.65 (3H, s), 2.44 (1H, quintet, *J* = 7.0 Hz), 2.37 (3H, s), 2.32 (3H, s), 2.16 (1H, sextet, *J* = 7.0 Hz), 1.97 (1H, sextet, *J* = 6.5 Hz), 1.84-1.72 (2H, m) 1.59-1.29 (1H, m). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 204.5 (C, *C*=O), 204.2 (C, *C*=O), 193.6 (C, *C*=O), 144.3 (C), 142.5 (C), 142.3 (C), 134.0 (CH), 126.4 (C), 122.9 (CH), 85.1 (C, *C*-OH), 73.6 (C), 61.8 (CH), 43.8 (CH), 33.3 (CH$_2$), 30.8 (CH$_3$), 27.4 (CH$_2$), 23.2 (CH$_2$), 22.8 (CH$_3$), 21.8 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{20}O_4H$ 313.1440; Found 313.1445.

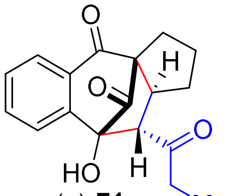
***N*-((3a*S*,9*S*,10*S*,10a*S*)-10-Acetyl-9-hydroxy-4,11-dioxo-2,3,4,9,10,10a-hexahydro-1H-3a,9-methanobenzo[*f*]azulen-6-yl)acetamide ((+)-71hb):** The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2.0:8.0), and isolated as a semi-solid. Yield: 62% (42.3 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 26.24 min (major), t_R = xx.xx min (minor). $[\alpha]_D^{28}$ = +22.7° (*c* = 0.15, CHCl$_3$, >99% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3339, 2954, 2925, 2854, 1767, 1686,1590, 1536, 1485, 1368, 1313, 1260, 1167, 1042, 909, 749 and 541 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.20 (1H, dd, *J* = 8.5, 2.0 Hz), 7.78 (1H, d, *J* = 2.0 Hz), 7.66 (1H, d, *J* = 8.5 Hz), 7.46 (1H, s), 3.77 (1H, s, O*H*), 3.02 (1H, d, *J* = 7.5 Hz),



(+)-**71ha**

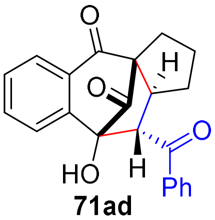
2.88 (1H, q, $J = 7.5$ Hz), 2.46 (1H, quintate, $J = 6.5$ Hz), 2.33 (3H, s), 2.19 (3H, s), 2.18-2.14 (1H, m), 2.04-1.97 (1H, m), 1.85-1.77 (2H, m), 1.39-1.34 (1H, m). ^{13}C {^{1}H}NMR (100 MHz, $CDCl_3$, DEPT-135): δ 204.2 (C, *C*=O), 204.1 (C, *C*=O), 192.5 (C, *C*=O), 168.5 (C, N-*C*=O), 139.0 (C), 135.8 (C), 130.97 (C), 126.1 (CH), 125.7 (CH), 117.3 (CH), 84.97 (C, *C*-OH), 73.0 (C), 61.4 (CH), 44.1 (CH), 33.3 (CH_2), 30.9 (CH_3), 27.6 (CH_2), 24.6 (CH_3), 22.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}NO_5H$ 342.1341; Found 342.1339.

(3a*S*,9*S*,10*S*,10a*S*)-9-hydroxy-10-propionyl-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione ((+)-71ac): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2:8), and isolated as a semi-solid. Yield: 69.0% (41.2 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.89 min (major), t_R = 11.73 min (minor). $[\alpha]_D^{25}$ = +45.3° (*c* = 0.10, $CHCl_3$, 83.7% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3445, 2961, 2935, 2865, 1767, 1715, 1688, 1598, 1454, 1407, 1374, 1283, 1258, 1183, 1116, 1028, 984, 800, 765, 743 and 524 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.07 (1H, d, $J = 7.5$ Hz), 7.66-7.62 (2H, m), 7.49-7.46 (1H, m), 3.75 (1H, s), 3.03 (1H, d, $J = 7.5$ Hz), 2.92-2.86 (2H, m), 2.52 (1H, q, $J = 7.5$ Hz), 2.48 (1H, quintet, $J = 6.5$ Hz), 2.17 (1H, td, $J = 13.0, 7.5$ Hz), 1.98 (1H, sextet, $J = 6.0$ Hz), 1.81 (2H, q, $J = 7.0$ Hz), 1.36 (1H, sextet, $J = 7.0$ Hz), 0.97 (3H, t, $J = 7.0$ Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, DEPT-135): δ 206.6 (C, *C*=O), 204.5 (C, *C*=O), 192.9 (C,

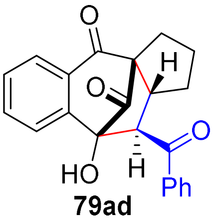


(+)-**71ac**

C=O), 140.9 (C), 134.9 (CH), 130.5 (C), 129.2 (CH), 127.6 (CH), 124.6 (CH), 85.3 (C, *C*-OH), 73.1 (C), 60.5 (CH), 44.3 (CH), 37.1 (CH_2), 33.3 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 7.2 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{18}O_4H$ 299.1283; Found 299.1280.



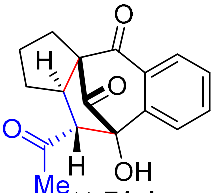
71ad
Major isomer



79ad
Minor isomer

(3a*S*,9*S*,10*S*,10a*S*)-10-Benzoyl-9-hydroxy-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione (71ad) and (3a*S*,9*S*,10*R*,10a*R*)-10-Benzoyl-9-hydroxy-1,2,3,9,10,10a-hexahydro-4H-3a,9-methanobenzo[*f*]azulene-4,11-dione (79ad): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2:8), and isolated as a semi-solid. Yield: 81.3% (56.3 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 19.19 min (major), t_R = 21.23 min (minor) [For major isomer], t_R = 62.34 min (major), t_R = 33.08 min (minor) [For minor isomer]. $[\alpha]_D^{25}$ = −12.8° (*c* = 0.22, $CHCl_3$, 94.02% *ee* and 1.65:1 *dr*). IR (Neat): ν_{max} 3441, 3067, 2959, 2871, 2846, 1762, 1687, 1666, 1595, 1445, 1367, 1301, 1270, 1218, 1182, 1151, 1085, 1042, 1017, 989, 962, 910, 887, 845, 796, 765, 732, 684, and 620 cm^{-1}. Isomer-1 ^1H NMR ($CDCl_3$, 400 MHz): δ 8.12 (1H, dd, *J* = 8.0, 1.2 Hz), 8.03-8.01 (2H, m), 7.95 (1H, dd, *J* = 8.0, 0.8 Hz), 7.90-7.88 (2H, m), 7.64-7.59 (1H, m), 7.56-7.44 (3H, m), 4.33 (1H, s), 4.21 (1H, d, *J* = 13.0 Hz), 2.80-2.74 (1H, m), 2.58-2.51 (1H, m), 2.15-2.08 (1H, m), 1.89-1.81 (1H, m), 1.64-1.57 (1H, m), 1.34-1.28 (2H, m). $^{13}C\{^1H\}$ NMR (100 MHz,

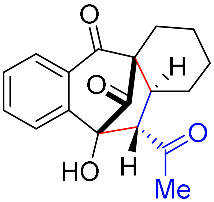
$CDCl_3$, DEPT-135): δ 204.0 (C, *C*=O), 200.5 (C, *C*=O), 193.9 (C, *C*=O), 144.6 (C), 136.9 (C), 135.3 (CH), 134.1 (CH), 129.7 (C), 128.9 (2xCH), 128.9 (CH), 128.4 (2xCH), 127.6 (CH), 124.8 (CH), 85.0 (C, *C*-OH), 72.9 (C), 51.3 (CH), 46.2 (CH), 30.2 (CH_2), 27.6 (CH_2), 22.99 (CH_2). Isomer-2 ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (1H, dd, *J* = 8.0, 1.2 Hz), 8.03-8.01 (1H, m), 7.74 (1H, dt, *J* = 7.6, 1.6 Hz), 7.64-7.59 (1H, m), 7.56-7.44 (4H, m), 7.30-7.28 (1H, m), 3.97 (1H, d, *J* = 7.2 Hz), 3.77 (1H, s), 3.12 (1H, q, *J* = 7.6 Hz), 2.58-2.51 (1H, m), 2.24 (1H, td, *J* = 14.0, 7.2 Hz) 2.02-1.96 (1H, m), 1.89-1.81 (2H, m), 1.49-1.39 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, DEPT-135): δ 204.8 (C, *C*=O), 196.5 (C, *C*=O), 193.0 (C, *C*=O), 141.2 (C), 137.3 (C), 134.8 (CH), 133.6 (CH), 130.7 (C), 129.3 (2xCH), 129.0 (CH), 128.4 (2xCH), 127.3 (CH), 125.1 (CH), 86.0 (C, *C*-OH), 73.2 (C), 56.2 (CH), 45.8 (CH), 33.3 (CH_2), 27.5 (CH_2), 22.97 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{18}O_4Na$ 369.1103; Found 369.1103.



(-)-**71ab**

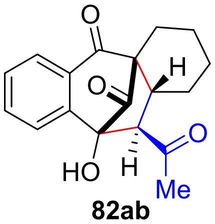
(3a*R*,9*R*,10*R*,10a*R*)-10-Acetyl-9-hydroxy-1,2,3,9,10,10a-hexahydro-4*H*-3a,9-methanobenzo[*f*]azulene-4,11-dione ((-)-71ab): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 1.5:8.5), and isolated as a semi-solid. Yield: 79% (45.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 48.25 min (major), t_R = 43.21 min (minor). $[\alpha]_D^{25} = -62.2^o$ (*c* = 0.27, $CHCl_3$, 66.6% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3428, 2968, 2921, 2851, 1762, 1692, 1619, 1595, 1450, 1363, 1336, 1299, 1269, 1188, 1161, 1117, 1075, 1042, 1019, 1001, 974, 953, 901, 885, 850, 798,776, 724, 680, 648, 631, 604, 580, and 560 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.07 (1H, dd, *J* = 7.5, 1.0 Hz), 7.72 (1H, dd, *J* = 7.5, 1.0 Hz), 7.65 (1H, dt, *J* = 7.5, 1.5 Hz), 7.48 (1H, dt, *J* = 7.5, 1.0 Hz), 3.79 (1H, s, O*H*), 3.03 (1H, d, *J* = 7.5 Hz), 2.88 (1H, q, *J* = 8.0 Hz), 2.48 (1H, quintate, *J* = 6.5 Hz), 2.32 (3H, s), 2.17 (1H, td, *J* = 14.0, 7.0 Hz), 2.03-1.96 (1H, m), 1.86-1.77 (2H, m), 1.39-1.32 (1H, m). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 204.4 (C, *C*=O), 203.9 (C, *C*=O), 192.8 (C, *C*=O), 140.7 (C), 134.99 (CH), 130.4 (C), 129.2 (CH), 127.7 (CH), 124.6 (CH), 85.0 (C, *C*-OH), 73.0 (C), 61.5 (CH), 44.1 (CH), 33.3 (CH$_2$), 30.8 (CH$_3$), 27.6 (CH$_2$), 22.9 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{18}O_3H$ 271.1334; Found 271.1335.

((4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methano dibenzo[a,d][7]annulene-5,12(2*H*)-dione ((+)-72ab):



(+)-**72ab**
Major isomer

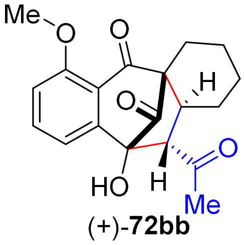
The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 78.7% (47.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.72 min (major), t_R = 12.10 min (minor). $[\alpha]_D^{25}$ = +96.4° (*c* = 0.05, CHCl$_3$, 99.0% *ee* and 5:1 *dr*). IR (Neat): ν_{max} 3455, 2930, 2856, 1765, 1712, 1679, 1596, 1453, 1357, 1329, 1300, 1276, 1231, 1172, 1085, 1037, 971, 953, 782, and 735 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.01 (1H, d, *J* = 8.0 Hz), 7.74 (1H, d, *J* = 8.0 Hz), 7.63 (1H, t, *J* = 7.5 Hz), 7.44 (1H, t, *J* = 7.5 Hz), 3.82 (1H, s), 3.02 (1H, d, *J* = 4.5 Hz), 2.65 (1H, td, *J* = 11.5, 5.0 Hz), 2.44-2.38 (1H, m), 2.11 (3H, s), 2.06 (1H, td, *J* = 14.5, 4.5 Hz), 1.94-1.90 (1H, m), 1.81 (1H, td, *J* = 13.5, 5.0 Hz), 1.66-1.62 (2H, m), 1.48-1.42 (1H, m), 1.37-1.28 (1H, m), 1.12 (1H, dq, *J* = 12.0, 4.0 Hz). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 205.7 (C, *C*=O), 203.9 (C, *C*=O), 194.9 (C, *C*=O), 141.2 (C), 134.7 (CH), 130.2 (C), 129.0 (CH), 128.0 (CH), 123.4 (CH), 81.5 (C, *C*-OH), 65.3 (CH), 64.4 (C), 34.8 (CH), 31.4 (CH$_2$), 30.2 (CH$_3$), 22.1 (CH$_2$), 20.2 (CH$_2$), 20.1 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for C$_{18}$H$_{18}$O$_4$Na 321.1103; Found 321.1103.



82ab
Minor Isomer

(4a*S*,10*S*,11*R*,11a*R*)-11-acetyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione (82ab): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 15.4% (9.2 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.25 min (major), t_R = 14.63 min (minor). IR (Neat): ν_{max} 3455, 2930, 2856, 1765, 1712, 1679, 1596, 1453, 1357, 1329, 1300, 1276, 1231, 1172, 1085, 1037, 971, 953, 782, and 735 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.07 (1H, d, *J* = 8.0 Hz), 7.82 (1H, d, *J* = 7.5 Hz), 7.70 (1H, dt, *J* = 7.5, 1.0 Hz), 7.48 (1H, dt, *J* = 8.0, 1.0 Hz), 3.55 (1H, s), 2.98 (1H, d, *J* = 11.0 Hz), 2.61-2.55 (1H, m), 2.47-2.35 (2H, m), 2.26 (3H, s), 1.88-1.78 (2H, m), 1.72-1.65 (1H, m), 1.56-1.55 (1H, m), 1.42(1H, tq, *J* = 13.0, 4.5 Hz), 1.29-1.28 (1H, m). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 204.5 (C, *C*=O), 204.4 (C, *C*=O), 196.3 (C, *C*=O), 147.4 (C), 135.2 (CH), 130.8 (C), 128.5 (CH), 127.9 (CH), 121.3 (CH), 79.2 (C, *C*-OH), 65.5 (C), 63.5 (CH), 42.9 (CH), 32.9 (CH_3), 27.2 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 21.4 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{18}O_4H$ 299.1283; Found 299.1283.

(4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-6-methoxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[a,d][7]annulene-5,12(2*H*)-dione ((+)-72bb): The compound

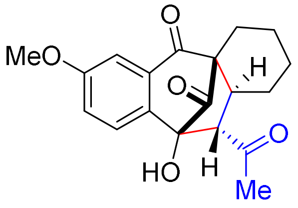


(+)-**72bb**

Major isomer

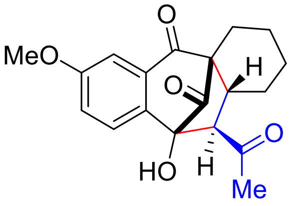
was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (2:8), and isolated as a semi-solid. Yield: 68.4% (45.0mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 21.11 min (major), t_R = xx.xx min (minor). $[\alpha]_D^{25}$ = +16.7° (*c* = 0.15, $CHCl_3$, >99% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3417, 2926, 2855, 1763, 1708, 1678, 1589, 1469, 1434, 1360, 1279, 1214, 1183, 1047, 1014, 914, 799, 730 and 522 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.54 (1H, t, *J* = 8.0 Hz), 7.35 (1H, dd, *J* = 8.0, 1.0 Hz), 6.96 (1H, d, *J* = 8.5 Hz), 3.91 (3H, s), 3.72 (1H, s), 2.99 (1H, d, *J* = 4.0 Hz), 2.70-2.66 (1H, m), 2.42-2.36 (1H, m), 2.10 (3H, s), 2.02 (1H, td, *J* = 14.0, 3.5 Hz), 1.92-1.87 (1H, m), 1.81-1.75 (1H, m), 1.64-1.61 (1H, m), 1.45-1.35 (1H, m), 1.34-1.30 (1H, m), 1.11-1.03 (1H, m). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 205.5 (C, *C*=O), 203.9 (C, *C*=O), 193.2 (C, *C*=O), 160.6 (C), 143.7 (C), 135.0 (CH), 118.9 (C), 115.2 (CH), 112.3 (CH), 81.5 (C, *C*-OH), 65.4 (C), 65.3 (CH), 56.1 (CH_3), 35.4 (CH), 31.5 (CH_2), 30.3 (CH_3), 22.3 (CH_2), 20.4 (CH_2), 20.3 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}O_5H$ 329.1389; Found 329.1384.

(4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-7-methoxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[a,d][7]annulene-5,12(2*H*)-dione ((+)-72cb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 77.0% (50.6 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.62 min (major), t_R = 11.4 min (minor). $[\alpha]_D^{25}$ = +192.7° (c = 0.22, $CHCl_3$, 99.1% *ee* and 5:1 *dr*). IR (Neat): ν_{max} 3443, 2936, 2860, 1760, 1709, 1683, 1603, 1487, 1423, 1359, 1329, 1277, 1245, 1180, 1032, 1014, 874, 841, 758, and 574 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.60 (1H, d, J = 8.5 Hz), 7.42 (1H, d, J = 2.5 Hz), 7.15 (1H, dd, J = 8.5, 2.5 Hz), 3.88 (1H, s), 3.82 (3H, s), 2.99 (1H, d, J = 4.5 Hz), 2.61 (1H, quintet, J = 5.5 Hz), 2.41-2.35 (1H, m), 2.10 (3H, s), 2.04 (1H, td, J = 14.5, 4.5 Hz), 1.90 (1H, qd, J = 13.0, 4.0 Hz), 1.82-1.75 (1H, m), 1.64-1.59 (1H, m), 1.45-1.36 (1H, m), 1.35-1.26 (1H, m), 1.10 (1H, dq, J = 12.0, 4.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 205.6 (C, *C*=O), 204.1 (C, *C*=O), 194.9 (C, *C*=O), 160.0 (C), 133.6 (C), 131.5 (C), 124.8 (CH), 122.7 (CH), 110.1 (CH), 81.3 (C, *C*-OH), 65.1 (CH), 64.3 (C), 55.5 (CH_3), 34.8 (CH), 31.3 (CH_2), 30.1 (CH_3), 22.1 (CH_2), 20.1 (2xCH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}O_5H$ 329.1389; Found 329.1385.



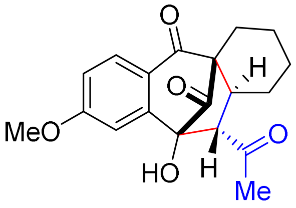
(+)-**72cb**
Major isomer

(4a*S*,10*S*,11*R*,11a*R*)-11-acetyl-10-hydroxy-7-methoxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(*2H*)-dione (82cb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 15.2% (10.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.59 min (major), t_R = 18.17 min (minor). IR (Neat): ν_{max} 3443, 2936, 2860, 1760, 1709, 1683, 1603, 1487, 1423, 1359, 1329, 1277, 1245, 1180, 1032, 1014, 874, 841, 758, and 574 cm^{-1}.^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.72 (1H, d, J = 8.5 Hz), 7.53 (1H, d, J = 3.0 Hz), 7.25 (1H, dd, J = 8.5, 3.0 Hz), 3.87 (3H, s), 3.51 (1H, s), 2.94 (1H, d, J = 11.0 Hz), 2.55 (1H, dt, J = 11.0, 3.0 Hz), 2.47-2.39 (1H, m), 2.38-2.33 (1H, s), 2.25 (3H, s), 1.88-1.78 (2H, m), 1.71-1.63 (1H, m), 1.56-1.55 (2H, m), 1.42 (1H, tq, J = 13.0, 4.5 Hz), 1.24 (1H, dq, J = 12.5, 3.5 Hz). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 204.9 (C, *C*=O), 204.1 (C, *C*=O), 196.2 (C, *C*=O), 159.9 (C), 140.2 (C), 132.0 (C), 123.1 (CH), 122.9 (CH), 110.1 (CH), 79.1 (C, *C*-OH), 65.4 (C), 63.6 (CH), 55.7 (CH$_3$), 43.0 (CH), 33.0 (CH$_3$), 27.3 (CH$_2$), 26.6 (CH$_2$), 26.3 (CH$_2$), 21.5 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{20}O_5H$ 329.1389; Found 329.1389.

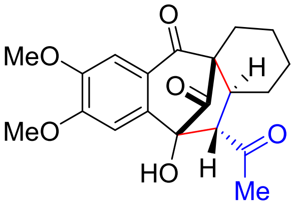


82cb
Minor isomer

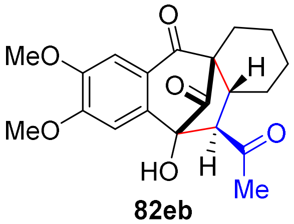
(4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-8-methoxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione ((+)-72db): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 88.3% (50.0+5.4 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 15.46 min (major), t_R = 24.62 min (minor) [For major isomer], t_R = 13.36 min (major), t_R = 15.12 min (minor) [For minor isomer]. $[\alpha]_D^{25}$ = +16.2° (*c* = 0.08, $CHCl_3$, 98.9% *ee* and 9:1 *dr*). IR (Neat): ν_{max} 3419, 2925, 2855, 1761, 1710, 1677, 1596, 1488, 1443, 1359, 1326, 1274, 1234, 1182, 1103, 1017, 756, and 573 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.96 (1H, d, J = 9.0 Hz), 7.16 (1H, d, J = 3.0 Hz), 6.91 (1H, dd, J = 9.0, 2.5 Hz), 3.87 (3H, s), 3.84 (1H, s), 2.99 (1H, d, J = 5.0 Hz), 2.64 (1H, quintet, J = 5.5 Hz), 2.43-2.37 (1H, m), 2.14 (3H, s), 2.04 (1H, td, J = 14.5, 4.5 Hz), 1.94-1.89 (1H, m), 1.83-1.76 (1H, m), 1.64-1.59 (1H, m), 1.45-1.35 (1H, m), 1.34-1.25 (1H, m), 1.09 (1H, dq, J = 12.0, 4.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 205.6 (C, *C*=O), 203.8 (C, *C*=O), 193.3 (C, *C*=O), 164.9 (C), 143.8 (C), 130.5 (CH), 123.5 (C), 115.0 (CH), 108.1 (CH), 81.6 (C, *C*-OH), 65.4 (CH), 63.9 (C), 55.7 (CH_3), 34.9 (CH), 31.6 (CH_2), 30.2 (CH_3), 22.2 (CH_2), 20.3 (CH_2), 20.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}O_5H$ 329.1389; Found 329.1384.


(+)-**72db**
Major isomer

(4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-7,8-dimethoxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[a,d][7]annulene-5,12(2*H*)-dione ((+)-72eb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid.


(+)-**72eb**
Major isomer

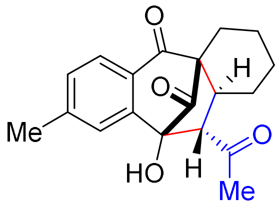
Yield: 64.7% (46.4 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 24.45 min (major), t_R = xx.xx min (minor). $[\alpha]_D^{25} = +53.0^o$ (*c* = 0.13, $CHCl_3$, >99% *ee* and 4.0:1 *dr*). IR (Neat): ν_{max} 3434, 2937, 2861, 2359, 2256, 1761, 1710, 1673, 1593, 1506, 1463, 1363, 1281, 1208, 1180, 1114, 1014, 910, 730 and 649 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.44 (1H, s), 7.15 (1H, s), 3.97 (3H, s), 3.91 (3H, s), 3.88 (1H, s), 2.99 (1H, d, *J* = 4.0 Hz), 2.62 (1H, quintet, *J* = 5.5 Hz), 2.45-2.39 (1H, m), 2.15 (3H, s), 2.05 (1H, td, *J* = 15.5, 4.0 Hz), 1.95-1.91 (1H, m), 1.84-1.78 (1H, m), 1.65-1.61 (1H, m), 1.46-1.27 (2H, m), 1.10 (1H, dq, *J* = 12.5, 4.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 205.0 (C, *C*=O), 203.7 (C, *C*=O), 193.6 (C, *C*=O), 154.7 (C), 149.6 (C), 136.1 (C), 123.6 (C), 108.99 (CH), 105.1 (CH), 81.3 (C, *C*-OH), 65.5 (CH), 64.0 (C), 56.4 (CH_3), 56.1 (CH_3), 35.0 (CH), 31.6 (CH_2), 30.2 (CH_3), 22.2 (CH_2), 20.3 (CH_2), 20.2 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}O_6H$ 359.1495; Found 359.1491.



82eb
Minor isomer

(4a*S*,10*S*,11*R*,11a*R*)-11-Acetyl-10-hydroxy-7,8-dimethoxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(*2H*)-dione (82eb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 15.3% (11.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.65 min (major), t_R = 15.57 min (minor). IR (Neat): ν_{max} 3434, 2937, 2861, 2359, 2256, 1761, 1710, 1673, 1593, 1506, 1463, 1363, 1281, 1208, 1180, 1114, 1014, 910, 730 and 649 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.51 (1H, s), 7.23 (1H, s), 4.03 (3H, s), 3.94 (3H, s), 3.65 (1H, s), 2.95 (1H, d, J = 10.5 Hz), 2.50 (1H, dt, J = 12.5, 2.5 Hz), 2.43 (1H, td, J = 13.5, 5.0 Hz), 2.39-2.35 (1H, m), 2.26 (3H, s), 1.88-1.77 (2H, m), 1.66 (2H, dt, J = 12.5, 4.5 Hz), 1.41 (1H, tq, J = 13.0, 4.5 Hz), 1.31-1.27 (1H, m). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 205.4 (C, *C*=O), 203.5 (C, *C*=O), 194.6 (C, *C*=O), 155.1 (C), 149.3 (C), 142.4 (C), 124.0 (C), 108.9 (CH), 103.0 (CH), 79.2 (C, *C*-OH), 65.0 (C), 63.6 (CH), 56.5 (CH$_3$), 56.2 (CH$_3$), 43.4 (CH), 33.0 (CH$_3$), 27.4 (CH$_2$), 26.6 (CH$_2$), 26.3 (CH$_2$), 21.5 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{22}O_6H$ 359.1495; Found 359.1499.

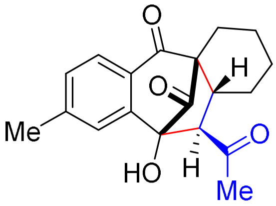
(4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-8-methyl-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[a,d][7]annulene-5,12(2*H*)-dione



(+)-**72fb**
Major isomer

((+)-72fb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 65.8% (41.1 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.99 min (major), t_R = 14.10 min (minor). $[\alpha]_D^{25}$ = +275.5° (c = 0.20, CHCl$_3$, 98.8% *ee* and 6:1 *dr*). IR (Neat): ν_{max} 3442, 2925, 2855, 2341, 2360, 1760, 1708, 1680, 1602, 1448, 1360, 1281, 1256, 1231, 1179, 1007, 910, 732, 443 and 411 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.89 (1H, dd, J = 7.5, 1.5 Hz), 7.52

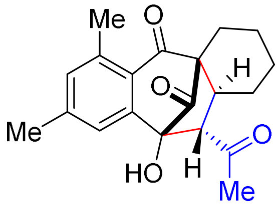
(1H, s), 7.23 (1H, d, *J* = 8.0 Hz), 3.82 (1H, s), 3.01 (1H, dd, *J* = 4.5, 2.0 Hz), 2.66-2.62 (1H, m), 2.43 (3H, s), 2.41-2.37 (1H, m), 3.13 (3H, s), 2.08-2.03 (1H, m), 1.93-1.90 (1H, m), 1.82-1.78 (1H, m), 1.67-1.58 (1H, m), 1.46-1.38 (1H, m), 1.35-1.29 (1H, m), 1.11 (1H, q, *J* = 13.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 205.9 (C, *C*=O), 203.9 (C, *C*=O), 194.5 (C, *C*=O), 146.1 (C), 141.3 (C), 130.0 (CH), 128.1 (CH), 127.9 (C), 123.7 (CH), 81.5 (C, *C*-OH), 65.3 (CH), 64.2 (C), 34.8 (CH), 31.5 (CH_2), 30.2 (CH_3), 22.1 (CH_2), 22.1 (CH_2), 20.2 (CH_2), 20.0 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}O_4H$ 313.1440; Found 313.1446.



82fb
Minor isomer

(4a*S*,10*S*,11*R*,11a*R*)-11-acetyl-10-hydroxy-8-methyl-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione (82fb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 11.2% (7.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.42 min (major), t_R = 9.36 min (minor). IR (Neat): ν_{max} 3442, 2925, 2855, 2341, 2360, 1760, 1708, 1680, 1602, 1448, 1360, 1281, 1256, 1231, 1179, 1007, 910, 732, 443 and 411 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) : δ 7.96 (1H, d, *J* = 8.0 Hz), 7.60 (1H, br s), 7.28-7.26 (1H, m), 3.54 (1H, s), 2.96 (1H, d, *J* = 10.8 Hz), 2.58-2.53 (1H, m), 2.48 (3H, s), 2.42 (1H, td *J* = 13.2, 4.8 Hz), 2.38-2.33 (1H, m), 2.26 (3H, s), 1.88-1.75 (2H, m), 1.71-1.62 (1H, m), 1.56 (1H, qd, *J* = 12.4, 3.2 Hz), 1.41 (1H, qt, *J* = 13.2, 4.4 Hz), 1.30-1.23 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, DEPT-135): δ 204.7 (C, *C*=O), 204.5 (C, *C*=O), 195.8 (C, *C*=O), 147.4 (C), 146.7 (C), 129.4 (CH), 128.6 (C), 128.0 (CH), 121.5 (CH), 79.2 (C, *C*-OH), 65.2 (C), 63.4 (CH), 43.1 (CH), 32.9 (CH_3), 27.2 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 22.1 (CH_3), 21.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}O_4H$ 313.1440; Found 313.1445.

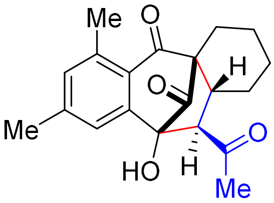
(4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-6,8-dimethyl-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione ((+)-72gb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 80.4% (52.5 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.89 min (major), t_R = 8.30 min (minor). $[\alpha]_D^{25}$ = +6.6° (*c* = 0.07, $CHCl_3$, 98.3% *ee* and 8:1 *dr*). IR (Neat): ν_{max} 3460, 3021, 2928, 1759, 1711, 1679, 1602, 1445, 1359, 1215, 1008, 909, 753 and 672 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 (1H, s), 7.01 (1H, s), 3.84 (1H, s), 2.99 (1H, d, *J* = 4.0 Hz), 2.66-2.61 (1H, m), 2.58 (3H, s), 2.39-2.32 (4H, m), 2.07 (3H, s), 2.01 (1H, td, *J* = 14.0, 4.0 Hz), 1.89 (1H, qd, *J* = 13.0, 3.5 Hz), 1.77 (1H, td, *J* = 13.5, 5.0 Hz), 1.62 (1H, td, *J* = 13.0, 4.0 Hz), 1.43-1.27 (2H, m), 1.07 (1H, dq, *J* = 12.0, 3.5 Hz. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 206.1 (C, *C*=O), 204.2 (C, *C*=O), 195.8 (C, *C*=O), 144.1 (C), 142.6 (C), 142.6 (C), 133.8 (CH), 126.2 (C), 121.7 (CH), 81.7 (C, *C*-OH), 65.4 (CH), 65.2 (C), 35.3 (CH), 31.7 (CH_2), 30.2 (CH_3), 22.8 (CH_3),



(+)-**72gb**
Major isomer

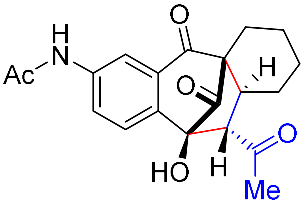
22.5 (CH_2), 21.8 (CH_3), 20.6 (CH_2), 20.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}O_4H$ 327.1596; Found 327.1591.

(4a*S*,10*S*,11*R*,11a*R*)-11-Acetyl-10-hydroxy-6,8-dimethyl-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dioneand (82gb): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 10.0% (6.5 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.79 min (major), t_R = 7.58 min (minor). IR (Neat): ν_{max} 3460, 3021, 2928, 1759, 1711, 1679, 1602, 1445, 1359, 1215, 1008, 909, 753 and 672 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (1H, s), 7.07 (1H, s), 3.48 (1H, s), 2.97 (1H, d, *J* = 11.0 Hz), 2.65 (3H, s), 2.51 (1H, dt, *J* = 12.0, 3.0 Hz), 2.43 (3H, s), 2.30 (1H, br dd, *J* = 14.0, 3.5 Hz), 2.25 (3H, s), 1.88-1.84 (1H, m), 1.79-1.74 (1H, m), 1.66 (1H, dt, *J* = 13.5, 5.5 Hz), 1.54-1.53 (1H, m), 1.41 (1H, td, *J* = 13.0, 4.5 Hz), 1.30 (2H, dq, *J* = 12.5, 3.5 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135) : δ 204.7 (C, *C*=O), 204.7 (C, *C*=O), 197.4 (C, *C*=O), 148.6 (C), 144.7 (C), 142.7 (C), 133.3 (CH), 126.8 (C), 119.5 (CH), 79.1 (C, *C*-OH), 65.1 (C), 63.3 (CH), 42.9 (CH), 32.9 (CH_3), 26.6 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 22.9 (CH_3), 21.9 (CH_3), 21.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}O_4H$ 327.1596; Found 327.1595.



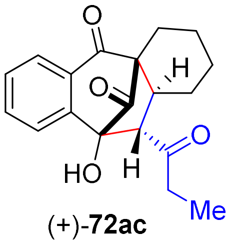
82gb
Minor isomer

***N*-((4a*S*,10*S*,11*S*,11a*S*)-11-Acetyl-10-hydroxy-5,12-dioxo-1,2,3,4,5,10,11,11a-octahydro-4a,10-methanodibenzo[*a,d*][7]annulen-7-yl)acetamide ((+)-72hb):** The compound was prepared following procedure **4a**, purified by column chromatography



(+)-**72hb**
Major isomer

using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 81.2% (57.7 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 23.57 min (major), t_R = 31.18 min (minor). $[\alpha]_D^{25}$ = +89.6° (*c* = 0.09, $CHCl_3$, 96.4% *ee* and >20:1 *dr*). IR (Neat): ν_{max} 3346, 2933, 2859, 1763, 1683, 1591, 1537, 1487, 1413, 1368, 1324, 1297, 1260, 910, 731 and 573 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (1H, dd, *J* = 8.5, 2.0 Hz), 7.73 (1H, s), 7.67 (1H, d, *J* = 2.5 Hz), 7.63 (1H, d, *J* = 8.5 Hz), 4.03 (1H, s), 3.01 (1H, d, *J* = 4.5 Hz), 2.60 (1H, quintet, *J* = 6.0 Hz), 2.38-2.32 (1H, m), 2.19 (3H, s), 2.11 (3H, s), 2.03 (1H, td, *J* = 14.5, 4.5 Hz), 1.91 (1H, qd, *J* = 13.0, 5.0 Hz), 1.81-1.77 (1H, m), 1.65-1.59 (1H, m), 1.45-1.38 (1H, m), 1.34-1.26 (1H, m), 1.12 (1H, dq, *J* = 12.0, 4.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 205.6 (C, *C*=O), 204.4 (C, *C*=O), 194.7 (C, *C*=O), 168.9 (C, N-*C*=O), 138.9 (C), 136.3 (C), 130.6 (C), 126.0 (CH), 124.3 (CH), 117.7 (CH), 81.5 (C, *C*-OH), 64.9 (CH), 64.5 (C), 34.8 (CH), 31.3 (CH_2), 30.3 (CH_3), 24.5 (CH_3), 22.1 (CH_2), 20.2 (CH_2), 20.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{21}NO_5H$ 356.1498; Found 356.1494.

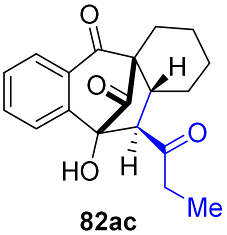


(+)-**72ac**
Major isomer

(4a*S*,10*S*,11*S*,11a*S*)-10-Hydroxy-11-propionyl-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[a,d][7]annulene-5,12(2*H*)-dione ((+)-72ac): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9 to 2:8), and isolated as a semi-solid. Yield: 34.9% (21.8 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.87 min (major), t_R = 12.64 min (minor). $[\alpha]_D^{25}$ = +2.8° (c = 0.07, $CHCl_3$, 98.5% *ee* and 1:1 *dr*). IR (Neat): ν_{max} 3445, 2927, 2854, 1761, 1711, 1683, 1597, 1455, 1283, 1259, ,1226, 1079, 963, 766, 718 and 493 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.00 (1H, dd, J = 7.6, 0.8 Hz), 7.68 (1H, dd, J = 8.0, 0.8), 7.61 (1H, dt, J = 7.2, 1.6 Hz), 7.43 (1H, dt, J = 7.6, 1.2 Hz), 3.78 (1H, s), 3.02 (1H, d, J = 4.4 Hz), 2.69-2.59 (2H, m), 2.45-2.31 (2H, m), 2.06 (1H, td, J = 14.4, 4.0 Hz), 1.95-1.88 (1H, m), 1.84-1.77 (1H, m), 1.66-1.60 (2H, m), 1.47-1.39 (1H, m), 1.14 (1H, dq, J = 11.6, 3.6 Hz), 0.76 (3H, t, J = 7.2 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, DEPT-135): δ 206.7 (C, *C*=O), 205.8 (C, *C*=O), 195.0 (C, *C*=O), 141.4 (C), 134.7 (CH), 130.4 (C), 130.4 (CH), 128.9 (CH), 123.2 (CH), 81.7 (C, *C*-OH), 64.5 (C), 64.1 (CH), 36.4 (CH_2), 35.0 (CH), 31.4 (CH_2), 22.2 (CH_2), 20.2 (CH_2), 20.1 (CH_2), 7.1 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}O_4H$ 313.1440; Found 313.1436.

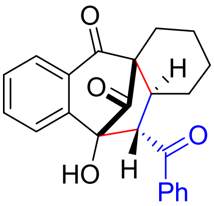
(4a*S*,10*S*,11*R*,11a*R*)-10-hydroxy-11-propionyl-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione (82ac): The compound was prepared following procedure **4a**, purified by column chromatography using

EtOAc/hexanes (1:9 to 2:8), and isolated as a semi-solid. Yield: 34.9% (21.8 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 28.00 min (major), t_R = 30.71 min (minor). IR (Neat): ν_{max} 3445, 2927, 2854, 1761, 1711, 1683, 1597, 1455, 1283, 1259, ,1226, 1079, 963, 766, 718 and 493 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.06 (1H, dd, *J* = 8.0, 1.2 Hz), 7.80 (1H, dd, *J* = 8.0, 0.8), 7.69 (1H, dt, *J* = 7.6, 1.6 Hz), 7.47 (1H, dt, *J* = 8.0, 1.2 Hz), 3.53 (1H, s), 2.98 (1H, d, *J* = 10.8 Hz), 2.70-2.60 (2H, m), 2.44-2.29 (2H, m), 1.87-1.73 (2H, m), 1.69 (1H, dt, *J* = 4.8 Hz), 1.56-1.52 (1H, m), 1.47-1.35 (1H, m), 1.30-1.20 (2H, m), 1.08 (3H, t, *J* = 7.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$, DEPT-135): δ 207.5 (C, *C*=O), 204.4 (C, *C*=O), 196.3 (C, *C*=O), 147.4 (C), 135.1 (CH), 130.8 (C), 128.4 (CH), 127.9 (CH), 121.4 (CH), 79.5 (C, *C*-OH), 65.5 (C), 62.6 (CH), 43.2 (CH), 39.3 (CH$_2$), 27.2 (CH$_2$), 26.5 (CH$_2$), 26.2 (CH$_2$), 21.4 (CH$_2$), 7.3 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{20}O_4H$ 313.1440; Found 313.1437.



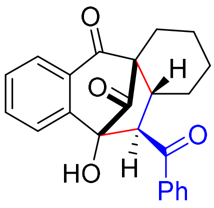
82ac
Minor isomer

(4a*S*,10*S*,11*S*,11a*S*)-11-Benzoyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione ((-)-72ad): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 62.4% (45 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm),



(-)-**72ad**
Major isomer

t_R = 17.06 min (major), t_R = 22.68 min (minor). $[\alpha]_D^{25}$ = –3.9° (c = 0.08, $CHCl_3$, 74.1% *ee* and 3.5:1 *dr*). IR (Neat): ν_{max} 3432, 3064, 2926, 2854, 1761, 1680, 1596, 1448, 1281, 1258, 1232, 1089, 1002, 798, 765, 733, 688, 475 and 413 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.99 (1H, dd, J = 7.5, 1.2 Hz), 7.89-7.87 (2H, m), 7.58-7.55 (1H, m), 7.42 (2H, t J = 7.5 Hz), 7.35-7.28 (2H, m), 7.10-7.08 (1H, m), 3.85 (1H, d, J = 3.0 Hz), 3.81 (1H, s), 2.92-2.88 (1H, m), 2.52-2.46 (1H, m), 2.13 (1H, td, J = 14.0, 3.0 Hz), 2.02-1.99 (1H, m), 1.86-1.82 (1H, m), 1.73-1.69 (1H, m), 1.52-1.43 (1H, m), 1.39-1.31 (1H, m), 1.23-1.20 (1H, m). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 206.1 (C, *C*=O), 196.8 (C, *C*=O), 195.4 (C, *C*=O), 141.2 (C), 136.9 (C), 134.2 (CH), 133.4 (CH), 130.7 (C), 129.0 (2xCH), 128.7 (CH), 128.3 (2xCH), 127.4 (CH), 123.5 (CH), 81.8 (C, *C*-OH), 64.9 (C), 60.3 (CH), 36.6 (CH), 31.9 (CH_2), 22.9 (CH_2), 20.8 (CH_2), 20.6 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{20}O_4H$ 361.1440; Found 361.1440

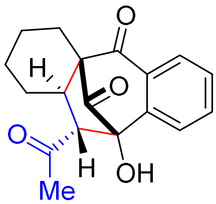


82ad
Minor isomer

(4a*S*,10*S*,11*R*,11a*R*)-11-Benzoyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(*2H*)-dione (82ad): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 17.2% (12.4 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 44.01 min (major), t_R = 13.71 min (minor). IR (Neat): ν_{max} 3432, 3064, 2926, 2854, 1761, 1680, 1596, 1448, 1281, 1258, 1232, 1089, 1002, 798, 765, 730, 688, 475 and 413 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.13 (1H, d, J = 7.5 Hz), 7.81 (3H, t, J =

7.5 Hz), 7.74 (1H, t, *J* = 7.5 Hz), 7.59 (1H, t, *J* = 7.0 Hz), 7.54 (1H, t, *J* = 7.5 Hz), 7.46 (2H, t, *J* = 7.5 Hz), 3.75 (1H, d, *J* = 11.0 Hz), 3.59 (1H, s), 2.84 (1H, dt, *J* = 12.0, 2.5 Hz), 2.51-2.38 (2H, m), 1.88-1.73 (3H, m), 1.57 (1H, dd, *J* = 12.0, 2.5 Hz), 1.43 (1H, tq, *J* = 13.5, 4.5 Hz), 1.31 (1H, dq, *J* = 12.0, 3.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 204.5 (C, *C*=O), 196.8 (C, *C*=O), 196.5 (C, *C*=O), 146.9 (C), 137.4 (C), 135.0 (CH), 133.7 (CH), 131.0 (C), 128.7 (2xCH), 128.6 (CH), 128.5 (2xCH), 128.0 (CH), 121.9 (CH), 79.9 (C, *C*-OH), 65.5 (C), 58.7 (CH), 43.9 (CH), 27.2 (CH_2), 26.7(CH_2), 26.3 (CH_2), 21.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{20}O_4H$ 361.1440; Found 361.1440

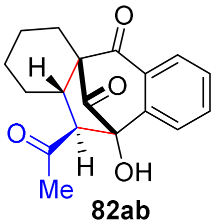
((4a*R*,10*R*,11*R*,11a*R*)-11-Acetyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methano dibenzo[*a,d*][7]annulene-5,12(2*H*)-dione ((-)-72ab): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 65.3% (39 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.49 min (major), t_R = xx.xx min (minor). $[\alpha]_D^{25}$ = −135.17° (*c* = 0.05, $CHCl_3$, 99.0% *ee* and 3:1 *dr*). IR (Neat): ν_{max} 3455, 2930, 2856, 1765, 1712, 1679, 1596, 1453, 1357, 1329, 1300, 1276, 1231, 1172, 1085, 1037, 971, 953, 782, and 735 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.00 (1H, dd, *J* = 8.0, 1.0 Hz), 7.73 (1H, d, *J* = 7.0 Hz), 7.63 (1H, dt, *J* = 7.5, 1.5 Hz), 7.44 (1H, dt, *J* = 7.5, 1.0 Hz), 3.79 (1H, s), 3.02 (1H, d, *J* = 4.5 Hz), 2.65 (1H, quintate, *J* = 5.5 Hz), 2.44-2.37 (1H, m), 2.11 (3H, s), 2.06 (1H, td, *J* = 14.5,



(-)-**72ab**
Major isomer

4.5 Hz), 1.92 (1H, qd, J = 13.0, 4.0 Hz), 1.84-1.77 (1H, m), 1.66-1.61 (1H, m), 1.47-1.38 (1H, m), 1.36-1.28 (1H, m), 1.12 (1H, dq, J = 12.0, 4.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, DEPT-135): δ 205.7 (C, *C*=O), 203.9 (C, *C*=O), 194.9 (C, *C*=O), 141.2 (C), 134.8 (CH), 130.2 (C), 129.0 (CH), 128.0 (CH), 123.4 (CH), 81.5 (C, *C*-OH), 65.3 (CH), 64.4 (C), 34.8 (CH), 31.4 (CH_2), 30.2 (CH_3), 22.1 (CH_2), 20.2 (CH_2), 20.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{18}O_4Na$ 321.1103; Found 321.1103.

(4a*R*,10*R*,11*S*,11a*S*)-11-acetyl-10-hydroxy-1,3,4,10,11,11a-hexahydro-4a,10-methanodibenzo[*a,d*][7]annulene-5,12(2*H*)-dione (82ab): The compound was prepared following procedure **4a**, purified by column chromatography using EtOAc/hexanes (1:9), and isolated as a semi-solid. Yield: 21.8% (13.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.47 min (major), t_R = 9.81 min (minor). IR (Neat): ν_{max} 3455, 2930, 2856, 1765, 1712, 1679, 1596, 1453, 1357, 1329, 1300, 1276, 1231, 1172, 1085, 1037, 971, 953, 782, and 735 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.06 (1H, d, J = 7.5 Hz), 7.82 (1H, d, J = 7.5 Hz), 7.70 (1H, t, J = 7.5 Hz), 7.48 (1H, t, J = 7.5 Hz), 3.58 (1H, s), 2.98 (1H, d, J = 10.5 Hz), 2.58 (1H, dt, J = 12.5, 2.5 Hz), 2.47-2.34 (2H, m), 2.26 (3H, s), 1.87-1.77 (2H, m), 1.71-1.64 (1H, m), 1.58-1.55 (1H, m), 1.41 (1H, tq, J = 7.5, 4.5 Hz), 1.25 (1H, dq, J = 12.0, 3.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 204.6 (C, *C*=O), 204.4 (C, *C*=O), 196.3 (C, *C*=O), 147.4 (C), 135.2 (CH), 130.8 (C), 128.5 (CH), 127.9 (CH), 121.3 (CH), 79.2 (C, *C*-OH), 65.4 (C), 63.4 (CH), 42.9 (CH), 32.9 (CH_3),



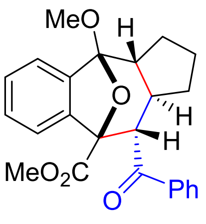
82ab
Minor Isomer

27.2 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 21.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{18}O_4Na$ 321.1103; Found 321.1103.

4c. General Procedures for Synthetic Transformation of Product 71ad into 84ad:

To a 25 mL of round bottom flask equipped with a magnetic stirring bar were added 0.2 mmol of **71ad** and 2 mL of methanol. Then, 0.4 mmol of K_2CO_3 was added in two portions with 0.5 h time intervals and the resulting mixture was allowed to stir at RT. After complete consumption of **71ad**, as monitored by TLC, methanol was removed by rotary evaporation. To this crude reaction mixture was added acetone (0.1 M), dimethyl sulfate (5 equiv.) and K_2CO_3 (5 equiv.) and the resulting mixture was allowed to stir at 60 °C for 12 h. Next, the reaction mixture was allowed to cool to RT and then the solvent was removed by rotary evaporation. The resulting product mixture was partitioned between aqueous and ethyl acetate layers and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product (-)-**84ad** was obtained after column chromatography purification using ethyl acetate/hexanes as an eluent system.

Methyl (3a*R*,4*S*,9*R*,10*S*,10a*R*)-10-benzoyl-4-methoxy-2,3,3a,4,10,10a-hexahydro-4,9-epoxybenzo[*f*]azulene-9(*1H*)-carboxylate ((-)-84ad):



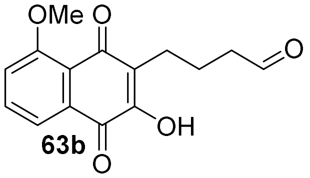
(-)-**84ad**

Prepared by following the procedure **4c** and purified by column chromatography using EtOAc/hexane and isolated as white semi-solid; Yield: 40% (31.4 mg). IR (Neat): ν_{max} 2947, 2872, 1767, 1728, 1685, 1447, 1311, 1236, 1212, 1171, 1111, 1020, 1006, 939, 754, 733 and 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (2H, dd, *J* = 8.0, 1.0 Hz), 7.56 (1H, tt, *J* = 7.5, 1.0 Hz), 7.46 (2H, t, *J* = 8.0 Hz), 7.44-7.40 (3H, m), 7.33-7.31 (1H, m), 3.83 (3H, s), 3.46 (3H, s), 2.58-2.55 (1H, m), 2.33-2.31 (1H, m), 1.89-1.82 (1H, m), 1.69-1.60 (2H, m), 1.34-1.29 (2H, m), 1.21-1.13 (1H, m), -0.21 to -0.29 (1H, m). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, DEPT-135): δ 199.6 (C, *C*=O), 171.1 (C, *C*=O), 142.7 (C), 138.7 (C), 135.7 (C), 133.0 (CH), 129.3 (CH), 128.6 (2xCH), 128.5 (3xCH), 123.6 (CH), 121.0 (CH), 111.6 (C, *O-C-OH*), 83.6 (C, *C-O*), 52.6 (CH), 51.1 (CH), 50.1 (CH), 41.73 (CH_3), 41.68 (CH_3), 32.7 (CH_2), 24.8 (CH_2), 24.1 (CH_2). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{24}O_5H$ 393.1702; Found 393.1703.

4d. Organocatalytic Reductive Coupling of Dialdehydes with 2-Hydroxy-1,4-naphthoquinone Derivatives:

To a 25 mL of round bottom flask equipped with a magnetic stirring bar were added 0.6 mmol of (*S*)-proline, 6.0 mmol of dialdehydes and 10.0 mL of anhydrous DCM. Then, 3.3 mmol of Hantzsch ester and 3.0 mmol of 2-hydroxy-1,4-naphthoquinone derivatives were added sequentially to a well stirred solution and the resulting mixture was allowed to stir for overnight. The solvent was removed under reduced pressure, the solid reaction mixture was dissolved in hexanes and the solvent was decanted and dried. Then, the solid product mixture was redissolved in 5-10% $CHCl_3$/hexanes mixtures and the solvent was decanted and dried. This process was repeated for 3-4 times to give the product with 80% purity. Further purification was carried out by passing the compound through short silica gel column using $CHCl_3$ as an eluent. The pure coupling products **63a-h** and **64a-h** were obtained upto 41% yields.

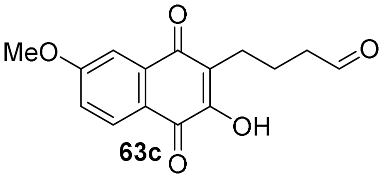
4-(3-hydroxy-8-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal (63b):



63b

The compound was prepared following procedure **4d**, purified by the column chromatography using EtOAc/hexane (2:8 to 2.5:7.5), and isolated as a yellow semi-solid. Yield: 10.0% (82.3 mg). IR (Neat): ν_{max} 3306, 2925, 2853, 1717, 1642, 1585, 1472, 1442, 1377, 1345, 1264, 1183, 1071, 1017, 908, 732 and 703 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.77 (1H, t, J = 1.5 Hz), 7.76 (1H, dd, J = 7.5, 1.0 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.34 (1H, d, J = 8.0 Hz), 7.19 (1H, s), 4.00 (3H, s), 2.63 (2H, t, J = 7.0 Hz), 2.49 (2H, dt, J = 7.5, 1.5 Hz), 1.89 (2H, quin, J = 7.5 Hz). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 202.4 (HC, H-*C*=O), 184.3 (C, *C*=O), 181.5 (C, *C*=O), 159.7 (C, *C*-OH), 151.6 (C), 134.1 (CH), 131.6 (C), 124.7 (C), 119.8 (C), 119.5 (CH), 119.1 (CH), 56.5 (CH$_3$), 43.5 (CH$_2$), 22.7 (CH$_2$), 20.7 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{14}O_5H$ 275.0919; Found 275.0915.

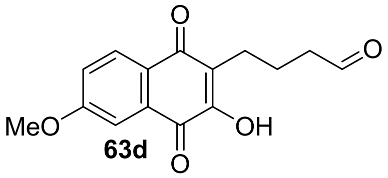
4-(3-hydroxy-7-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal (63c): The



63c

compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2:8), and isolated as a yellow solid. Mp: 130-135 °C. Yield: 26.8% (220.5 mg). IR (Neat): ν_{max} 3334, 2937, 2360, 1721, 1637, 1581, 1492, 1435, 1378, 1336, 1293, 1244, 1198, 1083, 1013, 985, 912, 843, 765, 748, 682, 619 and 597 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.79 (1H, br s), 8.03 (1H, d, J = 8.5 Hz), 7.58 (1H, d, J = 2.5 Hz), 7.50 (1H, br s), 7.13 (1H, dd, J = 8.5, 2.0 Hz), 3.96 (3H, s), 2.64 (2H, t, J = 7.5 Hz), 2.50 (2H, t, J = 7.5 Hz), 1.91 (2H, quintet, *J* = 7.5 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): *δ* 202.1 (HC, H-*C*=O), 184.5 (C, *C*=O), 179.9 (C, *C*=O), 165.3 (C, *C*-OH), 153.7 (C), 135.4 (C), 128.8 (CH), 122.6 (C), 122.3 (C), 119.1 (CH), 111.0 (CH), 56.0 (CH_3), 43.4 (CH_2), 22.5 (CH_2), 20.6 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}O_5H$ 275.0919; Found 275.0914.

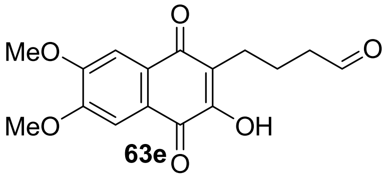
4-(3-hydroxy-6-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal (63d):



63d

The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane 1.5:8.5 to 2:8), and isolated as a yellow solid. Mp: 85-87 °C. Yield: 27.0% (222.1 mg). IR (Neat): ν_{max} 3337, 2939, 2843, 2719, 1717, 1668, 1640, 1593, 1493, 1454, 1437, 1364, 1350, 1326, 1278, 1233, 1200, 1172, 1085, 1020, 895, 881, 849, 751, 735 and 691 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): *δ* 9.79 (1H, br s), 8.05 (1H, d, *J* = 9.0 Hz), 7.52 (1H, d, *J* = 2.5 Hz), 7.29 (1H, br s), 7.21 (1H, dd, *J* = 8.5, 2.0 Hz), 3.94 (3H, s), 2.64 (2H, t, *J* = 7.5 Hz), 2.51 (2H, t, *J* = 7.5 Hz), 1.91 (2H, quintet, *J* = 7.5 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): *δ* 202.2 (HC, H-*C*=O), 183.9 (C, *C*=O), 181.4 (C, *C*=O), 163.4 (C, *C*-OH), 153.1 (C), 131.1 (C), 129.1 (CH), 126.1 (C), 122.9 (C), 120.9 (CH), 109.9 (CH), 55.9 (CH_3), 43.4 (CH_2), 22.5 (CH_2), 20.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}O_5H$ 275.0919; Found 275.0913.

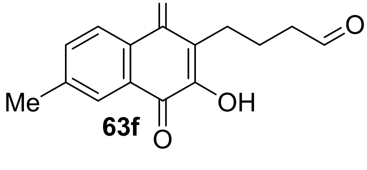
4-(3-hydroxy-6,7-dimethoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal (63e):



63e

The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (3:7 to 4:6), and isolated as a yellow semi-solid. Yield: 16.3% (148.8 mg). IR (Neat): ν_{max} 3263, 2948, 2926, 2843, 1713, 1655, 1642, 1577, 1505, 1458, 1339, 1301, 1280, 1264, 1202, 1180, 1120, 1092, 1016, 970, 887, 778, 752, 679, 638, 498, 450 and 422 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.78 (1H, t, *J* = 1.6 Hz), 7.54 (1H, s), 7.47 (1H, s), 7.39 (1H, br s), 4.02 (3H, s), 4.00 (3H, s), 2.61 (2H, t, *J* = 7.6 Hz), 2.49 (2H, dt, *J* = 7.2, 1.6 Hz), 1.89 (2H, quintet, *J* = 7.6 Hz). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$, DEPT-135): δ 202.3 (HC, H-*C*=O), 184.3 (C, *C*=O), 180.5 (C, *C*=O), 154.4 (C, *C*-OH), 153.2 (C), 152.6 (C), 128.0 (C), 123.4 (C), 121.8 (C), 108.7 (CH), 107.6 (CH), 56.5 (CH$_3$), 56.5 (CH$_3$), 43.4 (CH$_2$), 22.4 (CH$_2$), 20.7 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{16}O_6H$ 305.1025; Found 305.1019.

4-(3-hydroxy-6-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal (63f): The compound was prepared following procedure **4d**, purified by the column

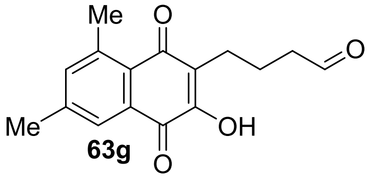


63f

chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as a yellow solid. Yield: 35.5% (275.0 mg). IR (Neat): ν_{max} 3166, 2923, 2852, 1718, 1701, 1640, 1599, 1437, 1346, 1276, 1230, 1183, 1162, 1085, 1032, 934, 847, 743, 692, 567 and 452 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.79 (1H, t, *J* = 1.5 Hz), 7.99 (1H, d, *J* = 8.0 Hz), 7.86 (1H, s), 7.55 (1H, dd, *J* = 8.0, 0.5 Hz), 7.48 (1H, br s), 2.65 (2H, t, *J* = 7.5

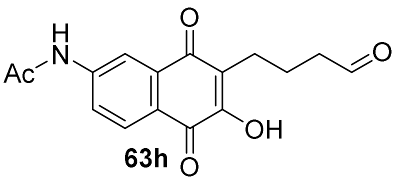
Hz), 2.52 (2H, dt, *J* = 7.5, 1.5 Hz), 2.48 (3H, s), 1.91 (2H, quintet, *J* = 7.5 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 202.4 (HC, H-*C*=O), 184.6 (C, *C*=O), 181.5 (C, *C*=O), 153.3 (C, *C*-OH), 144.0 (C), 135.6 (CH), 130.5 (C), 129.3 (C), 126.9 (CH), 126.6 (CH), 122.9 (C), 43.4 (CH_2), 22.5 (CH_2), 21.6 (CH_3), 20.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}O_4H$ 259.0970; Found 259.0974.

4-(3-hydroxy-6,8-dimethyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanal (63g): The compound was prepared following procedure **4d**, purified by the column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as a yellow semi-solid. Yield: 30.0% (245.0 mg). IR (Neat): ν_{max} 3354, 3053, 2967, 2927, 1719, 1661, 1643, 1601, 1371, 1341, 1290, 1264, 1190, 1105, 871, 733 and 702 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 9.79 (1H, t, *J* = 2.0 Hz), 7.83 (1H, s), 7.34 (1H, s), 7.24 (1H, s), 2.71 (3H, s), 2.63 (2H, t, *J* = 7.5 Hz), 2.51 (2H, dt, *J* = 7.5, 1.0 Hz), 2.43 (3H, s), 1.89 (2H, quintet, *J* = 7.5 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 202.3 (HC, H-*C*=O), 186.6 (C, *C*=O), 181.9 (C, *C*=O), 152.0 (C, *C*-OH), 142.8 (C), 141.7 (C), 139.9 (CH), 130.7 (C), 127.7 (C), 125.7 (CH), 123.9 (C), 43.5 (CH_2), 22.9 (CH_2), 22.7 (CH_3), 21.3 (CH_2), 20.8 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}O_4H$ 273.1127; Found 273.1122.



63g

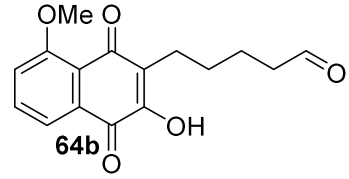
***N*-(6-hydroxy-5,8-dioxo-7-(4-oxobutyl)-5,8-dihydronaphthalen-2-yl)acetamide (63h):** The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as



63h

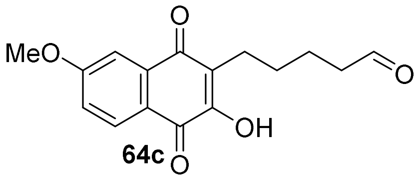
a yellow semi-solid. Yield: 11.0% (100 mg). IR (Neat): ν_{max} 3342, 2919, 2856, 1690, 1650, 1633, 1582, 1535, 1424, 1329, 1251, 1079, 1016, 802, 748, 623 and 539 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.78 (1H, t, *J* = 1.5 Hz), 8.26 (1H, d, *J* = 9.0 Hz), 8.07 (1H, d, *J* = 8.5 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 7.55 (1H, s), 7.44 (1H, s), 2.64 (2H, t, *J* = 7.5 Hz), 2.50 (2H, dt, *J* = 7.5, 1.5 Hz), 2.26 (3H, s), 1.90 (2H, quintet, *J* = 7.5 Hz). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 202.2 (HC, H-*C*=O), 184.0 (C, *C*=O), 179.8 (C, *C*=O), 168.5 (C, N-*C*=O), 153.7 (C, *C*-OH), 144.0 (C), 134.2 (C), 128.4 (CH), 124.8 (C), 122.7 (C), 122.7 (CH), 116.6 (CH), 43.4 (CH$_2$), 24.9 (CH$_3$), 22.5 (CH$_2$), 20.6 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M - H]$^+$ Calcd for $C_{16}H_{15}NO_5H$ 302.1028; Found 300.0804.

5-(3-hydroxy-8-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal (64b): The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as a yellow semi-solid. Yield: 9.8% (84.8 mg). IR (Neat): ν_{max} 2950, 2726, 2253, 1719, 1458, 1442, 1401, 1389, 1098, 1021, 907, 725, 647 and 517 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.76 (1H, t, *J* = 2.0 Hz), 7.76 (1H, d, *J* = 6.5 Hz), 7.62 (1H, t, *J* = 8.0 Hz), 7.33 (1H, d, *J* = 8.5 Hz), 7.10 (1H, s), 4.00 (3H, s), 2.60 (2H, t, *J* = 7.5 Hz), 2.47 (2H, dt, *J* = 7.5, 1.5 Hz), 1.71 (2H, quintet, *J* = 7.0 Hz), 1.59 (2H, quintet, *J* = 8.0 Hz). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 202.6 (HC, H-*C*=O), 184.4 (C, *C*=O), 181.6 (C, *C*=O), 159.7 (C, *C*-OH), 151.4 (C), 134.0 (CH), 131.6 (C), 125.3 (C), 119.8 (C), 119.5 (CH), 119.0 (CH), 56.5 (CH$_3$), 43.6 (CH$_3$), 27.7 (CH$_2$), 23.1 (CH$_2$), 22.0 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{16}O_5H$ 289.1076; Found 289.1073.



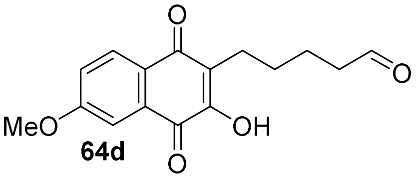
64b

5-(3-hydroxy-7-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal (64c):


64c

The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as a yellow solid. Mp: 102-125 °C. Yield: 29.0% (250.8 mg). IR (Neat): ν_{max} 3340, 2961, 2934, 2843, 2359, 2331, 1719, 1639, 1582, 1433, 1343, 1242, 1090, 966, 767, 750, 685 and 599 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.76 (1H, t, J = 1.5 Hz), 8.01 (1H, d, J = 8.5 Hz), 7.57 (1H, d, J = 2.5 Hz), 7.12 (1H, dd, J = 8.5, 3.0 Hz), 3.95 (3H, s), 2.60 (2H, t, J = 7.5 Hz), 2.48 (2H, dt, J = 7.0, 1.5 Hz), 1.71 (2H, quintet, J = 7.0 Hz), 1.59 (2H, quintet, J = 6.5 Hz). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 202.6 (HC, H-*C*=O), 184.6 (C, *C*=O), 180.0 (C, *C*=O), 165.2 (C, *C*-OH), 153.5 (C), 135.4 (C), 128.8 (CH), 122.9 (C), 122.6 (C), 119.0 (CH), 110.9 (CH), 55.9 (CH$_3$), 43.6 (CH$_2$), 27.6 (CH$_2$), 22.8 (CH$_2$), 21.9 (CH$_2$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{16}O_5H$ 289.1076; Found 289.1071.

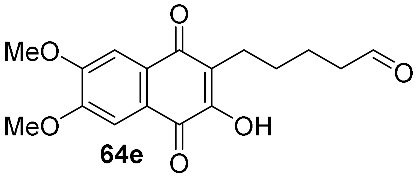
5-(3-hydroxy-6-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal (64d):


64d

The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and isolated as a yellow solid. Mp: 105-107 °C. Yield: 26.3% (227.4 mg). IR (Neat): ν_{max} 3231, 2933, 2836, 2747, 2359, 1709, 1664, 1643, 1590, 1493, 1458, 1362, 1330, 1279, 1231, 1192, 1167, 1099, 1025, 933, 848, 752, 689, 523, 459 and 429 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.77 (1H, t, J = 1.6 Hz), 8.04 (1H, d, J = 8.8 Hz), 7.51 (1H, d, J = 2.4 Hz), 7.20

(1H, dd, *J* = 8.4, 2.8 Hz), 3.94 (3H, s), 2.62 (2H, t, *J* = 7.2 Hz), 2.49 (2H, dt, *J* = 7.2, 1.6 Hz), 1.72 (2H, quintet, *J* = 6.8 Hz), 1.60 (2H, quintet, *J* = 6.8 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, DEPT-135): δ 202.6 (HC, H-*C*=O), 184.0 (C, *C*=O), 181.5 (C, *C*=O), 163.3 (C, *C*-OH), 152.9 (C), 131.1 (C), 129.0 (CH), 126.2 (C), 123.6 (C), 120.7 (CH), 109.8 (CH), 55.8 (CH_3), 43.6 (CH_2), 27.6 (CH_2), 22.8 (CH_2), 21.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}O_5H$ 289.1076; Found 289.1070.

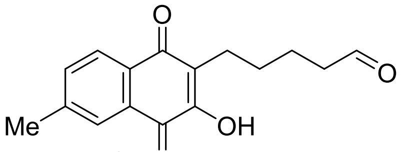
5-(3-hydroxy-6,7-dimethoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal



64e

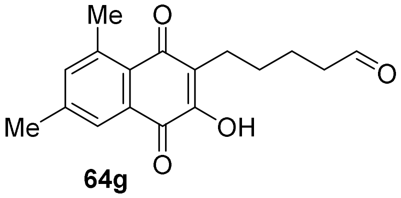
(64e): The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (3:7 to 4:6), and isolated as a yellow solid. Mp: 184-190 °C. Yield: 30.0% (286.5 mg). IR (Neat): ν_{max} 3315, 2925, 2853, 1710, 1650, 1579, 1508, 1461, 1334, 1269, 1218, 1201, 1122, 1096, 1021, 983, 888, 778 and 749 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 9.77 (1H, s), 7.54 (1H, s), 7.47 (1H, s), 7.37 (1H, br s), 4.03 (3H, s), 4.01 (3H, s), 2.59 (2H, t, *J* = 7.5 Hz), 2.50 (2H, t, *J* = 7.0 Hz), 1.71 (2H, quintet, *J* = 7.6 Hz), 1.59 (2H, quintet, *J* = 7.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135): δ 202.6 (HC, H-*C*=O), 184.4 (C, *C*=O), 180.5 (C, *C*=O), 154.3 (C, *C*-OH), 153.0 (C), 152.5 (C), 128.0 (C), 123.4 (C), 122.4 (C), 108.6 (CH), 107.6 (CH), 56.5 (CH_3), 56.4 (CH_3), 43.6 (CH_2), 27.6 (CH_2), 22.7 (CH_2), 21.8 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}O_6H$ 319.1182; Found 319.1176.

5-(3-hydroxy-6-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal (64f): The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (1:9 to 2:8), and isolated as a yellow solid. Mp: 88-90°C. Yield: 41.0% (335.0mg). IR (Neat): ν_{max} 3107, 2948, 2850, 1704, 1669, 1642, 1598, 1342, 1273, 1243, 1188, 1159, 1093, 908, 745, 691 and 454 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.78 (1H, br t, *J* = 1.4 Hz), 8.00-7.97 (1H, m), 7.86 (1H, s), 7.53 (1H, br d, *J* = 7.0 Hz), 7.45 (1H, br, s), 2.62 (2H, t, *J* = 6.8 Hz), 2.52-2.48 (2H, m), 2.48 (3H, s), 1.72 (2H, quintet, *J* = 7.2 Hz), 1.61 (2H, quintet, *J* = 7.6 Hz). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$, DEPT-135): δ 202.6 (HC, H-*C*=O), 184.6 (C, *C*=O), 181.6 (C, *C*=O), 153.1 (C, *C*-OH), 143.9 (C), 135.5 (CH), 130.6 (C), 129.3 (C), 126.9 (CH), 126.5 (CH), 123.6 (C), 43.6 (CH$_2$), 27.6 (CH$_2$), 22.8 (CH$_2$), 21.9 (CH$_2$), 21.6 (CH$_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{16}O_4H$ 273.1127; Found 273.1129.



64f

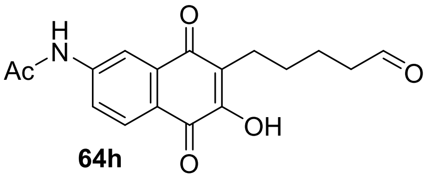
5-(3-hydroxy-6,8-dimethyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal (64g): The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (3:7 to 4:6), and isolated as a yellow semi-solid. Yield: 32.0% (275.0 mg). IR (Neat): ν_{max} 3230, 2932, 2834, 2359, 2334, 1709, 1664, 1642, 1590, 1493, 1458, 1362,1330, 1279, 1231, 1192, 1167, 1099, 1025, 933, 848, 752, 689, 523, 460 and 430 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.76 (1H, t, *J* = 1.5 Hz), 7.81 (1H, s), 7.32 (1H, s), 7.18 (1H, s), 2.69 (3H, s), 2.59 (2H, t, *J* = 7.5 Hz), 2.48 (2H, dt, *J* = 7.5, 1.5 Hz), 2.41 (3H, s), 1.71 (2H, quintet, *J* = 7.5 Hz), 1.57 (2H, quintet, *J* = 8.0 Hz). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, DEPT-135): δ 202.5 (HC, H-*C*=O), 186.7 (C, *C*=O), 181.9 (C, *C*=O), 151.8 (C, *C*-OH), 142.7 (C), 141.6



64g

(C), 139.8 (CH), 130.7 (C), 127.8 (C), 125.6 (CH), 124.6 (C), 43.6 (CH_2), 27.7 (CH_2), 23.0 (CH_2), 22.9 (CH_3), 22.0 (CH_2), 21.3 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}O_4H$ 287.1283; Found 287.1279.

***N*-(6-hydroxy-5,8-dioxo-7-(5-oxopentyl)-5,8-dihydronaphthalen-2-yl)acetamide (64h):** The compound was prepared following procedure **4d**, purified by column chromatography using EtOAc/hexane (5:5), and isolated as a yellow semi-solid. Yield: 18.0% (170.3 mg). IR (Neat): ν_{max} 3336, 2939, 2869, 2157, 2033, 2012, 1718, 1683, 1666, 1586, 1537, 1421, 1369, 1335, 1263, 1129, 731, 702 and 452 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): aldehyde: δ 9.66 (1H, t, *J* = 1.5 Hz), 8.17 (1H, br d, *J* = 8.5 Hz), 7.90 (1H, dd, *J* = 8.5, 3.0 Hz), 7.74 (1H, dd, *J* = 5.0, 2.0 Hz), 2.48 (2H, quintet, *J* = 7.5 Hz), 2.11 (3H, s), 1.58-1.54 (1H, m), 1.54-1.52 (1H, m), 1.51-1.48 (2H, m), 1.46-1.41 (2H, m). hemiacetal: δ 8.17 (1H, br d, *J* = 8.5 Hz), 7.90 (1H, dd, *J* = 8.5, 3.0 Hz), 7.74 (1H, dd, *J* = 5.0, 2.0 Hz), 4.41 (1H, t, *J* = 5.5 Hz), 2.48 (2H, quintet, *J* = 7.5 Hz), 2.41 (2H, dt, *J* = 7.0, 1.5 Hz), 2.11 (3H, s), 1.62 (2H, quintet, *J* = 7.5 Hz), 1.36 (2H, quintet, *J* = 7.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, DEPT-135) aldehyde: δ 203.4 (HC, H-*C*=O), 185.2 (C, *C*=O), 179.9 (C, *C*=O), 170.2 (C, *C*=O), 154.8 (C), 144.7 (C), 133.7 (C), 127.9 (CH), 124.7 (C), 123.9 (C), 122.5 (CH), 116.3 (CH), 43.4 (CH_2), 27.7 (CH_2), 24.4 (CH_2), 23.8 (CH_3), 22.5 (CH_2). hemiacetal: δ 185.1 (C, *C*=O), 179.9 (C, *C*=O), 170.2 (C, *C*=O), 154.7 (C), 144.6 (C), 133.7 (C), 127.8 (CH), 124.7 (C), 123.3 (C), 122.5 (CH), 116.3 (CH), 98.6 (CH), 36.3 (CH_2), 27.3 (CH_2),



64h

23.8 (CH_3), 22.8 (CH_2), 21.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}NO_5H$ 316.1185; Found 316.1182.

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LIST OF PUBLICATIONS

1. Organocatalytic Asymmetric Formal [3+2]-Cycloaddition as a Versatile Platform to Methanobenzo[7]annulenes. D. B. Ramachary, **Md. Anif Pasha**, and G. Thirupathi, *Angew. Chem. Int. Ed.* **2017**, *56*, 12930.

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POSTERS AND PRESENTATIONS

1. **Poster presentation:** "ChemFest -2020" (17th Annual In-House Symposium), School of Chemistry, University of Hyderabad. February 27 – 28th, 2020

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3. **Oral presentation:** "XV J-NOST (J - National Organic Symposium Trust) Conference" Department of Chemistry, University of Delhi, Delhi, India. October 18-21st 2019.

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4. **Participated:** "21st IUPAC International Conference on Organic Synthesis (ICOS-21)". December 11-16th 2016.

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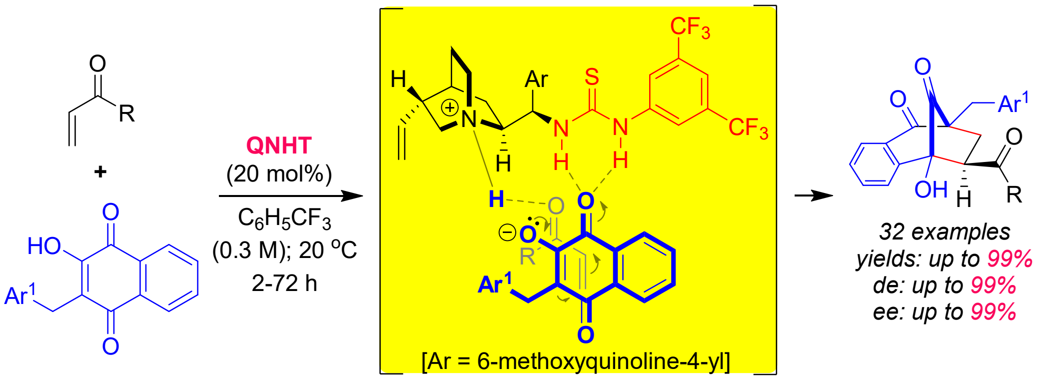

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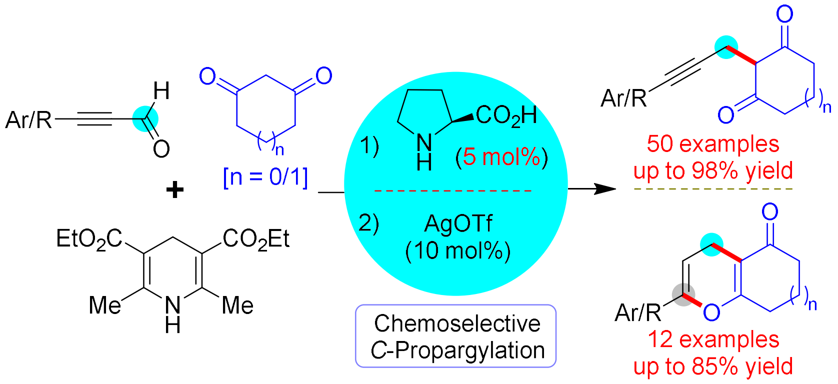

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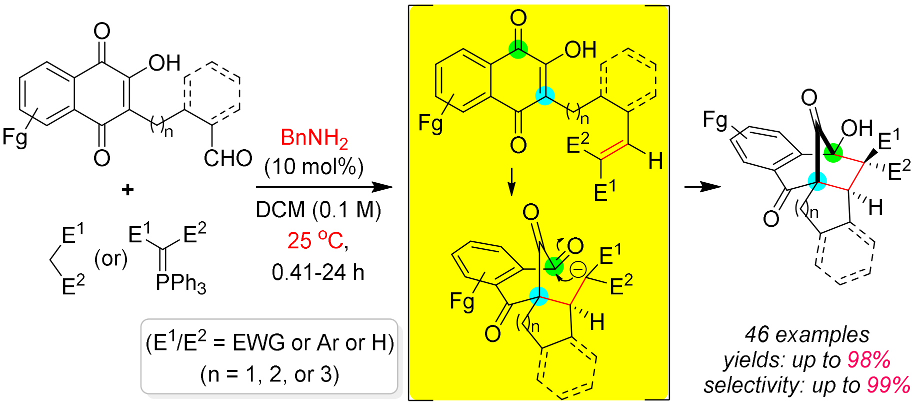

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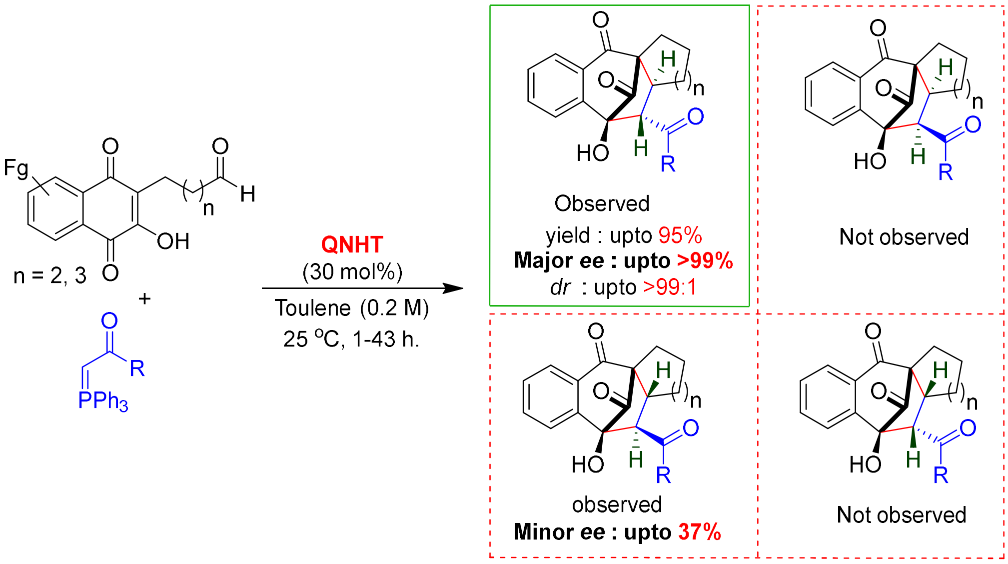

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