Development of Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules

A

Thesis

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By

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June 2023

Dedicated to…………..

My father Anugam Rama Krishna

and mother Anugam Uma

&

All enthusiastic chemists

DECLARATION

I hereby declare that the matter embodied in the thesis entitled **"Development of Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules"** is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Prof. Dhevalapally B. Ramachary.**

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CERTIFICATE

Certified that the work contained in the thesis entitled **"Development of Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules"** has been carried out by **Mr. Anugam Vamshi Krishna** 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.

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Anugam Vamshi Krishna

PREFACE

*In the last two decades, organocatalysis came into the limelight because of its huge importance and vast applicability in chemistry and biology. It became very important tool for the construction of chiral molecules and since nature designed itself in a more enantioselective manner, it will be the dream of every chemist to achieve such selectivity within the laboratory using synthetic methodologies. In earlier stages of asymmetric synthesis, the reactions were catalyzed by various metal catalysts in order to achieve the enantioselectivity. After few decades, organic chemists started using small organic molecules to catalyze a reaction. This popped up into a new area called "organocatalytic asymmetric synthesis" which enabled the scientific community to synthesize numerous complex molecules using simple organic molecules as the catalysts. In recognition, David MacMillan and Benjamin List shared the 2021 Nobel Prize for their enormous contribution in asymmetric organocatalysis. Besides its enormous contribution towards scientific community, still there is a huge vacuum which needs to be filled. Organocatalytic asymmetric annulation is one of the most important tools for the construction of various medicinally and materially important polycyclic systems. The present thesis entitled "**Development of Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules**" is an honest attempt to develop organocatalytic asymmetric annulation reactions for constructing various biologically important polycyclic scaffolds. A huge library of spiro, monocyclic, tricyclic, heterocyclic scaffolds were synthesized using our developed asymmetric protocols. Few natural products such as Parvaquone, Phthiocol were synthesized directly using our developed protocol. We have successfully developed the first catalytic asymmetric methodology for the synthesis of chiral Swaminathan ketones. 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 the first chapter, we engineered an enantioselective [3+3]-annulation reaction to furnish medicinally important 2,3-diazaspiro[4.5]deca-3,6-diene-1-ones by choosing specially designed substrates with multi nucleophilic and multi electrophilic centers. As a matter of fact, the increased number of electrophilic/nucleophilic sites in the substrates increase the possibility of different *product formations which makes it more challenging to achieve single desired product. Here, we successfully engineered the [3+3]-annulation of α-arylidene pyrazolinones with (E)-alkyl 2-oxo-4-aryl-but-3-enoates to furnish the desired products 2,3-diazaspiro[4.5]deca-3,6-diene-1-ones with good diastereoselectivity and excellent enantioselectivity under quinidine catalysis. The double sequence of in situ isoaromatization and dearomatization of α-arylidene pyrazolinones was the driving force for the reaction to furnish the desired products. Here, we successfully synthesized 40 examples with up to 83% yields, 99:1 dr and 96% ee using the developed protocol.*

In the second chapter, we have developed a seven-step, one-pot regioselective protocol for the synthesis of biologically important 3-aryllawsones. There are many medicinally important molecules and the direct drug candidates which possess 3-aryllawsones as the core skeleton. Not only this, all the previous reports on the synthesis of 3-aryllawsones suffered with low yields, less examples and usage of costly metal catalysts. This gave us enough motivation to take up this challenge. Here, we designed the reaction in a seven-step double cascade manner by combining Ramachary reductive coupling and the oxidative decarboxylation to furnish 3-aryllawsones. Owing to their structural importance, we successfully synthesized 41 differently functionalized 3-aryllawsones with up to 90% yields and >99% regioselectivity using commercially available starting materials. We have successfully investigated the substrate-controlled asymmetric aza-Michael/air-oxidation reaction on 2-arylnaphthalene-1,4-diones with chiral amines (S)-(-)-tert-butylsulfinamide and (R)-(+)-tert-butylsulfinamide under basic medium without affecting the enantioselectivity. For the first time, we have provided the crystallographic proof for the alkyl migration via the X-ray crystal structures of both starting material and the products.

In the third chapter, we have successfully developed a methodology for the regioselective C-alkylation of conformationally flexible cycloheptane-1,3-dione. We generated a huge library of 2-alkyl cycloheptane-1,3-diones which are the potential synthons for Swaminathan ketones. Besides, numerous applications, there is no catalytic asymmetric protocol available for the synthesis of chiral Swaminathan ketones. There are >450 natural products with a bicyclo[5.4.0]undecane core structure but achieving this skeleton in an enantioselective manner becomes challenging because of the highly conformationally flexible seven membered ring. Thus, we took it as a challenge and developed the first catalytic asymmetric protocol for the synthesis of chiral S. ketones from 2-alkyl *cycloheptane-1,3-diones in two steps. We successfully synthesised a library of more than 20 chiral S. ketones with up to 94% yields and >99.9% ee using our chiral asymmetric strategy.*

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
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
H-Ester	hantzsch ester
^{i}Pr	isopropyl
IR	infrared
$LiAlH_4$	lithium aluminum hydride
LUMO	lowest unoccupied molecular orbital
lit.	literature
m	multiplet
m-CPBA	*m*-chloro perbenzoic acid
M	molarity
Mp.	melting point
Me	methyl
mg	milligram (s)
mL	milliliter
mmol	millimole
MW	microwave
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
OrgRC	organocatalytic reductive coupling
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
py	pyridine
pr	propyl
q	quartet
rr	regioisomeric ratio
RT	room temperature
S. ketones	Swaminathan ketones
s	singlet
sec	secondary
t	triplet
TBHP	tertiary-butyl hydroperoxide
TCRA	three-component reductive alkylation
*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

Development of Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules

1. Abstract

Chapter 1 describes about engineering of an enantioselective [3+3]-annulation reaction to furnish medicinally important 2,3-diazaspiro[4.5]deca-3,6-diene-1-ones by choosing specially designed substrates with multi nucleophilic and multi-electrophilic centers. Here, we successfully engineered the [3+3]-annulation of α-arylidene pyrazolinones with (*E*)-alkyl 2-oxo-4-aryl-but-3-enoates to furnish the desired products 2,3-diazaspiro[4.5]deca-3,6-diene-1-ones with good diasteroselectivity and excellent enantioselectivity under quinidine catalysis. The double sequence of *in situ* isoaromatization and dearomatization of α-arylidene pyrazolinones was the driving force for the reaction to furnish the desired products. Here, we successfully synthesized 40 examples with up to 83% yields, 99:1 *dr* and 96% *ee* using the developed protocol.

Chapter 2 deals with the development of a seven-step, one-pot regioselective protocol for the synthesis of biologically important 3-aryllawsones. Here, we designed the reaction in a seven-step double cascade manner by combining Ramachary reductive coupling and the oxidative decarboxylation to furnish 3-aryllawsones. Owing to their structural importance, we successfully synthesized 41 differently functionalized 3-aryllawsones with up to 90% yields and >99% regioselectivity using commercially available starting materials. We have successfully investigated the substrate-controlled asymmetric *aza*-Michael/air-oxidation reaction on 2-arylnaphthalene-1,4-diones with chiral amines (*S*)-(-)-*tert*-butylsulfinamide and (*R*)-(+)-*tert*-butylsulfinamide under basic medium without affecting the enantioselectivity. For the first time, we have provided the crystallographic proof for the alkyl migration via the X-ray crystal structures of both starting material and the products.

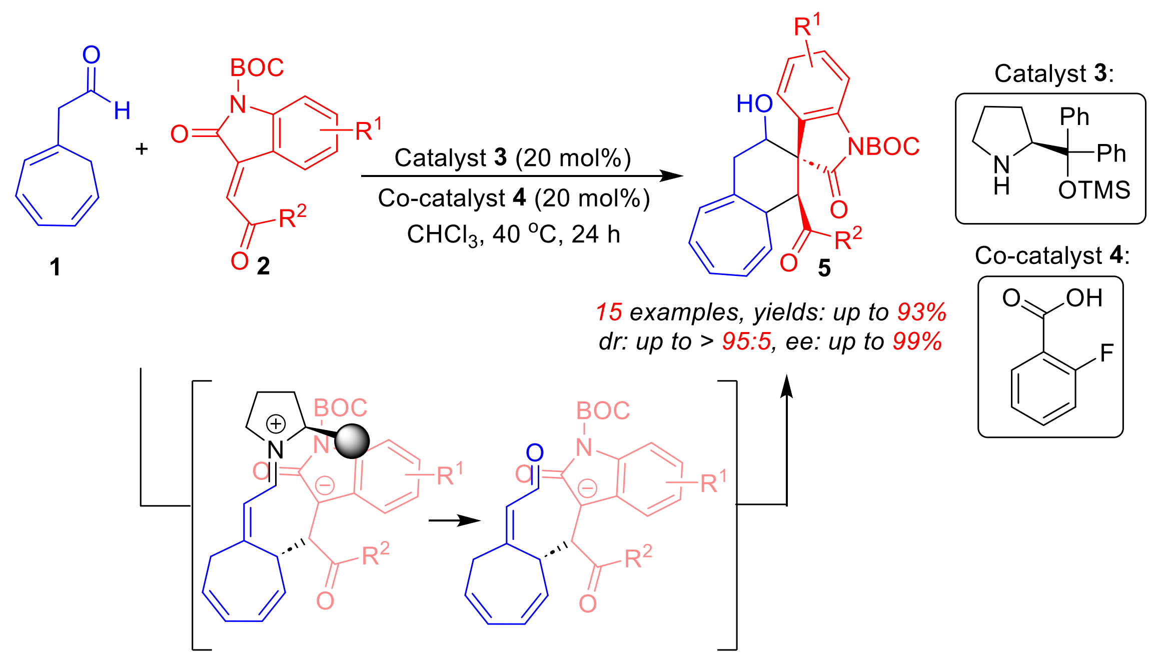
Chapter 3 deals with the development of a methodology for the regioselective *C*-alkylation of conformationally flexible cycloheptane-1,3-dione. We generated a huge library of 2-alkyl cycloheptane-1,3-diones which are the potential synthons for Swaminathan ketones. Besides, numerous applications, there is no catalytic asymmetric protocol available for the synthesis of chiral Swaminathan ketones. There are >450 natural products with a bicyclo[5.4.0]undecane core structure but achieving this skeleton in an enantioselective manner becomes challenging because

of the highly conformationally flexible seven membered ring. Thus, we took it as a challenge and developed the first catalytic asymmetric protocol for the synthesis of chiral S. ketones from 2-alkyl cycloheptane-1,3-diones in two steps. We successfully synthesised a library of more than 20 chiral S. ketones with up to 94% yields and >99% *ee* using our chiral asymmetric strategy.

2. Introduction

Organic reactions are all about breaking and making bonds of our interest using various synthetic techniques. Based on the mode of activation, reactions are classified into different types. The most interesting and challenging task for an organic chemist is to mimic the reactions that occur in the nature and perform them in the laboratory using synthetic methodologies. There are lot of hidden secrets in the nature which are yet to be discovered. As a matter of fact, in nature, all the natural products exist in their enantiomerically pure form. Interestingly, the two enantiomers of a same molecule can exhibit different biological properties. One of the best examples to understand this phenomenon is the “Thalidomide tragedy”.[1] In 1950s, Thalidomide was widely used in Germany as a drug for treating morning sickness in pregnant women. Shockingly, in between 1957 and 1962, around 10,000 children were born with birth defects and many of them even died. This was one of the biggest disasters of that time. The reason for this disaster remained unknown for 20 years but what scientists found after that was devastating. The common thing among all these pregnant women was, all of them consumed Thalidomide during their pregnancy. Since Thalidomide has both (*R*)- and (*S*)-enantiomers in it, (*R*)-Thalidomide has the biological properties to cure morning sickness and also possess sedative properties whereas (*S*)-Thalidomide has teratogenic properties which leads to the birth defects. This clearly showed the importance of enantiopurity among the drug candidates. This marks the beginning of new concept in organic chemistry called “asymmetric synthesis” where the reaction produces the products by creating a new chiral stereogenic unit into it, forming the stereoisomers in unequal amounts. In earlier stage of asymmetric synthesis, the reactions were catalyzed by various metal catalysts in order to achieve the enantioselectivity. After few decades, organic chemists started using small organic molecules to catalyze a reaction. This popped up into a new area called “organocatalytic asymmetric synthesis” which enabled the scientific community to synthesize numerous complex molecules using simple organic molecules as the catalysts. In 1970s, a break through reaction, namely Hajos-Parrish-Eder-Sauer-Wiechert reaction generated a bicyclo[3.4.0]nonane under chiral proline catalysis with excellent enantioselectivity followed by the discovery of chiral Weiland-Miescher ketone in 1985 which gave enough activation energy to the scientific community.[2, 3] After 1997, many chemists showed huge interest in organocatalytic asymmetric synthesis and produced many synthetic methodologies for various reactions till date. Because of the impact it created and the importance of it in constructing various medicinally and materially important molecules in a greener way, after the initiation of asymmetric organocatalysis by Prof. Carlos F. Barbas III, David MacMillan and Benjamin List were awarded 2021 Nobel prize in chemistry for their enormous contribution in asymmetric organocatalysis. Even though Nobel prize was awarded, there are lot more important reactions which are yet to be discovered. One of the important types of reaction in asymmetric organocatalysis is 'organocatalytic asymmetric annulations'. A reaction is said to be an 'organocatalytic asymmetric annulation reaction', if it furnishes an enantioselective product with an insertion of new ring into the existing starting material scaffold *via* new bonds using small organic molecules as the catalyst. Many complex polycyclic molecules and the molecules with important biological activities can be easily synthesized using these annulation reactions. There are many types of annulation reactions such as [3+2]-, [3+3]-, [4+2]-, [4+1]-annulations etc. in the literature. Herein, I am going to discuss few key annulation reactions which are recently developed.

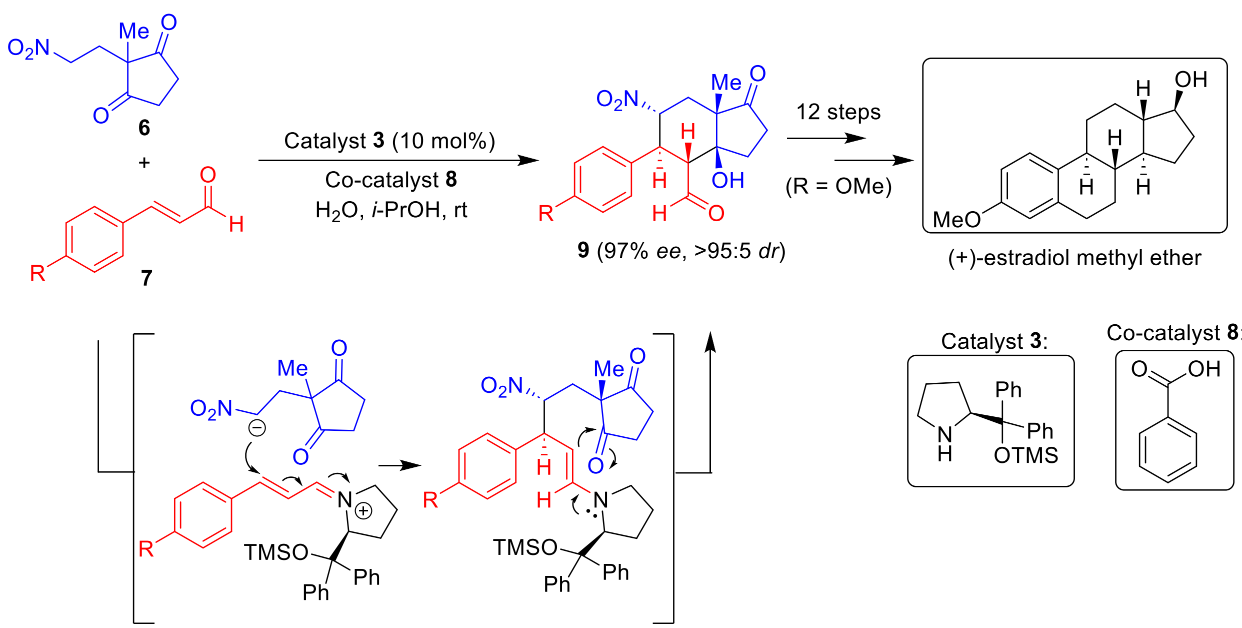
In 2014, Jorgensen et al. reported the [4+2]-annulation of 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde **1** with 3-olefinic oxindole **2** under TMS-protected prolinol catalysis (Scheme 1).[4]



Scheme 1: [4+2]-annulation of 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde **1** with 3-olefinic oxindoles **2**.

Initially, the catalyst **3** formed a reactive tetraenamine intermediate which underwent Michael reaction with 3-olefinic oxindole **2** forming a zwitter-ion intermediate. Further, hydrolysis happened by eliminating the catalyst followed by intramolecular cyclization and isomerization affording the desired spiro product **5**. They reacted 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde **1** with 3-olefinic oxindole **2** in the presence of catalyst **3** (20 mol%) and co-catalyst **4** (20 mol%) in $CHCl_3$ at 40 °C for 24 h and afforded the desired product **5** in 93% yield with >95:5 *dr* and 94% *ee*. They successfully demonstrated this [4+2]-annulation reaction on 15 examples and achieved up to 93% yield, >95:5 *dr* and up to 99% *ee* (Scheme 1).

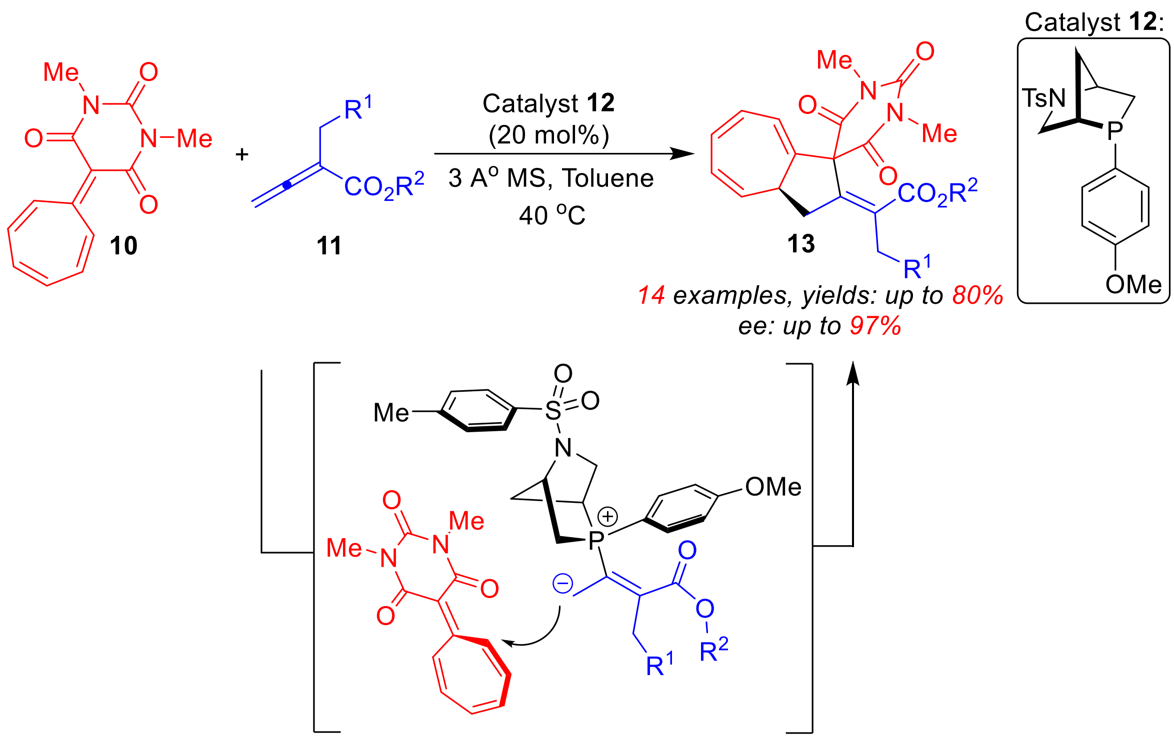
Next, in 2017, Hayashi et al. reported the [4+2]-annulation of nitroalkane **6** with substituted-cinnamaldehyde **7** under TMS-protected prolinol **3** catalysis (Scheme 2).[5] The reaction was initiated by the catalyst **3** forming iminium ion with the cinnamaldehyde **7**. The nucleophile generated on the nitroalkane attacked the iminium ion which further underwent intramolecular aldol reaction by regenerating the catalyst furnishing the desired product **9** with 97% *ee* and >95:5 *dr*. Further Hayashi et al. achieved the total synthesis of (+)-estradiol methyl ether from the product **9** in 12 steps proving its importance (Scheme 2).



Scheme 2. [4+2]-annulation of nitroalkanes **6** with substituted-cinnamaldehydes **7**.

In 2018, Guo et al. reported the [8+2]-annulation of heptafulvenes **10** with allenoates **11** under chiral phosphine catalysis (Scheme 3).[6] Here, the reaction got initiated by the attack of catalyst

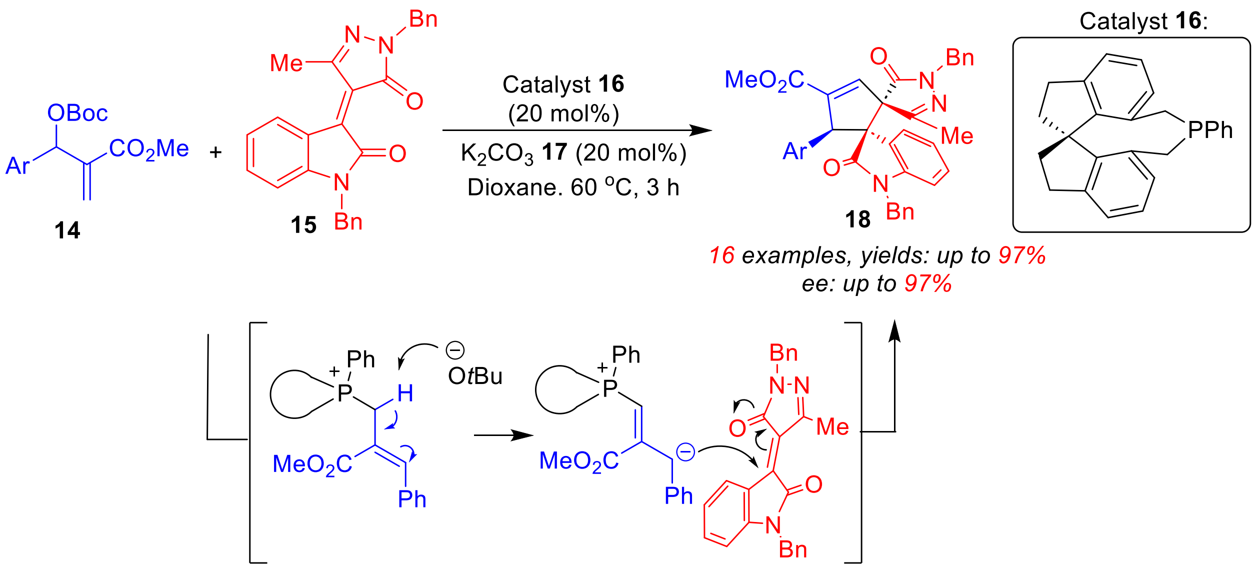
12 on to the allenoate **11** forming β-phosphonium dienolate. The formed enolate attacked the heptafulvene **10** involving all the **8** conjugated electrons in the reaction forming a carbanion which underwent nucleophilic substitution on to the allenoate regenerating the catalyst **12** furnishing the desired product **13**. They reacted the heptafulvene **10** with allenoate **11** in the presence of 20 mol% of catalyst **12** in toluene at 40 °C for 72 h and afforded the annulated product **13**. This methodology was successfully demonstrated on 14 examples with up to 80% yields and 97% *ee* showing the importance of the protocol (Scheme 3).



Scheme 3. [8+2]-annulation of Heptafulvene **10** with Allenoate **11**

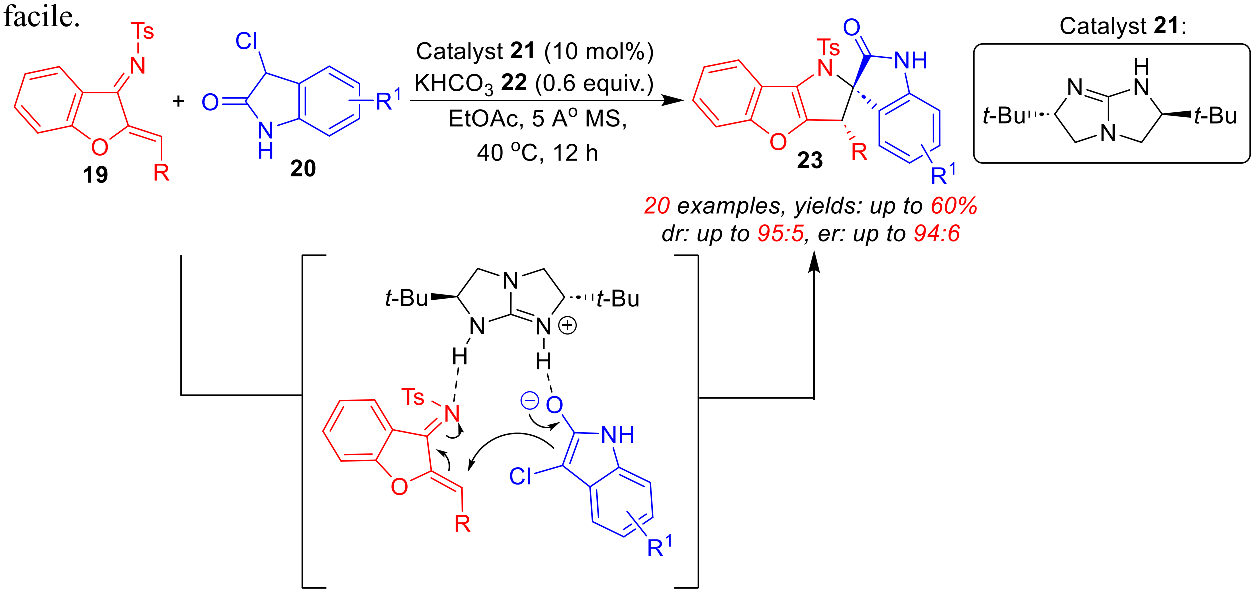
Later, in 2019, Lu et al. reported the [3+2]-annulation of MBH carbonates **14** with pyrazoloneylidene oxindoles **15** under chiral phosphorus **16** catalysis (Scheme 4).[7] Initially, the catalyst **16** attacked on to the alkene of MBH-carbonate **14** eliminating the OBoc group via decarboxylation leaving an active *tert*-butoxide anion in the reaction mixture. This active anion abstracted the proton α to the phosphinium ion forming an ylide. Then, the generated nucleophile went on to the electrophilic site of pyrazoloneylidene oxindoles **15** forming a nucleophile which in turn underwent intramolecular cyclization affording desired product **18** regenerating the catalyst **16**. They have performed the reaction of MBH carbonates **14** with pyrazoloneylidene oxindoles

15 in the presence of 20 mol% of catalyst **16** and 20 mol% of K_2CO_3 **17** in dioxane at 60 °C. In 3 h, the reaction afforded the desired product in excellent yields. They have successfully demonstrated this reaction over 16 examples with up to 97% yields and 97% *ee* (Scheme 4).



Scheme 4. [3+2]-annulation of MBH carbonates **14** with Pyrazoloneylidene oxindoles **15**.

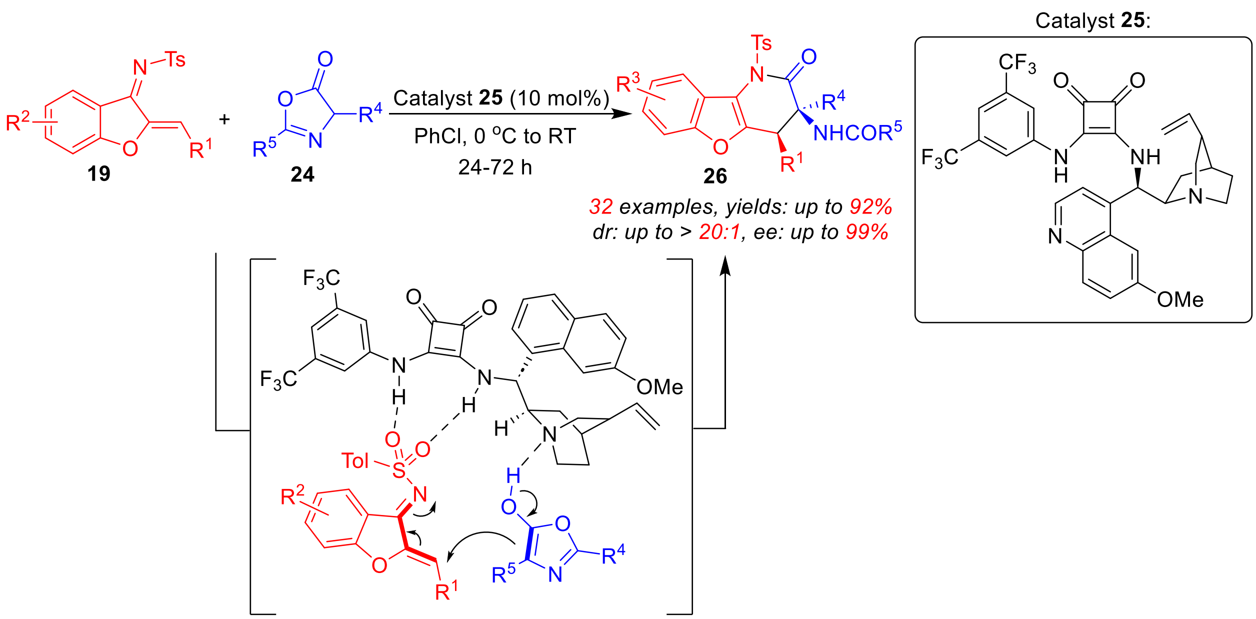
In 2019, Shi et al. reported an interesting [4+1]-annulation of azadienes **19** with 3-chloro oxindoles **20** under chiral guanidine **21** catalysis (Scheme 5).[8] Firstly, the chiral guanidine anchored both the substrates in to a close proximity *via* hydrogen bonding to make the reaction facile.



Scheme 5: [4+1]-annulation of Benzofuran derived azadienes **19** with 3-chloro oxindoles **20**.

Then, the 3-chloro oxindole **20** formed an enolate in the presence of chiral guanidine **19** generating a nucleophile which attacked on the electrophilic double bond of azadiene **19** creating a nucleophile on the nitrogen atom. This anion further underwent nucleophilic substitution reaction by replacing chlorine atom furnishing the desired product **23**. They performed the reaction of benzofuran derived azadiene **19** with 3-chloro oxindoles **20** in the presence of 10 mol% of catalyst **21** and 0.6 equiv. of $KHCO_3$ in ethyl acetate at 40 °C for 12 h using 5 A° MS to afford the desired annulation adducts **23** with excellent yield and selectivity. They have successfully synthesized 20 examples with up to 60% yields, 95:5 *dr* and 94:6 *er* using this protocol (Scheme 5).

Soon after Shi et al., Huang et al. in 2019, published a [4+2]-annulation reaction using the same azadienes **19** (Scheme 6).[9] Here, they reacted these azadienes **19** with azalactones **24** under square amide **25** catalysis.



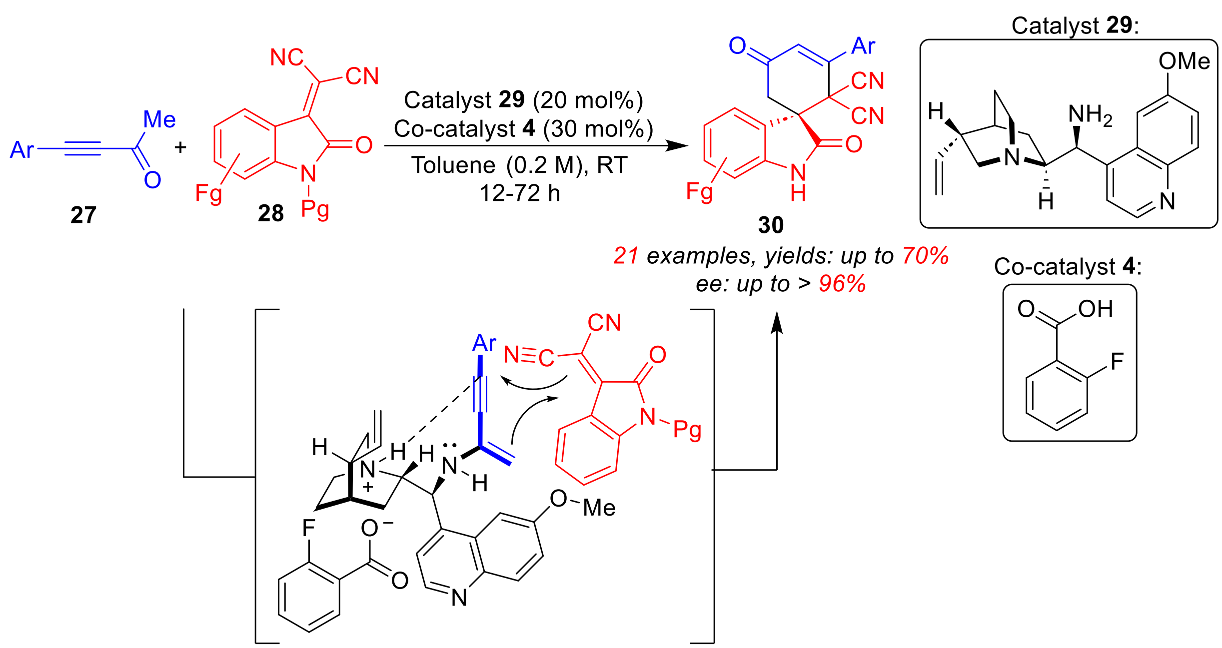
Scheme 6: [4+2]-annulation of Azadines **19** with Azalactones **24**.

Even here, the catalyst **25** anchored both the substrates *via* hydrogen bonding and brought them close for the reactivity. Azalactones **24** formed enolate in the presence of catalyst **25**, which attacked on to the electrophilic center of the azadiene **19** resulting a nucleophile on the nitrogen atom. Then, this nucleophile underwent aldol-type reaction with the keto group of azalactone **24** opening the ring and furnishing desired annulation products **26**. They performed the reaction of azadienes **19** with azalactones **24** in the presence of 10 mol% of catalyst **25** in chlorobenzene at 0 °C to rt for 24-72 h to afford desired products **26** with excellent yield and selectivity. The authors have successfully synthesized 32 examples with up to 92% yields, >20:1 *dr* and up to 99% *ee* using this protocol (Scheme 6).

2.1 Background

Till now we have discussed key annulation reactions reported by various research groups all over the world. Meanwhile, in past two decades, our laboratory has discovered various asymmetric organocatalytic methodologies for constructing structurally and biologically important complex ring systems. Not only this, our research group has also developed significant organocatalytic asymmetric annulation reactions to furnish antibiotic skeletons and interesting scaffolds. Herein, I am discussing a few key organocatalytic asymmetric annulation reactions developed from our laboratory which serves as the introduction as well as the background research work for the thesis.

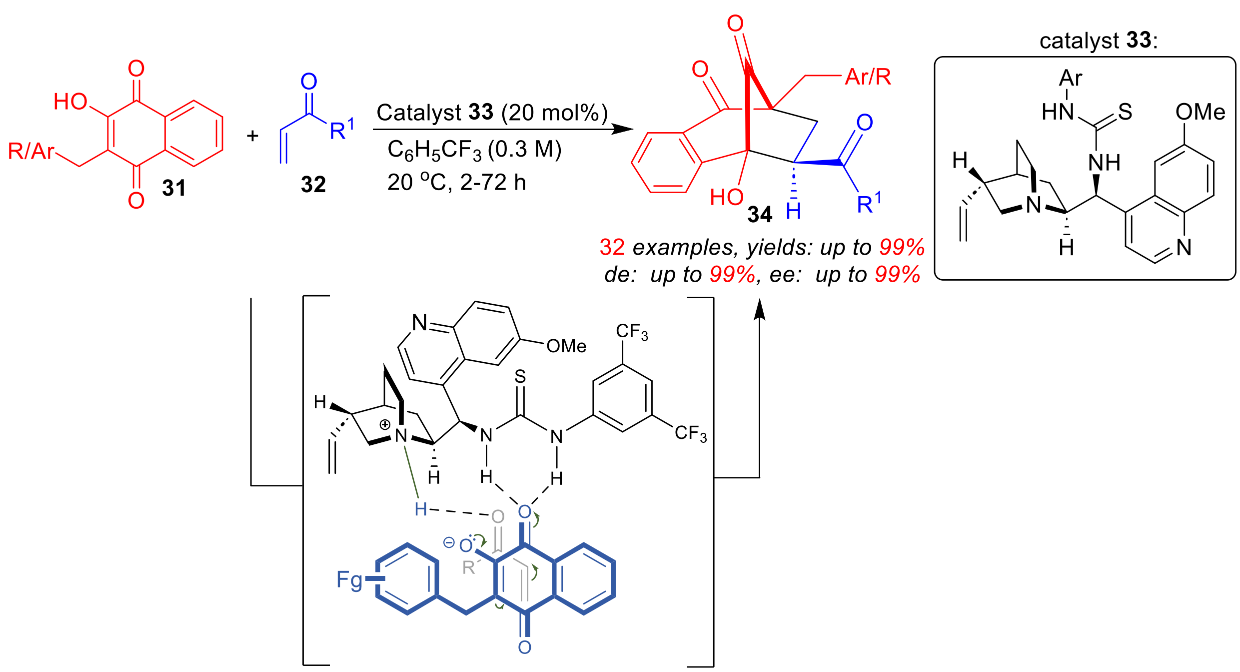
In 2013, our research group discovered a new mode of catalytic aminoenyne reactivity. In this, the authors has performed the [4+2]-annulation of ynones **27** with 2-(2-oxindolin-3-ylidene)malanonitriles **28** under quinine-NH_2 **29/4** catalysis (Scheme 7).[10]



Scheme 7: [4+2]-annulation of ynones **27** with 2-(2-oxoindolin-3-ylidene)malononitriles **28**.

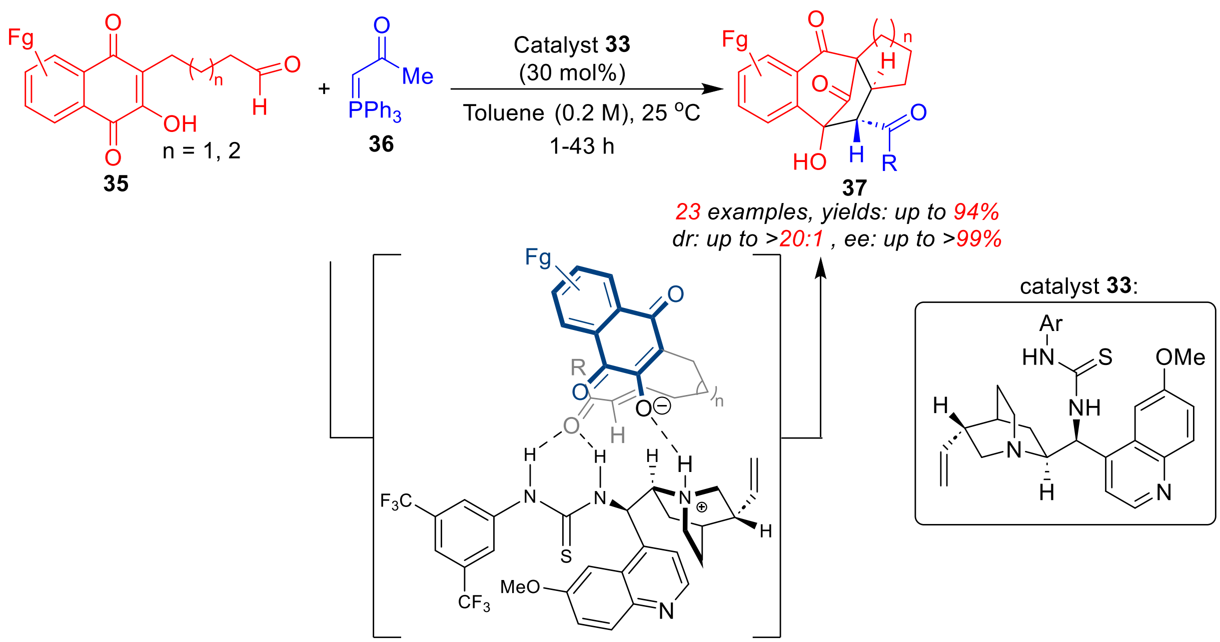
Here, the catalyst **29** along with the co-catalyst **4** formed aminoenyne species with the ynone **27** generating a terminal nucleophile. This underwent a nucleophilic attack on the electrophilic center of 2-(2-oxindolin-3-ylidene)malanonitriles **28** followed by intramolecular *reflexive*-Michael addition on to the electrophilic alkyne site furnishing the drug like six-membered spirooxindoles **30**. The reaction of 2-(2-oxindolin-3-ylidene)malanonitriles **28** with the ynones **27** in the presence of 20 mol% catalyst **29** and 30 mol% co-catalyst **4** in toluene at room temperature for 12-72 h afforded the drug like molecules **30** with good yields. The authors successfully synthesized 21 examples with up to 70% yields and >96% *ee* using this developed new protocol (Scheme 7).

Later, in 2017, our research group explored the interesting [3+2]-annulation of 3-alkyllawsones **31** with alkyl vinyl ketones **32** under quinine-thiourea **33** catalysis (Scheme 8).[11] Initially, both the substrates were anchored by the catalyst **33** *via* hydrogen bonding forming 3-alkyl-1,4-dioxo-1,4-dihydronaphthalen-2-olate which further underwent a Michael reaction with the alkyl vinyl ketones **32** forming a key Michael intermediate. The interesting part comes here, out of the three *keto*s present on lawsone core structure, only one *keto* group selectively involved in the subsequent aldol reaction furnishing the structurally and pharmaceutically important methanobenzo[7]annulenes. The reaction of 3-alkyllawsone **31** with alkyl vinyl ketone **32** in the presence of 20 mol% catalyst **33** in toluene at 20 °C for 2-72 h yielded the desired annulation products **34** in excellent yields. The authors successfully synthesized 32 examples with up to 99% yields, 99% *de* and 99% *ee* using the developed methodology (Scheme 8).



Scheme 8: [3+2]-annulation of 3-alkyllawsones **31** with alkyl vinyl ketones **32**.

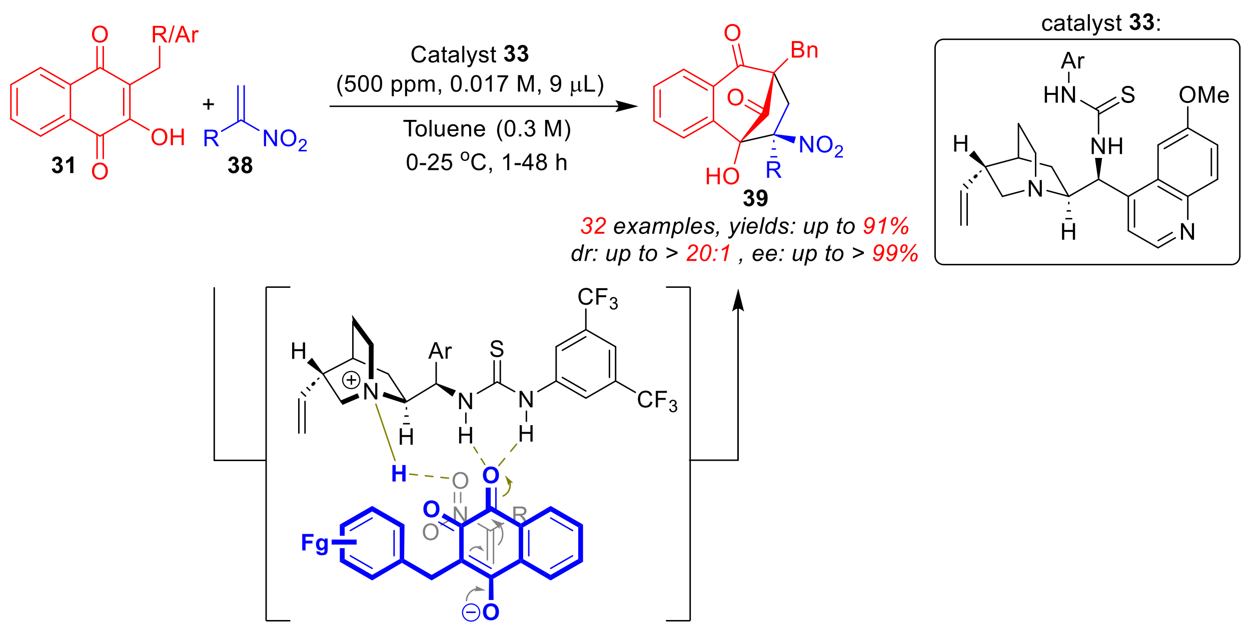
Next, in 2021, our laboratory published the intramolecular [3+2]-annulation of lawsone aldehydes **35** with acetylmethylene-triphosphoranes **36** under quinine-thiourea **33** catalysis (Scheme 9).[12] Here, the tertiary amine of catalyst anchored the lawsone by forming hydrogen bonding with the enolic part where as the terminal aldehyde was anchored and activated through the hydrogen bonding by two NH of the catalyst **33** facilitating the Wittig reaction followed by intramolecular Michael reaction and intramolecular aldol reaction furnishing the interesting skeletons of antibiotics **37**. The reaction of lawsone aldehyde **35** with the phosphoranes **36** in the presence of 30 mol% of catalyst **33** in toluene at 25 °C for 1-43 h furnished the desired products **37** in excellent yield and selectivity. The authors successfully synthesized 23 examples with up to 94% yields, > 20:1 *dr* and up to >99% *ee* (Scheme 9).



Scheme 9. [3+2]-annulation of lawsone aldehydes **35** with acetylmethylene-triphenyl-phosphoranes **36**.

Once again in 2021, our research group discovered an interesting ppm level catalyst loading asymmetric organocatalyzed [3+2]-annulation of 3-alkyllawsones **31** with nitroethylene **38** using quinine-thiourea **33** as the catalyst (Scheme 10).[13] Here, the protonated tertiary amine of the catalyst anchored and activated the nitroethylene whereas lawsone was anchored by the two NHs of the catalyst which facilitated the Michael reaction through the formation of enolate followed by the Henry reaction furnishing the desired products **39** with antibiotic skeleton. The reaction of 3-

alkyllawsones **31** with nitroethylene **38** in the presence of 500 ppm of catalyst **33** in toluene at 0-25 °C for 1-48 h furnished the desired products **39** with excellent yields and selectivity. The authors successfully synthesized 32 examples with up to 91% yield, > 20:1 *dr* and up to > 99% *ee* using the developed protocol (Scheme 10).



Scheme 10. [3+2]-annulation of 3-alkyllawsones **31** with nitroethylene **38**.

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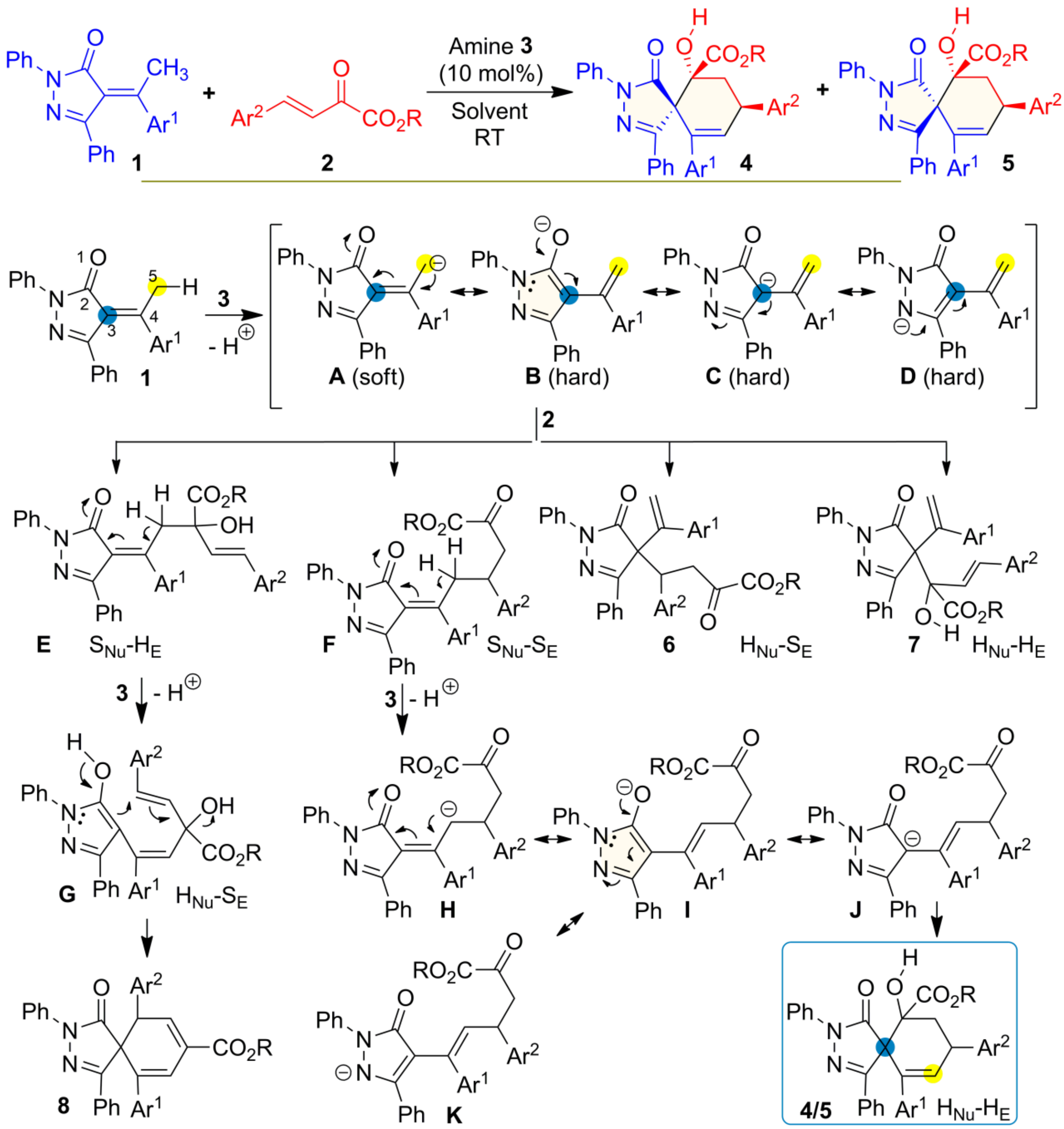
3. Organocatalytic Asymmetric [3+3]-Annulation to Access 2,3-Diazaspiro[4.5]deca-3,6-dien-1-ones

3.1 Introduction

Organocatalysis has its own charm in the realm of chemistry owing to its reliability and applicability. Recently, it emerged as one of the excellent tools to utilize the reactivity of mild functional groups through enamine, iminium and enolate formation. The fashion to mimic cellular type reactions in vial and to perform many selective new bond formations in one-pot has driven chemists to practice domino reactions to make drugs and natural products in sequential one-pot manner.[1] Recently, our group delved into the utilization of ambident lawsones in domino reactions.[2] To engineer complex domino/cascade/one-pot reactions, we are very much fascinated to investigate the new multi-centric nucleophiles and electrophiles under organocatalysis.[2] The huge challenge for an organic chemist is to engineer desired single drug/natural product from the ambident nucleophiles/electrophiles through selective bond formations in one-pot.[1]

The chemistry of α-arylidene pyrazolinone **1** with simple aldehydes and ketones under the organocatalysis is emerging area.[3] The availability of vinylogous protons of **1** made it more interesting which upon reacting with amine forms an enolate through isoaromatization, thus generating either a soft anion at C-5 (**A**) or a hard anion at C-3 (**C**). Owing to the fact that **1** behaves as an ambident nucleophile, we found an ambident electrophile **2** as a suitable substrate to study the reactivity and selectivity (Scheme 1). As **2** has soft and hard electrophilic sites within the molecule, there exists a competition between 1,4- versus 1,2-addition respectively upon nucleophilic attack. According to our design (Scheme 1), firstly amine **3** abstracts the vinylogous proton of **1** generating intermediate **A** having the character of a soft nucleophile which under the influence of heteroatoms in the ring undergo isoaromatization to form **B** to attain stability. Intermediate **A** can further undergo isomerization to form **C** and **D**, which behaves as relatively hard nucleophiles. Secondly, the *in situ* generated relatively hard nucleophile **C** may react with **2** through 1,4-addition or 1,2-addition to form the product **6** or **7** respectively. In the similar fashion, the *in situ* generated soft nucleophile **A** may react with **2** through 1,2-addition or 1,4-addition to form the intermediate **E** or **F** respectively.[4] Later, the intermediate **E** or **F** isoaromatizes to **G** or **I** by interacting with **3**, which further dearomatizes to proceed through cyclization by either intramolecular nucleophilic attack on the olefin followed by hydroxide ion elimination to form the product **8** or intramolecular aldol reaction through nucleophilic attack on the ketone to form products **4**/**5** respectively.



Scheme 1: Reaction design for spirocyclization through domino reactions.

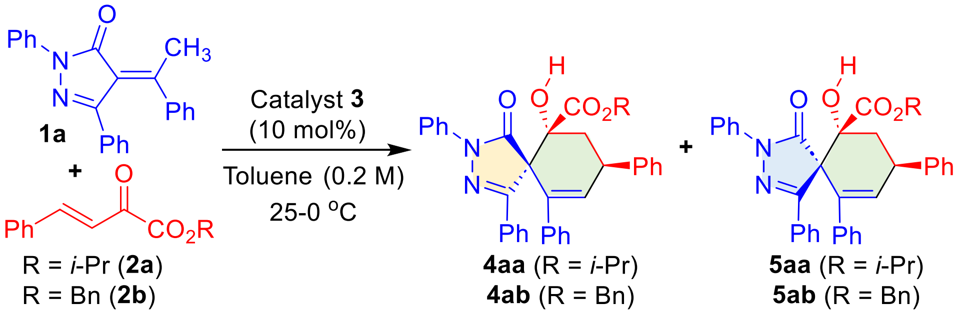
Observation of double isoaromatization-dearomatization phenomenon in an asymmetric domino reaction is novel and the possible formations of **4-8** made it more challenging to investigate the reaction in order to selectively synthesize the designed product (Scheme 1). Designed structures of **4**/**5** will be useful spirocycles in medicinal chemistry as analogues have many pharmaceutical applications.[5]

3.2 Results and Discussion

3.2.1 Reaction Preliminary Optimization

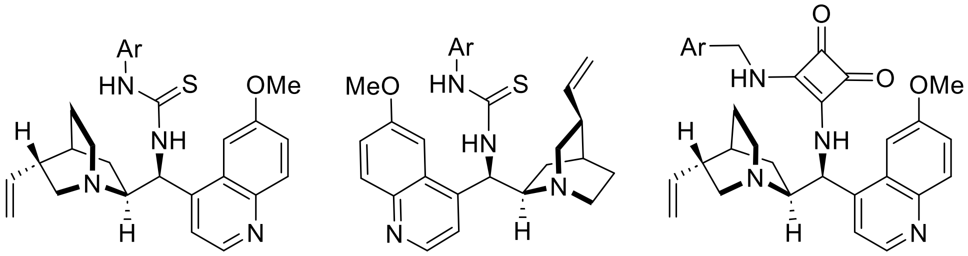
We have chosen **1a** and **2a/b** for the investigation of asymmetric domino reaction (Table 1). As ambident substrates are used in this reaction, to induce the chirality we opted multi-functionalized widely used quinine **3a** as a chiral catalyst for the investigation. Surprisingly, 1.0 equiv. of **1a** readily reacted with 1.2 equiv. of **2a** at 25 °C in the presence of 10 mol% **3a** in toluene (0.2 M) to furnish the products **4aa**/**5aa** in 83% yield with 80% *ee* and 5.8:1 *dr* within 1 h (Table 1, entry 1). With this exciting result, we screened the same reaction using quinidine **3b**, hydroquinidine **3c**, cinchonine **3d** and cinchonidine **3e** as catalyst and ending up in the desired products **4aa**/**5aa** with unvaried 75-86% yields, 79-83% *ee* and 5.5:1-5.8:1 *dr* within 1.0-1.15 h (Table 1, entries 2-5). When ratio of **1a**/**2a** is made to 1:1 instead of 1:1.2 with unaltered conditions resulted **4aa**/**5aa** in 83% yield, with increased *ee* (85%) and unchanged *dr* (5.8:1) which showed the clear dependence of *ee* on stoichiometry (Table 1, entry 6). Performing **3b**-catalyzed reaction of **1a** and **2a** at 0 °C for 2.5 h furnished **4aa/5aa** in reduced yield and *dr* with slightly increased *ee* (Table 1, entry 7). Even though **3b** resulted in reasonably good selectivity, we continued optimization by switching from **2a** to **2b** which can facilitate $\pi-\pi$ stacking through which selectivity can be improved further. Interestingly, when **1a** reacted with **2b** in the presence of 10 mol% **3b** at 25 °C in toluene furnished **4ab**/**5ab** with 80% yield, 80% *ee* and 3.6:1 *dr* within 1 h (Table 1, entry 8) whereas when the same reaction is performed at 0 °C for 1.8 h, there was a tremendous increase in *ee* of **4ab**/**5ab** from 80% to 91% (Table 1, entry 9). When 1.3 equiv. of **2b** was used at 0 °C, there is a fall in yield and selectivity to 68% and 85% *ee*, 3.7:1 *dr* respectively (Table 1, entry 10). Surprisingly, when the same reaction catalyzed by quinidine-OBn **3f**, even though the reaction time got doubled and furnished the product **4ab**/**5ab** in 78% yield and 3.5:1 *dr* with poor (30%) *ee* which clearly depicts the importance of quinidine's OH for the facial selectivity (Table 1, entry 11). Further, the same reaction didn't proceed when cupreidine **3g** was used as catalyst whereas quinine thiourea **3h**, quinidine thiourea **3i**, Rawal's catalyst **3j** slightly favoured the reaction with poor (34, 33, 34) yields and (28, 24, 24) *ee's* respectively (Table 1, entries 12-15).

Table 1: Reaction preliminary optimization[a]



Quinine (**3a**) Quinidine (**3b**) Hydroquinidine (**3c**) Cinchonine (**3d**)

Cinchonidine (**3e**) Quinidine-OBn (**3f**) Cupreidine (**3g**)



(**3h**) (**3i**) Ar = 3,5-$(CF_3)_2C_6H_3$ (**3j**)

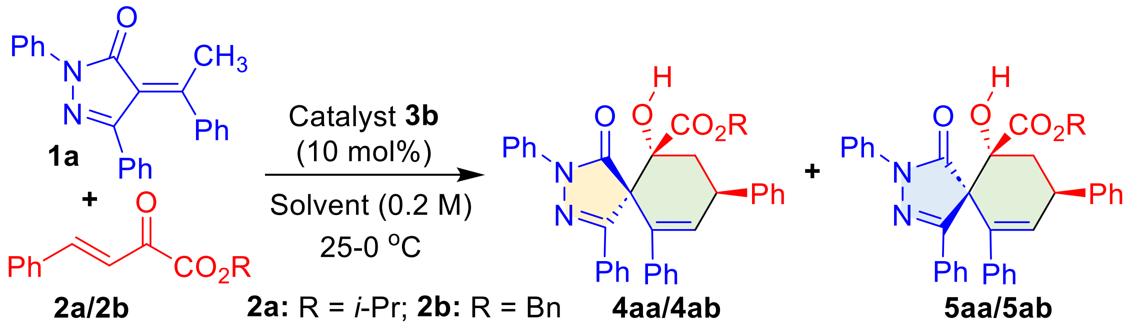
Entry	**2**	Catalyst [10 mol%]	*T* [°C]	*t* [h]	Yield [%][b] **[4+5]**	*dr*[c] **[4:5]**	*ee* [%][d] **[4]**
1[e]	**2a**	**3a**	25 °C	1	83	5.8:1	80
2[e]	**2a**	**3b**	25 °C	1	86	5.5:1	83
3[e]	**2a**	**3c**	25 °C	1	85	5.6:1	83
4[e]	**2a**	**3d**	25 °C	1.15	75	5.8:1	80
5[e]	**2a**	**3e**	25 °C	1	84	5.8:1	79
6	**2a**	**3e**	25 °C	1	83	5.8:1	85
7	**2a**	**3b**	0 °C	2.5	78	5.1:1	86
8	**2b**	**3b**	25 °C	1	80	3.6:1	80
9	**2b**	**3b**	0 °C	1.8	80	3.7:1	91
10[f]	**2b**	**3b**	0 °C	2	68	3.7:1	85
11	**2b**	**3f**	25 °C	2	78	3.5:1	30
12	**2b**	**3g**	25 °C	24	nr	-	-
13	**2b**	**3h**	25 °C	22	34	nd	28
14	**2b**	**3i**	25 °C	22	33	nd	24
15	**2b**	**3j**	25 °C	24	34	nd	24

[a] Reactions were carried out in solvent (0.2 M) with 1.0 equiv of **2a** relative to the **1a** (0.2 mmol) in the presence of 10 mol % of catalyst **3**. [b] Yields refers to the diastereomers **4** and **5** purified by coloumn chromatography. [c] dr was determined by ^{1}H NMR analysis of crude products. [d] *ee* determined by CSP HPLC analysis. [e] 1.2 equiv. of **2a** was used. [f] 1.3 equiv. of **2b** was used; nd = not determined.

With optimized catalyst **3b** in hand, we further screened various solvents (Table 2). DCM, DCE, and $CHCl_3$ solvents has similar impact on the selectivity to furnish the products

4ab/**5ab** in 72, 72, 78% yields with 82, 83, 82% *ee* respectively within 1.0 h (Table 2, entries 1-3). Similarly, diethyl ether failed to improve the yield and selectivity of **4ab**/**5ab** (Table 2, entry 4). The reaction in acetonitrile gave **4ab**/**5ab** in 82% yield with moderate (77%) *ee* within 0.4 h (Table 2, entry 5).

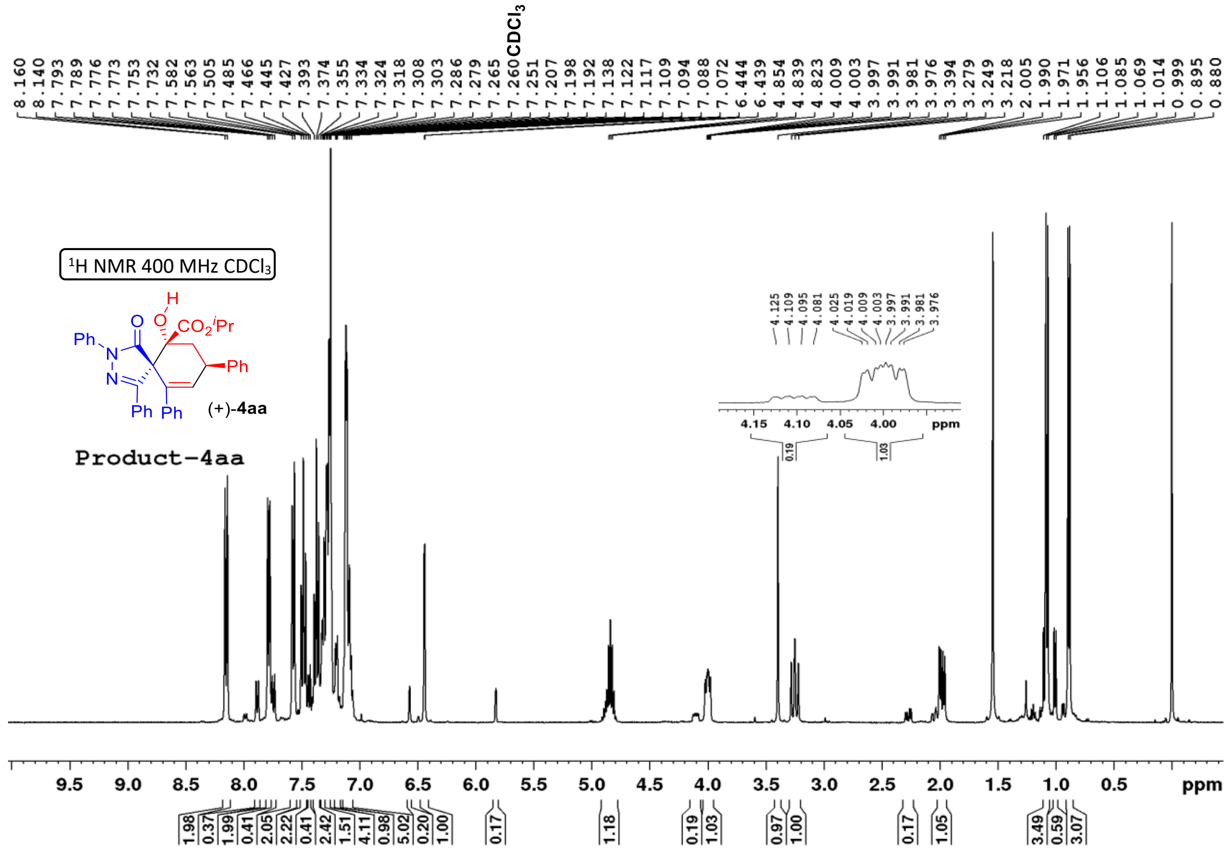
Table 2: Further reaction optimization[a]



Entry	Solvent [0.2 M]	2	T [°C]	t [h]	Yield [%][c] [4+5]	ee [%][d] [4]
1	DCM	**2b**	25 °C	1	72	82
2	DCE	**2b**	25 °C	1	72	83
3	$CHCl_3$	**2b**	25 °C	1	78	82
4	Et_2O	**2b**	25 °C	1.5	71	83
5	CH_3CN	**2b**	25 °C	0.4	82	77
6	DMSO	**2b**	25 °C	6	50	22
7	$CF_3C_6H_5$	**2b**	25 °C	1	70	86
8	C_6F_6	**2b**	25 °C	4	71	79
9	C_6H_6	**2b**	25 °C	1	73	89
10	$CH_3C_6H_5$:C_6H_6 (1:1)	**2b**	0 °C	1.8	67	92
11	C_6H_6	**2b**	4-8 °C	3	80	93
12[e]	C_6H_6	**2b**	4-8 °C	5	66	92
13[f]	C_6H_6	**2b**	4-8 °C	2.5	60	91
14[g]	C_6H_6	**2b**	4-8 °C	2	58	89
15[h]	C_6H_6	**2b**	4-8 °C	3	40	89
16[i]	C_6H_6	**2a**	4-8 °C	4	76	93

[a] Reactions were carried out in solvent (0.2 M) with 1.0 equiv. of **2b** relative to the **1a** (0.2 mmol) in the presence of 10 mol% of catalyst **3b**. [b] Diastereomeric ratio of all the products were maintained between 3.3:1 to 3.7:1 and confirmed by ^{1}H NMR analysis of crude products. [c] Yields refers to the diastereomers **4ab** and **5ab** purified by coloumn chromatography. [d] *ee* determined by CSP HPLC analysis. [e] 5 mol % of catalyst **3b** was used. [f] 15 mol % of catalyst **3b** was used. [g] 20 mol % of catalyst **3b** was used. [h] 0.5 mL H_2O was added. [i] 5.6:1 *dr* of **4aa**:**5aa** was observed.

Reaction was very sluggish in DMSO with 50% yield and extremely low (22%) *ee* may be due to the unavailability of directional **3b**-OH in DMSO for hydrogen bonding with incoming electrophile **2b** to control facial selectivity (Table 2, entry 6). Trifluorotoluene, hexafluorobenzene, and benzene solvents are facilitated the reaction at 25 °C to furnish **4ab**/**5ab** in 70, 71, 73% yields with 86, 79, 89% *ee* respectively (Table 2, entries 7-9). When we performed reaction in mixture of toluene and benzene (1:1) at 0 °C for 1.8 h furnished **4ab**/**5ab** in reduced (67%) yield with increased (92%) *ee* (Table 2, entry 10). When the same reaction was performed in benzene at 4-8 °C for 3 h furnished **4ab**/**5ab** in 80% yield with enhanced 93% *ee* (Table 2, entry 11). To know the effect of catalyst loading, we performed three reactions using 5/15/20 mol% **3b** in benzene at 4-8 °C (Table 2, entries 12-14). It clearly showed that the catalyst loading is inversely proportional to the reaction times/yields/selectivities of **4ab**/**5ab** with 5/2.5/2 h, 66/60/58% yields and 92/91/89% *ee* respectively. Thus, the reaction of **1a** with **2b** in 0.2 M benzene catalyzed by 10 mol% **3b** at 4-8 °C stood as the optimized conditions. Water (0.5 mL) addition to the reaction proved that yield (40%) affected without much change in (89%) *ee* (Table 2, entry 15). Reaction of **1a** with **2a** under the optimized conditions furnished **4aa/5aa** in reduced yield (76%) with 93% *ee* and 5.6:1 *dr*, which is confirming that benzyl is better than isopropyl group in the ester substrate **2** (Table 2, entry 16). The optimized product **4aa**/**5aa** was further confirmed by NMR spectroscopy (Figure 1) and HPLC analysis (Figure 2).



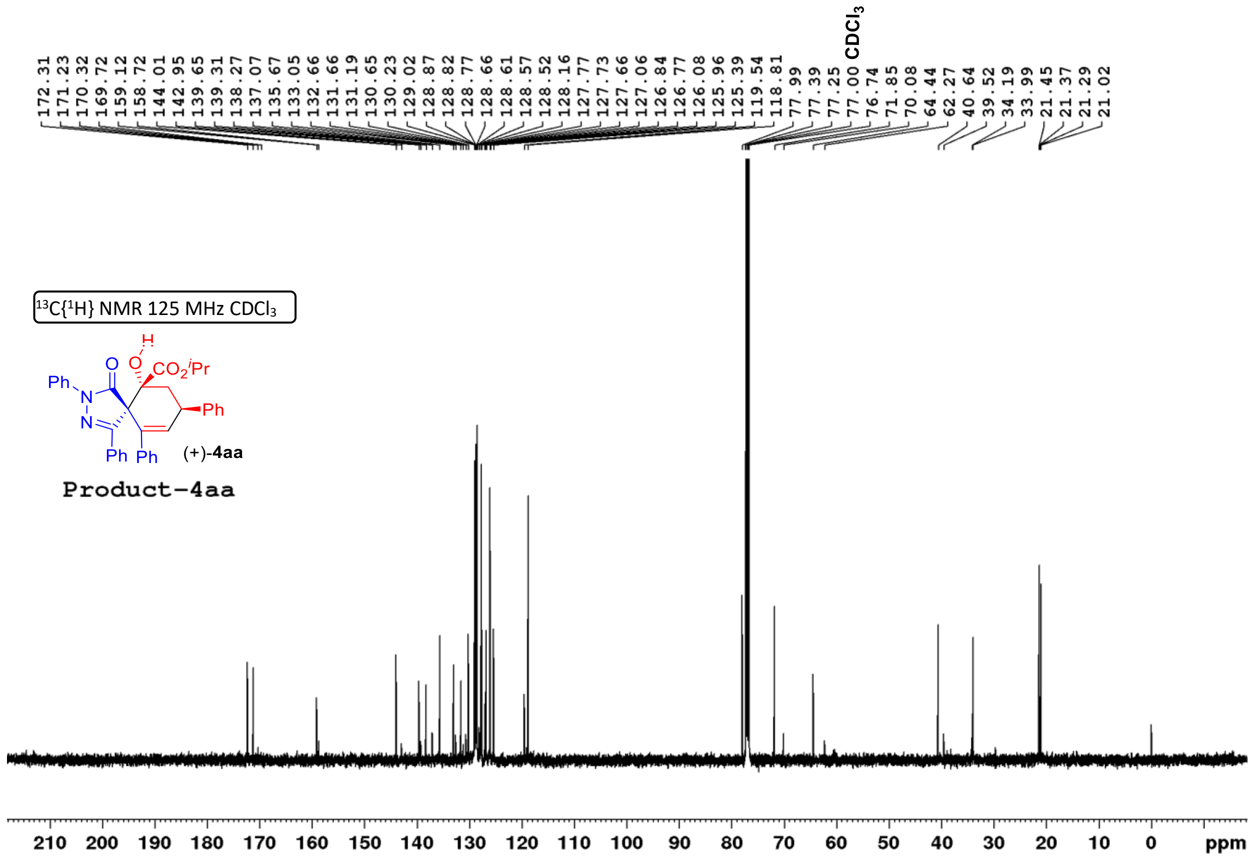
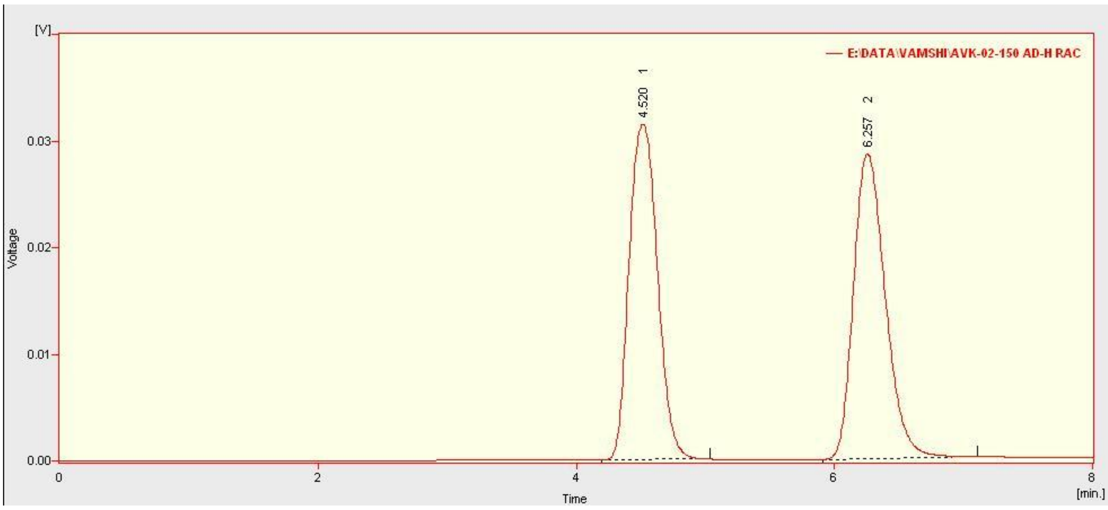


Figure 1: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4aa**.

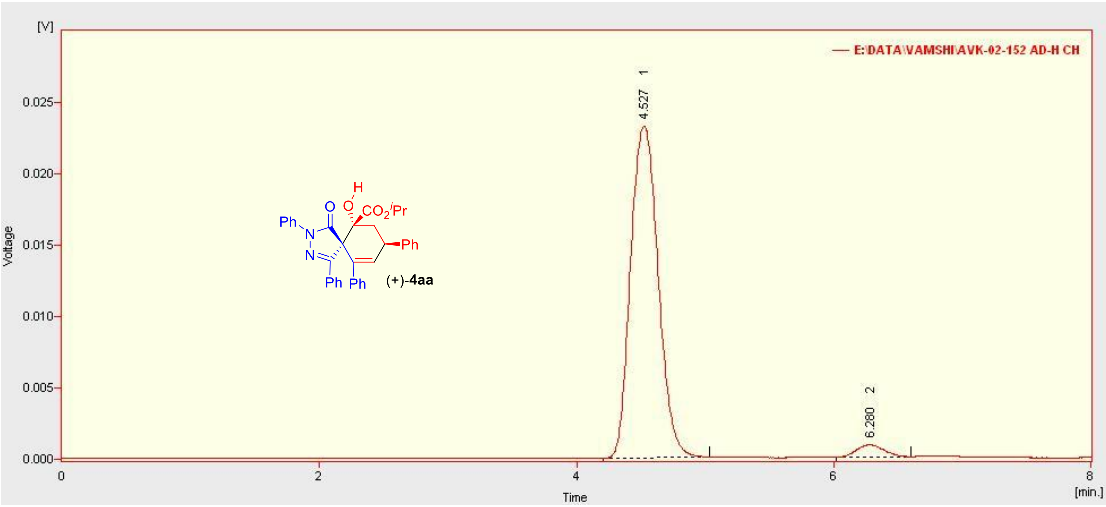
Racemic **(±)-4aa**:



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

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-150 AD-H RAC)						
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	4.520	480.717	31.468	49.6	52.4	0.25
2	6.257	488.205	28.553	50.4	47.6	0.27
	Total	968.923	60.021	100.0	100.0	

Chiral **(+)-4aa** (93% *ee*):



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

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-152 AD-H CH)						
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	4.527	346.266	23.269	96.5	96.5	0.24
2	6.280	12.690	0.854	3.5	3.5	0.24
	Total	358.956	24.123	100.0	100.0	

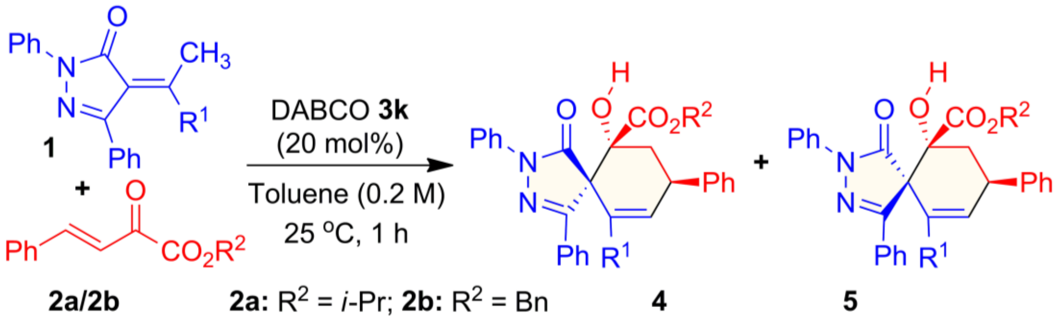
Figure 2: HPLC spectra of the product **4aa**.

3.2.2 Substrate Scope of the Organocatalytic Asymmetric [3+3]-Annulation Reaction

3.2.2.1 Racemic substrate scope with reference to the ambident nucleophiles 1

Before proceeding to the chiral substrate scope, we have synthesized a library of racemic products **4aa**/**5aa** to **4jb**/**5jb** by reacting **1** with **2** in the presence of 20 mol% of DABCO **3k** in 0.2 M toluene at 25 °C for 1.0 h. We successfully furnished all the racemic products with excellent yields and moderate *dr* (Table 3).

Table 3: Racemic substrate scope with reference to ambident nucleophiles **1**[a]



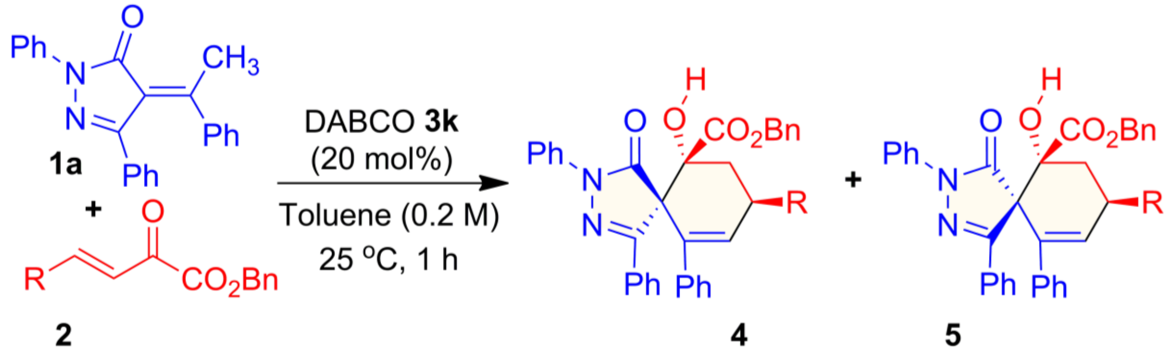
Entry	**1** [R^1]	**2** [R^2]	Yield [%][b] **[4+5]**	*dr*[c] **[4:5]**
1	**1a:** C_6H_5	**2a**	93 (**4aa+5aa**)	5.4:1
2	**1a:** C_6H_5	**2b**	91 (**4ab+5ab**)	3.0:1
3	**1b:** 4-FC_6H_4	**2b**	90 (**4bb+5bb**)	3.7:1
4	**1c:** 4-ClC_6H_4	**2b**	91 (**4cb+5cb**)	4.2:1
5	**1d:** 4-BrC_6H_4	**2b**	88 (**4db+5db**)	4.2:1
6	**1e:** 2,4-$Cl_2C_6H_3$	**2b**	78 (**4eb+5eb**)	3.3:1
7	**1f:** 4-MeC_6H_4	**2b**	87 (**4fb+5fb**)	3.2:1
8	**1g:** 4-$^tBuC_6H_4$	**2b**	92 (**4gb+5gb**)	3.3:1
9	**1h:** 3,4-$Me_2C_6H_3$	**2b**	87 (**4hb+5hb**)	3.7:1
10	**1i:** 4-$OMeC_6H_4$	**2b**	87 (**4ib+5ib**)	3.4:1
11	**1j:** 4-$CF_3C_6H_4$	**2b**	80 (**4jb+5jb**)	4.3:1

[a] Reactions were carried out in toluene (0.2 M) with 1.0 equiv. of **2** relative to the **1** (0.2 mmol) in the presence of 20 mol% of catalyst **3k**. [b] Yields refers to the diastereomers **4** and **5** purified by column chromatography. [c] dr was determined by ^{1}H NMR analysis of column purified products.

3.2.2.2 Racemic substrate scope with reference to the ambident electrophiles 2

We have then synthesized a library of racemic products **4ac**/**5ac** to **4al**/**5al** by reacting **1** with **2** in the presence of 20 mol% of DABCO **3k** in 0.2 M toluene at 25 °C for 1.0 h. We successfully furnished all the racemic products with excellent yields and moderate *dr* (Table 4).

Table 4: Racemic substrate scope with reference to ambident electrophiles **2**[a]



Entry	**2** (R)	Yield [%][b] [**4+5**]	*dr*[c] [**4:5**]
1	**2c:** R = 2-FC_6H_4	80 (**4ac+5ac**)	3.8:1
2	**2d:** R = 3-FC_6H_4	91 (**4ad+5ad**)	11.0:1
3	**2e:** R = 4-FC_6H_4	92 (**4ae+5ae**)	4.2:1
4	**2f:** R = 4-ClC_6H_4	90 (**4af+5af**)	3.0:1
5	**2g:** R = 4-BrC_6H_4	94 (**4ag+5ag**)	3.8:1
6	**2h:** R = 4-MeC_6H_4	81 (**4ah+5ah**)	2.9:1
7	**2i:** R = 2-Napthyl	90 (**4ai+5ai**)	3.2:1
8	**2j:** R = 4-OMeC_6H_4	92 (**4aj+5aj**)	3.3:1
9	**2k:** R = 4-CNC_6H_4	95 (**4ak+5ak**)	4.5:1
10	**2l:** R = 4-$CF_3C_6H_4$	89 (**4al+5al**)	4.0:1

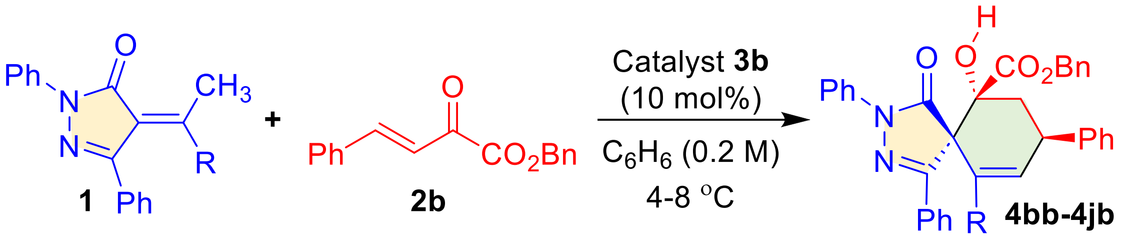
[a] Reactions were carried out in toluene (0.2 M) with 1.0 equiv. of **2** relative to the **1a** (0.2 mmol) in the presence of 20 mol % of catalyst **3k**. [b] Yields refers to the diastereomers **4** and **5** purified by column chromatography. [c] dr was determined by ^{1}H NMR analysis of column purified products.

3.2.2.3 Chiral substrate scope with reference to the ambident nucleophiles 1

With the best conditions in hand, we were fascinated to investigate the multi-centric nucleophiles **1** with electrophiles **2**. We initiated our investigation by varying substituted nucleophiles **1b-j** with **2b**. The reaction of 4-fluorophenyl, 4-chlorophenyl, and 4-bromophenyl substituted pyrazolinones **1b-d** with **2b** catalyzed by 10 mol% **3b** at 4-8 °C for 3.5 to 4.0 h furnished the products **4bb-db/5bb-db** in 67-70% yields with 3.3:1-4.2:1 *dr* and 92-94% *ee* (Table 5, entries 1-3). The reaction also well tolerated alkyl substitutions such as

4-methylphenyl, 4-*tert*-butylphenyl, and 3,4-dimethylphenyl substituted pyrazolinones **1f-h** for 3.5 h to furnish the products **4fb-hb**/**5fb-hb** in 71-79% yields with 3.6:1-4.8:1 *dr* and 94-92% *ee* (Table 5, entries 5-7).

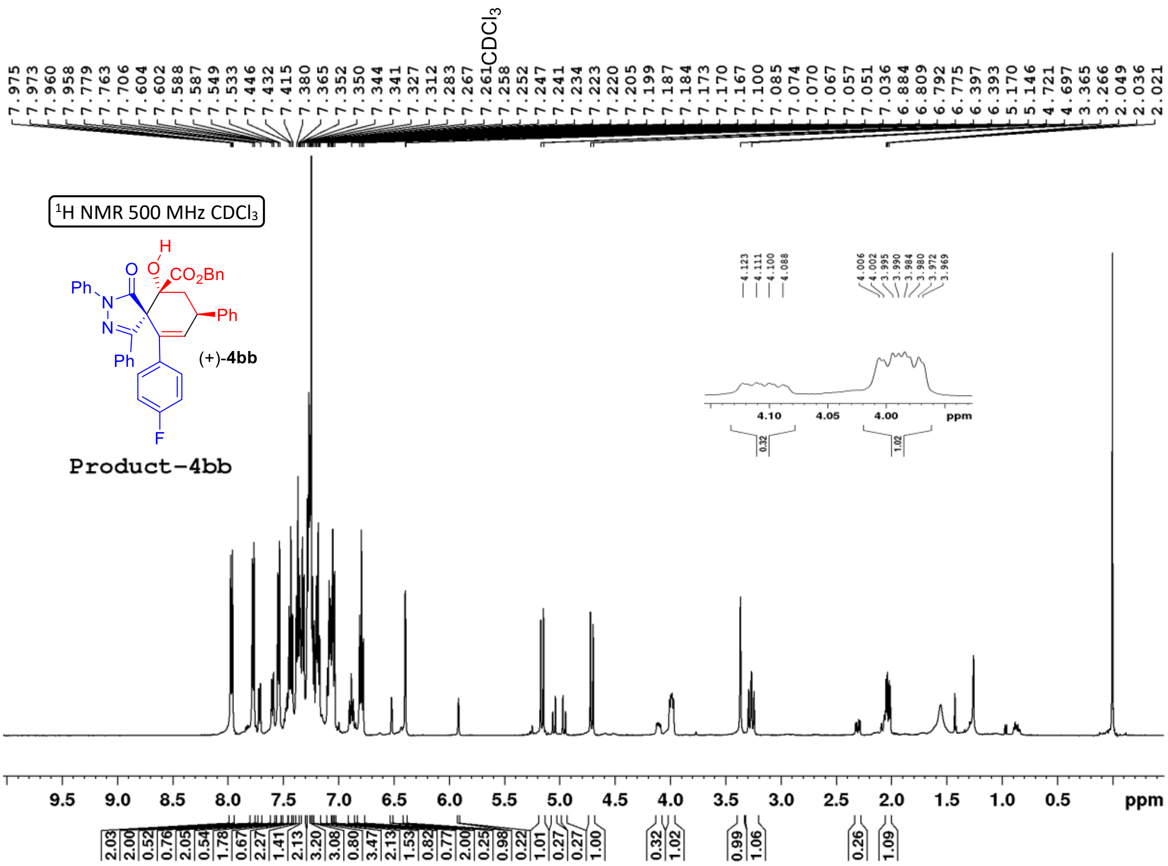
Table 5: Chiral substrate scope with reference to ambident nucleophiles **1**[a]



Entry	**1** (R)	*t* (h)	Yield [%][b] [4+5]	*dr*[c] [4:5]	*ee* [%][d] [4]
1	**1b:** 4-FC_6H_4	4.0	68 [**4bb+5bb**]	3.3:1	94
2	**1c:** 4-ClC_6H_4	3.5	70 [**4cb+5cb**]	4.2:1	92
3	**1d:** 4-BrC_6H_4	3.5	67 [**4db+5db**]	3.7:1	92
4	**1e:** 2,4-$Cl_2C_6H_3$	4.0	42 [**4eb+5eb**]	3.4:1	77
5	**1f:** 4-MeC_6H_4	3.5	74 [**4fb+5fb**]	3.6:1	94
6	**1g:** 4-$^t BuC_6H_4$	3.5	79 [**4gb+5gb**]	4.8:1	92
7	**1h:** 3,4-$Me_2C_6H_3$	3.5	71 [**4hb+5hb**]	4.0:1	93
8	**1i:** 4-$OMeC_6H_4$	3.5	83 [**4ib+5ib**]	3.3:1	96
9	**1j:** 4-$CF_3C_6H_4$	4.0	37 [**4jb+5jb**]	4.4:1	86

[a] Reactions were carried out in benzene (0.2 M) with 1.0 equiv of **2b** relative to the **1** (0.2 mmol) in the presence of 10 mol % of catalyst **3b**. [b] Yields refers to the diastereomers **4** and **5** purified by coloumn chromatography. [c] dr was determined by ^{1}H NMR analysis of coloumn purified products. [d] *ee* determined by CSP HPLC analysis.

Interestingly, 2,4-dichlorophenyl pyrazolinone **1e** yielded the product **4eb**/**5eb** for 4.0 h in poor (42%) yield with 3.4:1 *dr* and moderate (77%) *ee* showing the steric effect of *ortho*-substitution on yield and selectivity (Table 5, entry 4). Gratifyingly, 4-methoxyphenyl substituted pyrazolinone **1i** furnished the product **4ib**/**5ib** for 3.5 h in 83% yield with 3.3:1 *dr* and 96% *ee* (Table 5, entry 8); whereas trifluoromethylphenyl substituted pyrazolinone **1j** furnished **4jb**/**5jb** in low (37%) yield with 4.4:1 *dr* and 86% *ee* (Table 5, entry 9). This validates the effect of electronic factors on the product yields and selectivities. The spectroscopic and HPLC data for few selected substrates **4** were shown in Figures 3-10.



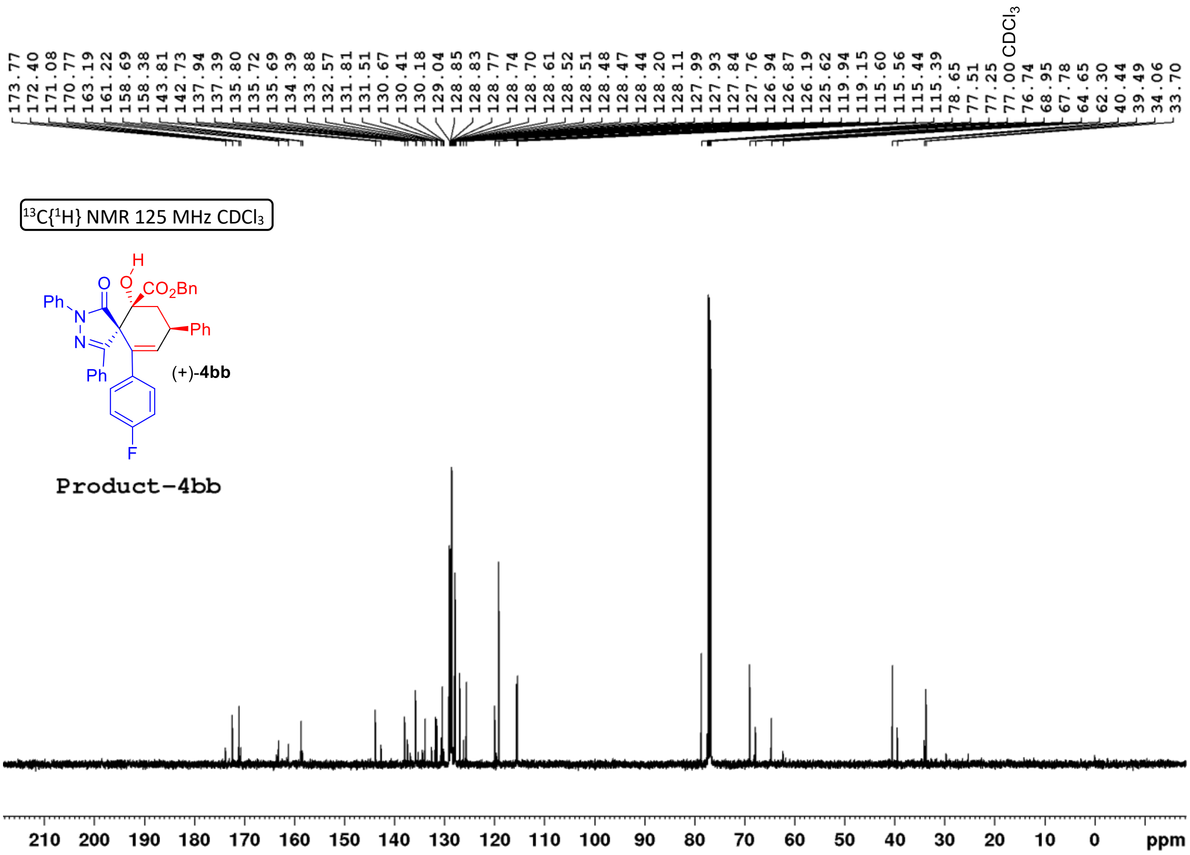
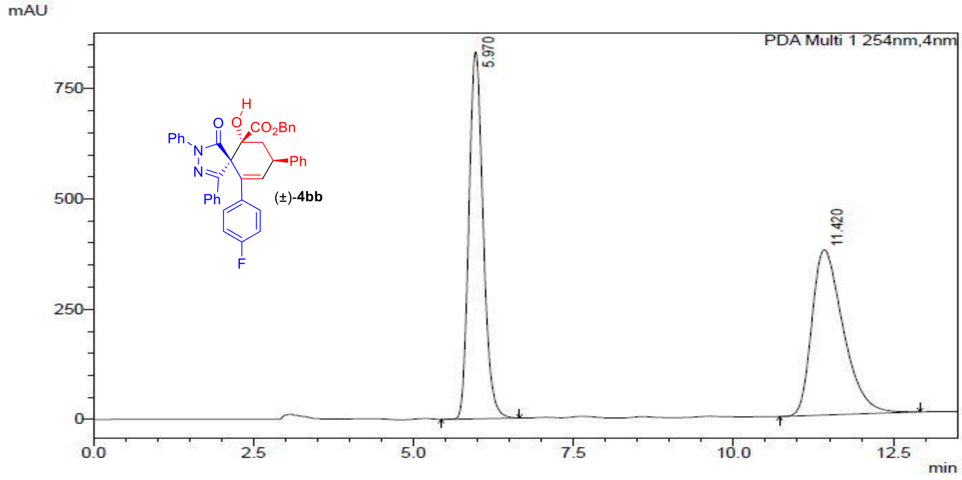


Figure 3: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4bb**.

Racemic **(±)-4bb**:



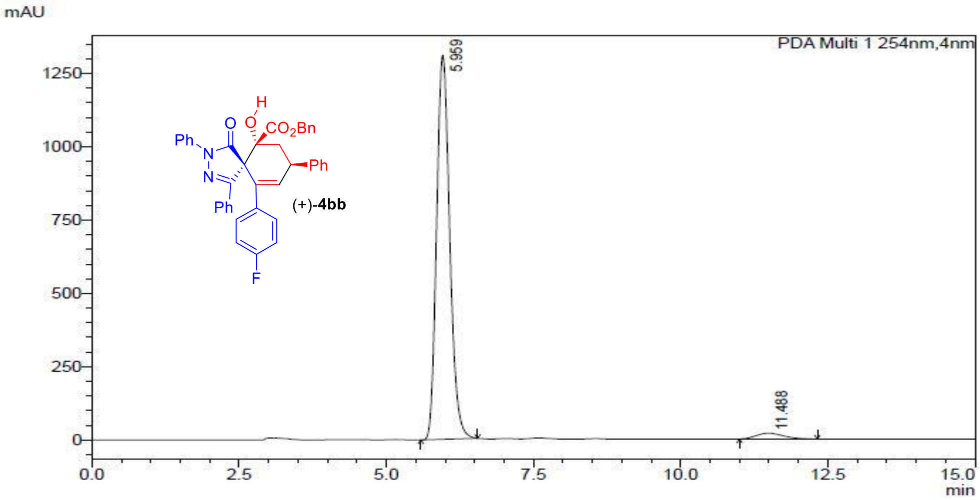
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:5.970	5.970	12931819	832577	50.304	68.947
2	RT:11.420	11.420	12775420	374978	49.696	31.053
Total			25707239	1207555	100.000	100.000

Chiral **(+)-4bb** (94% *ee*):



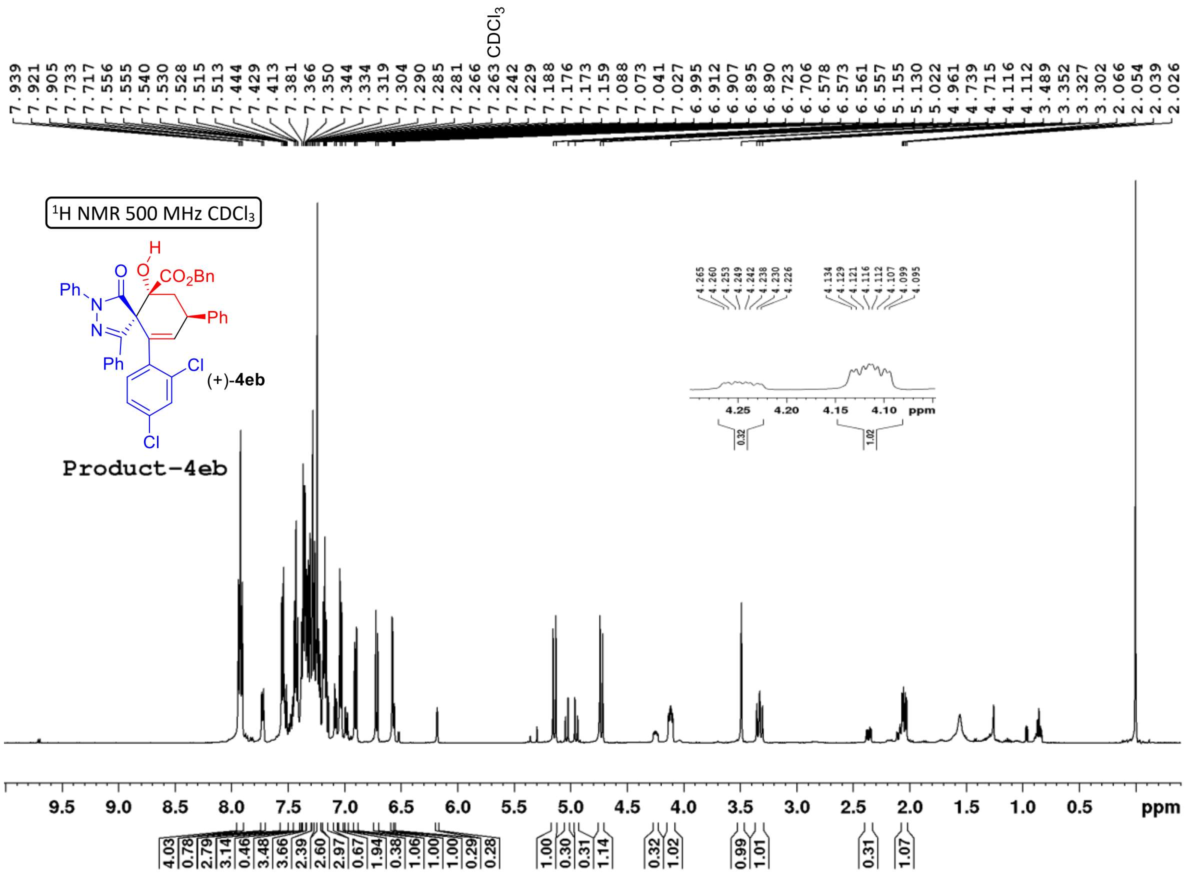
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:5.959	5.959	20309152	1310545	96.979	98.521
2	RT:11.488	11.488	632569	19677	3.021	1.479
Total			20941722	1330221	100.000	100.000

Figure 4: HPLC spectra of the product **4bb**.



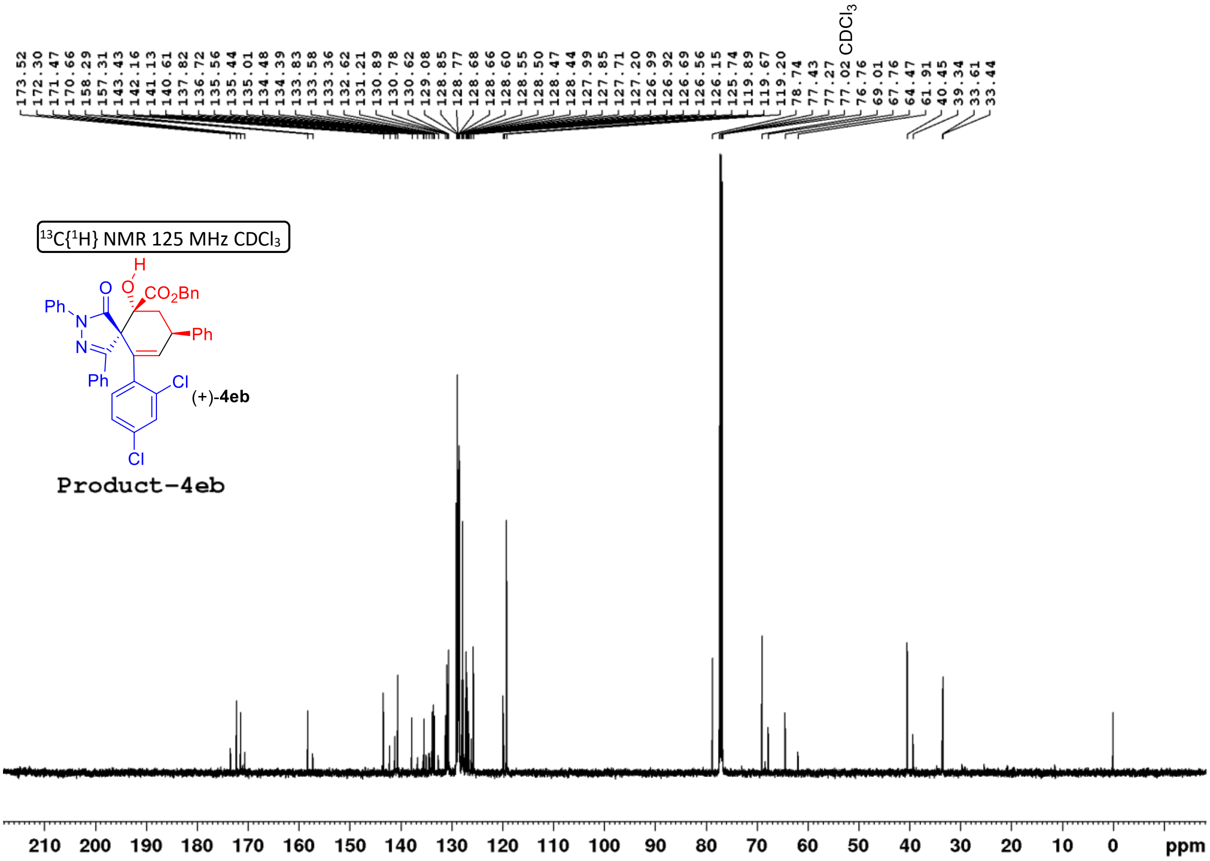
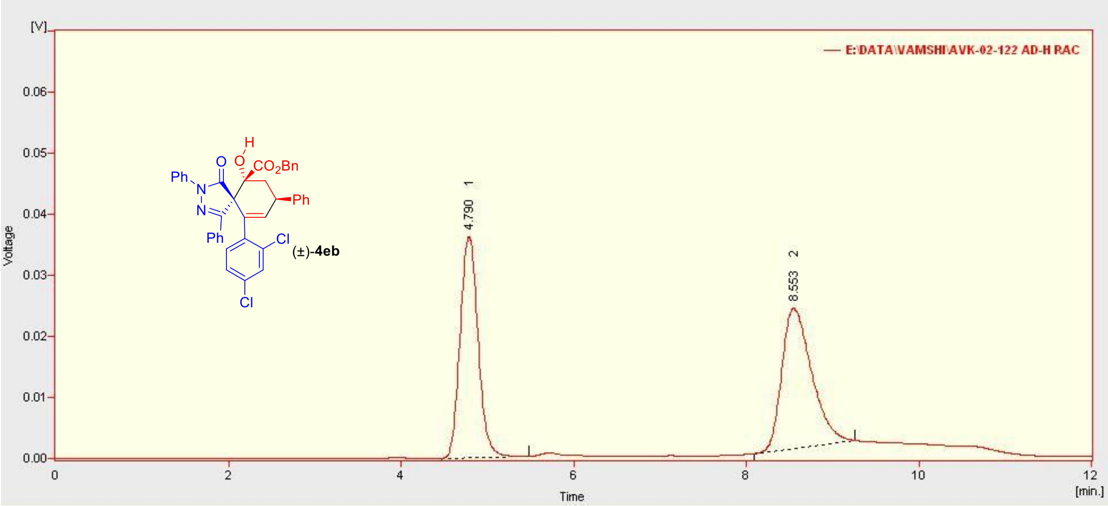


Figure 5: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4eb**.

Racemic **(±)-4eb**:

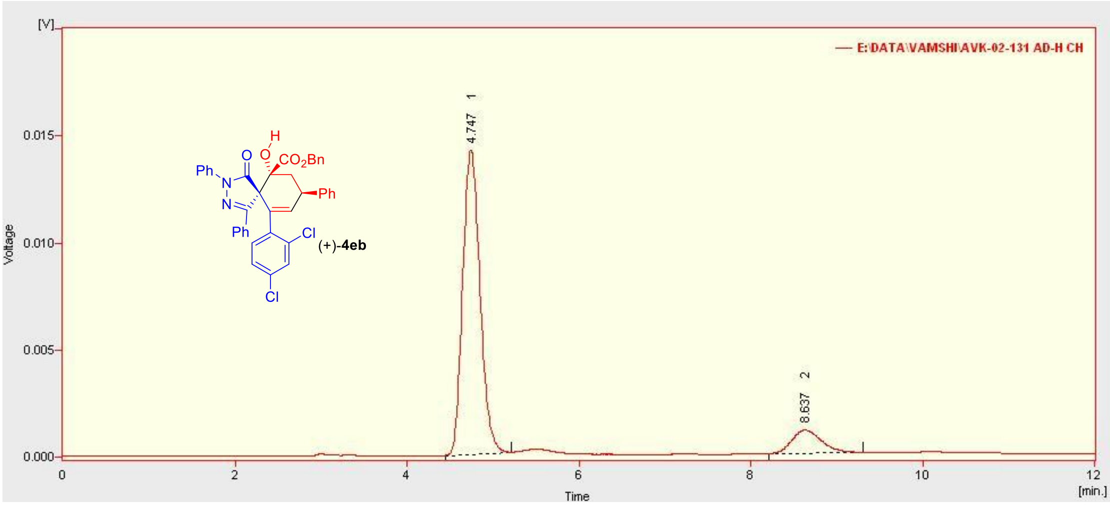


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-122 AD-H RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	4.790	521.088	36.178	48.7	61.2	0.23
2	8.553	548.516	22.906	51.3	38.8	0.38
	Total	1069.604	59.084	100.0	100.0	

Chiral **(+)-4eb** (77% *ee*):

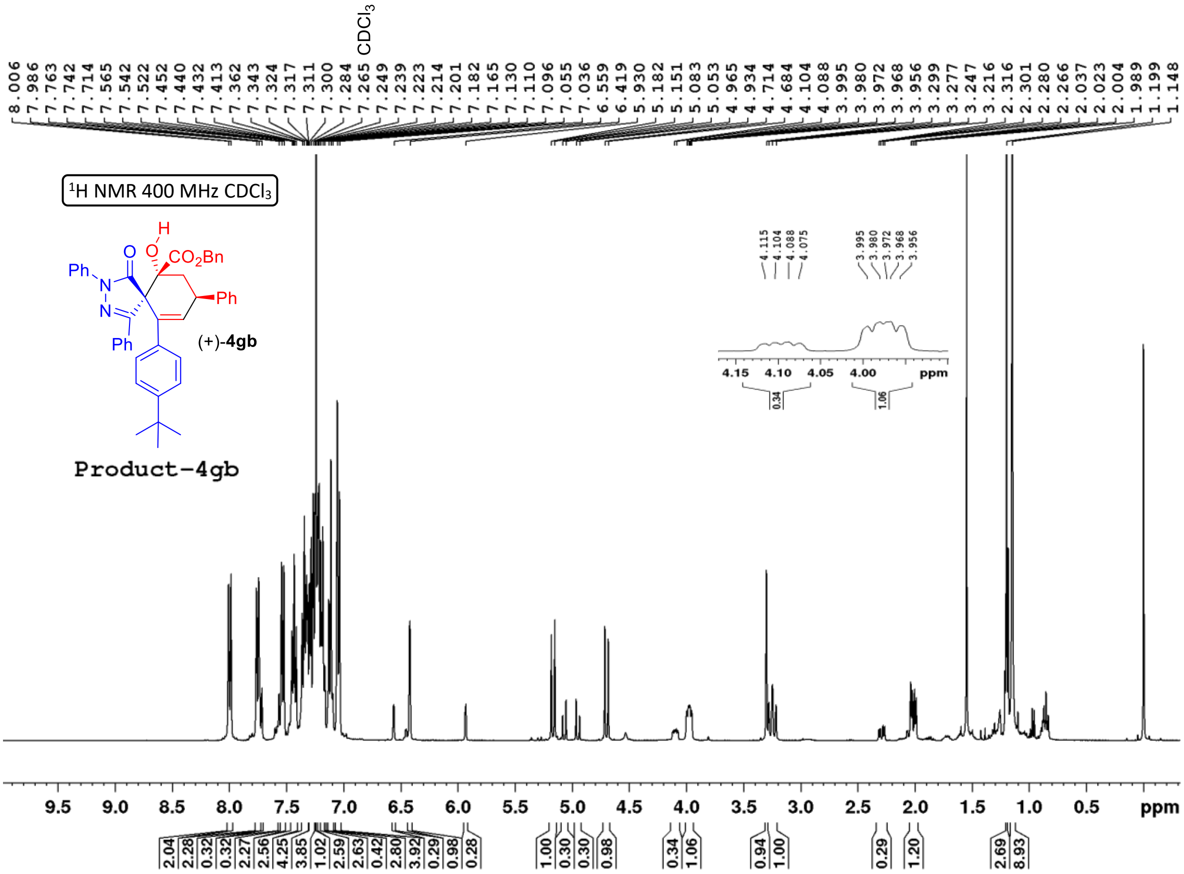


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-131 AD-H CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	4.747	198.428	14.201	88.5	93.0	0.22
2	8.637	25.791	1.075	11.5	7.0	0.37
	Total	224.220	15.276	100.0	100.0	

Figure 6: HPLC spectra of the product **4eb**.



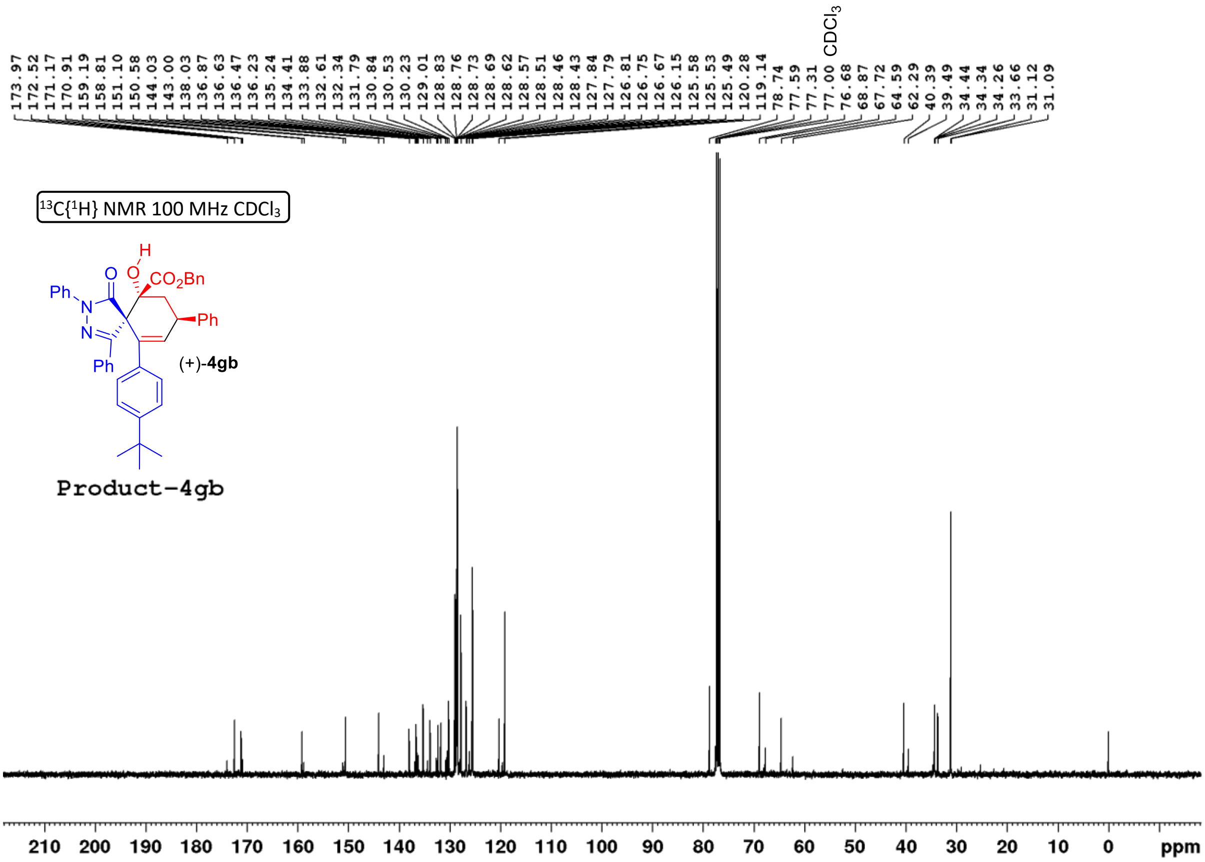
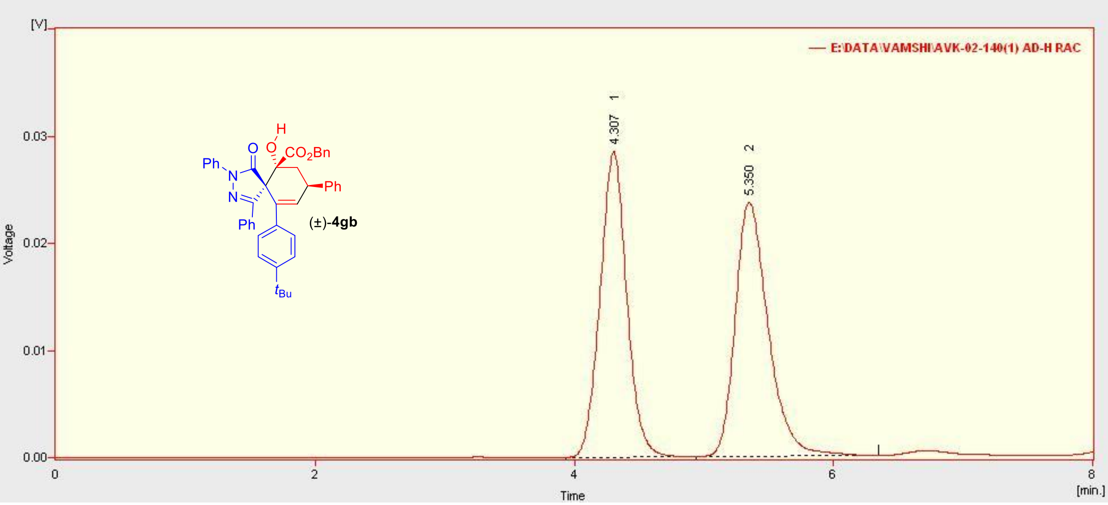


Figure 7: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4gb**.

Racemic **(±)-4gb**:

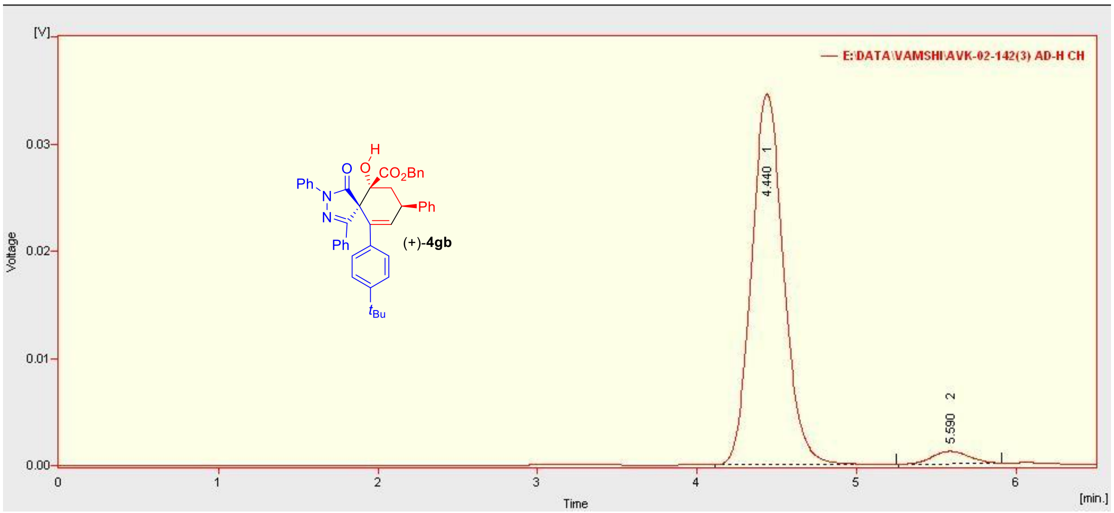


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-140(1) AD-H RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	4.307	407.022	28.481	49.2	54.6	0.22
2	5.350	419.592	23.705	50.8	45.4	0.27
	Total	826.614	52.186	100.0	100.0	

Chiral **(+)-4gb** (92% *ee*):

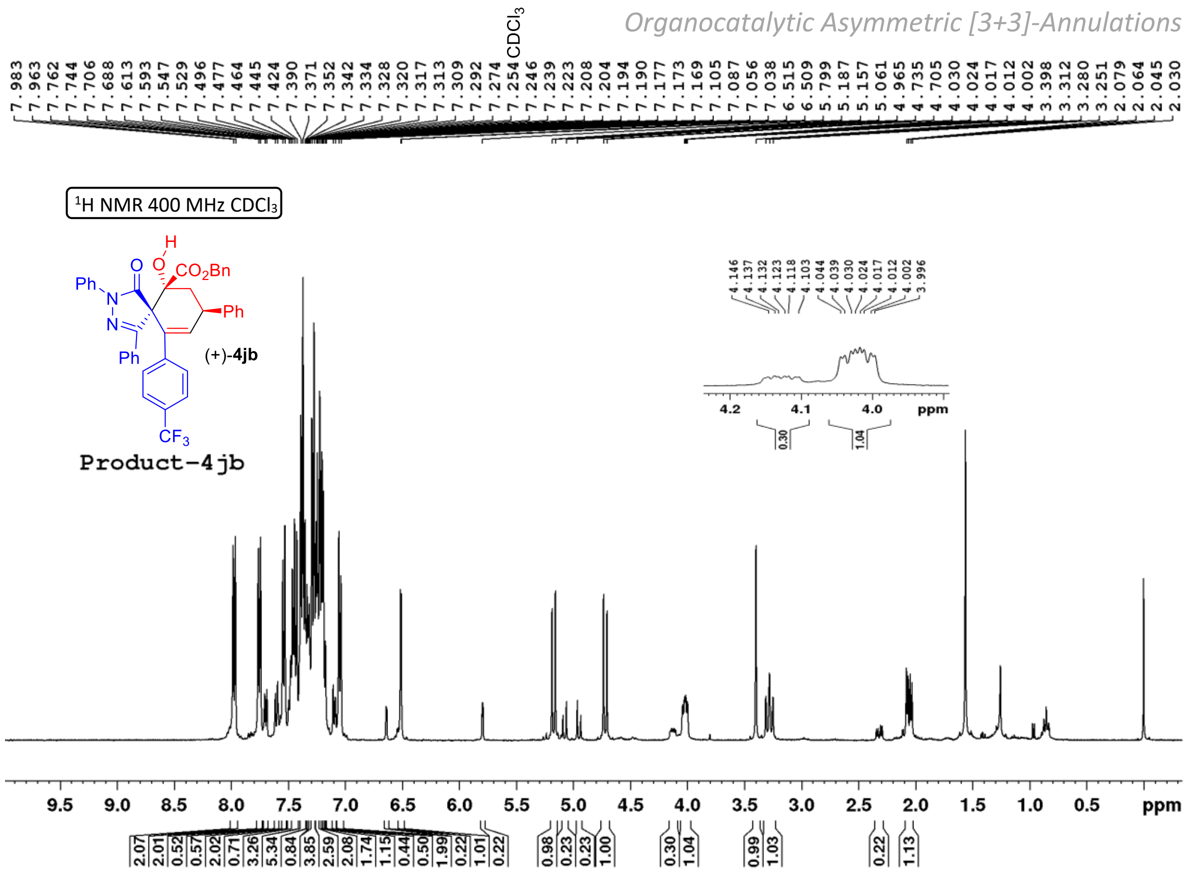


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-142(3) AD-H CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	4.440	480.451	34.561	96.3	96.8	0.22
2	5.590	18.252	1.151	3.7	3.2	0.26
	Total	498.704	35.713	100.0	100.0	

Figure 8: HPLC spectra of the product **4gb**.



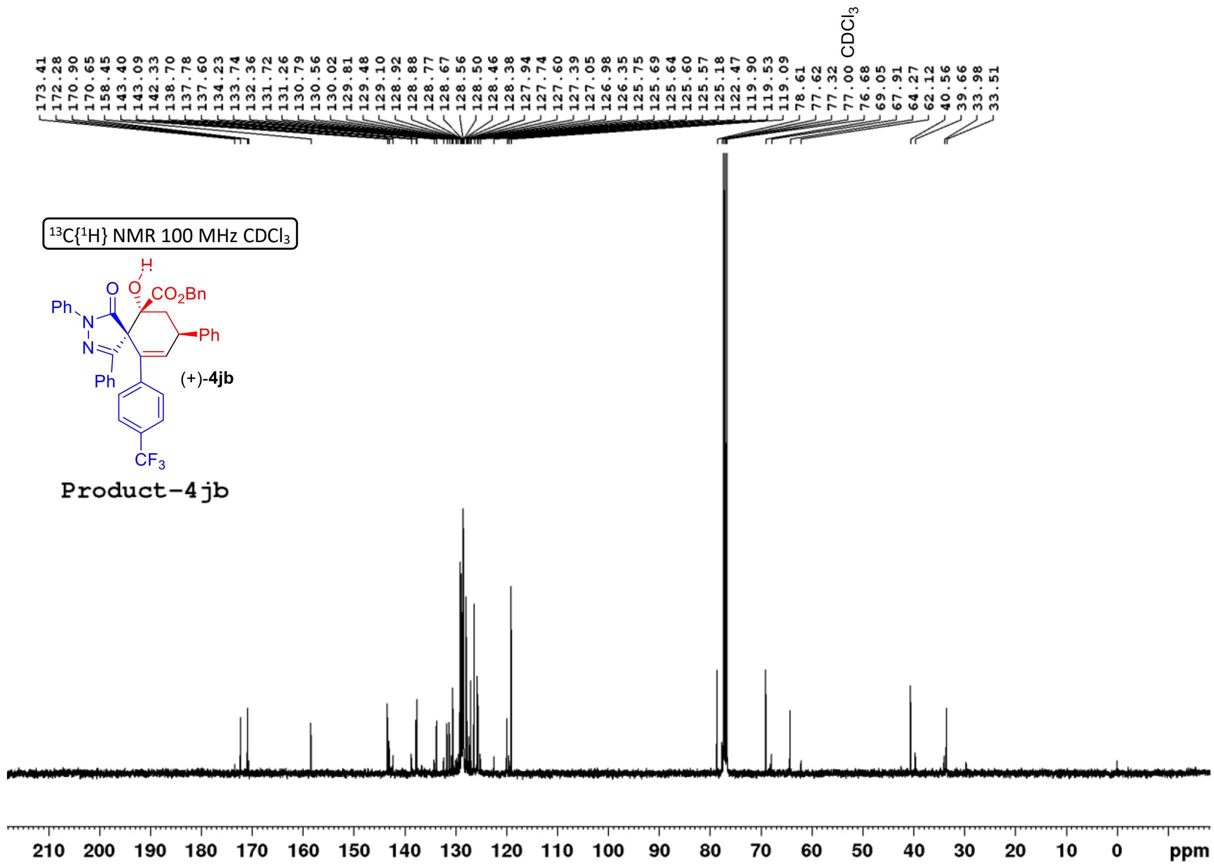
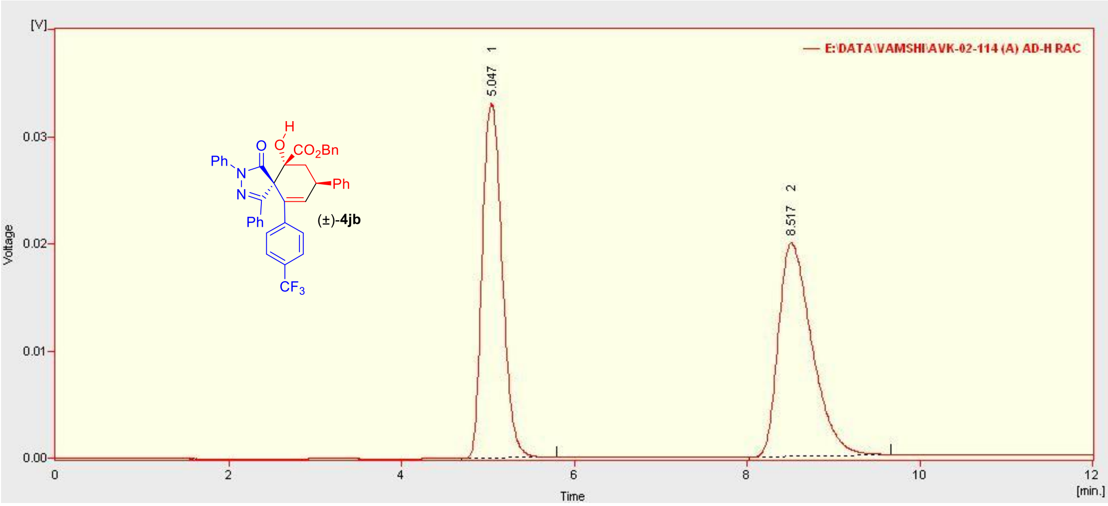


Figure 9: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4jb**.

Racemic **(±)-4jb**:

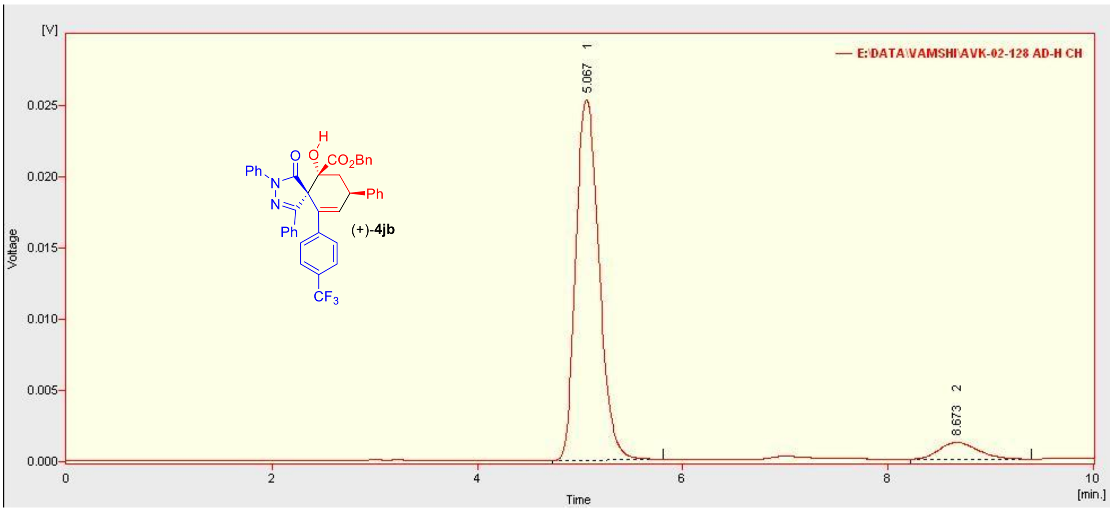


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-114 (A) AD-H RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	5.047	526.261	33.053	49.5	62.4	0.25
2	8.517	537.111	19.931	50.5	37.6	0.42
	Total	1063.372	52.984	100.0	100.0	

Chiral **(+)-4jb** (86% *ee*):



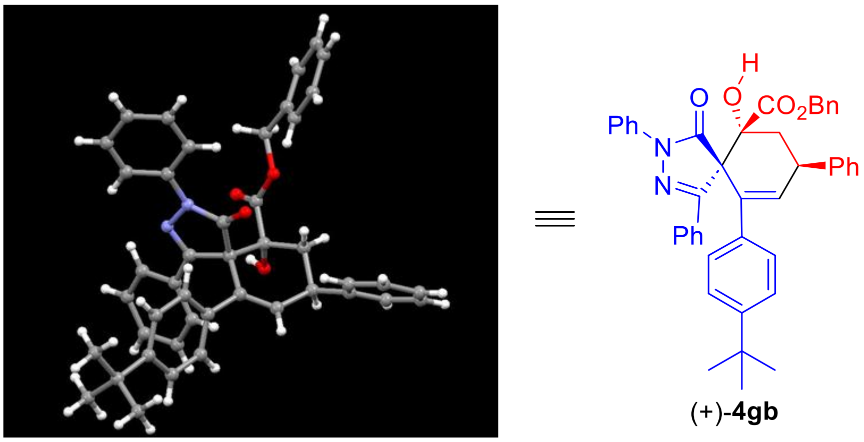
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-128 AD-H CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	5.067	398.296	25.297	92.9	95.6	0.25
2	8.673	30.510	1.173	7.1	4.4	0.41
	Total	428.806	26.469	100.0	100.0	

Figure 10: HPLC spectra of the product **4jb**.

The absolute structure of compound (+)-**4gb** was again confirmed by X-ray crystallography (Figure 11).[6]



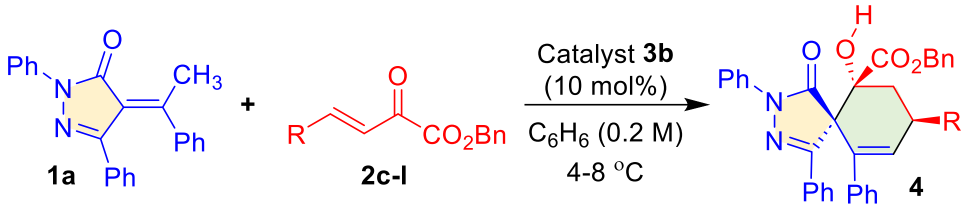
(+)-**4gb**

Figure 11: X-Ray crystal structure of Benzyl (5*S*,6*R*,8*R*)-10-(4-(tert-butyl)phenyl)-6-hydroxy-4-oxo-1,3,8-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate [(+)-**4gb**]

3.2.2.4 Chiral substrate scope with reference to the ambident electrophiles 2 and 9

Further, we investigated the reaction by varying electrophiles **2a-l** with **1a**. In order to understand the substituent positional effect on the yield and selectivity, we reacted 2-fluorophenyl, 3-fluorophenyl, and 4-fluorophenyl substituted keto-ester **2c-e** with **1a** under the optimal conditions for 3.5-4.0 h to furnish **4ac-ae/5ac-ae** in 56, 74, 70% yields with 4.2:1, 3.3:1, 4.2:1 *dr* and 91, 92, 90% *ee* respectively (Table 6, entries 1-3). This clearly revealed the effect of *ortho*-substitution on the yield. The reaction was well tolerated with other halo, alkyl, aryl substitutions such as 4-chlorophenyl, 4-bromophenyl, 4-methylphenyl, and 2-napthyl substituted keto-esters **2f-i** to furnish **4af-ai/5af-ai** in 64-76% yield with 2.8:1-4.2:1 *dr* and 90-92% *ee* for 3.0-4.0 h (Table 6, entries 4-7). Interestingly, the 4-methoxyphenyl **2j**, 4-cyanophenyl, and 4-trifluoromethylphenyl substituted keto-esters **2j-l** tolerated the reaction in the similar fashion to furnish **4aj-al/5aj-al** in 70-71% yield with 3.3:1-4.5:1 *dr* and 90-92% *ee* for 3.5-4.0 h (Table 6, entries 8-10). This clearly shows that the domino reaction selectivity is unaffected by the electronic factors of the substituted electrophiles **2**. Surprisingly, reaction of **1a** with cyclic keto-ester **9** under the optimal conditions at 25 °C for 12 h furnished the dispiro compound **10** in 47% yield with 99:1 *dr* and only 8% *ee* (Table 7, entry 1). Same reaction under the quinidine-thiourea **3i**-catalysis in benzene (0.2 M) at 25 °C for 14 h furnished the **10** in 77% yield with 99:1 *dr* and 75% *ee* (Table 7, entry 2). Reaction of **1a** with **9** under the **3h** or **3i**-catalysis in toluene (0.1 M) at 25 °C for 12 h furnished the dispiro compound **10** in 80-82% yield with 99:1 *dr* and 76% *ee* (Table 7, entries 3-5). These results clearly suggesting that structure of both **1** and **2/9** are involving more number of weak interactions with catalysts **3**, which is controlling the facial selectivity. The NMR and HPLC proofs for few selected compounds **4** and **10** are shown in Figures 12-25.

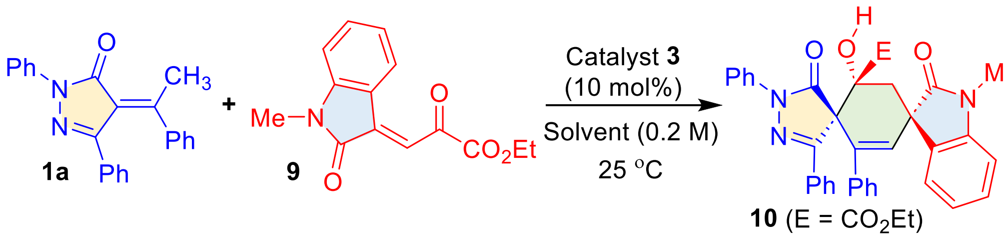
Table 6: Chiral substrate scope with reference to ambident electrophiles **2**[a]



Entry	**2** (R)	*t* (h)	Yield [%][b] **[4+5]**	*dr*[c] **[4:5]**	*ee* [%][d] **[4]**
1	**2c:** R = 2-FC_6H_4	3.5	56 [**4ac**+**5ac**]	4.2:1	91
2	**2d:** R = 3-FC_6H_4	3.5	74 [**4ad**+**5ad**]	3.3:1	92
3	**2e:** R = 4-FC_6H_4	4.0	70 [**4ae**+**5ae**]	4.2:1	90
4	**2f:** R = 4-ClC_6H_4	4.0	76 [**4af**+**5af**]	4.2:1	91
5	**2g:** R = 4-BrC_6H_4	4.0	64 [**4ag**+**5ag**]	3.3:1	92
6	**2h:** R = 4-MeC_6H_4	3.0	71 [**4ah**+**5ah**]	2.8:1	90
7	**2i:** R = 2-Napthyl	4.0	70 [**4ai**+**5ai**]	2.8:1	90
8	**2j:** R = 4-$OMeC_6H_4$	3.5	70 [**4aj**+**5aj**]	3.3:1	90
9	**2k:** R = 4-CNC_6H_4	4.0	70 [**4ak**+**5ak**]	3.7:1	92
10	**2l:** R = 4-$CF_3C_6H_4$	3.5	71 [**4al**+**5al**]	4.5:1	91

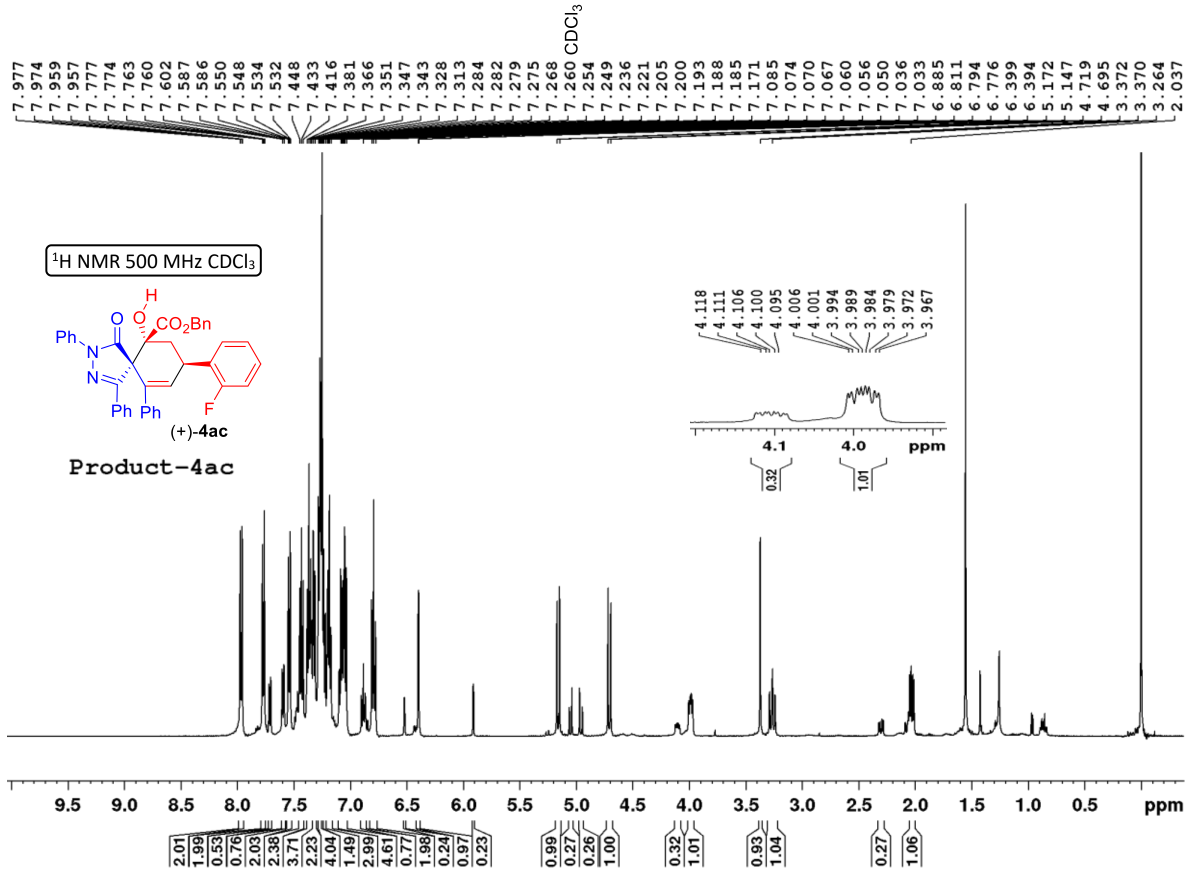
[a] Reactions were carried out in Benzene (0.2 M) with 1.0 equiv of **2a** relative to the **1a** (0.2 mmol) in the presence of 10 mol % of catalyst **3b**. [b] Yields refers to the diastereomers **4** and **5** purified by coloumn chromatography. [c] dr was determined by ^{1}H NMR analysis of coloumn purified products. [d] *ee* determined by CSP HPLC analysis.

Table 7: Chiral substrate scope with reference to ambident electrophiles **9**[a]



Entry	3	Solvent	*t* (h)	Yield [%][a]	*dr*[b]	*ee* [%][c]
1[d]	**3b**	C_6H_6	12	47	-	8
2[d]	**3i**	C_6H_6	14	77	-	75
3[d]	**3i**	$CH_3C_6H_5$	8.5	82	-	73
4[e]	**3i**	$CH_3C_6H_5$	12	80	-	76
5[e, f]	**3h**	$CH_3C_6H_5$	12	82	-	76

[a] Yields refers to the product purified by coloumn chromatography. [b] dr was determined by ^{1}H NMR analysis of crude products. [c] *ee* determined by CSP HPLC analysis. [d] Reactions were carried out in 0.2 M solvent. [e] Reactions were carried out in 0.1 M solvent. [f] *ee* represents the opposite enantiomer of **10**.



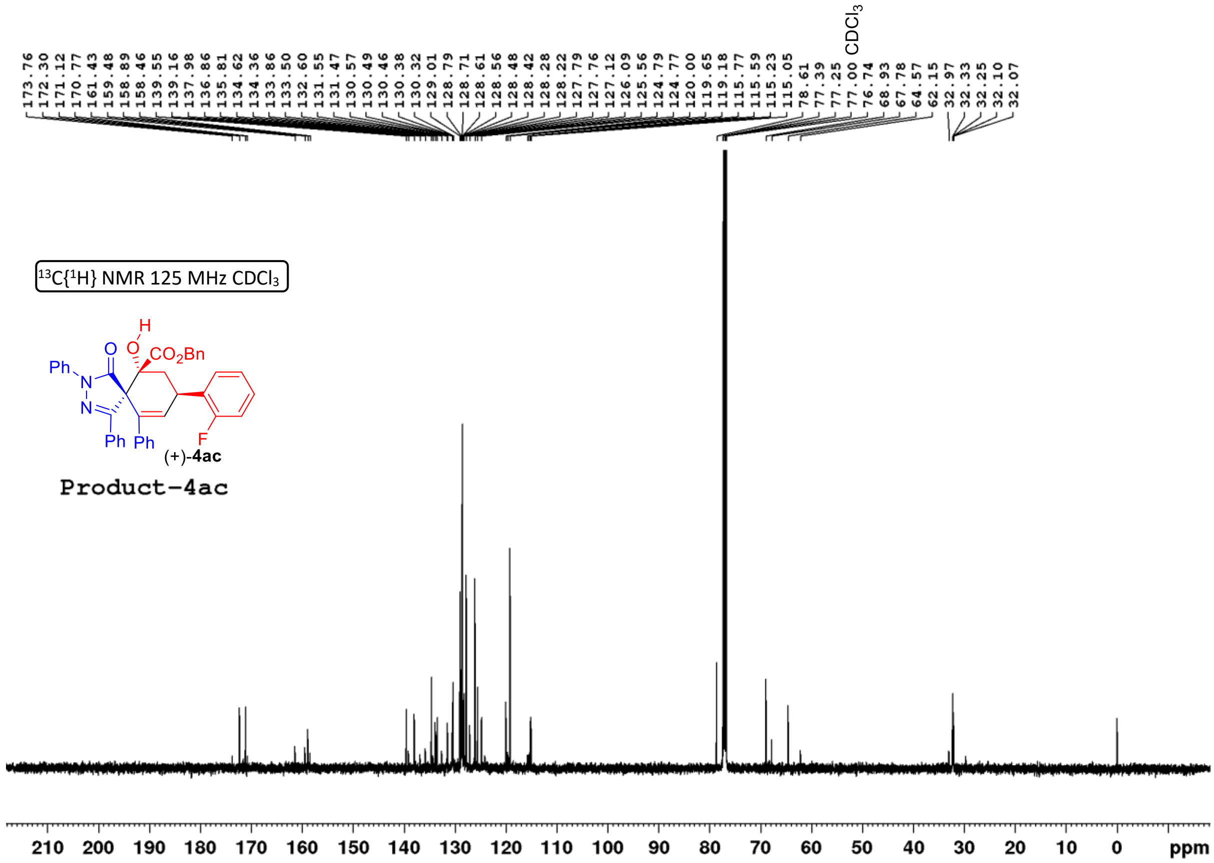
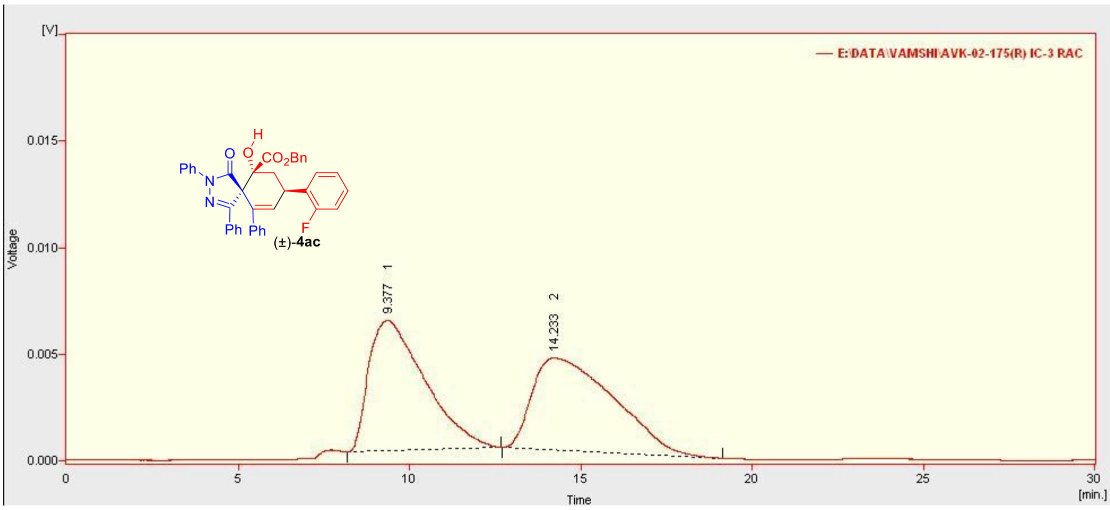


Figure 12: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4ac**.

Racemic **(±)-4ac**:

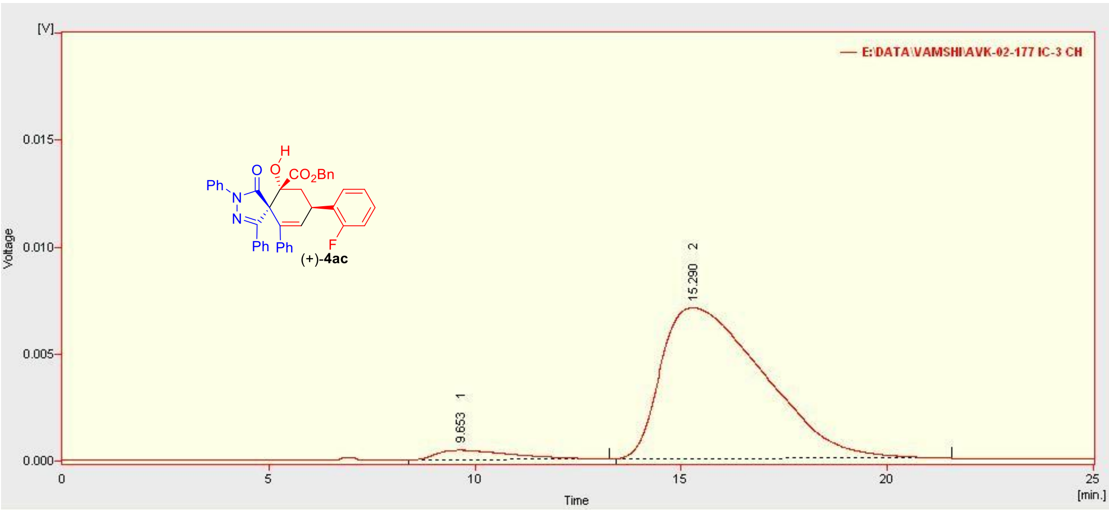


Chiralpak IC-3, Hexane/*i*-PrOH = 99:1, mL/Min, Flow Rate 0.5 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-175(R) IC-3 RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	9.377	695.973	6.127	49.1	58.7	1.83
2	14.233	720.272	4.317	50.9	41.3	2.67
	Total	1416.245	10.444	100.0	100.0	

Chiral **(+)-4ac** (91% *ee*):

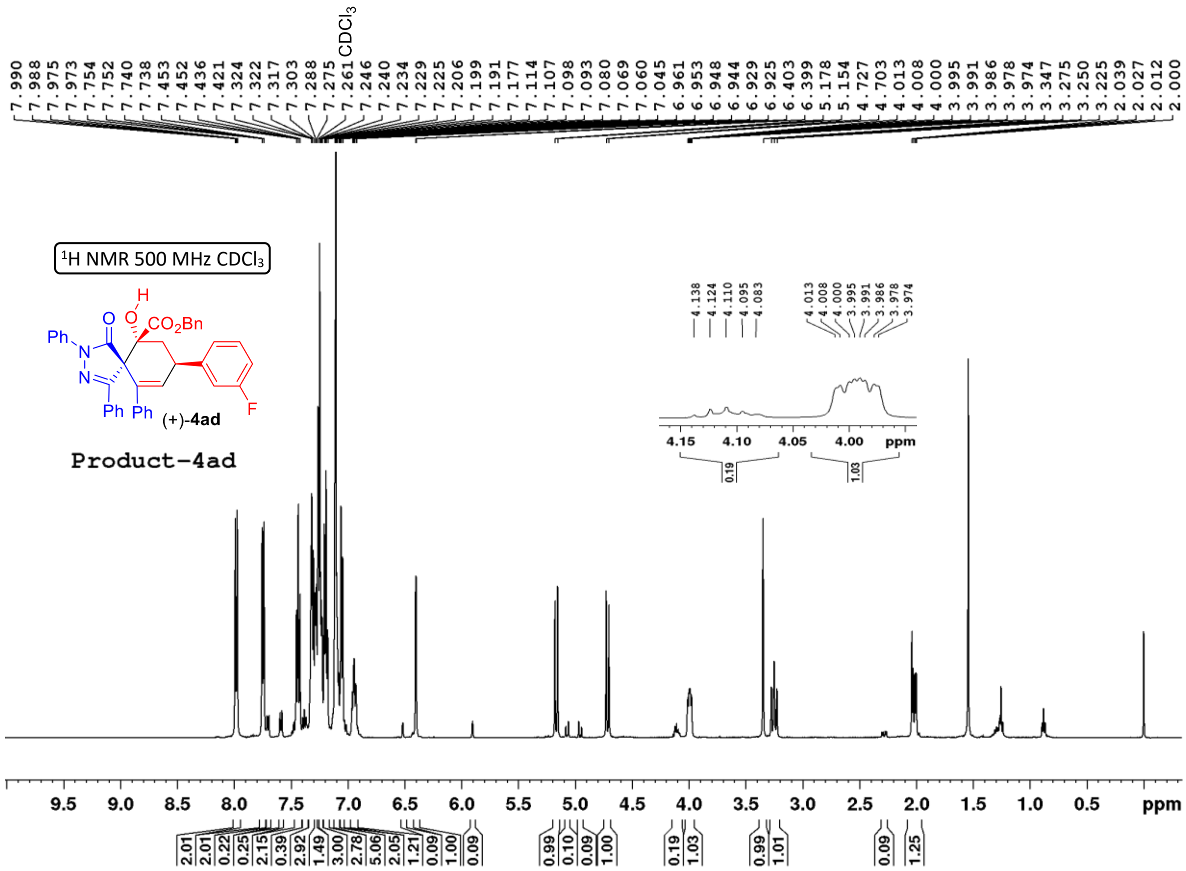


Chiralpak IC-3, Hexane/*i*-PrOH = 99:1, mL/Min, Flow Rate 0.5 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-177 IC-3 CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	9.653	56.858	0.443	4.4	5.9	2.10
2	15.290	1221.911	7.053	95.6	94.1	2.78
	Total	1278.769	7.496	100.0	100.0	

Figure 13: HPLC spectra of the product **4ac**.



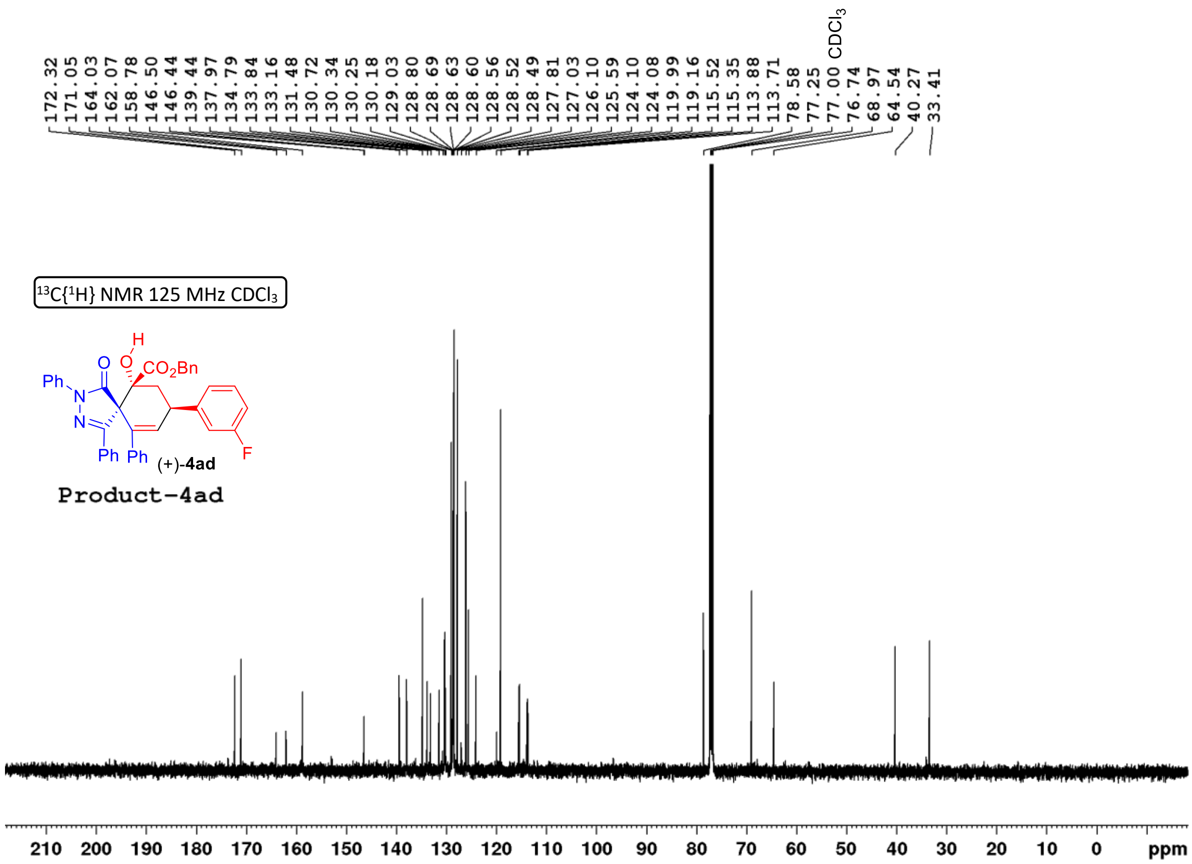
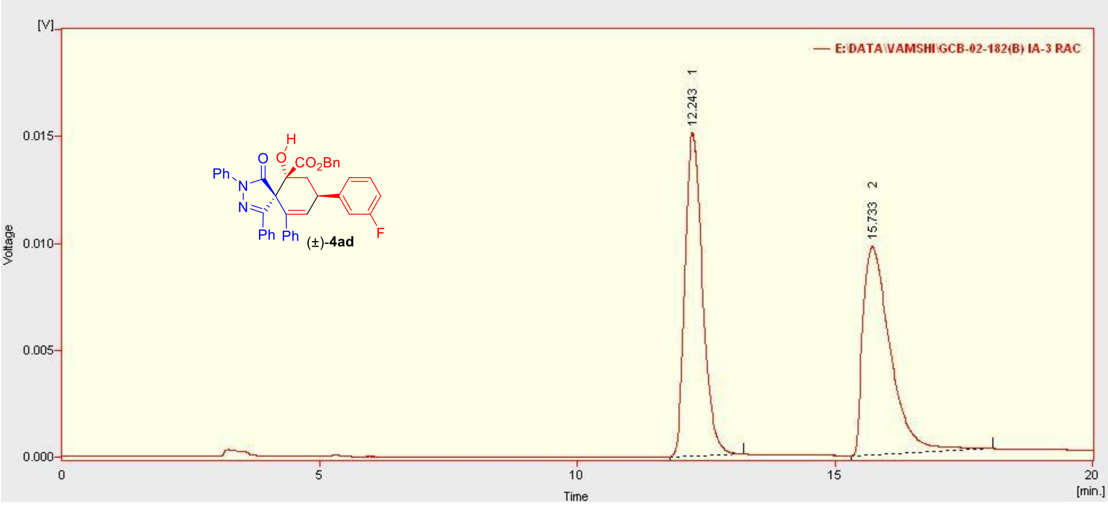


Figure 14: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4ad**.

Racemic **(±)-4ad**:

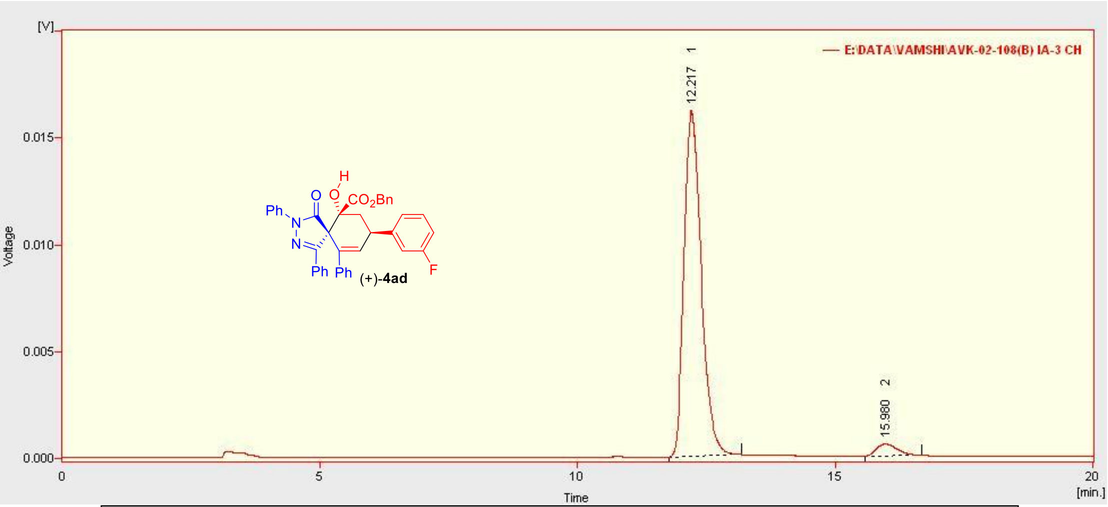


Chiralpak IA-3, Hexane/*i*-PrOH = 97:3, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\GCB-02-182(B) IA-3 RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	12.243	357.370	15.138	49.7	60.8	0.37
2	15.733	361.215	9.743	50.3	39.2	0.56
	Total	718.585	24.881	100.0	100.0	

Chiral **(+)-4ad** (92% *ee*):

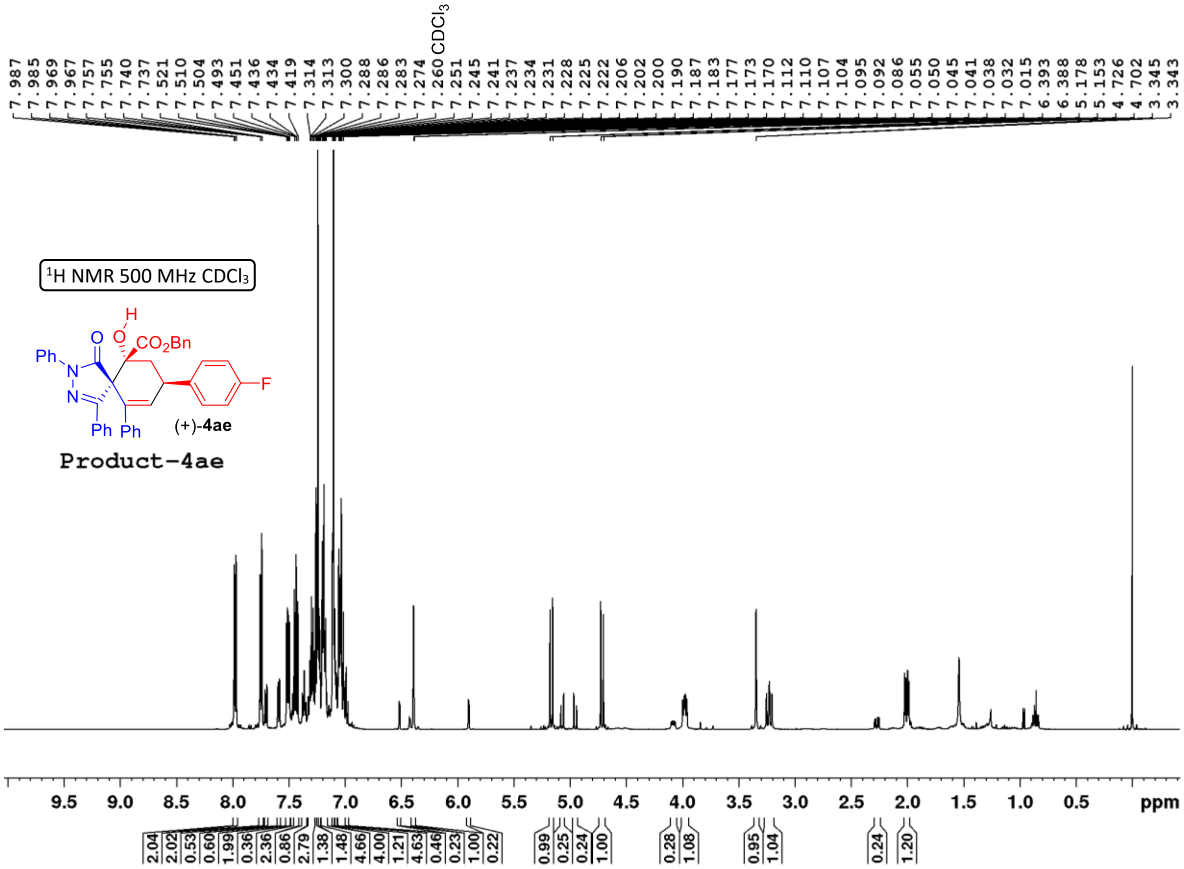


Chiralpak IA-3, Hexane/*i*-PrOH = 97:3, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-108(B) IA-3 CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	12.217	376.343	16.169	96.0	96.7	0.36
2	15.980	15.704	0.559	4.0	3.3	0.45
	Total	392.047	16.728	100.0	100.0	

Figure 15: HPLC spectra of the product **4ad**.



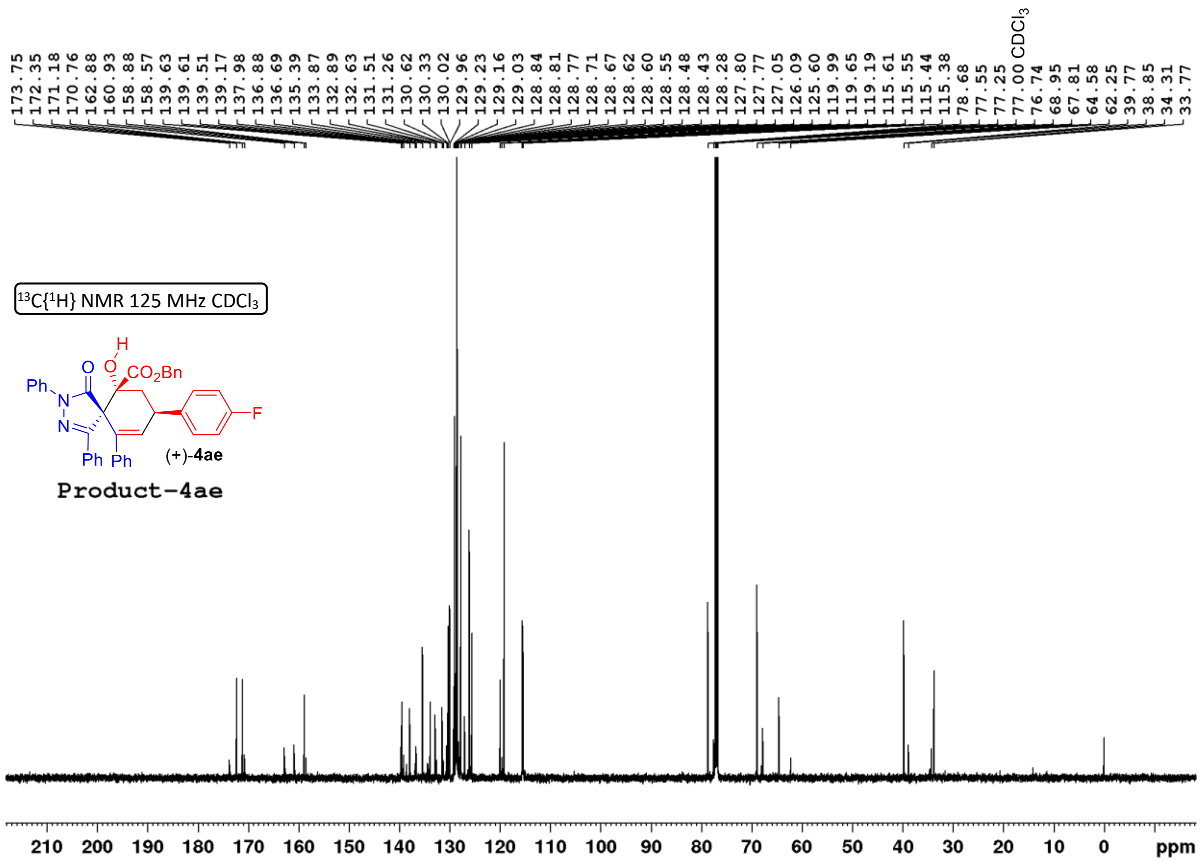
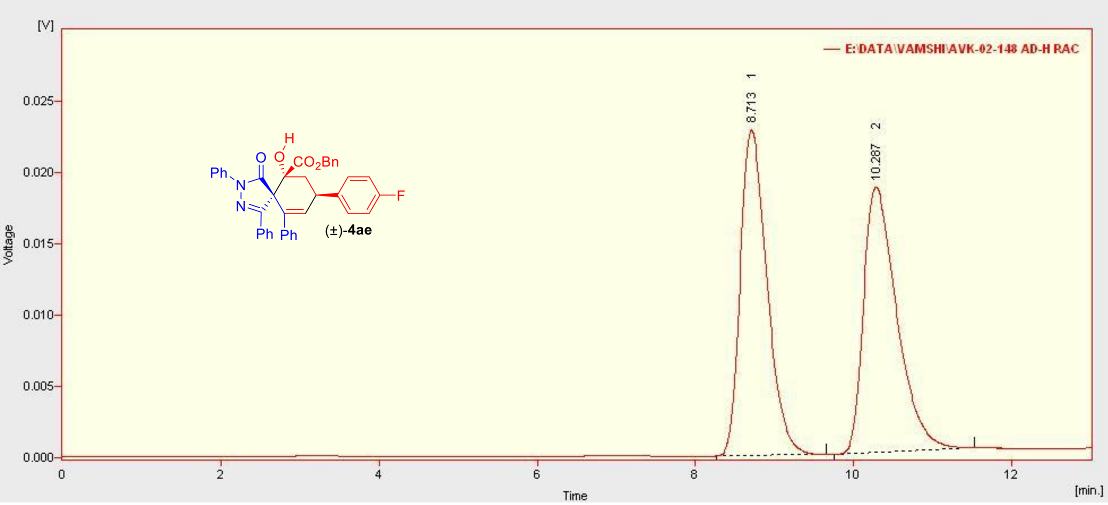


Figure 16: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4ae**.

Racemic **(±)-4ae**:

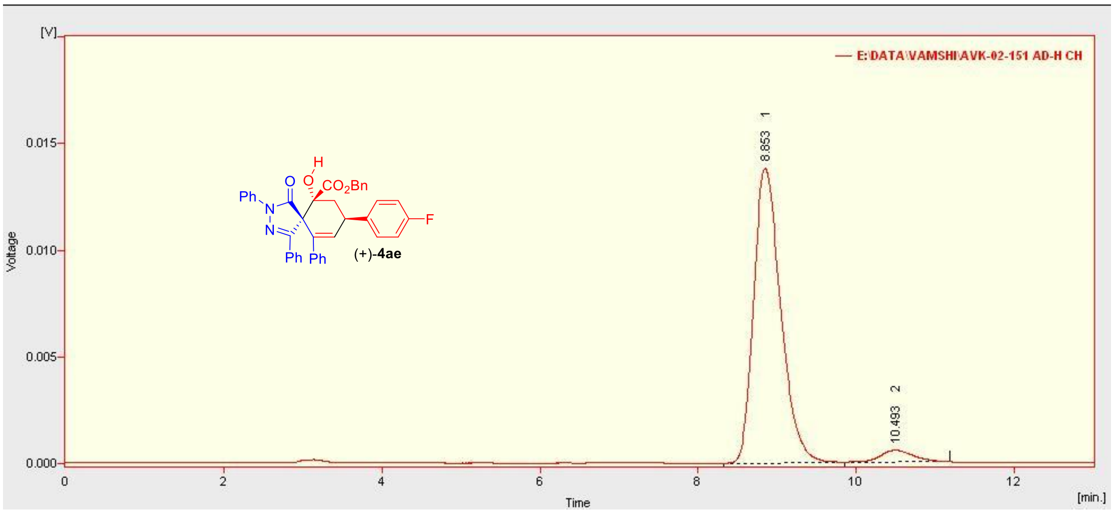


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-148 AD-H RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	8.713	536.369	22.847	49.6	55.1	0.37
2	10.287	544.740	18.619	50.4	44.9	0.45
	Total	1081.110	41.466	100.0	100.0	

Chiral **(+)-4ae** (90% *ee*):

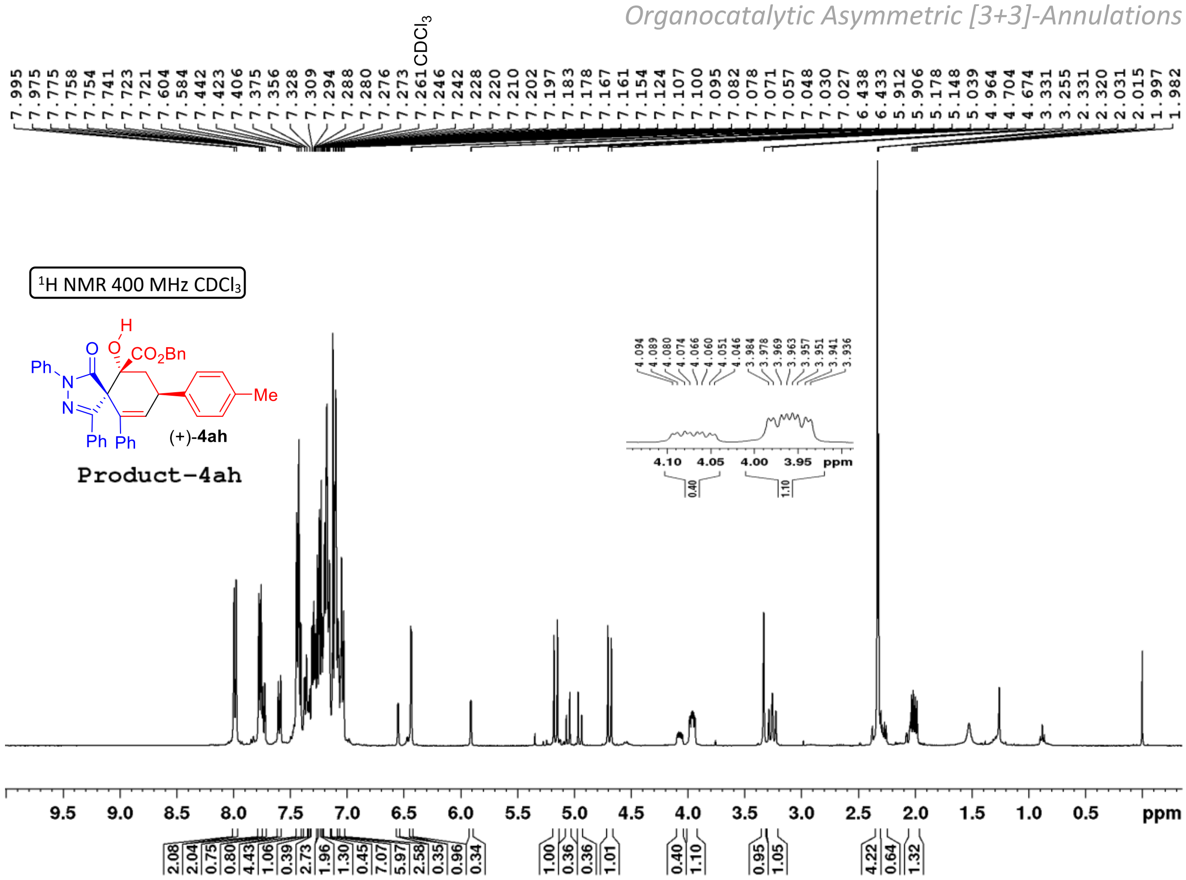


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-151 AD-H CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	8.853	327.902	13.789	95.2	96.1	0.37
2	10.493	16.522	0.556	4.8	3.9	0.45
	Total	344.425	14.345	100.0	100.0	

Figure 17: HPLC spectra of the product **4ae**.



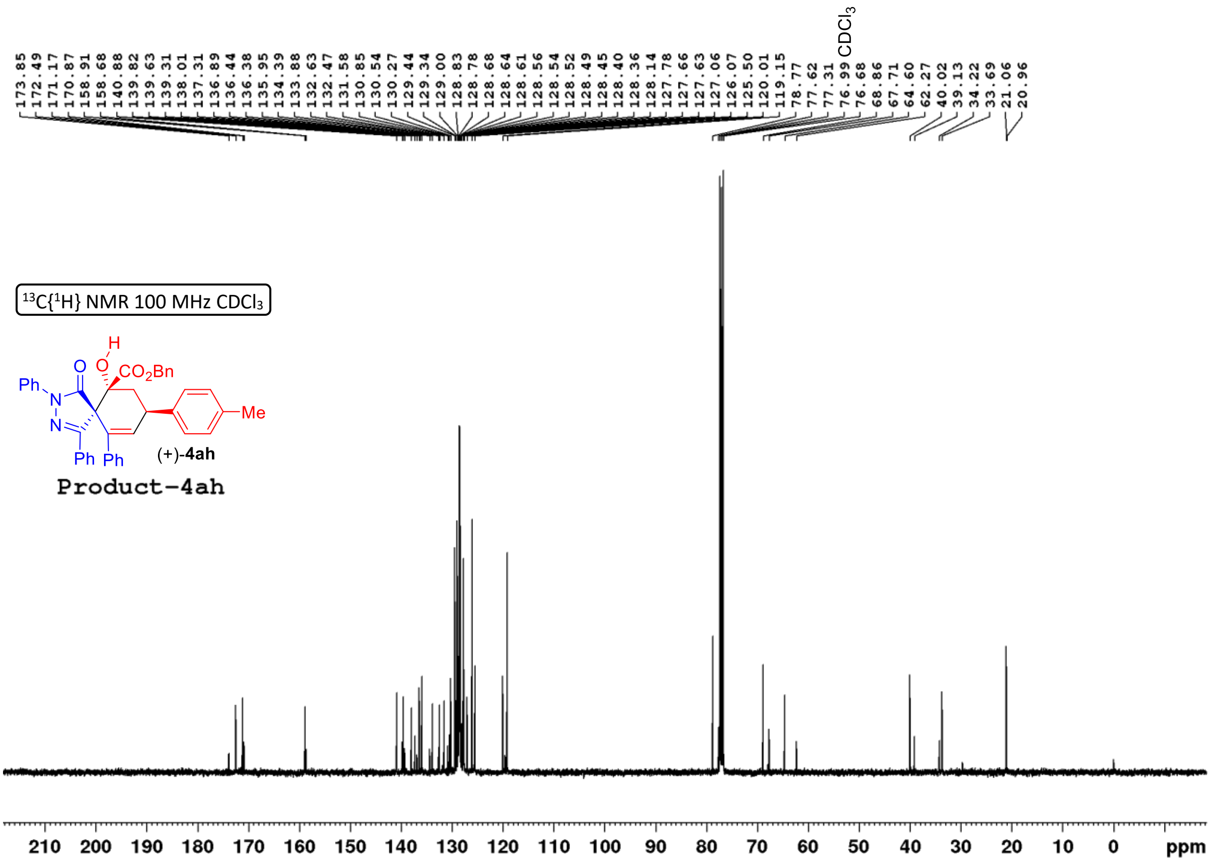
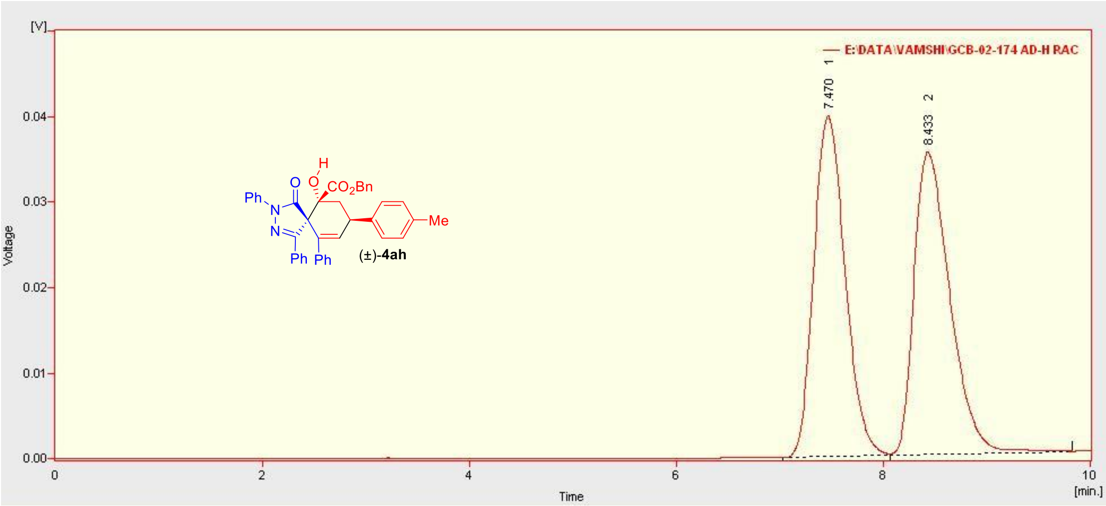


Figure 18: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4ah**.

Racemic **(±)-4ah**:

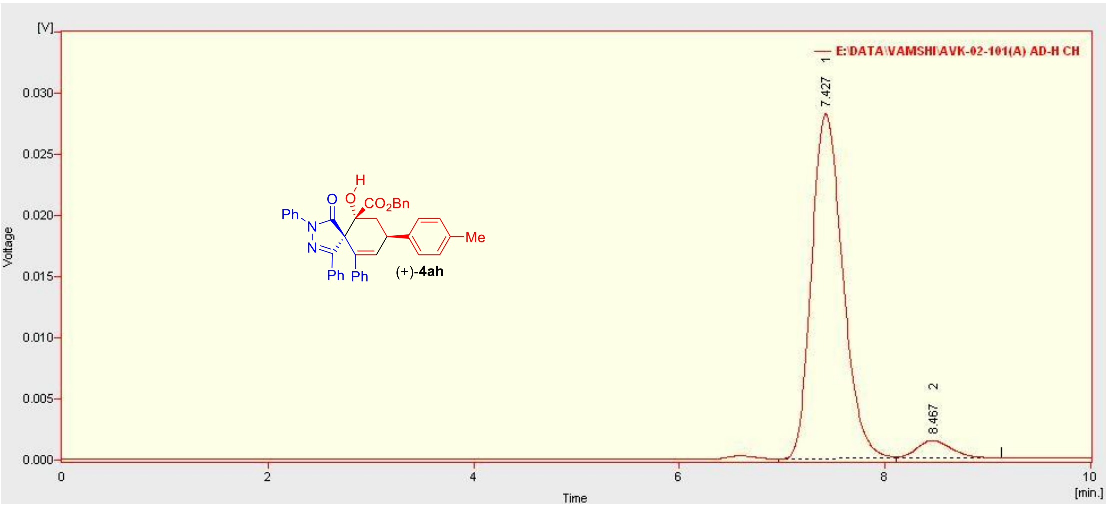


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\GCB-02-174 AD-H RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	7.470	838.571	39.874	49.6	53.0	0.33
2	8.433	850.787	35.325	50.4	47.0	0.37
	Total	1689.358	75.199	100.0	100.0	

Chiral **(+)-4ah** (90% *ee*):

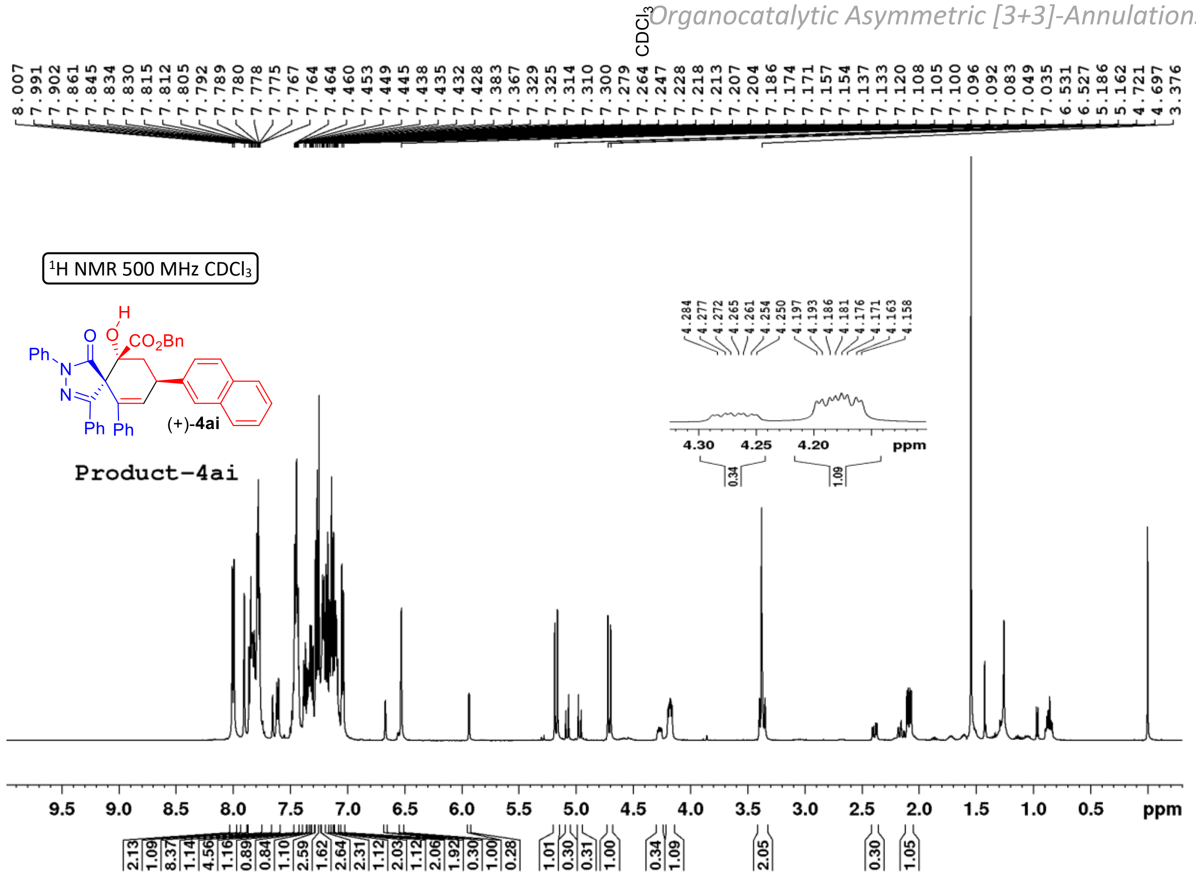


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-101(A) AD-H CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	7.427	594.922	28.266	94.7	95.2	0.33
2	8.467	33.350	1.434	5.3	4.8	0.36
	Total	628.272	29.700	100.0	100.0	

Figure 19: HPLC spectra of the product **4ah**.



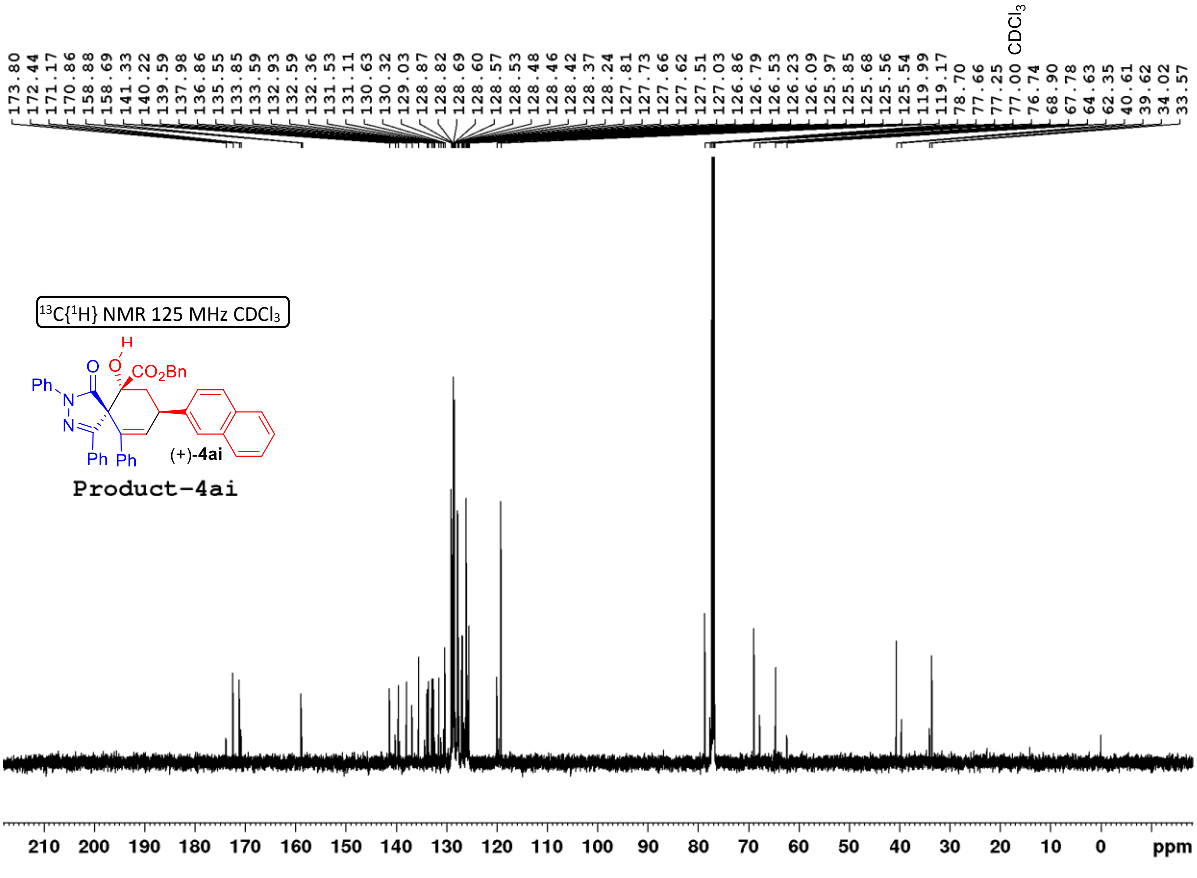
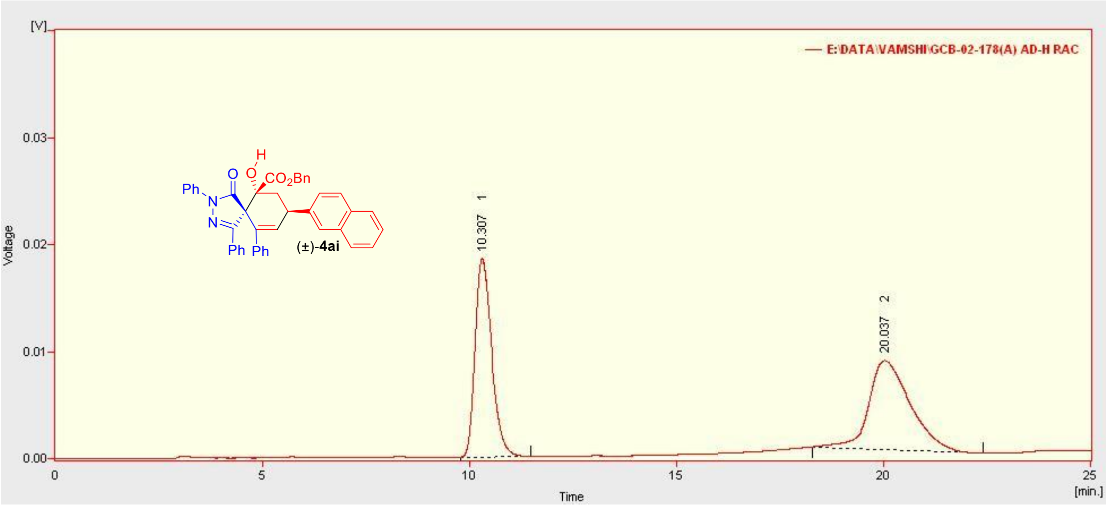


Figure 20: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4ai**.

Racemic **(±)-4ai**:

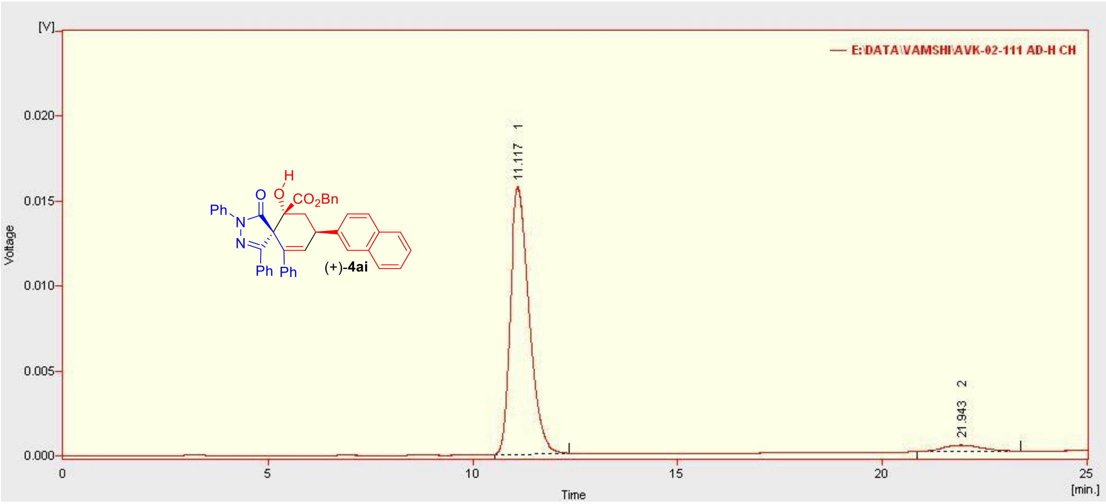


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\GCB-02-178(A) AD-H RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	10.307	519.255	18.566	47.3	69.1	0.43
2	20.037	577.919	8.311	52.7	30.9	1.02
	Total	1097.174	26.878	100.0	100.0	

Chiral **(+)-4ai** (90% *ee*):

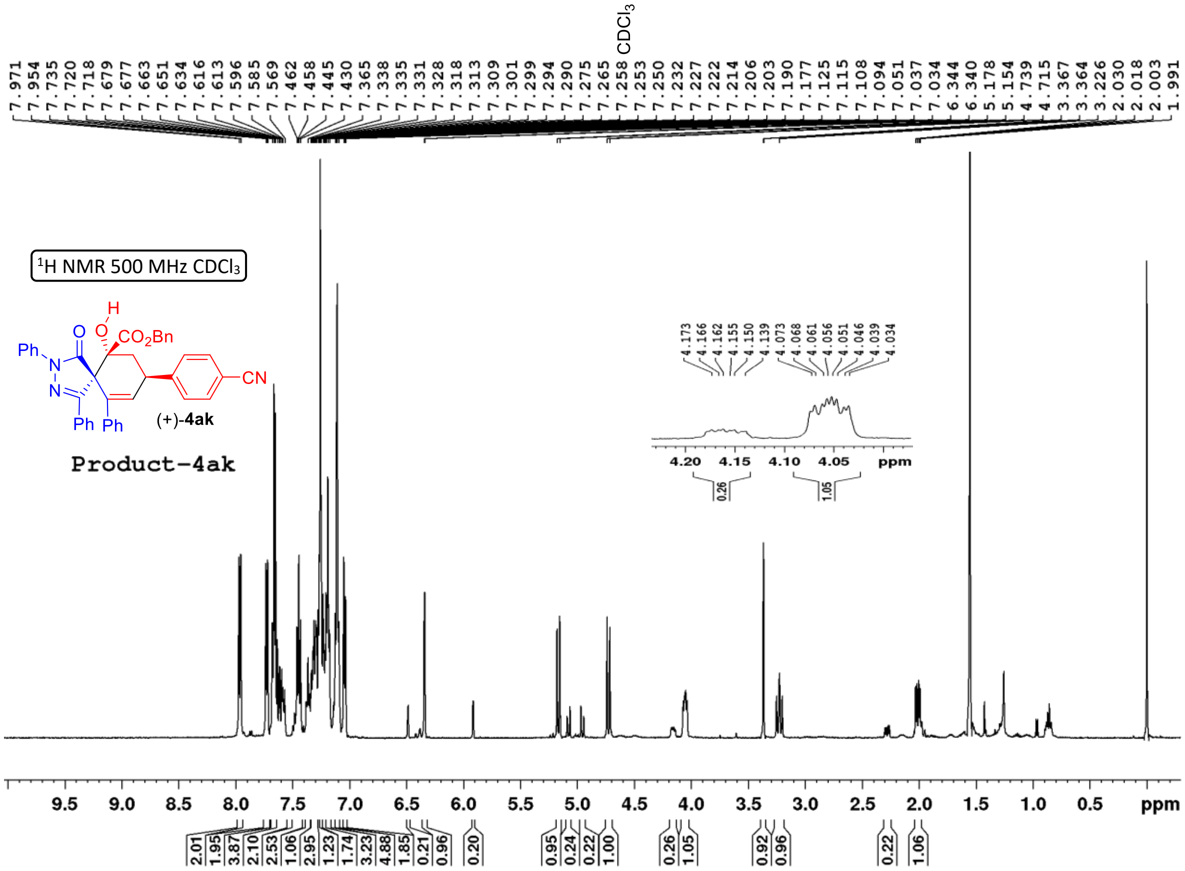


Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-111 AD-H CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	11.117	502.122	15.718	95.3	97.7	0.49
2	21.943	24.671	0.371	4.7	2.3	1.06
	Total	526.793	16.089	100.0	100.0	

Figure 21: HPLC spectra of the product **4ai**.



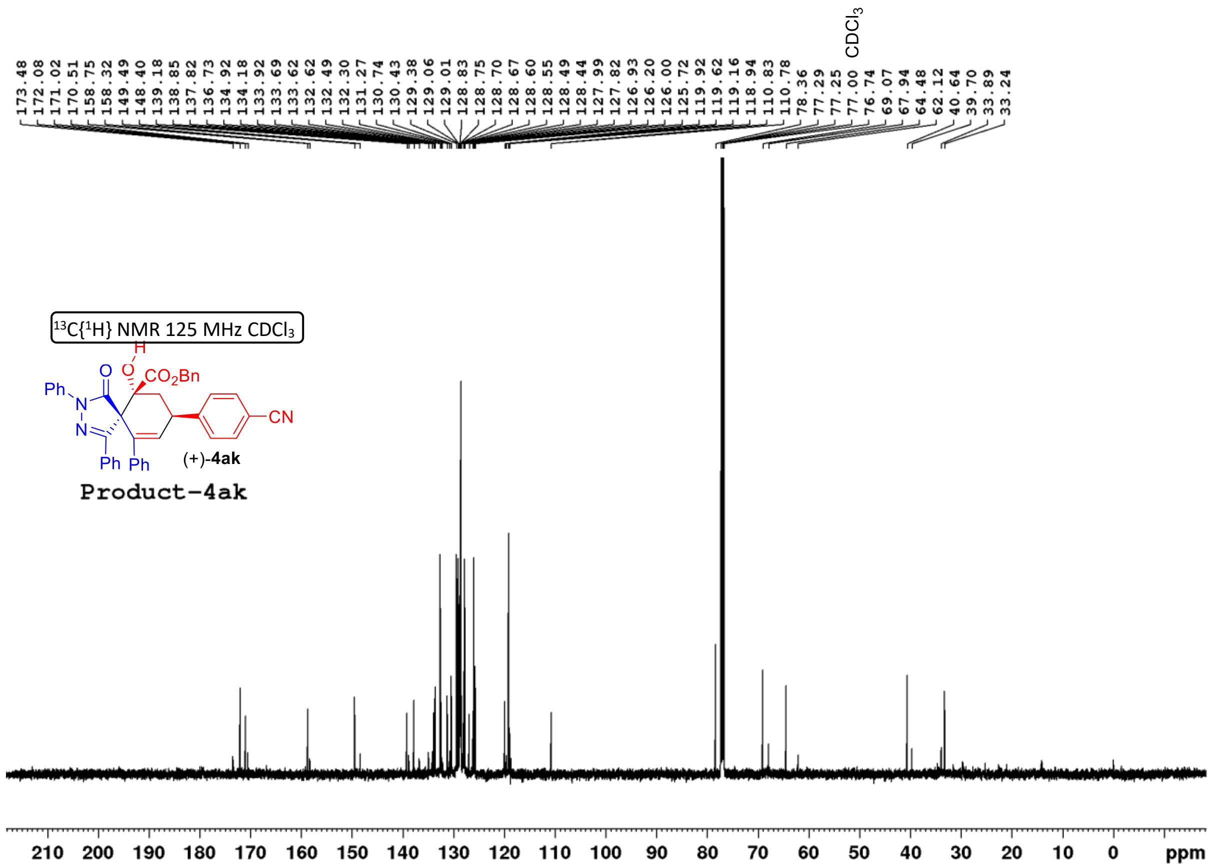
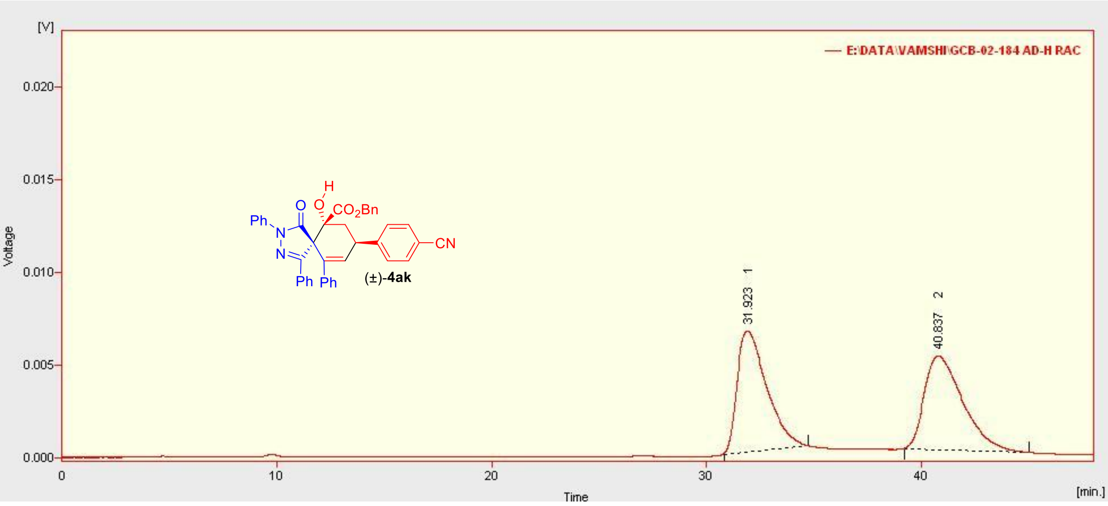


Figure 22: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**4ak**.

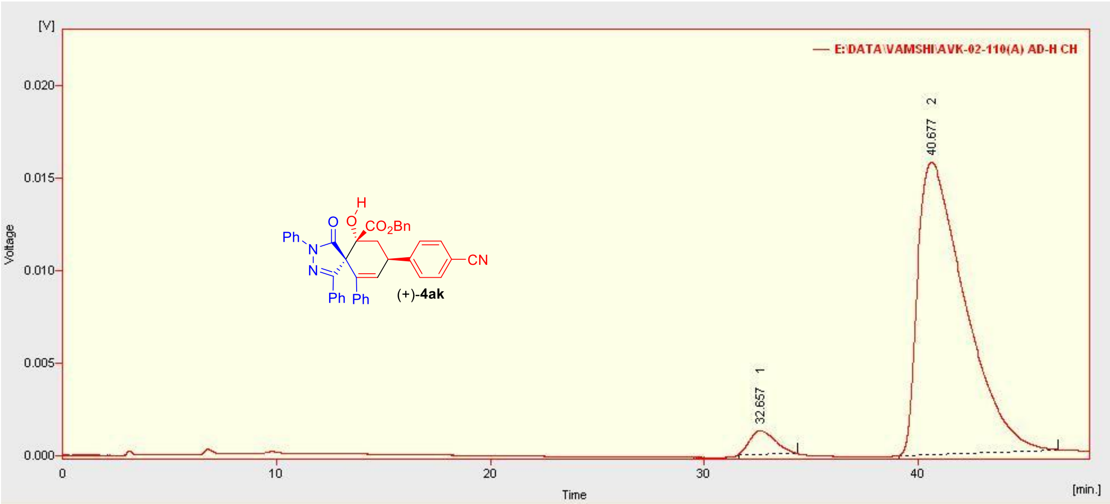
Racemic **(±)-4ak**:



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

Result Table (Uncal - E:\DATA\VAMSHI\GCB-02-184 AD-H RAC)						
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	31.923	621.158	6.510	49.6	56.3	1.51
2	40.837	630.468	5.055	50.4	43.7	1.91
	Total	1251.626	11.565	100.0	100.0	

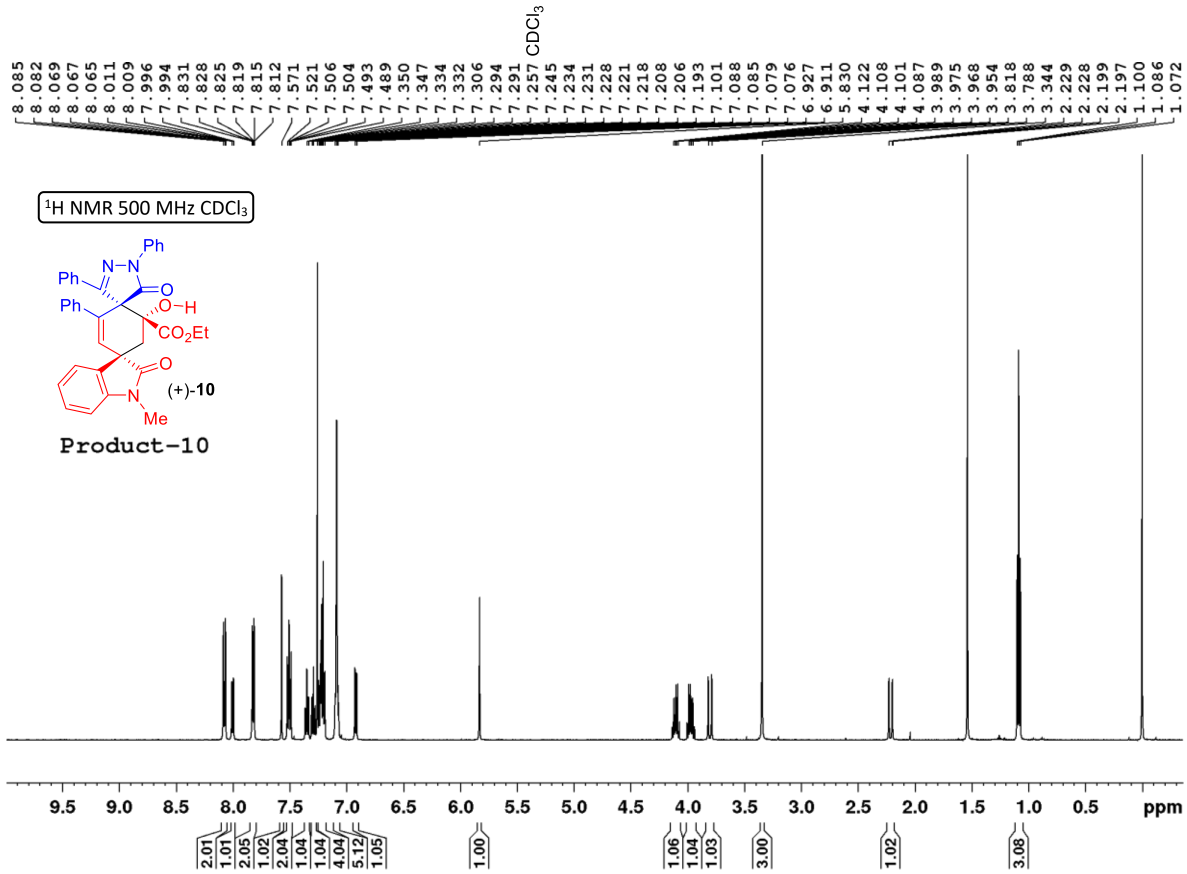
Chiral **(+)-4ak** (92% *ee*):



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

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-110(A) AD-H CH)						
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	32.657	104.019	1.262	4.1	7.4	1.36
2	40.677	2428.902	15.801	95.9	92.6	2.39
	Total	2532.921	17.063	100.0	100.0	

Figure 23: HPLC spectra of the product **4ak**.



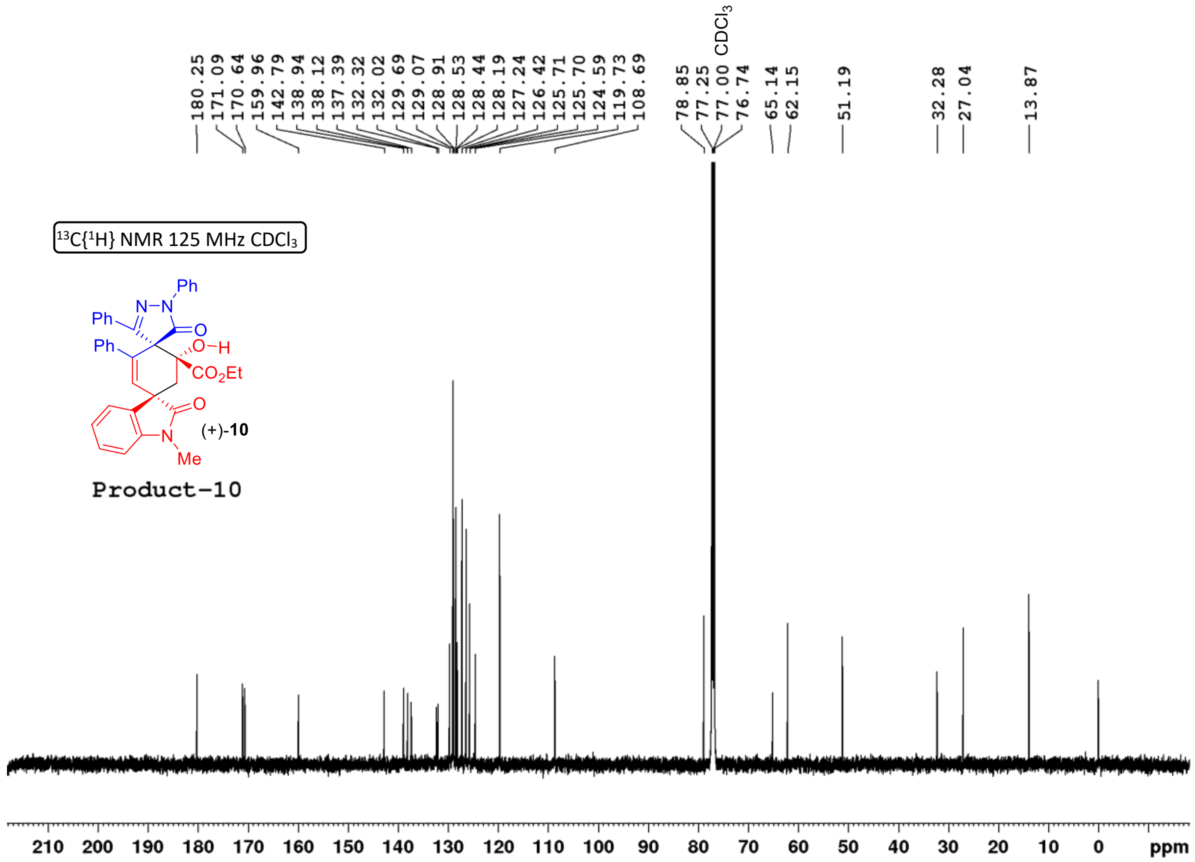
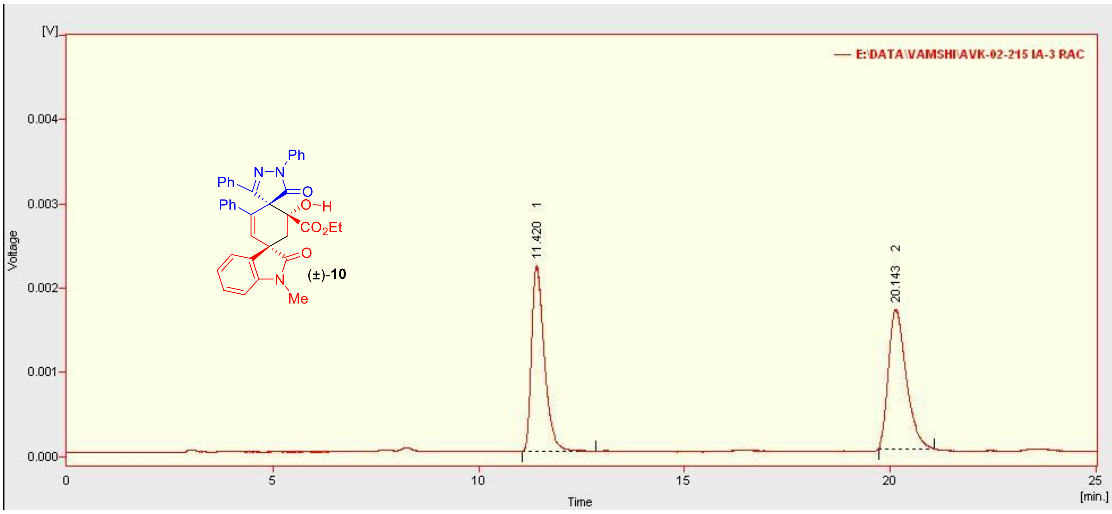


Figure 24: ^{1}H NMR and ^{13}C NMR spectrum of product-(+)-**10**.

Racemic **(±)-10**:

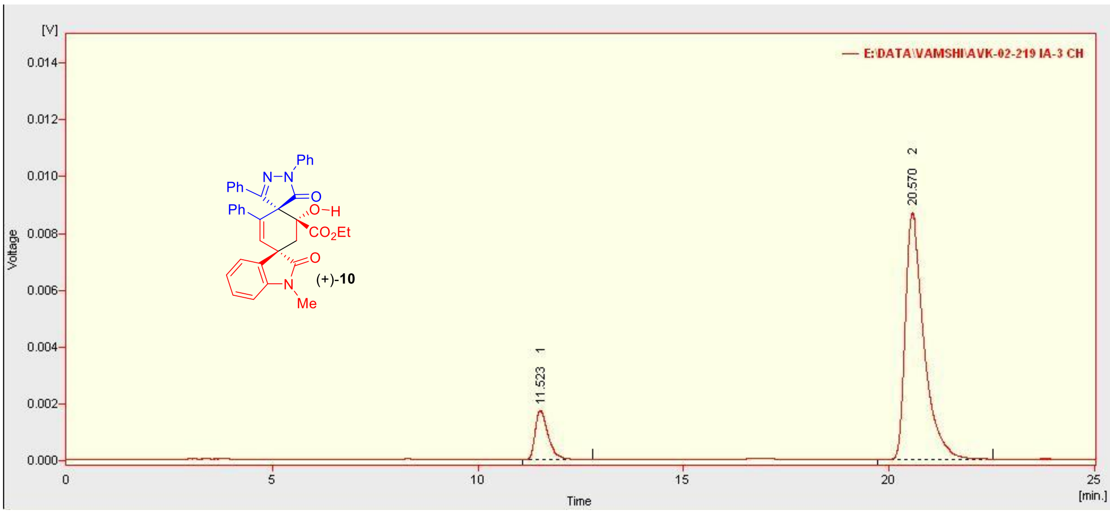


Chiralpak IA-3, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-215 IA-3 RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	11.420	46.607	2.207	48.9	57.1	0.32
2	20.143	48.718	1.658	51.1	42.9	0.45
	Total	95.325	3.864	100.0	100.0	

Chiral **(+)-10** (76% *ee*):



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

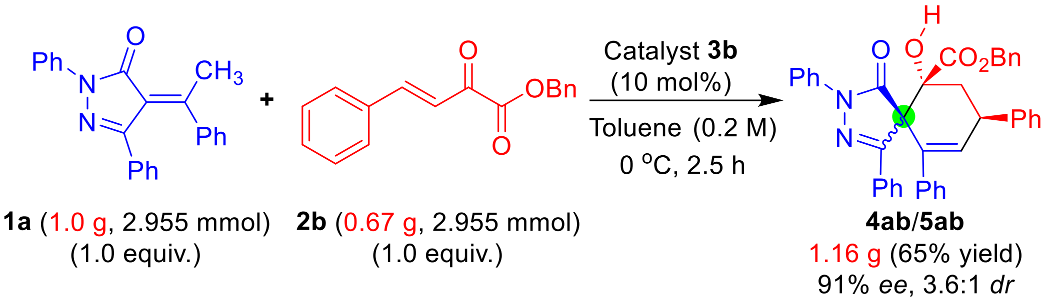
Result Table (Uncal - E:\DATA\VAMSHI\AVK-02-219 IA-3 CH)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	11.523	37.385	1.739	11.9	16.7	0.32
2	20.570	276.891	8.685	88.1	83.3	0.47
	Total	314.276	10.425	100.0	100.0	

Figure 25: HPLC spectra of the product **10**.

3.2.3 Gram-scale Organocatalytic Asymmetric [3+3]-Annulation Reaction

We planned a gram scale reaction of **1a** (1.0 g, 2.955 mmol) with **2b** (0.67 g, 2.955 mmol) catalyzed by **3b** (10 mol%) in toluene (14.8 mL, 0.2 M) at 0 °C for 2.5 h furnished the **4ab**/**5ab** in 65% (1.16 g) yield with uncompromised 91% *ee* and 3.6:1 *dr* which clearly demonstrates the industrial significance of the reaction (Scheme 2) and the pictorial representation of gram-scale reaction is shown in Figure 26.



Scheme 2: Gram-scale reaction of **1a** with **2b**.

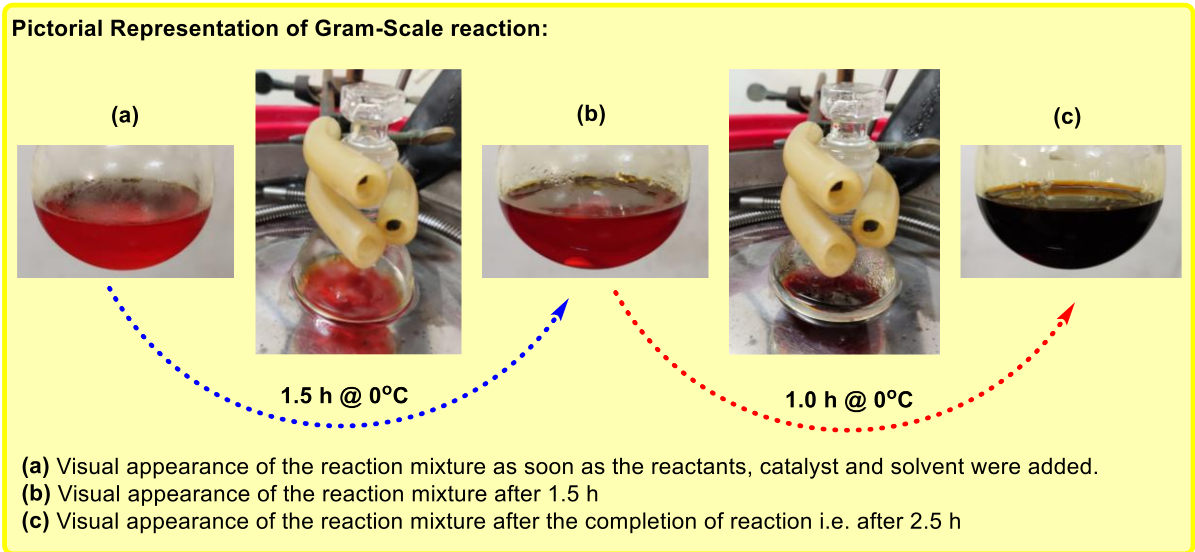
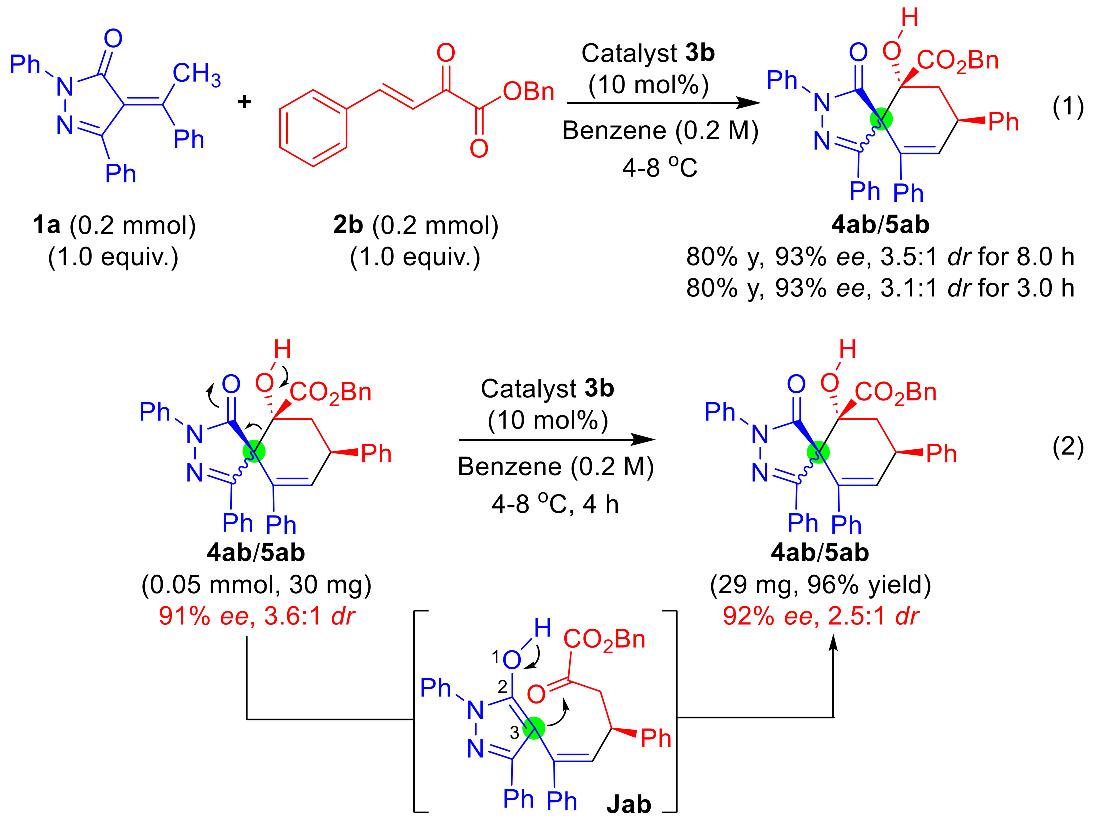


Figure 26: Pictorial representation of gram-scale reaction to furnish **4ab**/**5ab**.

3.2.4 Controlled Experiments to Understand the Diastereoselectivity of the Reaction

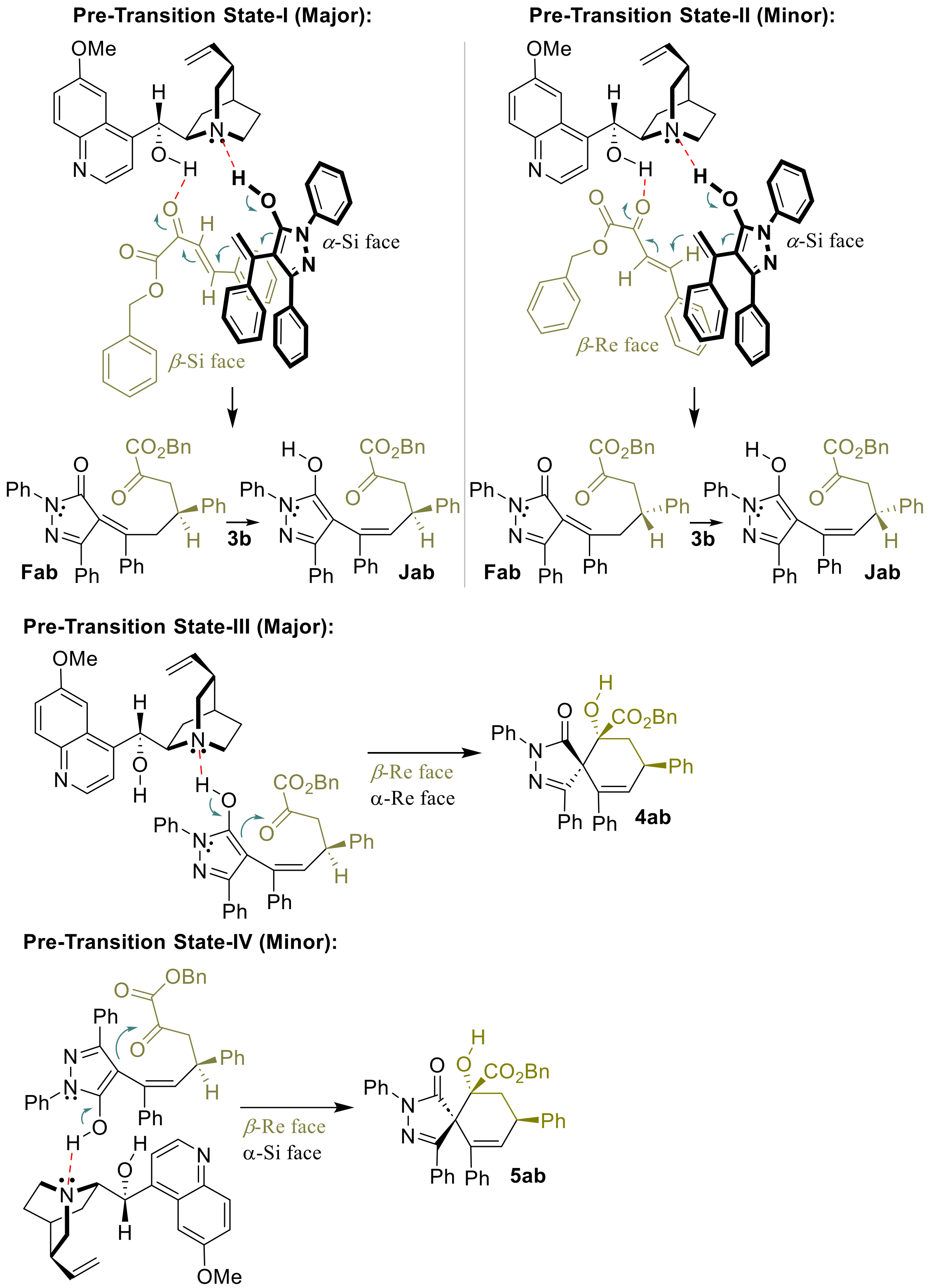
Further, to reveal the correlation of selectivity and reaction times, we have performed few control experiments in which we reacted **1a** (0.2 mmol) with **2b** (0.2 mmol) catalyzed by 10 mol% **3b** in benzene (0.2 M) at 4-8 °C for 8 h instead of optimized reaction time 3.0 h furnished **4ab**/**5ab** with unaltered 80% yield, 93% *ee* and 3.5:1 *dr* (Scheme 3, eq 1). In order to extend the investigation, the final product **4ab**/**5ab** (0.05 mmol, 30 mg) was taken and allowed to stir at 4-8 °C for 4 h under optimized conditions, which resulted in depletion of *dr* from 3.6:1 to 2.5:1 without affecting the *ee*/yield (Scheme 3, eq 2). This can be justified through the formation of *dr*'s *via* **Jab** by *retro*-aldol and aldol reactions catalyzed by **3b**. Surprisingly, minor isomers **5** couldn't observe through stationary phase chiral HPLC analysis may be due to its keto- and hydroxyl-groups are in the same plane, which facilitates the strong hydrogen bonding initiating the ring opening at C-3 by which isomers are disappearing.



Scheme 3: Controlled experiments.

3.2.5 Mechanistic Insights

With the crystal structural analysis and controlled experiments in hand, we can predict the plausible *pre*-transition states for domino reaction sequence (Scheme 4). The hydroxyl group of quinidine anchors through hydrogen bonding with keto-group of **2b**, whereas the amine of quinidine anchors through hydrogen bonding with hydroxyl group of isoaromatized **1a** as shown in *pre*-TS-I, which has strong π–π interactions between **1a** and **2b** through which α-Si face of **1a** approaches β-Si face of **2b** with close proximity for selective Michael addition. Unlike *pre*-TS-I, *pre*-TS-II does not have strong π–π interactions, which makes it less feasible for Michael addition (Scheme 4).



Scheme 4: Reaction mechanism.

Michael adduct **Fab** was isoaromatized into the intermediate **Jab** by *in situ* treatment with **3b**, further **3b** facilitates intramolecular conversion of **Jab** through the less sterically crowded attack from α-Re face of hard carbon nucleophile onto the β-Re face of hard carbonyl to give major aldol product **4ab** having spirocycles with vicinal quaternary carbon centers (*pre*-TS-III). In a minor route, **3b** facilitates the sterically crowded rotamer of **Jab** by attack of α-Si face of hard carbon nucleophile onto the β-Re face of the hard carbonyl to furnish the minor aldol product **5ab** also having spirocyclic vicinal quaternary carbon centers (*pre*-TS-IV).

3.3 Conclusions

In conclusion, for the first time, we have utilized the metal- and base-free *in situ* generated double sequence of isoaromatization and dearomatization steps as driving force for the construction of chiral 2,3-diazaspiro[4.5]deca-3,6-dien-1-ones having vicinal quaternary carbon centers in very good yields with high *ee*'s and *dr*'s through the quinidine-catalyzed domino Michael/aldol or formal [3+3]-cycloaddition from α-arylidene pyrazolinones and (*E*)-alkyl 2-oxo-4-arylbut-3-enoates. A library of 2,3-diazaspiro[4.5]deca-3,6-dien-1-ones in both achiral and chiral forms were constructed, which would be applicable in natural and medicinal chemistry. Further work in this line of exploring the potential of metal- and base-free *in situ* isoaromatization and dearomatization sequence from α-arylidene pyrazolinones with other ambident electrophiles is in progress.

3.4 Experimental Section

General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz or 400 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 silica gel (particle size: 0.063−0.200 mm). High-resolution mass spectra were recorded on a micromass ESI-TOF MS. IR spectra were recorded on FT/IR-5300 and 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 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 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. Starting materials α-arylidene pyrazolinone **1**[7], α, β-unsaturated keto ester **2**[8], and **10**[9] were synthesized according to reported literature procedures.

Procedure A: Preparation of racemic 2,3-diazaspiro[4.5]deca-3,6-dien-1-ones 4/5 under DABCO catalysis:

For Table-3 and Table-4: In an oven dried ordinary glass vial equipped with a magnetic stirring bar, α-arylidene pyrazolinones **1** (0.2 mmol, 1.0 equiv.) and keto-esters **2** (0.2 mmol, 1.0 equiv.) was added to 1.0 mL of toluene (0.2 M) and then DABCO **3k** (0.04 mmol, 20 mol%) was added and allowed to stir at room temperature for respective reaction times. The crude reaction mixture was directly loaded onto silica gel for column chromatography without aqueous workup and products **4**/**5** were obtained in respective yields.

Procedure B: Preparation of chiral 2,3-diazaspiro[4.5]deca-3,6-dien-1-ones 4/5 under quinidine catalysis:

For Table-1, 2, 5, and 6: In an oven dried ordinary glass vial equipped with a magnetic stirring bar, quinidine **3b** (0.02 mmol, 10 mol%) and benzene (1.0 mL, 0.2 M) was added and allowed to stir at 4-8 °C for few minutes, to which α-arylidene pyrazolinones **1** (0.2 mmol, 1.0 equiv.) and keto-esters **2** (0.2 mmol, 1.0 equiv.) were added and stirred at 4-8 °C for respective reaction times. The crude reaction mixture was directly loaded onto silica gel for column chromatography without aqueous work-up, and pure chiral products **4**/**5** were obtained in respective yields.

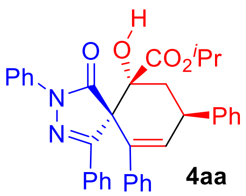
Procedure C: General procedure regarding gram-scale reaction for the preparation of chiral products 4ab/5ab under quinidine catalysis: To an oven dried round bottomed flask equipped with a magnetic stirring bar, catalyst quinidine **3b** (0.295 mmol, 95.7 mg) was added to 14.77 mL (0.2 M) toluene and allowed to stir for few minutes at 0 °C, to which α-arylidene pyrazolinone **1a** (2.955 mmol, 1.0 g, 1.0 equiv.) and keto-ester **2b** (2.955 mmol, 0.67 g, 1.0 equiv.) was added and stirred at 0 °C for 2.5 h. The excess solvent were removed using rotary evapourator and made slurry using silica gel, which was then loaded onto silica gel for column chromatography to obtain pure chiral products **4ab**/**5ab** in 65% (1.16 g) yield.

Procedure D: General procedure for preparation of racemic compound 10: In an oven dried ordinary glass vial equipped with a magnetic stirring bar, **1a** (0.1 mmol, 33.84 mg, 1.0 equiv.), **9** (0.1 mmol, 25.91 mg, 1.0 equiv.), **3b** (0.01 mmol, 3.24 mg, 10 mol%) and benzene (0.5 mL, 0.2 M) was added and allowed to stir for 12 h at room temperature. The crude reaction mixture was directly loaded onto silica gel for column chromatography without aqueous work-up and pure single product **10** was obtained in respective yield.

Procedure E: General procedure for preparation of compound (+)-10: In an oven dried ordinary glass vial equipped with a magnetic stirring bar, **1a** (0.1 mmol, 33.84 mg, 1.0 equiv.), **9** (0.1 mmol, 25.91 mg, 1.0 equiv.), quinidine-thiourea **3i** (0.01 mmol, 5.94 mg, 10 mol%) and toluene (1.0 mL, 0.1 M) was added and allowed to stir for 12 h at room temperature. The crude reaction mixture was directly loaded onto silica gel for column chromatography without aqueous workup, and pure chiral product (+)**-10** was obtained in respective yield.

Procedure F: General procedure for preparation of compound (-)-10: In an oven dried ordinary glass vial equipped with a magnetic stirring bar, **1a** (0.1 mmol, 33.84 mg, 1.0 equiv.), **9** (0.1 mmol, 25.91 mg, 1.0 equiv.), quinine-thiourea **3h** (0.01 mmol, 5.94, 10 mol%) and toluene (1.0 mL, 0.1 M) was added and allowed to stir for 12 h at room temperature. The crude reaction mixture was directly loaded onto silica gel for column chromatography without aqueous workup, pure chiral product (-)**-10** was obtained in respective yield.

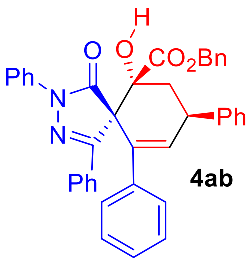
Isopropyl (5*S*,6*R*,8*R*)-6-hydroxy-4-oxo-1,3,8,10-tetraphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4aa): The title compound was prepared following procedure **B**,



4aa

purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 137-139 °C. Yield: 76% (84.61 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, $\lambda = 254$ nm), t_R = 4.53 min (major), t_R = 6.28 min (minor); $[\alpha]_D^{25}$ = +35.0° [*c* = 0.1, CH_2Cl_2, 93% *ee* and 5.4:1 *dr*]; IR (Neat): ν_{max} 3497, 3060, 2982, 2930, 1717, 1596, 1492, 1444, 1357, 1299, 1272, 1217, 1181, 1145, 1101, 1037, 908, 867, 814, 759, 732, 693, 639, 563 and 494 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 5.4:1 *dr*, major isomer): δ 8.15 (2H, br d, *J* = 8.0 Hz), 7.78 (2H, br dd, *J* = 6.6, 1.5 Hz), 7.57 (2H, br d, *J* = 7.6 Hz), 7.48 (2H, br t, *J* = 8.0 Hz), 7.37 (2H, br t, *J* = 7.6 Hz), 7.33-7.30 (1H, m), 7.27 (4H, br dd, J = 8.0, 2.8 Hz), 7.14-7.07 (5H, m), 6.44 (1H, d, J = 2.0 Hz, olefinic-H), 4.90-4.81 (1H, m), 4.0 (1H, ddd, J = 11.06, 6.32, 2.24 Hz), 3.39 (1H, s, OH), 3.25 (1H, t, J = 12.0 Hz), 1.98 (1H, dd, J = 13.6, 6.0 Hz), 1.08 (3H, d, J = 6.4 Hz), 0.89 (3H, d, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.3 (C, O-C=O), 171.2 (C, N-C=O), 159.1 (C, N=C), 144.0 (C), 139.6 (C), 138.3 (C), 135.7 (CH), 133.0 (C), 131.7 (C), 130.2 (CH), 129.0 (2 x CH), 128.8 (2 x CH), 128.6 (2 x CH), 128.57 (2 x CH), 128.51 (2 x CH), 127.7 (2 x CH), 127.6 (CH), 126.8 (CH), 126.0 (2 x CH), 125.4 (CH), 118.8 (2 x CH), 78.0 (C, C-OH), 71.8 (CH), 64.4 (C), 40.6 (CH), 34.0 (CH_2), 21.4 (CH_3), 21.0 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{32}N_2O_4H$ 557.2440. Found 557.2445.

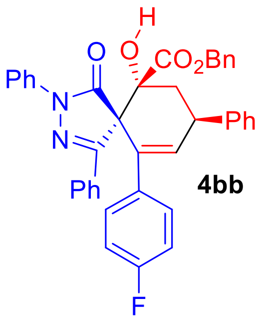
Benzyl (5*S*,6*R*,8*R*)-6-hydroxy-4-oxo-1,3,8,10-tetraphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ab): The title compound was prepared following procedure **B**,



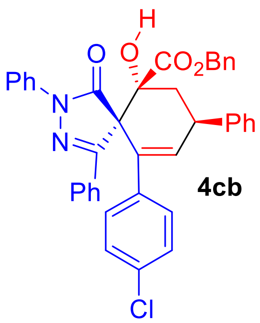
4ab

purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 103-105 °C. Yield: 80% (96.75 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 = 7.31 min (major), t_R = 12.41 min (minor); $[\alpha]_D^{25}$ = +87.0° [c = 0.1, $CHCl_3$, 93% *ee* and 3.6:1 *dr*]; IR (Neat): ν_{max} 3501, 3063, 3028, 1715, 1596, 1492, 1444, 1374, 1298, 1218, 1182, 1140, 1029, 930, 906, 865, 755, 691, 599, 564, 491 and 419 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, 3.6:1 *dr*, major isomer): δ 7.99 (2H, br d, J = 8.0 Hz), 7.76 (2H, br d, J = 7.0 Hz), 7.55 (2H, br d, J = 7.0 Hz), 7.45-7.42 (2H, m), 7.36 (2H, br t, J = 7.5 Hz), 7.32-7.29 (2H, m), 7.274-7.269 (1H, m), 7.24-7.22 (3H, m), 7.20-7.18 (4H, m), 7.12-7.11 (3H, m), 7.05 (2H, br d, J = 7.5 Hz), 6.45 (1H, d, J = 2.0 Hz, olefinic-H), 5.17 (1H, d, J = 12.0 Hz, OCH_2Ph), 4.70 (1H, d, J = 12.0 Hz, OCH_2Ph), 3.99 (1H, ddd, J = 11.0, 6.0, 2.0 Hz), 3.34 (1H, d, J = 1.0 Hz, OH), 3.27 (1H, t, J = 12.5 Hz), 2.03 (1H, dd, J = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.5 (C, O-C=O), 171.1 (C, N-C=O), 158.9 (C, N=C), 143.9 (C), 139.6 (C), 138.0 (C), 135.7 (CH), 133.9 (C), 132.7 (C), 131.6 (CH), 130.3 (C), 129.0 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.6 (CH), 128.55 (CH), 128.53 (2 x CH), 128.5 (3 x CH), 128.46 (2 x CH), 127.8 (3 x CH), 126.9 (CH), 126.1 (2 x CH), 125.5 (CH), 119.2 (2 x CH), 78.7 (C, C-OH), 68.9 (CH_2, OCH$_2$Ph), 64.6 (C), 40.5 (CH), 33.7 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{40}H_{32}N_2O_4H$ 605.2440. Found 605.2442.

Benzyl (5*S*,6*R*,8*R*)-10-(4-fluorophenyl)-6-hydroxy-4-oxo-1,3,8-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4bb): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 110-112 °C. Yield: 68% (84.69 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 = 5.96 min (major), t_R = 11.49 min (minor); $[\alpha]_D^{25}$ = +69.0° [*c* = 0.1, $CHCl_3$, 94% *ee*]; IR (Neat): ν_{max} 3581, 3507, 3062, 3030, 2925, 2854, 1717, 1597, 1454, 1493, 1373, 1299, 1234, 1142, 1046, 930, 836, 758, 694, 643 and 510 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 3.7:1 dr, major isomer): δ 7.97 (2H, br dd, *J* = 7.5, 1.0 Hz), 7.77 (2H, br d, *J* = 8.0 Hz), 7.54 (2H, br d, *J* = 8.0 Hz), 7.44 (2H, br d, *J* = 7.0 Hz), 7.37 (2H, br d, *J* = 7.5 Hz), 7.32 (2H, br d, *J* = 7.5 Hz), 7.27 (2H, br d, *J* = 8.0 Hz), 7.25 (2H, br s), 7.20-7.17 (3H, m), 7.09 (2H, br d, *J* = 7.5 Hz), 7.06-7.05 (1H, m), 6.79 (2H, t, *J* = 8.5 Hz), 6.39 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.16 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.71 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.0 (1H, ddd, *J* = 11.0, 5.75, 2.0 Hz), 3.36 (1H, br s, O*H*), 3.27 (1H, t, *J* = 12.5 Hz), 2.03 (1H, dd, *J* = 13.75, 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.4 (C, O-*C*=O), 171.1 (C, N-*C*=O), 162.2 (C, d, *J* = 246.25 Hz, *C*-F), 158.7 (C, N=*C*), 143.8 (C), 137.9 (C), 135.8 (CH), 135.7 (C, d, *J* = 3.38 Hz), 133.9 (C), 131.8 (C), 131.5 (C), 130.4 (CH), 129.0 (3 x CH), 128.8 (2 x CH), 128.6 (CH), 128.5 (3 x CH), 128.47 (4 x CH), 127.9 (2 x CH, d, *J* = 7.86 Hz), 127.8 (2 x CH), 126.9 (CH), 125.6 (CH), 119.1 (2 x CH), 115.5 (2 x CH, d, *J* = 21.25 Hz), 78.6 (C, *C*-OH), 68.9 (CH_2, OCH_2Ph), 64.6 (C), 40.4 (CH), 33.7 (CH_2); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −113.47 (minor), −114.23 (major); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{31}FN_2O_4H$ 623.2346. Found 623.2347.



4bb

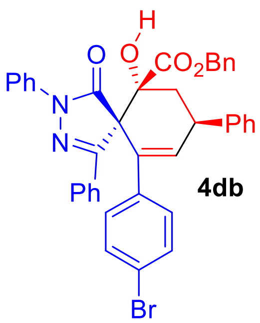


4cb

Benzyl (5*S*,6*R*,8*R*)-10-(4-chlorophenyl)-6-hydroxy-4-oxo-1,3,8-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4cb): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 113-115 °C. Yield: 70% (89.48 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, $\lambda = 254$ nm), t_R = 6.06 min (major), t_R = 11.07 min (minor); $[\alpha]_D^{25}$ = +46.6° [c = 0.1, $CHCl_3$, 92% *ee*]; IR (Neat): ν_{max} 3501, 3066, 3029, 2928, 1717, 1596, 1491, 1454, 1373, 1299, 1239, 1182, 1142, 1094, 1046, 930, 907, 868, 830, 758, 693, 640, 604, 539, 503, and 463 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.2:1 dr, major isomer): δ 7.96 (2H, br d, J = 8.0 Hz), 7.76 (2H, br d, J = 7.5 Hz), 7.58 (2H, br d, J = 7.5 Hz), 7.43 (2H, t, J = 7.5 Hz), 7.38-7.31 (4H, m), 7.28-7.25 (3H, m), 7.22 (2H, br d, J = 7.0 Hz), 7.20-7.16 (2H, m), 7.08-7.07 (2H, m), 7.05-7.02 (3H, m), 6.42 (1H, d, J = 2.5 Hz, olefinic-*H*), 5.16 (1H, d, J = 12.0 Hz, OCH_2Ph), 4.71 (1H, d, J = 12.0 Hz, OCH_2Ph), 3.99 (1H, ddd, J = 10.9, 6.0, 2.5 Hz), 3.37 (1H, br s, O*H*), 3.26 (1H, t, J = 12.0 Hz), 2.03 (1H, dd, J = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 171.0 (C, N-*C*=O), 158.6 (C, N=*C*), 143.7 (C), 138.1 (C), 137.9 (C), 136.2 (CH), 133.8 (C), 133.6 (C), 131.7 (C), 131.4 (C), 130.5 (CH), 129.0 (2 x CH), 128.3 (2 x CH), 128.7 (3 x CH), 128.6 (CH), 128.5 (2 x CH), 128.47 (6 x CH), 127.9 (2 x CH), 127.5 (2 x CH), 125.7 (CH), 119.1 (2 x CH), 78.6 (C, *C*-OH), 69.0 (CH_2, O*C*H_2Ph), 64.4 (C), 40.5 (CH), 33.6 (CH_2); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{40}H_{31}ClN_2O_4H$ 639.2051. Found 639.2052.

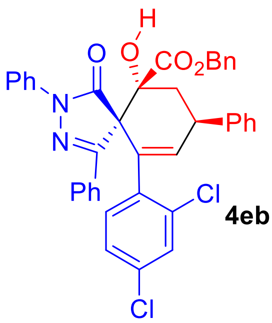
Benzyl (5*S*,6*R*,8*R*)-10-(4-bromophenyl)-6-hydroxy-4-oxo-1,3,8-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4db): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 133-135 °C. Yield: 67% (91.60 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, $\lambda = 254$ nm), t_R = 6.44 min (major), t_R = 11.88 min (minor); $[\alpha]_D^{25}$ = +75.4° [c = 0.1, $CHCl_3$, 92% *ee*]; IR (Neat): ν_{max} 3503, 3029, 2922, 2852, 1716, 1595, 1489, 1454, 1373, 1298, 1217, 1181, 1141, 1075, 1028, 1007, 906, 867, 827, 729, 691, 646, 601, 497 and 460 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.2:1 dr, major isomer): δ 7.97-7.95 (2H, m), 7.76-7.75 (2H, m), 7.53 (2H, br d, J = 8.0 Hz), 7.46-7.42 (2H, m), 7.38-7.30 (5H, m), 7.29-7.25 (3H, m), 7.23-7.22 (2H, m), 7.20-7.16 (2H, m), 7.04 (2H, br d, J = 8.0 Hz), 6.97 (2H, br dd, J = 8.5, 1.5 Hz), 6.43 (1H, s, olefinic-*H*), 5.16 (1H, d, J = 12.0 Hz, OCH_2Ph), 4.71 (1H, d, J = 12.0 Hz, OCH_2Ph), 3.99-3.96 (1H, m), 3.37 (1H, br s, O*H*), 3.26 (1H, br t, J = 13.0 Hz), 2.03 (1H, dd, J = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz,



4db

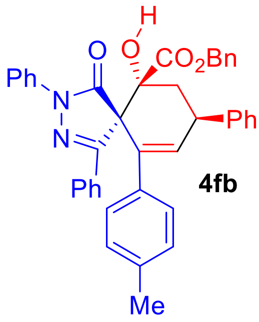
DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 171.0 (C, N-*C*=O), 158.6 (C, N=*C*), 143.6 (C), 138.5 (C), 137.8 (C), 136.3 (CH), 133.8 (C), 131.8 (C), 131.7 (2 X CH), 131.4 (C), 130.5 (CH), 129.0 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.6 (CH), 128.5 (2 x CH), 128.46 (4 x CH), 127.9 (2 x CH), 127.7 (3 x CH), 125.7 (CH), 121.8 (C), 119.1 (2 x CH), 78.6 (C, *C*-OH), 69.0 (CH_2, O*C*H_2Ph), 64.4 (C), 40.5 (CH), 33.6 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{31}BrN_2O_4H$ 683.1545. Found 683.1545.

Benzyl (5*S*,6*R*,8*R*)-10-(2,4-dichlorophenyl)-6-hydroxy-4-oxo-1,3,8-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4eb): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white semisolid. Yield: 42% (56.58 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 = 4.75 min (major), t_R = 8.64 min (minor); $[\alpha]_D^{25}$ = +177.2° [*c* = 0.1, $CHCl_3$, 77% *ee*]; IR (Neat): ν_{max} 3504, 3062, 2923, 2854, 1715, 1595, 1493, 1454, 1374, 1298, 1262, 1231, 1141, 1069, 1028, 907, 870, 821, 757, 730, 693, 634, 575, 507 and 479 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 3.3:1 dr, major isomer): δ 7.92 (3H, br t, *J* = 9.0 Hz), 7.56-7.51 (2H, m), 7.43 (2H, br t, *J* = 7.5 Hz), 7.36-7.34 (3H, m), 7.33-7.30 (3H, m), 7.29-7.28 (2H, m), 7.24-7.23 (2H, m), 7.19-7.16 (2H, m), 7.03 (2H, br d, *J* = 7.0 Hz), 6.90 (1H, dd, *J* = 8.5, 2.5 Hz), 6.71 (1H, d, *J* = 8.5 Hz), 6.57 (1H, d, *J* = 2.5 Hz, olefinic-*H*), 5.14 (1H, d, *J* = 12.5 Hz, OC*H*$_2$Ph), 4.95 (1H, d, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.11 (1H, ddd, *J* = 10.9, 6.5, 2.5 Hz), 3.49 (1H, br s, O*H*), 3.33 (1H, t, *J* = 12.5 Hz), 2.05 (1H, dd, *J* = 13.75, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 171.5 (C, N-*C*=O), 158.3 (C, N=*C*), 143.4 (C), 140.6 (CH), 137.8 (C), 135.4 (C), 133.8 (C), 133.6 (C), 133.4 (C), 131.2 (C), 130.9 (CH), 130.6 (CH), 129.1 (2 x CH), 128.8 (3 x CH), 128.7 (CH), 128.6 (2 x CH), 128.54 (CH), 128.5 (2 x CH), 128.47 (2 x CH), 128.0 (CH), 127.7 (2 x CH), 127.2 (CH), 127.0 (CH), 126.7 (C), 125.7 (CH), 119.2 (2 x CH), 78.7 (C, *C*-OH), 69.0 (CH_2, O*C*H_2Ph), 64.5 (C), 40.4 (CH), 33.4 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{30}Cl_2N_2O_4H$ 673.1661. Found 673.1661.



4eb

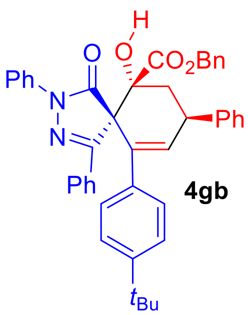
Benzyl (5*S*,6*R*,8*R*)-6-hydroxy-4-oxo-1,3,8-triphenyl-10-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4fb): The title compound was prepared following procedure **B**,



4fb

purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 125-127 °C. Yield: 74% (91.57 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 = 6.57 min (major), t_R = 14.98 min (minor); $[\alpha]_D^{25}$ = +151.7° [*c* = 0.1, $CHCl_3$, 94% *ee*]; IR (Neat): ν_{max} 3506, 3062, 3027, 2922, 2852, 1717, 1596, 1493, 1454, 1374, 1299, 1269, 1221, 1182, 1141, 1028, 907, 866, 822, 757, 730, 693, 662, 646, 630, 603, 535, 508 and 407 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 3.2:1 dr, major isomer): δ 7.98 (2H, br dd, *J* = 8.5, 1.0 Hz), 7.76 (2H, br dd, *J* = 7.2, 1.1 Hz), 7.54 (2H, br d, *J* = 7.0 Hz), 7.43 (2H, br t, *J* = 7.5 Hz), 7.35 (3H, br t, *J* = 7.5 Hz), 7.32-7.29 (1H, m), 7.27-7.23 (5H, m), 7.19 (2H, br d, *J* = 7.5 Hz), 7.05 (1H, br d, *J* = 7.0 Hz), 7.0 (2H, br d, *J* = 8.0 Hz), 6.91 (2H, br d, *J* = 8.0 Hz), 6.41 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.16 (1H, d, *J* = 12.5 Hz, OCH_2Ph), 4.70 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 3.98 (1H, ddd, *J* = 11.0, 6.25, 2.0 Hz), 3.32 (1H, br s, O*H*), 3.25 (1H, t, *J* = 12.5 Hz), 2.15 (3H, s, CH_3), 2.27 (1H, dd, *J* = 13.75, 5.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.5 (C, O-*C*=O), 171.2 (C, N-*C*=O), 159.0 (C, N=*C*), 144.0 (C), 138.0 (C), 137.4 (C), 136.7 (C), 135.0 (CH), 133.8 (C), 132.5 (C), 131.6 (C), 130.3 (CH), 129.3 (2 x CH), 129.0 (2 x CH), 128.8 (CH), 128.7 (2 x CH), 128.63 (CH), 128.56 (3 x CH), 128.5 (5 x CH), 127.8 (3 x CH), 125.9 (2 x CH), 119.1 (2 x CH), 78.7 (C, *C*-OH), 68.9 (CH_2, OCH_2Ph), 64.6 (C), 40.4 (CH), 33.6 (CH_2), 20.9 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{41}H_{34}N_2O_4H$ 619.2597. Found 619.2597.

Benzyl (5*S*,6*R*,8*R*)-10-(4-(*tert*-butyl)phenyl)-6-hydroxy-4-oxo-1,3,8-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4gb): The title

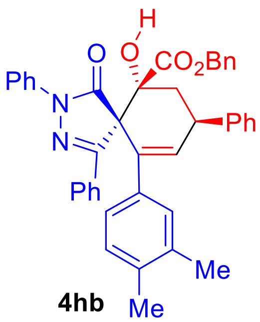


4gb

compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white semisolid. Mp.: 122-124 °C. Yield: 79% (104.40 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 = 4.44 min (major), t_R =

5.59 min (minor); $[\alpha]_D^{25}$ = +66.6° [*c* = 0.1, $CHCl_3$, 92% *ee*]; IR (Neat): ν_{max} 3508, 3059, 3030, 2960, 2862, 1717, 1596, 1492, 1455, 1372, 1299, 1235, 1141, 1045, 905, 864, 835, 748, 695, 578 and 543 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 3.3:1 dr, major isomer): δ 8.0 (2H, br d, *J* = 8.0 Hz), 7.75 (2H, brd, *J* = 8.4 Hz), 7.53 (2H, d, *J* = 8.0 Hz), 7.43 (2H, br t, *J* = 8.0 Hz) 7.36-7.31 (3H, m), 7.30-7.26 (3H, m), 7.25 (1H, br s), 7.22 (2H, br d, *J* = 3.5 Hz), 7.17 (2H, br d, *J* = 6.8 Hz), 7.13-7.10 (2H, m), 7.04 (3H, br d, *J* = 7.6 Hz), 6.42 (1H, br s, olefinic-*H*), 5.17 (1H, d, *J* = 12.4 Hz, OCH_2Ph), 4.70 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.0-3.96 (1H, m), 3.30 (1H, br s, O*H*), 3.25 (1H, t, *J* = 12.0 Hz), 2.01 (1H, dd, *J* = 13.4, 5.6 Hz), 1.15 (9H, 3 x CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135, major isomer) δ 172.5 (C, O-*C*=O), 171.2 (C, N-*C*=O), 159.2 (C, N=*C*), 150.6 (C), 144.0 (C), 138.0 (C), 136.6 (C), 135.2 (CH), 133.9 (C), 132.3 (C), 131.8 (C), 130.2 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 128.6 (3 x CH), 128.56 (CH), 128.5 (4 x CH), 128.46 (2 x CH), 127.8 (2 x CH), 126.8 (CH), 125.6 (2 x CH), 125.5 (2 x CH), 119.1 (2 x CH), 78.7 (C, *C*-OH), 68.9 (CH_2, OCH_2Ph), 64.6 (C), 40.4 (CH), 34.3 (C), 33.7 (CH_2), 31.1 (3 X CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{44}H_{40}N_2O_4H$ 661.3066. Found 661.3067.

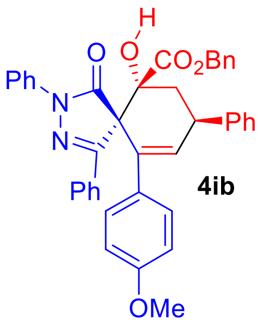
Benzyl (5*S*,6*R*,8*R*)-10-(3,4-dimethylphenyl)-6-hydroxy-4-oxo-1,3,8-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4hb): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white semisolid. Yield: 71% (89.85 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 = 5.48 min (major), t_R = 6.23 min (minor); $[\alpha]_D^{25}$ = +132.0° [*c* = 0.1, $CHCl_3$, 93% *ee*]; IR (Neat): ν_{max} 3507, 3027, 2921, 2851, 1716, 1596, 1492, 1452, 1374, 1299, 1262, 1221, 1181, 1141, 1027, 907, 861, 824, 729, 692, 661, 635, 587, 510 and 488 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 3.7:1 dr, major isomer): δ 7.99 (2H, br d, *J* = 8.0 Hz), 7.79 (2H, br d, *J* = 7.5 Hz), 7.57 (2H, br d, *J* = 7.5 Hz), 7.47 (2H, br t, *J* = 8.0 Hz), 7.38 (4H, br t, *J* = 7.5 Hz), 7.32-7.28 (5H, m), 7.25-7.21 (2H, m), 7.11 (2H, br d, *J* = 7.0 Hz), 6.90 (2H, br d, *J* = 5.0 Hz), 6.44 (1H, d, *J* = 2.5 Hz, olefinic-*H*), 5.21 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.79 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.01 (1H, ddd, *J* = 11.25, 5.75, 2.5 Hz), 3.33-3.28 (2H, m), 2.088 (1H, dd, *J* = 13.25, 6.5 Hz), 2.09 (3H, s, Ar-CH_3), 2.05 (3H, s, Ar-



4hb

CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.5 (C, O-*C*=O), 171.3 (C, N-*C*=O), 159.1 (C, N=*C*), 144.1 (C), 138 (C), 137.2 (C), 136.5 (C), 136.1 (C), 134.8 (CH), 134.0 (C), 132.6 (C), 131.8 (C), 130.2 (CH), 129.8 (CH), 129.0 (2 x CH), 128.72 (2 x CH), 128.67 (2 x CH), 128.56 (CH), 128.5 (4 x CH), 128.46 (2 x CH), 127.8 (2 x CH), 127.3 (CH), 126.8 (CH), 125.5 (CH), 123.5 (CH), 119.3 (2 x CH), 78.6 (C, *C*-OH), 68.8 (CH_2, O*C*H_2Ph), 64.6 (C), 40.4 (CH), 33.8 (CH_2), 19.7 (CH_3), 19.2 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{42}H_{36}N_2O_4H$ 633.2753. Found 633.2754.

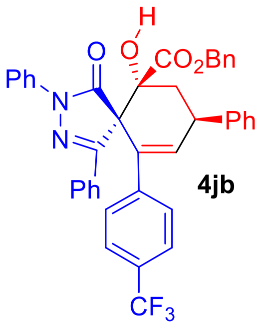
Benzyl (5*S*,6*R*,8*R*)-6-hydroxy-10-(4-methoxyphenyl)-4-oxo-1,3,8-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ib): The title compound was prepared



4ib

following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 112-114 °C. Yield: 83% (105.36 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 = 9.39 min (major), t_R = 20.14 min (minor); $[\alpha]_D^{25}$ = +82.7° [*c* = 0.1, $CHCl_3$, 96% *ee*]; IR (Neat): ν_{max} 3498, 2929, 2160, 1977, 1716, 1597, 1510, 1493, 1454, 1373, 1298, 1247, 1180, 1140, 1031, 928, 865, 831, 757, 692, 643, 627, 606, 567 and 495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 3.4:1 dr, major isomer): δ 7.99 (2H, br dd, *J* = 8.75, 1.0 Hz), 7.77 (2H, br dd, *J* = 7.0, 1.5 Hz), 7.54 (2H, br dd, *J* = 8.1, 1.5 Hz), 7.45-7.41 (2H, m), 7.37-7.34 (3H, m), 7.32-7.29 (1H, m), 7.28-7.26 (2H, m), 7.25-7.22 (3H, m), 7.20-7.16 (2H, m), 7.05-7.02 (3H, m), 6.46-6.61 (2H, m), 6.37 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.16 (1H, d, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.70 (1H, d, *J* = 12.0 Hz, OC*H*$_2$Ph), 3.97 (1H, ddd, *J* = 11.125, 6.0, 2.5 Hz), 3.62 (3H, s, OC*H*$_3$), 3.33 (1H, s, O*H*), 3.25 (1H, t, *J* = 12.5 Hz), 2.01 (1H, dd, *J* = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.5 (C, O-*C*=O), 171.2 (C, N-*C*=O),159.1 (C), 159.0 (C, N=*C*), 144.1 (C), 138.0 (C), 134.4 (CH), 134.3 (C), 133.8 (C), 132.1 (C), 131.6 (C), 130.3 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 128.6 (CH), 128.5 (3 x CH), 128.49 (2 x CH), 128.48 (CH), 128.45 (2 x CH), 127.8 (2 x CH), 127.2 (2 x CH), 126.8 (CH), 125.5 (CH), 119.1 (2 x CH), 113.9 (2 x CH), 78.7 (C, *C*-OH), 68.9 (CH_2, O*C*H_2Ph), 64.7 (C), 55.0 (CH_3, O*C*H_3), 40.3 (CH), 33.6 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{41}H_{34}N_2O_5H$ 635.2546. Found 635.2546.

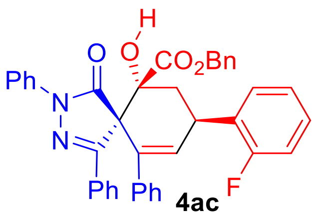
Benzyl (5*S*,6*R*,8*R*)-6-hydroxy-4-oxo-1,3,8-triphenyl-10-(4-(trifluoromethyl)phenyl)-2,3 diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4jb): The title compound was prepared



4jb

following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 105-107 °C. Yield: 37% (49.78 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 = 5.07 min (major), t_R = 8.67 min (minor); $[\alpha]_D^{25}$ = +141.3° [*c* = 0.1, $CHCl_3$, 86% *ee*]; IR (Neat): ν_{max} 3507, 2921, 2852, 1718, 1596, 1493, 1456, 1324, 1299, 1264, 1219, 1167, 1121, 1071, 1018, 907, 869, 732, 692, 643, 627, 606, 537, 498, and 455 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 4.3:1 dr, major isomer): δ 7.97 (2H, br d, *J* = 8.0 Hz), 7.75 (2H, br d, *J* = 7.2 Hz), 7.54 (2H, br d, *J* = 7.2 Hz), 7.44 (3H, br t, *J* = 7.6 Hz), 7.37 (4H, br t, *J* = 7.6 Hz), 7.28 (3H, br d, *J* = 7.2 Hz), 7.25-7.24 (2H, m), 7.22 (2H, br s), 7.20 (2H, br d, *J* = 1.8 Hz), 7.05 (2H, br d, *J* = 7.2 Hz), 6.51 (1H, d, *J* = 2.4 Hz, olefinic-*H*), 5.17 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.72 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.02 (1H, ddd, *J* = 11.0, 5.8, 2.0 Hz), 3.4 (1H, br s, O*H*), 3.28 (1H, t, *J* = 12.8 Hz), 2.05 (1H, dd, *J* = 13.6, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 170.9 (C, N-*C*=O), 158.4 (C, N=*C*), 143.4 (C), 143.1 (C), 137.8 (C), 137.6 (CH), 133.7 (C), 131.7 (C), 131.3 (C), 130.6 (CH), 129.6 (C, q, *J* = 32.4 Hz), 129.1 (2 x CH), 128.9 (2 x CH), 128.8 (CH), 128.7 (2 x CH), 128.5 (2 x CH), 128.49 (CH), 128.46 (2 x CH), 128.38 (CH), 129.9 (2 x CH), 127.0 (CH), 126.3 (2 x CH), 125.7 (CH), 125.6 (2 x CH, q, *J* = 3.7 Hz), 125.3 (C, q, *J* = 271.0 Hz, *C*F_3), 119.1 (2 x CH), 78.6 (C, *C*-OH), 69.0 (CH_2, O*C*H_2Ph), 64.3 (C), 40.6 (CH), 33.5 (CH_2); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –62.72 (major), –62.76 (minor); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{41}H_{31}F_3N_2O_4H$ 673.2314. Found 673.2314.

Benzyl (5*S*,6*R*,8*R*)-8-(2-fluorophenyl)-6-hydroxy-4-oxo-1,3,10-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ac) : The title compound was prepared

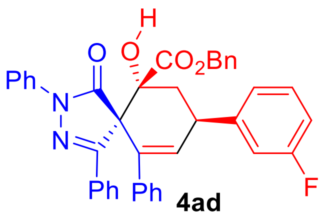


4ac

following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 193-195 °C. Yield: 56% (69.74 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IC-3 column (hexane/2-propanol = 99:1, flow rate 0.5

mL/min, λ = 254 nm), t_R = 9.65 min (minor), t_R = 15.29 min (major); $[\alpha]_D^{25}$ = +69.0° [*c* = 0.1, $CHCl_3$, 91% *ee*]; IR (Neat): ν_{max} 3507, 3482, 3061, 3028, 1714, 1595, 1491, 1444, 1374, 1298, 1224, 1182, 1142, 1032, 930, 906, 865, 756, 692, 661, 637, 499, 477 and 417 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 3.8:1 dr, major isomer): δ 7.97 (2H, br dd, *J* = 8.75, 1.5 Hz), 7.77 (2H, br dd, *J* = 7.0, 1.5 Hz), 7.54 (2H, br dd, *J* = 8.32, 1.0 Hz), 7.43 (2H, br t, *J* = 7.5 Hz), 7.38-7.34 (3H, m), 7.32 (2H, br d, *J* = 7.45 Hz), 7.28-7.25 (3H,m), 7.23 (1H, br d, *J* = 7.2 Hz), 7.20-7.17 (2H, m), 7.10-7.03 (3H, m), 6.79 (2H, br t, *J* = 8.5 Hz), 6.39 (1H, d, *J* = 2.5 Hz, olefinic-*H*), 5.16 (1H, d, *J* = 12.5 Hz, OCH_2Ph), 4.71 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 3.99 (1H, ddd, *J* = 11.0, 6.0, 2.5 Hz), 3.37 (1H, d, *J* = 1.0 Hz, O*H*), 3.29-3.24 (1H, m), 2.03 (1H, dd, *J* = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 171.1 (C, N-*C*=O), 160.4 (C, d, *J* = 243.75 Hz, *C*-F), 158.9 (C, N=*C*), 139.5 (C), 138.0 (C), 134.6 (CH), 133.9 (C), 133.5 (C), 131.5 (C), 130.47 (C, d, *J* = 22.8 Hz), 130.5 (CH, d, *J* = 4.02 Hz), 130.3 (CH), 129.0 (2 x CH), 128.8 (CH), 128.61 (3 x CH), 128.56 (4 x CH), 128.5 (2 x CH), 128.2 (CH, d, *J* = 7.8 Hz), 127.8 (2 x CH), 126.1 (3 x CH), 124.8 (CH, d, *J* = 2.5 Hz), 119.2 (2 x CH), 115.1 (CH, d, *J* = 22.5 Hz), 78.6 (C, *C*-OH), 68.9 (CH_2, OCH_2Ph), 64.6 (C), 32.2 (CH_2), 32.1 (CH, d, *J* = 3.75 Hz); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −117.51 (minor), −120.32 (major); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{31}FN_2O_4H$ 623.2346. Found 623.2346.

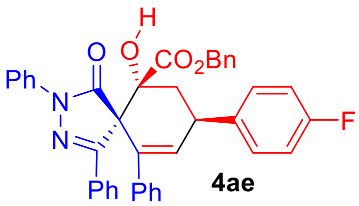
Benzyl (5*S*,6*R*,8*R*)-8-(3-fluorophenyl)-6-hydroxy-4-oxo-1,3,10-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ad): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and



4ad

isolated as an off-white solid. Mp.: 105-107 °C. Yield: 74% (92.16 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IA-3 column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.22 min (major), t_R = 15.98 min (minor); $[\alpha]_D^{25}$ = +73.0° [*c* = 0.1, $CHCl_3$, 92% *ee*]; IR (Neat): ν_{max} 3649, 3565, 3510, 3059, 3034, 1716, 1613, 1591, 1559, 1489, 1444, 1374, 1299, 1254, 1182, 1138, 1037, 963, 930, 906, 865, 757, 737, 661, 639, 556, 491 and 457 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 11:1 dr, major isomer): δ 7.98 (2H, br dd, *J* = 7.5, 1.0 Hz), 7.75 (2H, br dd, *J* = 7.0, 1.0 Hz), 7.44 (2H, br t, *J* = 8.0 Hz), 7.32-7.30 (3H, m), 7.29-7.27 (1H, m), 7.26-7.22 (3H, m), 7.21-7.18 (3H, m), 7.11-7.09 (5H, m), 7.05 (2H, br d, *J* = 7.5 Hz), 6.96-6.92 (1H, m), 6.40 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.17 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.71 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.0 (1H, ddd, *J* = 10.8, 6.5, 2.5 Hz), 3.35 (1H, br s, O*H*), 3.25 (1H, t, *J* = 12.5 Hz), 2.02 (1H, dd, *J* = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 171.0 (C, N-*C*=O), 163.0 (C, d, *J* = 245 Hz, *C*-F), 158.8 (C, N=*C*), 146.5 (C, d, *J* = 7.5 Hz), 139.4 (C), 138.0 (C), 134.8 (CH), 133.8 (C), 133.2 (C), 131.5 (C), 130.3 (CH), 130.2 (CH, d, *J* = 8.75 Hz), 129.0 (2 x CH), 128.63 (CH), 128.60 (2 x CH), 128.56 (2 x CH), 128.52 (2 x CH), 128.49 (2 x CH), 127.8 (3 x CH), 126.1 (2 x CH), 125.6 (CH), 124.1 (CH, d, *J* = 2.125 Hz), 119.2 (2 x CH), 115.4 (CH, d, *J* = 21.25 Hz), 113.8 (CH, d, *J* = 21.25 Hz), 78.6 (C, C-OH), 69.0 (CH_2, OCH_2Ph), 64.5 (C), 40.3 (CH), 33.4 (CH_2); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –112.67 (major), –112.78 (minor); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{40}H_{31}FN_2O_4Na$ 645.2166. Found 645.2168.

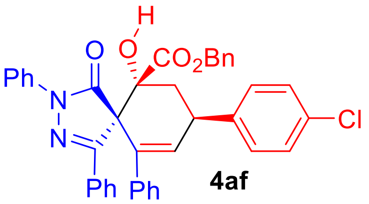
Benzyl (5*S*,6*R*,8*R*)-8-(4-fluorophenyl)-6-hydroxy-4-oxo-1,3,10-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ae): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 116-118 °C. Yield: 70% (87.18 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 = 8.85 min (major), t_R = 10.49 min (minor); $[\alpha]_D^{25}$ = +57.8° [*c* = 0.1, $CHCl_3$, 90% *ee*]; IR (Neat): ν_{max} 3504, 3460, 3061, 3037, 2360, 2338, 1714, 1596, 1494, 1444, 1374, 1298, 1218, 1183, 1141, 1070, 866, 836, 757, 738, 691, 528, 508, 487 and 415 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 4.2:1 *dr*, major isomer): δ 7.98 (2H, br dd, *J* = 9.0, 1.0 Hz), 7.56-7.34 (2H, m), 7.52-7.49 (2H, m), 7.45-7.42 (2H, m), 7.33-7.27 (2H, m), 7.26 (1H, br s), 7.24-7.22 (1H, m), 7.21-7.16 (4H, m), 7.11-7.10 (3H, m), 7.09-7.07 (1H, m), 7.06-7.0 (4H, m), 6.39 (1H, d, *J* = 2.5 Hz, olefinic-*H*), 5.16 (1H, d, *J* = 12.5 Hz, OCH_2Ph), 4.71 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 3.98 (1H, ddd, *J* = 11.125, 6.25, 2.0 Hz), 3.34 (1H, d, *J* = 1.0 Hz, O*H*), 3.23 (1H, t, *J* = 13.0 Hz), 2.0 (1H, dd, *J* = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 171.2 (C, N-*C*=O), 161.9 (C, d, *J* = 243.75 Hz, *C*-F), 158.9 (C, N=*C*), 139.6 (C, d, *J* = 2.5 Hz), 139.2 (C), 138.0 (C), 135.4 (CH), 133.9 (C), 132.9 (C), 131.5 (C), 130.6 (CH), 130.0 (2 x CH, d, *J* = 7.5 Hz), 129.0



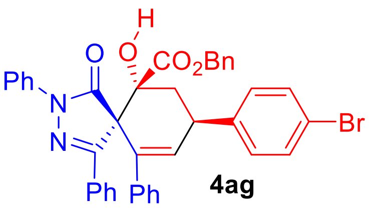
4ae

(2 x CH), 128.8 (CH), 128.7 (CH), 128.59 (2 x CH), 128.5 4 (4 x CH), 128.48 (2 x CH), 127.8 (2 x CH), 127.77 (CH), 126.1 (2 x CH), 119.2 (2 x CH), 115.5 (2 x CH, d, J = 21.25 Hz), 78.7 (C, *C*-OH), 68.9 (CH_2, OCH_2Ph), 64.6 (C), 39.8 (CH), 33.8 (CH_2); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −116.0 (minor), −116.1 (major); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{31}FN_2O_4H$ 623.2346. Found 623.2346.

Benzyl (5*S*,6*R*,8*R*)-8-(4-chlorophenyl)-6-hydroxy-4-oxo-1,3,10-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4af): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 104-106 °C. Yield: 76% (97.15 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IA-3 column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.55 min (major), t_R = 18.59 min (minor); $[\alpha]_D^{25}$ = +72.0° [c = 0.1, $CHCl_3$, 91% *ee*]; IR (Neat): ν_{max} 3503, 3060, 2922, 2852, 1715, 1595, 1491, 443, 1374, 1298, 1264, 1182, 1141, 906, 757, 736, 692, 494 and 419 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 4.2:1 dr, major isomer): δ 7.97 (2H, br d, J = 8.5 Hz), 7.74 (2H, br d, J = 7.0 Hz), 7.48 (2H, br d, J = 8.0 Hz), 7.43 (2H, br t, J = 8.0 Hz), 7.33-7.30 (3H, m), 7.29-7.27 (1H, m), 7.25 (2H, br s), 7.23-7.22 (1H, m), 7.21-7.17 (3H, m), 7.10-7.07 (4H, m), 7.05 (2H, br d, J = 7.0 Hz), 6.38 (1H, d, J = 2.5 Hz, olefinic-*H*), 5.16 (1H, d, J = 12.0 Hz, OCH_2Ph), 4.71 (1H, d, J = 12.0 Hz, OCH_2Ph), 3.97 (1H, ddd, J = 11.0, 6.0, 2.5 Hz), 3.34 (1H, s, O*H*), 3.22 (1H, t, J = 12.0 Hz), 2.0 (1H, dd, J = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 171.1 (C, N-*C*=O), 158.8 (C, N=*C*), 142.4 (C), 139.4 (C), 137.9 (C), 135.0 (CH), 133.8 (C), 133.1 (C), 132.6 (C), 131.4 (C), 130.4 (CH), 129.9 (2 x CH), 129.0 (2 x CH), 128.9 (2 x CH), 128.8 (CH), 128.63 (CH), 128.61 (2 x CH), 128.54 (2 x CH), 128.51 (2 x CH), 128.48 (2 x CH), 127.8 (3 x CH), 126.0 (2 x CH), 119.2 (2 x CH), 78.6 (C, *C*-OH), 69.0 (CH_2, OCH_2Ph), 64.5 (C), 39.9 (CH), 33.5 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{31}ClN_2O_4H$ 639.2051. Found 639.2051.



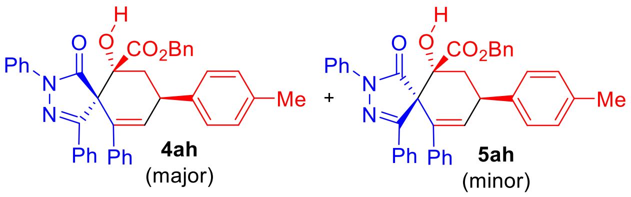
4af



4ag

Benzyl (5*S*,6*R*,8*R*)-8-(4-bromophenyl)-6-hydroxy-4-oxo-1,3,10-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ag): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 113-115 °C. Yield: 64% (87.50 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IA-3 column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.37 min (major), t_R = 18.83 min (minor); $[\alpha]_D^{25}$ = +69.0° [*c* = 0.1, $CHCl_3$, 92% *ee*]; IR (Neat): ν_{max} 3750, 3649, 3502, 3031, 1714, 1595, 1540, 1488, 1443, 1373, 1298, 1268, 1181, 1140, 1122, 1070, 1036, 1010, 930, 905, 865, 825, 756, 736, 690, 660, 644, 540, 491 and 406 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 3.8:1 dr, major isomer): δ 7.97 (2H, br d, *J* = 8.0 Hz), 7.74 (2H, br d, *J* = 7.5 Hz), 7.48-7.46 (2H, m), 7.44-7.41 (3H, m), 7.37-7.34 (1H, m), 7.33-7.28 (2H, m), 7.26-7.24 (3H, m), 7.23-7.27 (1H, m), 7.21-7.18 (3H, m), 7.11-7.10 (3H, m), 7.04 (2H, br d, *J* = 7.0 Hz), 6.38 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.17 (1H, d, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.71 (1H, d, *J* = 12.0 Hz, OC*H*$_2$Ph), 3.96 (1H, ddd, *J* = 11.0, 6.0, 2.5 Hz), 3.34 (1H, br s, O*H*), 3.21 (1H, t, *J* = 13.0 Hz), 2.0 (1H, dd, *J* = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.3 (C, O-*C*=O), 171.1 (C, N-*C*=O), 158.8 (C, N=*C*), 143.0 (C), 139.4 (C), 138.0 (C), 134.8 (C), 133.8 (C), 133.2 (C), 131.9 (2 x CH), 131.5 (C), 130.3 (2 x CH), 129.03 (2 x CH), 128.8 (CH), 128.7 (CH), 128.61 (2 x CH), 128.5 (5 x CH), 128.49 (2 x CH), 127.8 (3 x CH), 126.1 (2 x CH), 125.6 (CH), 120.7 (C), 119.2 (2 x CH), 78.6 (C, *C*-OH), 69.0 (CH_2, O*C*H$_2$Ph), 64.6 (C), 40.0 (CH), 33.6 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{31}BrN_2O_4H$ 705.1365. Found 705.1365.

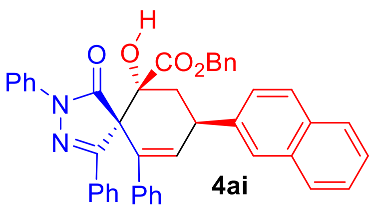
Benzyl (5*S*,6*R*,8*R*)-6-hydroxy-4-oxo-1,3,10-triphenyl-8-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ah): The title compound was prepared following procedure **B**,



purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 114-116 °C. Yield: 71% (87.86 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 = 7.43 min (major), t_R = 8.46 min (minor); $[\alpha]_D^{25}$ = +73.0° [*c* = 0.1, $CHCl_3$, 90% *ee*]; IR (Neat): ν_{max} 3648, 3507, 3062, 3030, 1717, 1653, 1558, 1540, 1496, 1456, 1374, 1300, 1143, 819, 758 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 2.8:1 dr, major isomer): δ 7.98 (2H, br d, *J* = 8.0 Hz), 7.76 (2H, br dd, *J* = 6.88, 1.4 Hz), 7.44-7.41 (4H, m), 7.30-7.27 (2H, m), 7.24 (2H, d, *J* = 1.6 Hz), 7.23-7.22 (1H, m), 7.20-7.15 (5H, m), 7.12-7.09 (4H, m), 7.06-7.03 (2H, m), 6.43 (1H, d, *J* = 2.0

Hz, olefinic-*H*), 5.16 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.69 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 3.96 (1H, ddd, *J* = 10.9, 6.0, 2.4 Hz), 3.33 (1H, s, O*H*), 3.25 (1H, t, *J* = 12.8 Hz), 2.33 (3H, s), 2.01 (1H, dd, *J* = 13.4, 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135, major isomer) δ 172.5 (C, O-*C*=O), 171.2 (C, N-*C*=O), 158.9 (C, N=*C*), 140.9 (C), 139.6 (C), 138.0 (C), 136.44 (C), 135.9 (CH), 133.9 (C), 132.5 (C), 131.6 (C), 130.3 (CH), 129.4 (2 x CH), 129.0 (2 x CH), 128.55 (CH), 128.53 (CH), 128.52 (3 x CH), 128.48 (2 x CH), 128.45 (2 x CH), 128.36 (2 x CH), 127.8 (2 x CH), 127.6 (2 x CH), 126.1 (2 x CH), 119.1 (2 x CH), 78.8 (C, *C*-OH), 68.9 (CH_2, O*C*H_2Ph), 64.6 (C), 40.0 (CH), 33.7 (CH_2), 21.1 (CH_3); ^{1}H NMR ($CDCl_3$, 400 MHz, 2.8:1 dr, minor isomer): δ 7.73 (2H, br d, *J* = 8.0 Hz), 7.59 (2H, br d, *J* = 8.0 Hz), 7.36 (3H, br d, *J* = 7.6 Hz), 7.33 (1H, br d, *J* = 3.6 Hz), 7.30.7.27 (2H, m), 7.23-7.22 (1H, m), 7.21 (1H, br s), 7.20-7.15 (6H, m), 7.12-7.09 (4H, m), 7.06-7.03 (2H, m), 6.55 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.91 (1H, d, *J* = 2.4 Hz, O*H*), 5.05 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.95 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.07 (1H, ddd, *J* = 11.4, 5.8, 2.0 Hz), 3.25 (1H, t, *J* = 12.8 Hz), 2.32 (3H, s), 2.28 (1H, dd, *J* = 13.4, 4.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135, minor isomer) δ 173.8 (C, O-*C*=O), 170.9 (C, N-*C*=O), 158.7 (C, N=*C*), 139.8 (C), 139.3 (C), 137.3 (CH), 136.9 (C), 136.38 (C), 134.4 (C), 132.6 (C), 130.8 (C), 130.5 (CH), 129.3 (2 x CH), 128.8 (3 x CH), 128.78 (3 x CH), 128.68 (2 x CH), 128.60 (3 x CH), 128.43 (CH), 128.4 (3 x CH), 127.1 (2 x CH), 125.5 (2 x CH), 120.0 (2 x CH), 77.6 (C, *C*-OH), 67.7 (CH_2, O*C*H_2Ph), 62.3 (C), 39.1 (CH), 34.2 (CH_2), 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{41}H_{34}N_2O_4Na$ 641.2416. Found 641.2417.

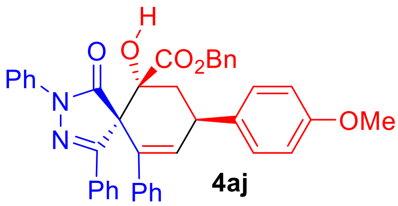
Benzyl (5*S*,6*R*,8*R*)-6-hydroxy-8-(naphthalen-2-yl)-4-oxo-1,3,10-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ai): The title compound was prepared



4ai

following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 129-131 °C. Yield: 70% (91.67 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 = 11.12 min (major), t_R = 21.94 min (minor); $[\alpha]_D^{25}$ = +121.0° [*c* = 0.1, $CHCl_3$, 90% *ee*]; IR (Neat): ν_{max} 3503, 3056, 2923, 2854, 1716, 1596, 1494, 1443, 1374, 1299, 1264, 1182, 1139, 1070, 1028, 906, 859, 820, 753, 736, 693, 509, 478 and 421 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 3.2:1 dr, major isomer): δ 8.0 (2H, br d, *J* = 8.0 Hz), 7.86-7.76 (6H, m), 7.65-7.60 (1H, m), 7.48-7.43 (3H, m), 7.37 (1H, br d, J = 8.0 Hz), 7.31-7.30 (1H, m), 7.27 (2H, br d, J = 7.5 Hz), 7.25 (1H, br s), 7.24-7.20 (2H, m), 7.18 (2H, br d, J = 7.5 Hz), 7.14-7.13 (2H, m), 7.11-7.08 (2H, m), 7.04 (2H, br d, J = 7.0 Hz), 6.55 (1H, d, J = 2.0 Hz, olefinic-H), 5.17 (1H, d, J = 12.0 Hz, OCH_2Ph), 4.71 (1H, d, J = 12.0 Hz, OCH_2Ph), 4.18 (1H, ddd, J = 11.1, 5.75, 2.0 Hz), 3.38 (2H, t, J = 9.0 Hz), 2.09 (1H, dd, J = 13.5, 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.4 (C, O-C=O), 171.2 (C, N-C=O), 158.9 (C, N=C), 141.3 (C), 139.6 (C), 138.0 (C), 135.5 (CH), 133.8 (C), 133.6 (C), 132.9 (C), 132.6 (C), 131.5 (C), 130.3 (CH), 129.0 (3 x CH), 128.7 (2 x CH), 128.6 (3 x CH), 128.5 (2 x CH), 128.48 (2 x CH), 128.46 (2 x CH), 127.8 (2 x CH), 127.7 (2 x CH), 126.8 (CH), 126.79 (CH), 126.1 (3 x CH), 125.5 (CH), 119.9 (2 x CH), 78.7 (C, C-OH), 68.9 (CH_2, OCH$_2$Ph), 64.6 (C), 40.6 (CH), 33.6 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{44}H_{34}N_2O_4Na$ 677.2416. Found 677.2416.

Benzyl (5*S*,6*R*,8*R*)-6-hydroxy-8-(4-methoxyphenyl)-4-oxo-1,3,10-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4aj): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 117-119 °C. Yield: 70% (88.86 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 = 13.28 min (major), t_R = 18.03 min (minor); $[\alpha]_D^{25}$ = +74.0° [c = 0.1, $CHCl_3$, 90% *ee*]; IR (Neat): ν_{max} 3853, 3711, 3689, 3675, 3066, 3031, 2835, 2360, 1716, 1653, 1558, 1510, 1490, 1457, 1443, 1374, 1298, 1247, 1177, 1247, 1141, 1069, 1032, 930, 866, 831, 757, 740, 692, 660, 641, 629, 539, 423, 413 and 406 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 3.3:1 dr, major isomer): δ 7.99 (2H, br dd, J = 8.75, 1.0 Hz), 7.76 (2H, br dd, J = 7.4, 1.7 Hz), 7.48-7.42 (4H, m), 7.38-7.36 (1H, m), 7.32-7.29 (2H, m), 7.27-7.22 (4H, m), 7.21-7.19 (2H, m), 7.11 (3H, br d, J = 4.5 Hz), 7.05-7.03 (2H, m), 6.90 (2H, br dd, J = 6.5, 2.0 Hz), 6.42 (1H, d, J = 2.5 Hz, olefinic-H), 5.17 (1H, d, J = 12.0 Hz, OCH_2Ph), 4.69 (1H, d, J = 12.0 Hz, OCH_2Ph), 3.94 (1H, ddd, J = 11.0, 6.0, 2.5 Hz), 3.79 (3H, s, OCH_3), 3.34 (1H, s, OH), 3.23 (1H, t, J = 12.5 Hz), 2.0 (1H, dd, J = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.5 (C, O-C=O), 171.2 (C, N-C=O), 158.9 (C, N=C), 158.6 (C), 139.6 (C), 138.0 (C), 136.1 (CH),



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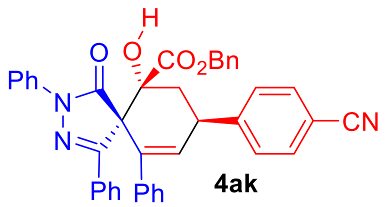
136.0 (C), 133.9 (C), 132.4 (C), 131.6 (C), 130.3 (CH), 129.5 (2 x CH), 129.0 (2 x CH), 128.7 (CH), 128.6 (CH), 128.57 (CH), 128.55 (2 x CH), 128.53 (CH), 128.51 (3 x CH), 128.46 (2 x CH), 127.8 (2 x CH), 126.1 (2 x CH), 119.2 (2 x CH), 114.2 (2 x CH), 78.8 (C, *C*-OH), 68.9 (CH_2, O*C*H_2Ph), 64.6 (C), 55.3 (CH_3, O*C*H_3), 39.6 (CH), 33.8 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{41}H_{34}N_2O_5Na$ 657.2365. Found 657.2363.

Benzyl (5*S*,6*R*,8*R*)-8-(4-cyanophenyl)-6-hydroxy-4-oxo-1,3,10-triphenyl-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4ak): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 122-124 °C. Yield: 70% (88.16 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 = 32.66 min (minor), t_R = 40.68 min (major); $[\alpha]_D^{25}$ = +90.8° [*c* = 0.1, $CHCl_3$, 92% *ee*]; IR (Neat): ν_{max} 3488, 2954, 2918, 2227, 1715, 1600, 1495, 1443, 1376, 1302, 1139, 761 and 691 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.5:1 dr, major isomer): δ 7.96 (2H, br d, *J* = 8.5 Hz), 7.73-7.72 (2H, m), 7.68-7.65 (2H, m), 7.63-7.57 (2H, m), 7.48-7.43 (2H, m), 7.34-7.29 (3H, m), 7.23-7.21 (2H, m), 7.20-7.18 (3H, m), 7.12-7.09 (4H, m), 7.05-7.03 (2H, m), 6.34 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.17 (1H, d, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.73 (1H, d, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.05 (1H, ddd, *J* = 11.0, 6.0, 2.5 Hz), 3.36 (1H, br s, O*H*), 3.23 (1H, t, *J* = 11.5 Hz), 2.01 (1H, dd, *J* = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.1 (C, O-*C*=O), 171.0 (C, N-*C*=O), 158.7 (C, N=*C*), 149.5 (C), 139.8 (C), 137.8 (C), 134.2 (C), 133.7 (C), 133.6 (CH), 132.6 (2 x CH), 131.3 (C), 130.7 (CH), 129.4 (2 x CH), 129.1 (2 x CH), 128.69 (CH), 128.7 (2 x CH), 128.66 (2 x CH), 128.59 (2 x CH), 128.54 (CH), 128.5 (3 x CH), 127.8 (2 x CH), 126.0 (2 x CH), 119.2 (2 x CH), 118.9 (C), 110.8 (C), 78.4 (C, *C*-OH), 69.1 (CH_2, O*C*H_2Ph), 64.5 (C), 40.6 (CH), 33.2 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{41}H_{31}N_3O_4Na$ 652.2212. Found 652.2214.



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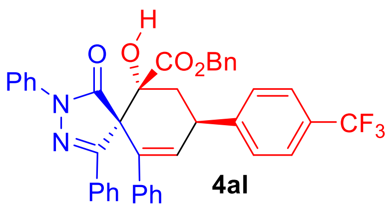
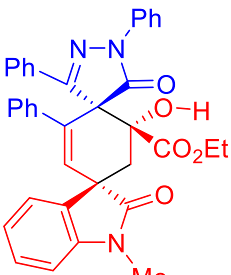


4al

Benzyl (5*S*,6*R*,8*R*)-6-hydroxy-4-oxo-1,3,10-triphenyl-8-(4-(trifluoromethyl)phenyl)-2,3-diazaspiro[4.5]deca-1,9-diene-6-carboxylate (4al): The title compound was prepared following procedure **B**, purified by column chromatography using EtOAc/hexane (1/19), and isolated as an off-white solid. Mp.: 109-111 °C. Yield: 71% (95.52 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralcel IA-3 column (hexane/2-propanol = 97:3, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.59 min (minor), t_R = 16.99 min (major); $[\alpha]_D^{25}$ = +67.0° [*c* = 0.1, $CHCl_3$, 91% *ee*]; IR (Neat): ν_{max} 3852, 3675, 3501, 3066, 2360, 1715, 1653, 1617, 1595, 1540, 1491, 1444, 1419, 1322, 1299, 1164, 1120, 1108, 1067, 1017, 930, 841, 757, 691, 643, 628, 604, 495, 420 and 412 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.5:1 dr, major isomer): δ 7.97 (2H, br dd, *J* = 7.5 Hz), 7.75 (2H, br d, *J* = 7.0 Hz), 7.70-7.66 (2H, m), 7.61 (2H, br d, *J* = 8.5 Hz), 7.44 (2H, br t, *J* = 8.0 Hz), 7.33-7.28 (2H, m), 7.25-7.24 (3H, m), 7.22-7.19 (4H, m), 7.11-7.10 (3H, m), 7.04 (2H, br d, *J* = 7.0 Hz), 6.39 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.17 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.72 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.06 (1H, ddd, *J* = 10.9, 6.25, 2.0 Hz), 3.37 (1H, d, *J* = 1.0 Hz, O*H*), 3.25 (1H, t, *J* = 13.0 Hz), 2.02 (1H, dd, *J* = 13.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, major isomer) δ 172.2 (C, O-*C*=O), 171.1 (C, N-*C*=O), 158.8 (C, N=*C*), 148.1 (C), 139.0 (C), 138.0 (C), 134.3 (CH), 133.8 (C), 133.6 (C), 131.5 (C), 130.4 (CH), 129.3 (C, q, *J* = 32.5 Hz), 129.0 (2 x CH), 128.9 (2 x CH), 128.8 (CH), 128.7 (CH), 128.6 (2 x CH), 128.57 (2 x CH), 128.56 (2 x CH), 128.50 (CH), 127.9 (CH), 127.8 (2 x CH), 126.1 (2 x CH), 125.7 (2 x CH, q, *J* = 3.8 Hz), 125.6 (CH), 124.3 (C, q, *J* = 270.1 Hz, CF_3), 119.2 (2 x CH), 78.5 (C, *C*-OH), 69.0 (CH_2, OCH_2Ph), 64.6 (C), 40.4 (CH), 33.5 (CH_2); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –62.40 (major), –62.43 (minor); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{41}H_{31}F_3N_2O_4Na$ 695.2134. Found 695.2134.

Ethyl(1′*R*,3*R*,6′*S*)-6′-hydroxy-1-methyl-2,5″-dioxo-1″,2′,3″-triphenyl-1″,5″dihydrodispiro[indoline-3,4′-cyclohexane-1′,4″-pyrazol]-2′-ene-6′-carboxylate 10:



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The title compound was prepared following procedure **D** or procedure **E** or procedure **F**, purified by column chromatography using EtOAc/hexane (4/16), and isolated as an off-white solid. Mp.: 251-253 °C. Yield: 47% (28.09 mg, procedure **D**), 80% (47.81 mg, procedure **E**), 82% (49.01 mg, procedure **F**). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralcel IA-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.52 min (minor), t_R = 20.57 min (major) for procedure **E**, t_R = 10.53 min (major), t_R = 20.12 min (minor) for procedure **F**;

$[\alpha]_D^{25}$ = +70.0º [*c* = 0.1, $CHCl_3$, 76% *ee*, procedure **E**], -63.0º [*c* = 0.1, $CHCl_3$, 76% *ee*, procedure **F**]; IR (Neat): ν_{max} 3229, 3062, 2923, 2853, 1709, 1681, 1609, 1493, 1470, 1444, 1376, 1302, 1255, 1166, 1132, 1091, 1033, 934, 880, 756, 692, 592 and 490 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.08-8.06 (2H, m), 8.00 (1H, dd, *J* = 7.5, 1.0 Hz), 7.83-7.81 (2H, m), 7.57 (1H, s), 7.52-7.49 (2H, m), 7.35 (1H, dt, *J* = 7.75, 1.0 Hz), 7.31-7.27 (1H, m), 7.25-7.19 (4H, m), 7.10-7.07 (5H, m), 6.92 (1H, d, *J* = 8.0 Hz, olefinic-H), 5.83 (1H, s, OH), 4.14-4.07 (1H, m, OCH_2CH_3), 4.00-3.94 (1H, m, OCH_2CH_3), 3.80 (1H, d, *J* = 15.0 Hz), 3.34 (3H, s, NCH_3), 2.21 (1H, dd, *J* = 15.25, 1.0 Hz), 1.09 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 180.2 (C, O-*C*=O), 171.1 (C, N-*C*=O), 170.6 (C, N-*C*=O), 160.0 (C, N=*C*), 142.8 (C), 138.9 (C), 138.1 (C), 137.4 (C), 132.3 (C), 132.0 (C), 129.7 (CH), 129.1 (3 x CH), 128.9 (2 x CH), 128.5 (CH), 128.4 (2 x CH), 128.2 (CH), 127.2 (2 x CH), 126.4 (2 x CH), 125.7 (2 x CH), 124.6 (CH), 119.7 (2 x CH), 108.7 (CH), 78.8 (C, C-OH), 65.1 (C), 62.1 (CH_2, OCH_2CH_3), 51.2 (C), 32.3 (CH_2), 27.0 (CH_3, NCH_3), 13.9 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{37}H_{31}N_3O_5H$ 598.2342. Found 598.2342.

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4. A Seven-Step, One-Pot Regioselective Synthesis of Biologically Important 3-Aryllawsones: Scope and Applications

4.1 Introduction

Naphthoquinones occupy a significant position in terms of their utility and surprising reactivity. Lawsone is the most naturally occurring naphthoquinone and is well known for its diverse reactivity. Our group has done thorough investigation regarding its reactivity pattern and application in the organocatalysis.[1] On the other hand, 3-aryllawsones have plenty of applications in terms of their biological activities and natural occurrence.[2]

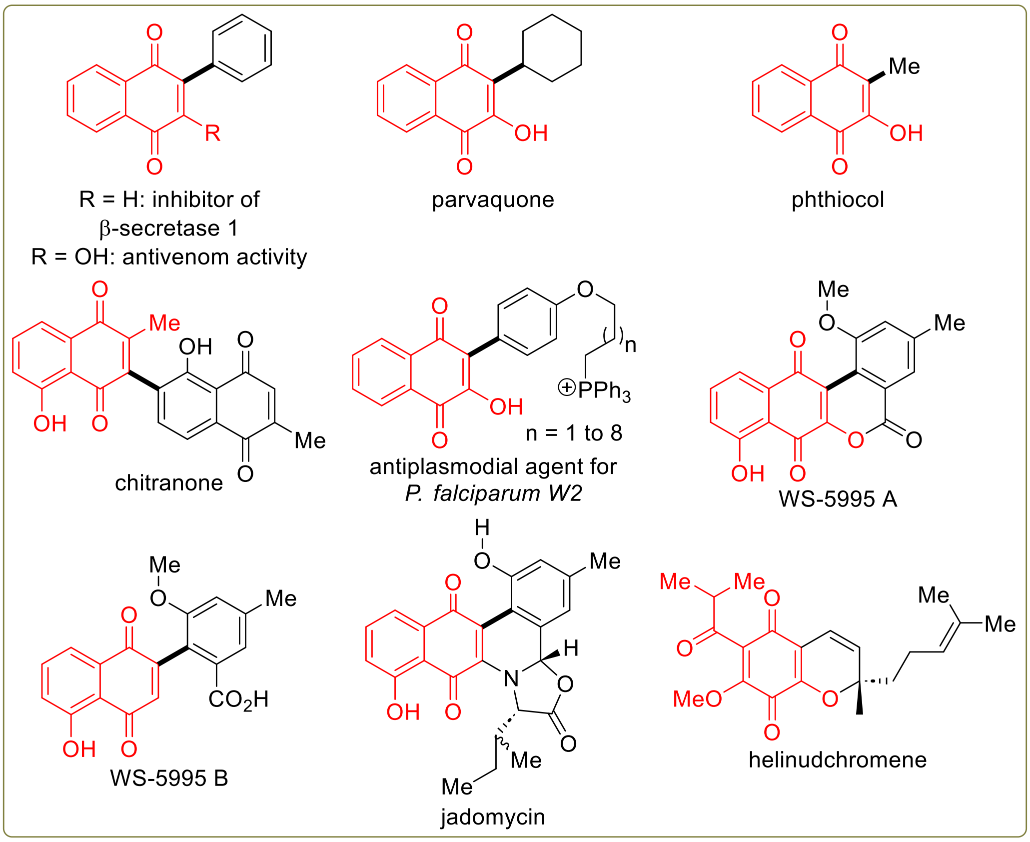
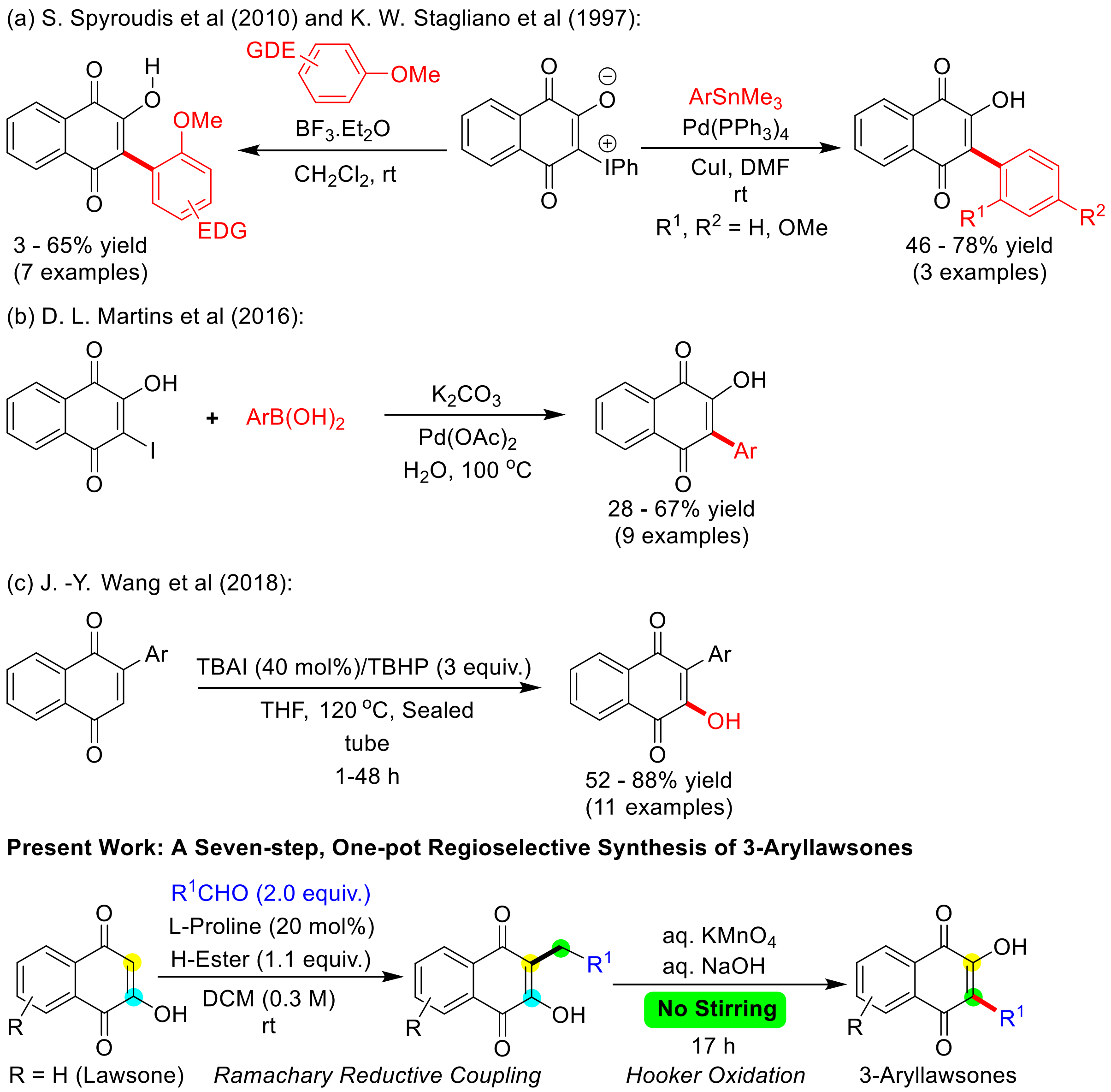


Figure 1: Biologically active naphthoquinone molecules.

For instance, parvaquone is a natural product, 2-phenylnaphthalene-1,4-dione is an inhibitor of β-secretase 1, 3-phenyllawsone has anti-venom activity, and phthiocol is having vitamin K activity, all of which can be synthesized in the laboratory. Apart from these, there are a lot more natural products and analogues (Figure 1).[2] As our laboratory develops new green one-pot protocols for drugs and natural products synthesis using organocatalysis,[1] herein we have taken up the challenge of synthesizing a library of 3-aryllawsones by using a green and sustainable seven-step double cascade one- or two-pot methodology.

4.1.1 Previous Reports on the Synthesis of 3-Aryllawsones

Earlier, Stagliano et al in 1997 reported the synthesis of 3-aryllawsones by reacting activated-lawsone with tin aryl substrates using palladium-catalysis and Spyroudis et al in 2010 demonstrated the reaction of activated-lawsone with electron-rich anisole under Lewis acid-catalysis, which gave poor to moderate yields of 3-aryllawsones (Scheme 1a).[3]



Scheme 1: Previous reports on the synthesis of 3-aryllawsones and present work.

Later, in 2016, Martins et al reported the synthesis of 3-aryllawsones in moderate yields by reacting iodo-lawsone with arylboronic acids in the presence of palladium (Scheme 1b).[4]

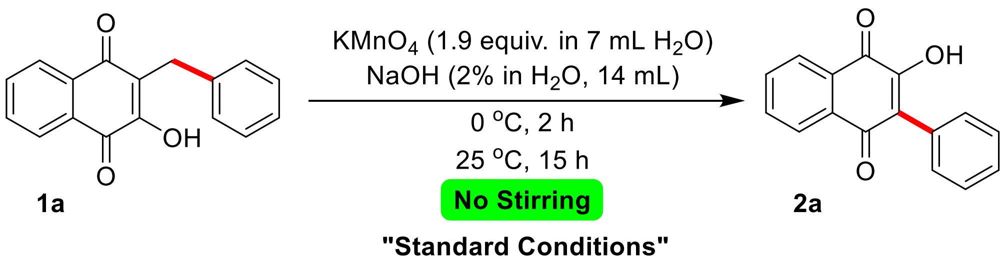
Then, in 2018, Wang et al reported the synthesis of the same through hydroxylation of 2-arylnaphthoquinones using TBAI as a catalyst and TBHP as an oxidant, but the reaction conditions are little harsh and the reaction was demonstrated on limited substrates (Scheme 1c).[5] All the above mentioned protocols are substrate specific, used highly activated starting materials, costly catalyst, and harsh reaction conditions and the yields were obtained in poor to moderate. Thus, absence of proper protocol for the synthesis of 3-aryllawsones and broad applications of many of these compounds propelled us to investigate this problem.

4.2 Results and Discussion

4.2.1 Reaction Preliminary Optimization

With a desire to achieve 3-aryllawsones *via* methylenearyl transfer reaction, first we have chosen 3-benzyllawsone (0.2 mmol, **1a**) and treated it with 14 mL of 2% aq. NaOH and 1.9 equiv. of $KMnO_4$ in 7 mL H_2O at 0 °C for 2 h followed by 15 h at 25 °C as standard reaction condition (Table 1, entry 1).

Table 1: Optimization for the Hooker oxidation[a]

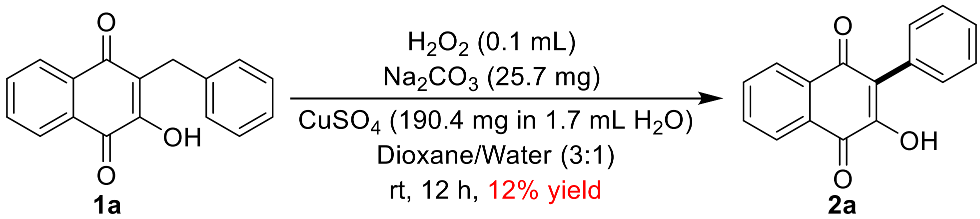


Entry	Deviation from standard conditions	Yield (%)[b]	Yield (%)[c]
1	No deviation	78	93
2	$KMnO_4$ (1.9 equiv., 7.0 mL); 2% LiOH (14 mL)	60	-
3	$KMnO_4$ (1.9 equiv., 7.0 mL); 2% KOH (14 mL)	60	-
4	$KMnO_4$ (2.0 equiv., 7.0 mL); 2% NaOH (14 mL)	52	86
5	$KMnO_4$ (1.8 equiv., 7.0 mL); 2% NaOH (14 mL)	64	89
6	$KMnO_4$ (1.7 equiv., 7.0 mL); 2% NaOH (14 mL)	68	71
7	$KMnO_4$ (1.7 equiv., 5.0 mL); 5% NaOH (10 mL)	46	84
8	$KMnO_4$ (1.7 equiv., 3.0 mL); 5% NaOH (6 mL)	53	82
9	$KMnO_4$ (2.0 equiv., 4.0 mL); 5% NaOH (6 mL)	53	56
10	$KMnO_4$ (2.0 equiv., 4.0 mL); 3% NaOH (8 mL)	60	-

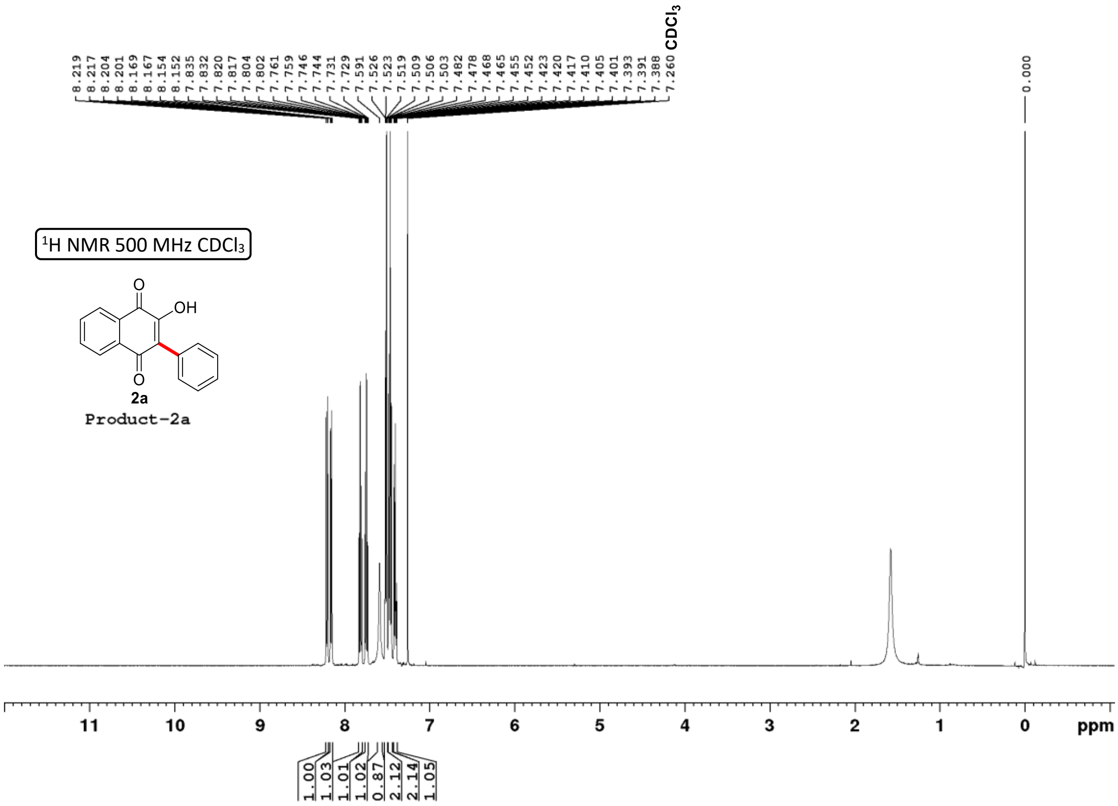
[a] Reactions were carried out in 0.2 mmol scale. [b] Yield refers to the overall yield of the column purified products. [c] Yield calculated based on the recovery of the starting material **1**.

Stunningly, the reaction yielded the Hooker oxidation product **2a** in a very good yield of 78% along with 16% **1a** (93% based on **1a** recovery) which was confirmed by NMR spectroscopy (Figure 2). In order to understand the effect of each component on the oxidation reaction, we studied the reaction by altering different parameters such as a base, equivalents and concentration (Table 1, entries 2-10). We thoroughly investigated the Hooker oxidation reaction by varying bases (LiOH and KOH), equivalents of $KMnO_4$ and concentration of the alkali medium from low to high as mentioned in the Table 1 (entries 2-10). But none of the deviations from entry 1 gave us fruitful result, with respect to time and yield. Besides moderate yield in the above conditions, we were able to recover the unreacted **1a** as mentioned in the Table 1. Since none of the deviations from the standard reaction condition gave fruitful result, we finalized our standard condition [1.9 equiv. of $KMnO_4$ in 7 mL H_2O and 14 mL of 2% NaOH] as the optimized condition.

Apart from Hooker oxidation, we have also tried synthesizing 3-aryllawsones by using Fischer's method. Here, we have performed Fischer's modified procedure by choosing 3-benzyllawsone (0.2 mmol, **1a**) and treated with H_2O_2 (0.1 mL), Na_2CO_3 (25.7 mg), $CuSO_4$ (190.4 mg in 1.7 mL H_2O) in dioxane/water (3:1) at room temperature for 12 h. Disappointingly, the reaction furnished 3-aryllawsone **2a** in only 12% yield (Scheme 2).



Scheme 2: Performing oxidative decarboxylation (OD) through Fieser's modified conditions (H_2O_2 / $CuSO_4$).



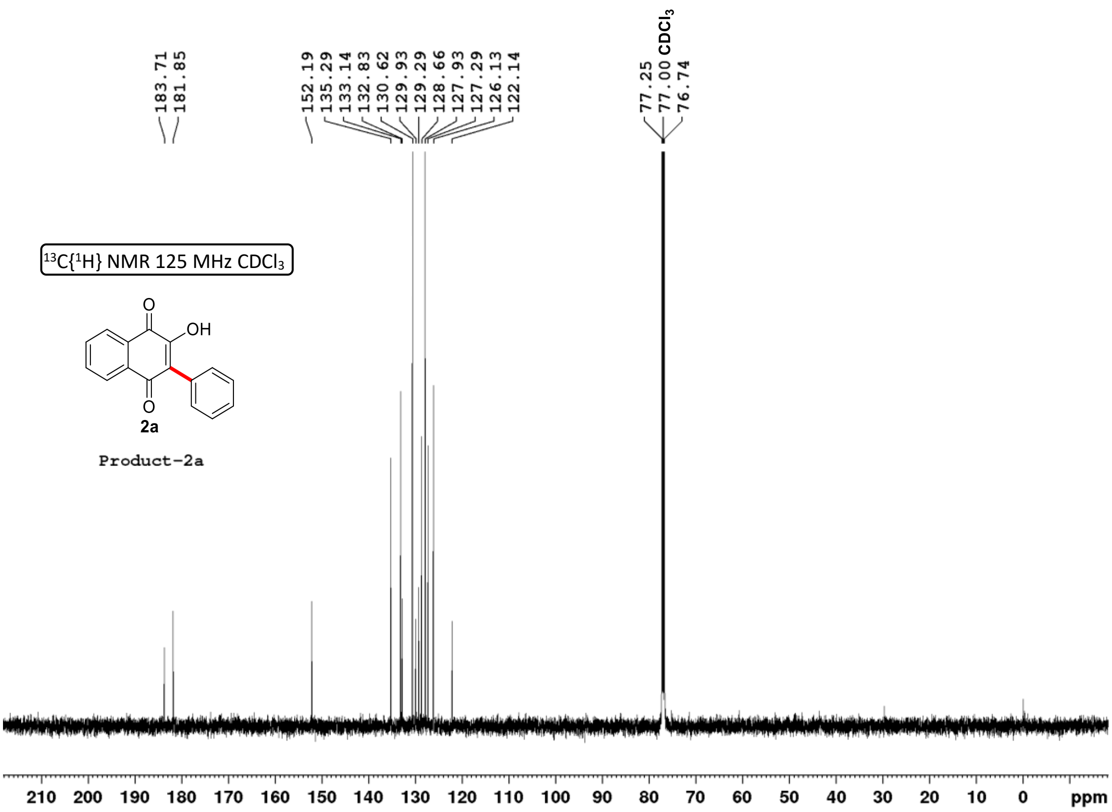


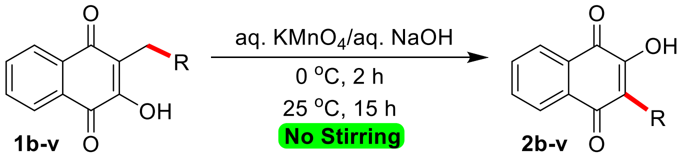
Figure 2: ^{1}H NMR and ^{13}C NMR spectrum of product **2a**.

4.2.2 Reaction Scope for the Synthesis of Functionalized 3-Aryllawsones

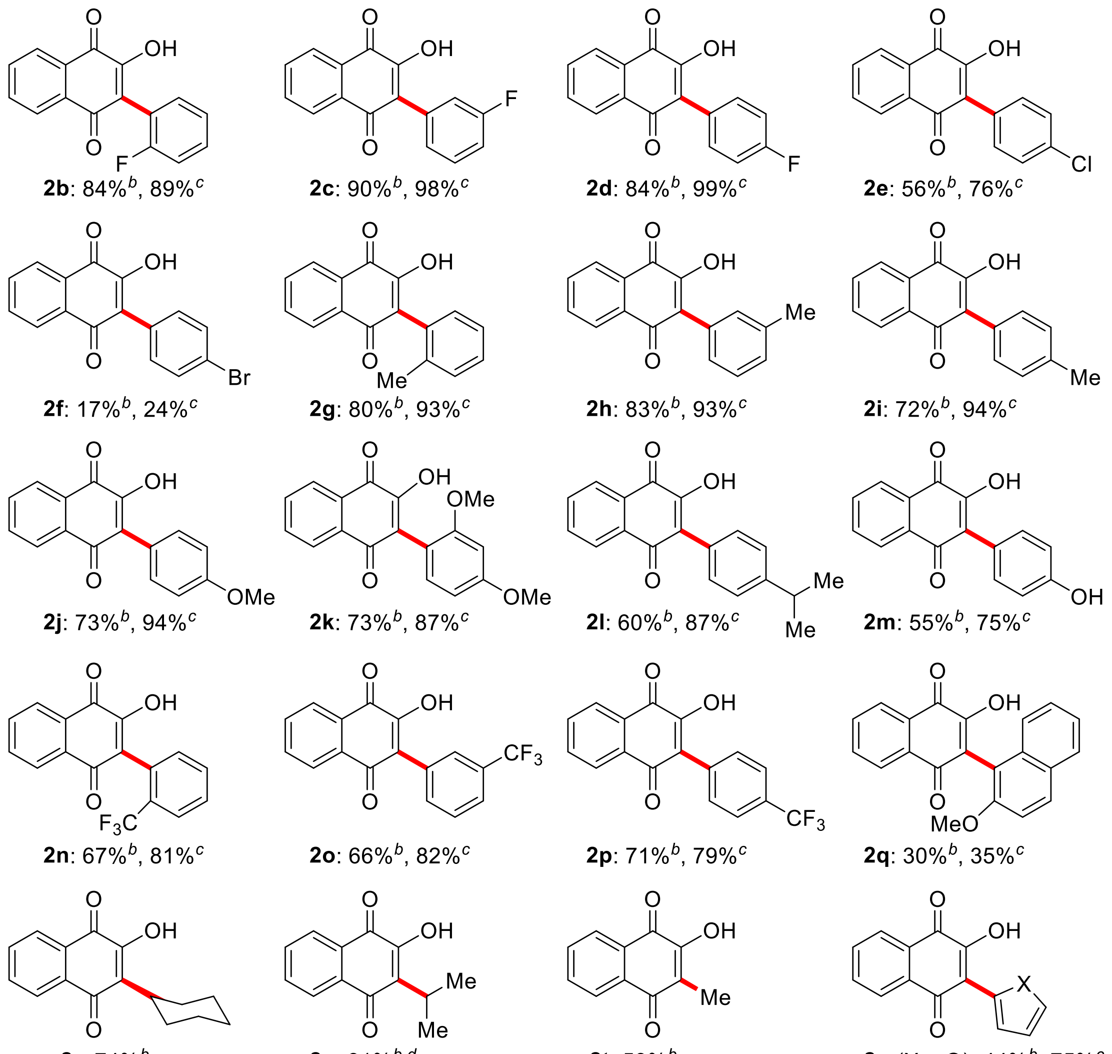
4.2.2.1 Reaction scope with respect to various functionalized alkyl substituents R

With the optimized condition in hand, we determined to analyse the effect of electronic factors on this protocol by screening various functionalized substrates **1b-1v** which were synthesized by using the two-step reductive coupling strategy (Table 2).[1a-d]

Table 2: Reaction scope for the synthesis of functionalized 3-aryllawsones[a]



1b-v → **2b-v**



2b: 84%[b], 89%[c]; **2c**: 90%[b], 98%[c]; **2d**: 84%[b], 99%[c]; **2e**: 56%[b], 76%[c]

2f: 17%[b], 24%[c]; **2g**: 80%[b], 93%[c]; **2h**: 83%[b], 93%[c]; **2i**: 72%[b], 94%[c]

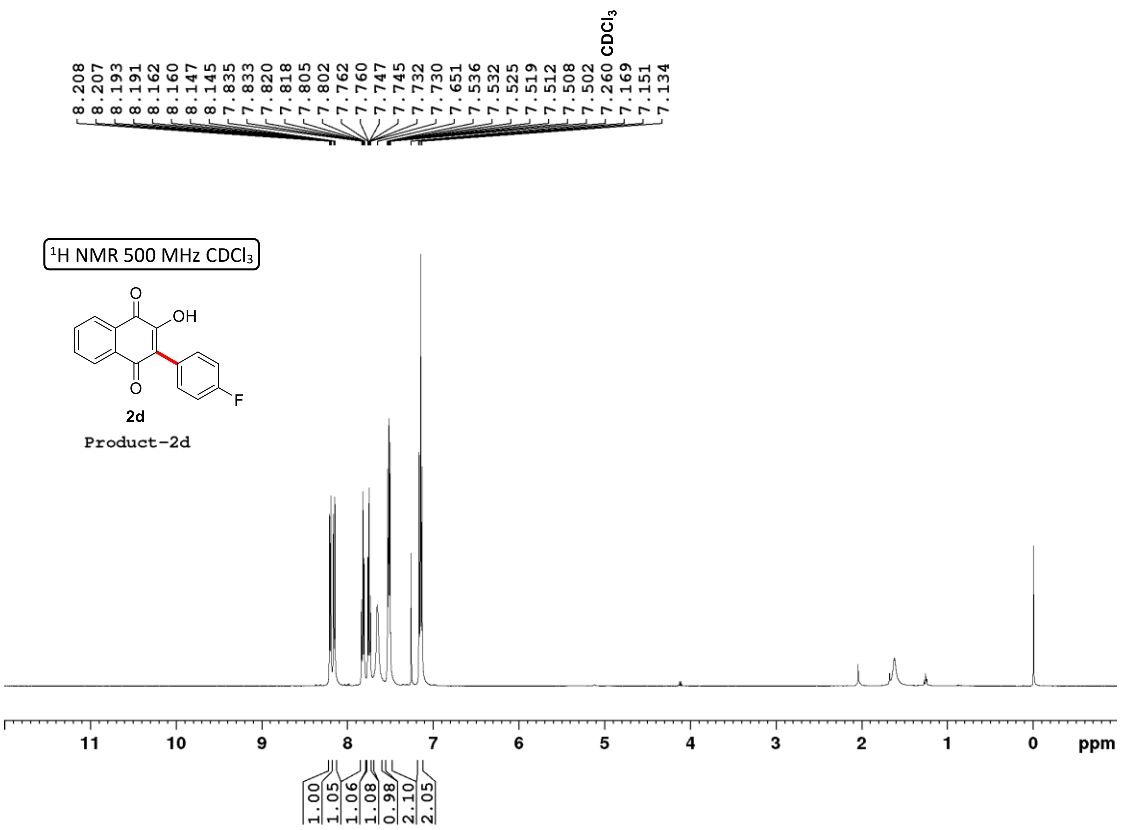
2j: 73%[b], 94%[c]; **2k**: 73%[b], 87%[c]; **2l**: 60%[b], 87%[c]; **2m**: 55%[b], 75%[c]

2n: 67%[b], 81%[c]; **2o**: 66%[b], 82%[c]; **2p**: 71%[b], 79%[c]; **2q**: 30%[b], 35%[c]

2r: 74%[b] *parvaquone*; **2s**: 81%[b,d]; **2t**: 53%[b] *phthiocol*; **2u** (X = O): 44%[b], 75%[c]; **2v** (X = S): 47%[b], 63%[c]

[a] Reactions were carried out on 0.2 mmol scale in 14 mL of 2% aq. NaOH and 1.9 equiv. of $KMnO_4$ in 7 mL H_2O at 0 °C for 2 h followed by 25 °C for 15 h. [b] Yield refers to the overall yield of the column purified products. [c] Yield calculated based on the recovery of the starting material **1**. [d] 21 mL of 2% aq. NaOH and 2.85 equiv. of $KMnO_4$ in 10.5 mL H_2O were used.

The reaction showed good tolerance towards various functional groups such as halogens, electron donating, electron withdrawing, heteroaryl and alkyl groups with moderate to excellent yields (Table 2). In the case of halogen, *ortho*-, *meta*- and *para*-fluorine functionalized substrates **1b-d** smoothly afforded products **2b-d** with excellent yields proving its tolerance. When we see the trend in the yields of halogen substituted 3-aryllawsones **2d-f**, it is evident that the reaction is very well tolerated towards fluorine derivative **2d** (84%) compared to chlorine derivative **2e** (56%) and bromine derivative **2f** (17%). Since halogens have affinity towards oxidation, the yield of **2d-2f** are inversely proportional to their tendency towards oxidation which justifies the low yield of **2f**. Electron donating groups such as methyl, methoxy, isopropyl, hydroxyl and electron withdrawing groups such as trifluoromethyl **1g-1p** underwent excellent Hooker alkyl transfer reaction to furnish the 3-aryllawsones **2g-2p** in good to excellent yields (Table 2). 2-Methoxy-substituted naphthalene derivative **1q** afforded **2q** but only with 30% yield because of its steric hindrance. Since, 3-alkyllawsones **2r-2t** have huge importance in medicinal chemistry, we performed the Hooker oxidation strategy on few important higher alkyllawsones **1r-1t** and successfully achieved the oxidized products parvaquone **2r**, analogue **2s**, and phthiocol **2t** with moderate to good yields (Table 2). The NMR spectra of few selected compounds **2** were shown in Figures 3-10. Compared to previous methods where used costly catalysts, reactive reagents or harsh conditions to prepare medicinally important **2a**/**2r**/**2s**/**2t**;[3-5] present method used simple commercially available substrates by using friendly reaction conditions. Thus, Hooker oxidation is the best protocol to achieve **2a**/**2r-2t** in a simple and efficient manner. We have also investigated the Hooker oxidation importance by synthesizing 3-heteroaryllawsones **2u-v** in very good yields (75% and 63%) respectively (Table 2).



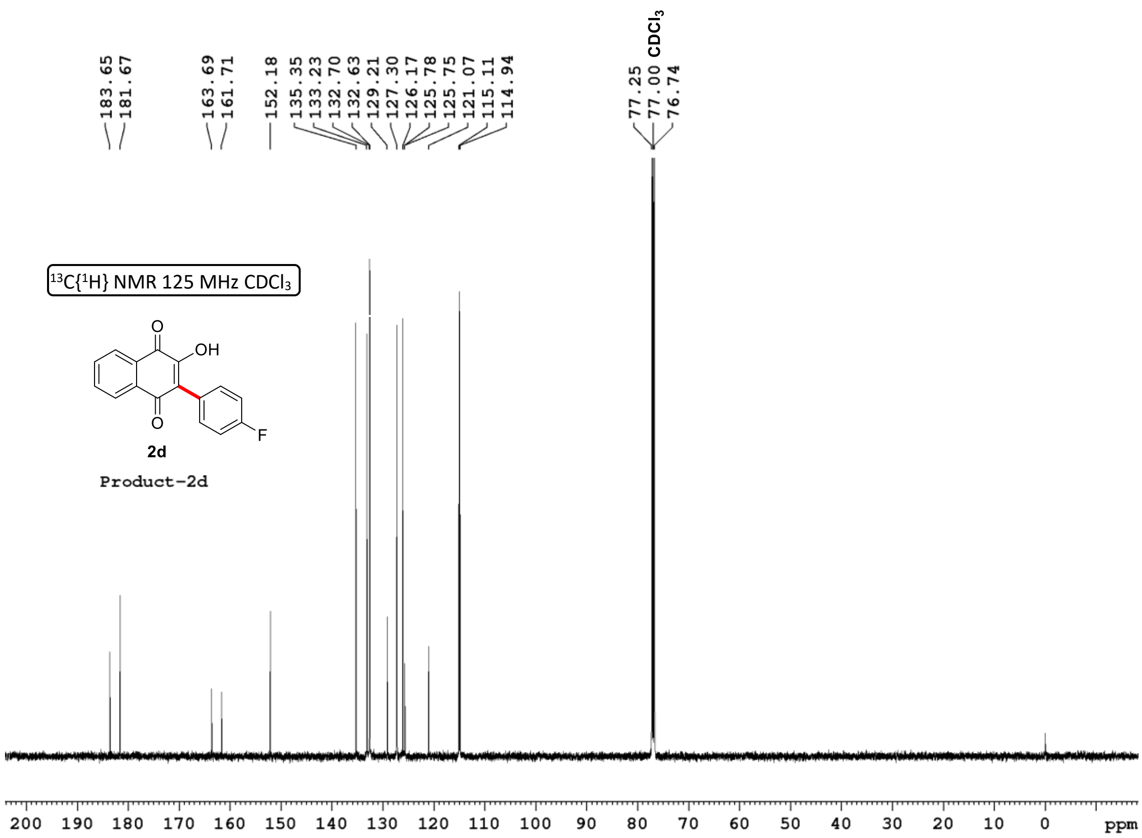
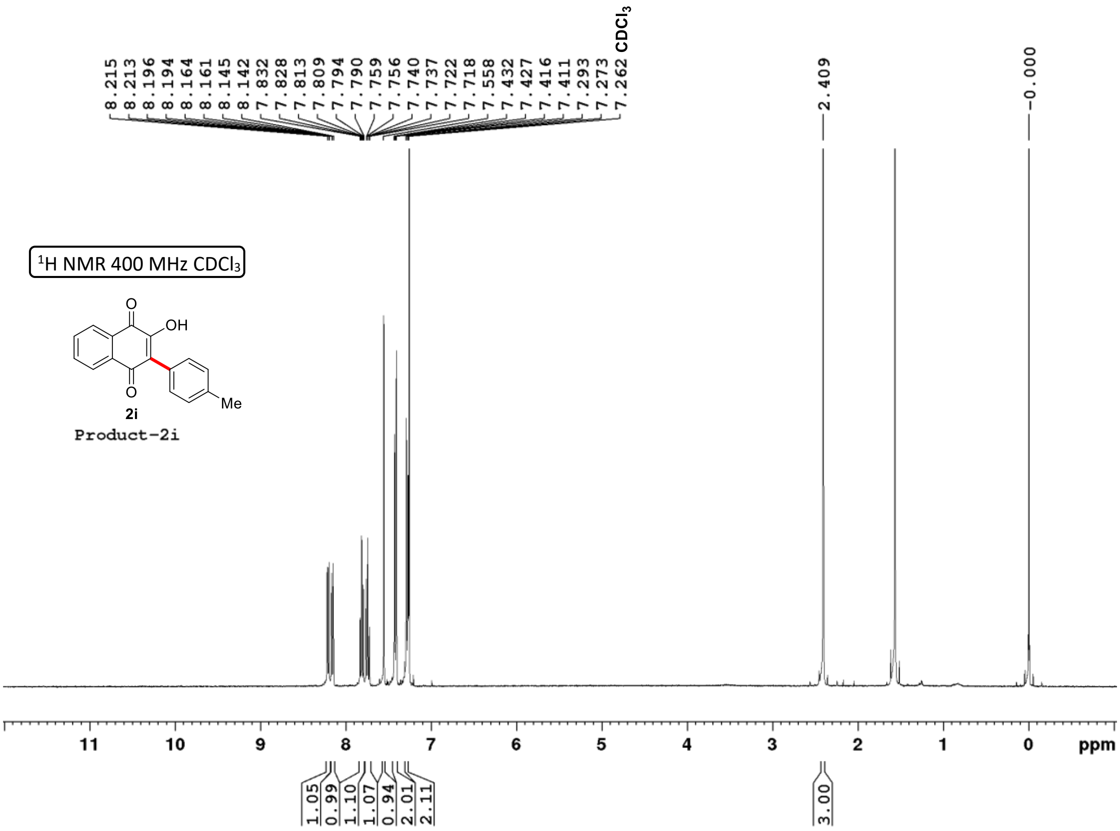


Figure 3: ^{1}H NMR and ^{13}C NMR spectrum of product **2d**.



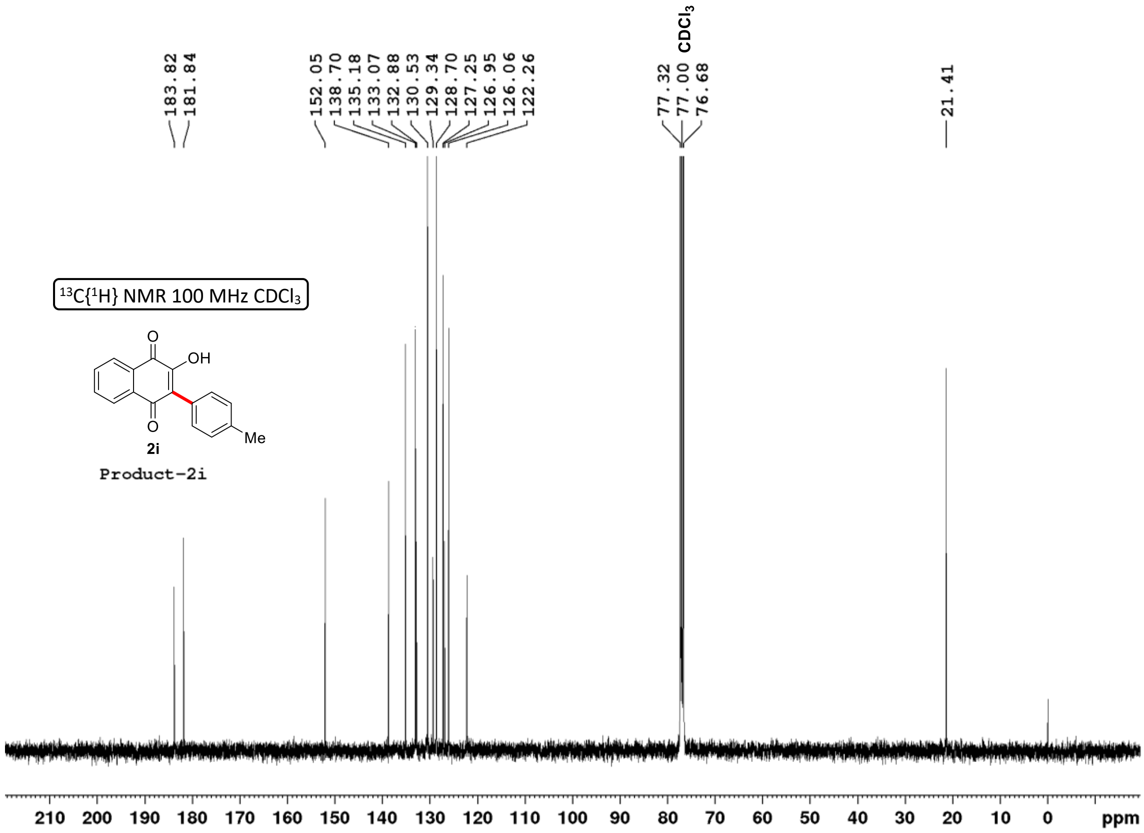
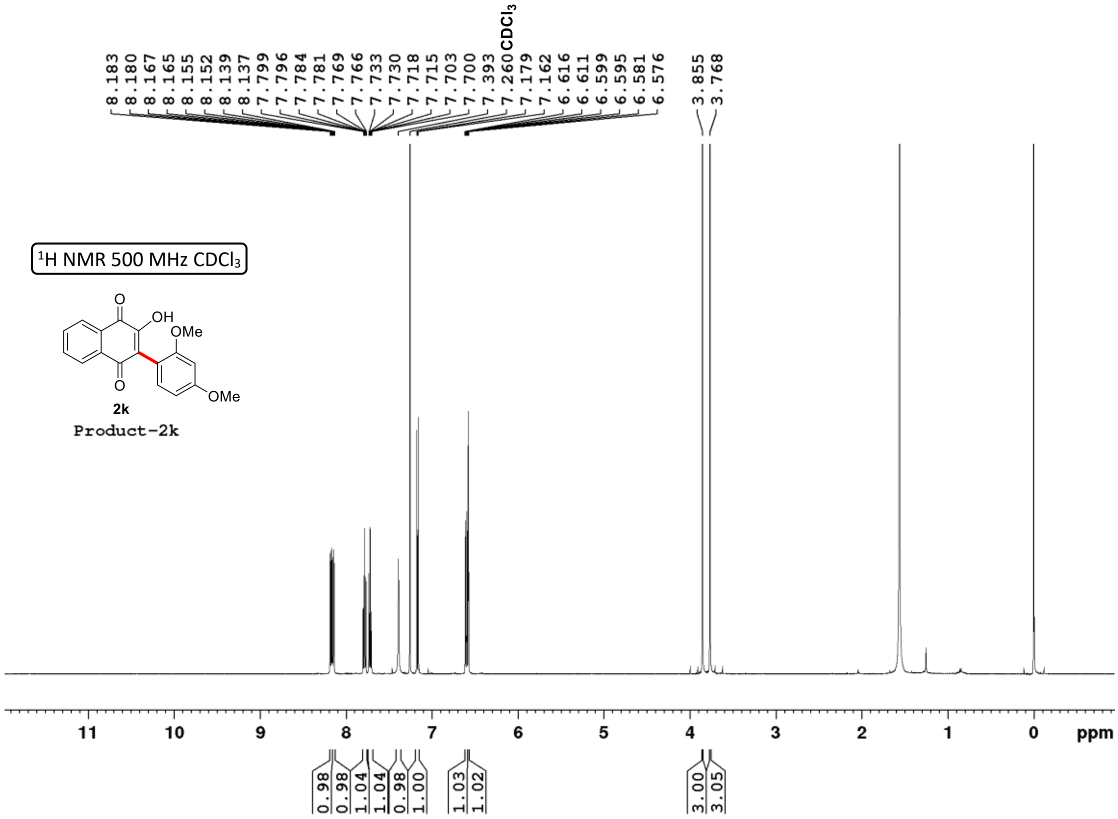


Figure 4: ^{1}H NMR and ^{13}C NMR spectrum of product **2i**.



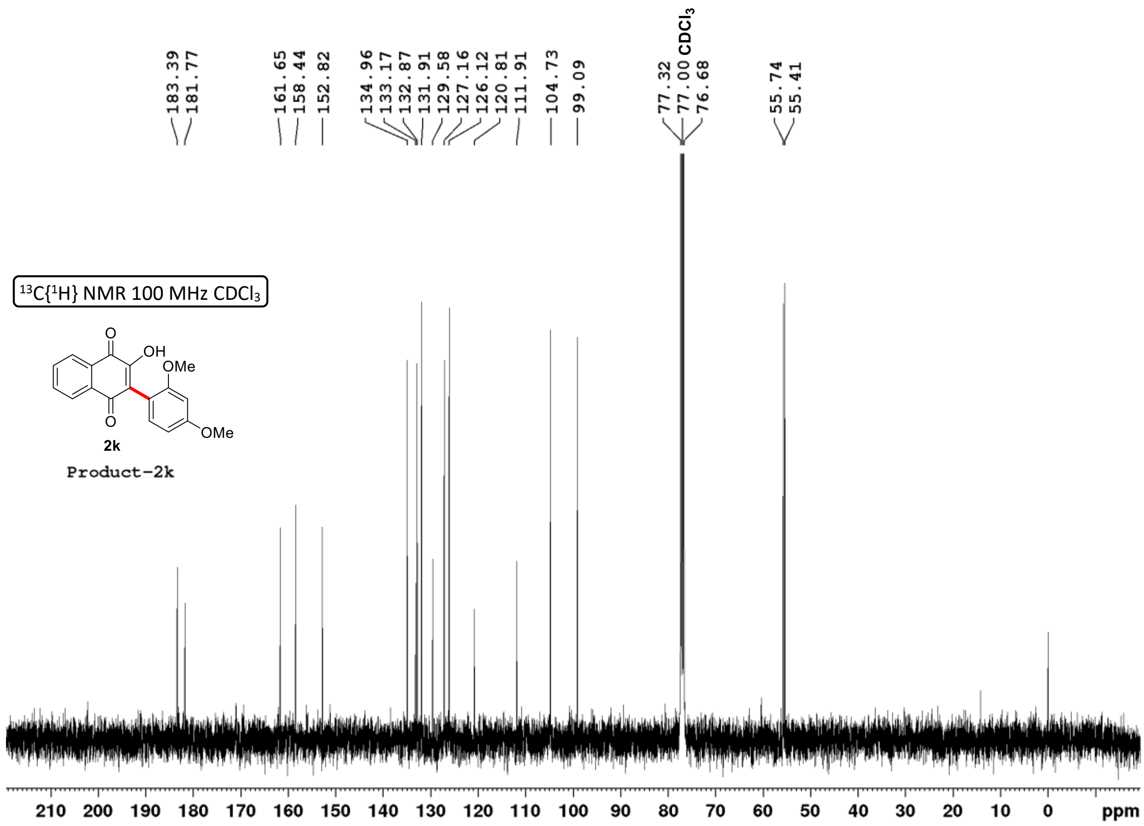
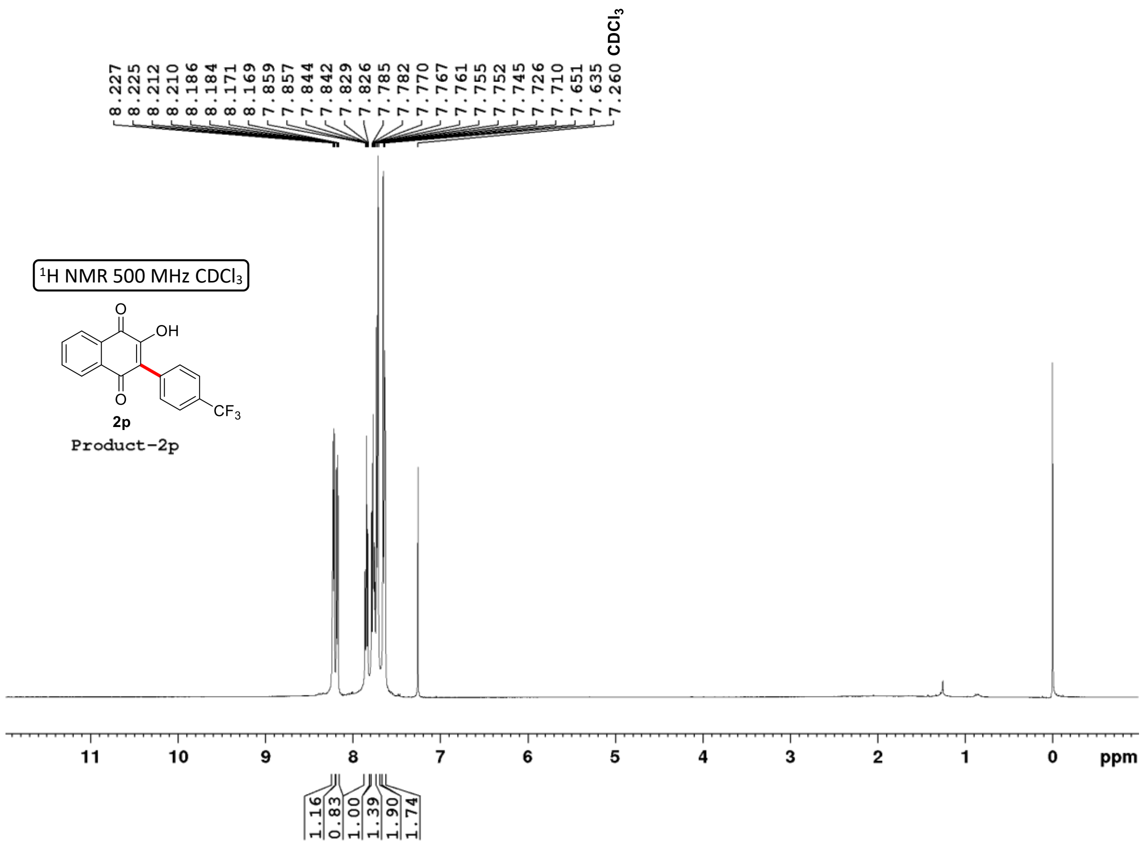


Figure 5: ^{1}H NMR and ^{13}C NMR spectrum of product **2k**.



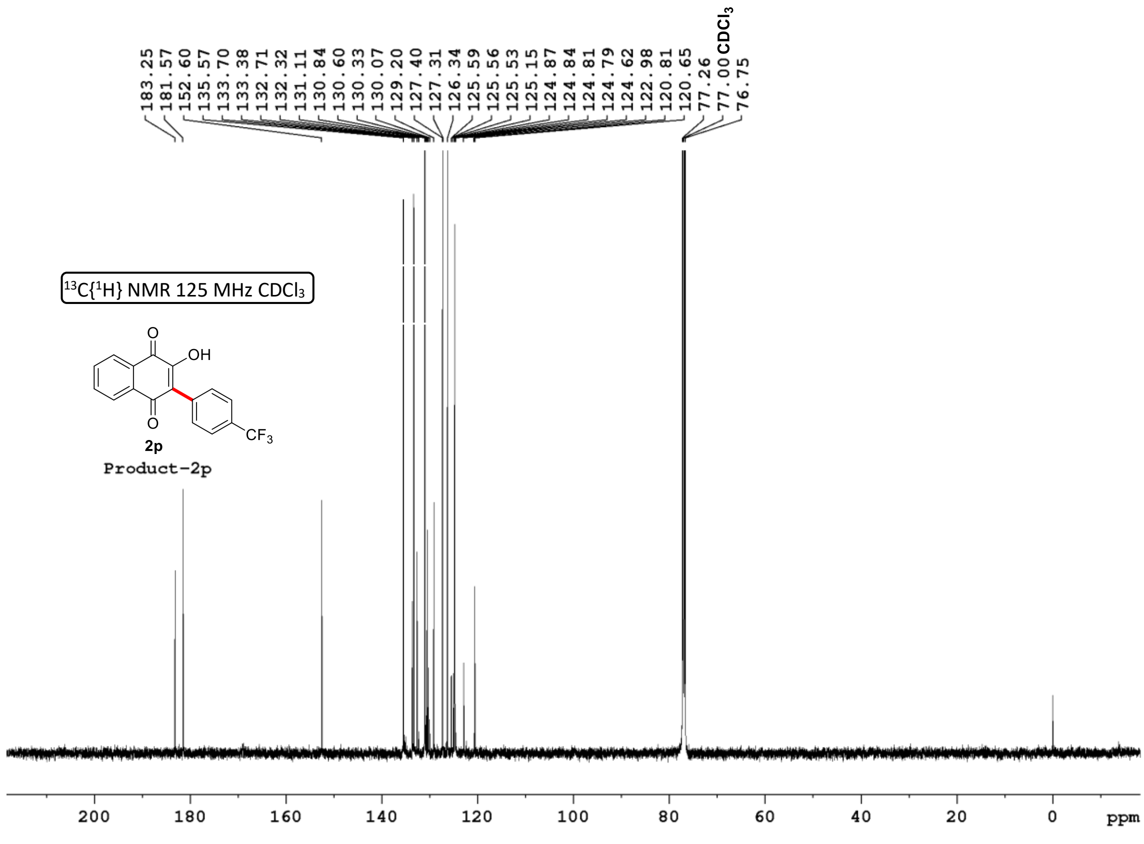
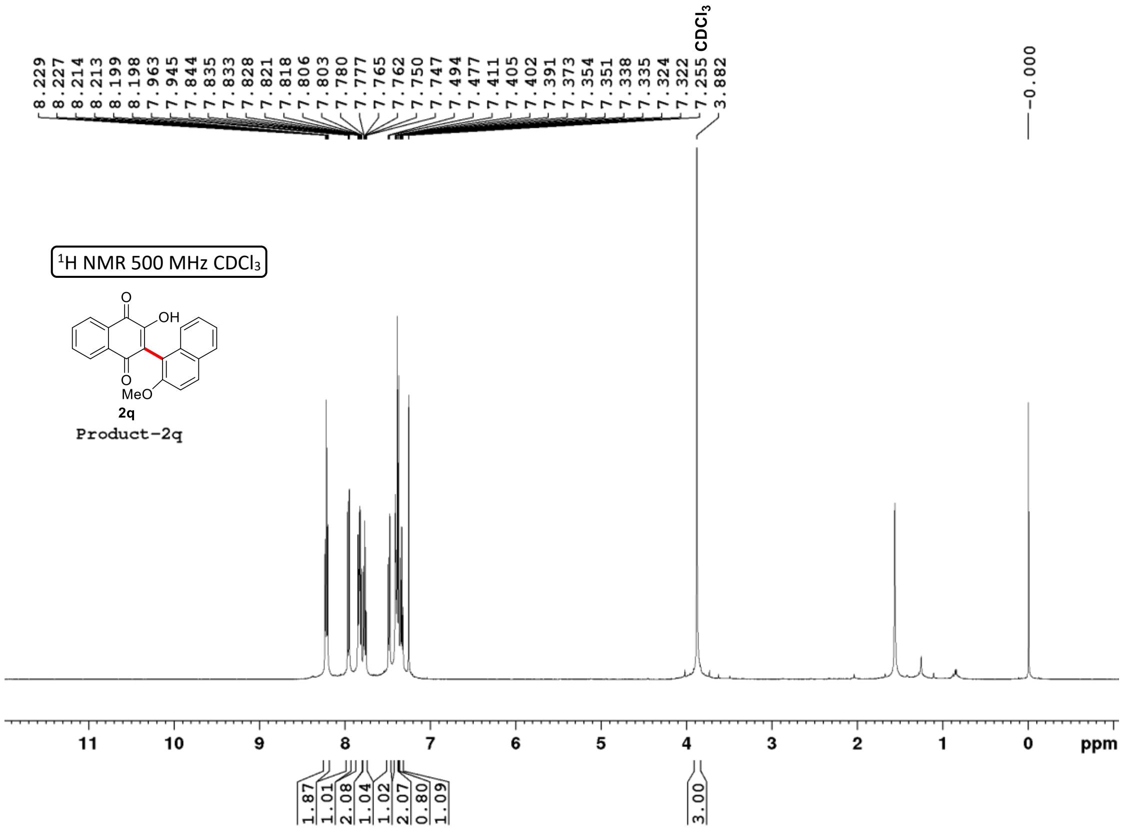


Figure 6: ^{1}H NMR and ^{13}C NMR spectrum of product **2p**.



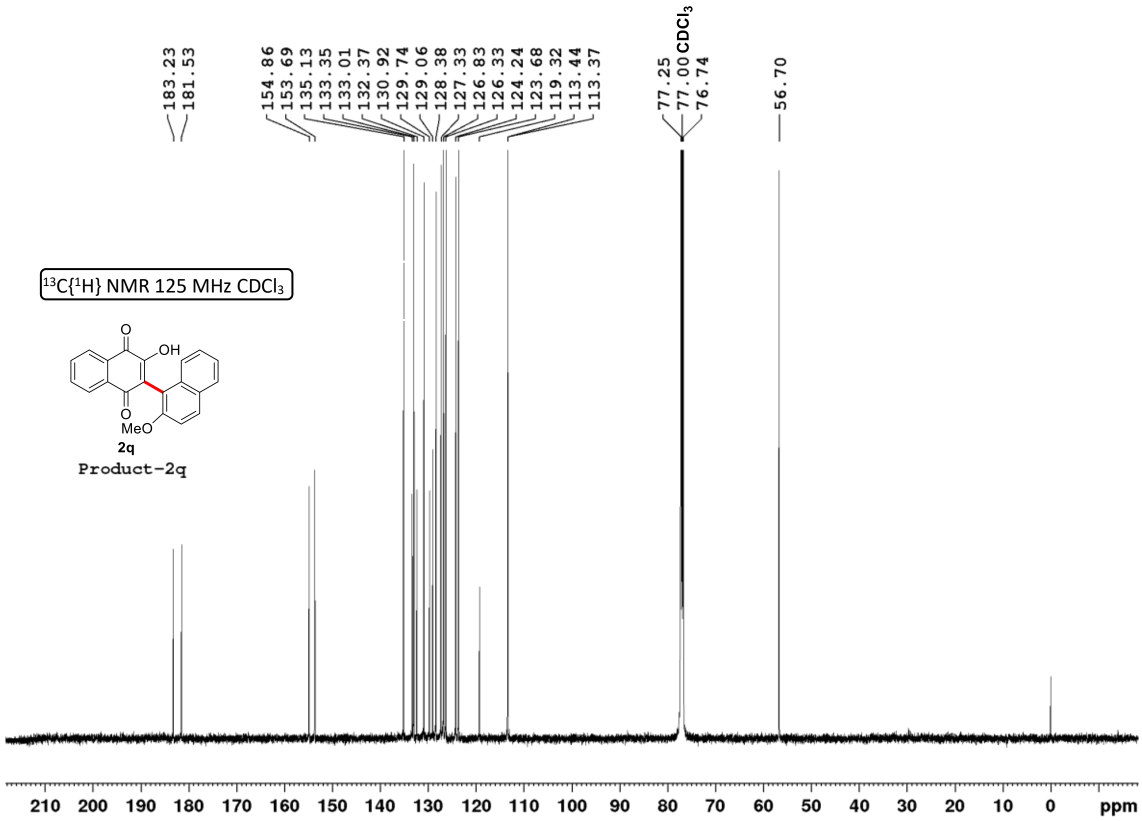
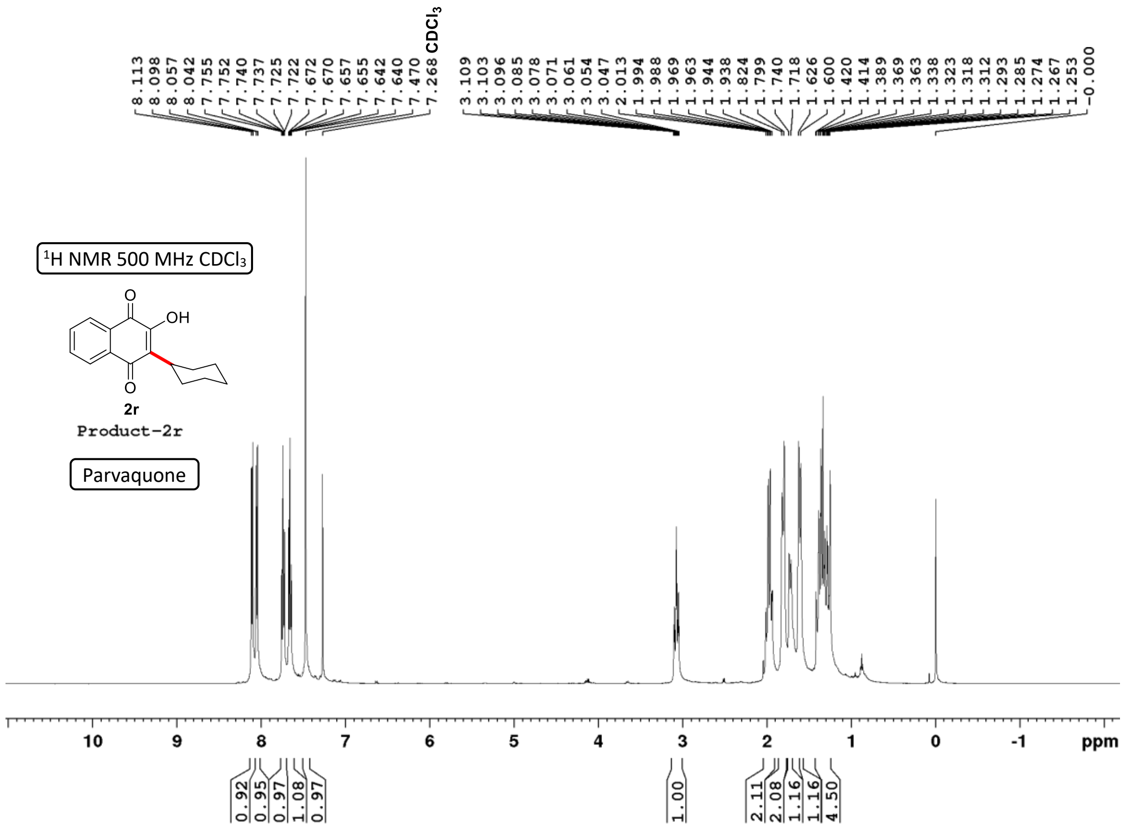


Figure 7: ^{1}H NMR and ^{13}C NMR spectrum of product **2q**.



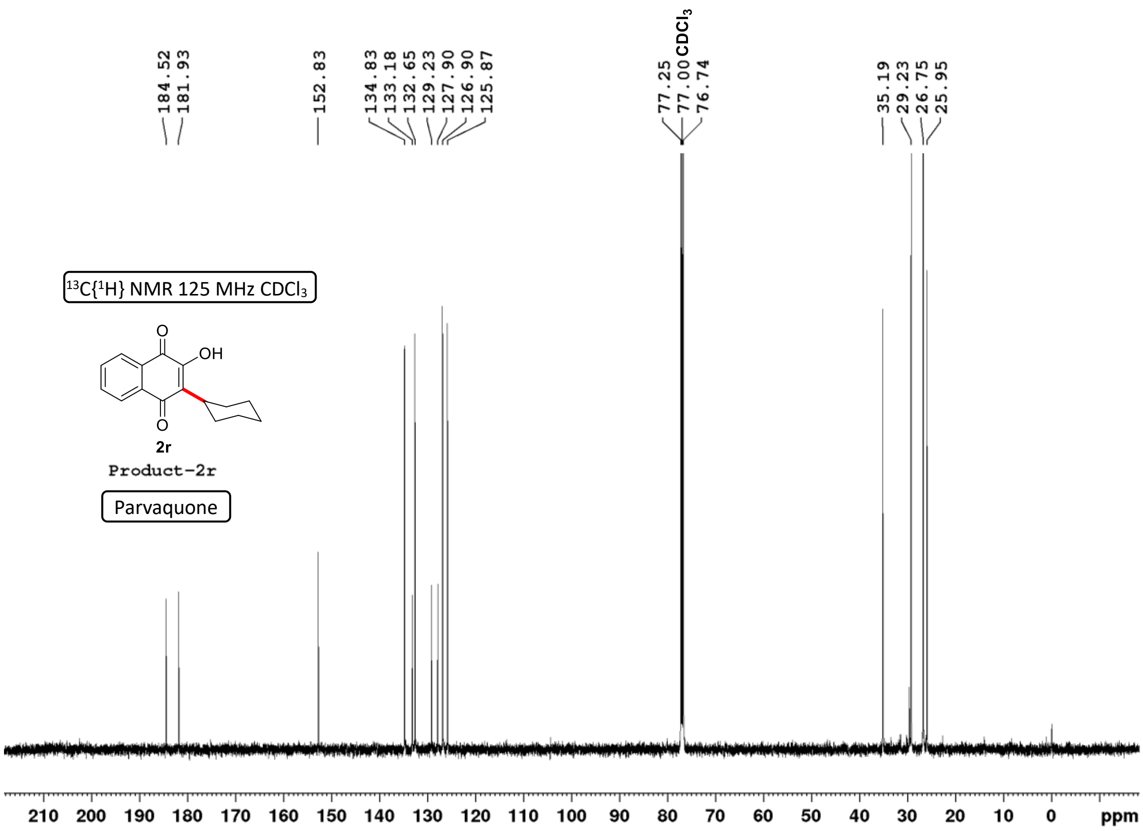
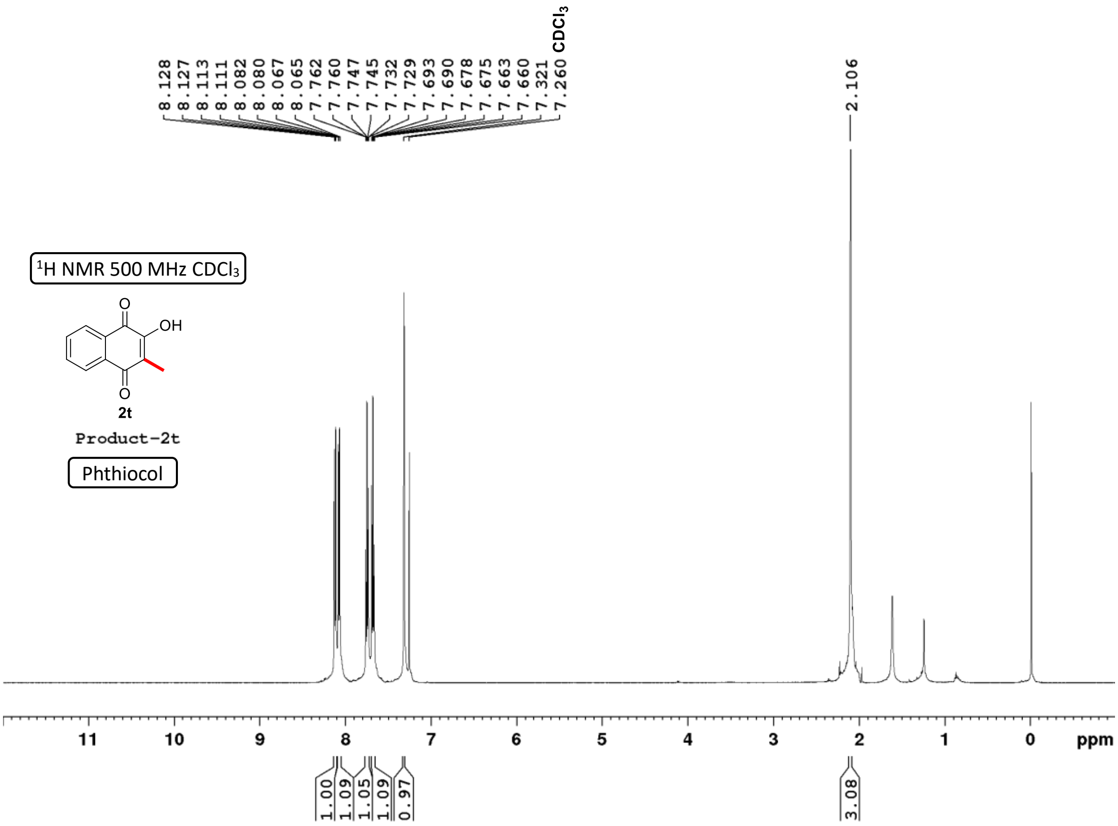


Figure 8: ^{1}H NMR and ^{13}C NMR spectrum of product **2r**.



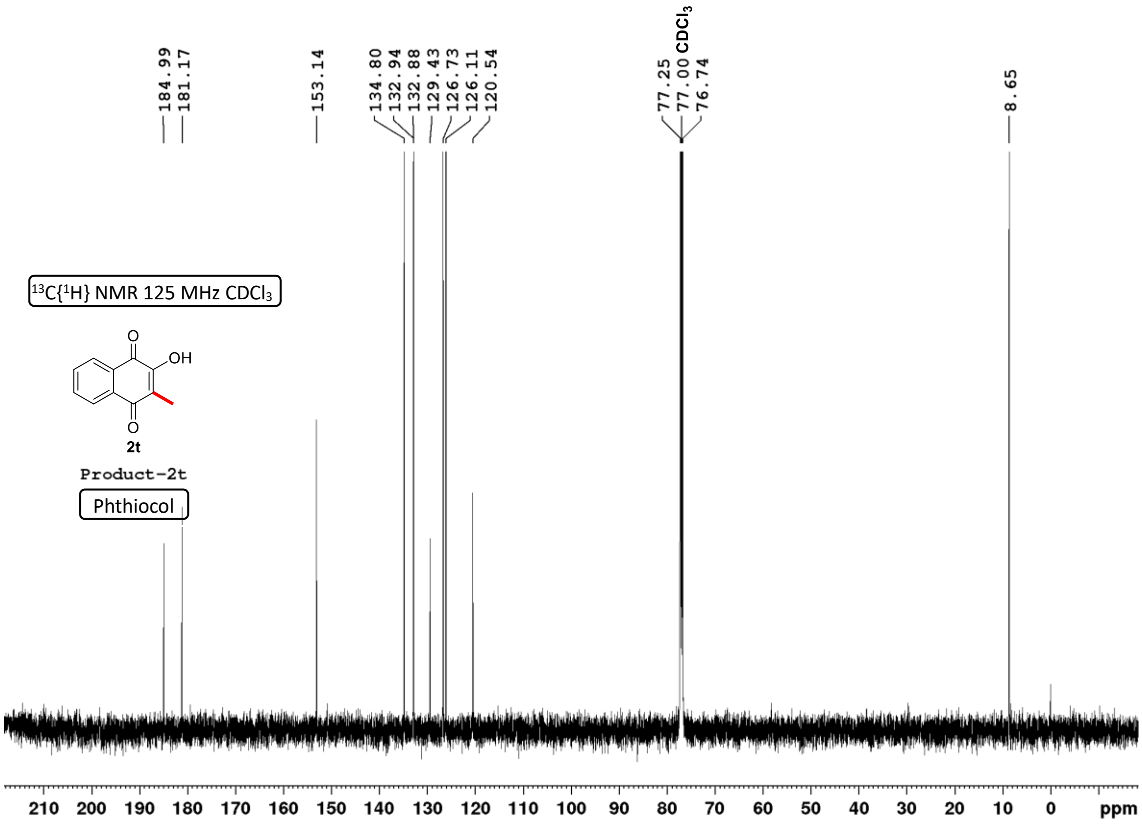
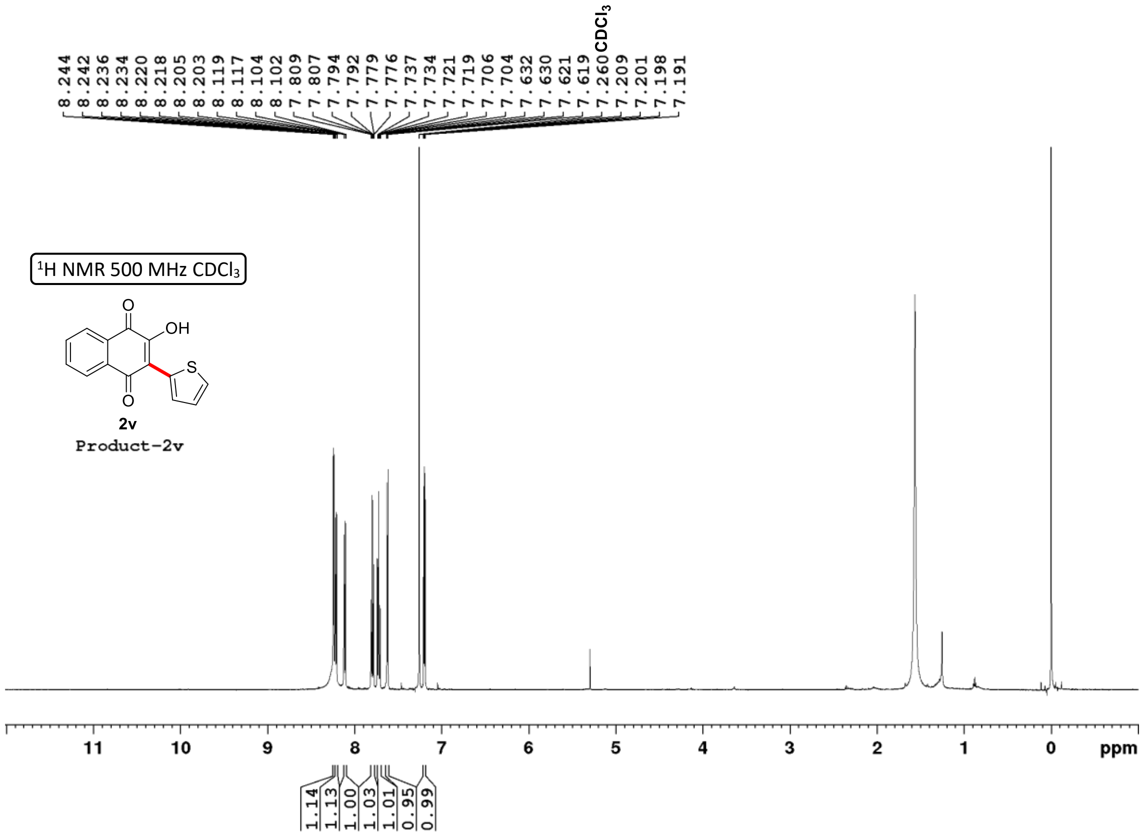


Figure 9: ^{1}H NMR and ^{13}C NMR spectrum of product **2t**.



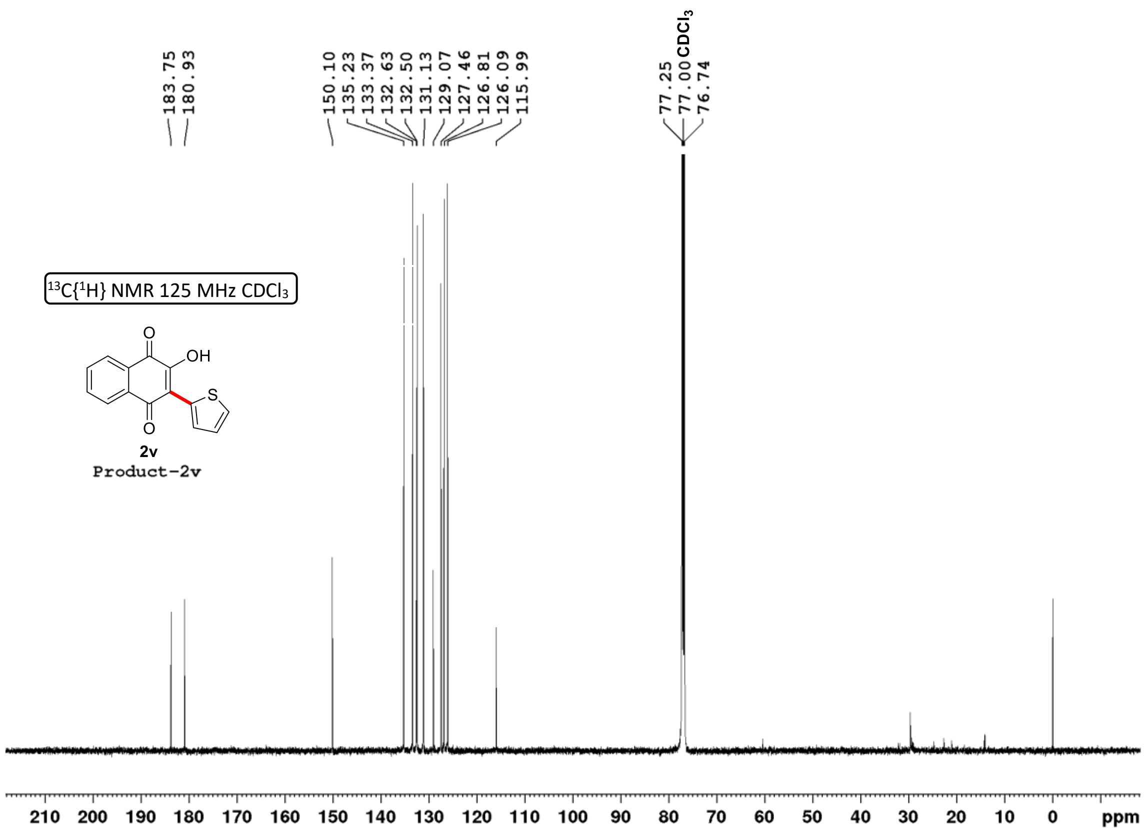
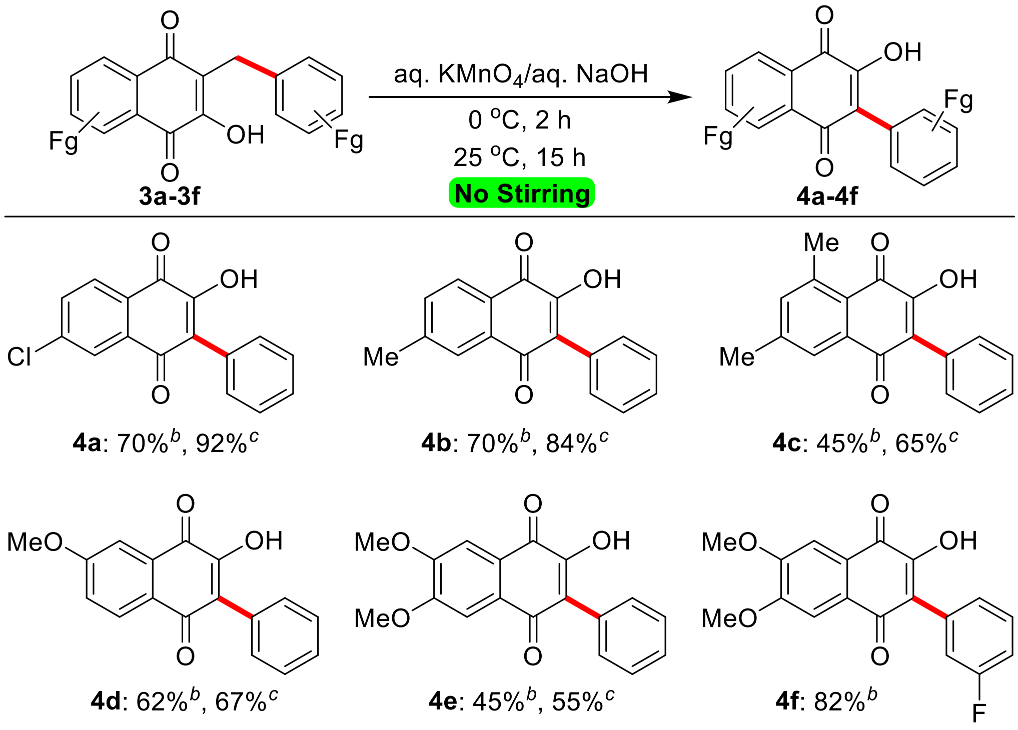


Figure 10: ^{1}H NMR and ^{13}C NMR spectrum of product **2v**.

4.2.2.2 Reaction scope for the synthesis of functionally rich 3-aryllawsones

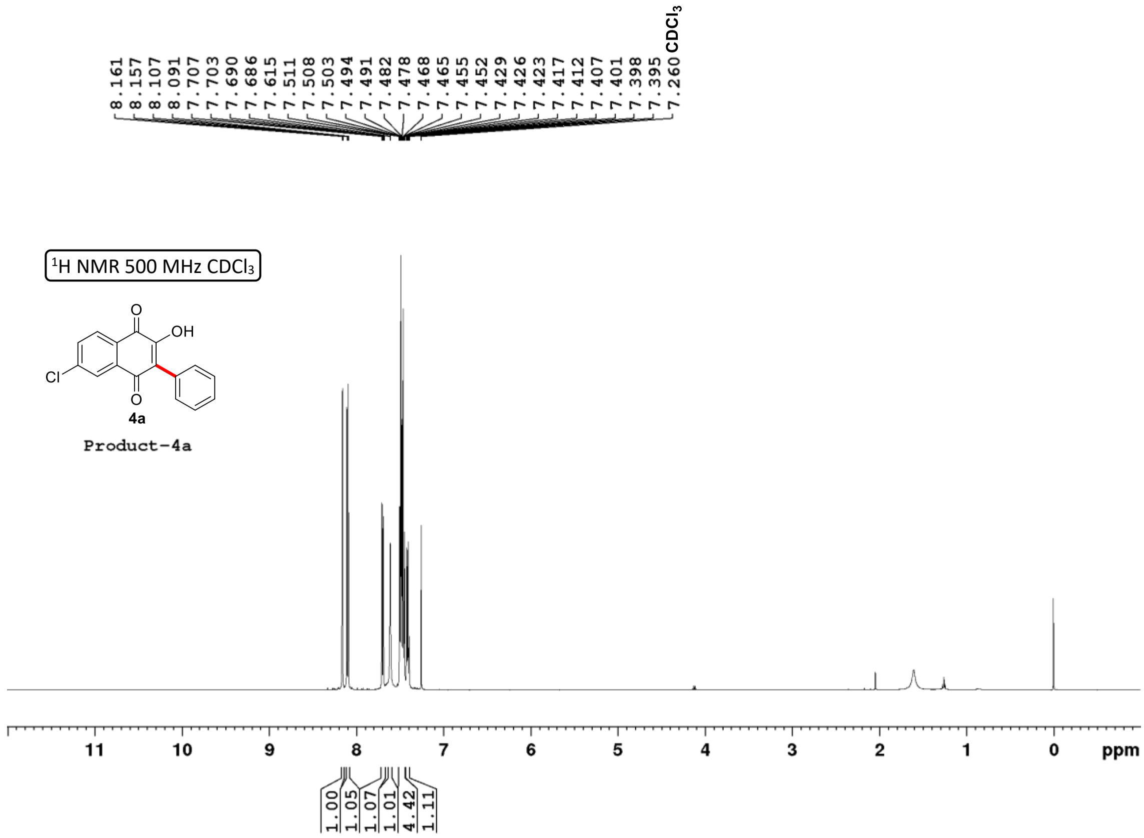
In order to prove the sustainability and regioselectivity of oxidation protocol, we have extended the substrate scope of simple lawsone to various functionalized lawsones **3a-3f**. All the substrates underwent Hooker reaction smoothly yielding oxidized products **4a-4f** with moderate to very good yields (Table 3). The designed reaction of 2-benzyl-3-hydroxy-6-methylnaphthalene-1,4-dione (**3b**) and 3-benzyl-2-hydroxy-6-methoxynaphthalene-1,4-dione (**3d**) under the standard condition furnished the products of 2-hydroxy-6-methyl-3-phenylnaphthalene-1,4-dione (**4b**) and 3-hydroxy-6-methoxy-2-phenylnaphthalene-1,4-dione (**4d**), respectively in >99% regioselectivity (Table 3).

Table 3: Reaction scope for the synthesis of functionally rich 3-aryllawsones[a]



[a] Reactions were carried out on 0.2 mmol scale in 14 mL of 2% aq. NaOH and 1.9 equiv. of $KMnO_4$ in 7 mL H_2O at 0 °C for 2 h followed by 25 °C for 15 h. [b] Yield refers to the overall yield of the column purified products. [c] Yield calculated based on the recovery of the starting material **3**.

The regioselectivity was further confirmed by NMR (Figures 11-15) and X-ray crystal structure analysis of both starting materials (**3b**/**3d**) and final Hooker oxidation products (**4b**/**4d**) (Figure 16-20).[7] This is first time to give crystallographic proof for regioselective alkyl transfer in the mechanism of Hooker oxidation reaction.[6]



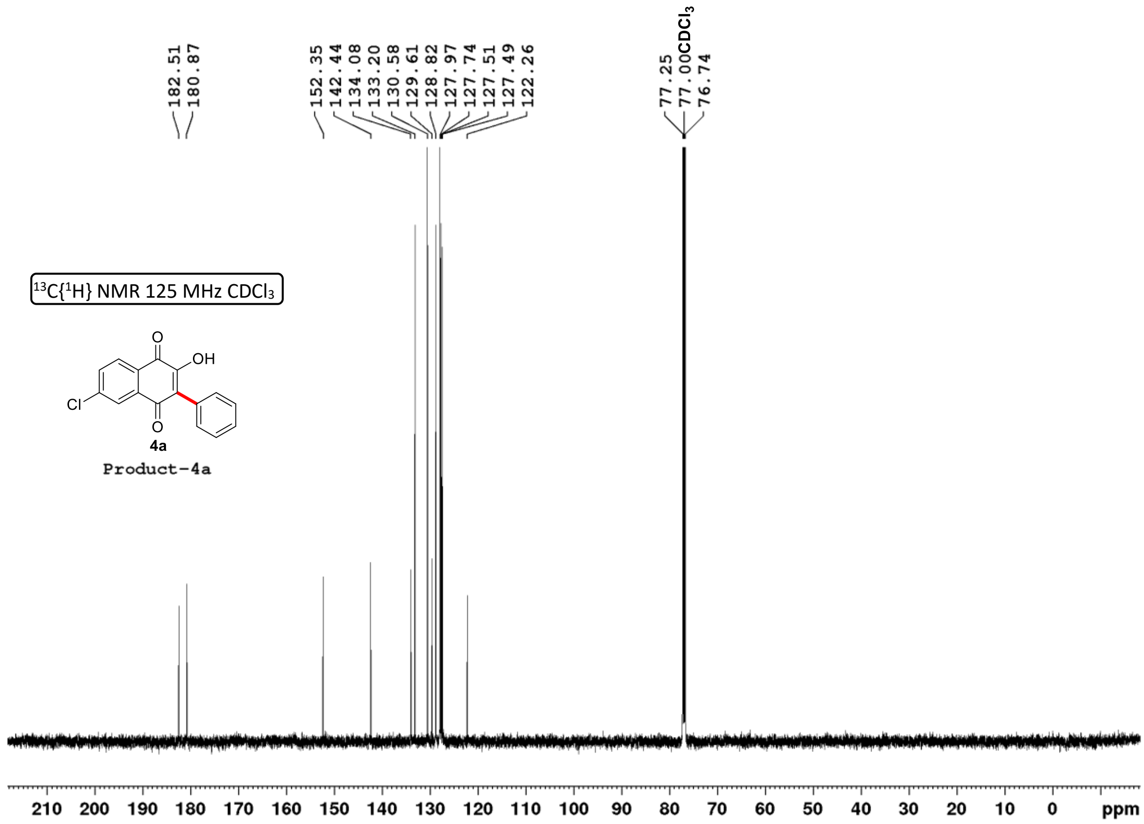
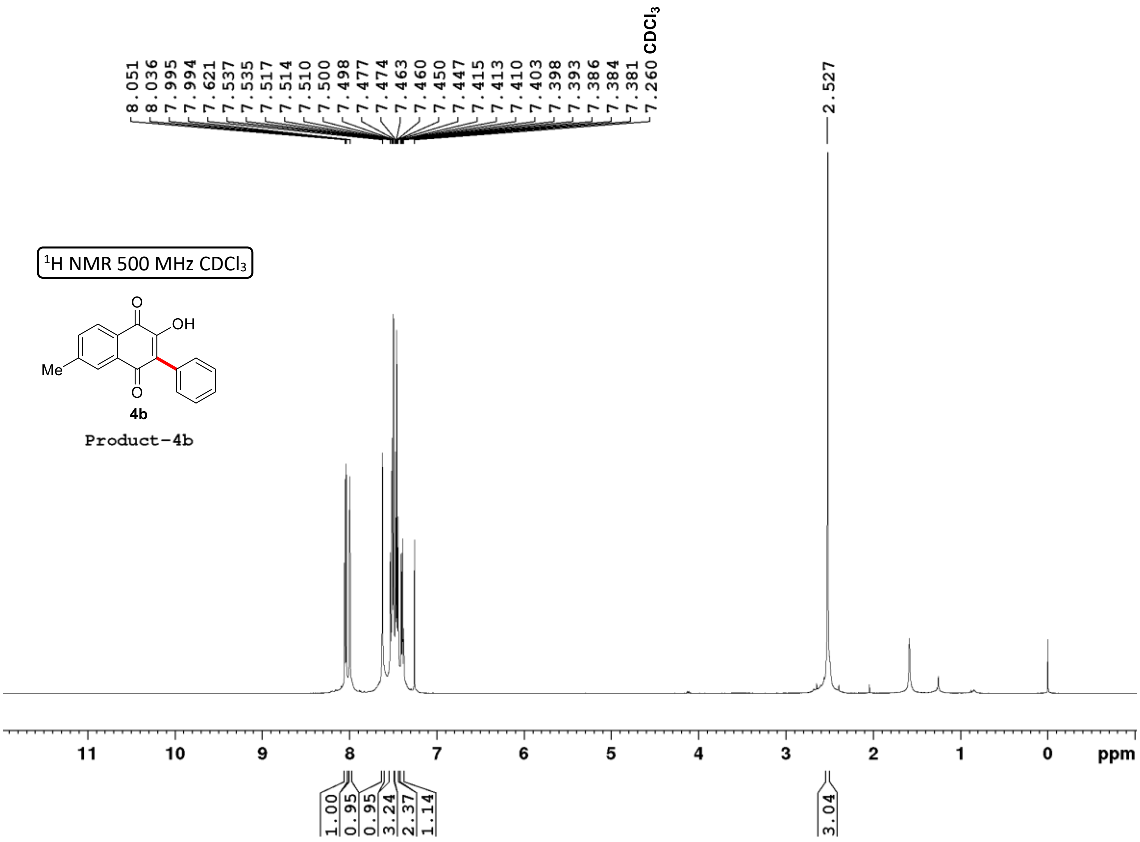


Figure 11: ^{1}H NMR and ^{13}C NMR spectrum of product **4a**.



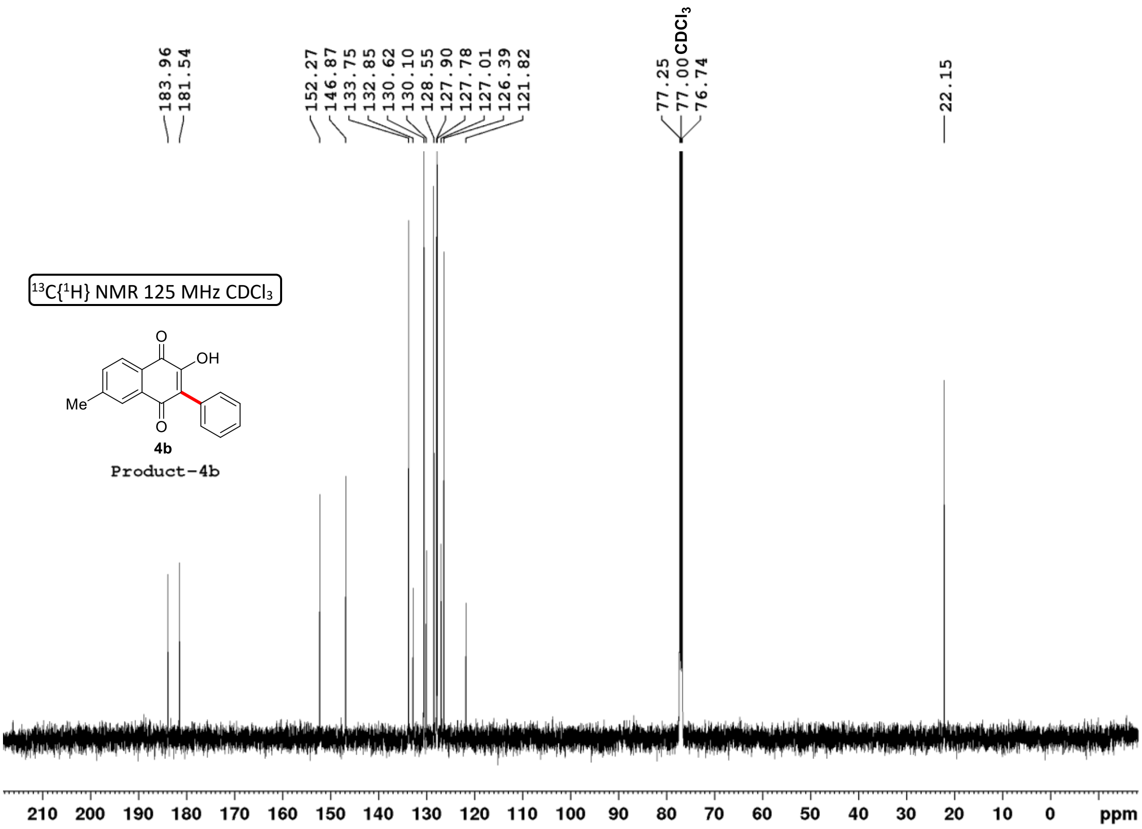
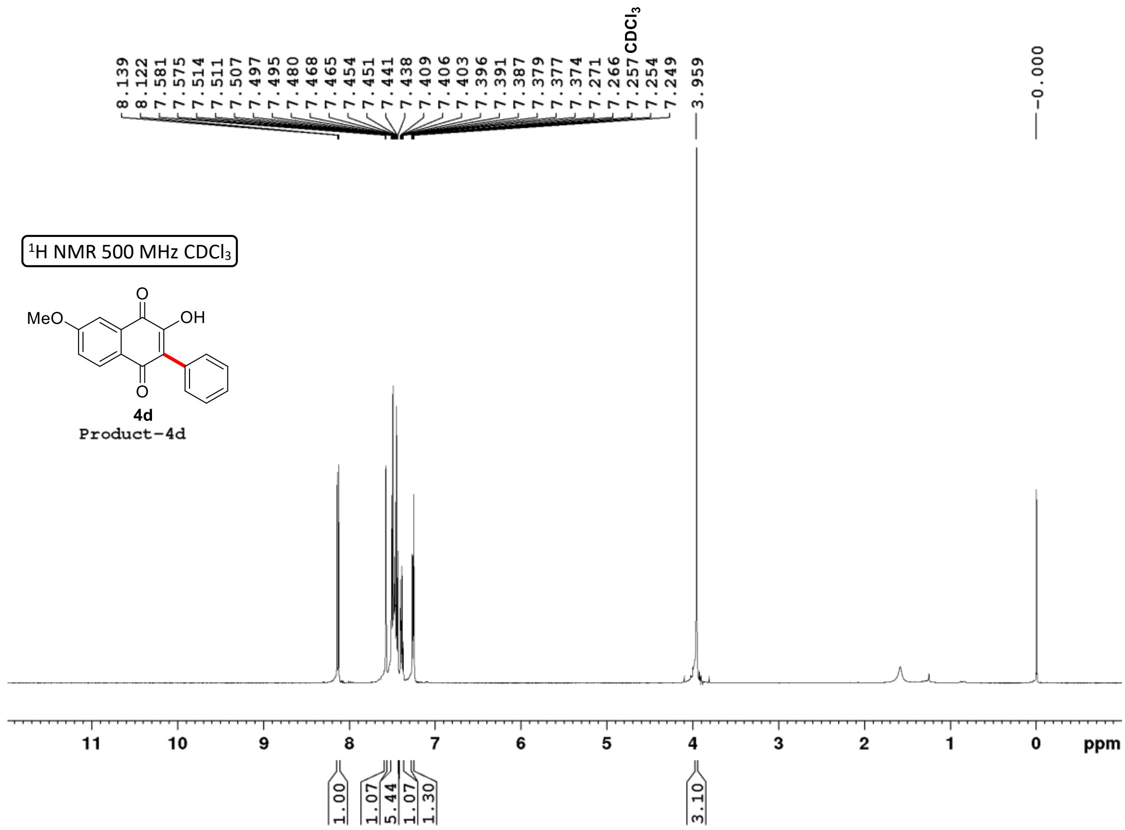


Figure 12: ^{1}H NMR and ^{13}C NMR spectrum of product **4b**.



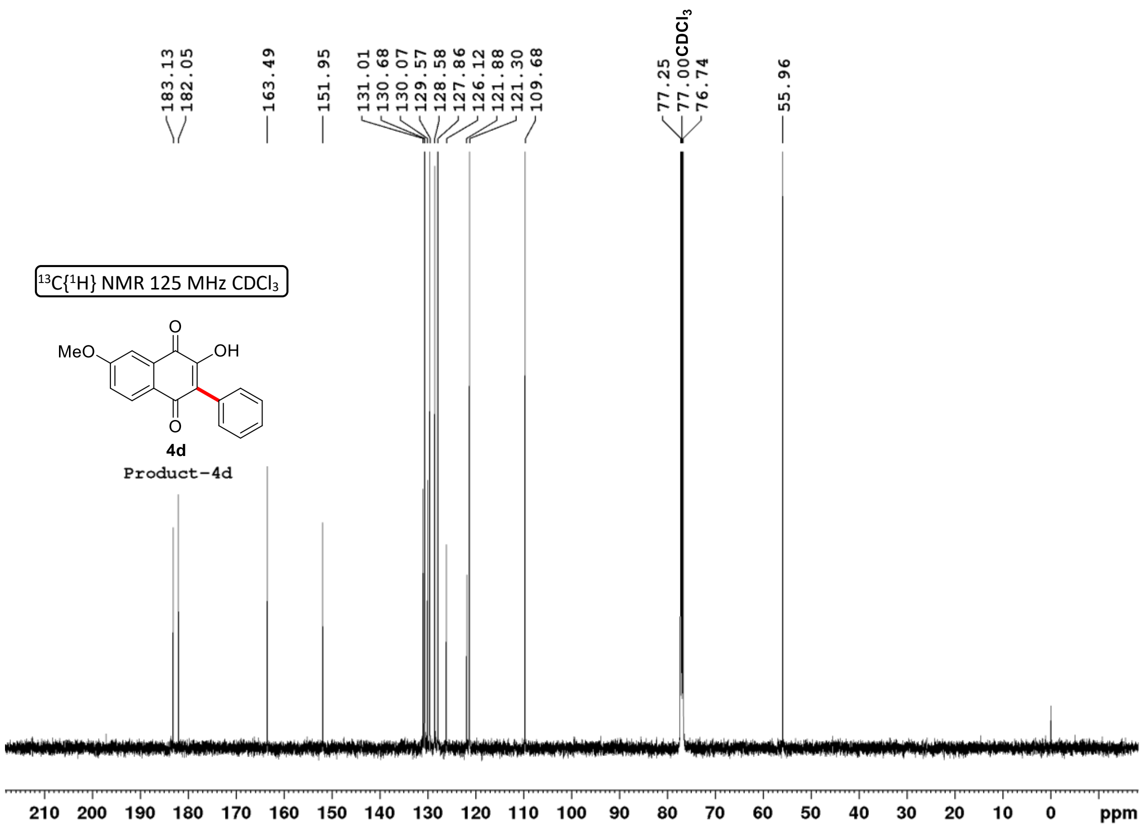
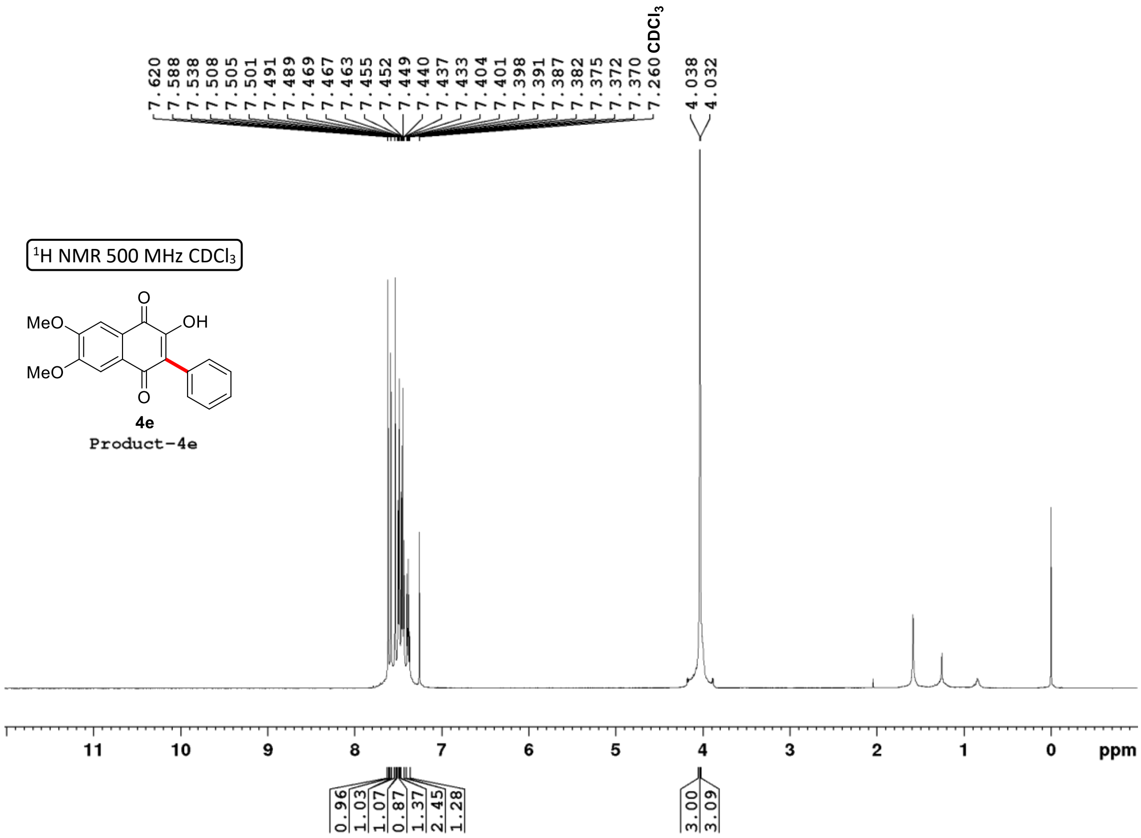


Figure 13: ^{1}H NMR and ^{13}C NMR spectrum of product **4d**.



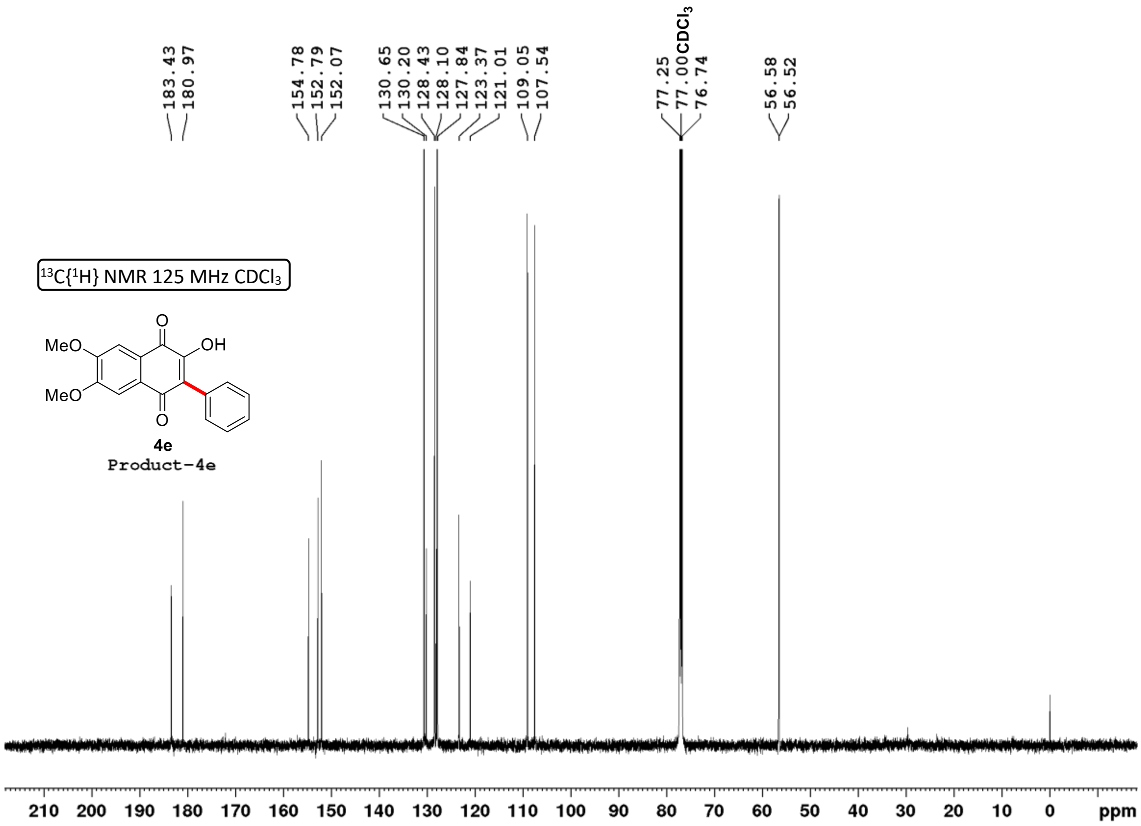
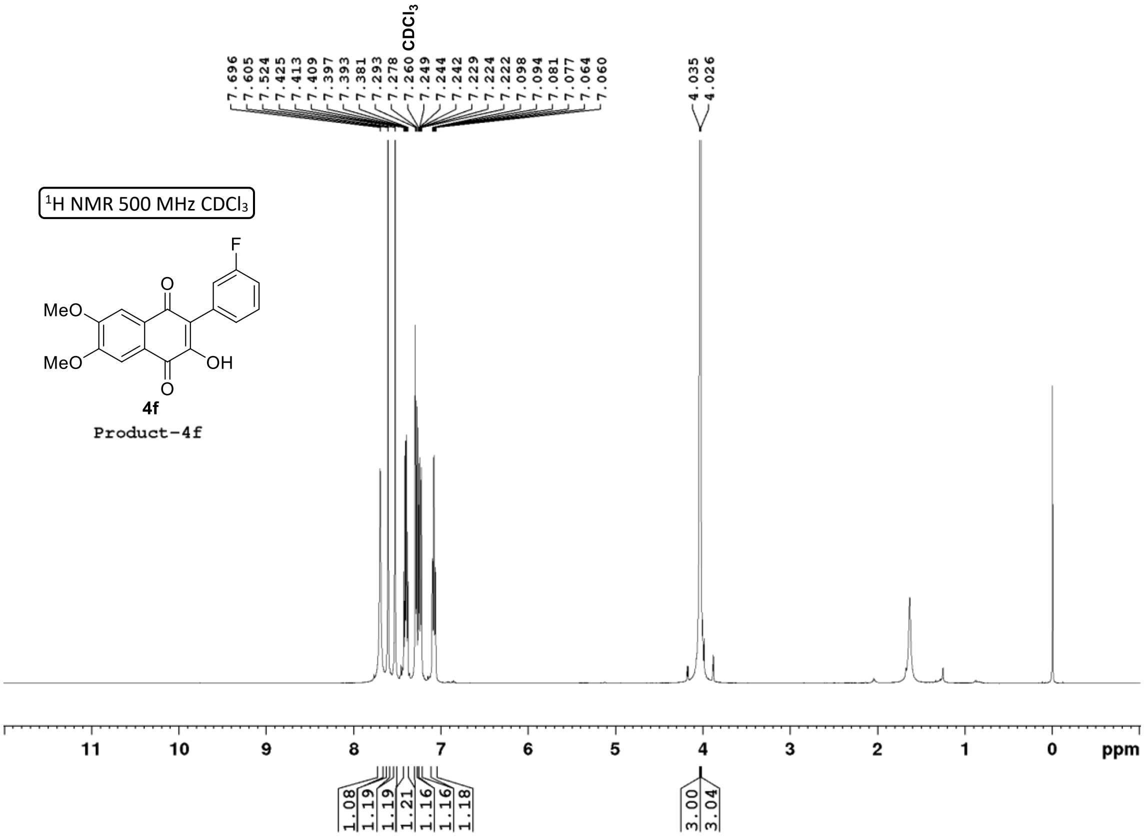


Figure 14: ^{1}H NMR and ^{13}C NMR spectrum of product **4e**.



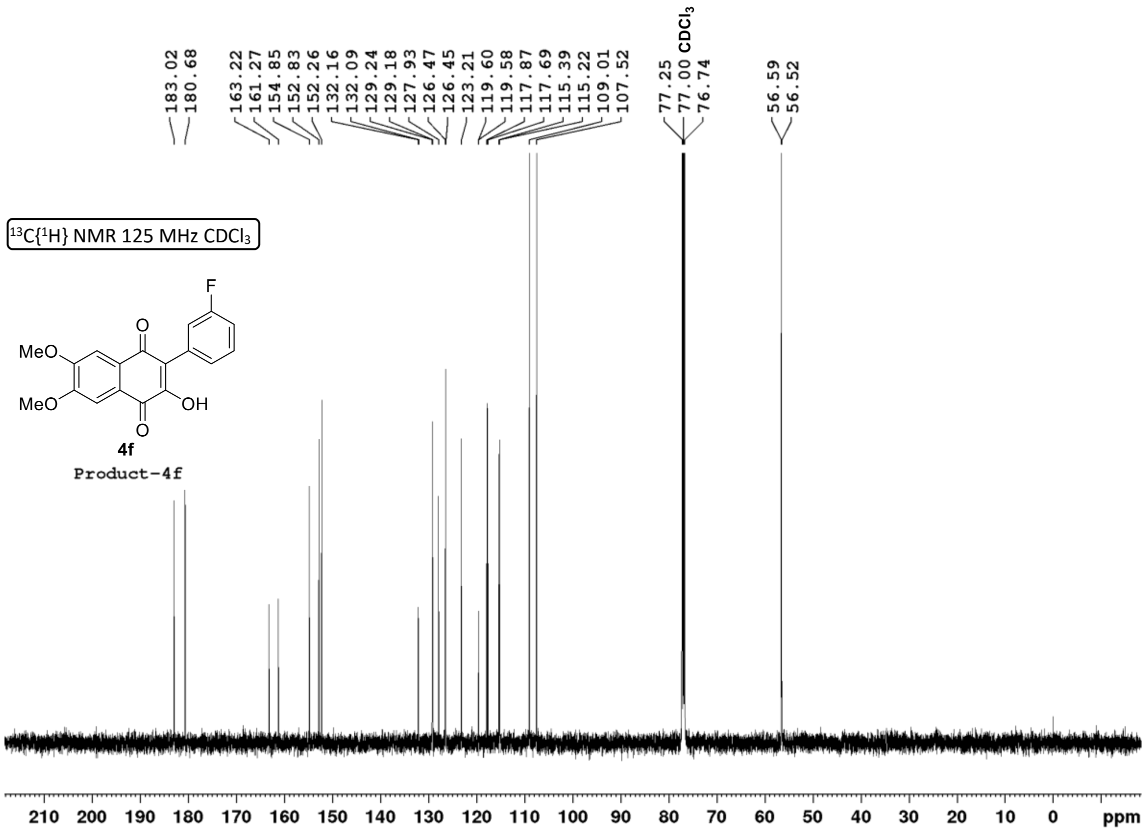


Figure 15: ^{1}H NMR and ^{13}C NMR spectrum of product **4f**.

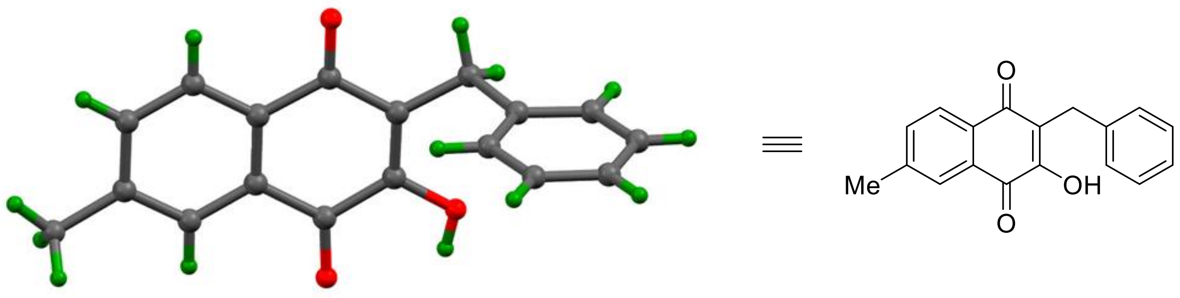


Figure 16: X-Ray crystal structure of 2-Benzyl-3-hydroxy-6-methylnaphthalene-1,4-dione (3b). [7]

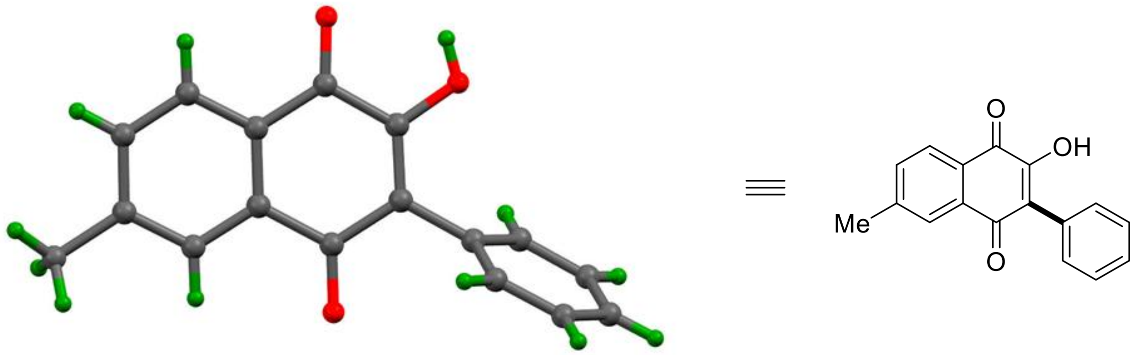


Figure 17: X-Ray crystal structure of 2-Hydroxy-6-methyl-3-phenylnaphthalene-1,4-dione (4b). [7]

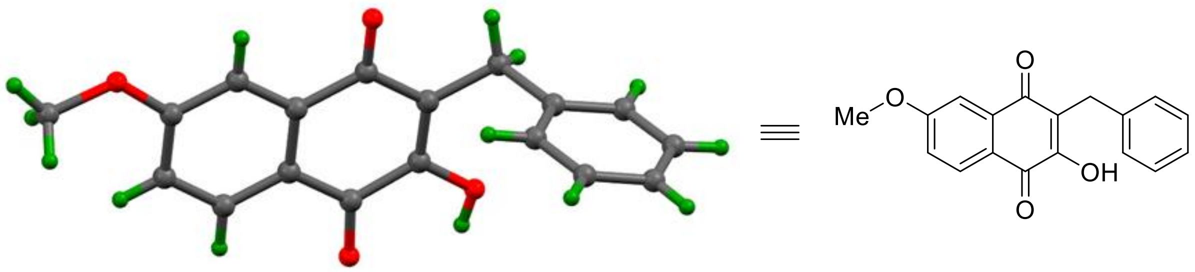


Figure 18: X-Ray crystal structure of 3-Benzyl-2-hydroxy-6-methoxynaphthalene-1,4-dione (3d). [7]

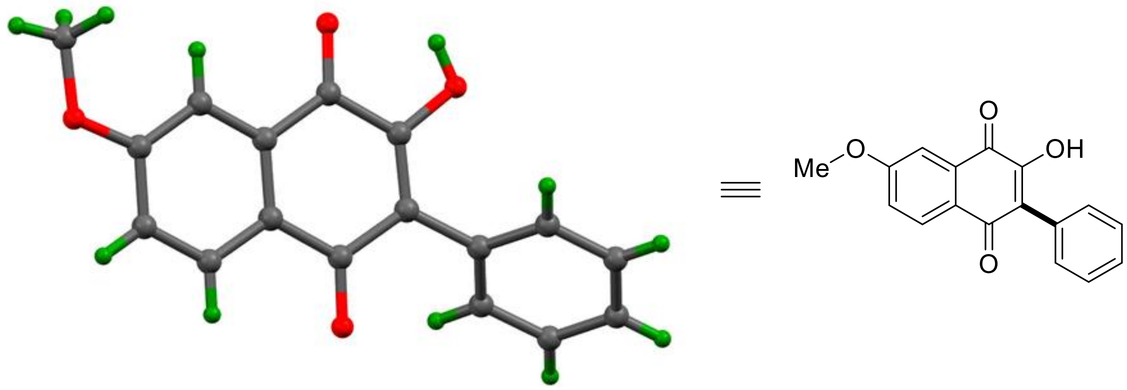


Figure 19: X-Ray crystal structure of 3-Hydroxy-6-methoxy-2-phenylnaphthalene-1,4-dione (4d).[7]

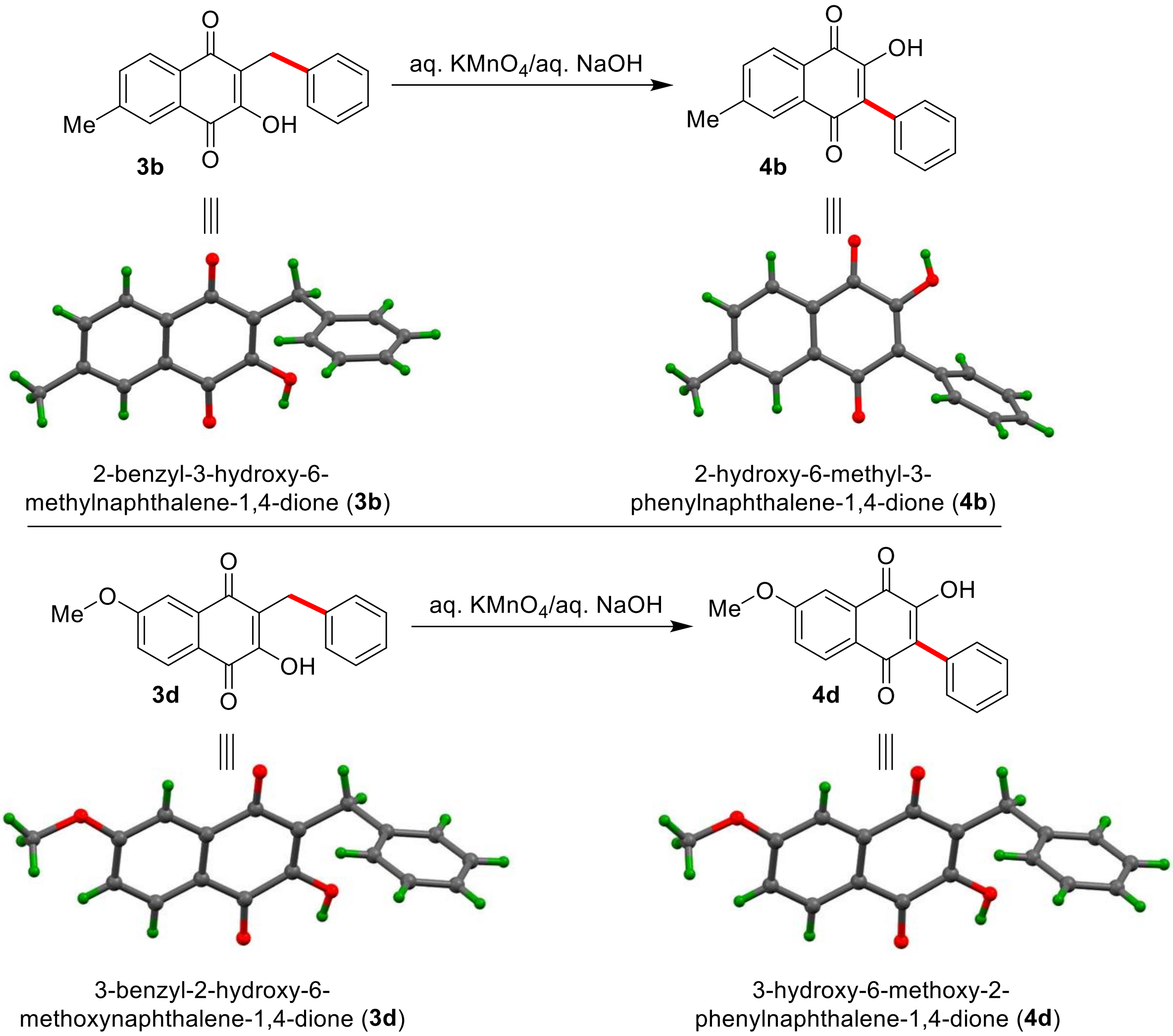
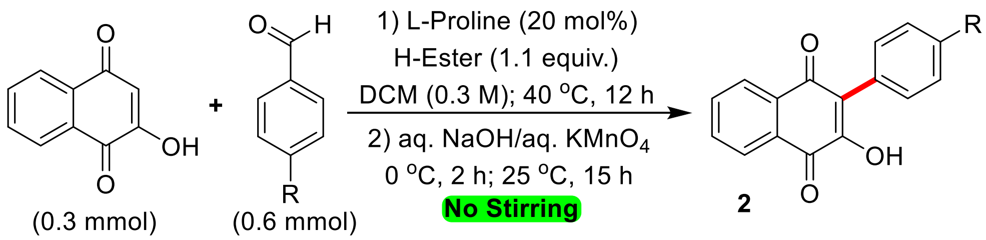


Figure 20: Providing proof for the alkyl 1,4-migratory insertion into the lawsones through correlation of X-ray crystal structures of OrgRC and OD products **3b**, **4b**, **3d** and **4d**.[7]

4.2.3 A Seven-step One-pot Synthesis of 3-Aryllawsones

To simplify our oxidation protocol, we were anxious to perform reductive coupling and Hooker reactions in one-pot. As reductive coupling is a very clean approach for selective alkylation on lawsones,[1a-d] the pyridine byproduct formed during reductive coupling should not interfere with Hooker oxidation since it proceeds in alkaline medium. With this ray of hope, we have chosen five different substrates consisting electron donating, electron withdrawing and halogen groups for performing one-pot reductive coupling/Hooker oxidation reactions (Table 4). Astonishingly, the sequential seven-step one-pot double cascade reaction proceeded very smoothly affording **2** from lawsone and corresponding benzaldehydes in moderate to good yields. This clearly enhances the utility and sustainability of the 3-aryllawsones **2** synthesis.

Table 4: 3-Aryllawsone synthesis in a seven-step one-pot manner[a]



Entry	R	$KMnO_4/H_2O$ mg (mL)[b]	2% aq. NaOH (mL)[b]	Yield (%)[c]	Yield (%)[d]
1	H	80.8 (9.4)	18.9	**2a**: 68	**2a**: 76
2	Cl	70.4 (8.2)	16.4	**2e**: 39	**2e**: 47
3	Me	63.0 (7.3)	14.7	**2i**: 50	**2i**: 58
4	OMe	43.1 (5.0)	10.0	**2j**: 34	**2j**: 38
5	CF_3	61.7 (7.2)	14.4	**2p**: 39	**2p**: 43

[a] Reactions were carried out in one-pot mode. TCRA for 12 h at 40° C followed by removal of DCM and proceeding for second step without any purification or filteration.[b] The amount of $KMnO_4$ and NaOH is taken based on the TCRA yields. [c] Yield refers to the overall yield of the column purified products. [d] Yield calculated based on the recovery of the TCRA product.

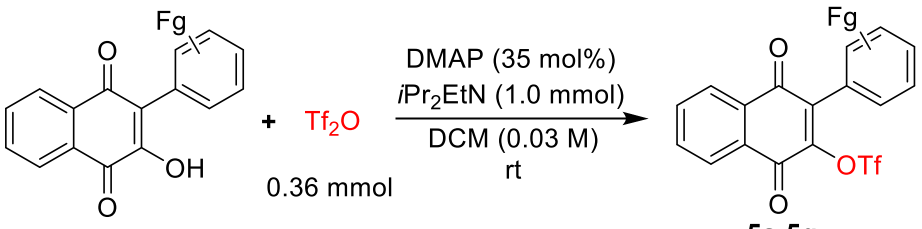
4.2.4 Scope and Applications of 3-Aryllawsones

4.2.4.1 Investigation of thia-Michael reaction on the 3-aryllawsonetriflates

After the development of the Hooker oxidation reaction, we were interested in the real-time applications of the molecules **2**. Initially we reacted **2a** with thiophenol **6a** in the presence of base expecting a Michael adduct, but the reaction was not fruitful. In order to tune the thia-Michael reaction rate, we have transformed 3-aryllawsones **2** into the 3-

aryllawsonetriflates **5**. When 0.2 mmol of 3-aryllawsones were reacted with 1.8 equiv. of Tf_2O (0.36 mmol) in the presence of DMAP (35 mol%), *i*Pr_2EtN (5.0 equiv., 1.0 mmol) in DCM (0.03 M) at room temperature, the reaction afforded aryllawsone-triflates **5** with 62-82% yields in 30-60 minutes (Table-5). The structure of **5a** was further conformed by NMR analysis (Figure 21).

Table 5: Synthesis of 3-aryllawsone-trifluoromethanesulfonates[a]

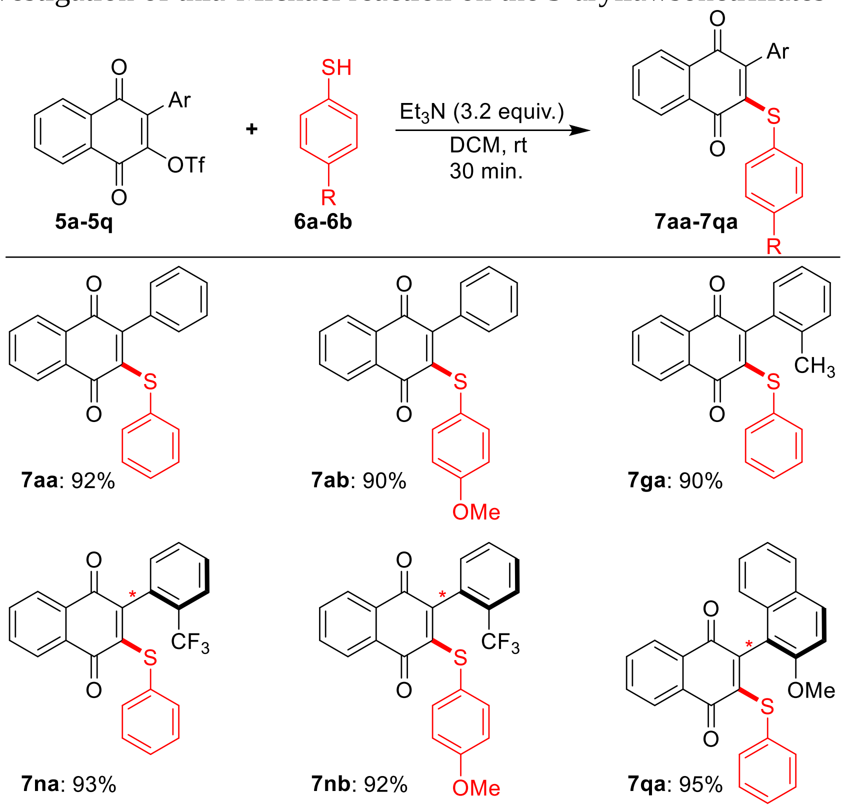


entry	Fg	Time	yield (%)[a]
1	H (**2a**)	40	**5a**: 82
2	4-F (**2d**)	30	**5d**: 70
3	4-CF_3 (**2p**)	30	**5p**: 74
4	4-Me (**2i**)	40	**5i**: 76
5	3-Me (**2h**)	40	**5h**: 75
6	2-Me (**2g**)	30	**5g**: 72
7	2-CF_3 (**2n**)	30	**5n**: 70
8	2-methoxynaphthalen-1-yl (**2q**)	60	**5q**: 62

[a] Yield refers to the column purified products.

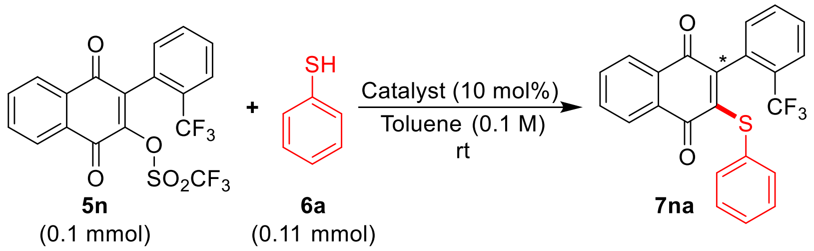
When we reacted 3-phenyllawsonetriflate **5a** with **6a** in the presence of triethylamine in DCM at 25 °C for 30 min furnished the thia-Michael product **7aa** in 92% yield (Table 6). We tested the generality of thia-Michael reaction by reacting five more examples of **5a-5q** with **6a-b** to furnish the products **7ab-7qa** in excellent yields (Table 6). Especially, when there is an *ortho*-CF_3/*ortho*-OCH_3 substitution on the aromatic ring of **5**, the Michael reaction generated interesting axial chirality in the molecules **7na**, **7nb**, and **7qa** owing to the fact that there is a restriction in the bond rotation due to steric hindrance making the molecules as atropisomers and all the enantiomers were well separated using HPLC analysis. The NMR spectra and HPLC analysis of few selected compounds **7** were shown in Figures 22-27. Our efforts to enhance the enantioselectivity of these molecules under the chiral amine catalysis and hydrogen bonding catalysis were not fruitful (Table 7).

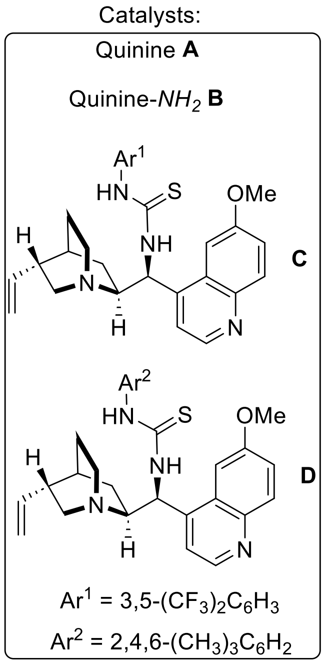
Table 6: Investigation of thia-Michael reaction on the 3-aryllawsonetriflates[a]



[a] Reactions were carried out in DCM (0.0065 M) with 1.0 equiv. **5** relative to **6** (1.01 equiv.) in the presence of Et_3N (3.2 equiv.). [b] Yield refers to the column-purified product.

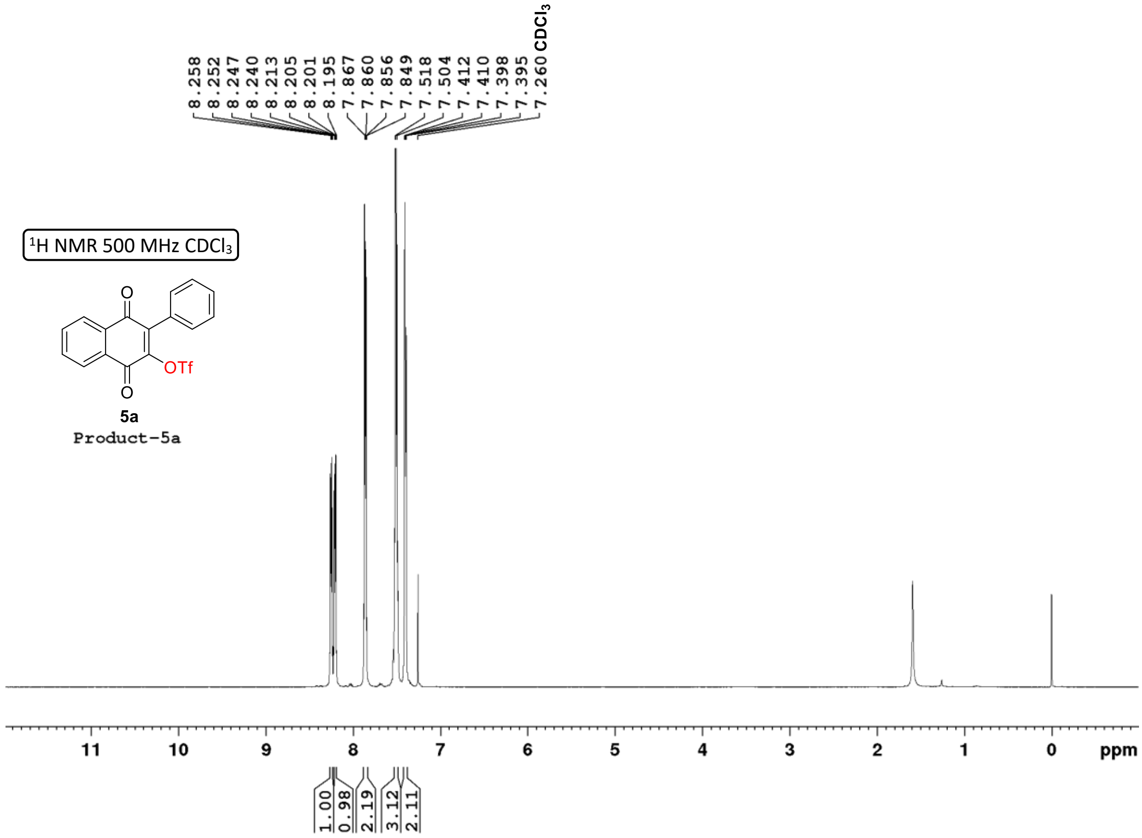
Table 7: Optimization for the asymmetric synthesis of 2,3-diaryl-naphthalene-1,4-diones[a]





entry	catalyst	time (h)	yield (%)[c]	*ee* (%)
1[b]	**A**	12	77	10
2[b]	**B**	48	77	1
3	**C**	6	80	1
4	**D**	3	82	2

[a]Reactions were carried out in 0.1 mmol scale. [b]Reaction was carried out at 0 °C. [c]Yield refers to the overall yield of the column purified products.



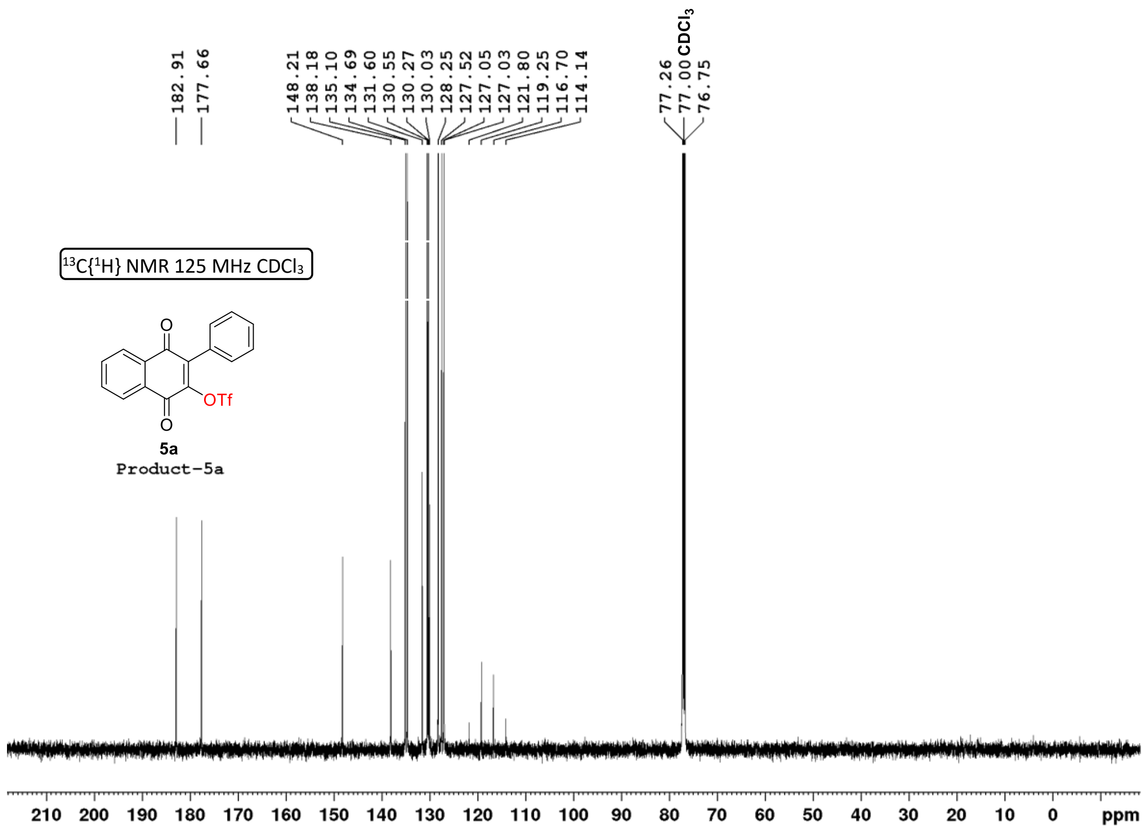
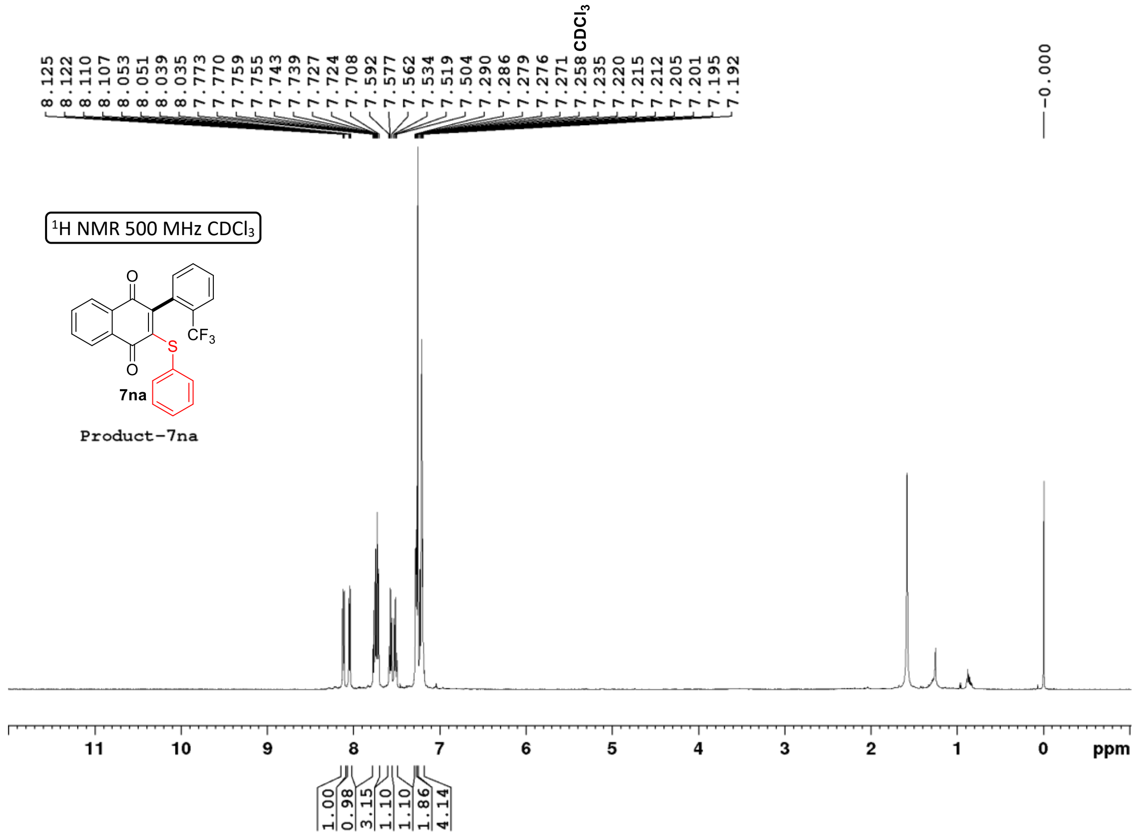


Figure 21: ^{1}H NMR and ^{13}C NMR spectrum of product **5a**.



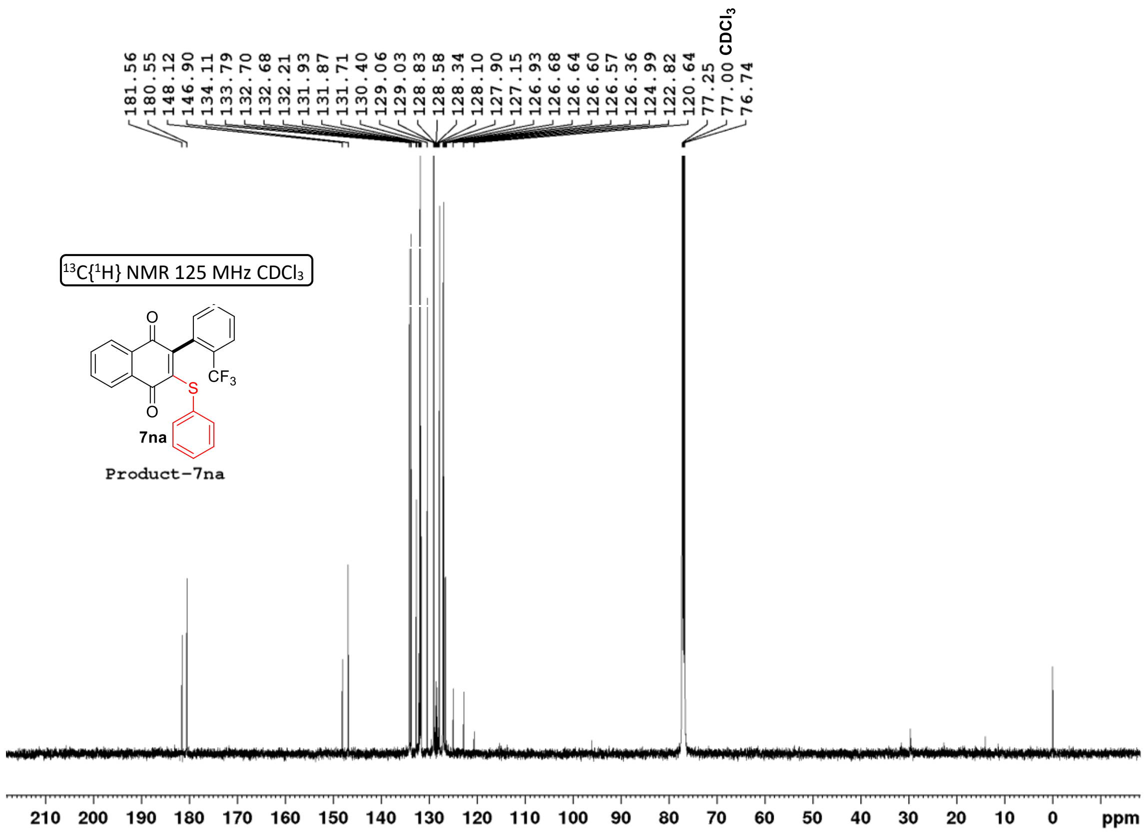
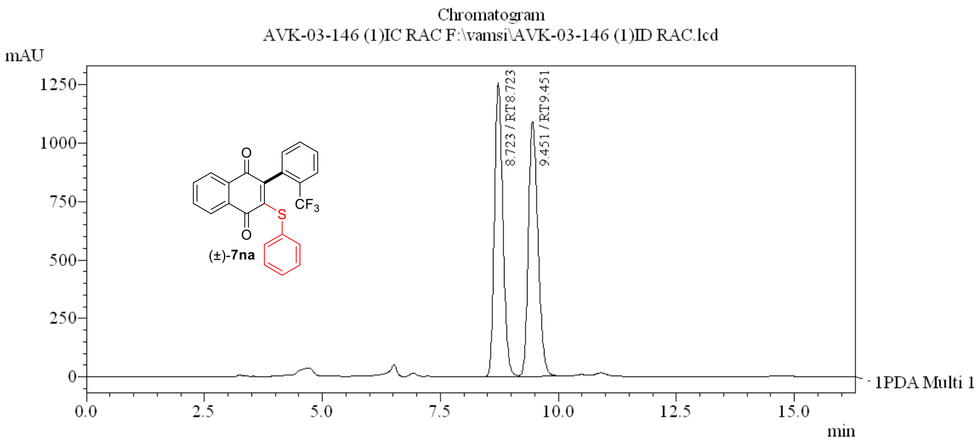


Figure 22: ^{1}H NMR and ^{13}C NMR spectrum of product **7na**.

Racemic (±)-**7na**:



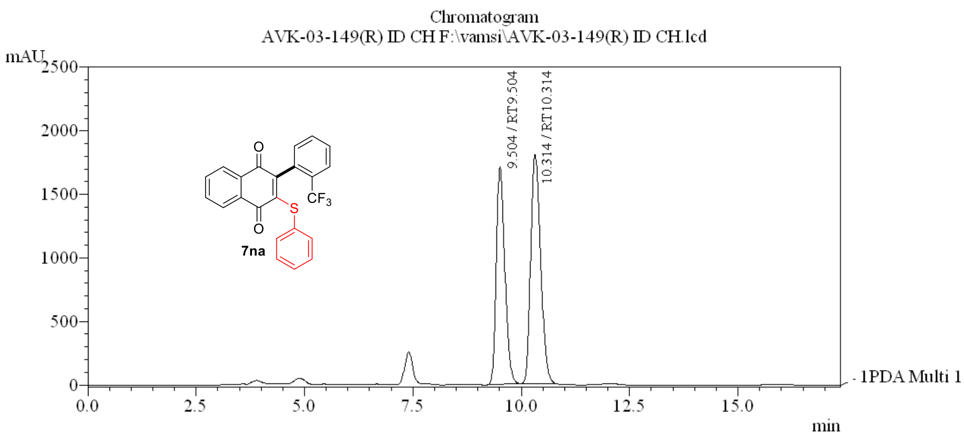
Chiralpak ID, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT8.723	8.723	15450357	1256571	50.123	53.615
2	RT9.451	9.451	15374611	1087115	49.877	46.385
Total			30824968	2343685	100.000	100.000

Chiral **7na** (10% *ee*) [Table 7, entry 1]:



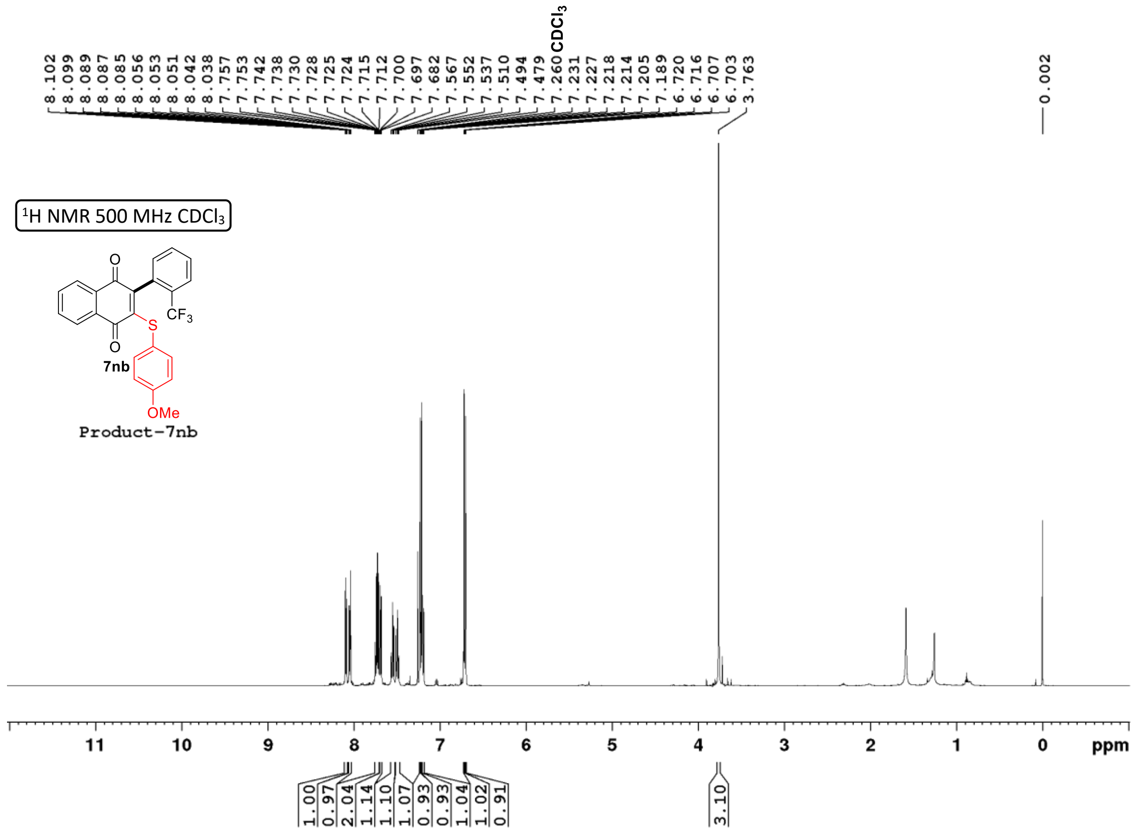
Chiralpak ID, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT9.504	9.504	23551743	1710998	45.060	48.673
2	RT10.314	10.314	28715414	1804261	54.940	51.327
Total			52267156	3515258	100.000	100.000

Figure 23: HPLC spectra of the product **7na**.



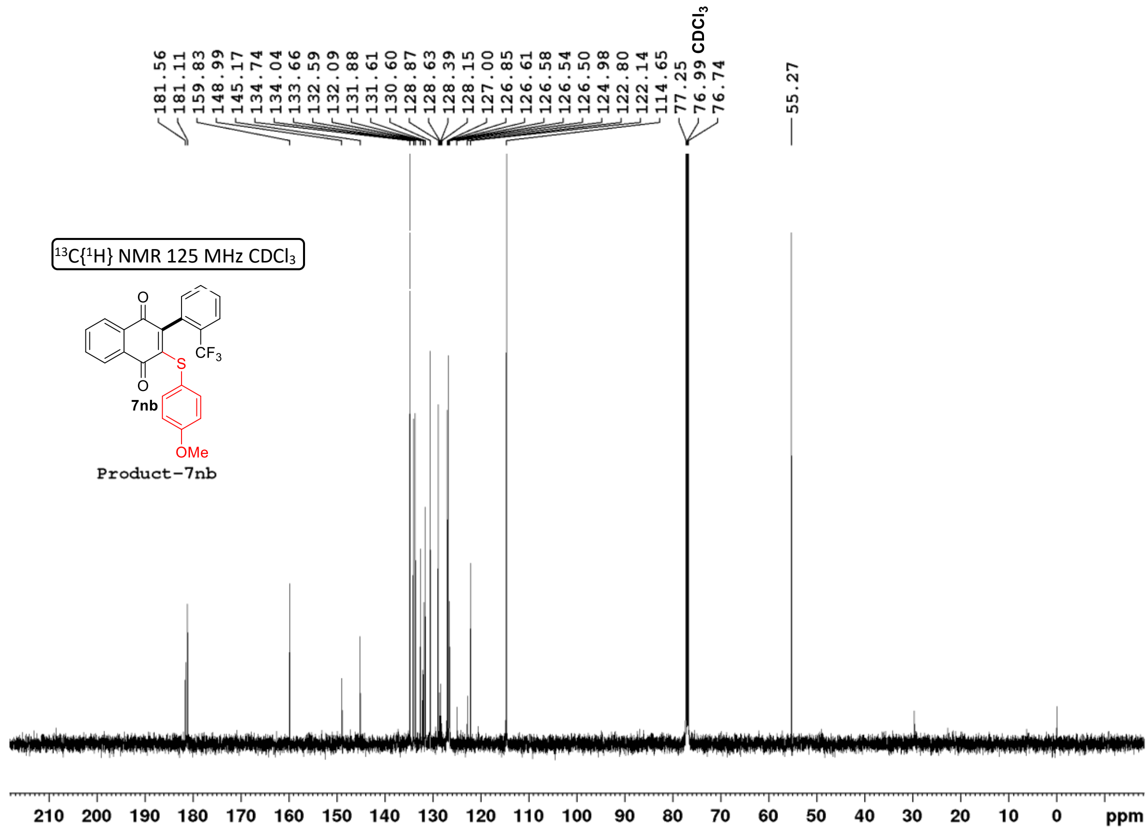
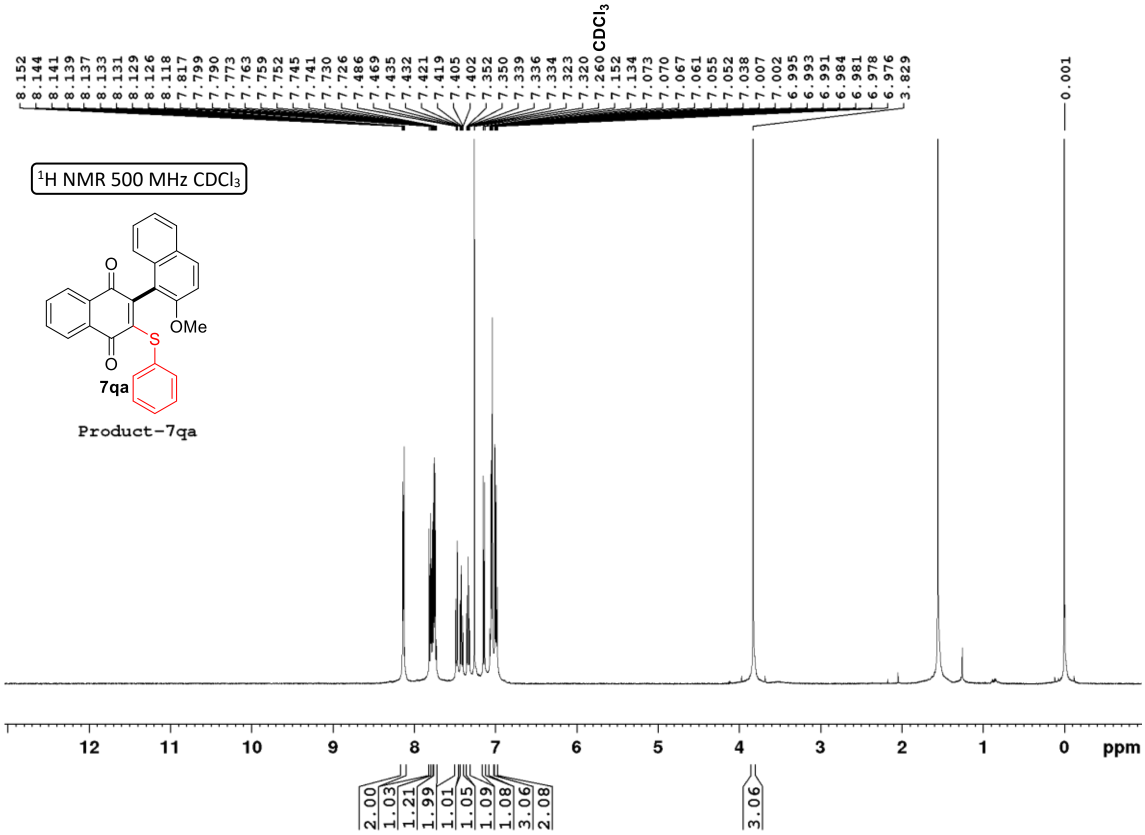


Figure 24: ^{1}H NMR and ^{13}C NMR spectrum of product **7nb**.



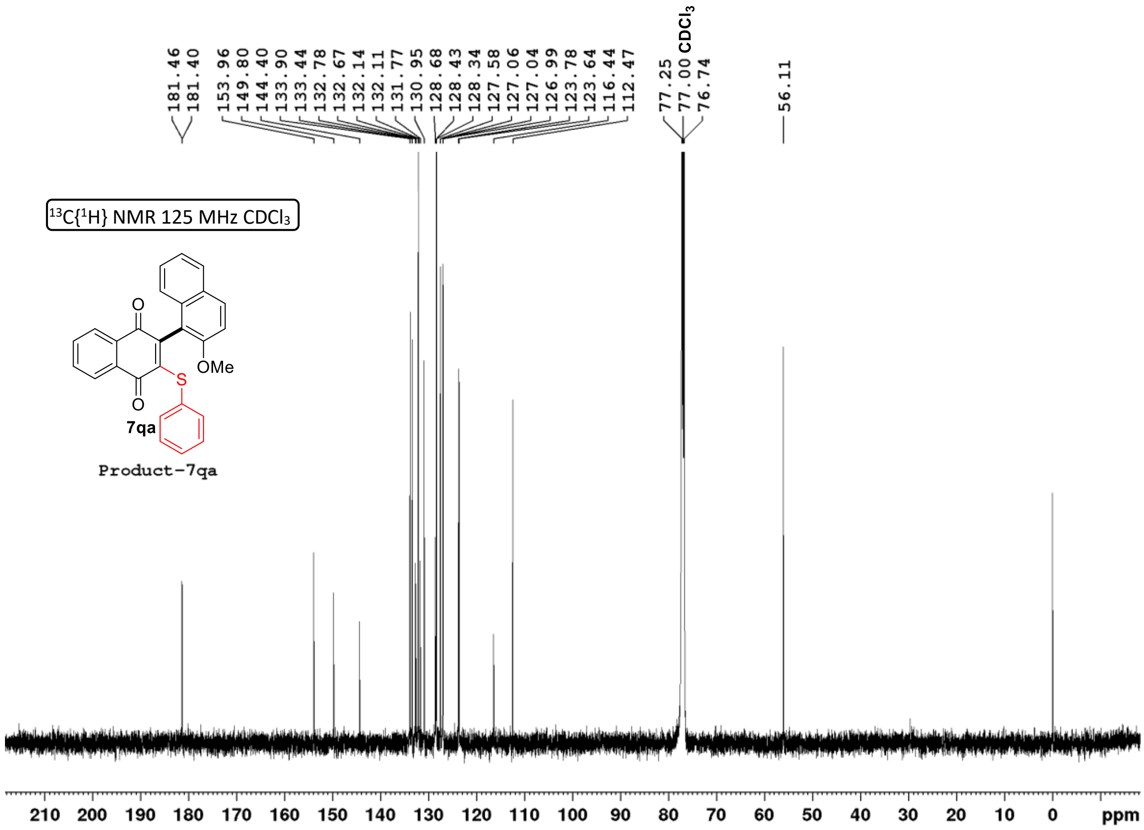
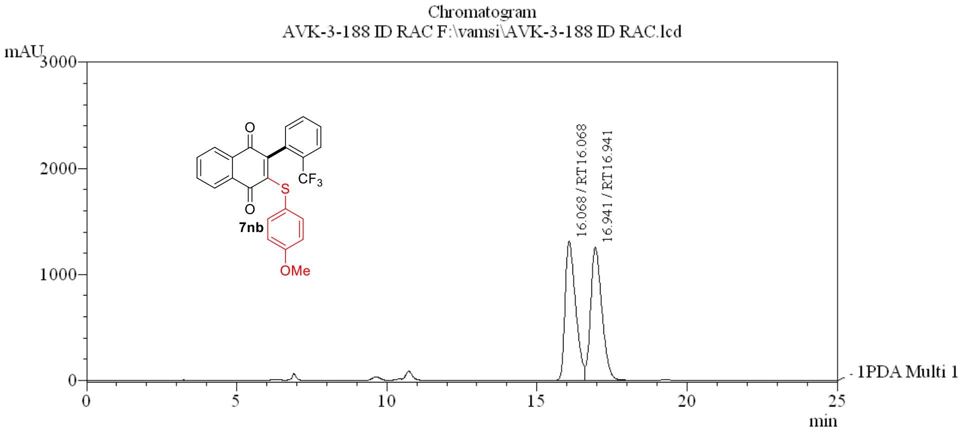


Figure 25: ^{1}H NMR and ^{13}C NMR spectrum of product **7qa**.

Racemic (±)-**7nb**:



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

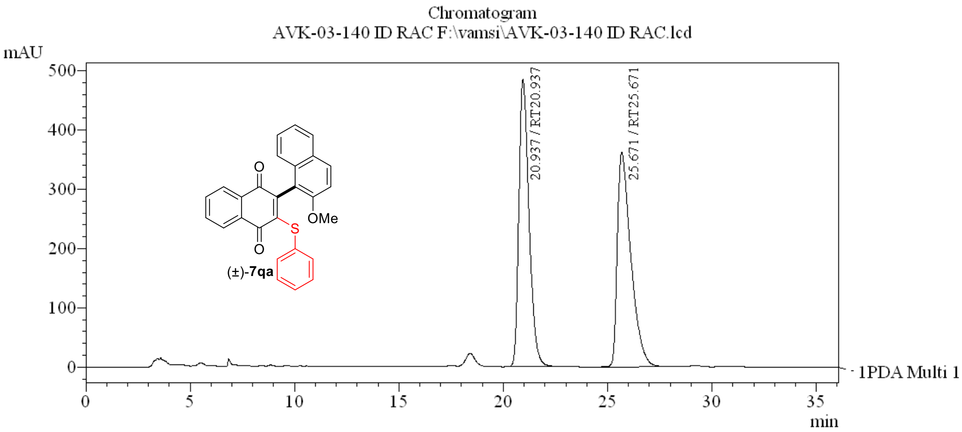
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT16.068	16.068	31951879	1310647	49.316	51.076
2	RT16.941	16.941	32837559	1255442	50.684	48.924
Total			64789438	2566089	100.000	100.000

Figure 26: HPLC spectra of the product **7nb**.

Racemic (±)-**7qa**:



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

PeakTable

PDA Ch1 254nm 4nm

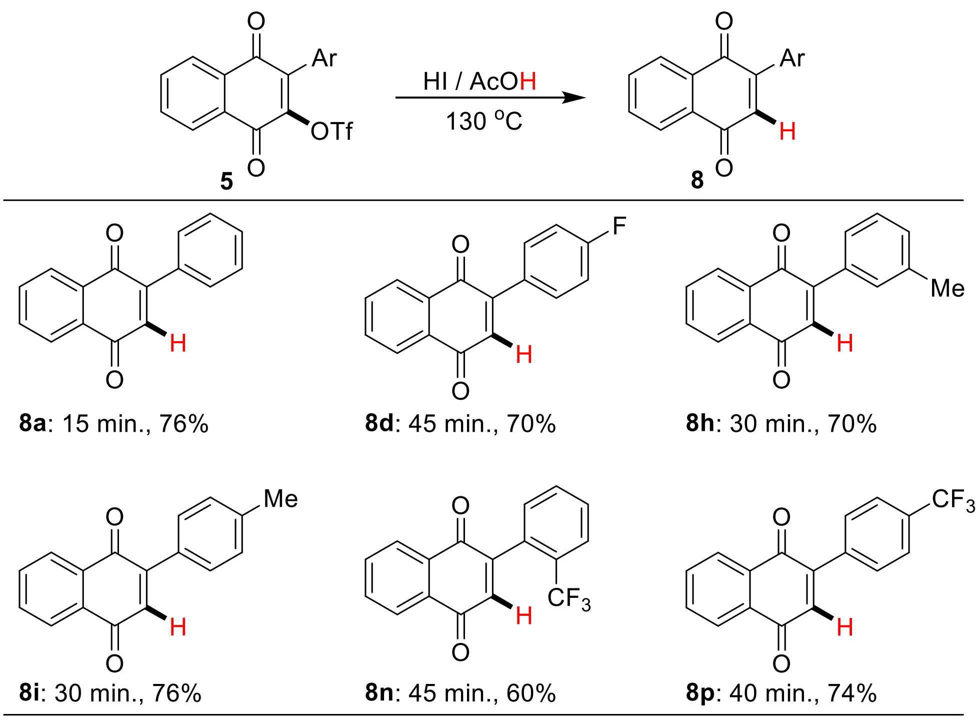
Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT20.937	20.937	16446164	485143	50.122	57.242
2	RT25.671	25.671	16366176	362392	49.878	42.758
Total			32812340	847535	100.000	100.000

Figure 27: HPLC spectra of the product **7qa**.

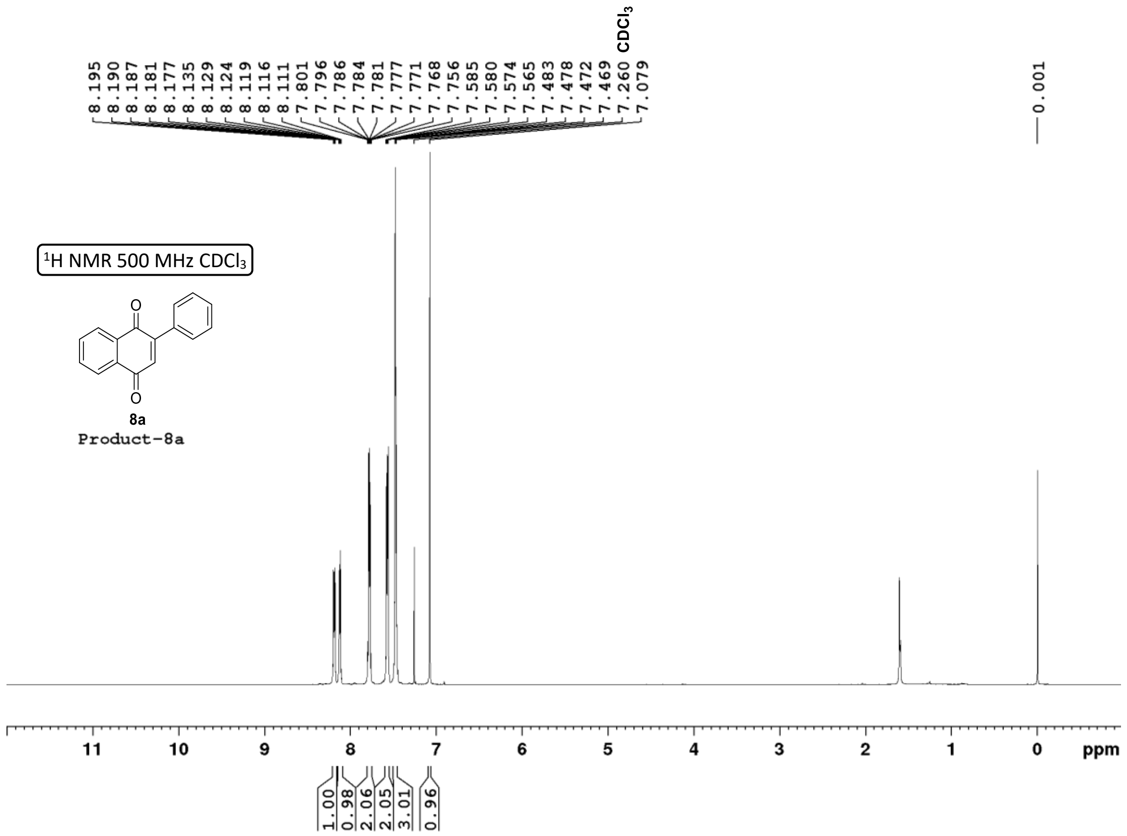
4.2.4.2 Investigation of reductive detriflation on the 3-aryllawsonetriflates

On our way to explore further applications, we started investigating reductive detriflation of **5**. The resulting 2-arylnaphthalene-1,4-diones **8** are very important molecules in medicinal/organic chemistry (Figure 1). Since it is not easy to remove a hydroxyl group from lawsone backbone, there are no reports in the literature as of today. This gave us inspiration to develop a new metal-free tool for the reductive detriflation of 3-aryllawsonetriflates **5** to furnish the products **8** (Table 8). When 3-phenyllawsonetriflate **5a** was reacted with excess HI/AcOH at 130 °C for 15 min, 2-phenylnaphthalene-1,4-dione **8a** formed in 76% yield, which is useful as inhibitor of β-secretase 1. Acetic acid-induced nucleophilic substitution of iodide anion followed by OTf elimination on **5a** with HI, further deiodination and protonation with HI through higher reaction rates furnished **8a** with excellent yield (Table 8) which was confirmed by NMR analysis as shown in Figure 28. This metal-free reductive detriflation was further confirmed with five more examples and furnished the expected products **8d-8p** in very good yields within shorter reaction times (Table 8) (for NMR analysis, see Figures 29-31).

Table 8: Investigation of reductive detriflation reaction on the 3-aryllawsonetriflates[a]



[a] Reactions were carried with 0.115 mmol of **5** in the presence of HI (0.44 mL) and AcOH (0.44 mL). [b] Yield refers to the column-purified product.



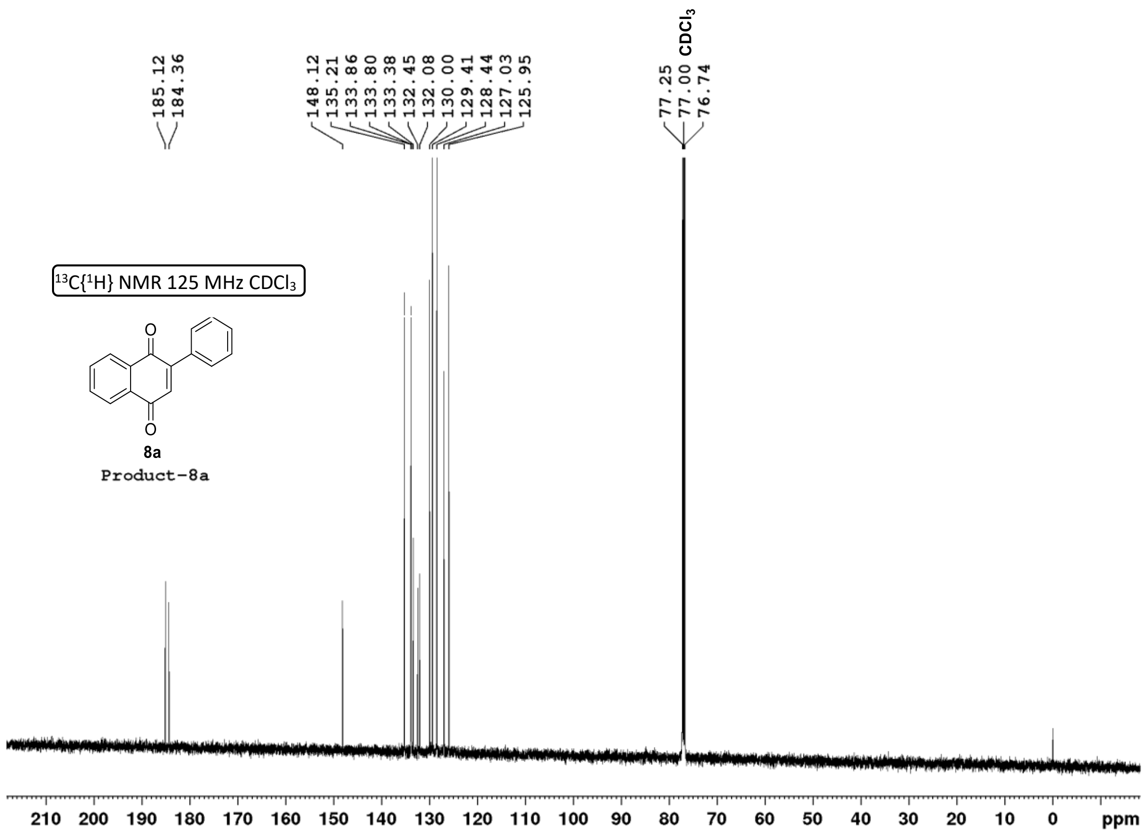
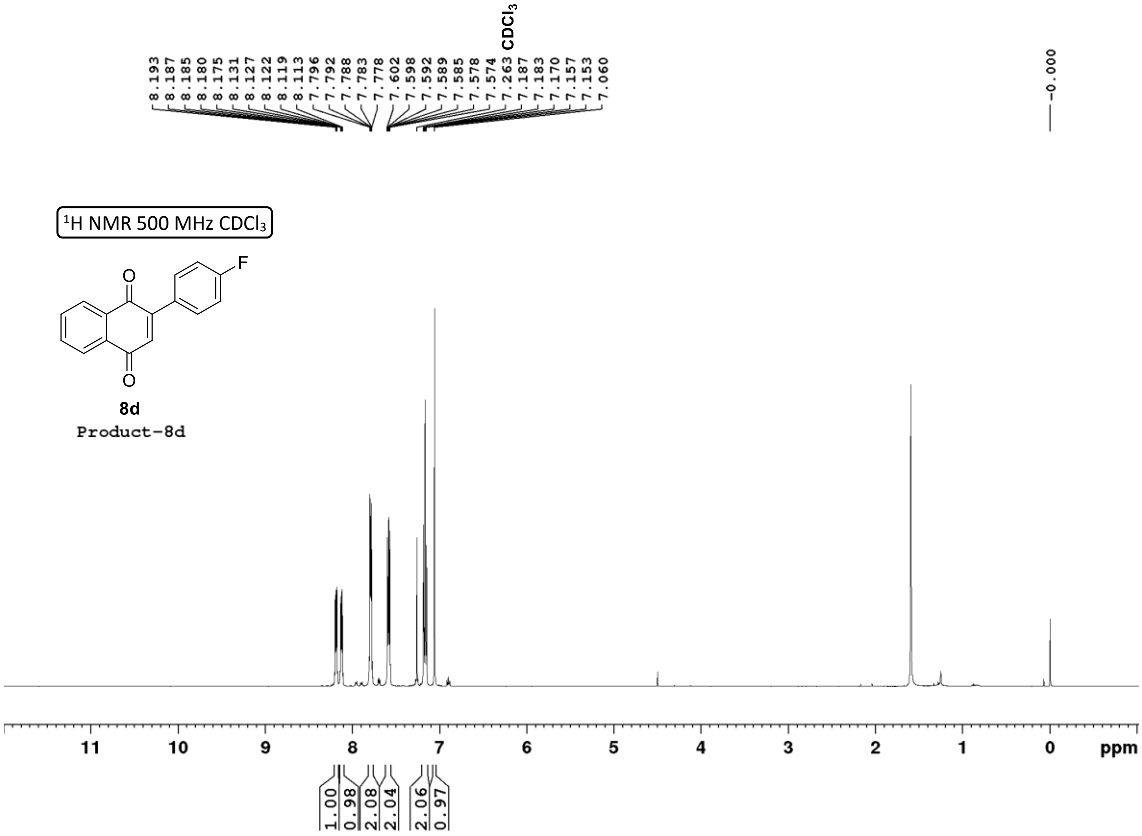


Figure 28: ^{1}H NMR and ^{13}C NMR spectrum of product **8a**.



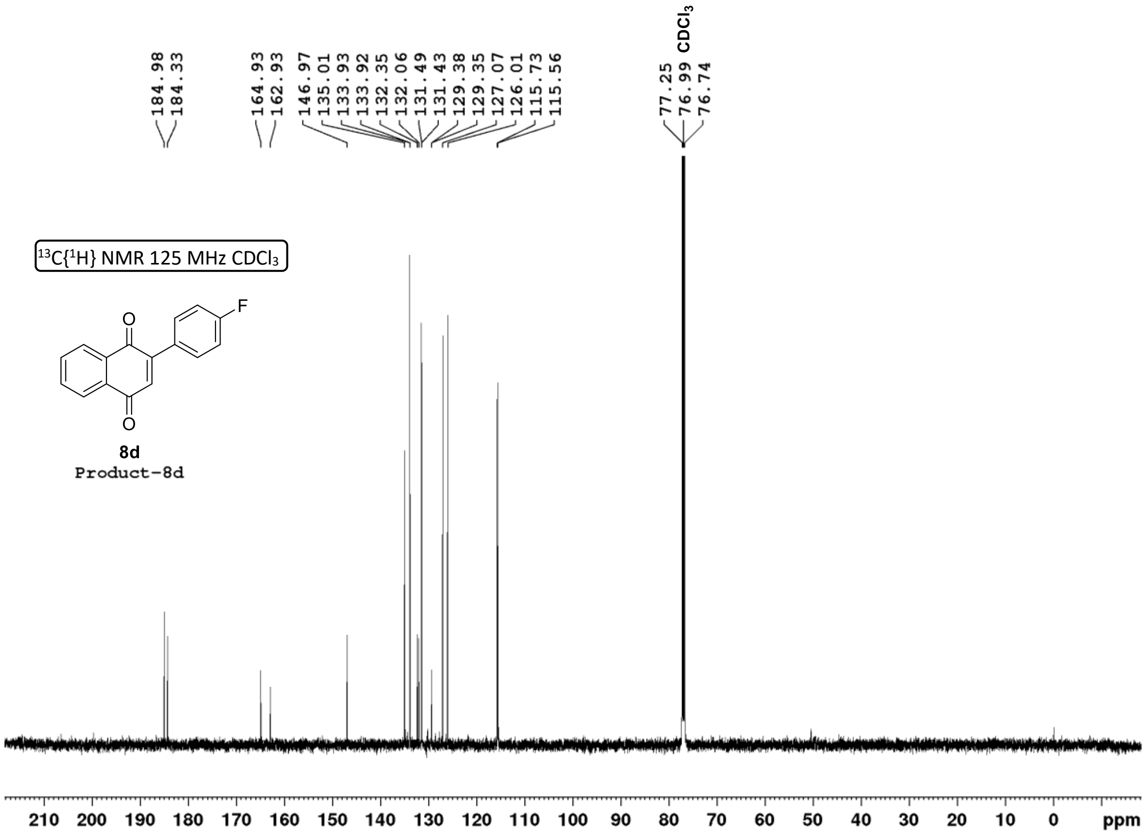
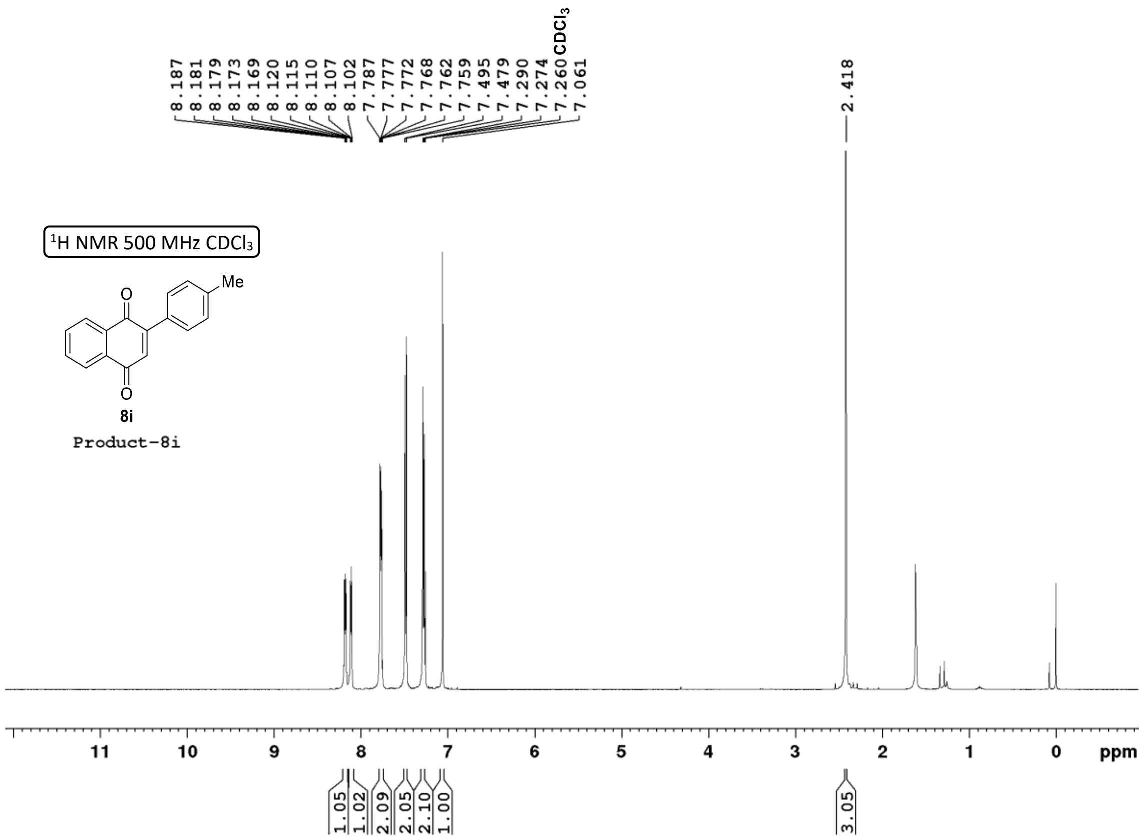


Figure 29: ^{1}H NMR and ^{13}C NMR spectrum of product **8d**.



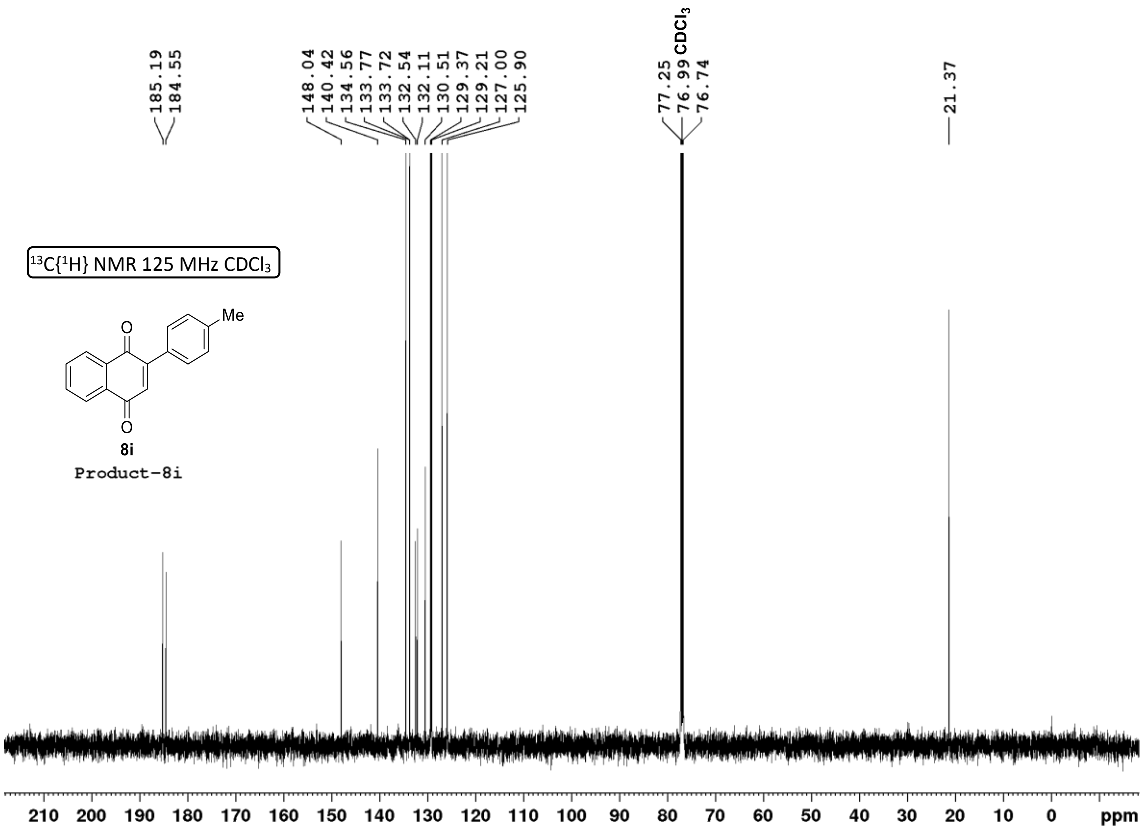
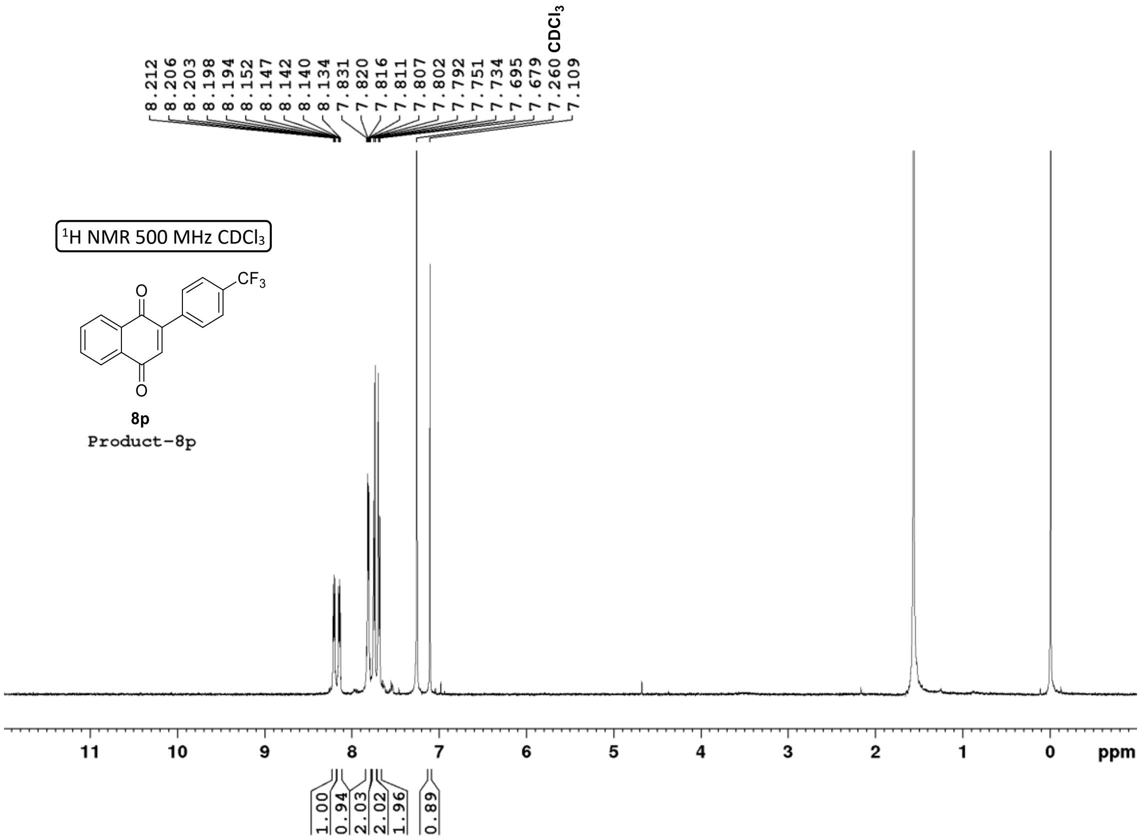


Figure 30: ^{1}H NMR and ^{13}C NMR spectrum of product **8i**.



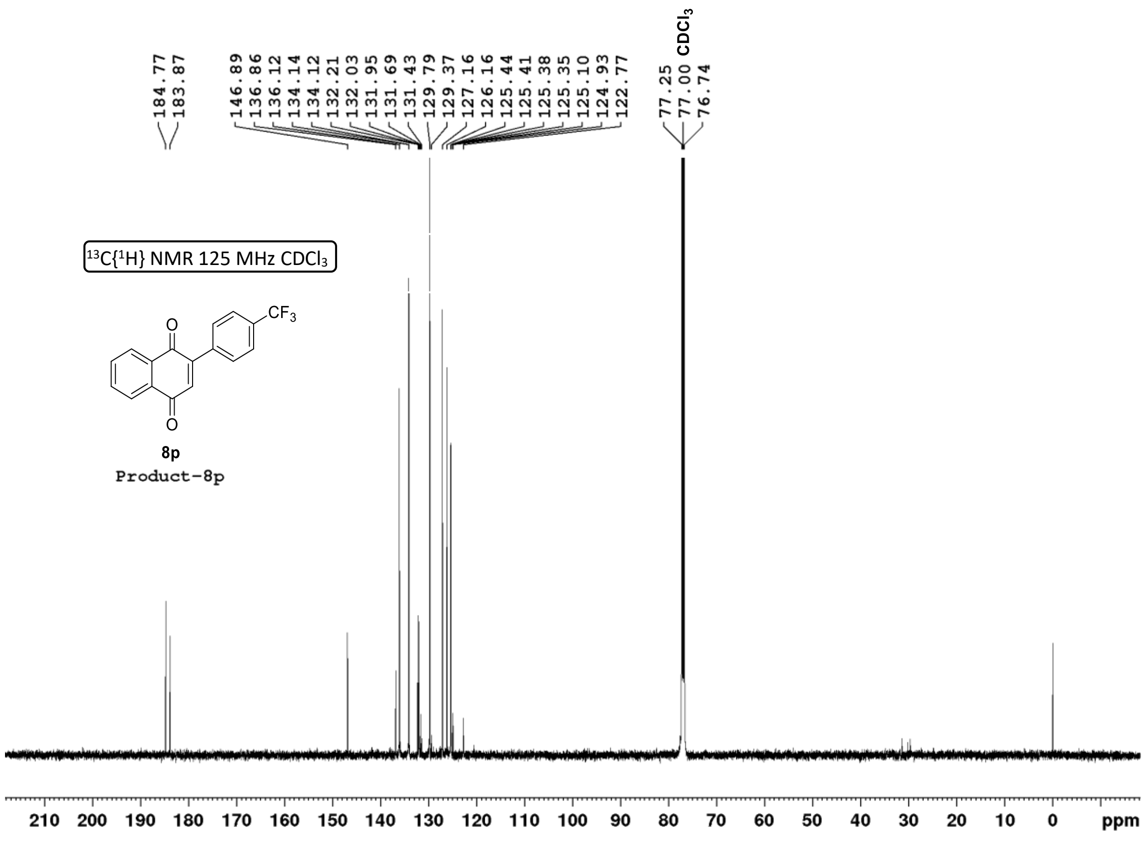
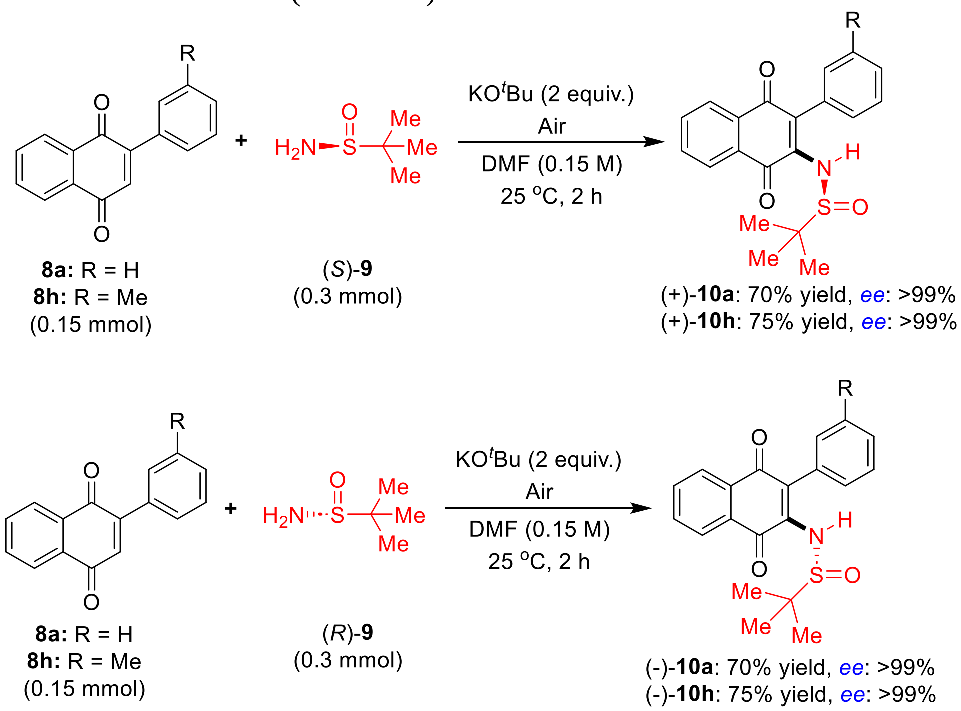


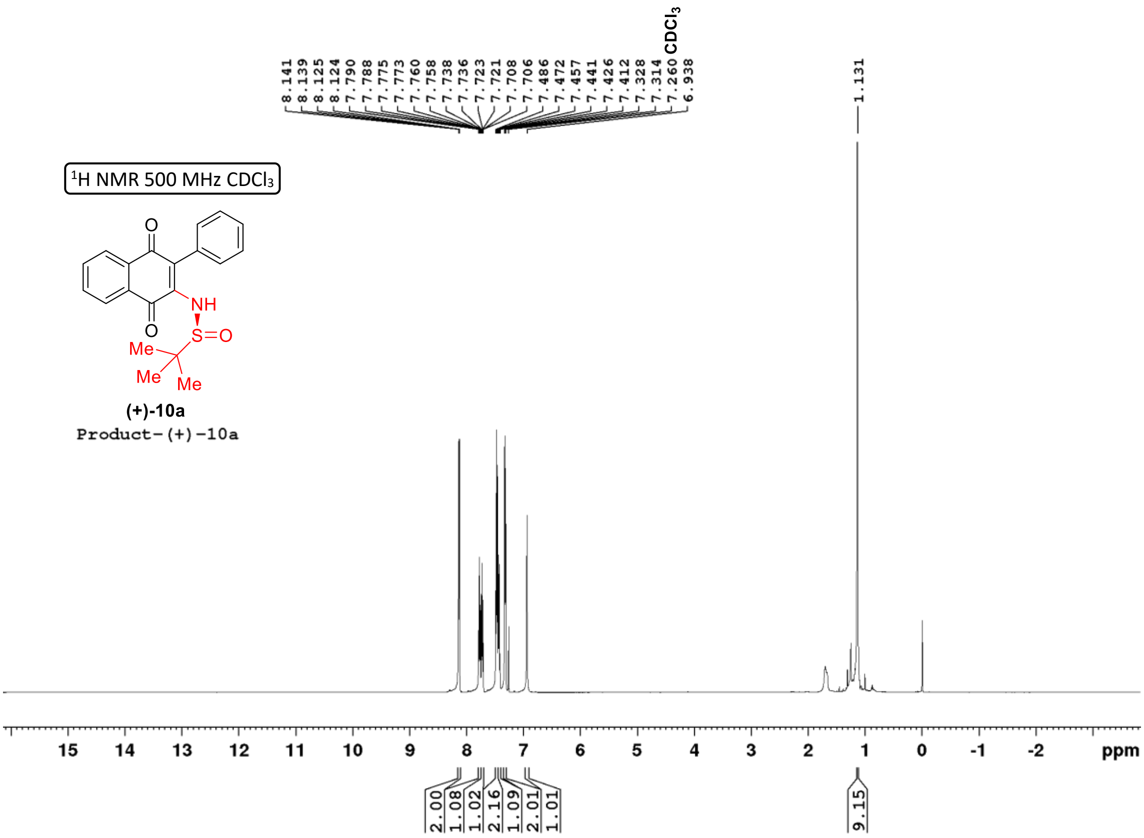
Figure 31: ^{1}H NMR and ^{13}C NMR spectrum of product **8p**.

4.2.4.3 Investigation of *aza*-Michael/air-oxidation reaction on 2-arylnaphthalene-1,4-diones 8

After the synthesis of **8**, we further investigated its reactivity with chiral amines **9**. Similar to the thia-Michael reaction, we investigated an *aza*-Michael reaction of chiral amines (*S*)-/(*R*)-**9** with **8**. Reaction of chiral primary amine (*S*)-(-)-*tert*-butylsulfinamide with 2-arylnaphthalene-1,4-diones **8a**/**8h** in the presence of KO^{t}Bu in DMF at 25 °C for 2 h furnished the optically pure chiral products (+)-**10a** and (+)-**10h** with the yields of 70 and 75% without affecting the enantioselectivity respectively which were confirmed by NMR spectroscopy and HPLC analysis (Figures 32-35). Similarly, the reaction of chiral primary amine (*R*)-(+)-*tert*-butylsulfinamide with 2-arylnaphthalene-1,4-diones **8a**/**8h** in the presence of KO^{t}Bu in DMF at 25 °C for 2 h furnished the optically pure chiral products (-)-**10a**, and (-)-**10h** in very good yields of 70 and 75% with >99% *ee*, respectively through domino *aza*-Michael/air-oxidation reactions (Scheme 3).



Scheme 3: Aza-Michael/air-oxidation reactions of 2-arylnaphthalene-1,4-diones with chiral amines.



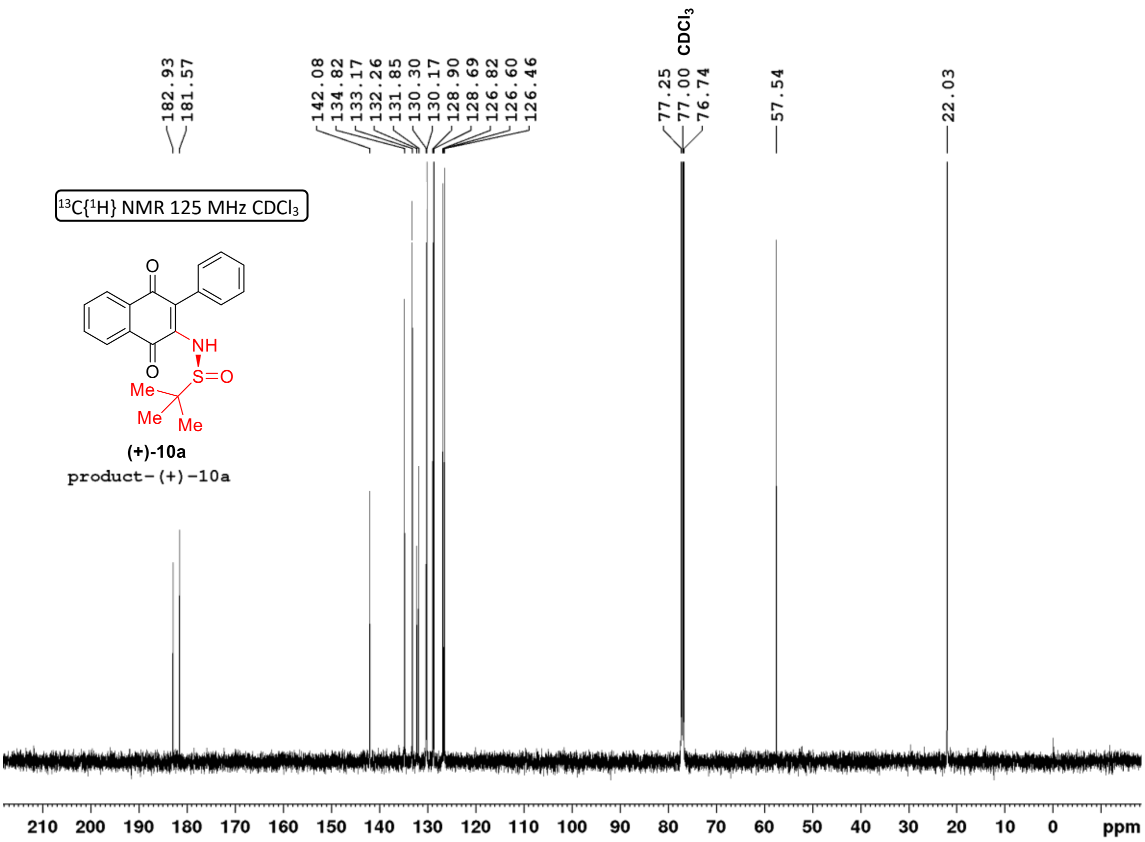
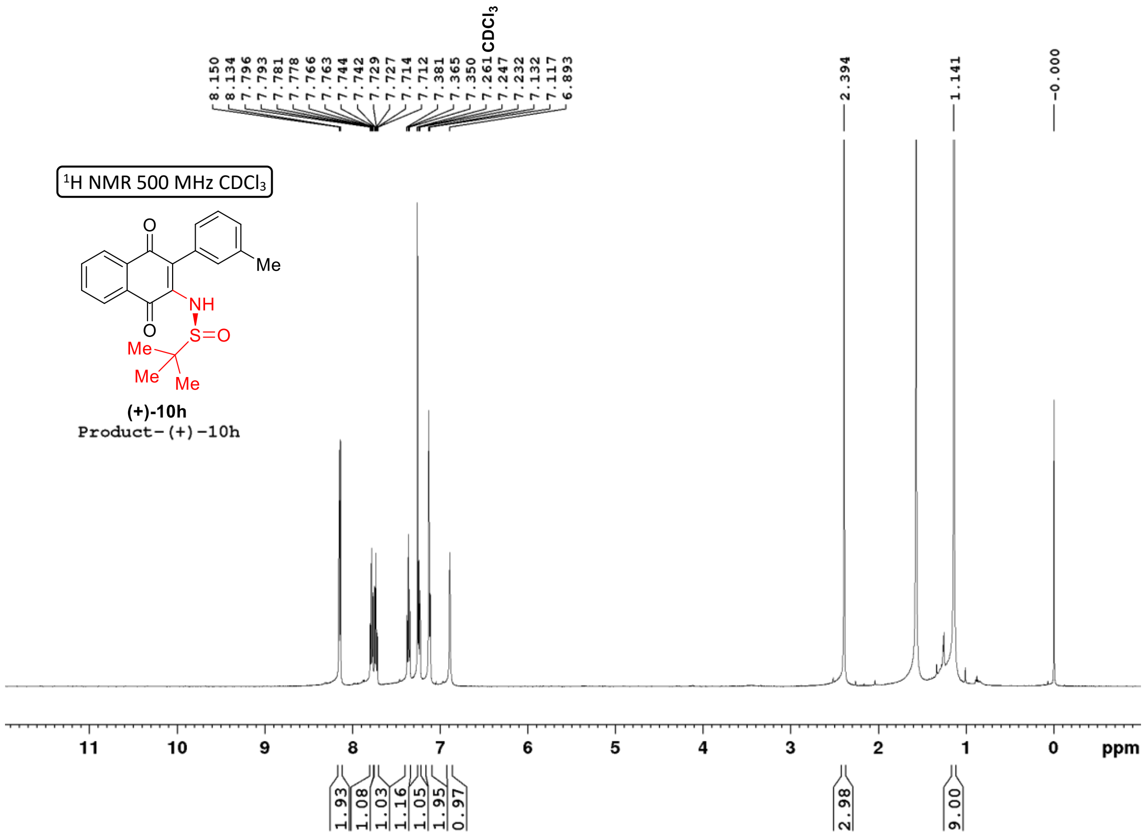


Figure 32: ^{1}H NMR and ^{13}C NMR spectrum of product **10a**.



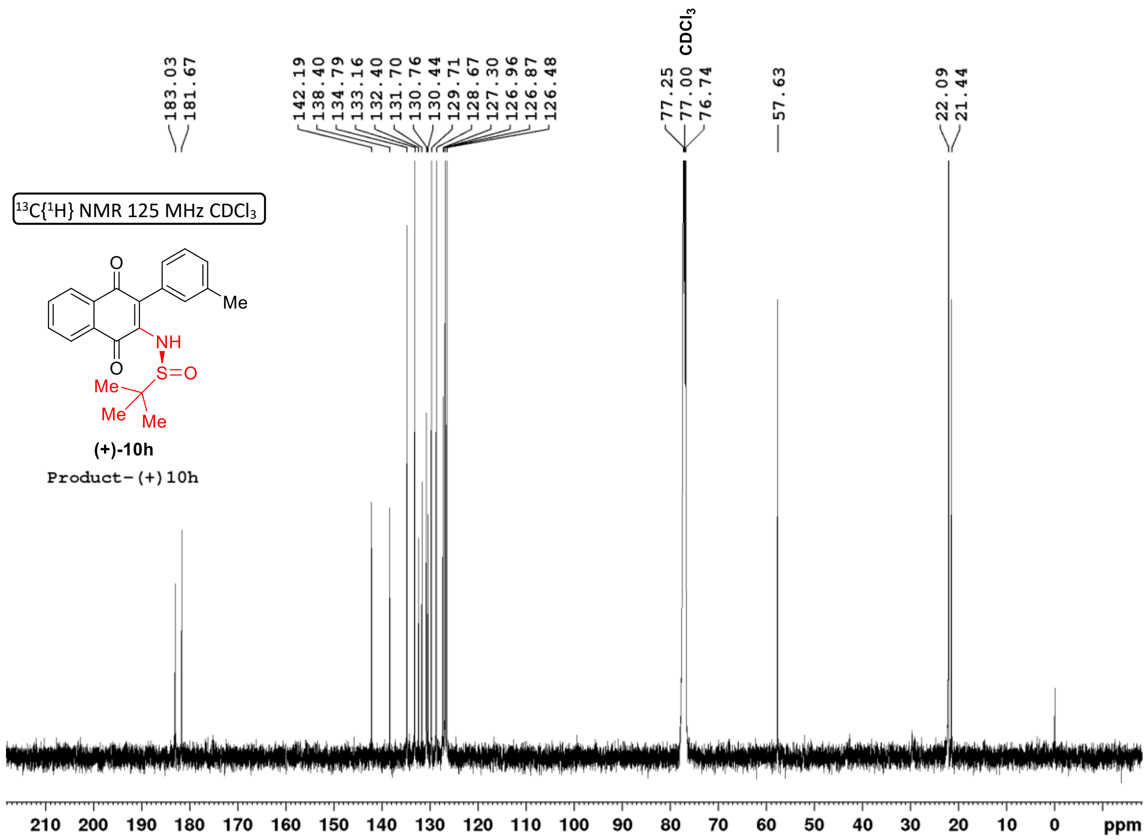
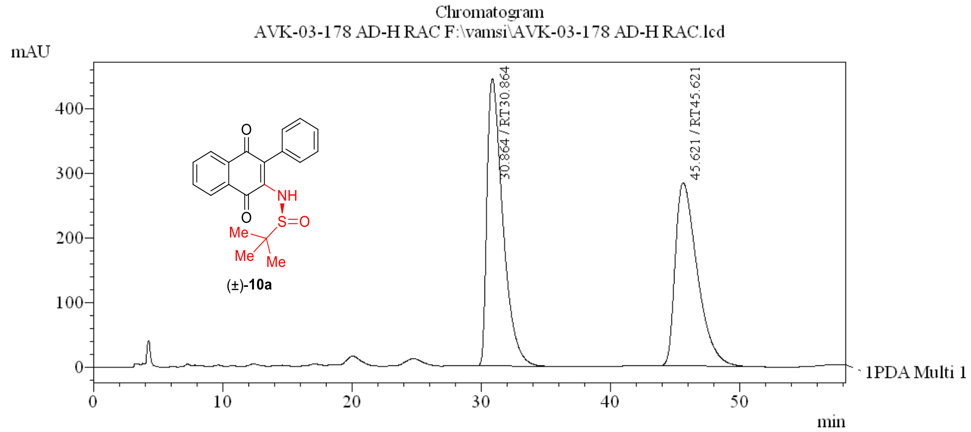


Figure 33: ^{1}H NMR and ^{13}C NMR spectrum of product **10h**.

Racemic (±)-**10a**:



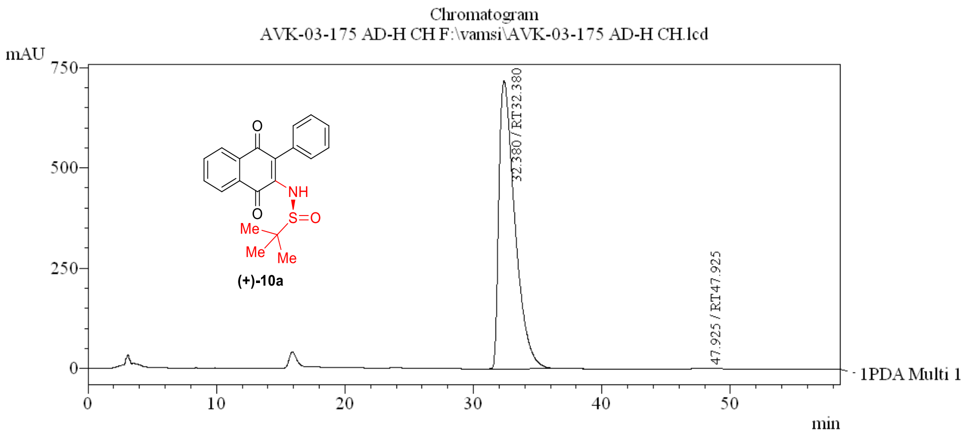
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT30.864	30.864	37868786	445101	52.812	61.043
2	RT45.621	45.621	33835855	284062	47.188	38.957
Total			71704642	729163	100.000	100.000

Chiral (+)-**10a** (>99% *ee*):



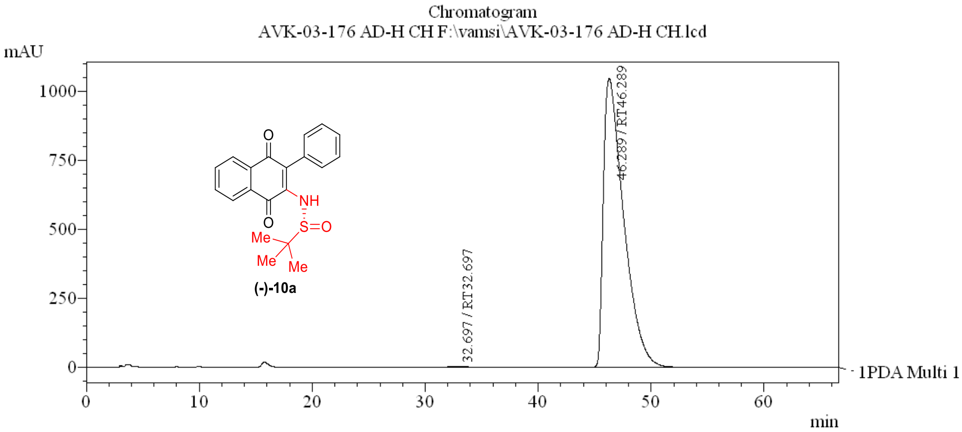
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT32.380	32.380	62181933	717156	99.787	99.768
2	RT47.925	47.925	132891	1665	0.213	0.232
Total			62314824	718820	100.000	100.000

Chiral (-)-**10a** (>99% *ee*):



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

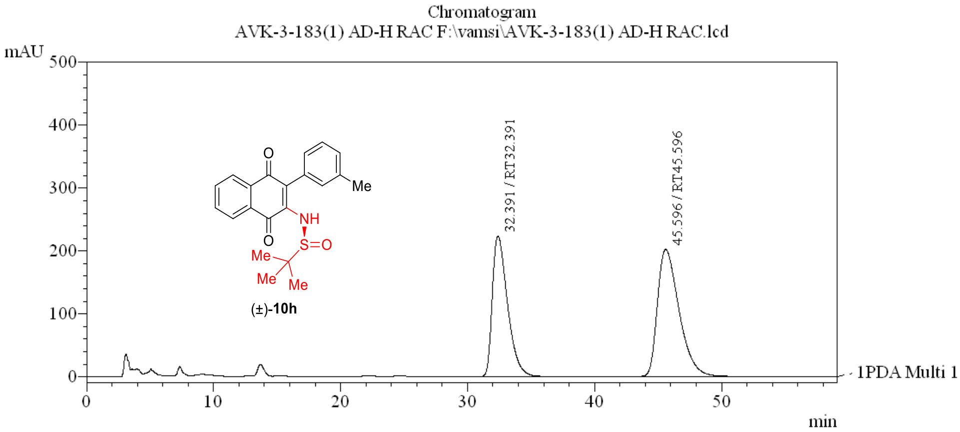
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT32.697	32.697	244402	3471	0.187	0.331
2	RT46.289	46.289	130575989	1045182	99.813	99.669
Total			130820391	1048653	100.000	100.000

Figure 34: HPLC spectra of the product **10a**.

Racemic (±)-**10h**:



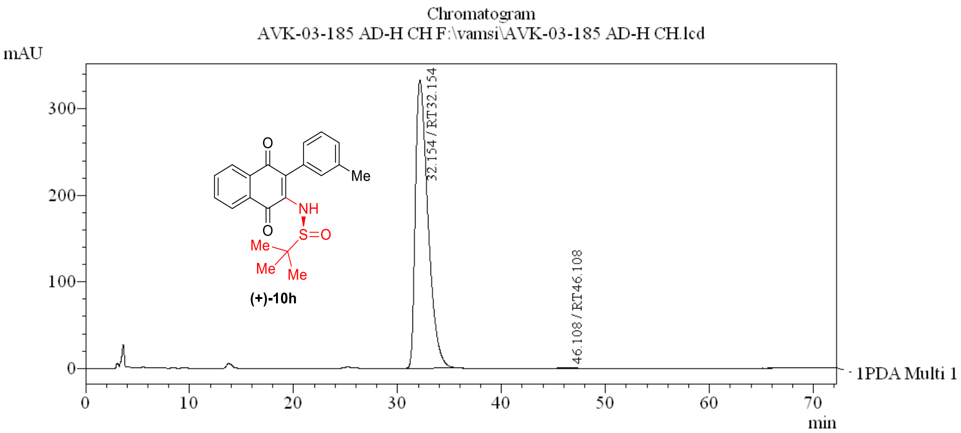
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT32.391	32.391	18523697	223563	43.845	52.558
2	RT45.596	45.596	23724710	201800	56.155	47.442
Total			42248407	425363	100.000	100.000

Chiral (+)-**10h** (>99% *ee*):



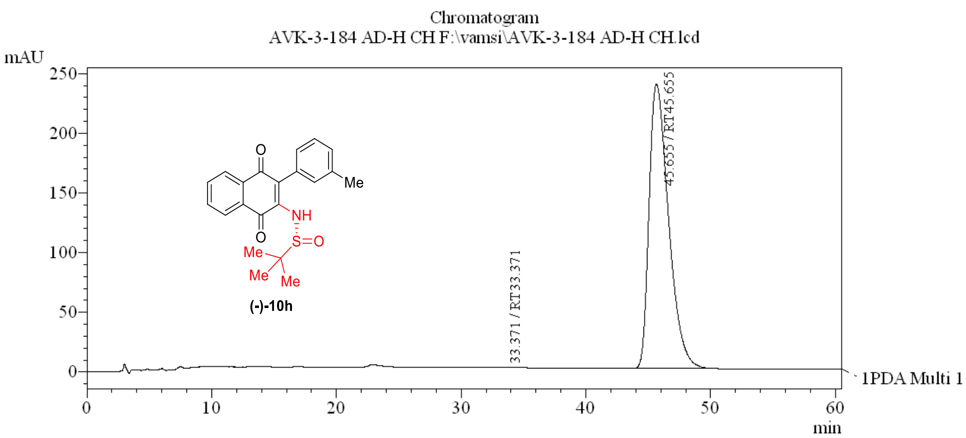
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT32.154	32.154	28067308	332796	99.825	99.857
2	RT46.108	46.108	49334	477	0.175	0.143
Total			28116642	333273	100.000	100.000

Chiral (-)-**10h** (>99% *ee*):



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

PeakTable

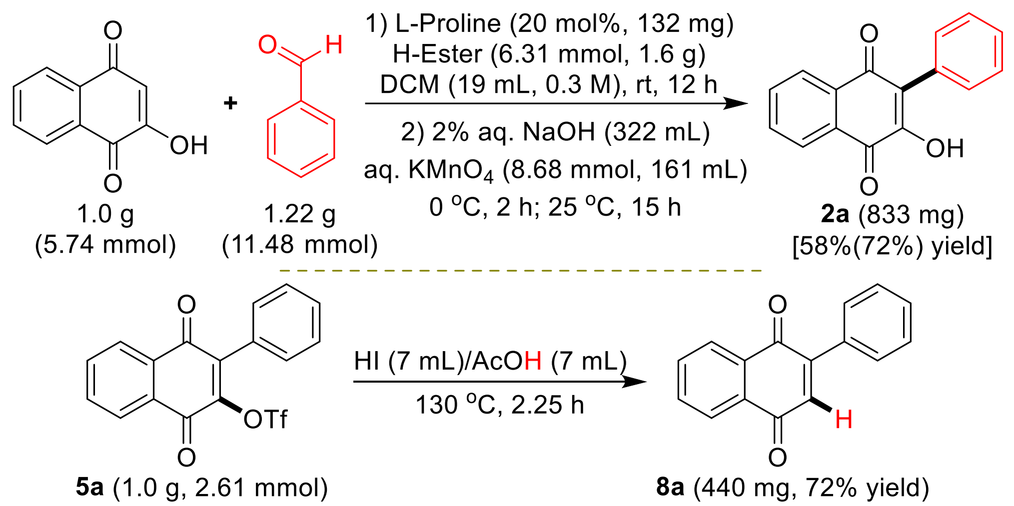
PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT33.371	33.371	32449	432	0.125	0.181
2	RT45.655	45.655	25853392	238156	99.875	99.819
Total			25885840	238588	100.000	100.000

Figure 35: HPLC spectra of the product **10h**.

4.2.5 Gram-scale Reductive Coupling/Hooker Oxidation and Reductive Detriflation Reactions

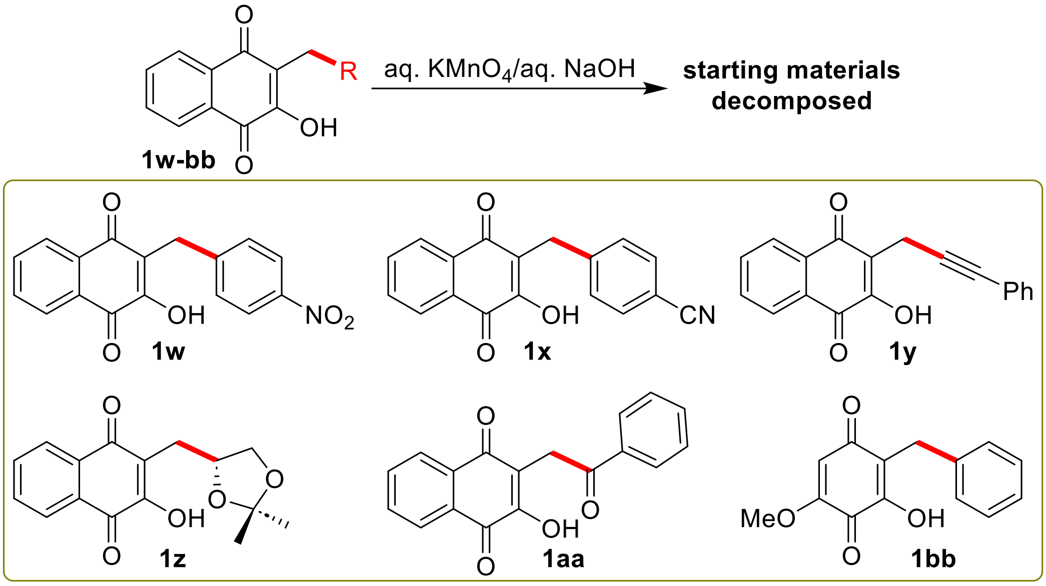
Since many of these 3-aryllawsones have wide range of applications, we have performed a gram-scale reductive coupling/Hooker oxidation and reductive detriflation reactions. Sequential seven-step double cascade one-pot reductive coupling/Hooker oxidation of lawsone (1.0 g) with benzaldehyde (1.22 g) for 29 h furnished the anti-venom drug 3-phenyllawsone **2a** in 0.833 g with slightly reduced yield (Scheme 4). At the same time reductive detriflation reaction of 1.0 g of **5a** with HI (7.0 mL, 55-58% in H_2O) and AcOH (7.0 mL) at 130 °C for 2.25 h furnished the drug molecule **8a** in 0.44 g with 72% yield. Astonishingly, both the gram-scale reactions afforded the corresponding drug products in very good yields (Scheme 4).



Scheme 4: Gram-scale reactions.

4.2.6 Controlled Experiments for the Hooker Oxidation

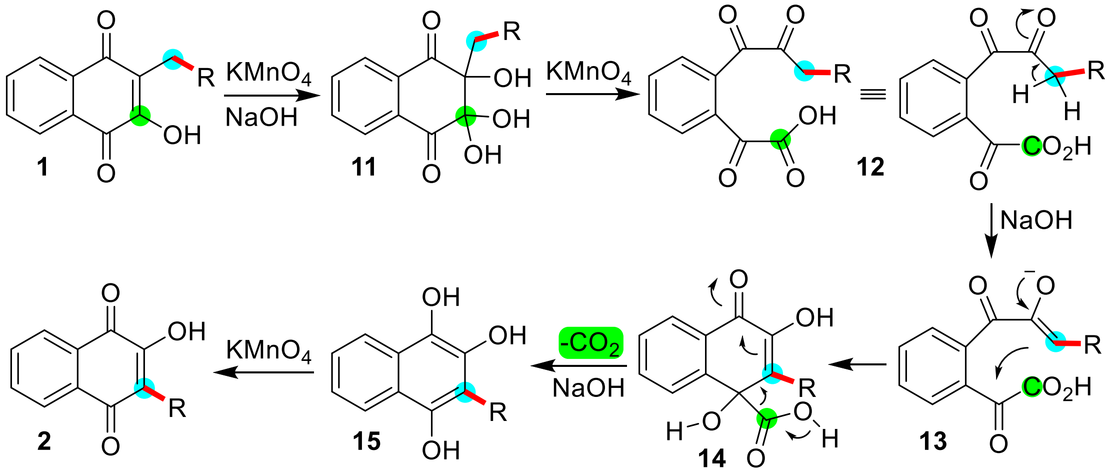
Further to understand the Hooker oxidation reaction mechanism, we performed few experiments to find out the sensitivity of the functional groups on lawsone or aryl. Hooker oxidation struggles to afford the products when there are functional groups which are prone to oxidation or induce the oxidation at methylene group (Scheme 5). We have chosen functional groups such as nitro and cyano (**1w-x**), which can effectively increase the acidity of the methylene group and performed Hooker reaction using standard conditions. Surprisingly, there is no product formation, but complete decomposition of the starting materials was observed. We further continued our investigation by keenly choosing specifically designed starting materials (**1y-1bb**) which contain an acidic methylene group or active olefin or protected alcohols. Here too, the substrates **1y-1bb** followed the same pattern of **1w-1x** no product formation but decomposition (Scheme 5).



Scheme 5: Controlled experiments for the Hooker oxidation.

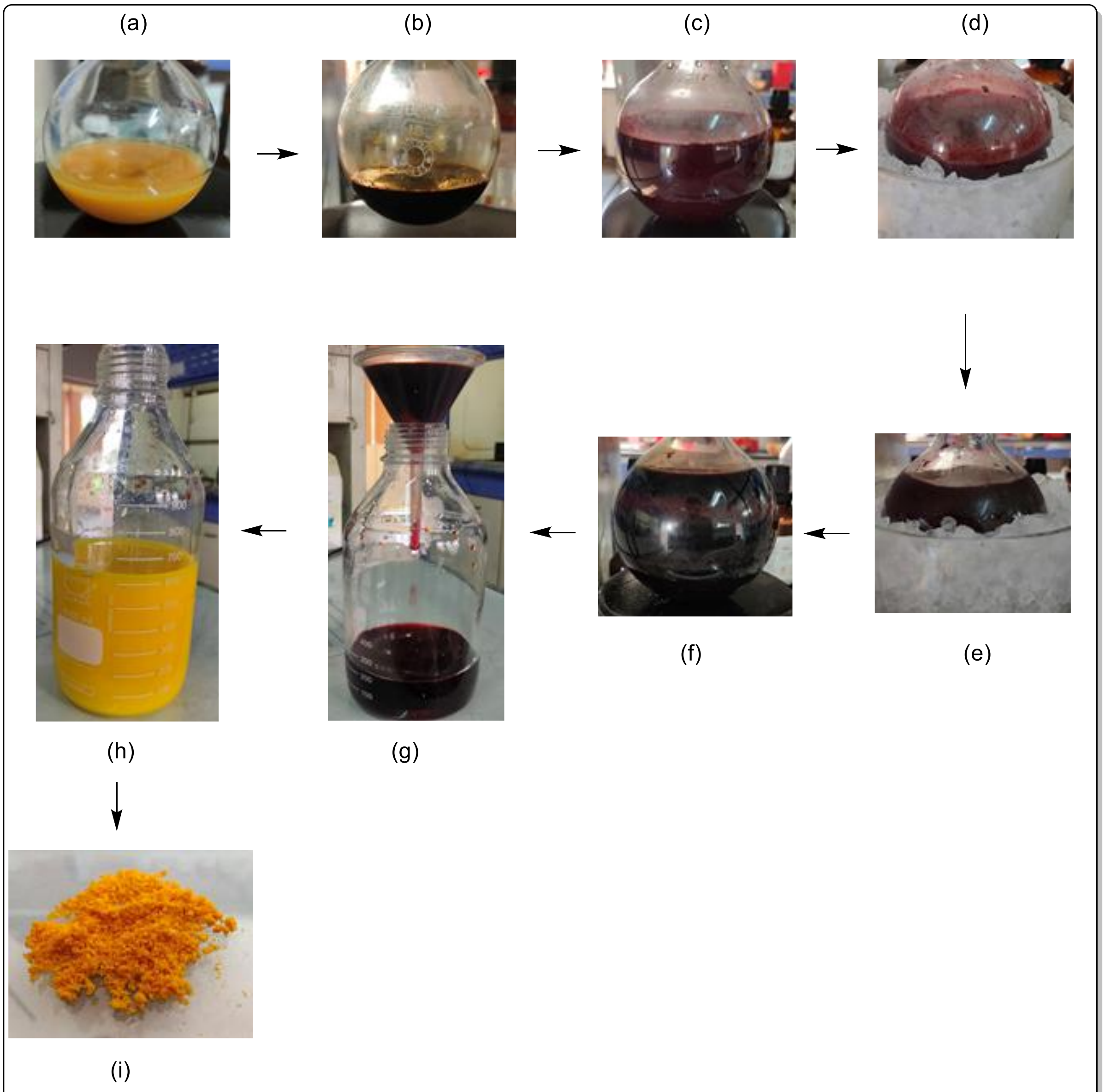
4.2.7 Mechanistic Insights

Herein we discussed the mechanism of Hooker oxidation through alkyl transfer based on the control experiments (Scheme 6).[6] Reaction of 3-arylmethylenelawsones **1** with $KMnO_4$ in the presence of NaOH furnish the dihydroxylated intermediate **11**, which on further in situ treatment with $KMnO_4$ gives the oxidative C-C bond cleavage intermediate **12**. Base-mediated in situ enolization followed by intramolecular aldol reaction of **12** furnished the alkyl transfer intermediate **14**, which on base-induced decarboxylation followed by oxidation delivers the 3-aryllawsones **2**.



Scheme 6: Proposed mechanism for Hooker reaction.

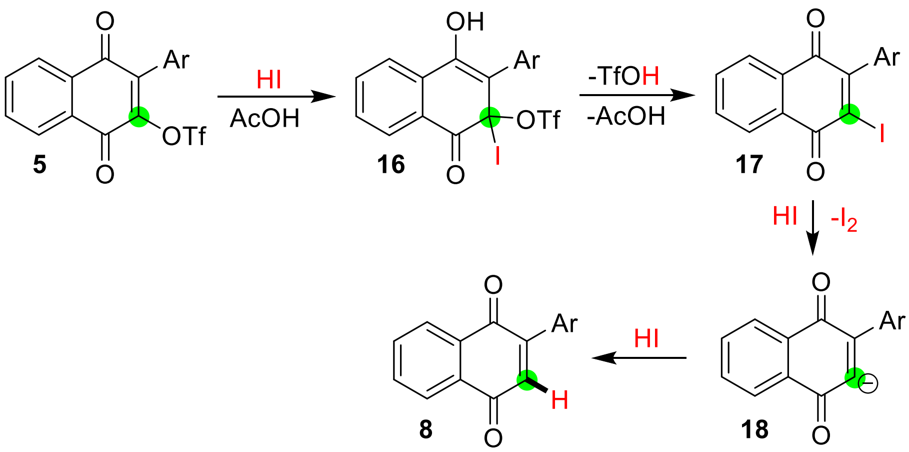
As mentioned in Scheme 5, these five cascade sequential one-pot reactions are highly selective to perform on the 3-arylmethylenelawsones **1**/**3** to give final products **2**/**4** in good yields.



(a) 5.74 mmol Lawsone is treated with 11.48 mmol benzaldehyde in the presence of 20 mol% L-proline and 6.31 mmol Hantzsch ester for 12 h (b) RRC was sucessfully completed and then DCM was evapourated. (c) After evaporating DCM, 322 mL of 2% aq. NaOH was added (d) reaction mixture was then cooled to zero degree (e) Then, 8.68 mmol of potassium permanganate in 161 mL of water which was already cooled to zero degree was added and stirred for 30 seconds and maintained undisturbed at 0 oC for 2 h (f) Then, the reaction mixture was allowed to stay undisturbed for 15 h at room temperature (g) The reaction mixture was filtered in order to remove manganese dioxide (h) Then, the filtrate was acidified with 20% HCl (i) After neutralising this way, workup should be done using ethyl acetate, combined organic layers were dried and concentrated, purified through colom chromatography to achieve pure 3-phenyllawsone.

Figure 36: Pictorial representation of seven-step one-pot synthesis of 3-aryllawsones.

Metal-free reductions always inspire the green chemistry practitioners; herein we explained the mechanism of excess HI/AcOH-mediated reductive detriflation reaction of 3-aryllawsonetriflates **5** (Scheme 7).[8] Acetic acid-induced iodination of **5** in the presence of hydroiodic acid (HI) furnish the iodo-enol **16**, which on further heat-mediated elimination of TfOH gave the key intermediate iodo-enone **17**.[8] Deiodination of **17** with excess hydroiodic acid (HI) followed by protonation furnished the final reductive detriflation product **8**, which is evidenced by iodine formation as violet colour of the reaction mixture. Same time this reaction represents for one of the best laboratory protocols for metal-free reductive deiodination reaction.



Scheme 7: Proposed mechanism for reductive detriflation.

4.3 Conclusions

In conclusion, we have developed a seven-step [olefination/transfer hydrogenation/dihydroxylation/oxidative C-C bond cleavage/aldol reaction/decarboxylation/oxidation] general protocol for the synthesis of important 3-aryllawsones through combination of two domino processes of organocatalytic reductive coupling and Hooker oxidation reactions from the easily available aldehydes and lawsones in one- or two-pot manner. In this paper, first time we have given crystallographic proof for the regioselective alkyl transfer in the Hooker oxidation reaction. Same time, we have also demonstrated many synthetic applications of 3-aryllawsones, which are of high importance in medicinal chemistry. Further studies are focused towards enhancing the selectivity of atropisomers **7** through specially designed catalysts and to study the medicinal properties of compounds **2** to **10** are under progress.

4.4 Experimental Section

General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 500 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. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-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. 3-Alkyllawsones **1/3** were prepared according to the literature procedure.[9]

Procedure A: **General procedure for oxidative decarboxylation**: In an oven dried round bottomed flask equipped with a magnetic stirring bar at 0 °C was taken 3-alkyllawsones **1** or **3** **(**0.2 mmol, 1.0 equiv.), to which $KMnO_4$ (0.38 mmol, 1.9 equiv. in 7.0 mL of H_2O) and 14.0 mL of 2% NaOH in H_2O was added and stirred vigorously for 20 seconds and left unstirred at 0 °C for 2 h followed by 25 °C for 15 h. The aq. $KMnO_4$ and aq. NaOH should be cooled to 0 °C prior to its addition to 3-alkyllawsones **1** or **3**. After 15 h, the reaction mixture was filtered in order to remove the precipitated MnO_2, the filtrate was acidified with 20% HCl and then extracted with ethyl acetate thrice. The combined organic layers were dried

(Na_2SO_4), and concentrated. Pure products of 3-aryllawsones **2** or **4** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

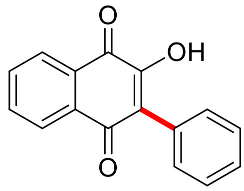
Procedure B: **General procedure for the OTf protection of 2/4**: In an oven dried round bottom flask was taken the mixture of 3-aryllawsones **2/4** (0.2 mmol, 1.0 equiv.) and DMAP (0.07 mmol, 35 mol%) in DCM (0.03 M) and cooled to 0 °C. To this (*i*Pr)$_2$EtN (1.0 mmol, 5.0 equiv.) and triflic anhydride (0.36 mmol, 1.8 equiv.) were added respectively and allowed to stir for 1 h at 0 °C. Then the reaction mixture was diluted with DCM and washed with saturated aq. NH_4Cl twice. The organic layer was separated and dried (Na_2SO_4), and concentrated. Pure products 3-aryllawsone-triflates **5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure C: **General procedure for the thia-Michael reaction**: In an oven dried round bottom flask was taken the mixture of 3-aryllawsone-triflates **5** (0.065 mmol, 1.0 equiv.) and thiophenol **6** (0.06565 mmol, 1.01 equiv.) in DCM (0.0065 M). The reaction mixture was stirred for 30 min. and then added Et_3N (0.21 mmol, 3.2 equiv.) and further stirred for another 30 min. Then the reaction mixture was diluted with DCM and washed with saturated aq. NH_4Cl twice. The organic layer was separated and dried (Na_2SO_4), and concentrated. Pure thia-Michael products **7** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure D: **General procedure for the preparation of 2-arylnaphthalene-1,4-diones 8**: In an oven dried round bottom flask was taken 3-aryllawsone-triflates **5** (0.115 mmol, 1.0 equiv.). To this 0.44 mL HI and 0.44 mL AcOH were added and stirred at 130 °C for respective times. Then, the reaction mixture was cooled to 0 °C and added water (7.0 mL) slowly and extracted with ethyl acetate thrice. The combined organic layers were dried (Na_2SO_4), and concentrated. Pure products **8** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure E: **General procedure for aza-Michael reaction**: In an oven dried round bottom flask was taken the mixture of 2-arylnaphthalene-1,4-diones **8** (0.15 mmol, 1.0 equiv.) and chiral (*R*)-*tert*-butylsulfinamide or (*S*)-*tert*-butylsulfinamide **9** (0.3 mmol, 2.0 equiv.) in DMF (0.15 M). To this, potassium *tert*-butoxide (0.3 mmol, 2.0 equiv.) was added and allowed to stir for 2 h under air atmosphere. Allow it to stir for 30 min. and then added Et_3N (0.21 mmol, 3.2 equiv.) and further stir for another 30 min. Then the reaction mixture is diluted with DCM and washed with saturated aq. NH_4Cl twice. The organic layer was separated and dried (Na_2SO_4), and concentrated. Pure chiral products **10** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

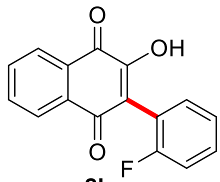
2-Hydroxy-3-phenylnaphthalene-1,4-dione (2a): Prepared by following the procedure **A**



2a

and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 78% (39.0 mg); Mp.: 116-118 °C; IR (Neat): ν_{max} 3339, 2931, 1640, 1587, 1428, 1366, 1344, 1309, 1217, 1019, 756 and 724 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.21 (1H, dd, *J* = 7.75, 1.0 Hz), 8.16 (1H, dd, *J* = 7.5, 1.0 Hz), 7.82 (1H, dt, *J* = 7.5, 1.5 Hz), 7.74 (1H, dt, *J* = 7.5, 1.0 Hz), 7.59 (1H, s, O*H*), 7.53-7.50 (2H, m), 7.46 (2H, dt, *J* = 6.75, 1.5 Hz), 7.40 (1H, tt, *J* = 7.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.7 (C, *C*=O), 181.8 (C, *C*=O), 152.2 (C, *C*-OH), 135.3 (CH), 133.1 (CH), 132.8 (C), 130.6 (2 x CH), 129.9 (C), 129.3 (C), 128.7 (CH), 127.9 (2 x CH), 127.3 (CH), 126.1 (CH), 122.1 (C); HRMS m/z 251.0706 (M + H^+), calcd for $C_{16}H_{10}O_3H$ 251.0708.

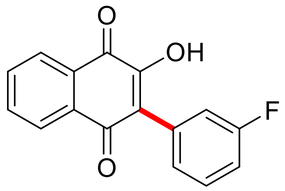
(2-(2-Fluorophenyl)-3-hydroxynaphthalene-1,4-dione (2b): Prepared by following the



2b

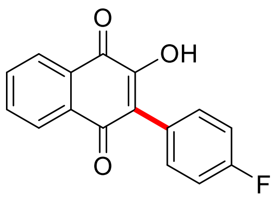
procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 84% (45.0 mg); Mp 110-112 °C; IR (Neat): ν_{max} 3343, 2924, 1660, 1610, 1592, 1337, 1264, 1214, 1117, 1001, 790, 756, and 724 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.20 (1H, dd, *J* = 7.75, 1.0 Hz), 8.18 (1H, dd, *J* = 7.5, 1.0 Hz), 7.82 (1H, dt, *J* = 7.75, 1.0 Hz), 7.75 (1H, dt, *J* = 7.75, 1.0 Hz), 7.63 (1H, s, O*H*), 7.44-7.40 (1H, m), 7.37 (1H, dt, *J* = 7.25, 1.5 Hz), 7.26-7.23 (1H, m), 7.20-7.16 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 182.7 (C, *C*=O), 181.4 (C, *C*=O), 160.1 (C, d, *J* = 248.75 Hz, *C*-F), 153.2 (C, *C*-OH), 135.4 (CH), 132.2 (CH), 132.8 (C), 132.0 (CH, d, *J* = 3.75 Hz), 130.7 (CH, d, *J* = 8.75 Hz), 129.3 (C), 127.3 (CH), 126.4 (CH), 123.7 (CH, d, *J* = 3.75 Hz), 117.9 (C, d, *J* = 16.25 Hz), 117.6 (C), 115.7 (CH, d, *J* = 21.25 Hz); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –110.6; HRMS m/z 269.0617 (M + H^+), calcd for $C_{16}H_9FO_3H$ 269.0614.

2-(3-Fluorophenyl)-3-hydroxynaphthalene-1,4-dione (2c): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 90% (48.3 mg); Mp 138-140 °C; IR (Neat): ν_{max} 3219, 2921, 2360, 2340, 1668, 1644, 1580, 1331, 1242, 1170, 1100, 1003, 893, 879, and 713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (1H, d, *J* = 8.0 Hz), 8.16 (1H, d, *J* = 7.5 Hz), 7.83 (1H, t, *J* = 7.0 Hz), 7.75 (1H, t, *J* = 7.5 Hz), 7.70 (1H, s, O*H*), 7.44-7.40 (1H, m), 7.30 (1H, d, *J* = 8.0 Hz), 7.25 (1H, d, *J* = 7.5 Hz), 7.10 (1H, dt, *J* = 8.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.3 (C, *C*=O), 181.6 (C, *C*=O), 163.3 (C, d, *J* = 243.75 Hz, *C*-F), 153.4 (C, *C*-OH), 135.4 (CH), 132.3 (CH), 132.7 (C), 131.9 (C, d, *J* = 8.75 Hz), 129.3 (CH, d, *J* = 8.75 Hz), 129.2 (C), 127.3 (CH), 126.5 (CH, d, *J* = 3.75 Hz), 126.2 (CH), 120.8 (C, d, *J* = 2.5 Hz), 117.8 (CH, d, *J* = 22.5 Hz), 115.5 (CH, d, *J* = 21.25 Hz); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −113.4; HRMS m/z 269.0613 (M + H^+), calcd for $C_{16}H_9FO_3H$ 269.0614.



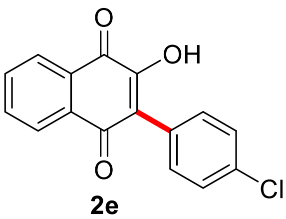
2c

2-(4-Fluorophenyl)-3-hydroxynaphthalene-1,4-dione (2d): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 84% (45.0 mg); Mp 180-182 °C; IR (Neat): ν_{max} 3330, 2926, 1664, 1645, 1593, 1352, 1233, 1079, 823 and 570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (1H, dd, *J* = 7.75, 1.0 Hz), 8.15 (1H, dd, *J* = 7.5, 1.0 Hz), 7.82 (1H, dt, *J* = 7.5, 1.0 Hz), 7.75 (1H, dt, *J* = 7.5, 1.0 Hz), 7.65 (1H, s, O*H*), 7.54-7.50 (2H, m), 7.15 (2H, t, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.6 (C, *C*=O), 181.7 (C, *C*=O), 162.7 (C, d, *J* = 247.5 Hz, *C*-F), 152.2 (C, *C*-OH), 135.3 (CH), 133.2 (CH), 132.7 (C), 132.66 (2 x CH, d, *J* = 8.75 Hz), 129.2 (C), 127.3 (CH), 126.2 (CH), 125.8 (C, d, *J* = 3.75 Hz), 121.1 (C), 115.0 (2 x CH, d, *J* = 21.25 Hz); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −112.2; HRMS m/z 269.0615 (M + H^+), calcd for $C_{16}H_9FO_3H$ 269.0614.



2d

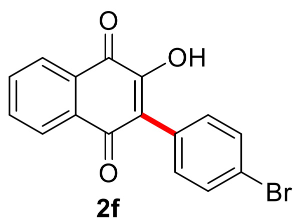
2-(4-Chlorophenyl)-3-hydroxynaphthalene-1,4-dione (2e): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 56% (31.9 mg); Mp.: 160-162 °C; IR (Neat): ν_{max} 3327,



2e

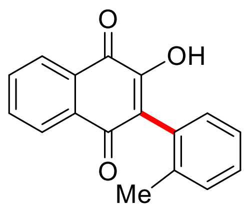
2922, 2852, 1664, 1592, 1491, 1357, 1336, 1280, 1235 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (1H, d, *J* = 7.5 Hz), 8.16 (1H, d, *J* = 7.5 Hz), 7.82 (1H, t, *J* = 7.5 Hz), 7.75 (1H, t, *J* = 7.5 Hz), 7.67 (1H, s, O*H*), 7.47 (2H, d, *J* = 8.5 Hz), 7.43 (2H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.4 (C, *C*=O), 181.6 (C, *C*=O), 152.3 (C, *C*-OH), 135.4 (CH), 134.7 (C), 133.3 (CH), 132.7 (C), 132.1 (2 x CH), 129.2 (C), 128.3 (C), 128.2 (2 x CH), 127.3 (CH), 126.2 (CH), 120.9 (C); HRMS m/z 285.0317 (M + H^+), calcd for $C_{16}H_9ClO_3H$ 285.0318.

2-(4-Bromophenyl)-3-hydroxynaphthalene-1,4-dione (2f): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 17% (11.9 mg); Mp.: 168-170 °C; IR (Neat): ν_{max} 3357, 2923, 2852, 2188, 2163, 1730, 1659, 1459, 1364, 1281, 1072 and 727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (1H, d, *J* = 7.5 Hz), 8.16 (1H, d, *J* = 7.0 Hz), 7.82 (1H, dt, *J* = 7.5, 1.0 Hz), 7.75 (1H, dt, *J* = 7.5, 1.0 Hz), 7.65 (1H, s, O*H*), 7.59 (2H, d, *J* = 8.5 Hz), 7.41 (2H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.4 (C, *C*=O), 181.6 (C, *C*=O), 152.2 (C, *C*-OH), 135.4 (CH), 133.3 (CH), 132.8 (C), 132.4 (2 x CH), 131.2 (2 x CH), 129.2 (C), 128.8 (C), 127.3 (CH), 126.2 (CH), 123.0 (C), 120.9 (C); HRMS m/z 328.9814 (M + H^+), calcd for $C_{16}H_9BrO_3H$ 328.9813.



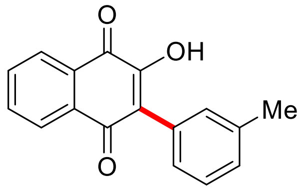
2f

2-Hydroxy-3-(o-tolyl)naphthalene-1,4-dione (2g): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 80% (42.3 mg); Mp.: 104-106 °C; IR (Neat): ν_{max} 3271, 2918, 2849, 1664, 1647, 1632, 1590, 1457, 1333, 1295, 1273, 1236, 1206, 1127, 1097, 997 and 720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (2H, dt, *J* = 7.4, 1.2 Hz), 7.82 (1H, dt, *J* = 7.8, 1.2 Hz), 7.75 (1H, dt, *J* = 7.6, 1.2 Hz), 7.46 (1H, s, O*H*), 7.35-7.26 (3H, m), 7.18 (1H, d, *J* = 7.2 Hz), 2.21 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.6 (C, *C*=O), 181.7 (C, *C*=O), 152.5 (C, *C*-OH), 137.0 (C), 135.3 (CH), 133.1 (CH), 132.9 (C), 130.1 (CH), 129.9 (CH), 129.8 (C), 129.4 (C), 128.8 (CH), 127.2 (CH), 126.2 (CH), 125.5 (CH), 123.1 (C), 20.0 (CH_3); HRMS m/z 265.0867 (M + H^+), calcd for $C_{17}H_{12}O_3H$ 265.0865.



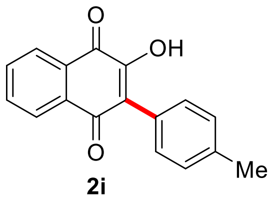
2g

2-Hydroxy-3-(m-tolyl)naphthalene-1,4-dione (2h): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 83% (43.8 mg); Mp.: 110-112 °C; IR (Neat): ν_{max} 3270, 2920, 1710, 1644, 1458, 1232, 777, 714, 663 and 527 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (1H, td, *J* = 7.0, 0.5 Hz), 8.15 (1H, td, *J* = 7.5, 0.5 Hz), 7.81 (1H, dt, *J* = 7.75, 1.5 Hz), 7.73 (1H, dt, *J* = 7.5, 1.5 Hz), 7.60 (1H, s, O*H*), 7.36 (1H, t, *J* = 8.0 Hz), 7.31-7.29 (2H, m), 7.23-7.21 (1H, m), 2.41 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.7 (C, *C*=O), 181.8 (C, *C*=O), 152.2 (C, *C*-OH), 137.5 (C), 135.2 (CH), 133.1 (CH), 132.8 (C), 131.1 (CH), 129.8 (C), 129.5 (CH), 129.3 (C), 127.8 (CH), 127.6 (CH), 127.2 (CH), 126.1 (CH), 122.4 (C), 21.5 (CH_3); HRMS m/z 265.0864 (M + H$^+$), calcd for $C_{17}H_{12}O_3H$ 265.0865.



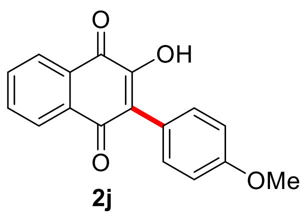
2h

2-Hydroxy-3-(p-tolyl)naphthalene-1,4-dione (2i): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 72% (38.0 mg); Mp.: 142-144 °C; IR (Neat): ν_{max} 3361, 2922, 2360, 2340, 1648, 1591, 1512, 1360, 1334, 1280, 1001, 820 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (1H, dd, *J* = 7.6, 0.8 Hz), 8.15 (1H, dd, *J* = 7.6, 1.2 Hz), 7.81 (1H, dt, *J* = 7.6, 1.6 Hz), 7.74 (1H, dt, *J* = 7.6, 1.2 Hz), 7.56 (1H, s, O*H*), 7.42 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 8.0 Hz), 2.40 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.8 (C, *C*=O), 181.8 (C, *C*=O), 152.0 (C, *C*-OH), 138.7 (C), 135.2 (CH), 133.1 (CH), 132.9 (C), 130.5 (2 x CH), 129.3 (C), 128.7 (2 x CH), 127.2 (CH), 126.9 (C), 126.1 (CH), 122.3 (C), 21.4 (CH_3); HRMS m/z 265.0869 (M + H$^+$), calcd for $C_{17}H_{12}O_3H$ 265.0865.



2i

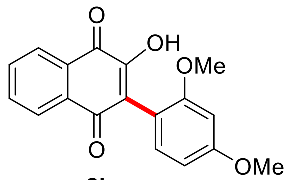
2-Hydroxy-3-(4-methoxyphenyl)naphthalene-1,4-dione (2j): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as red solid. Yield: 73% (40.9 mg); Mp.: 134-136 °C; IR (Neat): ν_{max} 3360, 2922, 2851, 1648, 1605, 1590, 1359, 1277, 1251, 1180, 1028, 819 and 723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (1H, d, *J* = 7.6 Hz), 8.13 (1H, d, *J* = 7.6 Hz), 7.80 (1H, t, *J* = 7.6 Hz), 7.72 (1H, t, *J* = 7.2 Hz), 7.61 (1H, s, O*H*), 7.51 (2H, d, *J* = 8.8 Hz), 7.00 (2H, d, *J* = 8.8 Hz), 3.86 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.0 (C,



2j

C=O), 181.7 (C, *C*=O), 159.8 (C), 151.8 (C, *C*-OH), 135.1 (CH), 133.1 (CH), 132.8 (C), 132.2 (2 x CH), 129.3 (C), 127.2 (CH), 126.0 (CH), 122.1 (C), 121.8 (C), 113.4 (2 x CH), 55.3 (CH_3, O*C*H_3); HRMS m/z 281.0815 (M + H^+), calcd for $C_{17}H_{12}O_4H$ 281.0814.

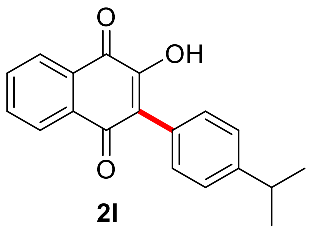
2-(2,4-Dimethoxyphenyl)-3-hydroxynaphthalene-1,4-dione (2k): Prepared by following



2k

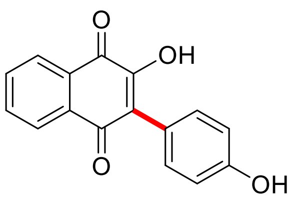
the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 73% (45.3 mg); Mp.: 178-180 °C; IR (Neat): ν_{max} 3308, 2924, 1663, 1648, 1608, 1507, 1367, 1333, 1302, 1256, 1207, 1037, 998 and 724 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.17 (1H, dd, *J* = 7.5, 1.5 Hz), 8.14 (1H, dd, *J* = 7.75, 1.5 Hz), 7.78 (1H, dt, *J* = 7.5, 1.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.5 Hz), 7.39 (1H, s, O*H*), 7.17 (1H, d, *J* = 8.5 Hz), 6.60 (1H, dd, *J* = 8.25, 2.5 Hz), 6.58 (1H, d, *J* = 2.5 Hz), 3.85 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.4 (C, *C*=O), 181.8 (C, *C*=O), 161.6 (C), 158.4 (C), 152.8 (C, *C*-OH), 135.0 (CH), 133.2 (C), 132.9 (CH), 131.9 (CH), 129.6 (C), 127.2 (CH), 126.1 (CH), 120.8 (C), 111.9 (C), 104.7 (CH), 99.1 (CH), 55.7 (CH_3, O*C*H_3), 55.4 (CH_3, O*C*H_3); HRMS m/z 311.0920 (M + H^+), calcd for $C_{18}H_{14}O_5H$ 311.0919.

2-Hydroxy-3-(4-isopropylphenyl)naphthalene-1,4-dione (2l): Prepared by following the



2l

procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 60% (35.1 mg); Mp.: 130-132 °C; IR (Neat): ν_{max} 2919, 2850, 1697, 1610, 1462, 1423, 1283, 935 and 777 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.20 (1H, d, *J* = 7.6 Hz), 8.15 (1H, d, *J* = 7.6 Hz), 7.82-7.79 (1H, m), 7.73 (1H, t, *J* = 7.60 Hz), 7.47 (2H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 8.4 Hz), 2.96 (1H, septet, *J* = 7.2 Hz), 1.29 (6H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.9 (C, *C*=O), 181.8 (C, *C*=O), 152.0 (C, *C*-OH), 149.4 (C), 135.2 (CH), 133.1 (CH), 132.8 (C), 130.6 (2 x CH), 129.3 (C), 127.3 (CH), 127.2 (C), 126.1 (2 x CH), 126.0 (CH), 122.2 (C), 34.4 (CH), 23.8 (2 x CH_3); HRMS m/z 315.0998 (M + Na^+), calcd for $C_{19}H_{16}O_3Na$ 315.0997.

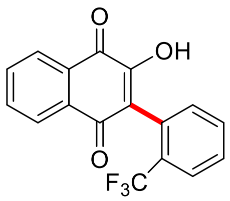


2m

2-Hydroxy-3-(4-hydroxyphenyl)naphthalene-1,4-dione (2m): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as brown solid.

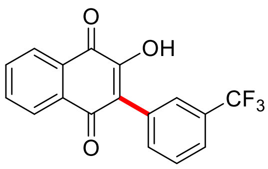
Yield: 55% (29.3 mg); Mp.: 200-202 °C; IR (Neat): ν_{max} 3338, 2480, 2012, 1655, 1578, 1513, 1340, 1234, 1174, 1084, 1002 824 and 713 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 8.10 (2H, d, *J* = 6.5 Hz), 7.79 (2H, td, *J* = 22.0, 7.0 Hz), 7.35 (2H, d, *J* = 8.0 Hz), 6.87 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 186.3 (C, *C*=O), 183.0 (C, *C*=O), 158.5 (C, *C*-OH), 155.7 (C), 135.7 (CH), 134.3 (CH), 134.2 (C), 133.6 (2 x CH), 131.7 (C), 127.7 (CH), 126.8 (CH), 123.9 (C), 123.4 (C), 115.6 (2 x CH); HRMS m/z 289.0485 (M + Na$^+$), calcd for $C_{16}H_{10}O_4Na$ 289.0477.

2-Hydroxy-3-(2-(trifluoromethyl)phenyl)naphthalene-1,4-dione (2n): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 67% (42.6 mg); Mp.: 172-174 °C; IR (Neat): ν_{max} 3376, 1641, 1586, 1368, 1352, 1308, 1231, 1145, 1037, 792 and 727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (1H, dd, *J* = 4.25, 1.0 Hz), 8.18 (1H, dd, *J* = 4.0, 1.0 Hz), 7.83 (1H, dt, *J* = 7.5, 1.0 Hz), 7.80 (1H, d, *J* = 8.0 Hz), 7.77 (1H, dt, *J* = 8.0, 1.5 Hz), 7.64 (1H, t, *J* = 7.5 Hz), 7.56 (1H, t, *J* = 7.5 Hz), 7.46 (1H, s, O*H*), 7.30 (1H, d, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.3 (C, *C*=O), 181.4 (C, *C*=O), 152.7 (C, *C*-OH), 135.4 (CH), 133.3 (CH), 132.7 (C), 131.7 (CH), 131.3 (CH), 129.4 (C, q, *J* = 30.0 Hz), 129.3 (C), 128.8 (C), 127.3 (C), 126.47 (2 x CH, q, *J* = 15.0 Hz), 126.5 (2 x CH), 123.9 (C, q, *J* = 268.75 Hz, *C*F_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –60.8; HRMS m/z 341.0405 (M + Na$^+$), calcd for $C_{17}H_9F_3O_3Na$ 341.0401.



2n

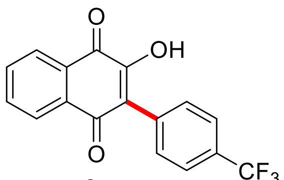
(2-Hydroxy-3-(3-(trifluoromethyl)phenyl)naphthalene-1,4-dione (2o): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 66% (42.0 mg); Mp.: 90-92 °C; IR (Neat): ν_{max} 3356, 2922, 2564, 1686, 1420, 1331, 1265, 1168, 1119, 1091, 1070, 919 and 683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.21 (1H, dd, *J* = 7.75, 1.0 Hz), 8.17 (1H, dd, *J* = 7.5, 1.0 Hz), 7.84 (1H, dt, *J* = 7.5, 1.5 Hz), 7.81 (1H, s), 7.76 (1H, dt, *J* = 7.5, 1.5 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.65 (1H, d, *J* = 7.5 Hz), 7.58 (1H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.3 (C, *C*=O), 181.6 (C, *C*=O), 152.6 (C, *C*-OH), 135.5 (CH), 134.1 (CH), 133.4 (CH), 132.7 (C), 130.8 (C), 130.5 (C), 130.4 (C, q, *J* = 32.5 Hz), 129.2 (C), 128.3 (CH), 127.7 (CH, q, *J* = 3.75



2o

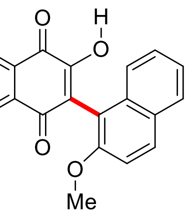
Hz), 127.4 (CH), 126.3 (CH), 125.3 (CH, q, J = 3.75 Hz), 124.1 (C, q, J = 270.0 Hz, CF_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −62.6; HRMS m/z 319.0579 (M + H^+), calcd for $C_{17}H_9F_3O_3H$ 319.0582.

2-Hydroxy-3-(4-(trifluoromethyl)phenyl)naphthalene-1,4-dione (2p): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 71% (45.2 mg); Mp.: 208-210 °C; IR (Neat): ν_{max} 3330, 3116, 2918, 2849, 1666, 1632, 1591, 1359, 1327, 1280, 1079, 1064, 1002, 887 and 723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (1H, dd, J = 7.5, 1.0 Hz), 8.18 (1H, dd, J = 7.5, 1.0 Hz), 7.84 (1H, dt, J = 7.5, 1.0 Hz), 7.77 (1H, dt, J = 7.5, 1.5 Hz), 7.72 (2H, d, J = 8.0 Hz), 7.64 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.2 (C, *C*=O), 181.6 (C, *C*=O), 152.6 (C, *C*-OH), 135.6 (CH), 133.7 (C), 133.4 (CH), 132.7 (C), 131.1 (2 x CH), 130.6 (C), 130.5 (C, q, J = 32.5 Hz), 129.2 (C), 127.4 (CH), 126.3 (CH), 124.8 (2 x CH, q, J = 3.75 Hz), 124.1 (C, q, J = 271.2 Hz, CF_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −62.8; HRMS m/z 319.0586 (M + H^+), calcd for $C_{17}H_9F_3O_3H$ 319.0582.

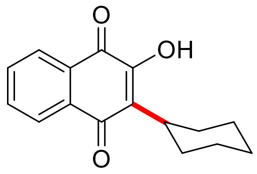


2p

(3'-Hydroxy-2-methoxy-[1,2'-binaphthalene]-1',4'-dione (2q): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 30% (19.8 mg); Mp.: 128-130 °C; IR (Neat): ν_{max} 3351, 2923, 2859, 2125, 1736, 1666, 1593, 1509, 1266, 1073, 1043, 993, and 727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.21 (2H, dt, J = 7.25, 1.0 Hz), 7.95 (1H, d, J = 9.0 Hz), 7.84 (1H, d, J = 8.0 Hz), 7.82 (1H, dt, J = 7.25, 1.5 Hz), 7.76 (1H, dt, J = 7.5, 1.5 Hz), 7.48 (1H, d, J = 8.5 Hz), 7.41-7.39 (2H, m), 7.37 (1H, s, O*H*), 7.34 (1H, dt, J = 8.0, 1.5 Hz), 3.88 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.2 (C, *C*=O), 181.5 (C, *C*=O), 154.9 (C), 153.7 (C, *C*-OH), 135.1 (CH), 133.3 (C), 133.0 (CH), 132.4 (C), 130.9 (CH), 129.7 (C), 129.1 (C), 128.4 (CH), 127.3 (CH), 126.8 (CH), 126.3 (CH), 124.2 (CH), 123.7 (CH), 119.3 (C), 113.4 (C), 113.37 (CH), 56.7 (CH_3, O*C*H_3); HRMS m/z 331.0972 (M + H^+), calcd for $C_{21}H_{14}O_4H$ 331.0970.

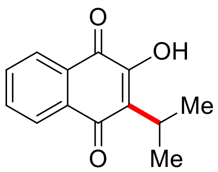
2q


2-Cyclohexyl-3-hydroxynaphthalene-1,4-dione (2r): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 74% (37.9 mg); Mp.: 98-100 °C; IR (Neat): ν_{max} 3360, 2923, 2851, 2360, 1646, 1595, 1382, 1338, 1274, 1238, 1056, 1003, 939 and 724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (1H, d, J = 7.5 Hz), 8.05 (1H, d, J = 7.5 Hz), 7.74 (1H, dt, J = 7.5, 1.5 Hz), 7.66 (1H, dt, J = 7.5, 1.0 Hz), 7.50 (1H, s, O*H*), 3.08 (1H, tt, J = 12.5, 5.0 Hz), 2.01-1.94 (2H, m), 1.81 (2H, d, J = 12.5 Hz), 1.73 (1H, d, J = 11.0 Hz), 1.61 (1H, d, J = 13.0 Hz), 1.42-1.25 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.5 (C, *C*=O), 181.9 (C, *C*=O), 152.8 (C, *C*-OH), 134.8 (CH), 133.2 (C), 132.6 (CH), 129.2 (C), 127.9 (C), 126.9 (CH), 125.9 (CH), 35.2 (CH), 29.2 (2 x CH_2), 26.7 (2 x CH_2), 25.9 (CH_2); HRMS m/z 257.1177 (M + H^+), calcd for $C_{16}H_{16}O_3H$ 257.1178.



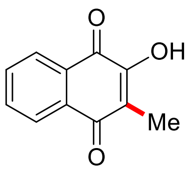
2r

2-Hydroxy-3-isopropylnaphthalene-1,4-dione (2s): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 81% (35.0 mg); Mp.: 145-147 °C; IR (Neat): ν_{max} 3368, 2921, 2851, 1710, 1661, 1595, 1269, 1121, 1013 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (1H, dd, J = 8.0, 1.0 Hz), 8.06 (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, 1.5 Hz), 7.43 (1H, d, J = 2.0 Hz, O*H*), 3.42 (1H, septet, J = 7.5 Hz), 1.31 (6H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.4 (C, *C*=O), 181.9 (C, *C*=O), 152.7 (C, *C*-OH), 134.9 (CH), 133.1 (C), 132.7 (CH), 129.2 (C), 128.7 (C), 126.9 (CH), 125.9 (CH), 24.6 (C), 19.8 (2 x CH_3); HRMS m/z 217.0858 (M + H^+), calcd for $C_{13}H_{12}O_3H$ 217.0865.



2s

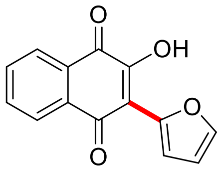
2-Hydroxy-3-methylnaphthalene-1,4-dione (2t): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as brown solid. Yield: 53% (19.9 mg); Mp.: 128-130 °C; IR (Neat): ν_{max} 3321, 2920, 1738, 1651, 1588, 1457, 1390, 1339, 1302, 1274, 1204, 1178, 1069, 1026, 935 and 721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (1H, dd, J = 7.75, 0.5 Hz), 8.07 (1H, dd, J = 7.25, 0.5 Hz), 7.75 (1H, dt, J = 7.5, 1.0 Hz), 7.68 (1H, dt, J = 7.5, 1.5 Hz), 7.32 (1H, s, O*H*), 2.11 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 185.0 (C, *C*=O), 181.2 (C, *C*=O), 153.1 (C, *C*-OH), 134.8 (CH), 132.9 (C), 132.88 (CH),



2t

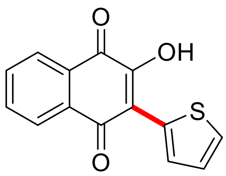
129.4 (C), 126.7 (CH), 126.1 (CH), 120.5 (C), 8.6 (CH_3); HRMS m/z 189.0553 (M + H^+), calcd for $C_{11}H_8O_3H$ 189.0552.

2-(Furan-2-yl)-3-hydroxynaphthalene-1,4-dione (2u): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as brown solid. Yield: 44% (21.1 mg); Mp.: 128-130 °C; IR (Neat): ν_{max} 3326, 1656, 1620, 1591, 1458, 1394, 1357, 1331, 1282, 1039, 1008, 874 and 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (1H, d, J = 7.5 Hz), 8.14 (1H, s), 8.11 (1H, d, J = 7.5 Hz), 7.79 (1H, dt, J = 7.5, 0.5 Hz), 7.72 (1H, dt, J = 7.5, 0.5 Hz), 7.69 (1H, s, O*H*), 7.43 (1H, d, J = 3.5 Hz), 6.62 (1H, q, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 182.3 (C, *C*=O), 181.0 (C, *C*=O), 150.0 (C, *C*-OH), 145.9 (C), 143.9 (CH), 135.1 (CH), 133.3 (CH), 132.8 (C), 129.2 (C), 127.1 (CH), 126.1 (CH), 117.0 (CH), 112.3 (C), 112.1 (CH); HRMS m/z 263.0324 (M + Na^+), calcd for $C_{14}H_8O_4Na$ 263.0320.



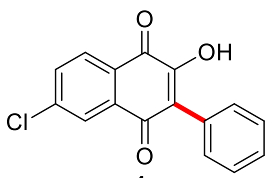
2u

2-Hydroxy-3-(thiophen-2-yl)naphthalene-1,4-dione (2v): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as brown solid. Yield: 47% (24.1 mg); Mp 138-140 °C; IR (Neat): ν_{max} 3316, 2920, 1647, 1589, 1375, 1352, 1325, 1281, 1229, 877 and 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (1H, dd, J = 4.0, 1.0 Hz), 8.21 (1H, dd, J = 7.5, 1.0 Hz), 8.11 (1H, dd, J = 7.5, 1.0 Hz), 7.79 (1H, dt, J = 7.5, 1.0 Hz), 7.72 (1H, dt, J = 7.75, 1.5 Hz), 7.62 (1H, dd, J = 5.5, 1.0 Hz), 7.20 (1H, dd, J = 5.5, 4.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.7 (C, *C*=O), 180.9 (C, *C*=O), 150.1 (C, *C*-OH), 135.2 (CH), 133.4 (CH), 132.6 (C), 132.5 (CH), 131.1 (C), 131.1 (CH), 129.1 (C), 127.5 (CH), 126.8 (CH), 126.1 (CH), 116.0 (C); HRMS m/z 257.0276 (M + H^+), calcd for $C_{14}H_8O_3SH$ 257.0272.



2v

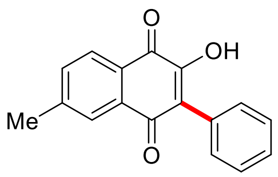
6-Chloro-2-hydroxy-3-phenylnaphthalene-1,4-dione (4a): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as red solid. Mp 106-108 °C; Yield: 70% (39.8 mg); IR (Neat): ν_{max} 3336, 2921, 2851, 2359, 1701, 1663, 1639, 1620, 1308, 1285, 1119, 768 and 743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500



4a

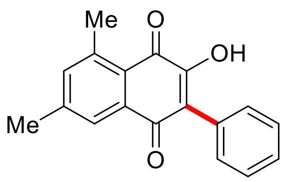
MHz) δ 8.16 (1H, d, J = 2.0 Hz), 8.10 (1H, d, J = 8.0 Hz), 7.70 (1H, dd, J = 8.5, 2.0 Hz), 7.61 (1H, s, OH), 7.51-7.45 (4H, m), 7.41 (1H, tt, J = 4.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 182.5 (C, C=O), 180.9 (C, C=O), 152.3 (C, C-OH), 142.4 (C), 134.1 (C), 133.2 (CH), 130.6 (2 x CH), 129.6 (C), 128.8 (CH), 128.0 (2 x CH), 127.7 (CH), 127.5 (C), 127.49 (CH), 122.3 (C); HRMS m/z 285.0316 (M + H^+), calcd for $C_{16}H_9ClO_3H$ 285.0318.

2-Hydroxy-6-methyl-3-phenylnaphthalene-1,4-dione (4b): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 70% (37.0 mg); Mp.: 140-142 °C; IR (Neat): ν_{max} 3348, 2961, 2150, 2031, 1652, 1595, 1366, 1259, 1089, 1015, 797 and 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (1H, d, J = 7.5 Hz), 8.00 (1H, brs), 7.62 (1H, s, OH), 7.54-7.50 (3H, m), 7.48-7.45 (2H, m), 7.40 (1H, tt, J = 7.5, 1.0 Hz), 2.53 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.0 (C, C=O), 181.5 (C, C=O), 152.3 (C, C-OH), 146.9 (C), 133.7 (CH), 132.8 (C), 130.6 (2 x CH), 130.1 (C), 128.5 (CH), 127.9 (2 x CH), 127.8 (CH), 127.0 (C), 126.4 (CH), 121.8 (C), 22.1 (CH_3); HRMS m/z 265.0865 (M + H^+), calcd for $C_{17}H_{12}O_3H$ 265.0865.

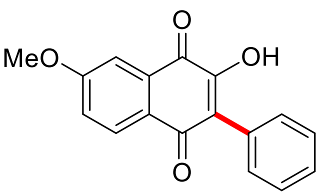


4b

3-Hydroxy-5,7-dimethyl-2-phenylnaphthalene-1,4-dione (4c): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 54% (30.0 mg); Mp.: 160-162 °C; IR (Neat): ν_{max} 3326, 3045, 2918, 1738, 1644, 1596, 1362, 1342, 1232, 1073, 1040, 999 and 682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (1H, d, J = 0.5 Hz), 7.91 (1H, s), 7.53-7.51 (2H, m), 7.45 (2H, tt, J = 7.5, 1.0 Hz), 7.38 (1H, tt, J = 7.5, 1.5 Hz), 7.32 (1H, s, OH), 2.77 (3H, s, CH_3), 2.47 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.1 (C, C=O), 182.5 (C, C=O), 152.7 (C, C-OH), 145.9 (C), 142.0 (C), 137.3 (CH), 134.4 (C), 130.6 (2 x CH), 130.2 (C), 128.4 (CH), 127.9 (2 x CH), 126.8 (CH), 124.5 (C), 120.3 (C), 22.6 (CH_3), 21.9 (CH_3); HRMS m/z 279.1022 (M + H^+), calcd for $C_{18}H_{14}O_3H$ 279.1021.



4c

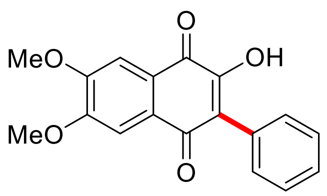


4d

3-Hydroxy-6-methoxy-2-phenylnaphthalene-1,4-dione (4d): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as red solid.

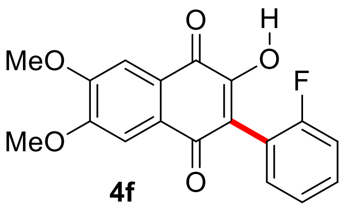
Yield: 62% (34.7 mg); Mp.: 197-199 °C; IR (Neat): ν_{max} 3373, 2947, 1656, 1588, 1366, 1319, 1260, 1166, 1033, 925, 877 and 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (1H, d, *J* = 8.5 Hz), 7.58 (1H, d, *J* = 3.0 Hz), 7.51-7.44 (5H, m), 7.39 (1H, tt, *J* = 7.5, 1.5 Hz), 7.26 (1H, dd, *J* = 8.5, 2.5 Hz), 3.96 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.1 (C, *C*=O), 182.0 (C, *C*=O), 163.5 (C), 151.9 (C, *C*-OH), 131.0 (C), 130.7 (2 x CH), 130.1 (C), 129.6 (CH), 128.6 (CH), 127.9 (2 x CH), 126.1 (C), 121.9 (C), 121.3 (CH), 109.7 (CH), 56.0 (CH_3, OCH_3); HRMS m/z 281.0818 (M + H^+), calcd for $C_{17}H_{12}O_4H$ 281.0814.

2-Hydroxy-6-methoxy-7-methyl-3-phenylnaphthalene-1,4-dione (4e): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as red solid. Yield: 60% (35.2 mg); Mp.: 200-202 °C; IR (Neat): ν_{max} 3319, 2362, 1640, 1573, 1506, 1312, 1270, 1219, 1154, 1071, 977 and 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (1H, s), 7.59 (1H, s), 7.53 (1H, s, O*H*), 7.50 (1H, t, *J* = 1.5 Hz), 7.49 (1H, d, *J* = 1.0 Hz), 7.45 (2H, tt, *J* = 7.5, 1.5 Hz), 7.39 (1H, tt, *J* = 7.0, 1.5 Hz), 4.04 (3H, s, OCH_3), 4.03 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.4 (C, *C*=O), 181.0 (C, *C*=O), 154.8 (C), 152.8 (C, *C*-OH), 152.1 (C), 130.6 (2 x CH), 130.2 (C), 128.4 (CH), 128.1 (C), 127.8 (2 x CH), 123.4 (C), 121.0 (C), 109.0 (CH), 107.5 (CH), 56.6 (CH_3, OCH_3), 56.52 (CH_3, OCH_3); HRMS m/z 311.0919 (M + H^+), calcd for $C_{18}H_{14}O_5H$ 311.0919.



4e

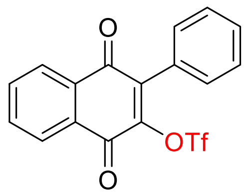
2-(3-Fluorophenyl)-3-hydroxy-6,7-dimethoxynaphthalene-1,4-dione (4f): Prepared by following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as dark orange solid. Yield: 82% (53.8 mg); Mp.: 208-210 °C; IR (Neat): ν_{max} 3318, 2923, 2174, 2037, 1989, 1646, 1580, 1510, 1362, 1325, 1303, 1280, 1213, 1041, 891 and 784 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1H, s, O*H*), 7.60 (1H, s), 7.52 (1H, s), 7.42-7.38 (1H, m), 7.28 (1H, d, *J* = 7.5 Hz), 7.23 (1H, td, *J* = 10.0, 1.0 Hz), 7.08 (1H, dt, *J* = 8.5, 2.0 Hz), 4.03 (3H, s, OCH_3), 4.026 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.0 (C, *C*=O), 180.6 (C, *C*=O), 162.2 (C, d, *J* = 243.75 Hz, *C*-F), 154.8 (C, *C*-OH), 152.8 (C), 152.3 (C), 132.1 (C, d, *J* = 8.75 Hz), 129.2 (CH, d, *J* = 7.5 Hz), 127.9 (C), 126.4 (CH, d, *J* = 2.5 Hz), 123.2 (C), 119.6 (C, d, *J* = 2.5 Hz), 117.7 (CH, d, *J* = 22.5 Hz),



4f

115.3 (CH, d, J = 21.25 Hz), 109.0 (CH), 107.5 (CH), 56.6 (CH_3, OCH_3), 56.5 (CH_3, OCH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ □113.6; HRMS m/z 329.0828 (M + H^+), calcd for $C_{18}H_{13}FO_5H$ 329.0825.

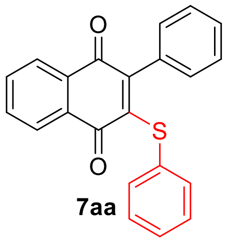
1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate (5a):



5a

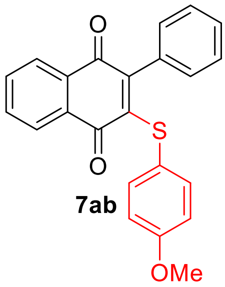
Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 82% (62.7 mg); Mp.: 150-152 °C; IR (Neat): ν_{max} 2920, 2851, 1742, 1671, 1621, 1592, 1493, 1267, 1046, 968, 846 and 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (1H, dd, J = 5.75, 3.0 Hz), 8.14 (1H, dd, J = 5.5, 4.0 Hz), 7.86 (2H, dd, J = 5.5, 3.5 Hz), 7.51 (3H, d, J = 7.0 Hz), 7.40 (2H, dd, J = 7.25, 1.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 182.9 (C, C=O), 177.7 (C, C=O), 148.2 (C), 138.2 (C), 135.1 (CH), 134.7 (CH), 131.6 (C), 130.5 (CH), 130.3 (2 x CH), 130.0 (C), 128.2 (2 x CH), 127.5 (CH), 127.05 (C), 127.03 (CH), 118.0 (C, q, J = 318.75 Hz, CF_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –74.51; HRMS m/z 405.0022 (M + Na^+), calcd for $C_{17}H_9F_3O_5SNa$ 405.0020.

2-Phenyl-3-(phenylthio)naphthalene-1,4-dione (7aa): Prepared by following the procedure



7aa

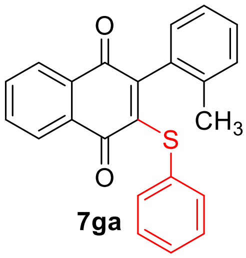
C and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 92% (20.5 mg); Mp.: 124-126 °C; IR (Neat): ν_{max} 3052, 1669, 1650, 1584, 1492, 1470, 1312, 1278, 1253, 1121, 1067, 1023, 807 and 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (1H, dd, J = 7.25, 1.5 Hz), 8.06 (1H, dd, J = 7.5, 1.0 Hz), 7.76 (1H, dt, J = 7.5, 1.5 Hz), 7.72 (1H, dt, J = 7.5, 1.5 Hz), 7.37-7.35 (3H, m), 7.24-7.19 (4H, m), 7.17-7.14 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 182.1 (C, C=O), 181.4 (C, C=O), 148.1 (C), 147.9 (C), 134.0 (CH), 133.65 (CH), 133.6 (C), 133.4 (C), 132.6 (C), 132.1 (C), 131.6 (2 x CH), 129.7 (2 x CH), 128.9 (2 x CH), 128.9 (CH), 127.8 (2 x CH), 127.5 (CH), 126.93 (CH), 126.9 (CH); HRMS m/z 343.0791 (M + H^+), calcd for $C_{22}H_{14}O_2SH$ 343.0793.



7ab

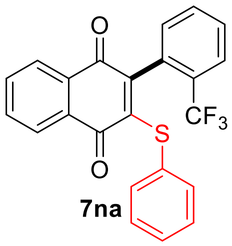
2-((4-Methoxyphenyl)thio)-3-phenylnaphthalene-1,4-dione (7ab): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane and isolated as red solid. Yield: 90% (21.8 mg); Mp.: 120-122 °C; IR (Neat): ν_{max} 2988, 1731, 1372, 1222, 1036, 829, 662, and 608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.12-8.10 (1H, m), 8.06-8.04 (1H, m), 7.74 (1H, dt, J = 7.25, 1.5 Hz), 7.71 (1H, dt, J = 7.0, 1.0 Hz), 7.36-7.34 (3H, m), 7.19-7.17 (2H, m), 7.15 (1H, d, J = 2.0 Hz), 7.14 (1H, d, J = 2.0 Hz), 6.67 (1H, d, J = 2.0 Hz), 6.66 (1H, d, J = 2.0 Hz), 3.75 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 182.1 (C, C=O), 181.9 (C, C=O), 159.5 (C), 148.8 (C), 146.6 (C), 134.3 (2 x CH), 133.9 (CH), 133.5 (CH), 133.47 (C), 132.6 (C), 132.1 (C), 129.7 (2 x CH), 128.7 (CH), 127.8 (2 x CH), 126.9 (CH), 126.8 (CH), 123.4 (C), 114.5 (2 x CH), 55.3 (CH_3, OCH_3); HRMS m/z 373.0896 (M + H^+), calcd for $C_{23}H_{16}O_3SH$ 373.0898.

2-(Phenylthio)-3-(o-tolyl)naphthalene-1,4-dione (7ga): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane and isolated as red semi-solid. Yield: 90% (20.8 mg); IR (Neat): ν_{max} 2921, 2852, 2360, 2337, 1668, 1591, 1276, 1255, 1128, 1084, 1128, 819, 748 and 716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.13-8.11 (1H, m), 8.07-8.05 (1H, m), 7.75 (1H, dt, J = 7.25, 1.5 Hz), 7.72 (1H, dt, J = 7.5, 1.5 Hz), 7.27 (1H, dt, J = 7.5, 1.5 Hz), 7.24-7.21 (2H, m), 7.20-7.17 (5H, m), 7.04 (1H, d, J = 1.5 Hz), 2.13 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 181.7 (C, C=O), 181.2 (C, C=O), 148.5 (C), 148.4 (C), 135.8 (C), 134.0 (CH), 133.6 (CH), 133.59 (C), 132.9 (C), 132.7 (C), 132.2 (C), 131.9 (2 x CH), 130.3 (CH), 128.93 (CH), 128.9 (2 x CH), 128.8 (CH), 127.7 (CH), 127.0 (CH), 126.9 (CH), 125.6 (CH), 20.0 (CH_3); HRMS m/z 357.0948 (M + H^+), calcd for $C_{23}H_{16}O_2SH$ 357.0949.



7ga

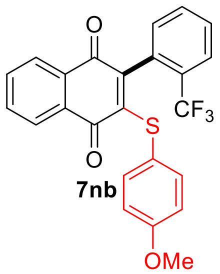
2-(Phenylthio)-3-(2-(trifluoromethyl)phenyl)naphthalene-1,4-dione (7na): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane and isolated as red solid. Yield: 93% (24.8 mg); Mp.: 141-143 °C; The enantiomers of **7na** were seperated by chiral stationary phase HPLC using a Daicel chiralpak ID column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R =



7na

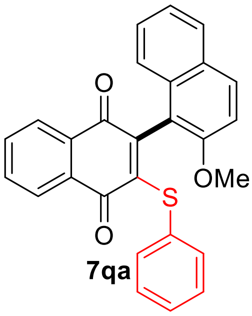
8.72 min (enantiomer I), t_R = 9.45 min (enantiomer II); IR (Neat): ν_{max} 3072, 2964, 2167, 1730, 1660, 1591, 1315, 1277, 1170, 1127, 1074, 768 and 747 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.12 (1H, dd, *J* = 7.5, 1.5 Hz), 8.06 (1H, dd, *J* = 7.5, 2.0 Hz), 7.77-7.71 (3H, m), 7.58 (1H, t, *J* = 7.5 Hz), 7.52 (1H, t, *J* = 7.5 Hz), 7.29-7.27 (2H, m), 7.23-7.19 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 181.6 (C, *C*=O), 180.5 (C, *C*=O), 148.1 (C), 146.9 (C), 134.1 (CH), 133.8 (CH), 132.7 (C), 132.68 (C), 132.2 (C), 131.93 (C), 131.87 (2 x CH), 131.7 (CH), 130.4 (CH), 129.1 (2 x CH), 129.0 (CH), 128.5 (C, q, *J* = 30.0 Hz), 127.9 (CH), 127.1 (CH), 126.9 (CH), 126.6 (CH, q, *J* = 5.0 Hz), 123.9 (C, q, *J* = 271.25 Hz, CF_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –59.6; HRMS m/z 411.0666 (M + H^+), calcd for $C_{23}H_{13}F_3O_2SH$ 411.0667.

2-((4-Methoxyphenyl)thio)-3-(2-(trifluoromethyl)phenyl)naphthalene-1,4-dione (7nb): Prepared by following the procedure **C** and purified by column chromatography using



7nb

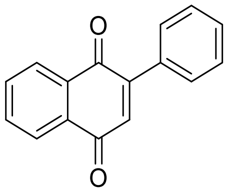
EtOAc/hexane and isolated as red semi solid; Yield: 92% (26.3 mg); The enantiomers of **7nb** were seperated by chiral stationary phase HPLC using a Daicel chiralpak ID column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.07 min (enantiomer I), t_R = 16.94 min (enantiomer II); IR (Neat): ν_{max} 2929, 1658, 1591, 1493, 1314, 1277, 1249, 1170, 1126, 1075, 1050, 767 and 716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.10-8.08 (1H, m), 8.06-8.04 (1H, m), 7.76-7.71 (2H, m), 7.70-7.68 (1H, m), 7.55 (1H, t, *J* = 7.5 Hz), 7.49 (1H, t, *J* = 8.0 Hz), 7.28 (1H, d, *J* = 2.0 Hz), 7.22 (1H, d, *J* = 2.0 Hz), 7.20 (1H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 2.0 Hz), 6.71 (1H, d, *J* = 2.0 Hz), 3.76 (3H, s, OC*H*3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 181.6 (C, *C*=O), 181.1 (C, *C*=O), 159.8 (C), 149.0 (C), 145.2 (C), 134.7 (2 x CH), 134.0 (CH), 133.7 (CH), 132.6 (CH), 132.1 (C), 131.9 (C), 131.6 (C), 130.6 (CH), 128.9 (CH), 128.3 (C, q, *J* = 30.0 Hz), 127.0 (CH), 126.8 (CH), 126.6 (CH, q, *J* = 5.0 Hz), 123.9 (C, q, *J* = 272.5 Hz, CF_3), 122.1 (C), 114.6 (2 x CH), 55.3 (CH_3, OCH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –59.6; HRMS m/z 441.0773 (M + H^+), calcd for $C_{24}H_{15}F_3O_3SH$ 441.0772.



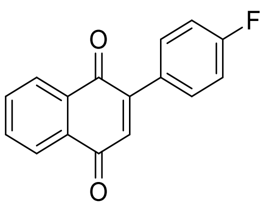
7qa

2-Methoxy-3'-(phenylthio)-[1,2'-binaphthalene]-1',4'-dione (7qa): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane and isolated as orange solid. Yield: 95% (26.08 mg); Mp.: 146-148 °C; The enantiomers of **7qa** were seperated by chiral stationary phase HPLC using a Daicel chiralpak ID column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 20.94 min (enantiomer I), t_R = 25.67 min (enantiomer II); IR (Neat): ν_{max} 2982, 2001, 1736, 1462, 1446, 1235, 1044, 934, 846, 787 and 723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.14-8.12 (2H, m), 7.81 (1H, d, J = 9.0 Hz), 7.78 (1H, d, J = 8.5 Hz), 7.76-7.73 (2H, m), 7.48 (1H, d, J = 8.5 Hz), 7.42 (1H, dt, J = 6.75, 1.5 Hz), 7.35-7.32 (1H, m), 7.14 (1H, d, J = 9.0 Hz), 7.07-7.04 (3H, m), 7.01-6.98 (2H, m), 3.83 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 181.46 (C, C=O), 181.40 (C, C=O), 154.0 (C), 149.8 (C), 144.4 (C), 133.9 (CH), 133.4 (CH), 132.8 (C), 132.7 (C), 132.14 (C), 132.1 (2 x CH), 131.8 (C), 131.0 (CH), 128.7 (C), 128.4 (CH), 128.3 (2 x CH), 127.6 (CH), 127.06 (CH), 127.04 (CH), 126.99 (CH), 123.8 (CH), 123.6 (CH), 116.4 (C), 112.5 (CH), 56.1 (CH_3, OCH_3); HRMS m/z 423.1054 (M + H^+), calcd for $C_{27}H_{18}O_3SH$ 423.1055.

2-Phenylnaphthalene-1,4-dione (8a): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid; Yield: 76% (20.5 mg); Mp.: 97-99 °C; IR (Neat): ν_{max} 2922, 2852, 1662, 1587, 1331, 1304, 1242, 1081, 898 and 756 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.19-8.18 (1H, m), 8.13-8.11 (1H, m), 7.80-7.76 (2H, m), 7.57 (2H, dd, J = 7.5, 2.5 Hz), 7.47 (3H, dd, J = 5.0, 1.5 Hz), 7.08 (1H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 185.1 (C, C=O), 184.4 (C, C=O), 148.1 (C), 135.2 (CH), 133.9 (CH), 133.8 (CH), 133.4 (C), 132.4 (C), 132.1 (C), 130.0 (CH), 129.4 (2 x CH), 128.4 (2 x CH), 127.0 (CH), 125.9 (CH); HRMS m/z 235.0755 (M + H^+), calcd for $C_{16}H_{10}O_2H$ 235.0759.



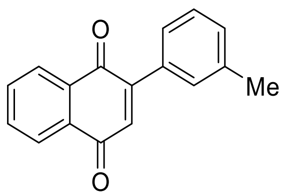
8a



8d

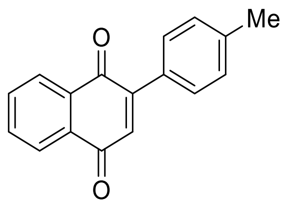
2-(4-Fluorophenyl)naphthalene-1,4-dione (8d): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid; Yield: 70% (20.3 mg); Mp.: 116-118 °C; IR (Neat): ν_{max} 2921, 2851, 1667, 1589, 1545, 1505, 1327, 1252, 1226, 1160, 1111, 1001, 793 and 726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19-8.17 (1H, m), 8.13-8.11 (1H, m), 7.80-7.78 (2H, m), 7.60-7.57 (2H, m), 7.17 (2H, tt, J = 8.5, 2.5 Hz), 7.06 (1H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 185.0 (C, *C*=O), 184.3 (C, *C*=O), 163.9 (C, d, J = 250.0 Hz, *C*-F), 147.0 (C), 135.0 (CH), 133.9 (2 x CH, d, J = 1.25 Hz), 132.3 (C), 132.10 (C), 131.5 (2 x CH, d, J = 7.5 Hz), 129.4 (C, d, J = 3.75 Hz), 127.1 (CH), 126.0 (CH), 115.6 (2 x CH, d, J = 21.25 Hz); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –110.28; HRMS m/z 253.0659 (M + H^+), calcd for $C_{16}H_9FO_2H$ 253.0665.

2-(m-Tolyl)naphthalene-1,4-dione (8h): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid; Yield: 70% (20.0 mg); Mp.: 126-128 °C; IR (Neat): ν_{max} 3301, 2920, 1663, 1589, 1480, 1457, 1325, 1307, 1260, 1245, 1219, 1119, 1082, 910 and 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19-8.17 (1H, m), 8.12-8.10 (1H, m), 7.79-7.45 (2H, m), 7.38-7.34 (3H, m), 7.30-7.26 (1H, m), 7.06 (1H, s), 2.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 185.1 (C, *C*=O), 184.4 (C, *C*=O), 148.3 (C), 138.1 (C), 135.1 (CH), 133.8 (CH), 133.7 (CH), 133.2 (C), 132.5 (C), 132.0 (C), 130.8 (CH), 130.0 (CH), 128.3 (CH), 127.0 (CH), 126.5 (CH), 125.9 (CH), 21.4 (CH_3); HRMS m/z 249.0913 (M + H^+), calcd for $C_{17}H_{12}O_2H$ 249.0916.



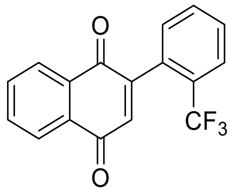
8h

2-(p-Tolyl)naphthalene-1,4-dione (8i): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid; Yield: 76% (21.7 mg); Mp.: 130-132 °C; IR (Neat): ν_{max} 3459, 2922, 2854, 1688, 1651, 1593, 1510, 1346, 1301, 1247, 1208, 1187, 1047, 966, 828, 796 and 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19-8.17 (1H, m), 8.12-8.10 (1H, m), 7.79-7.56 (2H, m), 7.49 (2H, d, J = 8.0 Hz), 7.28 (2H, d, J = 8.0 Hz), 7.06 (1H, s), 2.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 185.2 (C, *C*=O), 185.1 (C, *C*=O), 148.0 (C), 140.4 (C), 134.6 (CH), 133.8 (CH), 133.7 (CH), 132.5 (C), 132.1 (C), 130.5 (C), 129.4 (2 x CH), 129.2 (2 x CH), 127.0 (CH), 125.9 (CH), 21.4 (CH_3); HRMS m/z 249.0914 (M + H^+), calcd for $C_{17}H_{12}O_2H$ 249.0916.



8i

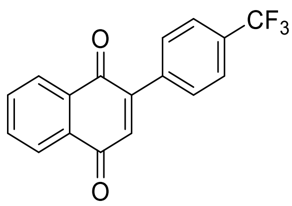
2-(2-(Trifluoromethyl)phenyl)naphthalene-1,4-dione (8n): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane and isolated as



8n

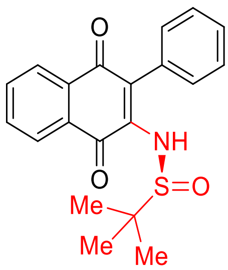
yellow solid; Yield: 60% (20.8 mg); Mp.: 122-124 °C; IR (Neat): ν_{max} 2921, 2851, 2359, 1666, 1619, 1594, 1447, 1344, 1313, 1254, 1169, 1109, 1068, 1035, 1020, 767 and 716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.16-8.14 (2H, m), 7.81-7.77 (3H, m), 7.63 (1H, t, *J* = 7.5 Hz), 7.58 (1H, t, *J* = 8.0 Hz), 7.31 (1H, d, *J* = 7.5 Hz), 6.94 (1H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.6 (C, *C*=O), 183.8 (C, *C*=O), 148.4 (C), 136.70 (C), 136.69 (CH), 134.08 (CH), 134.04 (CH), 132.1 (C), 131.58 (C), 131.5 (CH), 130.6 (CH), 129.3 (CH), 128.9 (C, q, *J* = 30.0 Hz), 127.0 (CH), 126.5 (CH, q, *J* = 3.75 Hz), 126.3 (CH), 126.0 (C, q, *J* = 272.5 Hz, *C*F_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –57.96; HRMS m/z 303.0635 (M + H^+), calcd for $C_{17}H_9F_3O_2H$ 303.0633.

2-(4-(Trifluoromethyl)phenyl)naphthalene-1,4-dione (8p): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane and isolated as



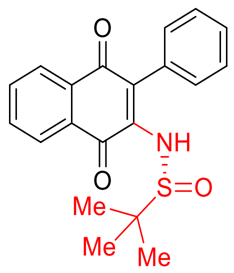
8p

yellow solid; Yield: 74% (25.7 mg); Mp.: 132-134 °C; IR (Neat): ν_{max} 3069, 2361, 1664, 1618, 1593, 1343, 1312, 1299, 1269, 1209, 1107, 1068, 1035, 810 and 766 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.21-8.19 (1H, m), 8.15-8.13 (1H, m), 7.83-7.99 (2H, m), 7.74 (2H, d, *J* = 8.5 Hz), 7.69 (2H, d, *J* = 8.0 Hz), 7.11 (1H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.8 (C, *C*=O), 183.9 (C, *C*=O), 146.9 (C), 136.9 (C), 136.1 (CH), 134.14 (CH), 134.12 (CH), 132.2 (C), 132.0 (C), 131.8 (C, q, *J* = 32.5 Hz), 129.8 (2 x CH), 127.2 (CH), 126.0 (C, q, *J* = 270.0 Hz, *C*F_3), 126.2 (CH), 125.4 (2 x CH, q, *J* = 3.75 Hz); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –62.89; HRMS m/z 303.0638 (M + H^+), calcd for $C_{17}H_9F_3O_2H$ 303.0633.



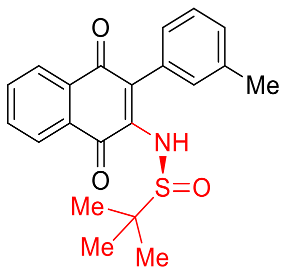
(+)-10a

(*S*)-N-(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)-2-methylpropane-2-sulfinamide (+)-10a: Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as orange solid; Yield: 70% (37.1 mg); Mp.: 138-140 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 32.38 min (major), t_R = 47.92 min (minor); $[\alpha]_D^{25}$ = +110.0° [c = 0.1, $CHCl_3$, 99.6% *ee*]; IR (Neat): ν_{max} 2921, 2851, 1734, 1663, 1615, 1328, 1291, 1173, 1085, 1042, 997, 843, 721 and 704 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.12 (2H, dd, J = 7.75, 1.0 Hz), 7.77 (1H, dt, J = 7.5, 1.0 Hz), 7.72 (1H, dt, J = 7.5, 1.0 Hz), 7.47 (2H, t, J = 7.0 Hz), 7.43 (1H, t, J = 7.5 Hz), 7.32 (2H, d, J = 7.0 Hz), 6.94 (1H, s, N*H*), 1.13 (9H, s, 3 x CH_3) ; ^{13}C NMR ($CDCl_3$, DEPT-135) δ 182.9 (C, *C*=O), 181.6 (C, *C*=O), 142.1 (C), 134.8 (CH), 133.2 (CH), 132.3 (C), 131.8 (C), 130.3 (C), 130.2 (2 x CH), 128.9 (CH), 128.7 (2 x CH), 126.8 (CH), 126.6 (C), 126.5 (CH), 57.7 (C), 22.0 (3 x CH_3); HRMS m/z 354.1164 (M + H^+), calcd for $C_{20}H_{19}NO_3SH$ 354.1164.



(-)-10a

(*R*)-N-(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)-2-methylpropane-2-sulfinamide (-)-10a: Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as orange solid; Yield: 70% (37.1 mg); Mp.: 138-140 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 32.70 min (minor), t_R = 46.29 min (major); $[\alpha]_D^{25}$ = -97.0° [c = 0.1, $CHCl_3$, 99.6% *ee*].

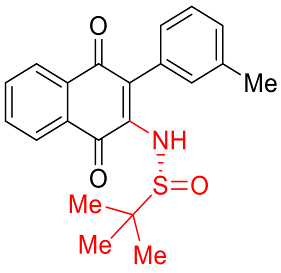


(+)-10h

(*S*)-N-(1,4-Dioxo-3-(m-tolyl)-1,4-dihydronaphthalen-2-yl)-2-methylpropane-2-sulfinamide (+)-10h: Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as orange solid; Yield: 75% (41.3 mg); Mp.: 138-140 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 32.15 min (major), t_R = 46.11 min (minor); $[\alpha]_D^{25}$ = +103.0° [c = 0.1, $CHCl_3$, 99.6% *ee*]; IR (Neat): ν_{max} 2922, 2852, 1735, 1664, 1595, 1460, 1406, 1362, 1292, 1237, 1185, 1091, 1042, 1005, 782 and 719 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.14 (2H, d, J = 8.0 Hz), 7.78 (1H, dt, J = 7.5, 1.5 Hz), 7.73 (1H, dt, J = 7.5, 1.0 Hz), 7.36 (1H, t, J = 8.0 Hz), 7.24 (1H, d, J = 7.5 Hz), 7.12 (2H, d, J = 7.5 Hz), 6.89 (1H, s, N*H*), 2.39 (3H, s, CH_3), 1.13 (9H, s, 3 x CH_3) ; ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.0 (C, *C*=O), 181.7 (C, *C*=O), 142.2

(C), 138.4 (C), 134.8 (CH), 133.2 (CH), 132.4 (C), 131.7 (C), 130.8 (CH), 130.4 (C), 129.7 (CH), 128.7 (CH), 127.3 (CH), 127.0 (C), 126.9 (CH), 126.5 (CH), 57.6 (C), 22.1 (3 x CH_3), 21.4 (CH_3); HRMS m/z 368.1320 ($M + H^+$), calcd for $C_{21}H_{21}NO_3SH$ 368.1320.

(*R*)-N-(1,4-Dioxo-3-(m-tolyl)-1,4-dihydronaphthalen-2-yl)-2-methylpropane-2-sulfinamide (-)-10h: Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as orange solid; Yield: 75% (41.3 mg); Mp.: 138-140 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 33.37 min (minor), t_R = 45.65 min (major); $[\alpha]_D^{25}$ = -124.0º [c = 0.1, $CHCl_3$, 99.6% *ee*].



(-)-10h

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7 CCDC 2127414–2127417 (**3b**, **4b**, **4d** and **3d**) contain the supplementary crystallographic data for this chapter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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5. Conformation-Controlled Catalytic Asymmetric Synthesis of Swaminathan Ketones

5.1 Introduction

Organic chemistry is all about mimicking nature and constructing complex molecules that could be natural products or potential building blocks for their synthesis. Over the last two decades, organocatalytic asymmetric synthesis has become one of the powerful tools for constructing complex natural products with excellent enantioselectivities. Besides enormous contribution from the scientific community towards constructing potential chiral bicyclic systems such as Wieland-Miescher ketones[1a-c] and Hajos-Parrish ketones[2a-e] which were well-proven to be the core structures of many natural products, there are lot more complex polycyclic/ring systems, whose asymmetric synthetic methodologies were yet to be discovered. Meanwhile, our laboratory majorly focuses on developing organocatalytic asymmetric methodologies for synthesizing complex polycyclic compounds, which serve as the building blocks for natural products, drugs and drug-like molecules.

Our interest in natural products made us come across Daphniphyllum alkaloids in literature which were mainly extracted from the genus Daphniphyllum. These plants were geographically distributed in South-East Asia, South China and used in Chinese herbal medicine to treat various illnesses as they exhibit anti-cancer, anti-HIV, anti-oxidant, and vasorelaxant properties significantly. To date, over 320 Daphniphyllum alkaloids have been isolated and characterized.[3a] Interestingly, the core skeleton of these alkaloids is bicyclo[5.4.0]undecane. After a thorough literature search, we found that more than 450 natural products possessed the bicyclo[5.4.0]undecane core structure (Scheme 1, A). [3b-e] With this excitement, we searched the literature for synthetic strategies to construct bicyclo[5.4.0]undecane systems.[3f-o]

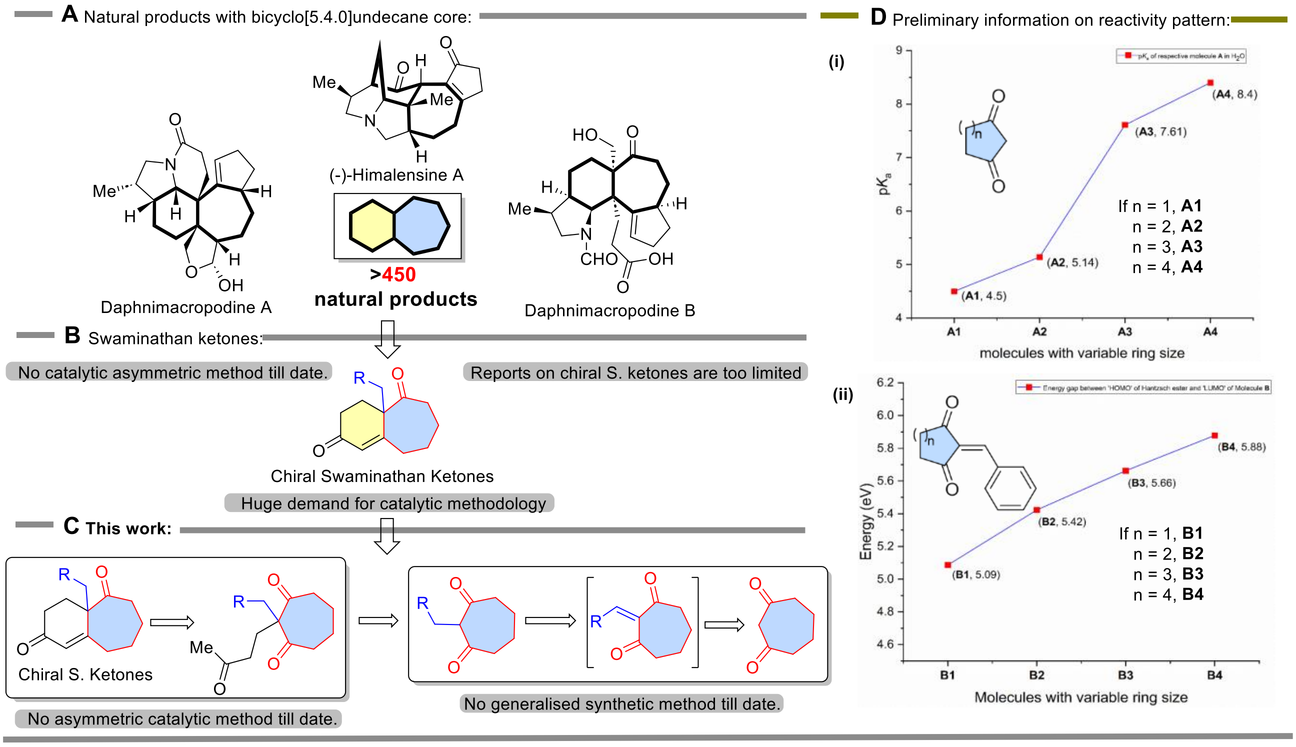
5.1.1 Previous Reports on the Swaminathan Ketones

In 1966, for the first time, Swaminathan et al. synthesized the racemic bicyclo[5.4.0]undecane system under pyrrolidine catalysis in the presence of acetic acid, which was later coined as Swaminathan ketone (S. ketone).[4a] They also attempted the asymmetric synthesis of S. ketones under secondary amine catalysis but were unsuccessful.

Later, in 2005[4d] and 2007[5b], Nagamine, Inomata and Paquette investigated the same under various amino acid, primary amine catalysis along with co-catalysts, but failed in achieving considerable enantioselectivities. After that, in 2016, Uwai et al. investigated the asymmetric synthesis of chiral S. ketones under lipase-catalysis, but unfortunately, these efforts were also not fruitful.[5e] Recently, Xu et al. in 2019 and 2021, published the total synthesis of (-)-Himalensine A and the racemic versions of two key intermediates for the synthesis of Daphnimacropodines by either proceeding with the less enantioselective S. ketones or with racemic S. ketones.[4f,4h,5g] Moreover, all these existing protocols used stoichiometric amounts of catalyst/co-catalyst, and none achieved excellent selectivity.[5a-h] This gave a clear insight to the scientific community that the construction of bicyclo[5.4.0]undecane core is much more difficult and not in comparable with the construction of bicyclo[4.4.0]decane and bicyclo[4.3.0]nonane core structures. As a matter of fact, W-M and H-P ketones were extensively studied and constructed by well-established proline catalysis and were successfully utilized in the total synthesis of several natural products. On the other hand, S. ketones undoubtedly possess numerous applications but not more than three chiral S. ketone and analogues were known in the literature,[5h] and there is no catalytic protocol available for the synthesis of chiral S. ketones to date. This indicates an immense need to discover a new organocatalytic asymmetric methodology for synthesizing chiral S. ketones (Scheme 1, B).

With this motivation, we have decided to tackle the challenge of constructing chiral S. ketones in an organocatalytic asymmetric fashion. To begin with, chiral S. ketones can be synthesized through intramolecular aldol condensation by asymmetric desymmetrization of the corresponding triketones, whereas these triketones can be synthesized by the Michael addition of 2-alkylcycloheptane-1,3-dione with methyl vinyl ketone. And now, the 2-alkylcycloheptane-1,3-diones can be synthesized from cycloheptane-1,3-dione using our laboratory established organocatalytic reductive coupling with different aldehydes and Hantzsch ester (Scheme 1, C).

In the past two decades, our lab has been developing organocatalytic reductive coupling methodologies for various five and six-membered cyclic-1,3-diones.[6a-c] But investigating the reductive coupling reaction on cycloheptane-1,3-dione will be more interesting and challenging since it has more conformers which can easily affect the acidity of methylene alpha to the two carbonyls. Organocatalytic reductive coupling proceeds through the amine-catalyzed *in situ* olefination, which depends on the rate of enolization followed by transfer hydrogenation. Before the core experiments, we performed a few preliminary experiments and DFT calculations in order to understand the reactivity pattern of cyclic-1,3-diones in organocatalytic reductive coupling for which we have chosen 5, 6, 7, and 8 membered cyclic-1,3-diones for our studies.



Scheme 1: A) Natural products containing bicyclo[5.4.0]undecane as the core structure. B) Huge demand for catalytic asymmetric methodology to synthesize chiral Swaminathan ketone and analogues. C) This work deals with organocatalytic asymmetric synthesis of Swaminathan ketone and analogues. D) Preliminary information on the reactivity patterns for (i) acidity versus ring size for olefination of various ring sized cyclic-1,3-diones **A** with benzaldehyde, (ii) energy gap for transfer hydrogenation of various ring sized benzylidene-cyclic-1,3-diones **B** with Hantzsch ester.

Firstly, we have determined the pK_a of cyclic-1,3-diones using the potentiometry technique, to reveal the rate of olefination. As we move from 5 to 8 membered ring, the pK_a order of cyclic-1,3-diones is **A1**<**A2**<**A3**<**A4**, which implies, the acidity of the methylene proton kept reducing drastically [Scheme 1, D(i)]. This is because of the increased conformational flexibility of the molecule as the ring size increases. *In support of this, the NMR spectra of cycloheptane-1,3-dione showed exclusively the keto form in $CDCl_3$*. Since the rate of enolization is directly proportional to the rate of olefination, the rate of olefination of cycloheptane-1,3-dione with benzaldehyde is relatively much lower compared to cyclopentane- and cyclohexane-1,3-diones. After olefination with benzaldehyde, the next challenge is regarding the rate of transfer hydrogenation which depends on the energy gap between HOMO of Hantzsch ester and LUMO of olefin. Here, we have done DFT studies and calculated the $\text{HOMO}_{\text{(Hantzsch ester)}}$-$\text{LUMO}_{\text{(olefin)}}$ energy gap using "CAM-B3LYP/6-311++G*". It clearly showed that the ring's conformational flexibility impacts the $\text{HOMO}_{\text{(Hantzsch ester)}}$-$\text{LUMO}_{\text{(olefin)}}$ gap (Figure 1). As the ring size increased, the HOMO-LUMO gap increased in the order **B1<B2<B3<B4**. In support of this, the single crystal structure of 2-(4-nitrobenzylidene)cycloheptane-1,3-dione revealed that the keto groups and the olefin were not in the same plane (Figure 2). This again suggests that the rate of transfer hydrogenation decreases as the ring-size increases [Scheme 1, D(ii)]. These two preliminary studies clearly implied that cycloheptane-1,3-dione is completely different from cyclopentane-, cyclohexane-1,3-diones, and thus, it is very important to investigate organocatalytic reductive coupling on cycloheptane-1,3-dione to develop a sustainable protocol.

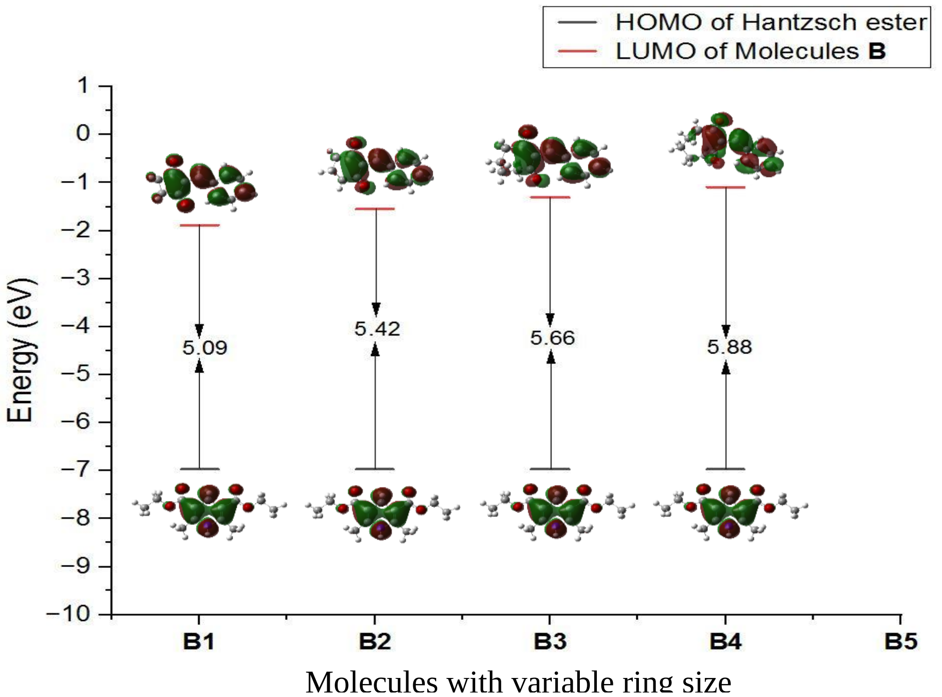


Figure 1: Graph showing the trends in $\text{HOMO}_{\text{(Hantzsch ester)}}$-$\text{LUMO}_{\text{(olefins with variable ring size)}}$ gap.

The structure of compound **5n** was again confirmed by X-ray crystallography (Figure 2).[7]

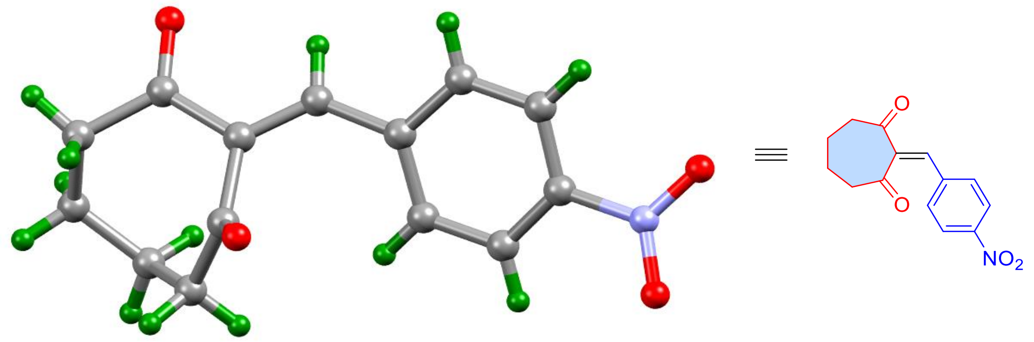


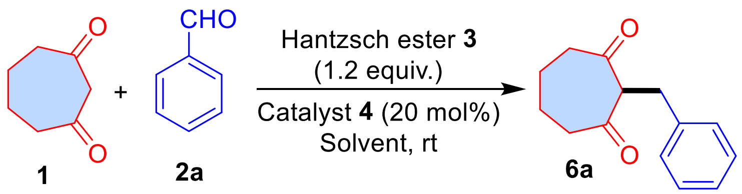
Figure 2: X-Ray crystal structure of 2-(4-nitrobenzylidene)cycloheptane-1,3-dione (**5n**).

5.2 Results and Discussion

5.2.1 Reaction Optimization for Reductive Alkylation of Cycloheptane-1,3-dione 1

With this pre-knowledge, we have chosen cycloheptane-1,3-dione **1** and benzaldehyde **2a** to investigate organocatalytic reductive coupling. Initially, we reacted 1.0 equiv. of cycloheptane-1,3-dione **1** with 2.0 equiv. of benzaldehyde **2a** in the presence of 20 mol% of proline **4a** and 1.2 equiv. Hantzsch ester **3** in DCM (0.3 M) at 25 °C. After 24 h, we got the desired product **6a** through olefin **5a**, but the yield was only 26% which clearly indicates that the reaction rate is in accordance with our preliminary reaction kinetic/DFT studies (Table 1, entry 1). Changing the solvent to $CHCl_3$ didn't improve the reaction yield (Table 1, entry 2). With this understanding of chlorinated solvents, we further investigated reaction in alcoholic solvents. Interestingly, the reductive alkylation reaction performed excellently, furnishing 85% of **6a** in 12 h, 93% of **6a** in 6 h, 78% of **6a** in 4.5 h, 91% of **6a** in 4.5 h, 81% of **6a** in 5.5 h, and 40% of **6a** in 24 h in methanol, ethanol, 1-propanol, 1-butanol, propane-2-ol and hexafluoro-2-propanol solvents respectively (Table 1, entries 3-8) which was confirmed by NMR spectroscopy (Figure 3). Further, we changed the solvent to DMSO and acetonitrile, which yielded **6a** in 79 and 83% in 24 and 12 h, respectively, proving 1-butanol to be the best solvent (Table 1, entry 9-10). Altering the catalyst loading to 15, 10, and 5 mol% resulted in a reduced yield and increased reaction times (Table 1, entries 11-13). In order to further optimize the reaction, we screened various catalysts **4**. Surprisingly, in the case of aniline **4c**, the reaction furnished **6a** in just 1.5 h with a 90% yield, whereas in the case of glycine **4b**, benzylamine **4d**, and pyrrolidine **4e**, the reaction did not perform better than **4c** in terms of yield and reaction times (Table 1, entries 14-17). Varying the catalyst **4c** loading to 15, 10 mol% or using 1.2 equiv. of **2a** did not contribute to any betterment (Table 1, entries 18-20). Thus, reacting cycloheptane-1,3-dione **1** with 2.0 equiv. of **2a** in the presence of **4c** (20 mol%) and 1.2 equiv. of **3** in 1-butanol (0.3 M) at room temperature for 1.5 h was finalized as the standard optimized alkylation reaction conditions.

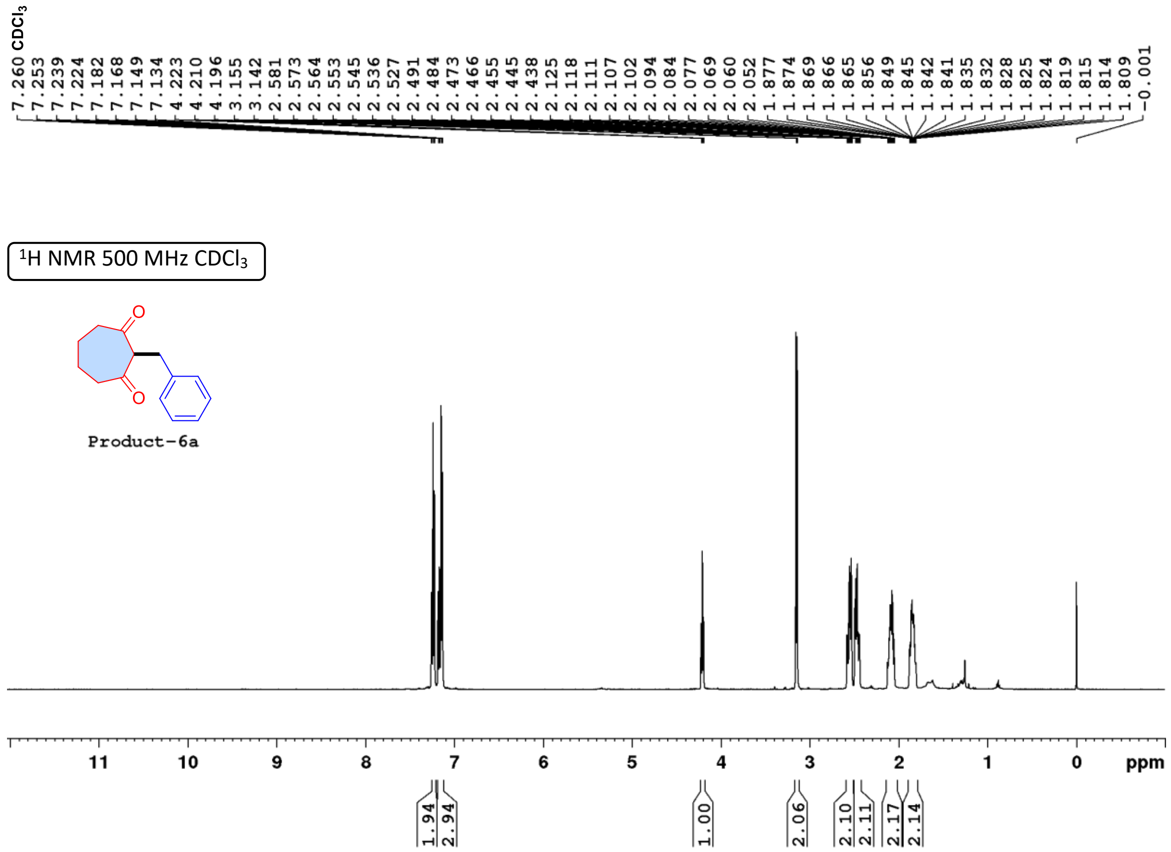
Table 1: Optimization for the reductive alkylation of cycloheptane-1,3-dione **1**.[a]



Proline (**4a**) Glycine (**4b**) Aniline (**4c**) Benzylamine (**4d**) Pyrrolidine (**4e**)

Entry	Catalyst	Solvent [0.3 M]	*t* [h]	Yield [%][b]
1	**4a**	DCM	24	26
2	**4a**	$CHCl_3$	24	23
3	**4a**	MeOH	12	85
4	**4a**	EtOH	6	93
5	**4a**	1-propanol	4.5	78
6	**4a**	1-butanol	4.5	91
7	**4a**	propan-2-ol	5.5	81
8	**4a**	$(CF_3)_2CHOH$	24	40
9	**4a**	DMSO	24	79
10	**4a**	CH_3CN	12	83
11[c]	**4a**	1-butanol	4.5	86
12[d]	**4a**	1-butanol	7	86
13[e]	**4a**	1-butanol	10	84
14	**4b**	1-butanol	24	80
15	**4c**	1-butanol	1.5	90
16	**4d**	1-butanol	19	75
17	**4e**	1-butanol	12	83
18[f]	**4c**	1-butanol	2	85
19[g]	**4c**	1-butanol	2.5	84
20[h]	**4c**	1-butanol	2	83

[a] Reactions were carried out in solvent (0.3 M) with 2.0 equiv. of **2a** and 1.2 equiv. of **3** relative to the **1** (0.3 mmol) in the presence of 20 mol% of catalyst **4**. [b] Yield refers to the column-purified product of **6a**. [c] 15 mol% of **4a** was used. [d] 10 mol% of **4a** was used. [e] 5 mol% of **4a** was used. [f] 15 mol% of **4c** was used. [g] 10 mol% of **4c** was used. [h] 1.2 equiv. of **2a** was used instead of 2.0 equiv.



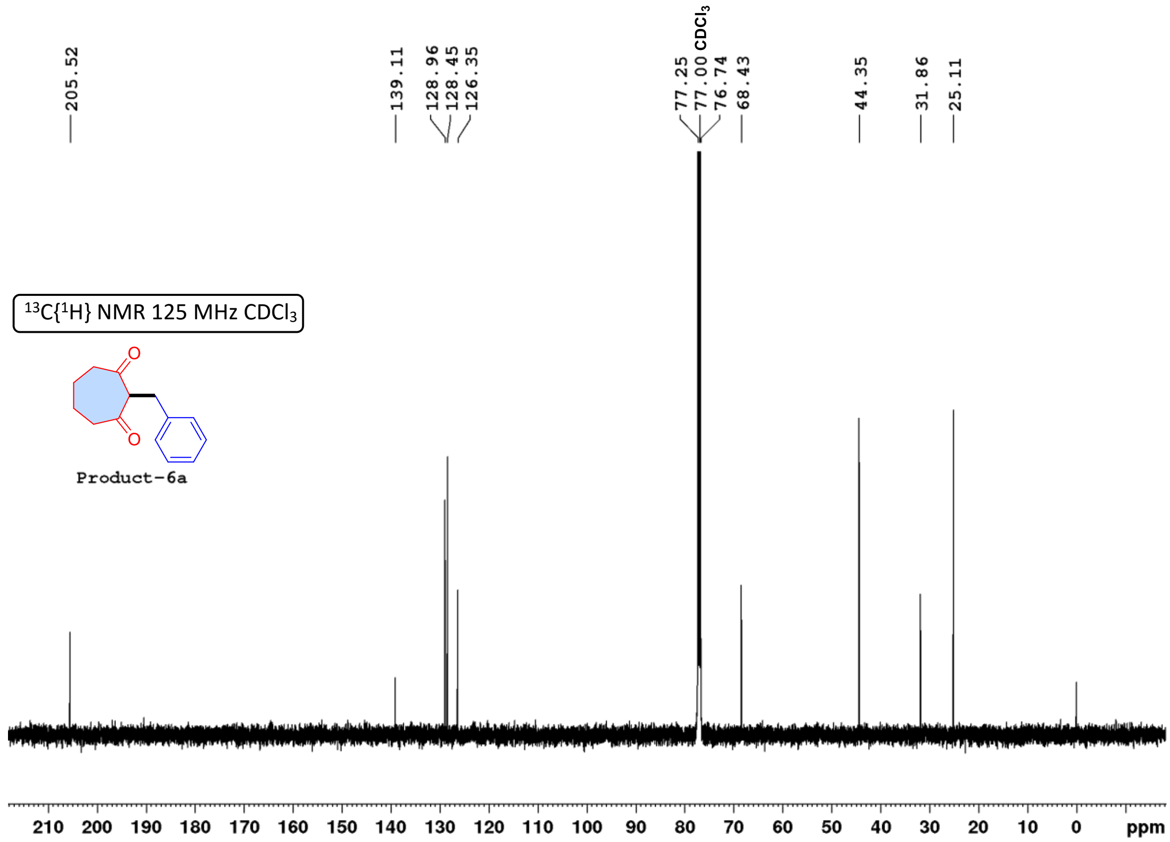


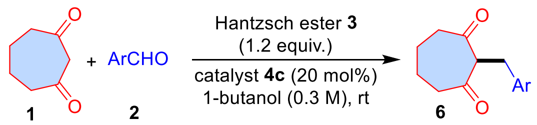
Figure 3: ^{1}H NMR and ^{13}C NMR spectrum of product **6a**.

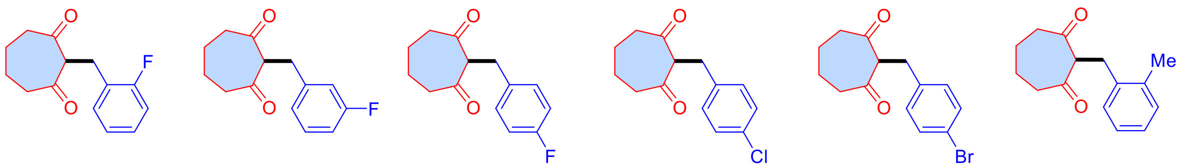
5.2.2 Reaction Scope for the Synthesis of Functionalized 3-Aryllawsones

5.2.2.1 Reaction scope with respect to various aromatic and heteroaromatic aldehydes 2

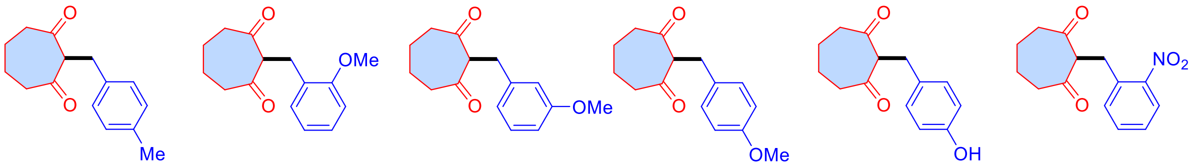
After successful optimization, we investigated the reductive alkylation for the effect of various electronic/steric factors using differently substituted aromatic/hetero-aromatic aldehydes **2**. The reaction of **1** with *o*-, *m*- and *p*-fluorobenzaldehydes **2b-d** in the presence of 1.2 equiv. of **3** and 20 mol% **4c** in 1-butanol (0.3 M) furnished the alkylation products **6b-d** in 80, 84, and 85% yields respectively, in just 1.0 h (Table 2). Likewise, 4-chloro- and 4-bromobenzaldehydes **2e-f** afforded 80 and 82% of **6e-f** respectively, under the optimized conditions (Table 2).

Table 2: Substrate scope for the reductive alkylation of cycloheptane-1,3-dione **1** with various aromatic and heteroaromatic aldehydes **2**.[a]

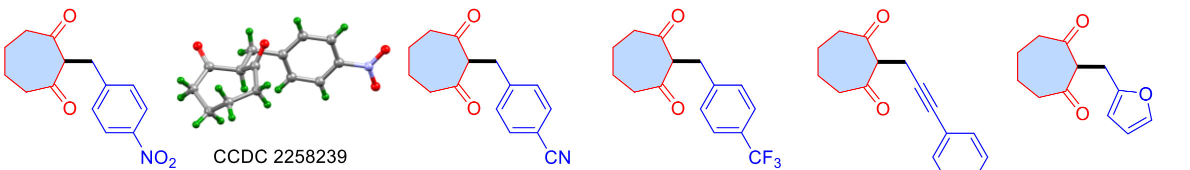




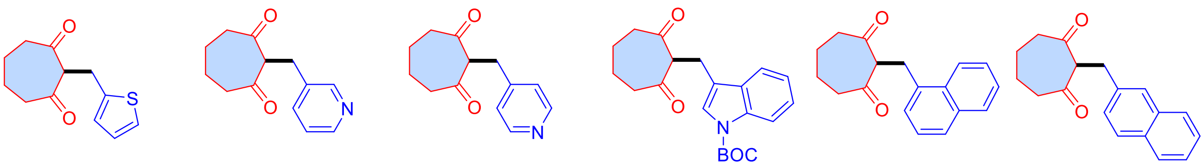
6b (1 h, 80%) **6c** (1 h, 84%) **6d** (1 h, 85%) **6e** (1 h, 80%) **6f** (1 h, 82%) **6g** (5 h, 90%)



6h (1.5 h, 94%) **6i** (6 h, 86%) **6j** (2 h, 90%) **6k** (2 h, 93%) **6l** (8 h, 85%) **6m** (1 h, 95%)



6n (1 h, 93%) CCDC 2258239 **6n**, X-ray structure **6o** (0.75 h, 97%) **6p** (0.75 h, 91%) **6q** (3 h, 83%) **6r** (1 h, 94%)



6s (1 h, 95%) **6t** (3 h, 81%) **6u** (3 h, 89%) **6v** (4 h, 70%) **6w** (6 h, 83%) **6x** (4 h, 91%)

[a] Reactions were carried out in 1-butanol (0.3 M) with 2.0 equiv. of **2** and 1.2 equiv. of **3** relative to **1** (0.3 mmol) in the presence of 20 mol% of aniline **4c**.

Coming to electron-donating groups, 2-methylbenzaldehyde **2g** afforded the desired product **6g** in 90% yield but with a longer reaction time of 5 h when compared to 4-methylbenzaldehyde **2h** which yielded **6h** with 94% yield in just 1.5 h because of the steric effects. Following the same pattern, the reaction with *o*-methoxybenzaldehyde **2i** took 6 h for the completion and afforded **6i** with 86% yield, whereas *m*-, and *p*-methoxybenzaldehyde **2j-k** furnished the desired products **6j-k** with 90 and 93% yield in just 2 h (Table 2). Surprisingly, 4-hydroxybenzaldehyde **2l** afforded the alkylation product **6l** with 85% yield but in 8 h. As expected, benzaldehydes with electron-withdrawing substitutions such as nitro, cyano, and trifluoromethyl **2m-p** performed excellently under optimized conditions to furnishing **6m-p** with >90% yield in less than 1.0 h (Table 2). The reductive coupling reaction was well tolerated towards phenylpropargyl aldehyde **2q** and the five different hetero-aromatic aldehydes **2r-v**, affording the desired alkylation products **6q-v** with the yields of 70-95% in 1-4 h. Same time the reaction smoothly proceeded in the case of 1- and 2-naphthaldehydes **2w-x**, affording **6w** and **6x** with 83 and 91% yield in 6 and 4 h, respectively (Tabe 2). The NMR spectra of few selected compounds **6** were shown in Figures 5-14.

The structure of compound **6n** was again confirmed by X-ray crystallography (Figure 4).[7]

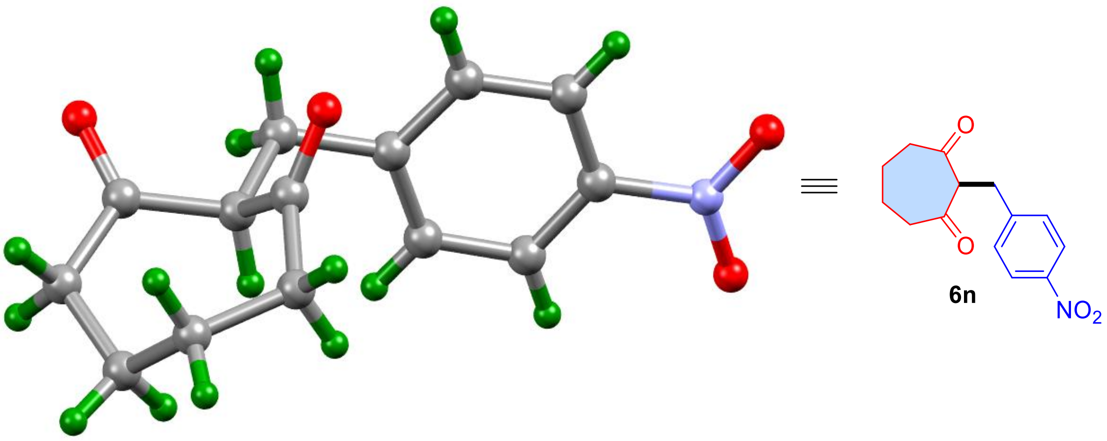
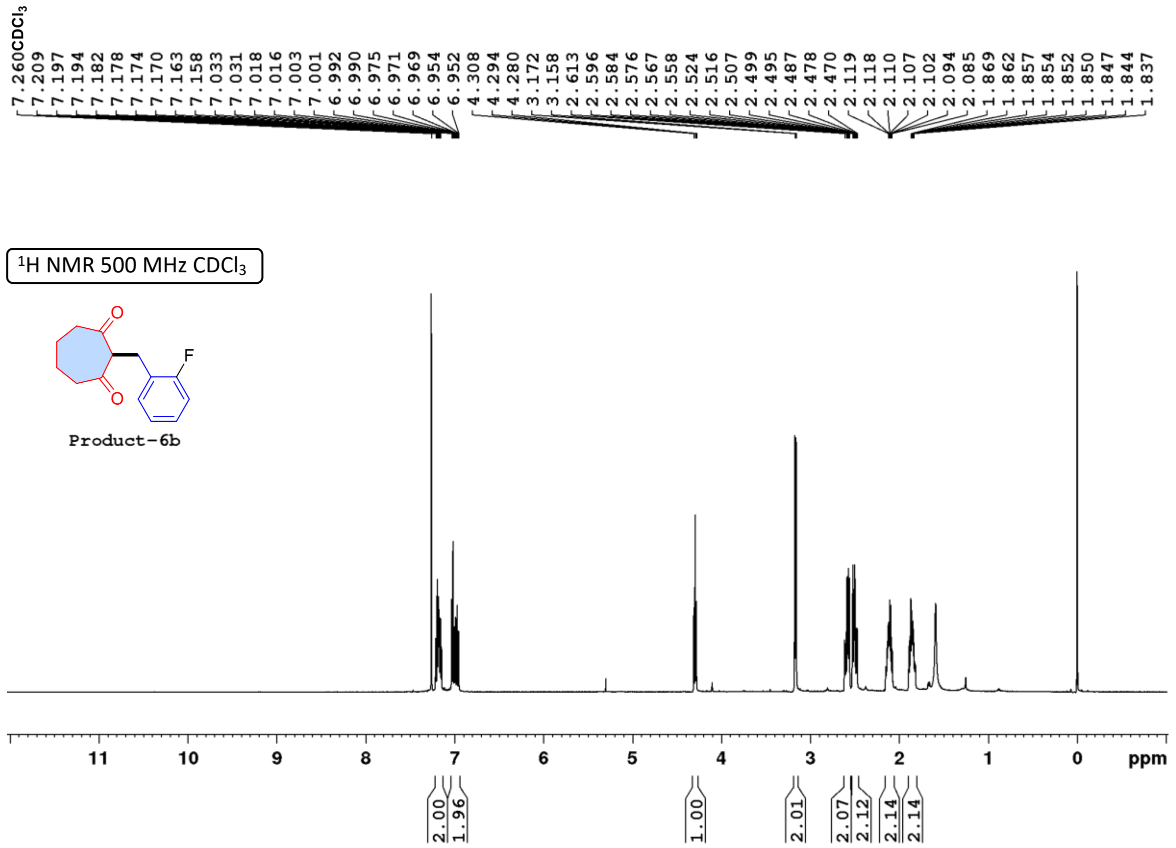


Figure 4: X-Ray crystal structure of 2-(4-nitrobenzyl)cycloheptane-1,3-dione (**6n**).



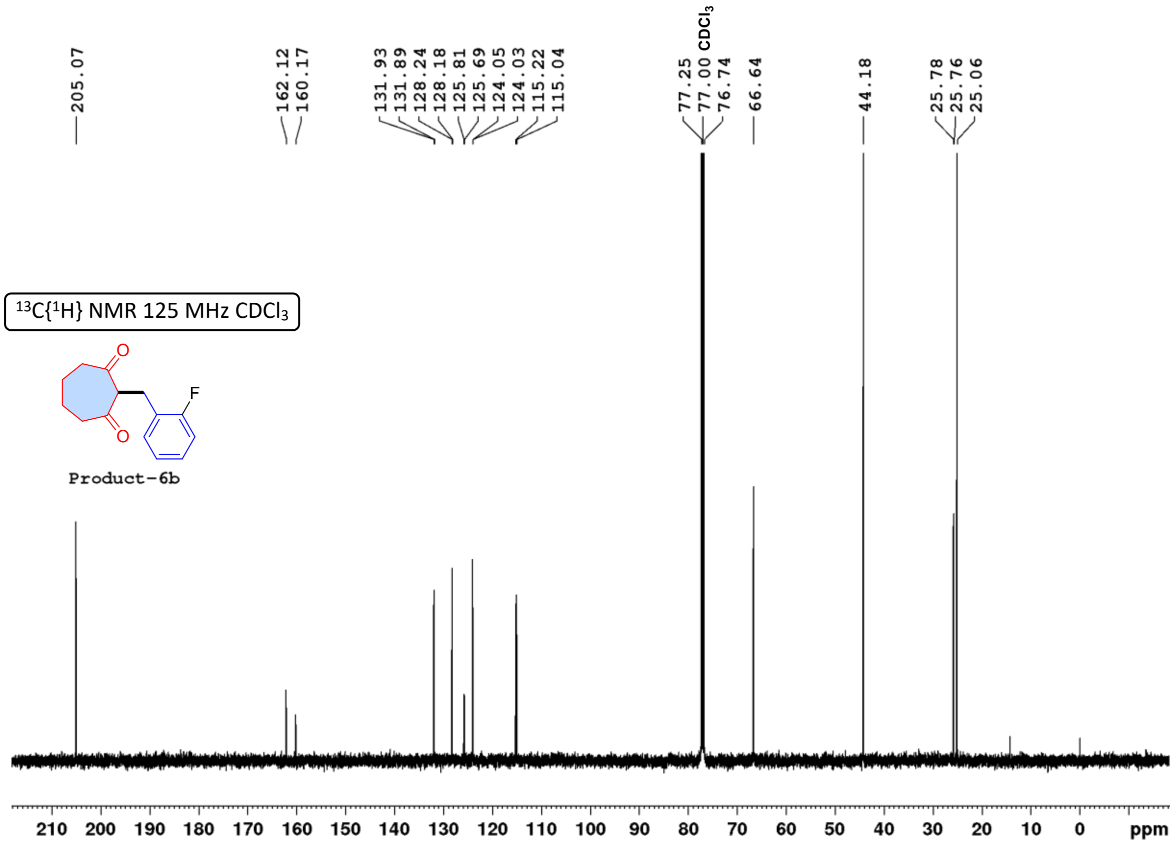
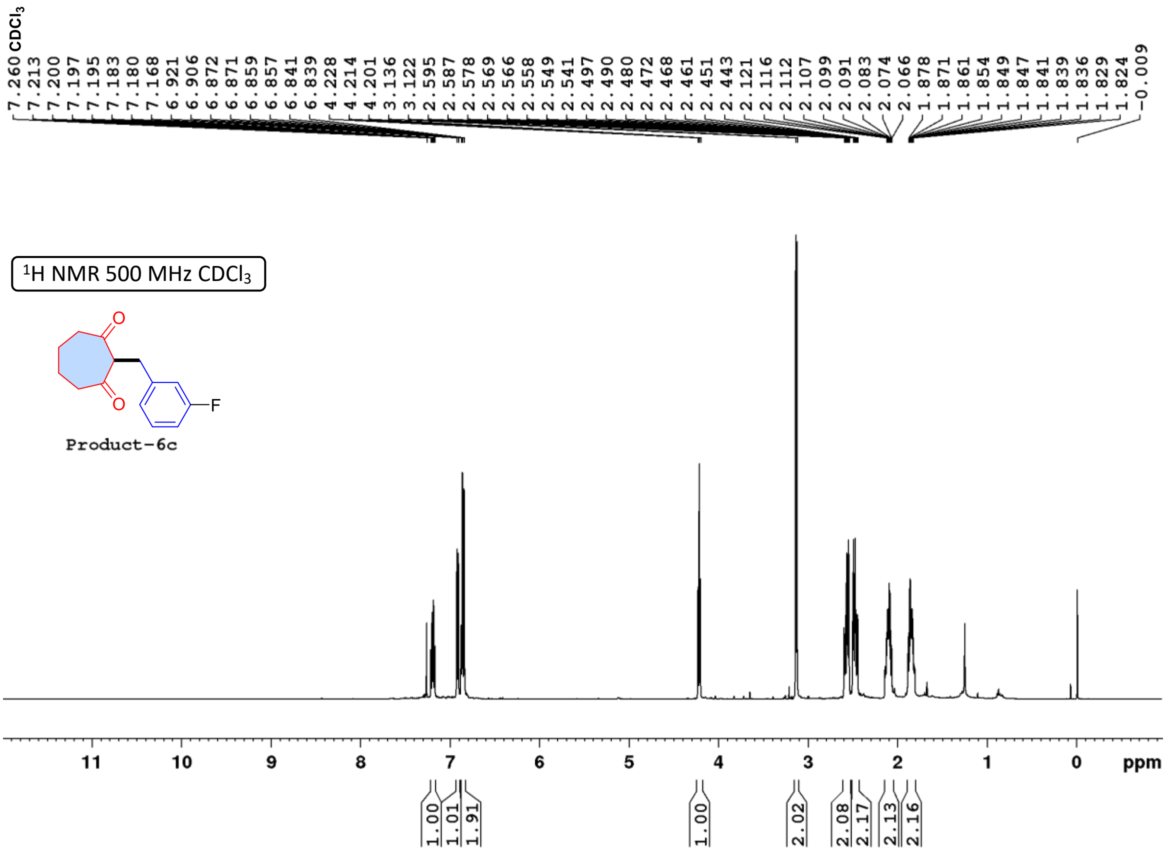


Figure 5: ^{1}H NMR and ^{13}C NMR spectrum of product **6b**.



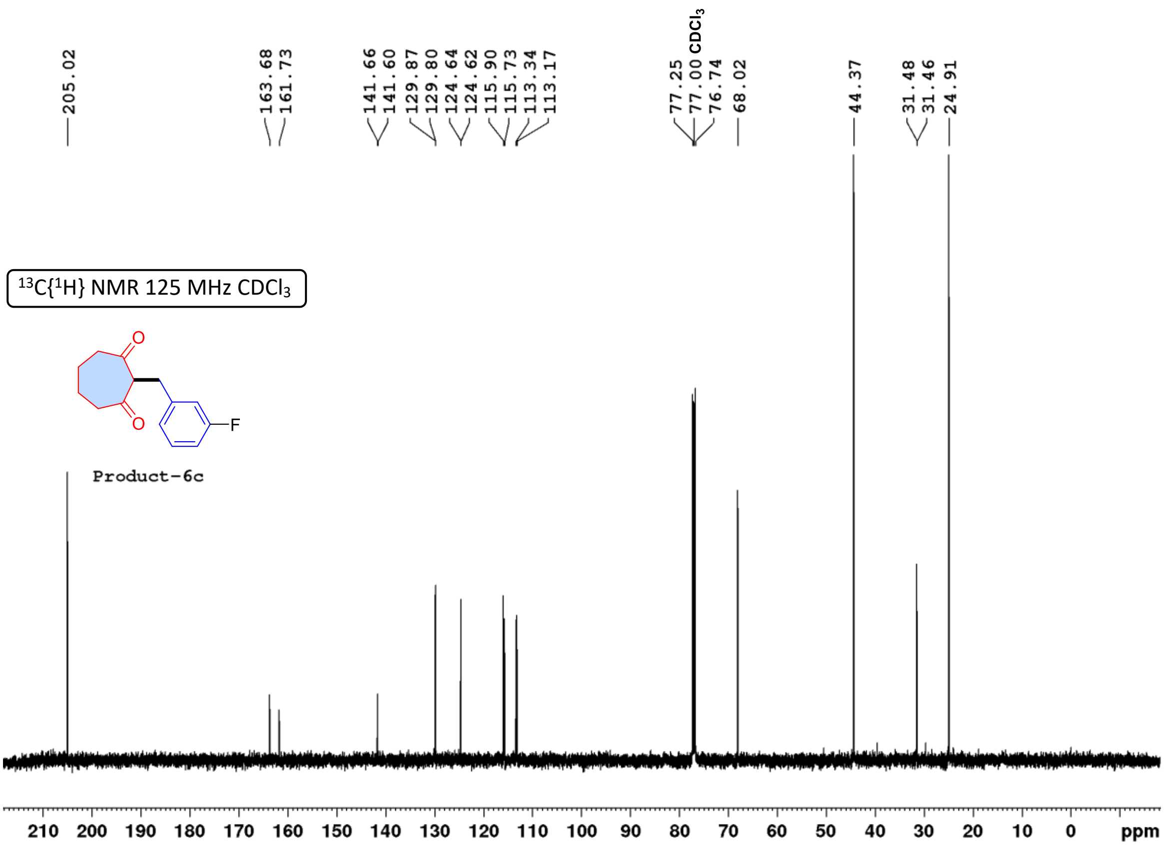
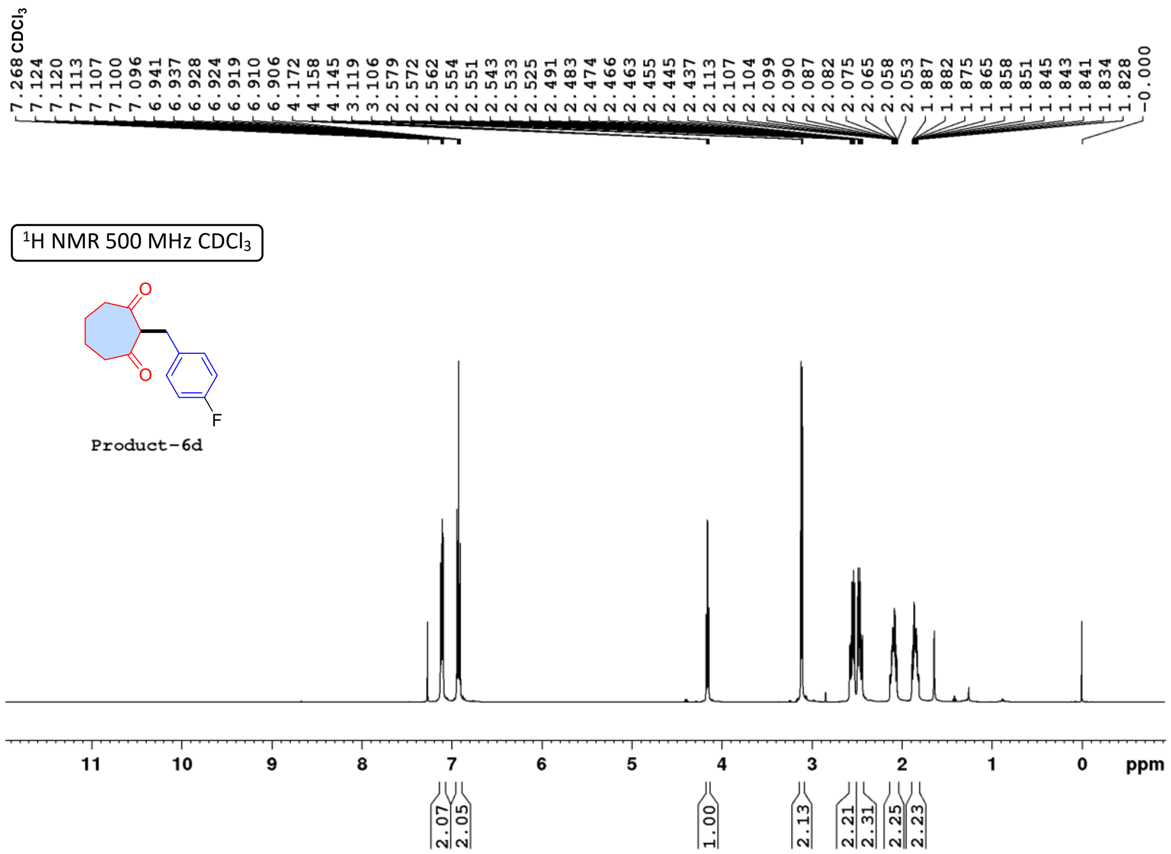


Figure 6: ^{1}H NMR and ^{13}C NMR spectrum of product **6c**.



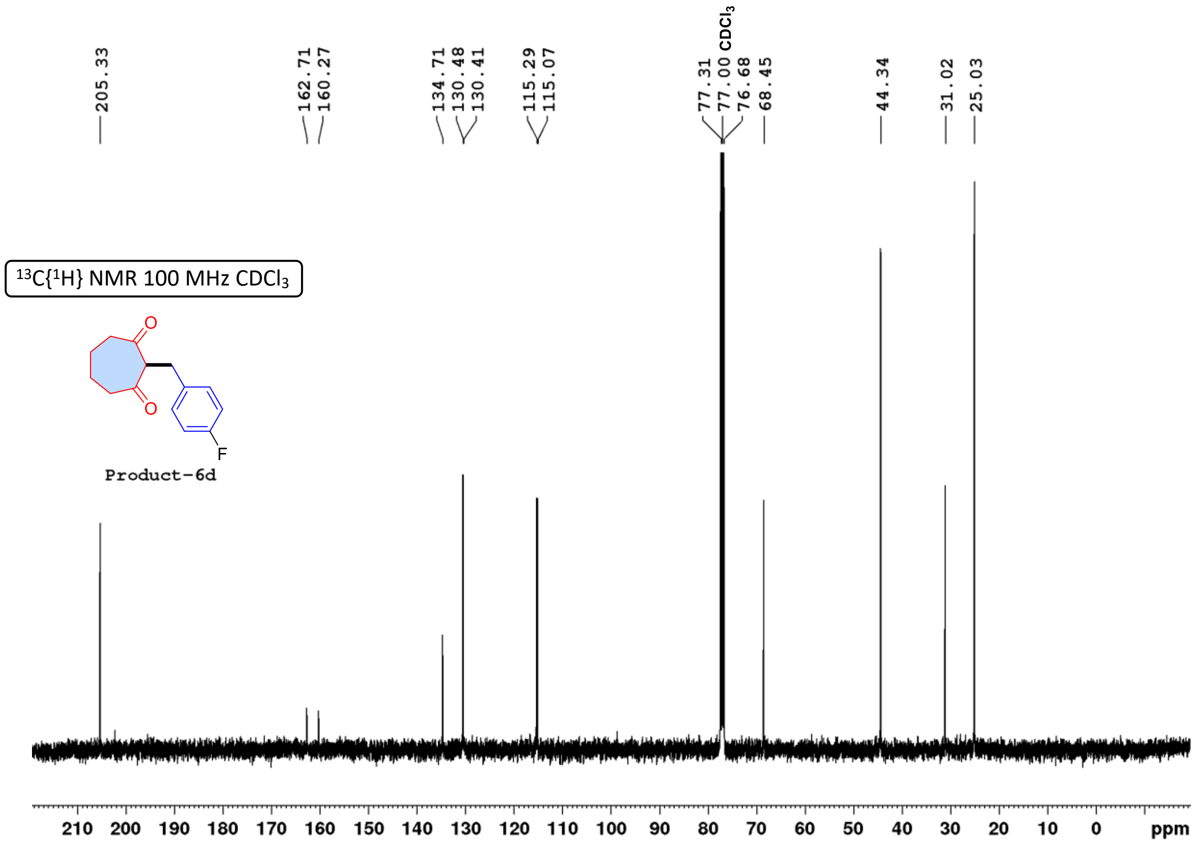
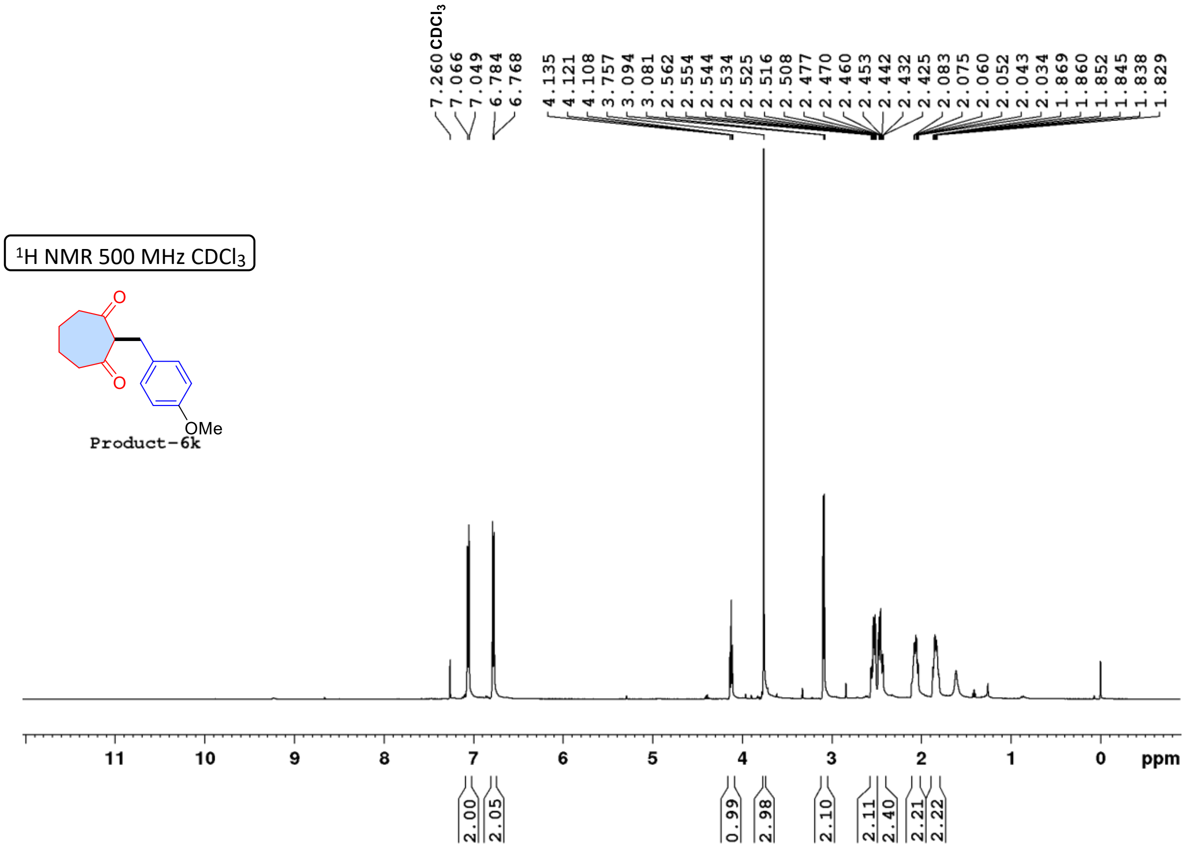


Figure 7: ^{1}H NMR and ^{13}C NMR spectrum of product **6d**.



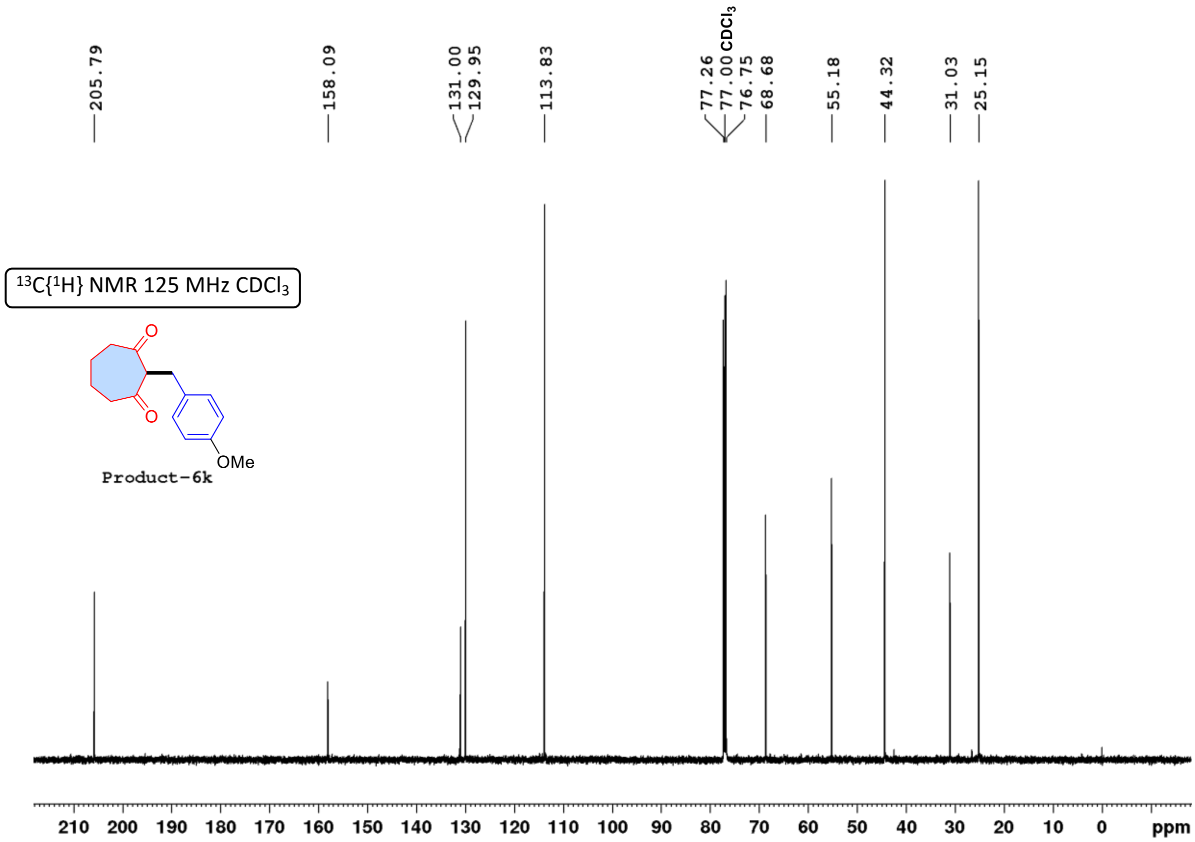
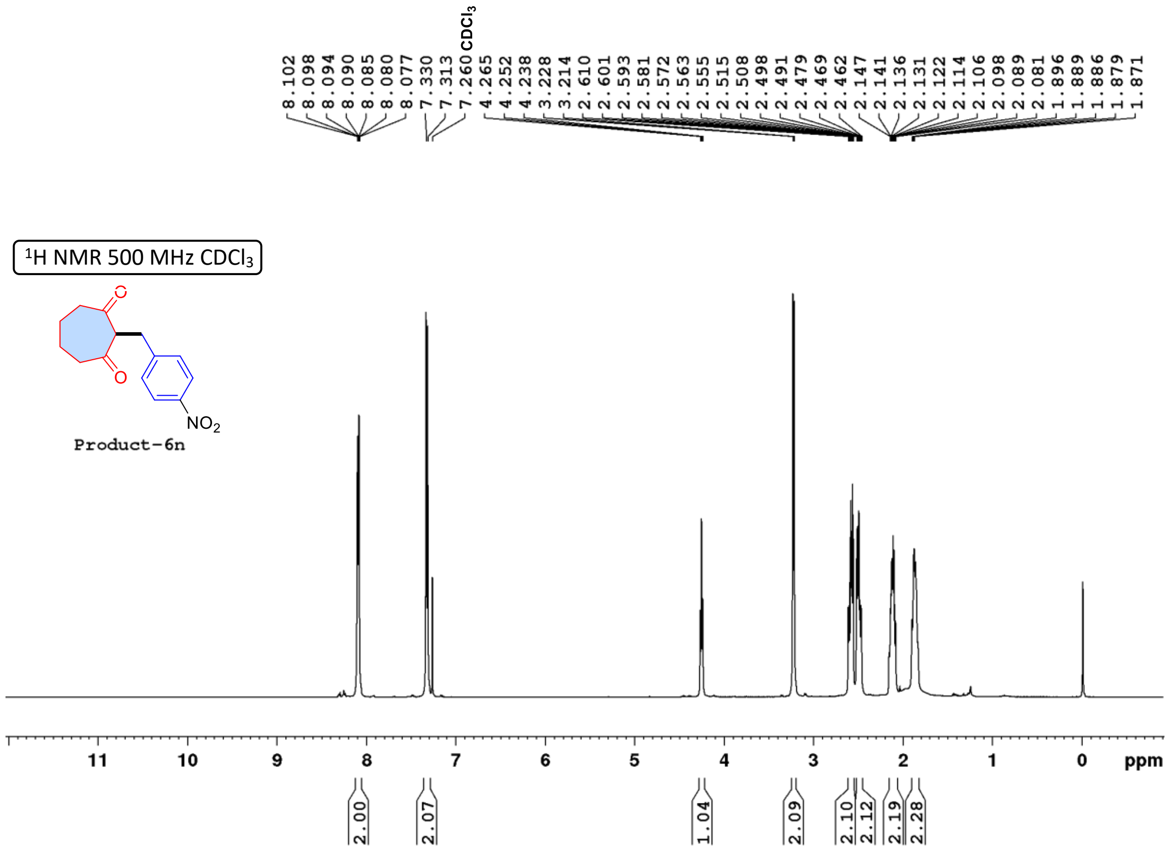


Figure 8: ^{1}H NMR and ^{13}C NMR spectrum of product **6k**.



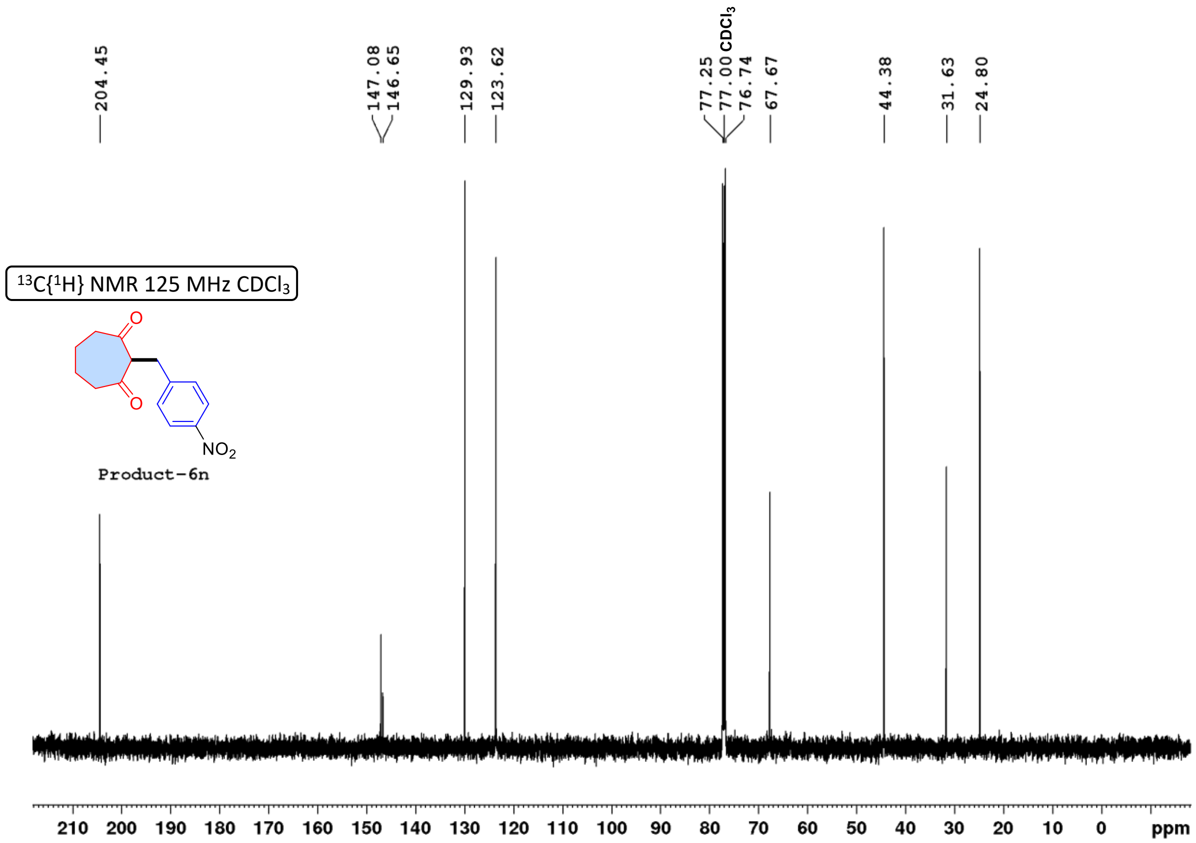
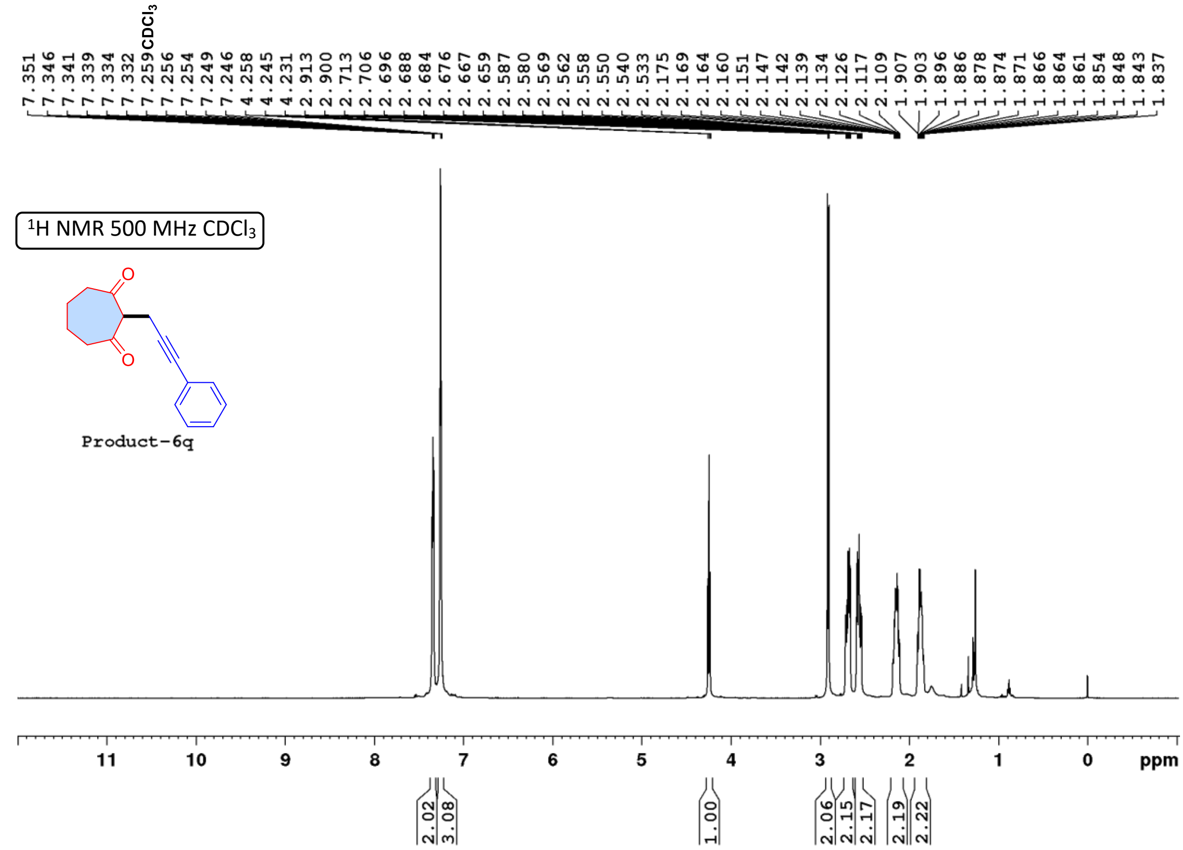


Figure 9: ^{1}H NMR and ^{13}C NMR spectrum of product **6n**.



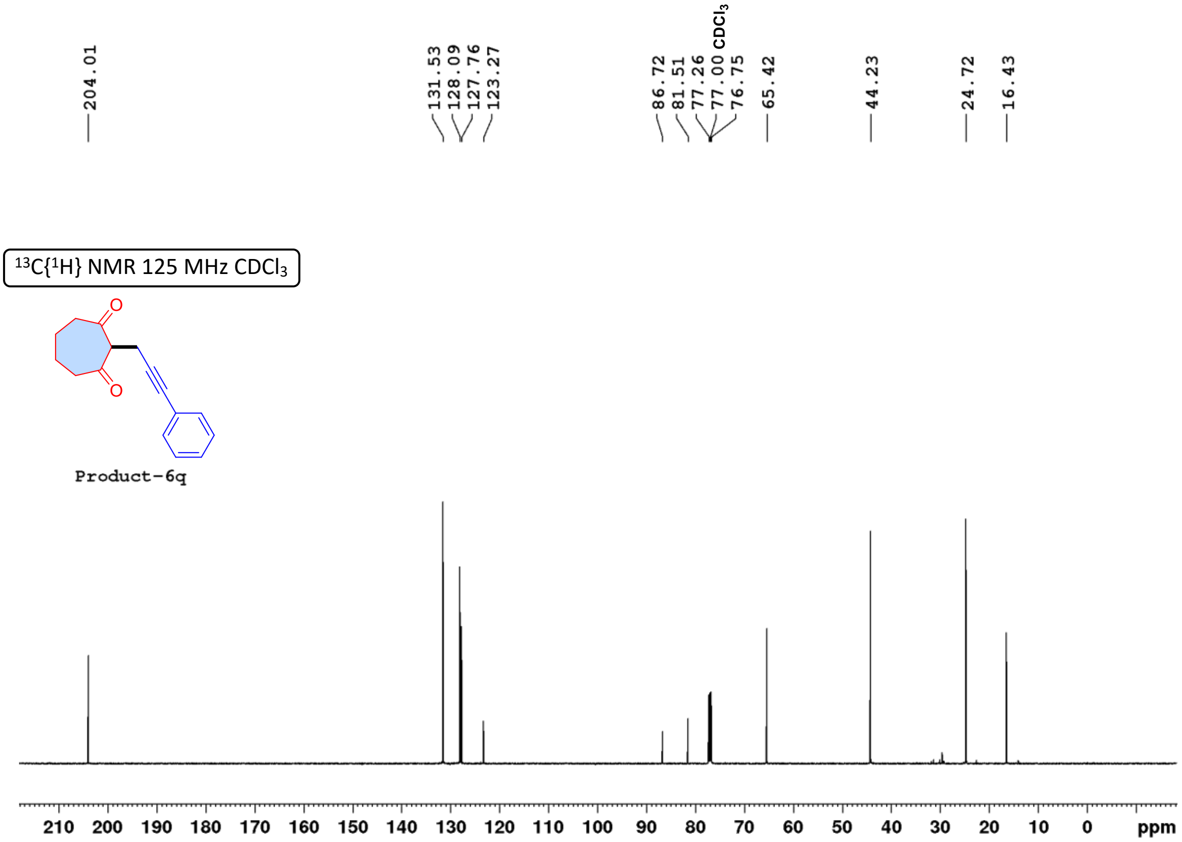
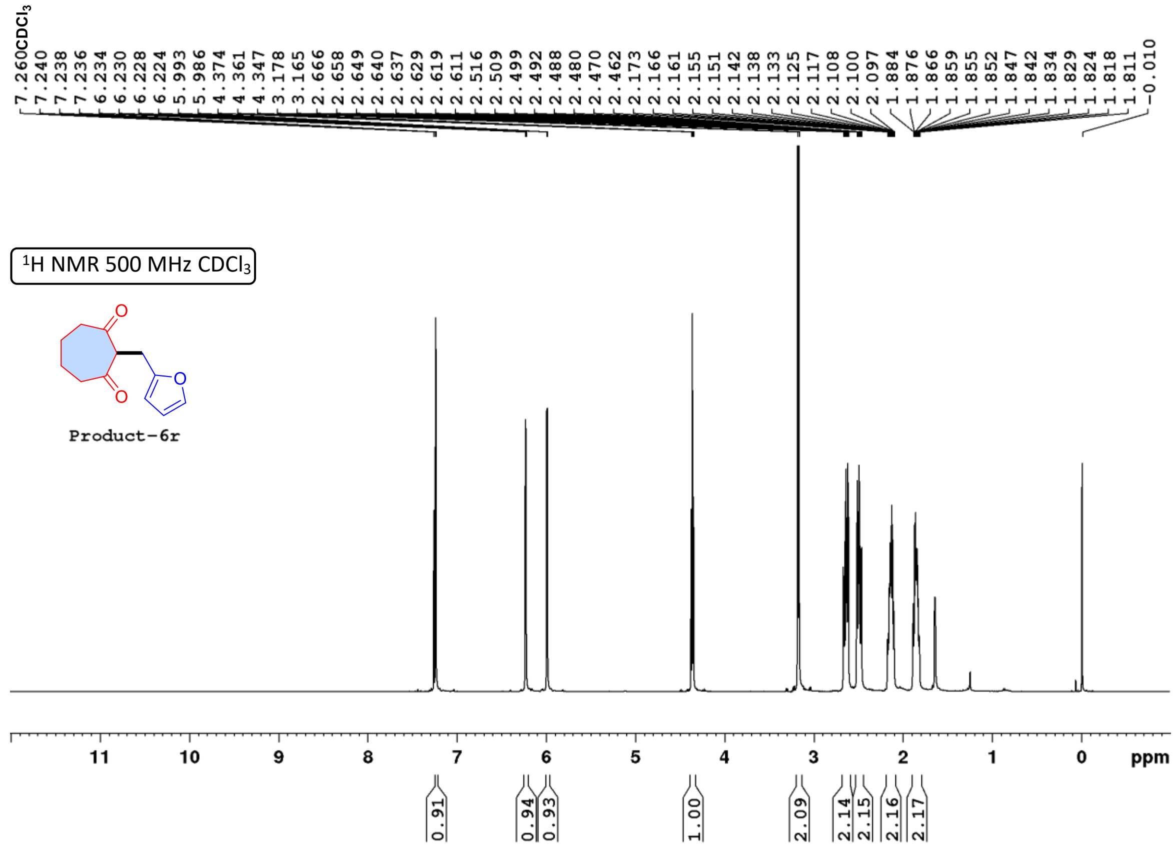


Figure 10: ^{1}H NMR and ^{13}C NMR spectrum of product **6q**.



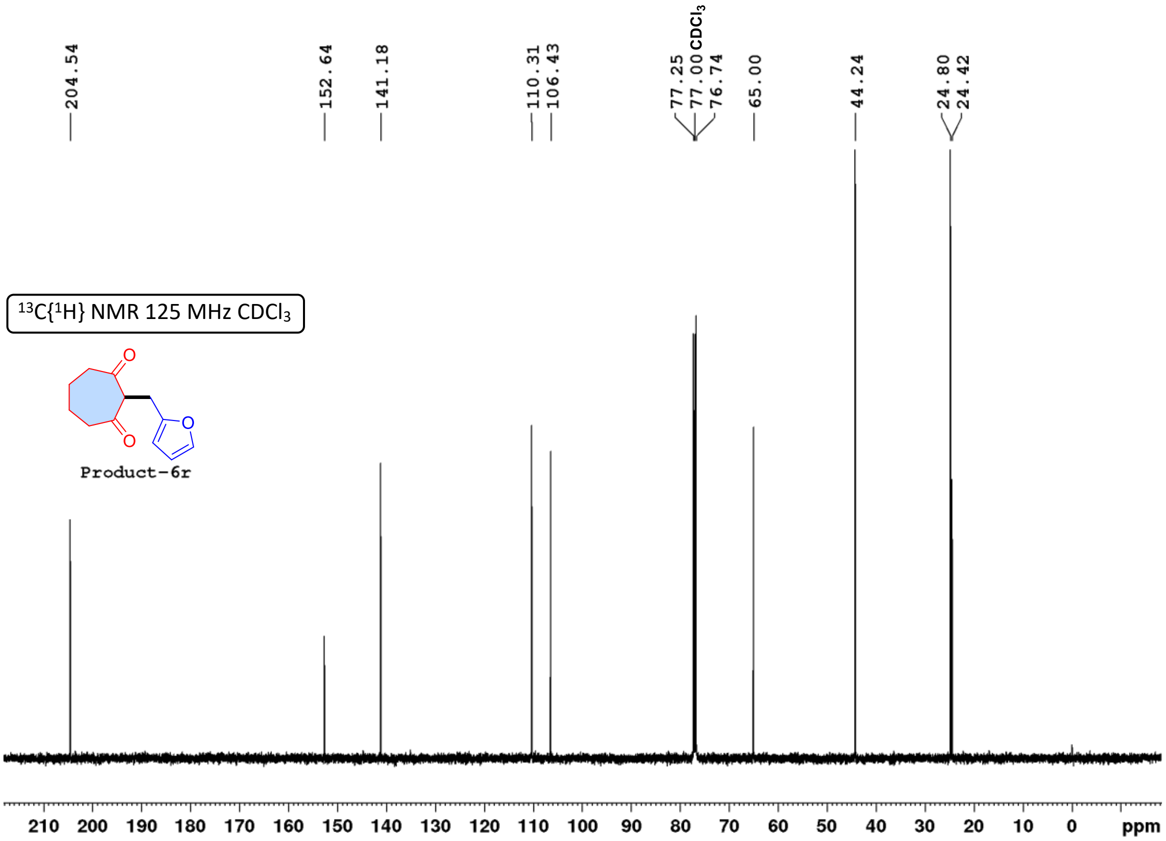


Figure 11: ^{1}H NMR and ^{13}C NMR spectrum of product **6r**.

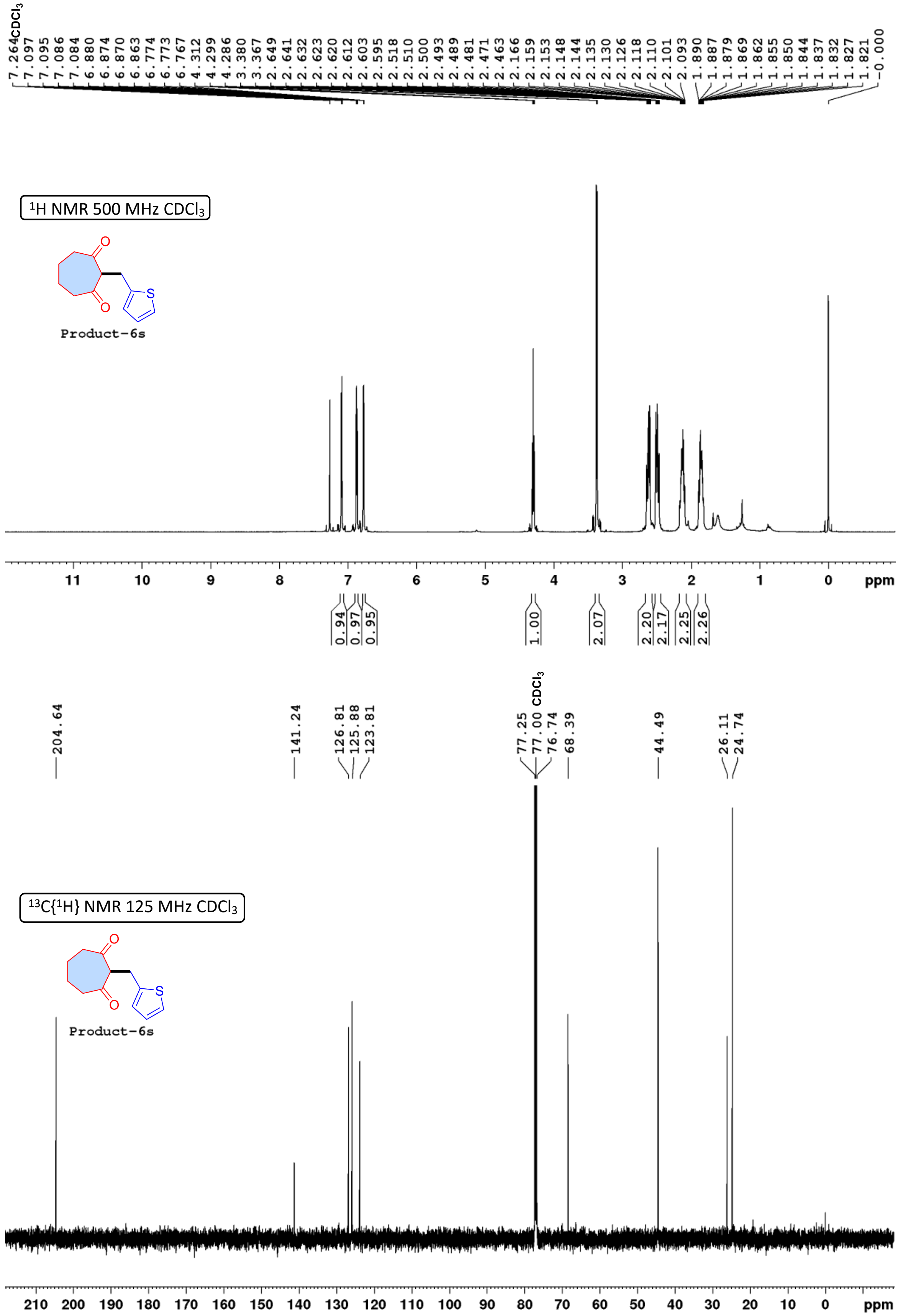
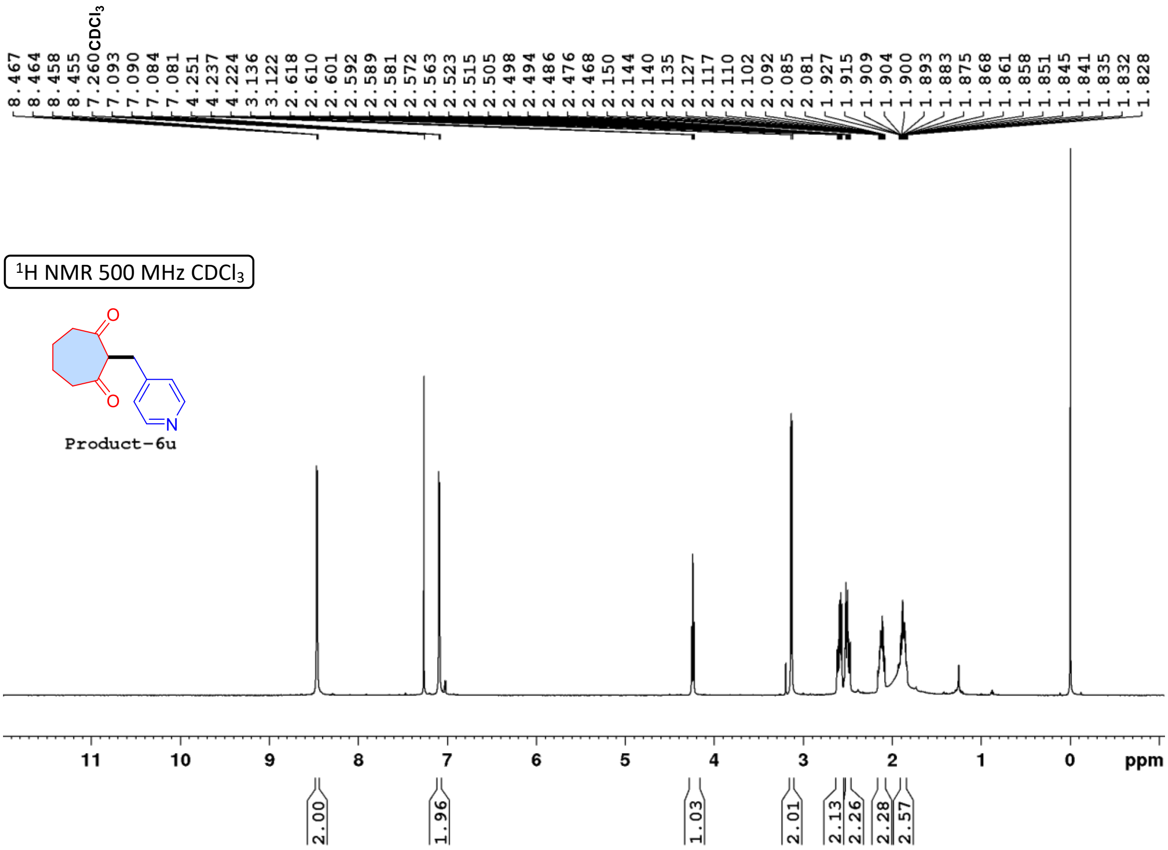


Figure 12: ^{1}H NMR and ^{13}C NMR spectrum of product **6s**.



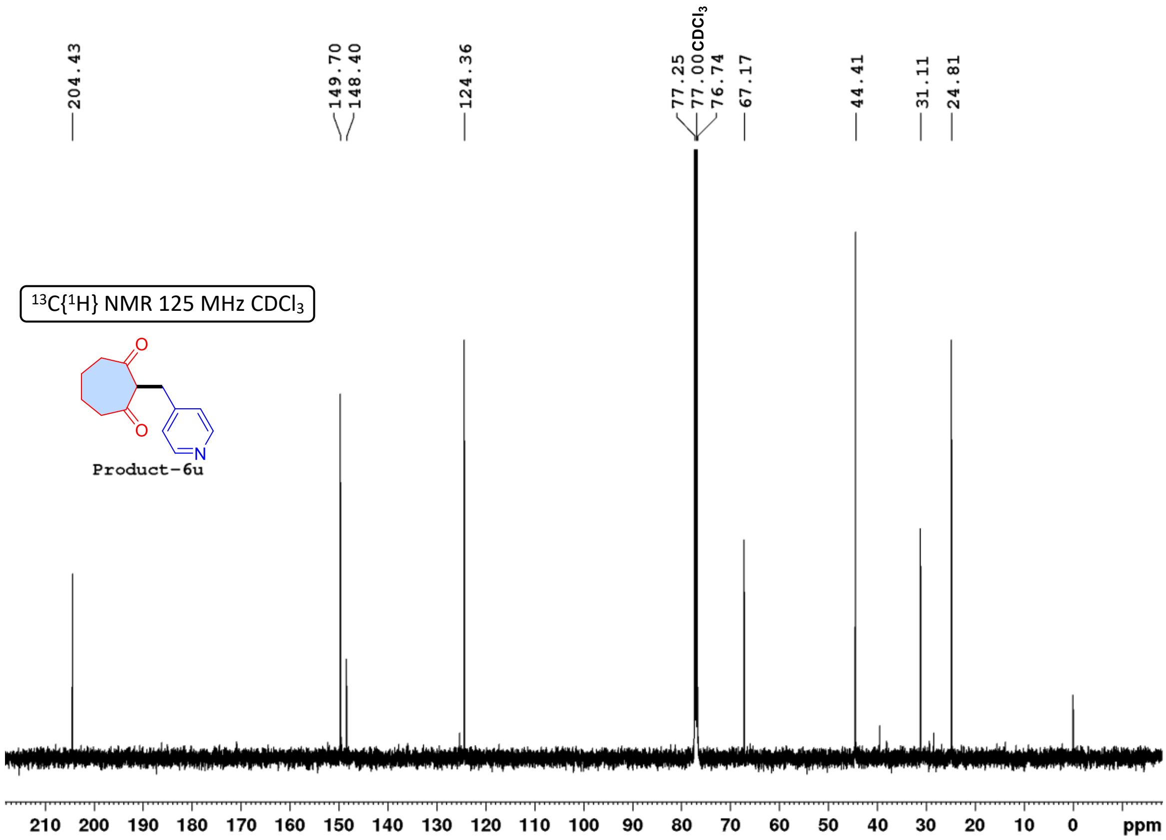


Figure 13: ^{1}H NMR and ^{13}C NMR spectrum of product **6u**.

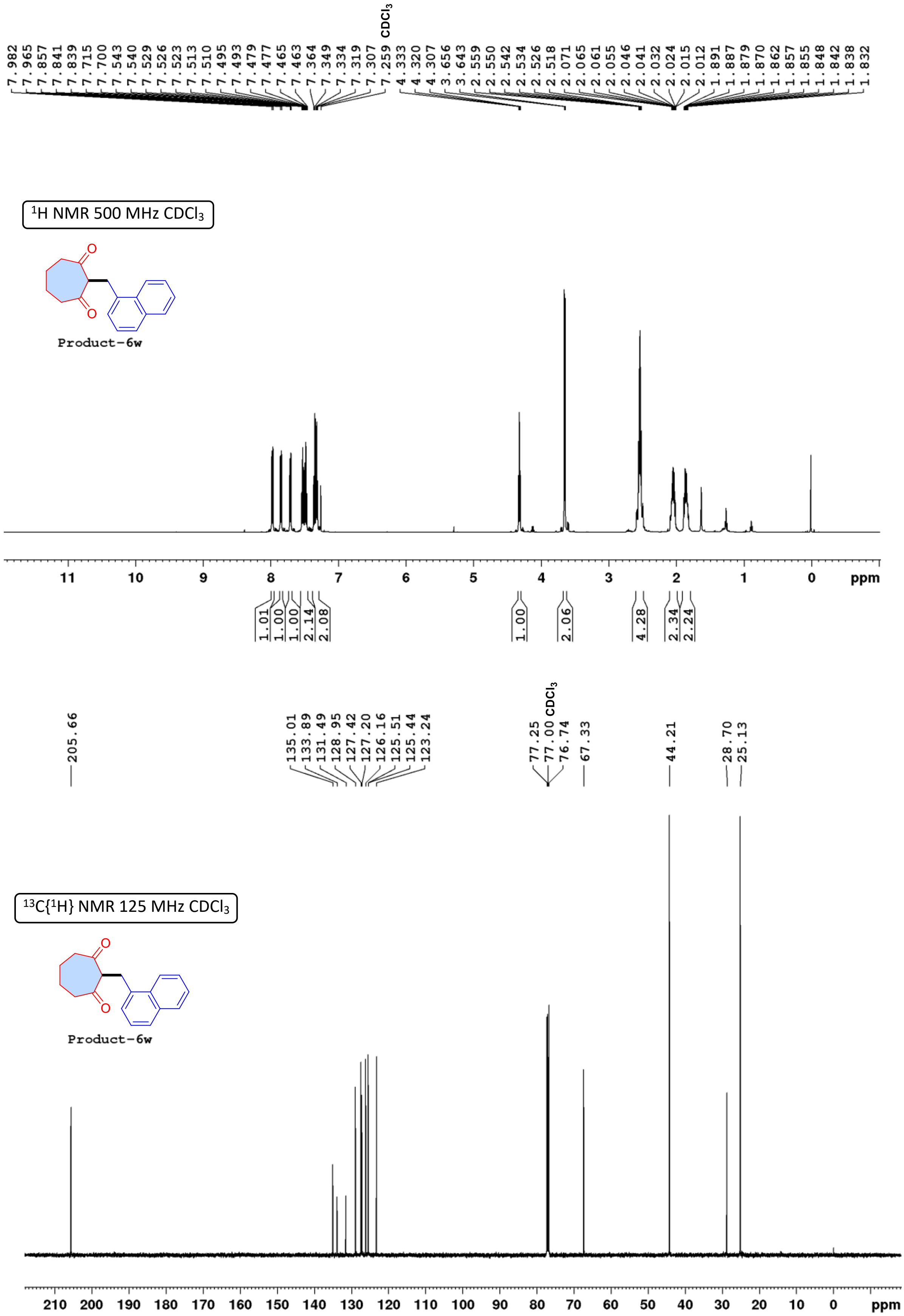
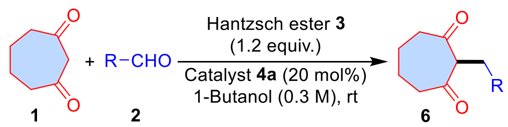


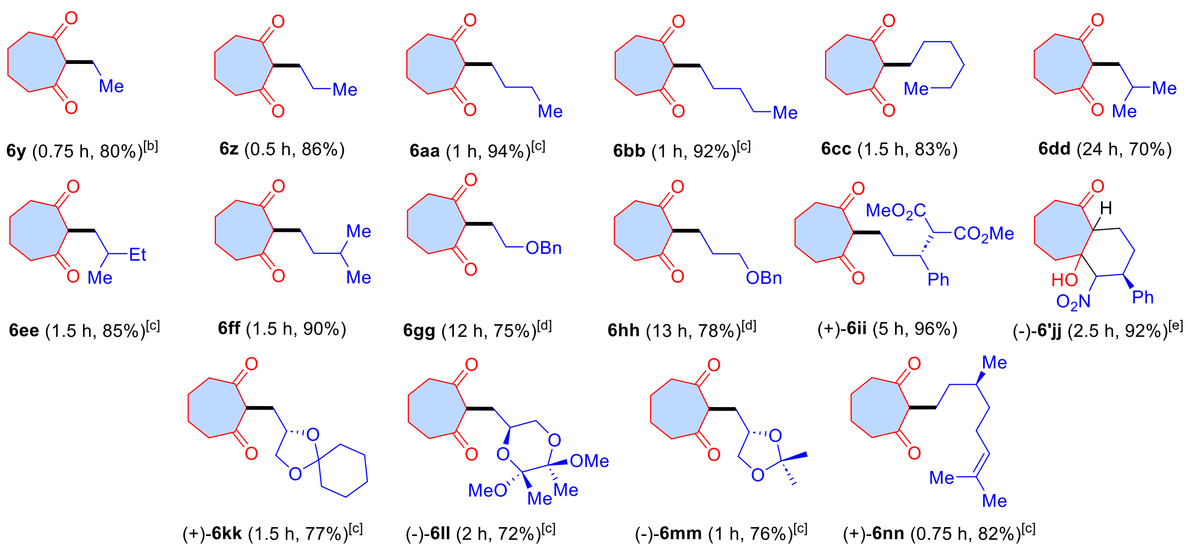
Figure 14: ^{1}H NMR and ^{13}C NMR spectrum of product **6v**.

5.2.2.2 Reaction scope with respect to various aliphatic and chiral aldehydes 2

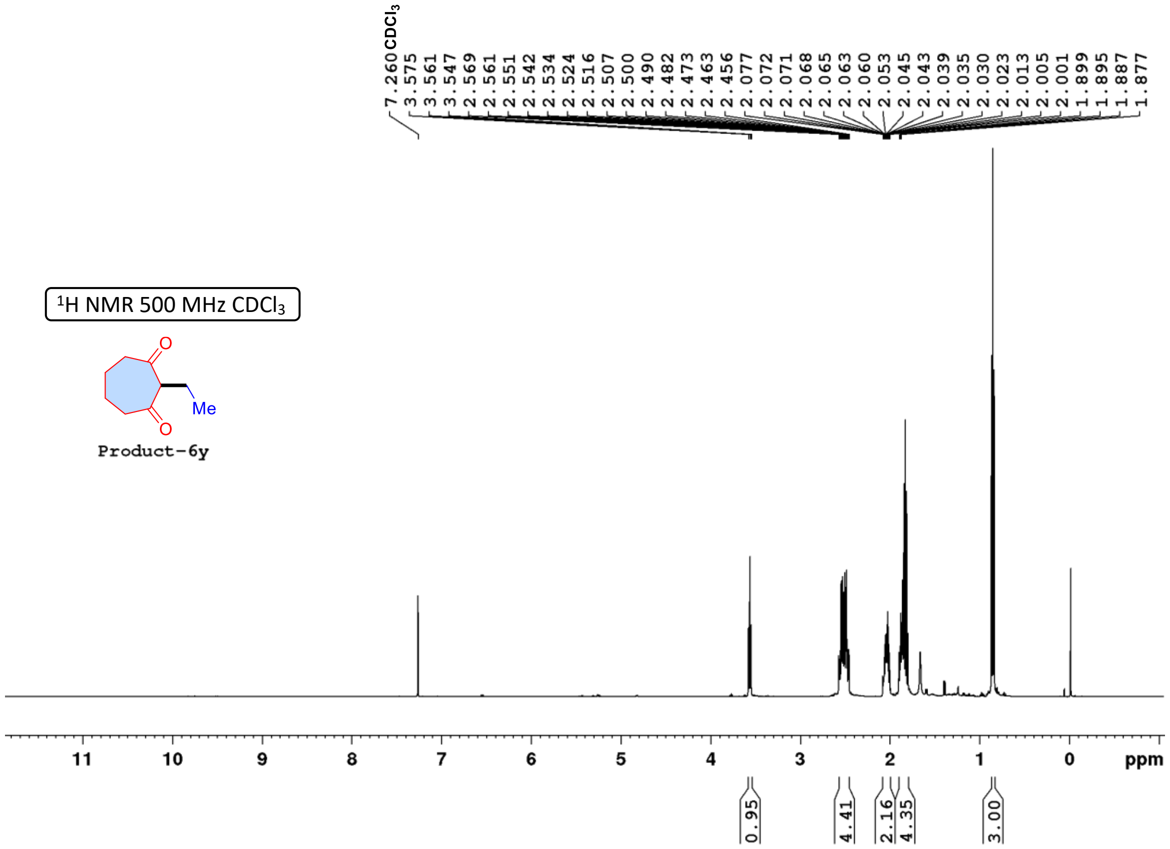
Extending the investigation of substrate scope, we further performed the reaction with various aliphatic and chiral aldehydes **2y-nn**. The reaction of **1** with **2y-nn** in the presence of 1.2 equiv. of **3** and 20 mol% **4a**/**4c** in 1-butanol (0.3 M) furnished the desired alkylation products **6y-nn** in excellent yields (Table 3). Interestingly, almost half of the aliphatic aldehydes, namely **2y**, **2z**, **2cc**, **2dd**, **2ff**, **2gg**, **2hh**, and **2ii** (91% *ee*)[8a], performed better under less reactive proline **4a**-catalysis rather than highly reactive aniline **4c**-catalysis to furnish the corresponding alkylation products **6y**, **6z**, **6cc**, **6dd**, **6ff**, **6gg**, **6hh**, and (+)-**6ii** with the yields of 70-96% in 0.5-24 h (Table 3). When cycloheptane-1,3-dione **1** was reacted with the chiral aldehyde **2jj** (95% *ee*)[8b] under proline **4a**-catalysis, the reaction directly afforded the cyclized product (-)-**6'jj** in 92% yield within 2.5 h which was the result of intramolecular cyclization of the corresponding reductive alkylation product (-)-**6jj** (Table 3). The remaining aliphatic and chiral aldehydes **2aa**, **2bb**, **2ee**, **2kk**, **2ll**, **2mm**, and **2nn** performed well under aniline **4c**-catalysis to furnish the corresponding products **6aa**, **6bb**, **6ee**, (+)-**6kk**, (-)-**6ll**, (-)-**6mm** and (+)-**6nn** with 72-94% yields in 0.75-2 h (Table 3) which were confirmed by NMR spectroscopy as shown in Figures 15-20. In case of **2gg** and **2hh**, DCM was used as a solvent since the reaction was not fruitful in 1-butanol (Table 3).

Table 3: Substrate scope for the reductive alkylation of cycloheptane-1,3-dione **1** with various aliphatic and chiral aldehydes **2.**[a]





[a] Reactions were carried out in 1-butanol (0.3 M) with 2.0 equiv. of **2** and 1.2 equiv. of **3** relatives to the **1** (0.3 mmol) in the presence of 20 mol% of **4a**. [b] 5.0 equiv. of aldehyde **2y** was used. [c] **4c** was used instead of **4a** as catalyst. [d] DCM was used as solvent. [e] TCRA product **6jj** underwent in situ cyclization to give single isomer of (-)-**6'jj**.



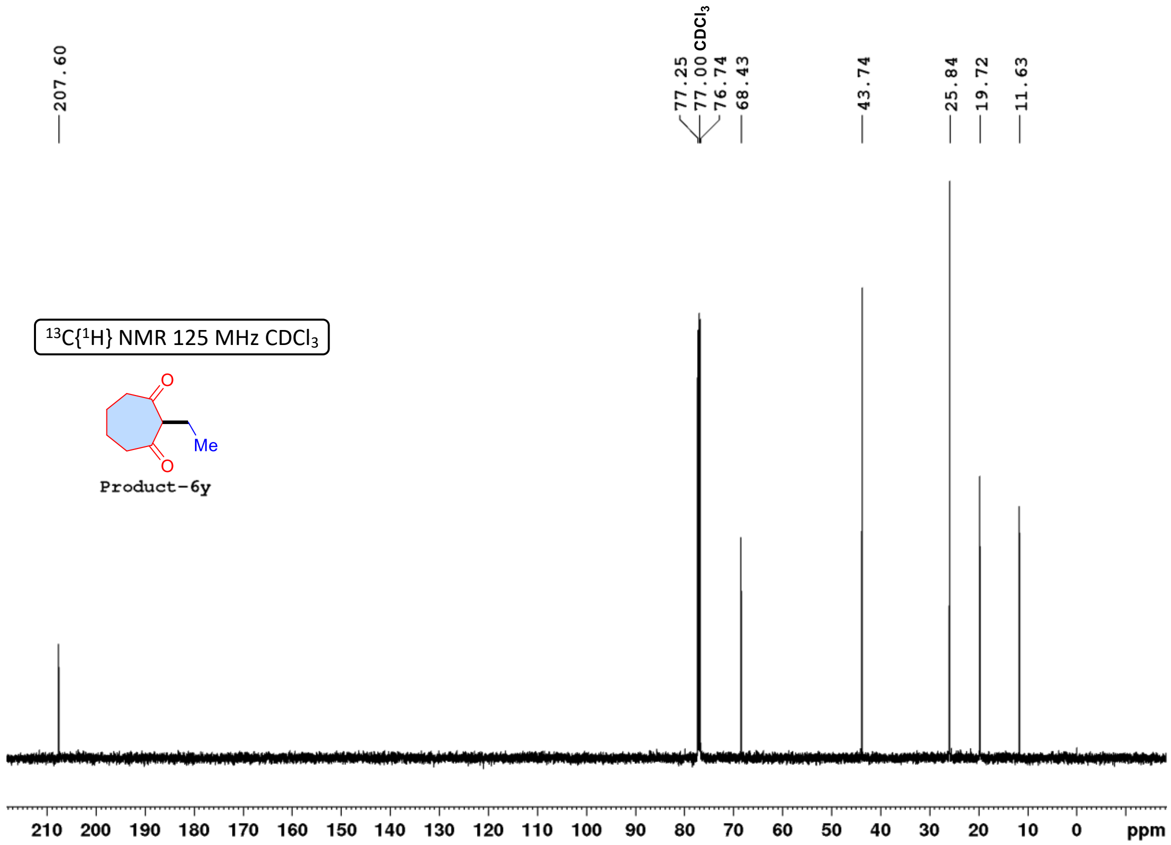
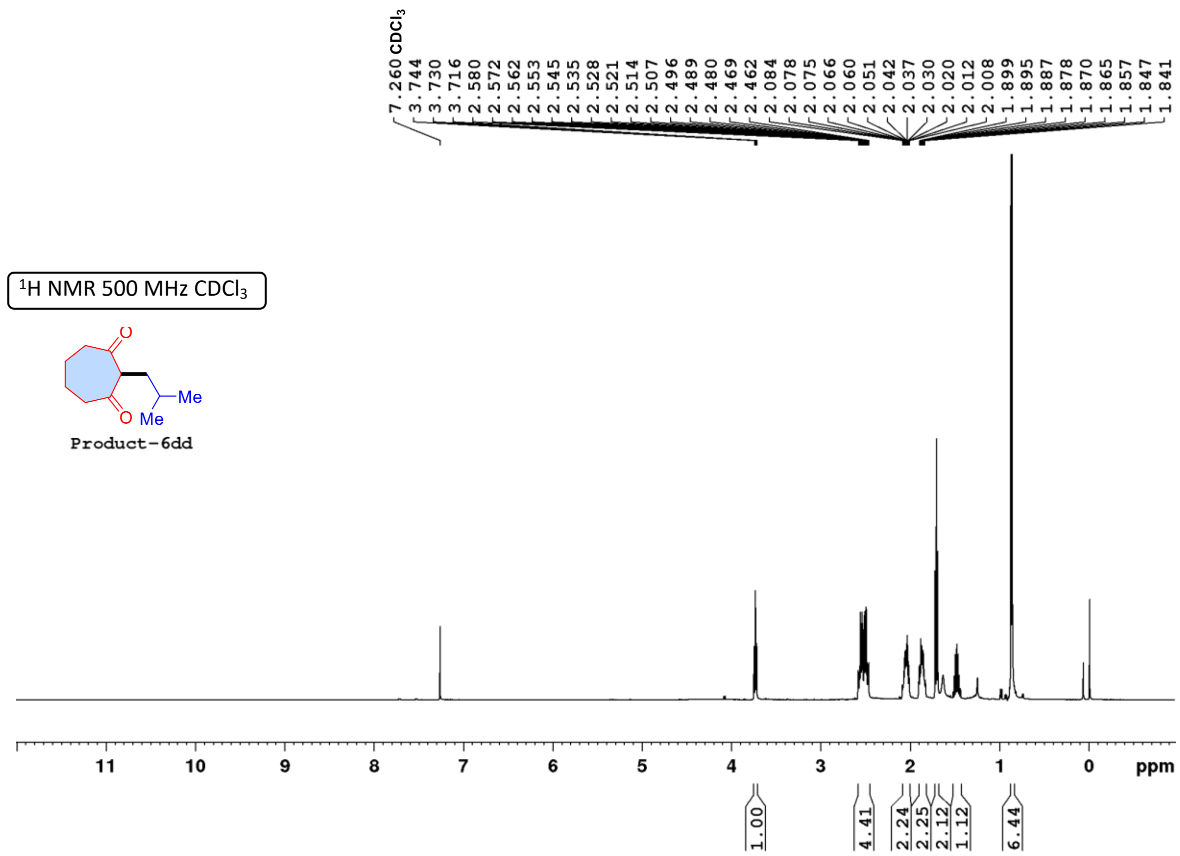


Figure 15: ^{1}H NMR and ^{13}C NMR spectrum of product **6y**.



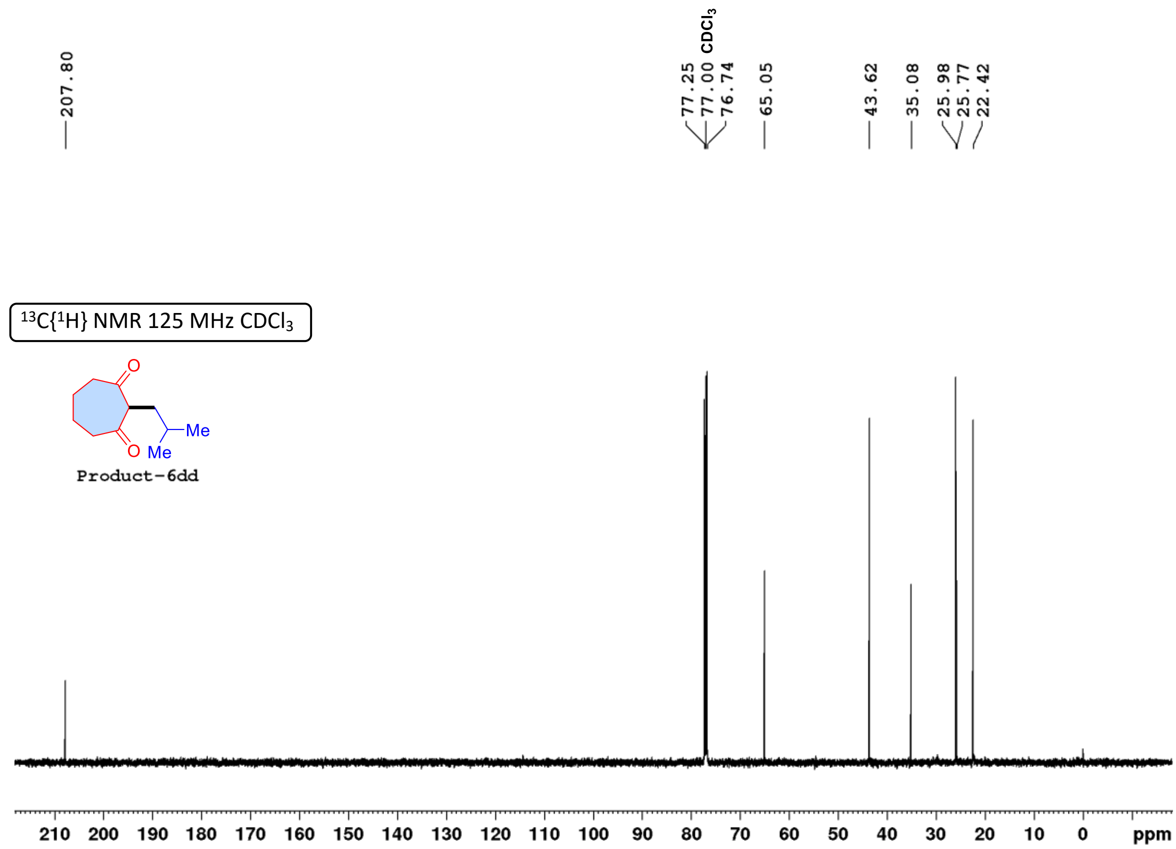


Figure 16: ^{1}H NMR and ^{13}C NMR spectrum of product **6dd**.

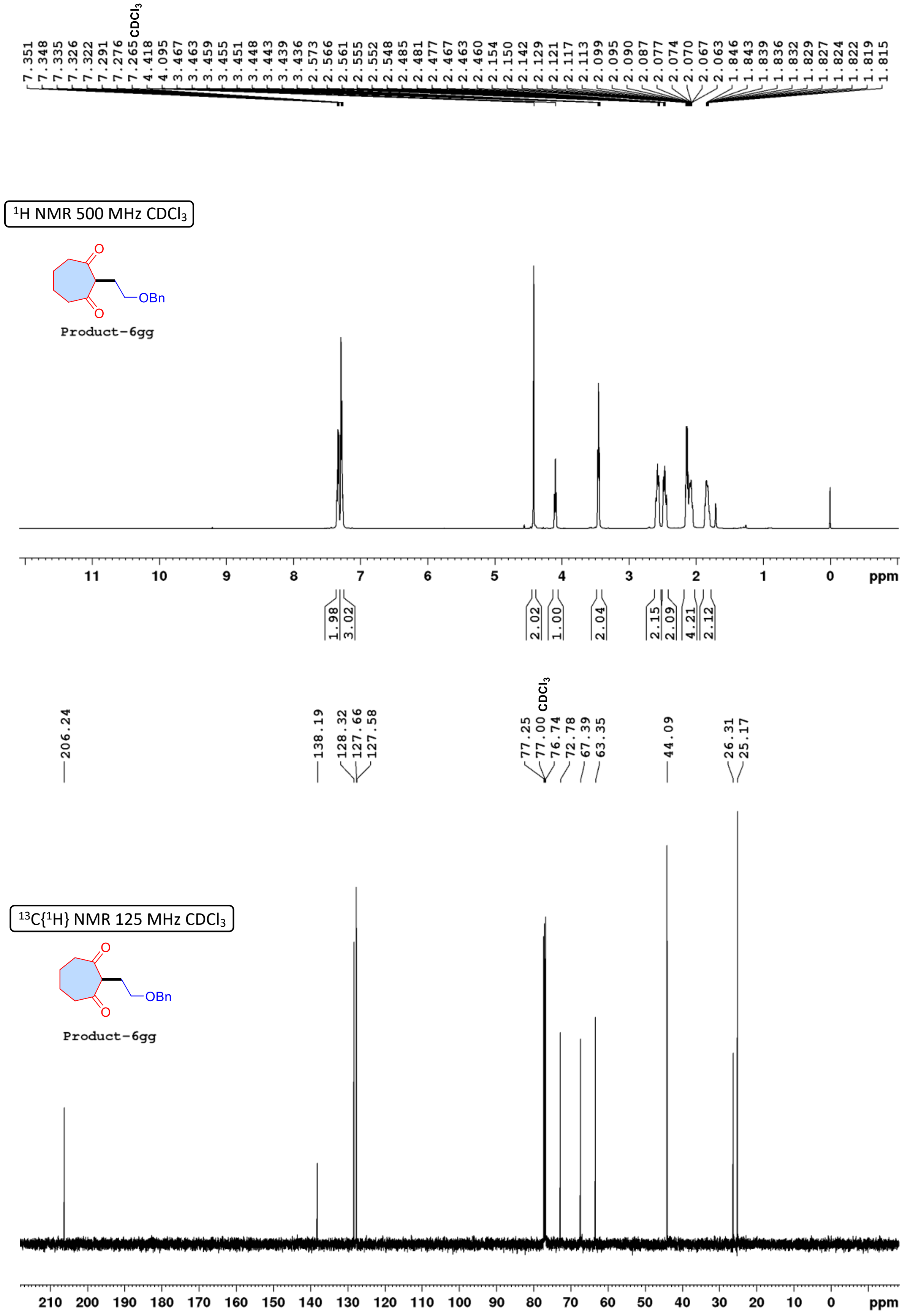
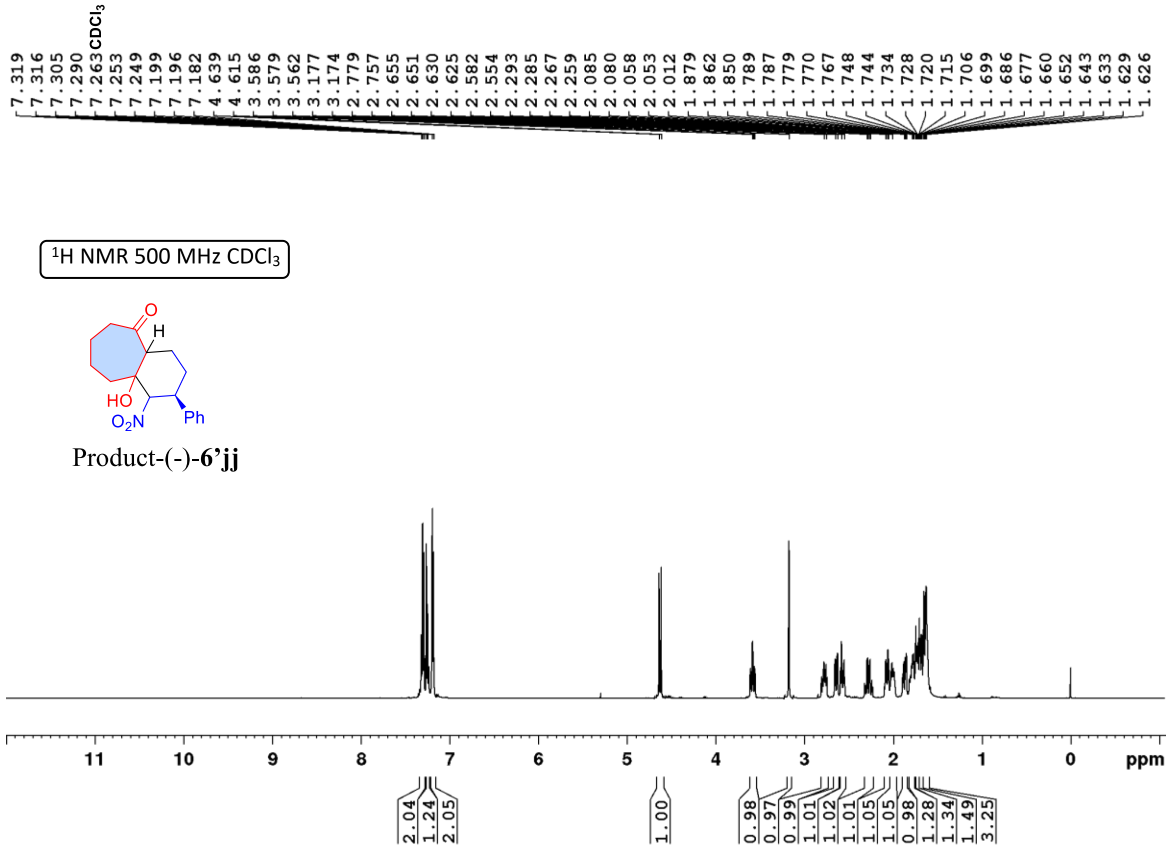


Figure 17: ^{1}H NMR and ^{13}C NMR spectrum of product **6gg**.



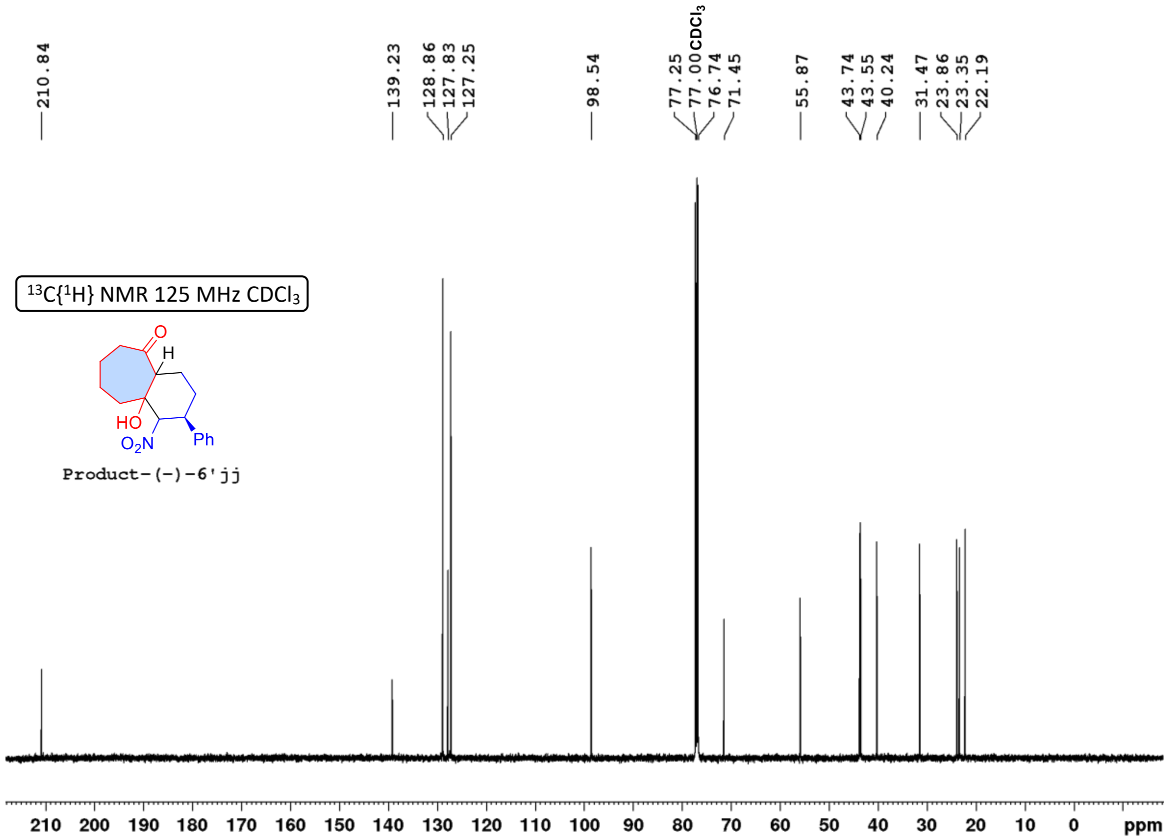
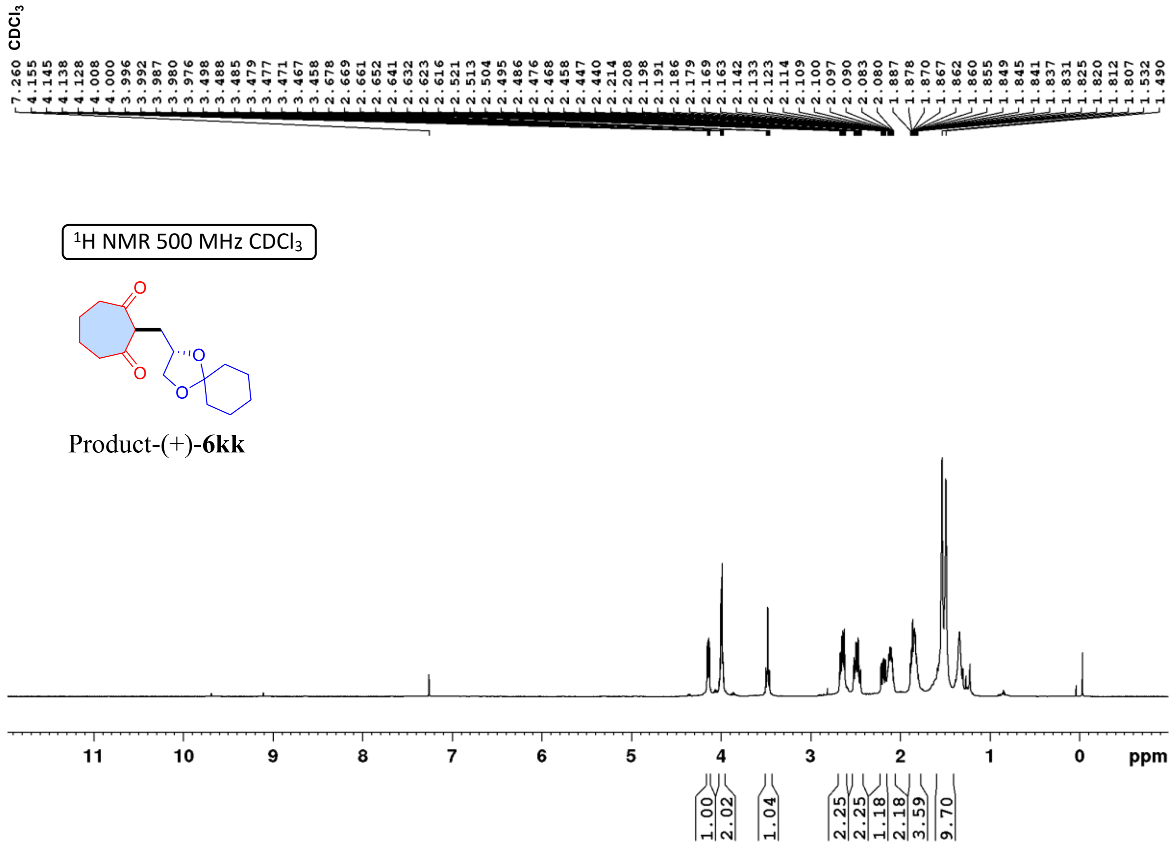


Figure 18: ^{1}H NMR and ^{13}C NMR spectrum of product (-)-**6'jj**.



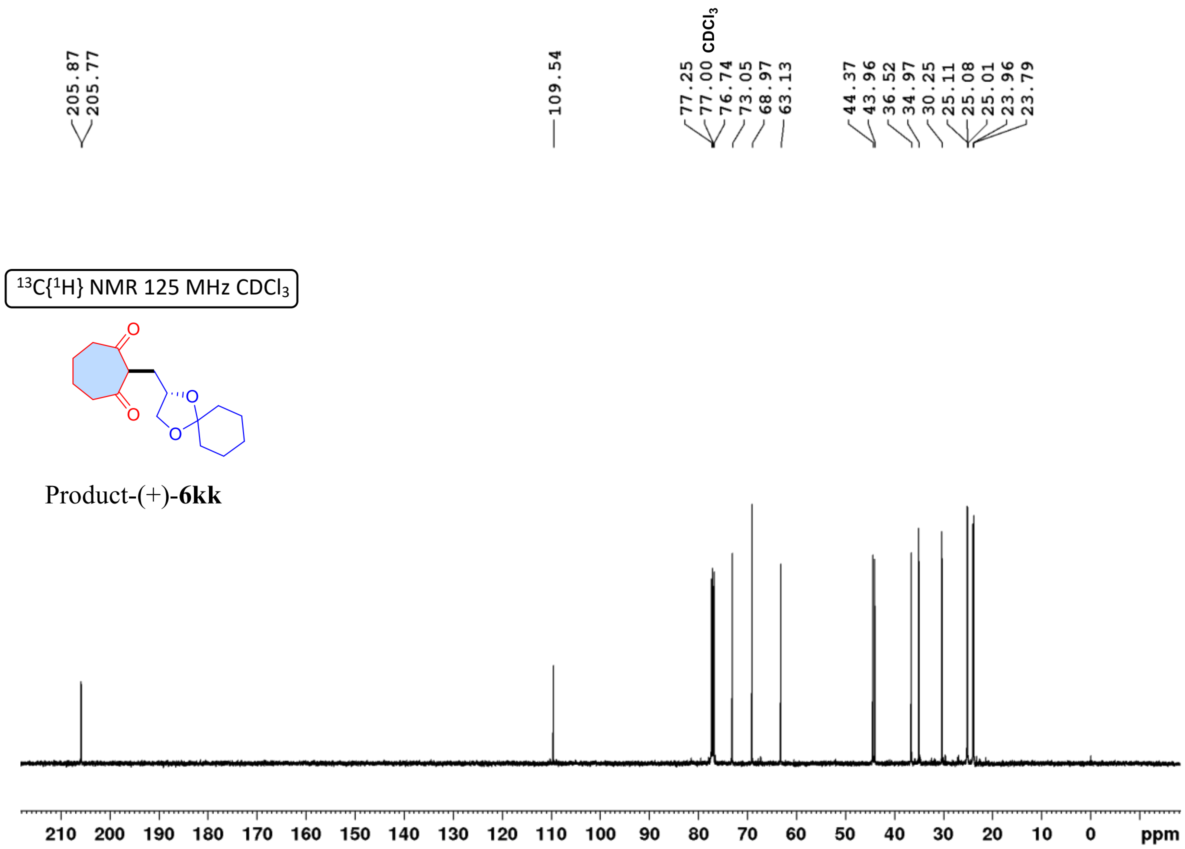


Figure 19: ^{1}H NMR and ^{13}C NMR spectrum of product (+)-**6kk**.

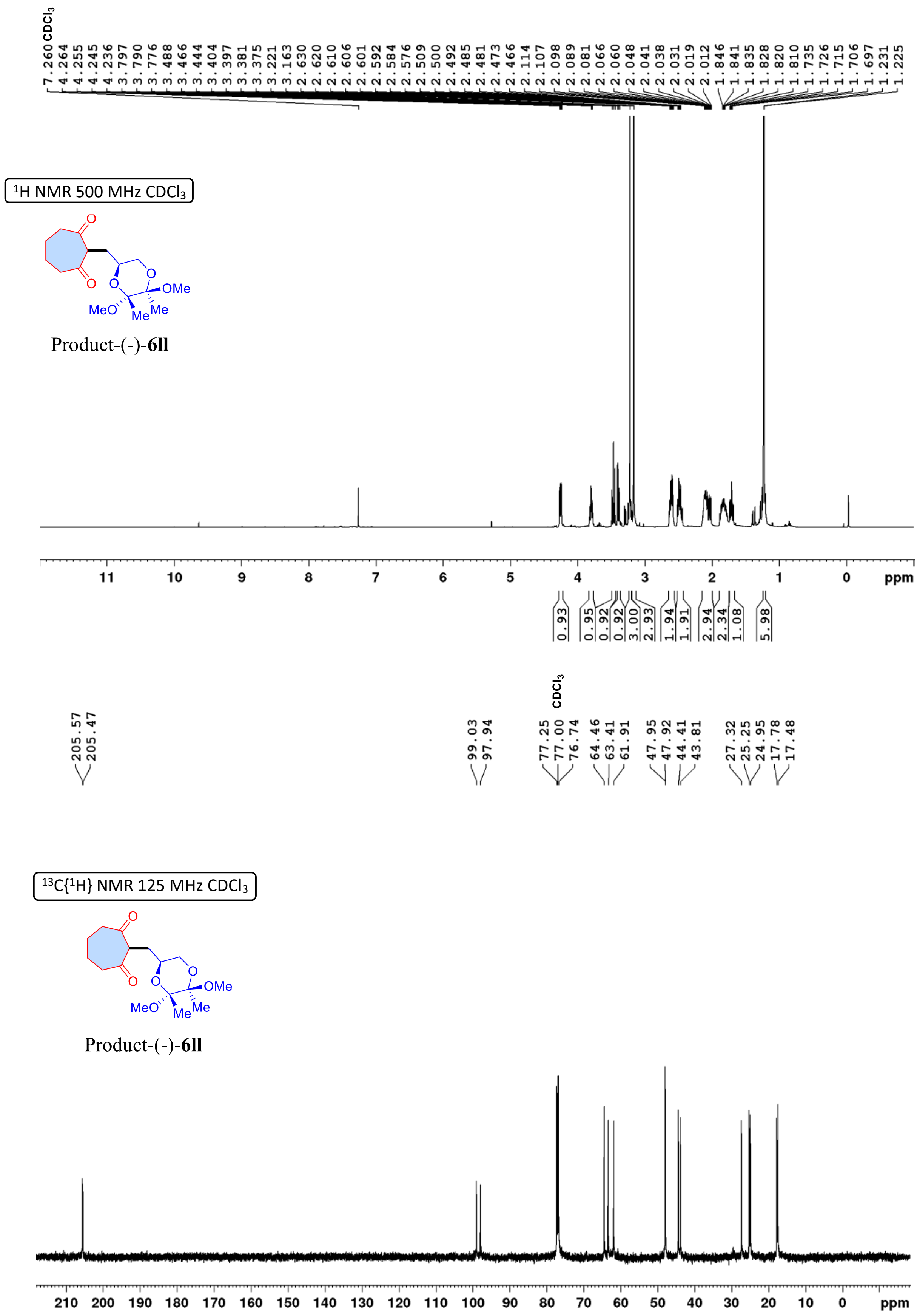
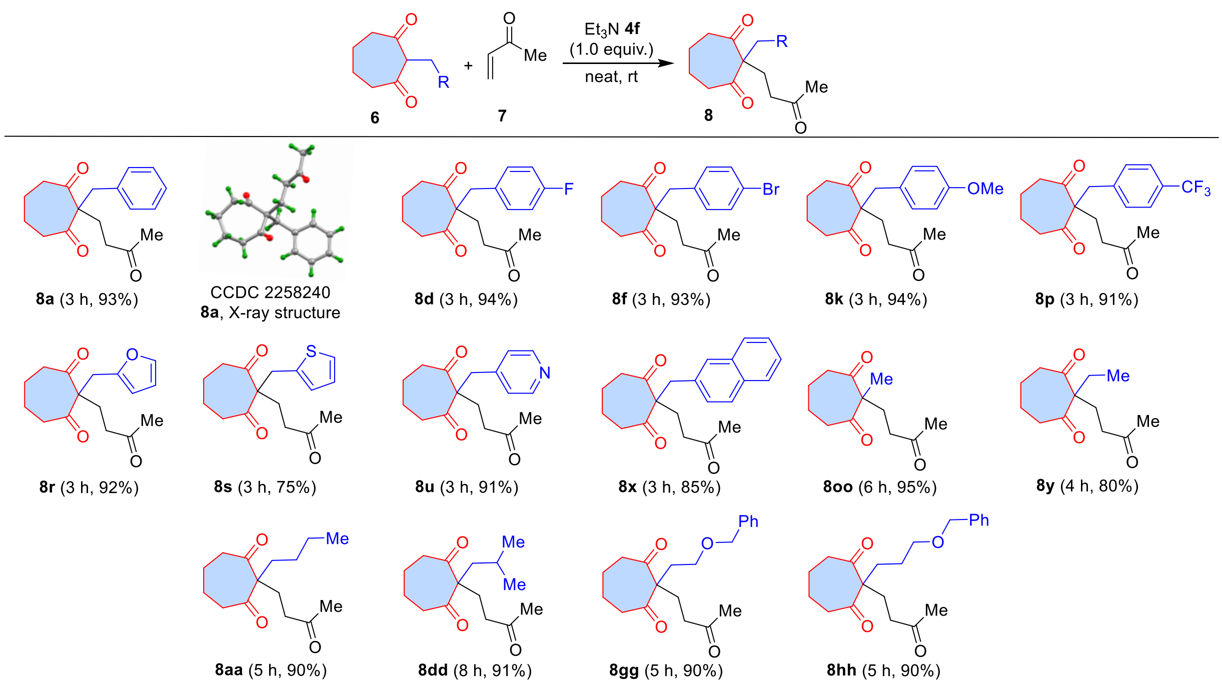


Figure 20: ^{1}H NMR and ^{13}C NMR spectrum of product (-)-**6ll**.

5.2.3 Investigation of Michael Addition on 2-alkylcycloheptane-1,3-diones 6 to Access Functionally Rich Triketones 8

After successful investigation of organocatalytic reductive coupling on **1** with **2** and **3**, our next target was to achieve high-yielding functionally rich triketones **8** through Michael addition of 2-alkylcycloheptane-1,3-diones **6** with methyl vinyl ketone **7**. Based on our previous laboratory experience on Michael addition, we had chosen Et_3N **4f** as a base to catalyze the Michael addition of various functionalized 2-alkylcycloheptane-1,3-dione **6** with methyl vinyl ketone **7** under neat conditions.[6c] The reaction of 2-benzylcycloheptane-1,3-dione **6a** with 3.0 equiv. of methyl vinyl ketone **7** in the presence of Et_3N **4f** (1.0 equiv.) afforded the Michael adduct **8a** with an excellent yield of 93% in 3 h (Table 4). Then, functionalized 2-alkylcycloheptane-1,3-diones **6** such as 2-(4-fluorobenzyl)-, 2-(4-bromobenzyl)-, 2-(4-methoxybenzyl)- and 2-(4-trifluoromethylbenzyl)-cycloheptane-1,3-diones (**6d**, **6f**, **6k**, **6p**) reacted readily with methyl vinyl ketone **7** under Et_3N **4f** catalysis affording the corresponding triketones **8d**, **8f**, **8k**, and **8p** with excellent yields of 94%, 93%, 94%, and 91% respectively in just 3 h (Table 4).

Table 4: Michael addition of 2-alkylcycloheptane-1,3-diones **6** with methyl vinyl ketone **7**[a]



[a] Reactions were carried out with 3.0 equiv. of **7** relative to the compound **6** (0.2 mmol) in the presence of 1.0 equiv. of Et_3N **4f**.

The Michael reaction was also well tolerated towards 2-(furan-2-ylmethyl)-, 2-(thiophene-2-ylmethyl)-, 2-(pyridine-4-ylmethyl)-, and 2-(naphthalen-2-ylmethyl)-cycloheptane-1,3-diones (**6r**, **6s**, **6u** and **6x**) yielding the desired triketones **8r**, **8s**, **8u** and **8x** with 92%, 75%, 91% and 85% in 3 h respectively (Table 4). Further, the Michael reactions were performed on various 2-alkyl substituted cycloheptane-1,3-diones **6oo**, **6y**, **6aa**, **6dd**, **6gg,** and **6hh**, where all of them furnished the corresponding triketones **8oo**, **8y**, **8aa**, **8dd**, **8gg** and **8hh** with 80-95% yields in 4-8 h (Table 4) (for NMR spectra, see Figures 22-29). The 2-methylcycloheptane-1,3-dione **6oo** used in this reaction was synthesized using the reported protocol.[4a] Henceforth, we successfully created a library of functionally diverse potential triketone synthons **8** in order to investigate catalytic conformation-controlled intramolecular aldol condensation reaction through asymmetric desymmetrization.

The structure of compound **8a** was again confirmed by X-ray crystallography (Figure 21).[7]

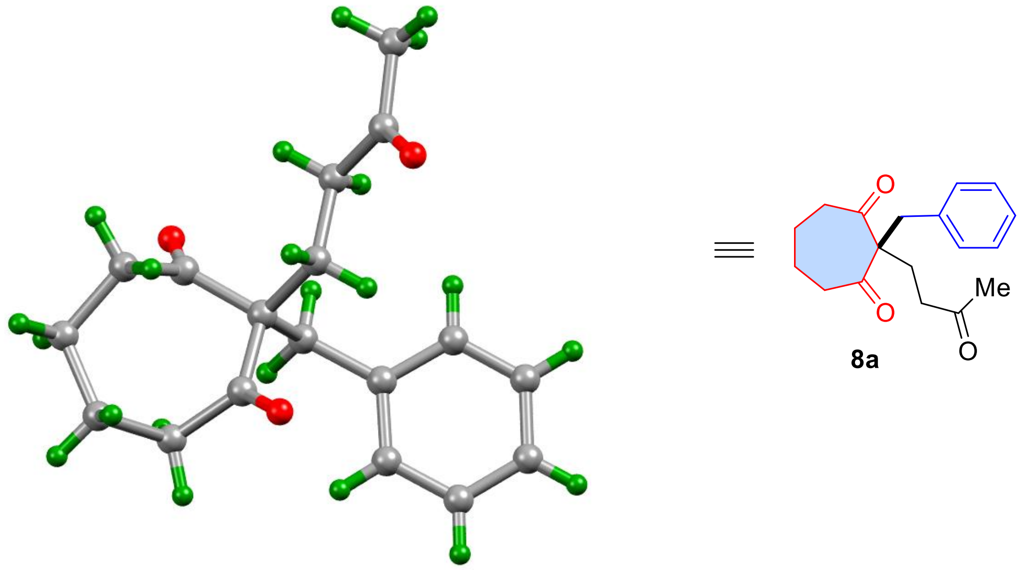
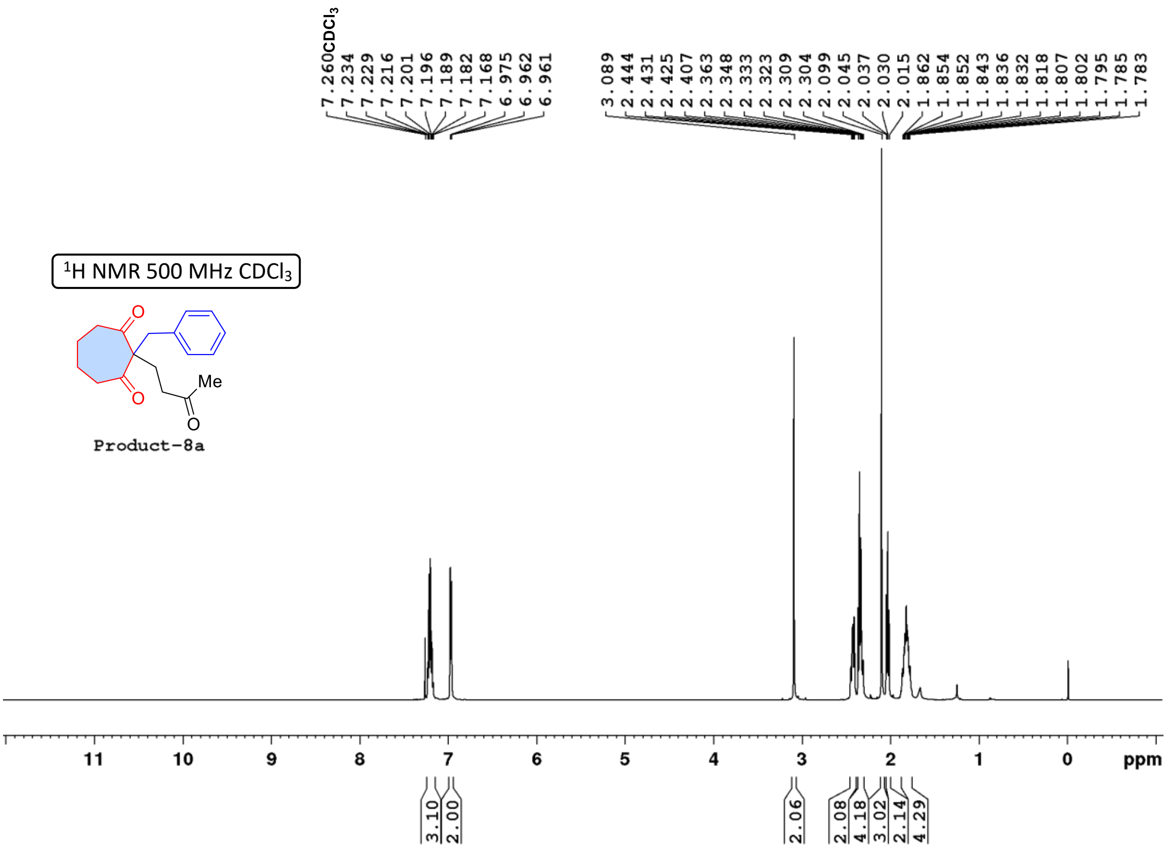


Figure 21: X-Ray crystal structure of 2-benzyl-2-(3-oxobutyl)cycloheptane-1,3-dione (**8a**).



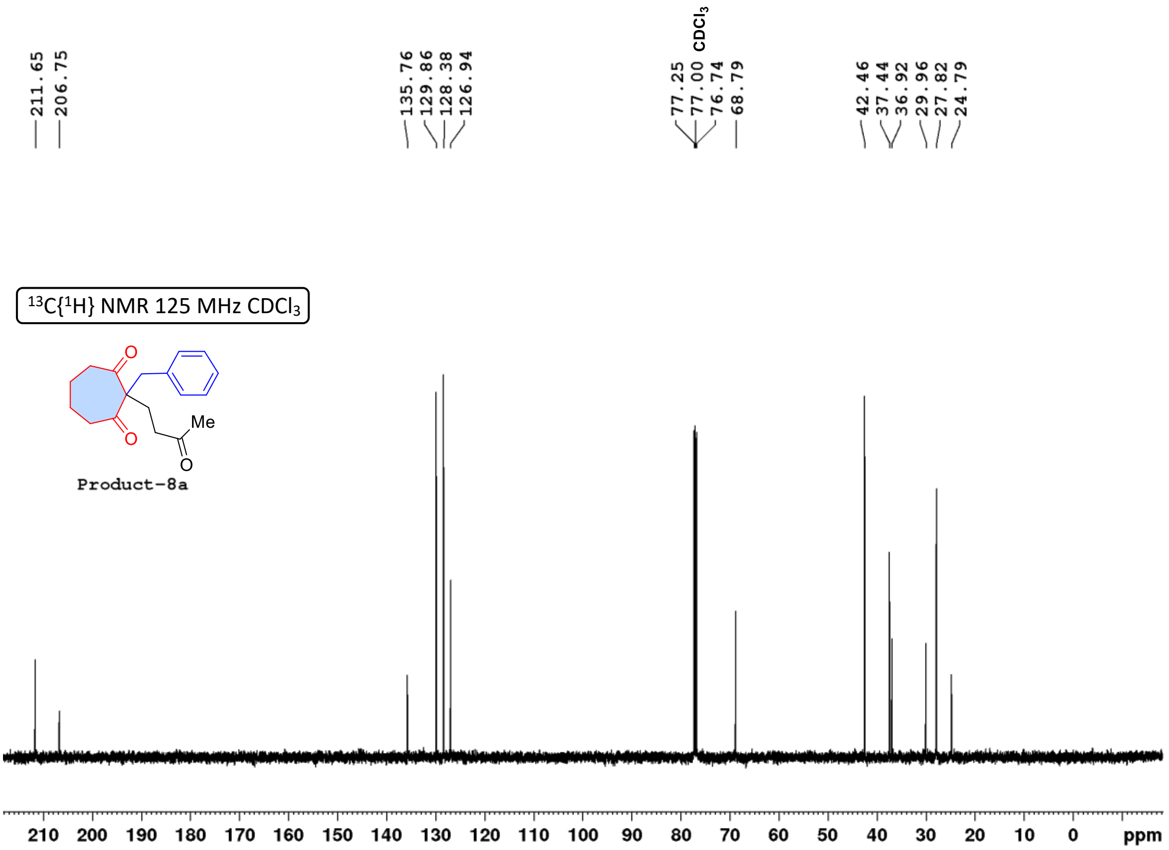
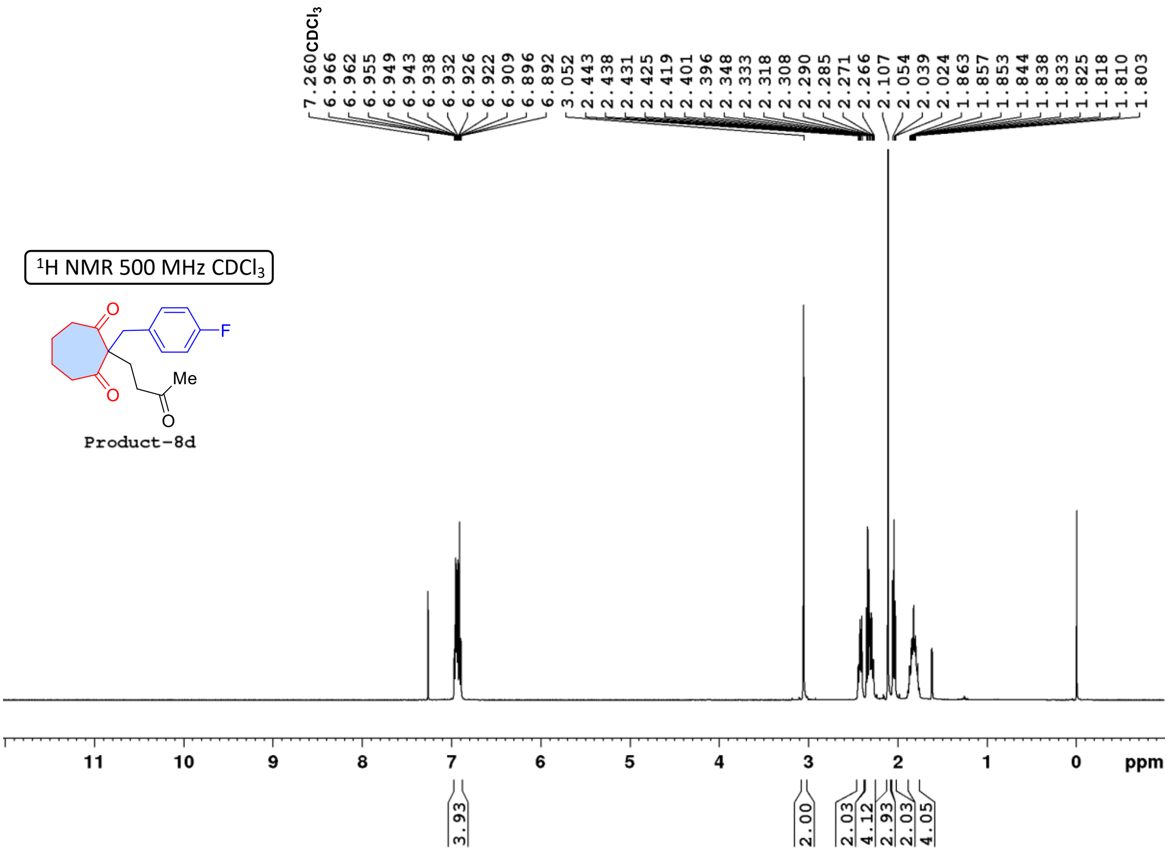


Figure 22: ^{1}H NMR and ^{13}C NMR spectrum of product **8a**.



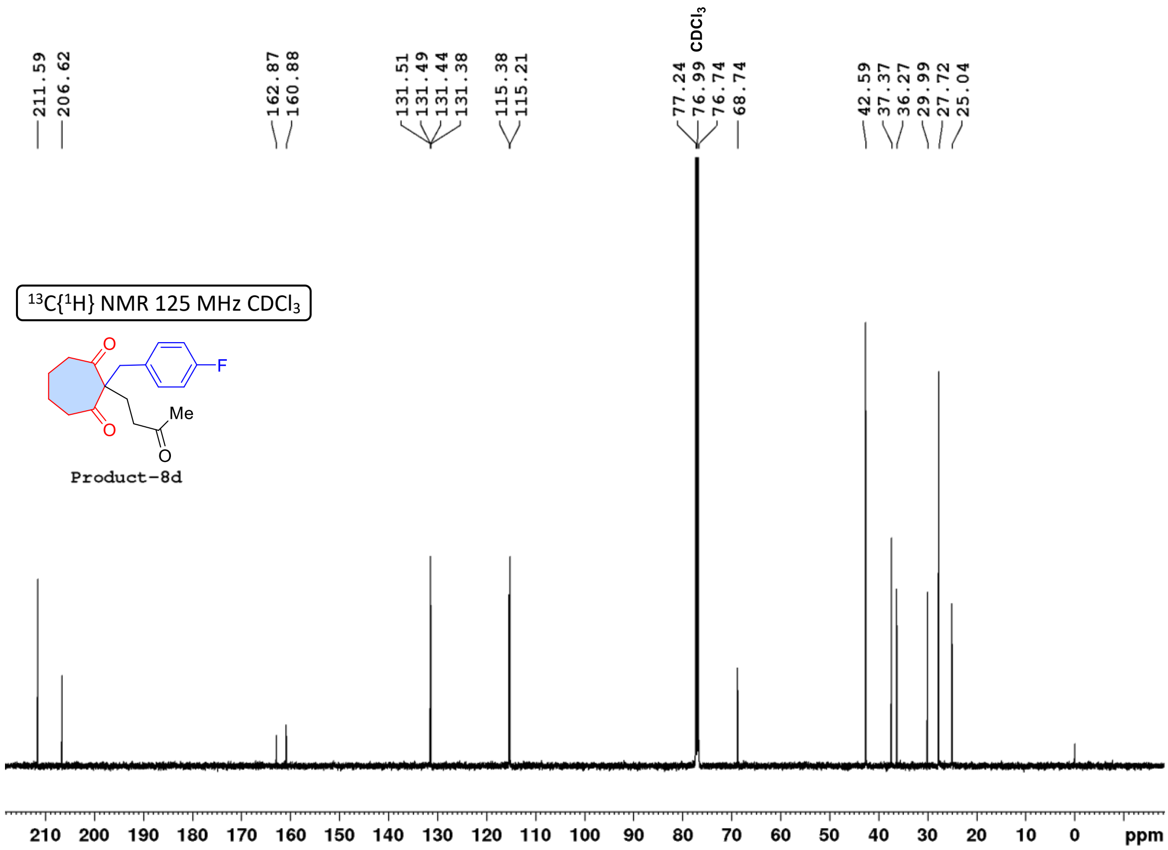
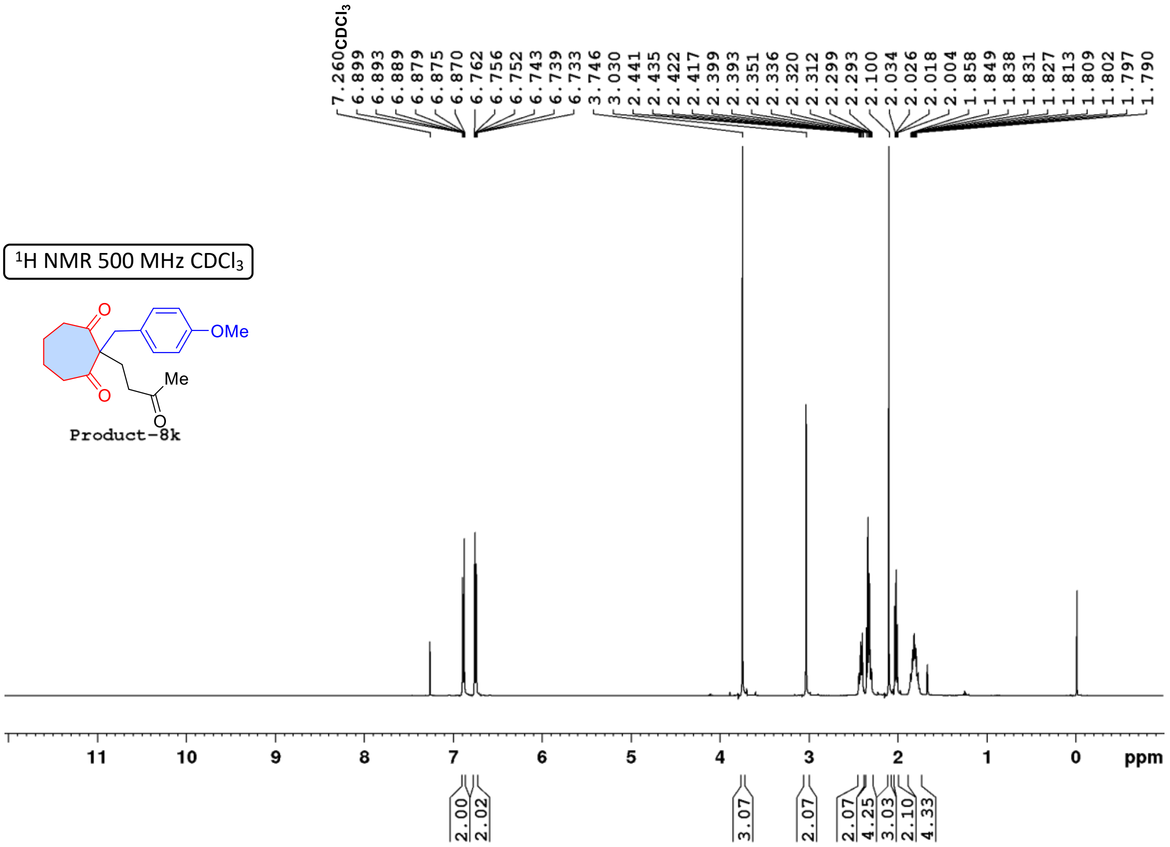


Figure 23: ^{1}H NMR and ^{13}C NMR spectrum of product **8d**.



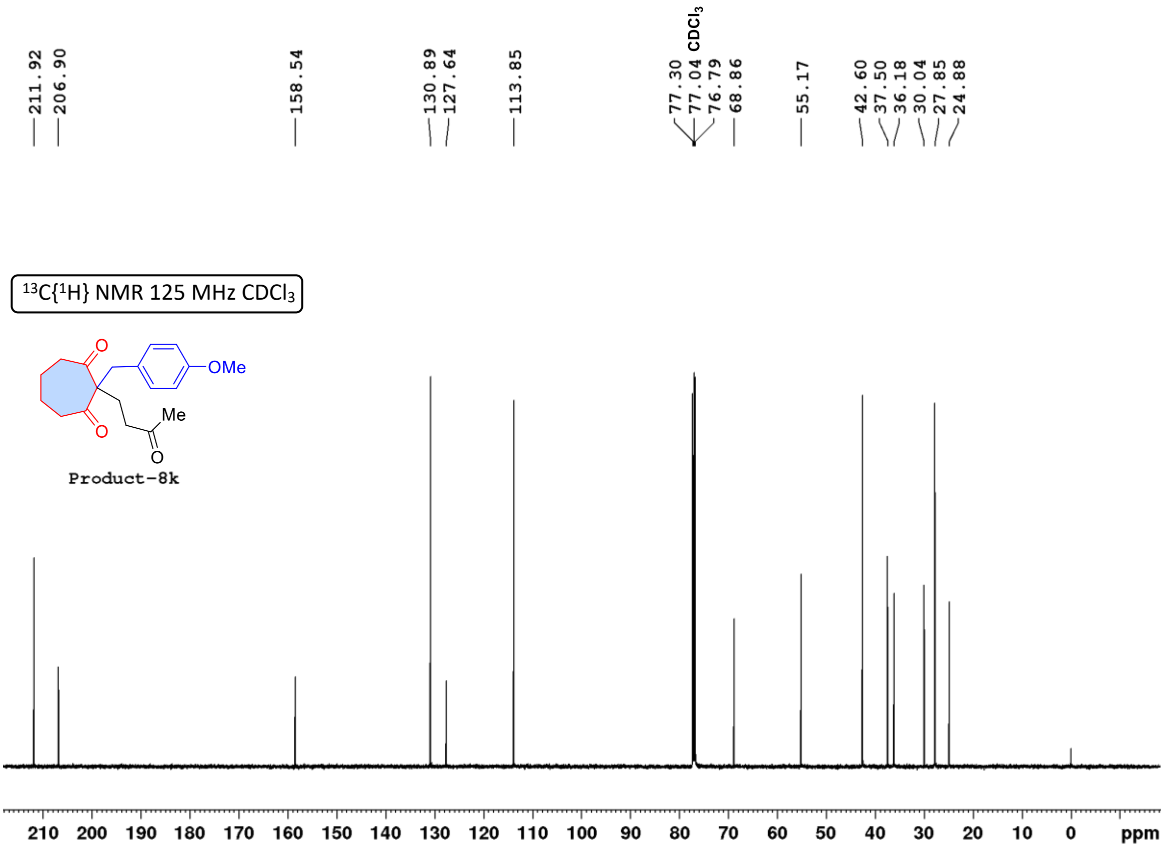
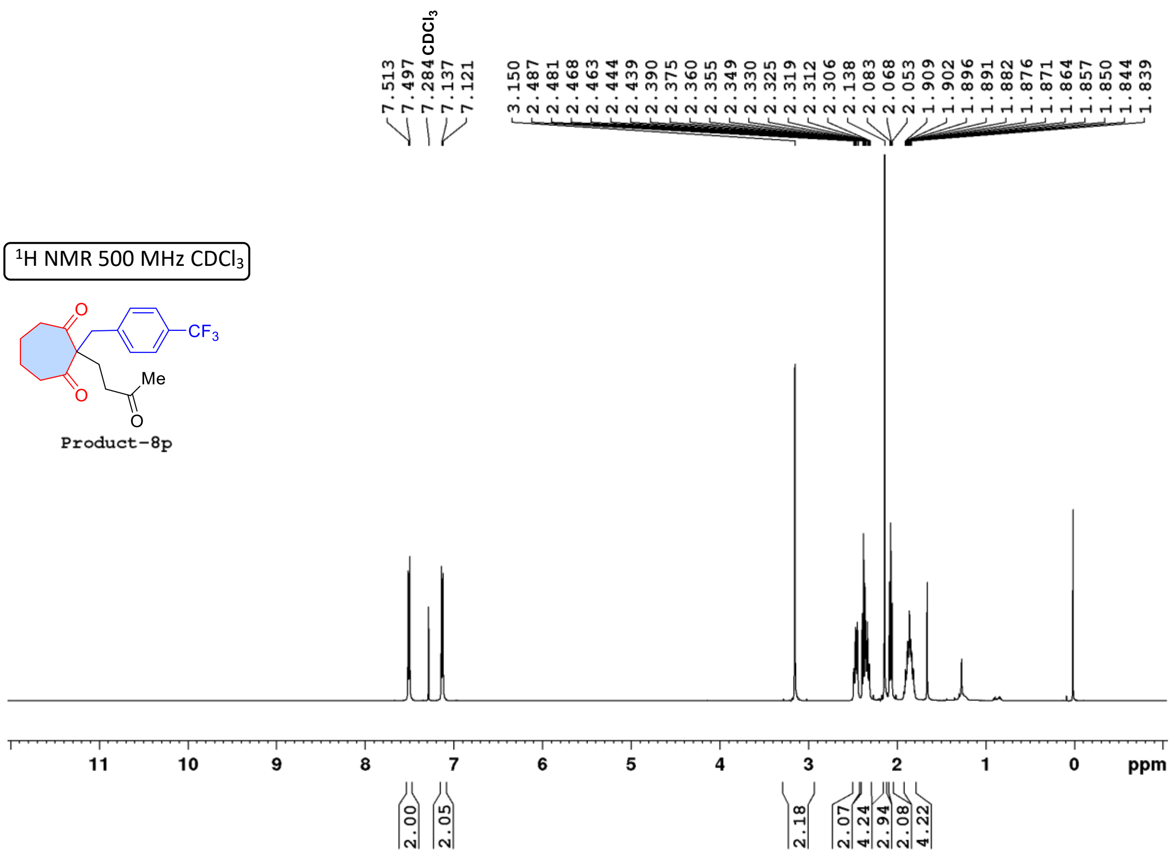


Figure 24: ^{1}H NMR and ^{13}C NMR spectrum of product **8k**.



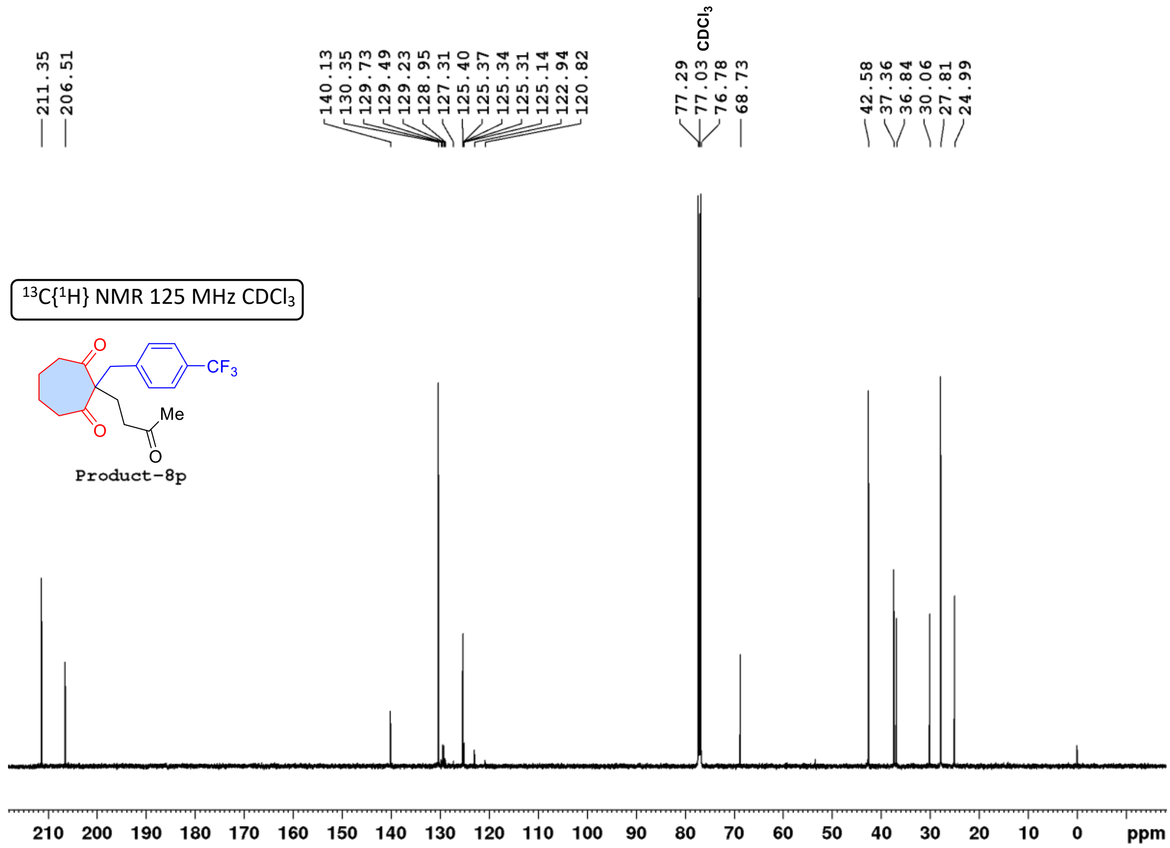
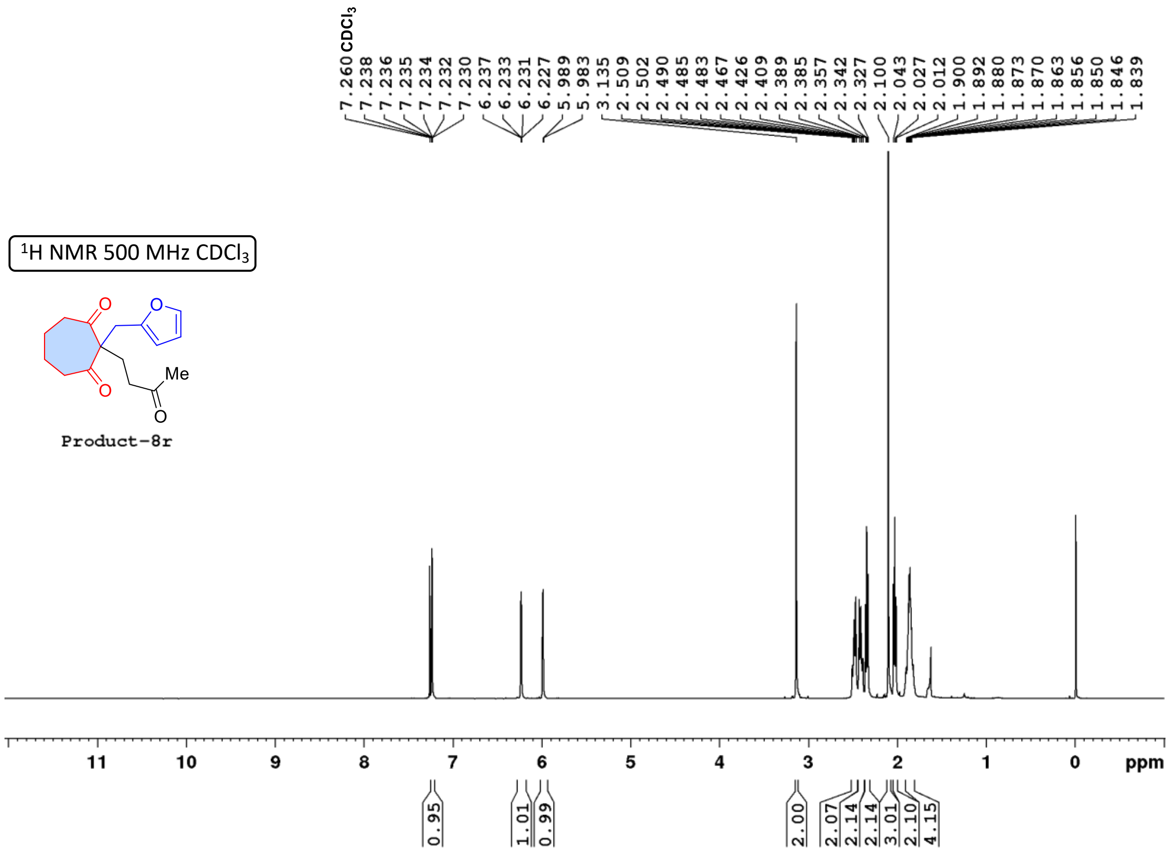


Figure 25: ^{1}H NMR and ^{13}C NMR spectrum of product **8p**.



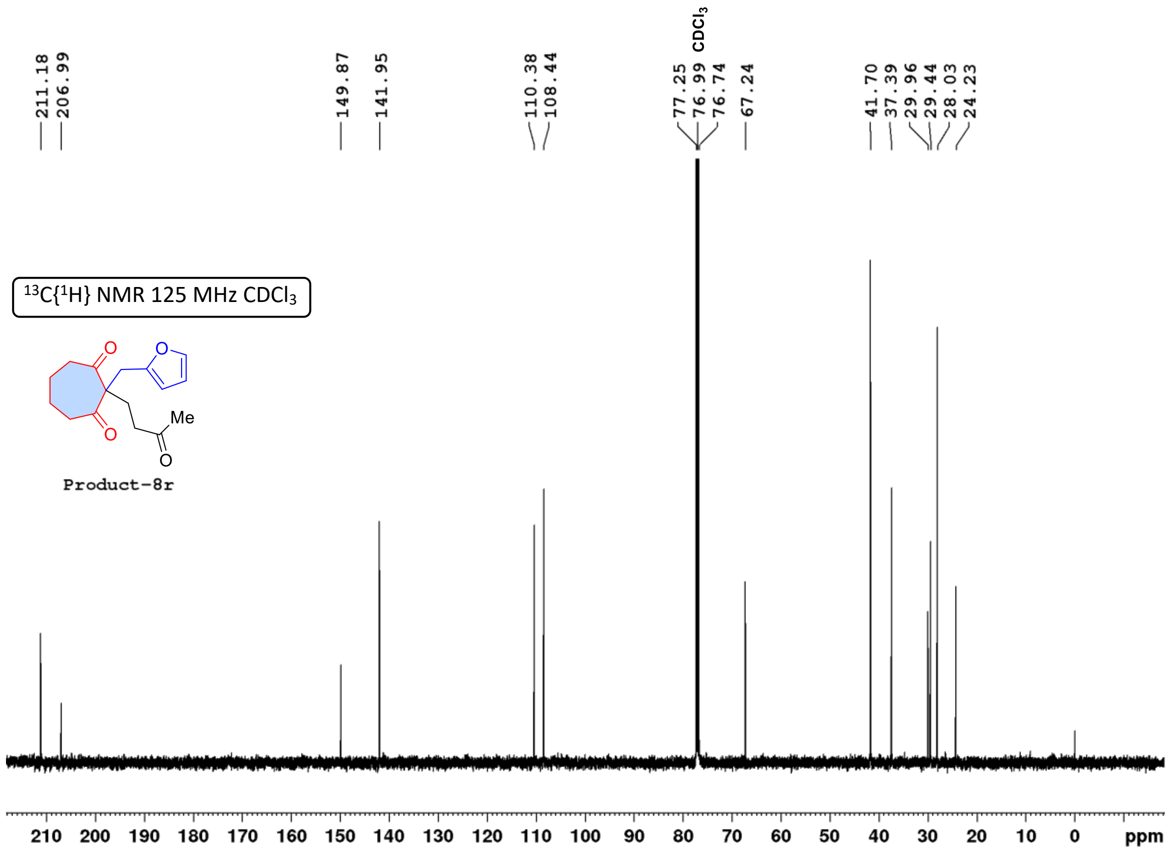
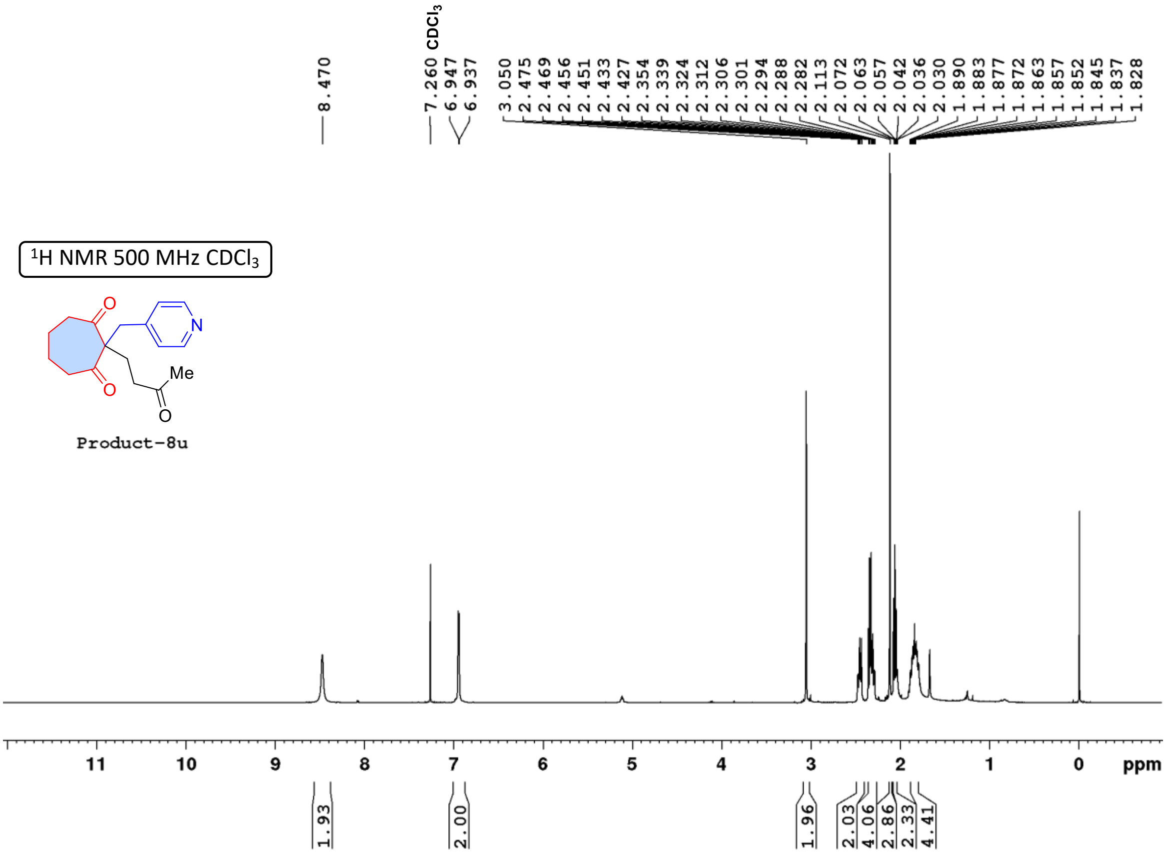


Figure 26: ^{1}H NMR and ^{13}C NMR spectrum of product **8r**.



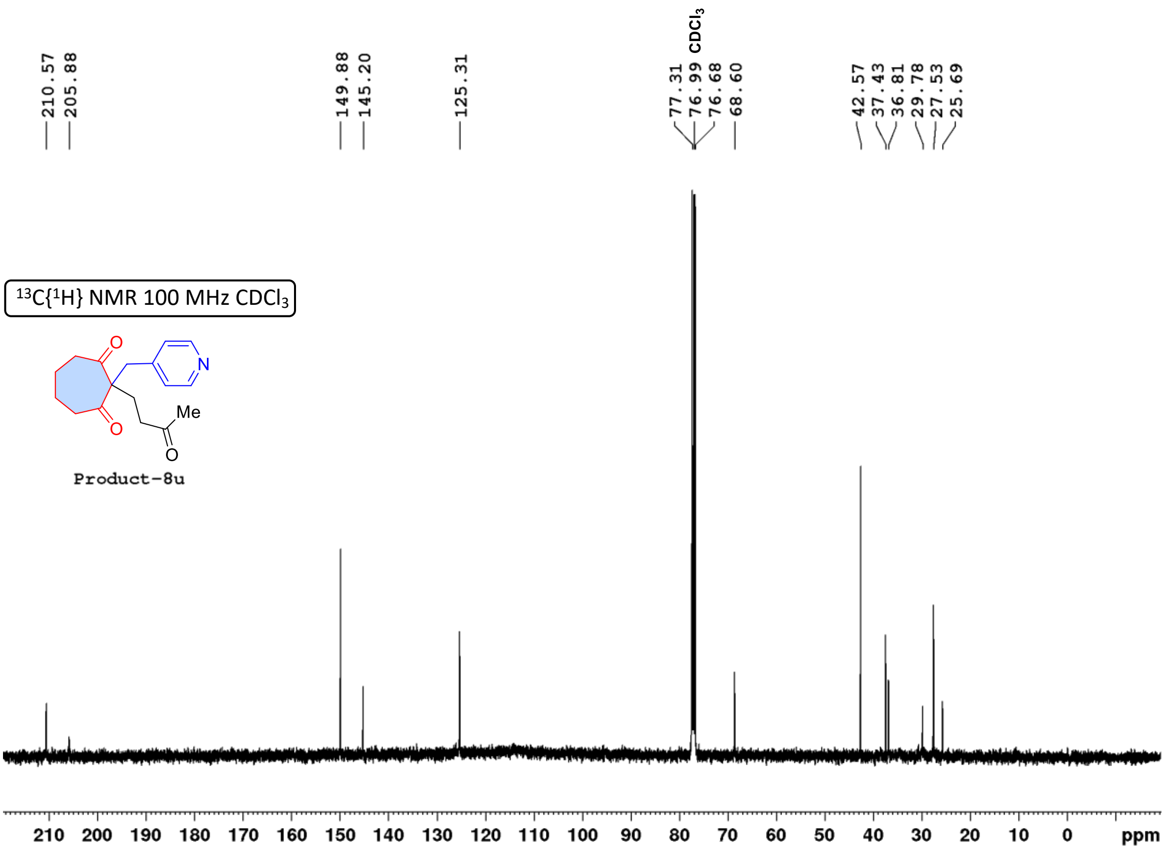
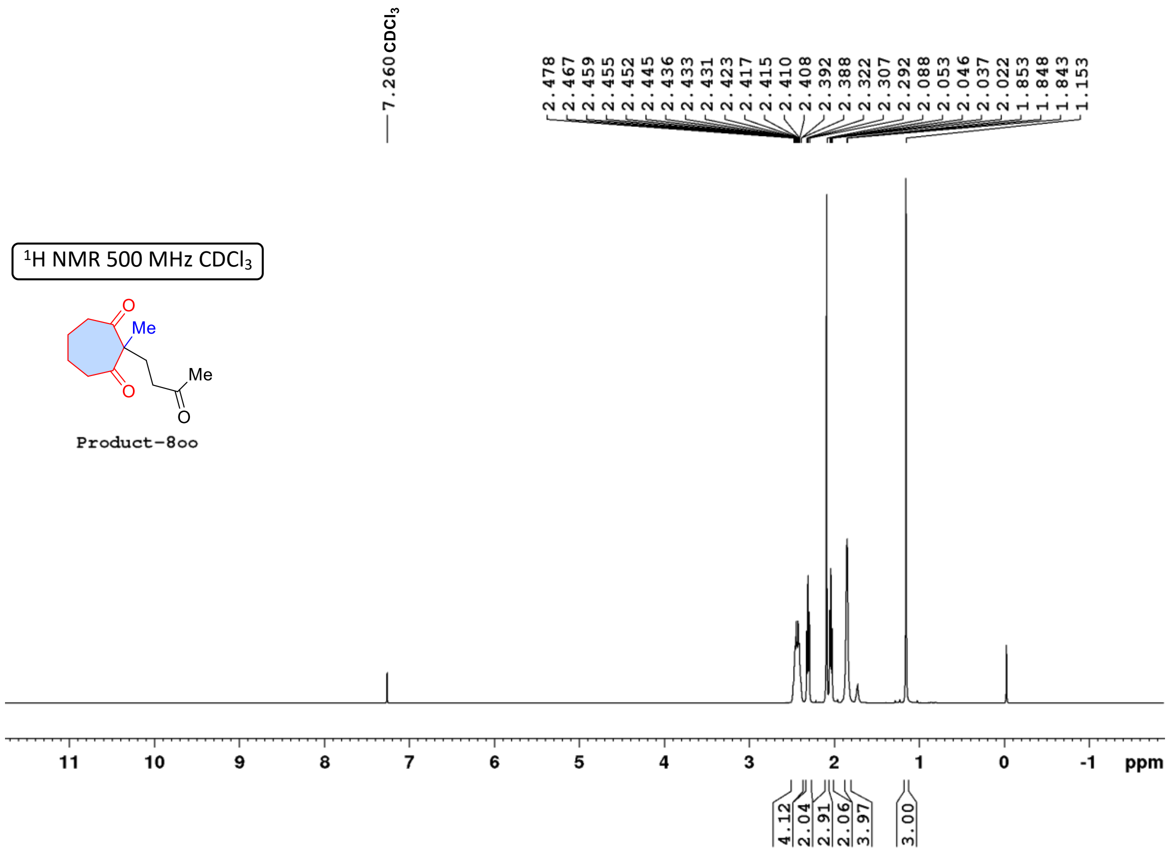


Figure 27: ^{1}H NMR and ^{13}C NMR spectrum of product **8u**.



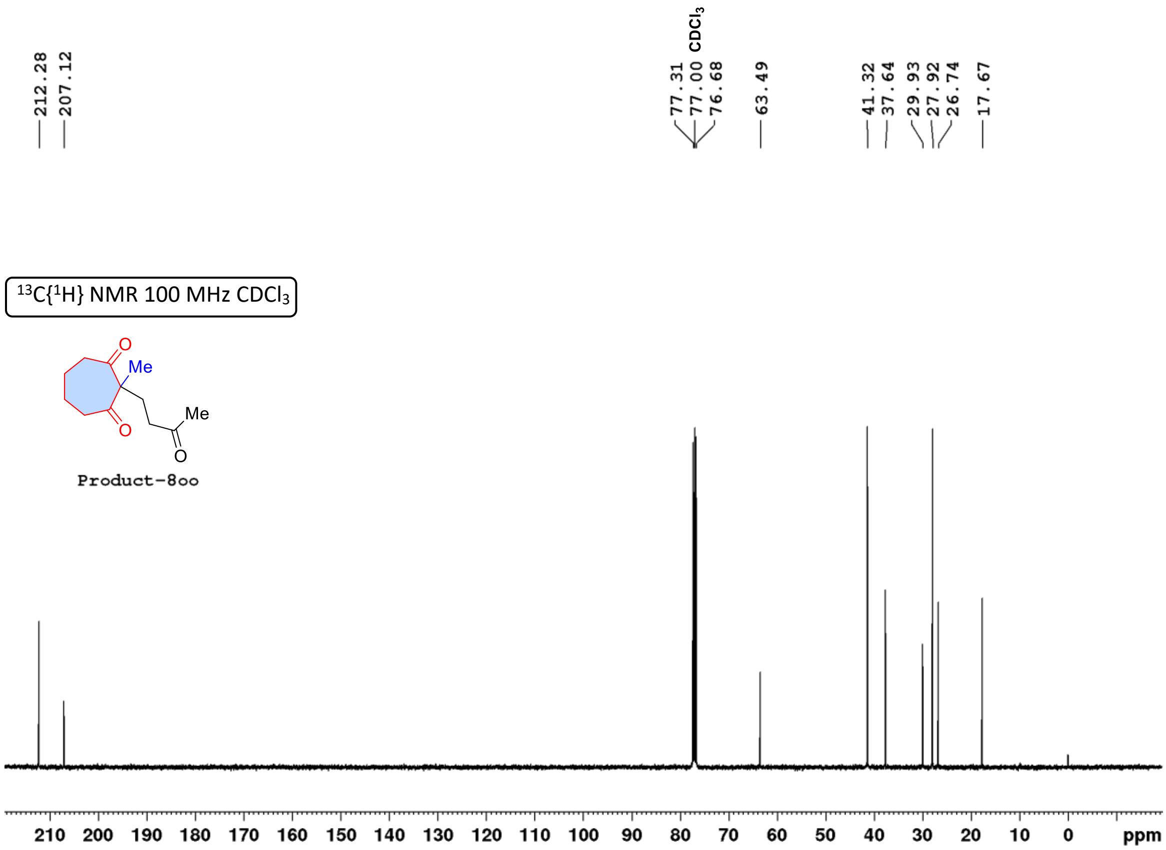
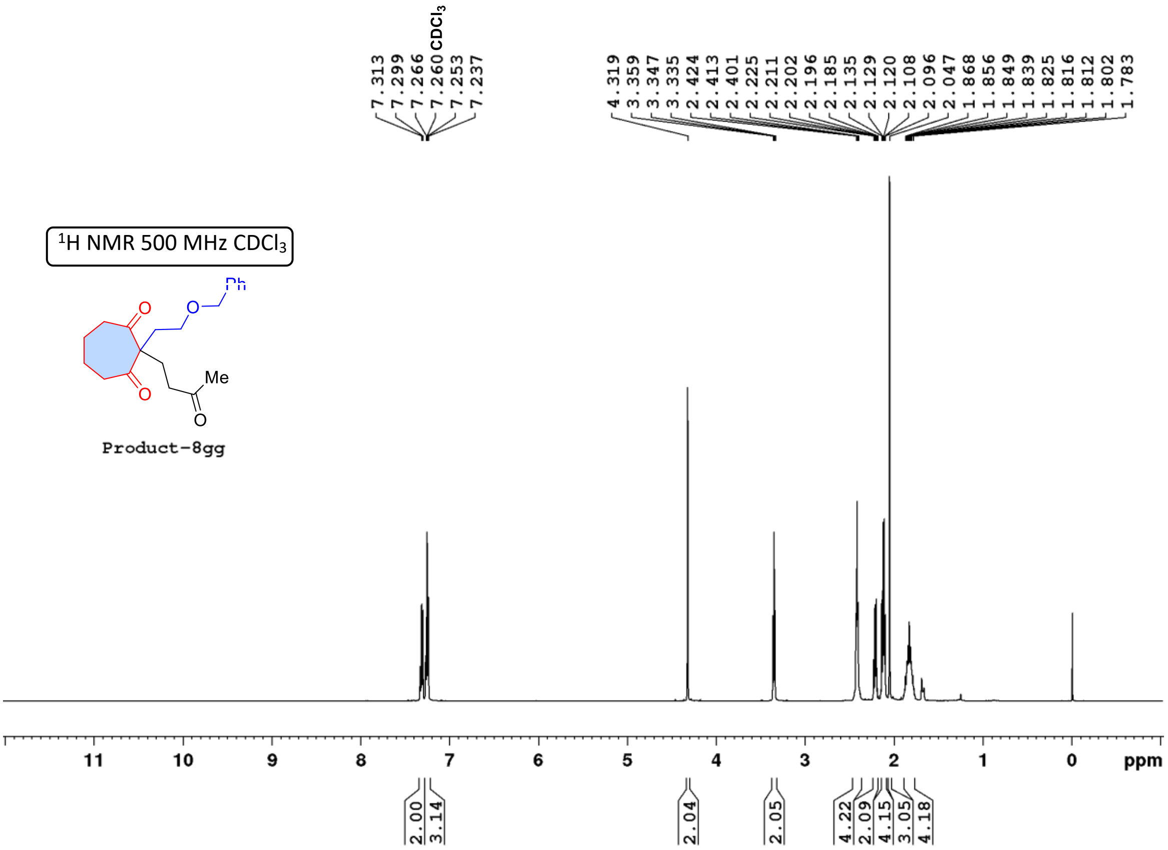


Figure 28: ^{1}H NMR and ^{13}C NMR spectrum of product **8oo**.



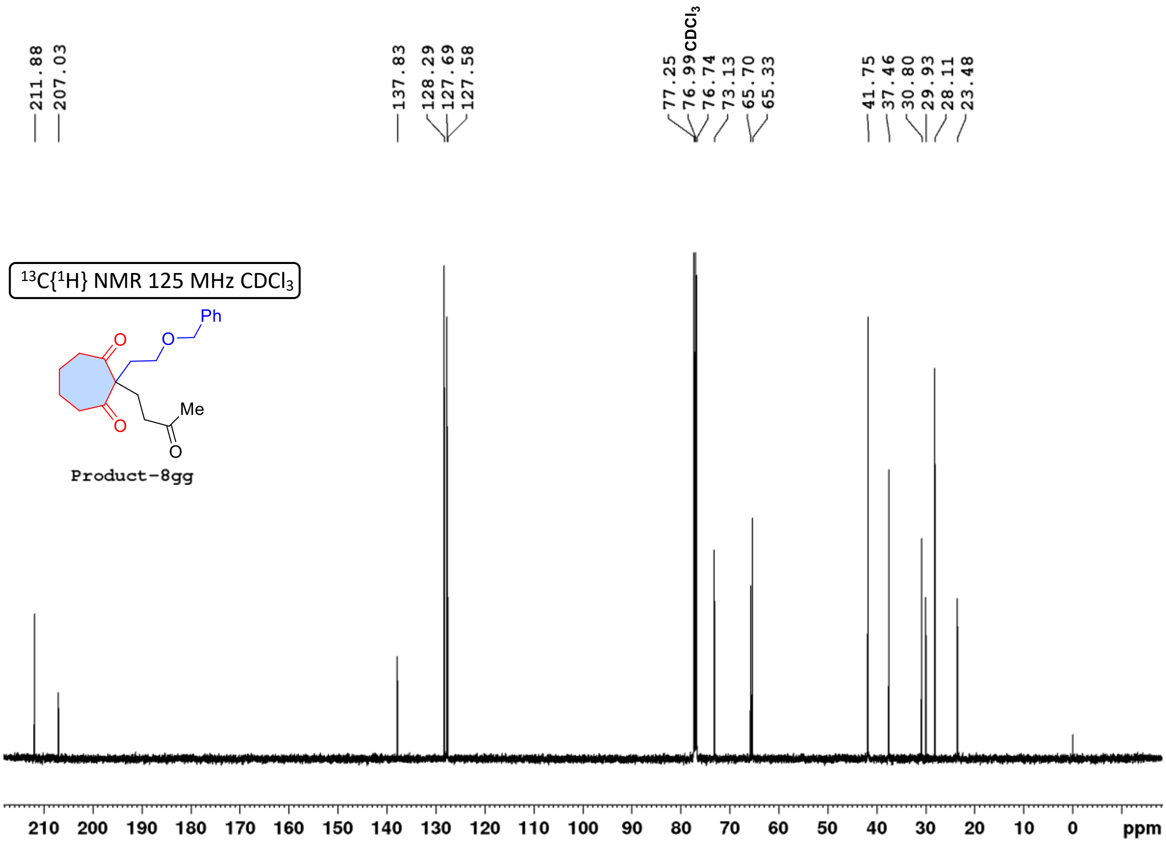
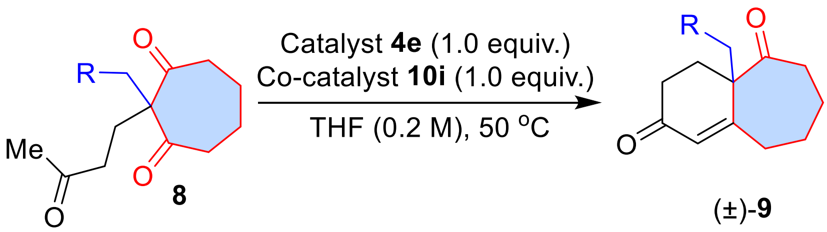


Figure 29: ^{1}H NMR and ^{13}C NMR spectrum of product **8gg**.

5.2.4 Synthesis of Racemic S. Ketone and Analogues (±)-9

Before investigating the chiral version of intramolecular aldol reaction, we prepared a library of racemic S. ketones (±)-**9** under equivalent amount of pyrrolidine **4e**/acetic acid **10i** in THF at 50 °C for 5-16 h to understand the steric/electronic factors involved in the reaction (Table 5).

Table 5: Racemic substrate scope with respect to various functionalized triketones **8** to furnish racemic S. ketone and analogues (±)-**9**.[a]



8 (±)-**9**

Entry	R	*t* [h]	Yield [%][b]
1[c]	C_6H_5 (±)-**9a**	16	90
2	4-FC_6H_4 (±)-**9d**	7	85
3	4-BrC_6H_4 (±)-**9f**	7	81
4	4-$OMeC_6H_4$ (±)-**9k**	7	87
5	4-$CF_3C_6H_4$ (±)-**9p**	7	84
6	2-furfuryl (±)-**9r**	7	84
7	2-thiophenyl (±)-**9s**	7	80
8	4-pyridinyl (±)-**9u**	7	83
9	2-napthyl (±)-**9x**	10	78
10	H (±)-**9oo**	5	90
11	CH_3 (±)-**9y**	7	80
12[c]	$CH_2CH_2CH_3$ (±)-**9aa**	16	85
13[c]	$CH(CH_3)_2$ (±)-**9dd**	16	84
14[c]	CH_2OCH_2Ph (±)-**9gg**	16	81
15[c]	$CH_2CH_2OCH_2Ph$ (±)-**9hh**	15	80

[a] Reactions were carried out in THF (0.2 M) at 50 °C with 1.0 equiv of **4e** and 1.0 equiv. of AcOH relative to the compound **8** (0.1 mmol). [b] yield refers to the coloum purified product. [c] Reactions were carried out at rt using Et_2O (0.2 M) as solvent

The reaction of benzyl substituted triketone **8a** in the presence of 1.0 equiv. of pyrrolidine **4e** and 1.0 equiv. of acetic acid **10i** in diethylether (0.2 M) at room temperature afforded the desired racemic S. ketone analogue (±)-**9a** with 90% yield in 16 h (Table 5, entry 1). Interestingly, all the aromatic, heteroaromatic substituted triketones **8d**, **8f**, **8k**, **8p**, **8r**, **8s**, **8u** and **8x** proceeded smoothly in THF (0.2 M) at 50 ^{o}C because of the solubility issues affording the racemic S. ketones (±)-**9d**, (±)-**9f**, (±)-**9k**, (±)-**9p**, (±)-**9r**, (±)-**9s**, (±)-**9u** and (±)-**9x** in 7-10 h with 78-90% yields (Table 5, entries 2-9). Whereas, aliphatic substituted triketones **8oo**, **8y**, **8aa**, **8dd**, **8gg** and **8hh** performed well in dietheylether (0.2 M) furnishing the corresponding racemic S. ketones (±)-**9oo**, (±)-**9y**, (±)-**9aa**, (±)-**9dd**, (±)-**9gg** and (±)-**9hh** in 5-16 h with 80-90% yield (Table 5, entries 10-15).

5.2.5 Journey Towards the Synthesis of Chiral Swaminathan Ketones

After synthesizing a library of racemic S. ketones (±)-**9** in high yields, we were interested in synthesizing chiral S. ketones. To optimize the designed asymmetric intramolecular aldol reaction under cinchona alkaloid primary amine catalysis,[9a-d] we chosen 2-benzyl-2-(3-oxobutyl)cycloheptane-1,3-dione **8a** for optimization studies.

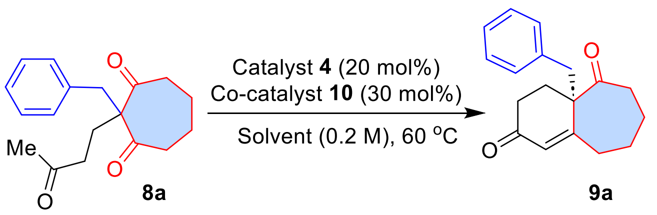
5.2.5.1 Investigation of proposed organocatalytic asymmetric reaction to access chiral S. ketone analogue 9a

Initially, we reacted the triketone **8a** in the presence of 20 mol% of catalyst **4g** and 40 mol% of co-catalyst **10i** in DCM (0.2 M) at room temperature. Disappointingly, the reaction didn’t yield desired product **9a** even after 24 h (Table 6, entry 1). Using our past laboratory experiences on primary amine catalysis,[9d] we predicted toluene could be the best solvent and *o*-fluorobenzoic acid **10a** could be the best co-catalyst. With this hope, we performed the intramolecular aldol reaction of **8a** (0.1 mmol) in the presence of 20 mol% of catalyst **4g** and 40 mol% of co-catalyst **10a** in toluene (0.2 M) at 60 °C. Stunningly, the reaction afforded the desired product (-)-**9a** in 91% yield with 81% *ee* (Table 6, entry 2). Next, the co-catalyst **10a** loading was varied to 30 and 20 mol% keeping the remaining parameters constant to see its effect on the reaction. In the case of 30 mol%, the reaction furnished the (-)-**9a** with an improved yield of 94% and improved selectivity of 82% *ee* in 14 h (Table 6, entry 3), whereas 20 mol% co-catalyst loading resulted in (-)-**9a** with a reduced yield of 85% leaving the enantioselectivity unchanged (Table 6, entry 4) declaring 30 mol% as the best loading. When the same reaction was performed at 50 °C, it afforded (-)-**9a** with 93% yield and 84% *ee* (Table 6, entry 5). As a part of solvent optimization, we performed the reaction of **8a** in benzene and toluene with 20 mol% **4g** and 30 mol% **10a** where the reaction afforded (-)-**9a** with 82% and 70% yield, 83% and 75% *ee* in 18 and 26 h respectively (Table 6, entries 6-7). Interestingly, hexafluorobenzene enhanced the selectivity by furnishing (-)-**9a** with 88% *ee* but with a reduced yield of 80% in 24 h (Table 6, entry 8). The reaction took longer times of 72 h in DMSO at 60 °C to afford (-)-**9a** in 50% yield with a reduced 64% *ee* (Table 6, entry 9). The selectivity got drastically affected when THF was used as a solvent, affording the product **9a** in almost racemic form with 2% *ee* and 60% yield after 48 h (Table 6, entry 10). Increasing the temperature to 60 °C, the reaction performed well in hexafluorobenzene affording (-)-**9a** with an increased 90% yield and 86% *ee* in 20 h (Table 6, entry 11). Later, when the reaction of **8a** was performed in toluene at 60 °C by changing the catalyst to **4j** and **4i**, keeping the co-catalyst **10a** constant, the reaction yielded (-)-**9a** in 94% and 95% yield with 82% and 84% *ee*, respectively in just 12 h declaring that **4i** as the best catalyst (Table 6, entries 12-13).

Extending the optimization further, we screened the reaction for the best co-catalyst with a series of substituted aromatic benzoic acids like *o*-bromo, 2,4,6-trifluoro, 2,6-dimethyl, *o*-nitro, and *p*-trifluoromethyl benzoic acids **10b-10f**. In all the cases, the reaction did not perform better than in entry 11, producing the desired product (-)-**9a** in 70-95% yields with 69-82% *ee* in 10-48 h (Table 6, entries 14-18). Surprisingly, the reaction performed exceptionally well when simple unsubstituted benzoic acid **10g** was used as co-catalyst, furnishing the product (-)-**9a** within 12 h in a high yield of 94% with good enantioselectivity of 85% (Table 6, entry 19). Similarly, 2-naphthoic acid **10h** gave similar results as benzoic acid by affording (-)-**9a** in 93% yield with 84% *ee* in 14 h (Table 6, entry 20). The co-catalyst investigation further continued testing with different aliphatic acids, such as trichloroacetic acid **10j**, diphenylacetic acid **10k** and (±)-BINOL-phosphoric acid **10l**, but none of them gave better results compared to the entry 11 (Table 6, entries 21-23). *When the reaction was performed without a co-catalyst, the reaction rate was very slow and only 25% of desired product (-)-**9a** was formed in 72 h with 31% ee (Table 6, entry 24), showing the importance of co-catalyst for the aldol reaction.* Since hexafluorobenzene improved the selectivity in entry 11, we have curiously employed hexafluorobenzene as solvent in entry 19 conditions instead of toluene. The intramolecular aldol reaction of **8a** in the presence of 20 mol% of catalyst **4i** and 30 mol% of co-catalyst **10g** in C_6F_6 (0.2 M) at 60 °C afforded the desired chiral S. ketone analogue (-)-**9a** with 93% yield and 88% *ee* in 24 h which was confirmed by NMR and HPLC analysis (Figures 30-31) making it as the best-optimized condition (Table 6, entry 25).

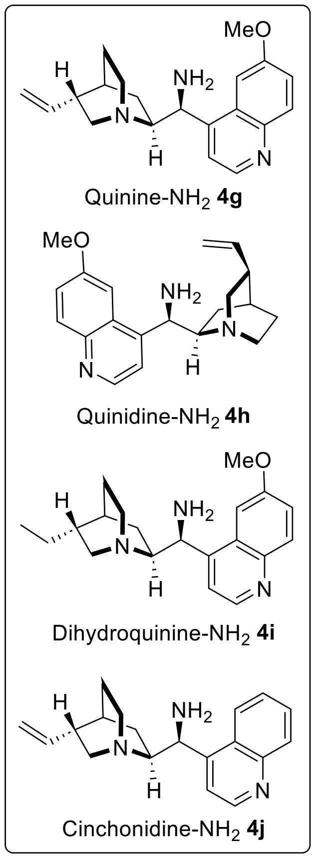
When the reaction was performed using the catalyst **4h**, which is an opposite epimer of **4g** under optimized reaction conditions, the reaction was very sluggish because of the solubility issues and afforded only 43% of (+)-**9a** with 65% *ee* (Table 6, entry 26).

Table 6: Investigation of proposed organocatalytic asymmetric reaction to access chiral S. ketone analogue **9a**.[a]



Entry	Catalyst/Co-catalyst (20/30 mol%)	Solvent [0.2 M]	*t* [h]	Yield [%][b]	*ee* (%)[c]
1[d]	**4g/10i**	DCM	24	-	-
2[d]	**4g/10a**	Toluene	12	91	81
3	**4g/10a**	Toluene	14	94	82
4[e]	**4g/10a**	Toluene	16	85	81
5[f]	**4g/10a**	Toluene	20	93	84
6[f]	**4g/10a**	Benzene	18	82	83
7[f]	**4g/10a**	CF_3-Toluene	26	70	75
8[f]	**4g/10a**	C_6F_6	24	80	88
9	**4g/10a**	DMSO	72	50	64
10	**4g/10a**	THF	48	60	2
11	**4g/10a**	C_6F_6	20	90	86
12	**4j/10a**	Toluene	12	94	82
13	**4i/10a**	Toluene	12	95	84
14	**4i/10b**	Toluene	12	95	81
15	**4i/10c**	Toluene	12	93	81
16	**4i/10d**	Toluene	48	70	69
17	**4i/10e**	Toluene	10	95	78
18	**4i/10f**	Toluene	12	92	82
19	**4i/10g**	Toluene	12	94	85
20	**4i/10h**	Toluene	14	93	84
21	**4i/10j**	Toluene	48	58	50
22	**4i/10k**	Toluene	12	92	63
23	**4i/10l**	Toluene	48	40	34
24	**4i**	Toluene	72	25	31
25	**4i/10g**	C_6F_6	24	93	88
26	**4h/10g**	C_6F_6	48	43	65

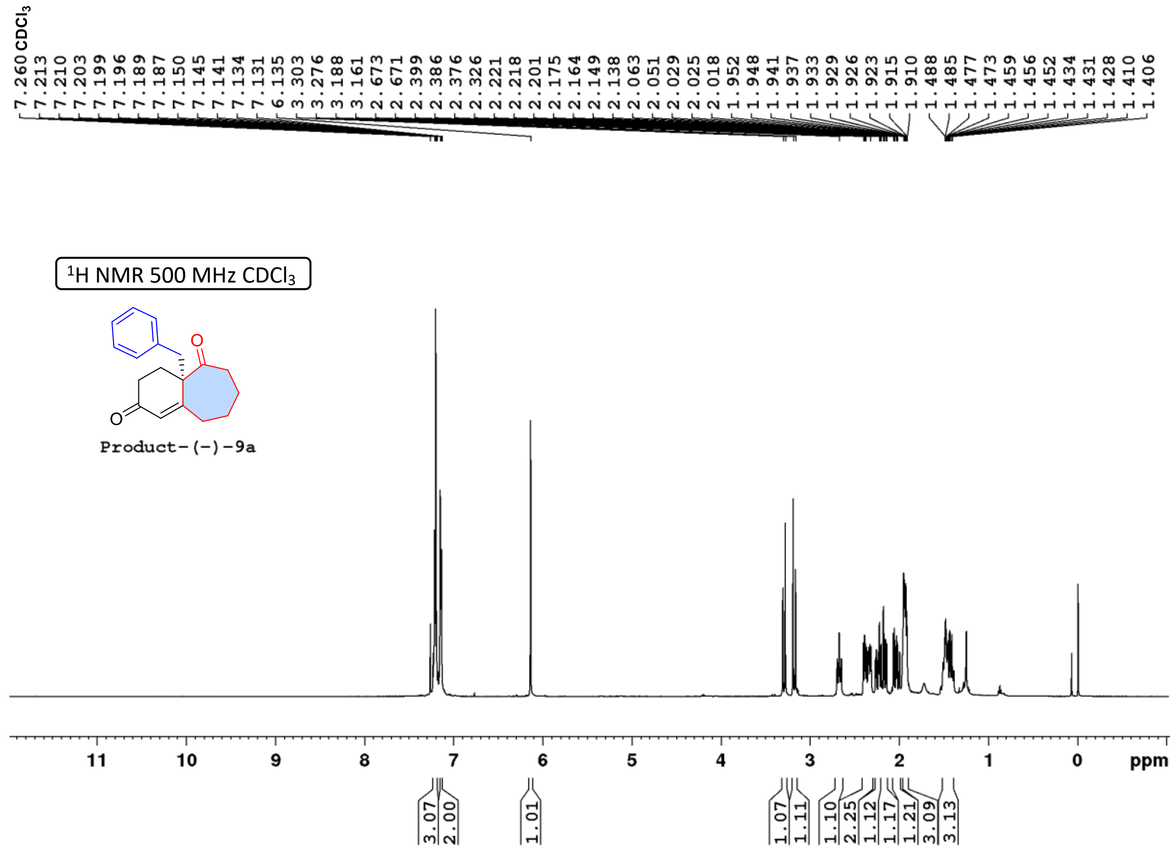
Catalysts:



Co-catalysts:

o-$FC_6H_4CO_2H$ (**10a**)
o-$BrC_6H_4CO_2H$ (**10b**)
2,4,6-trifluorobenzoic acid (**10c**)
2,6-$(CH_3)_2C_6H_3CO_2H$ (**10d**)
o-$NO_2C_6H_4CO_2H$ (**10e**)
p-$CF_3C_6H_4CO_2H$ (**10f**)
benzoic acid (**10g**)
2-naphthoic acid (**10h**)
CH_3CO_2H (**10i**)
CCl_3COOH (**10j**)
$(C_6H_5)_2CHCOOH$ (**10k**)
(±)-BINOL-phosphoric acid (**10l**)

[a] Reactions were carried out in solvent (0.2 M) with 20 mol% of catalyst **4** and 30 mol% of co-catalyst **10** relative to compound **8a** (0.1 mmol). [b] Yield refers to the column-purified product of **9a**. [c] Determined by CSP-HPLC analysis. [d] 40 mol% of co-catalyst was used. [e] 20 mol% of co-catalyst was used. [f] Reactions were carried out at 50 °C.



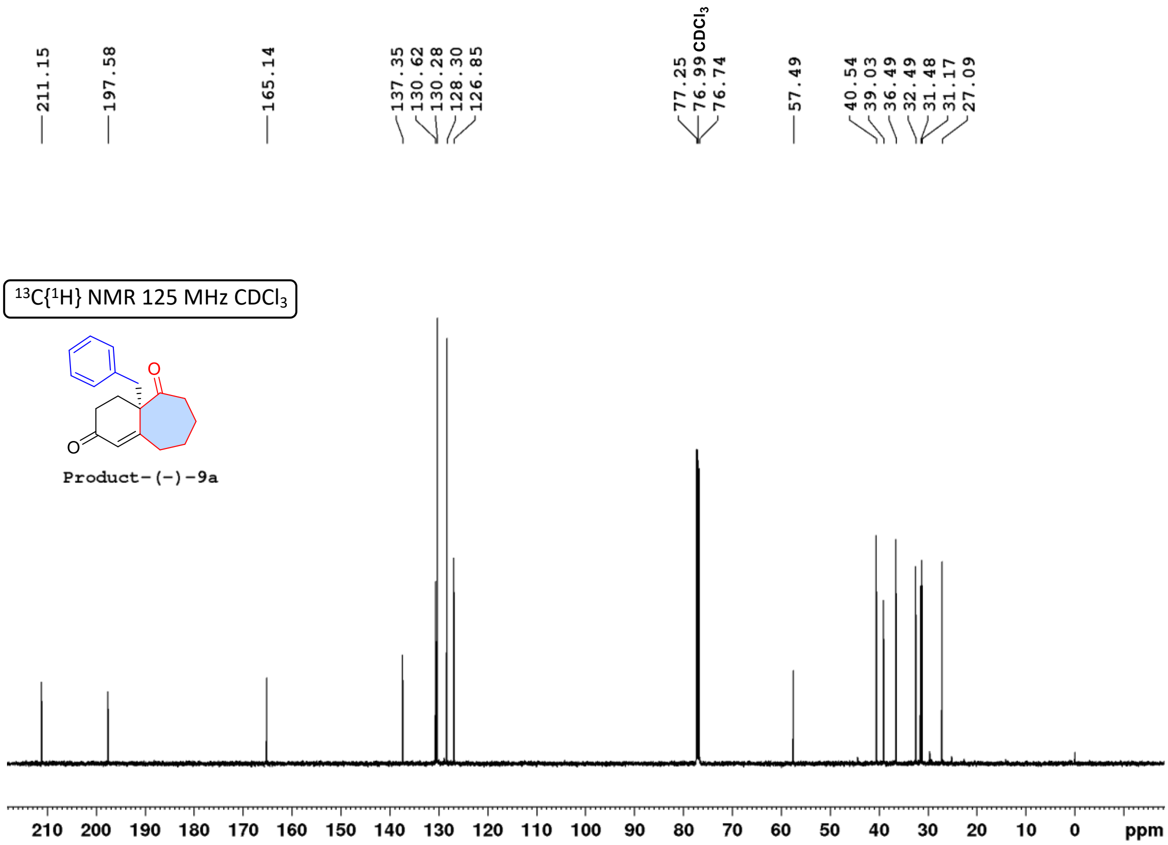
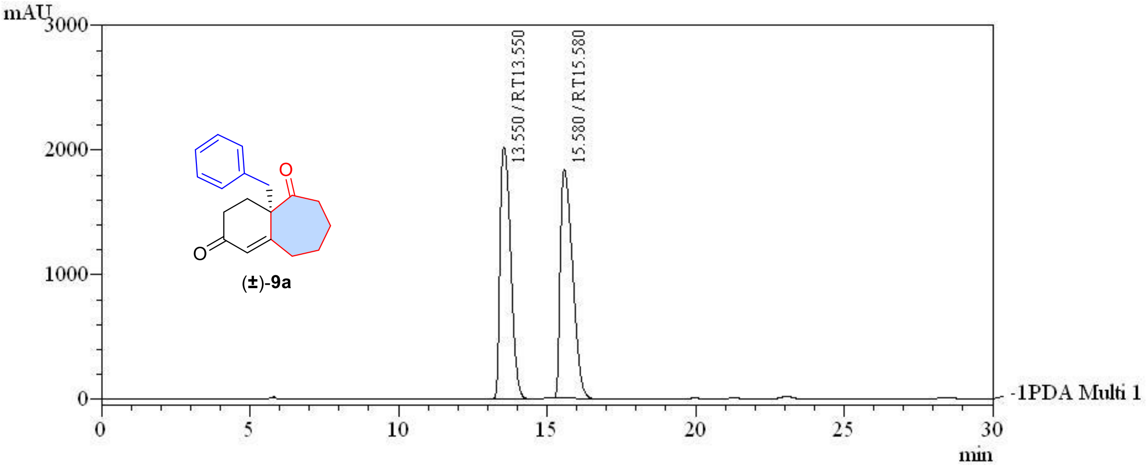


Figure 30: ^{1}H NMR and ^{13}C NMR spectrum of product **9a**.

Racemic **(±)-9a**:



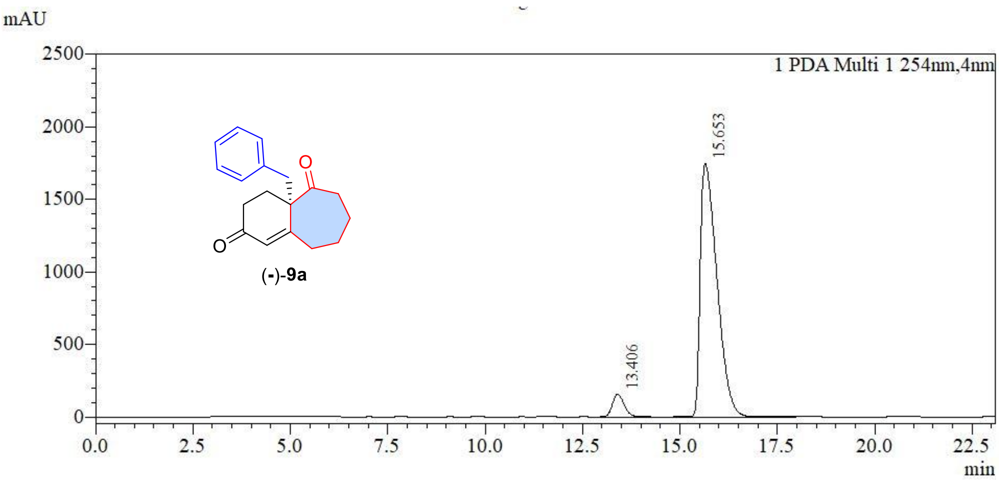
Chiralpak IG, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT13.550	13.550	50568890	2022666	48.892	52.378
2	RT15.580	15.580	52861884	1838985	51.108	47.622
Total			103430774	3861651	100.000	100.000

Chiral **(-)-9a** (88% *ee*):



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

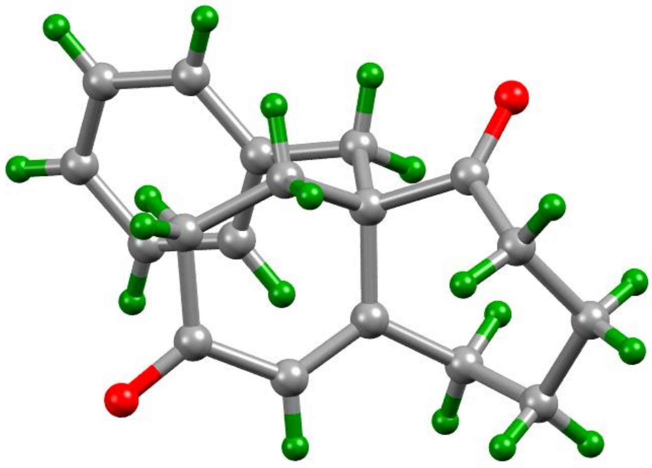
Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:13.406	13.406	3479047	157892	6.216	8.295
2	RT:15.653	15.653	52488616	1745667	93.784	91.705
Total			55967663	1903559	100.000	100.000

Figure 31: HPLC spectra of the product **9a**.

The absolute structure of compound (-)-**9a** was again confirmed by X-ray crystallography (Figure 32).[7]



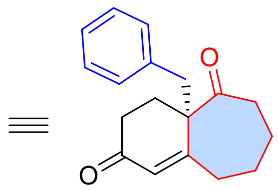


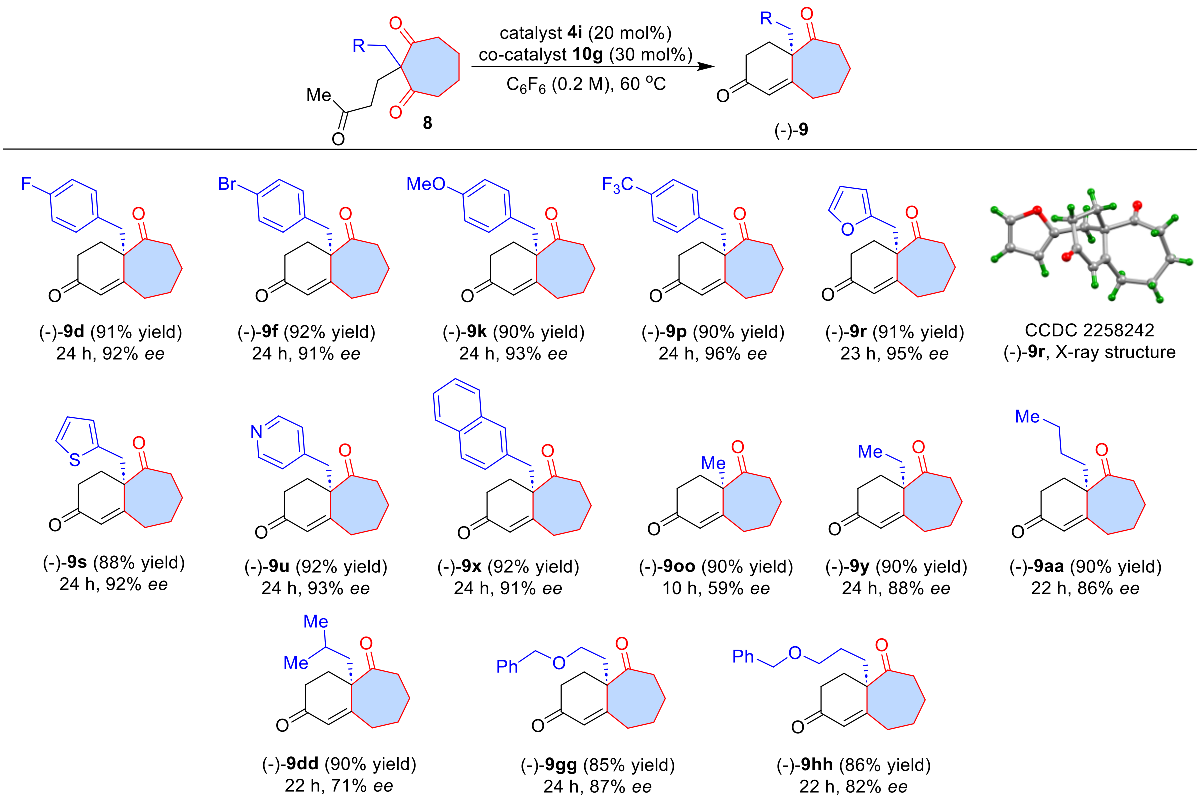
Figure 32: X-Ray crystal structure of (*S*)-4a-benzyl-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione (-)-**9a**.

5.2.5.2 Synthesis of chiral S. ketone and analogues (-)-9

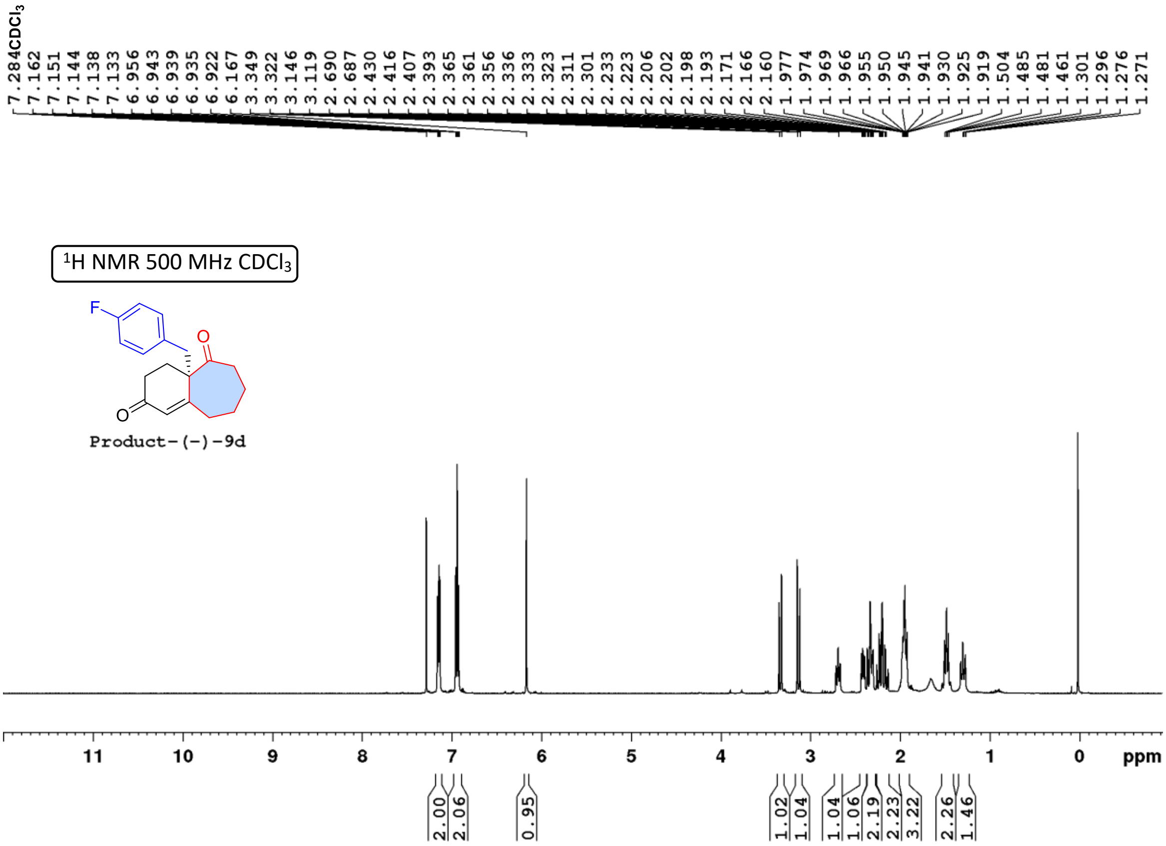
After thorough optimization, we were delighted to implement optimized asymmetric reaction conditions on the library of functionalized triketones **8** since we were just one step away from achieving chiral S. ketone and analogues **9**. Surprisingly, the intramolecular aldol reaction of 2-(4-fluorobenzyl)-, 2-(4-bromobenzyl)-, and 2-(4-methoxybenzyl)-substituted triketones **8d**, **8f**, and **8k** under optimized reaction conditions furnished the corresponding chiral S. ketone analogues (-)-**9d**, (-)-**9f** and (-)-**9k** in 24 h with excellent 91%, 92%, 90% yields and 92%, 91%, 93% *ee*, respectively (Table 7). Electron withdrawing group 2-(4-(trifluoromethyl)benzyl substituted triketone **8p** afforded the desired product (-)-**9p** with a stunning 90% yield and 96% *ee* in 24 h. The asymmetric reaction was also well tolerated in the case of heteroaromatic substituted triketones **8r**, **8s**, and **8u** furnishing (-)-**9r**, (-)-**9s**, and (-)-**9u** in 91%, 88%, and 92% yield with 95%, 92% and 93% *ee*, respectively (Table 7). In a similar fashion, 2-naphthyl substituted triketone **8x** furnished the desired chiral S. ketone analogue (-)-**9x** with 92% yield and 91% *ee* (Table 7). Disappointingly, 2-methyl substituted triketone **8oo** furnished the chiral S. ketone (-)-**9oo** with an excellent yield of 90% in just 10 h but with a lower enantioselectivity of 59% (Table 7), which indicates the importance of substituent induced steric strain control as a conformation-control at the 2-alkyl of triketone **8** for asymmetric desymmetrization. In support of this concept, ethyl-substituted triketone **8y** furnished the corresponding chiral S. ketone analogue (-)-**9y** with an excellent yield of 90%

and increased enantioselectivity of 88%. Similarly, 2-butyl, 2-isobutyl, 2-(2-(benzyloxy)ethyl) and 2-(3-(benzyloxy)propyl) substituted triketones **8aa**, **8dd**, **8gg**, and **8hh** furnished the corresponding chiral S. ketone analogues (-)-**9aa**, (-)-**9dd**, (-)-**9gg** and (-)-**9hh** in 90%, 90%, 85% and 84% yields with 86%, 71%, 87% and 82% *ee*'s, respectively in 22-24 h (Table 7). The NMR spectra and HPLC analysis of few selected compounds **9** were shown in Figures 33-48.

Table 7: Substrate scope with respect to various functionalized triketones **8** to furnish chiral S. ketone and analogues **9**.[a]



[a] Reactions were carried out in C_6F_6 (0.2 M) at 60 °C with 20 mol% of catalyst **4i** and 30 mol% of co-catalyst **10g** relative to the triketone **8** (0.1 mmol).



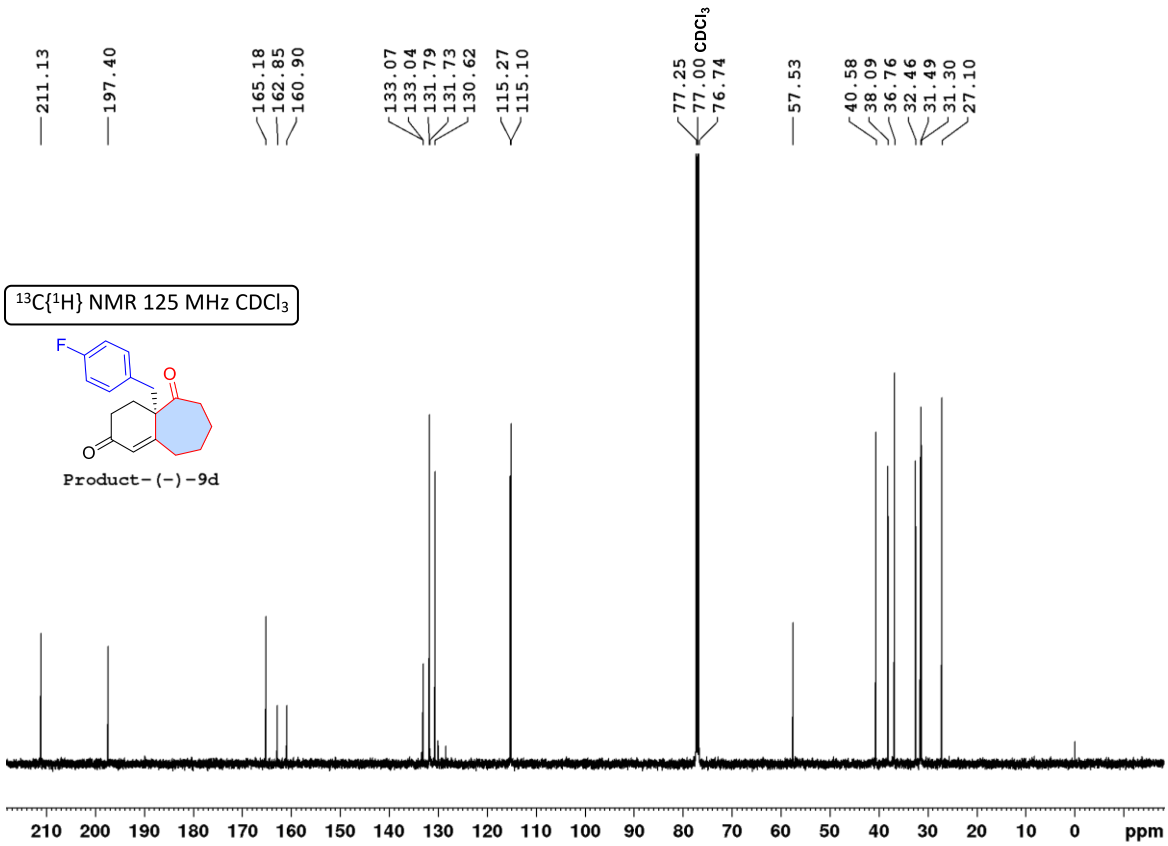
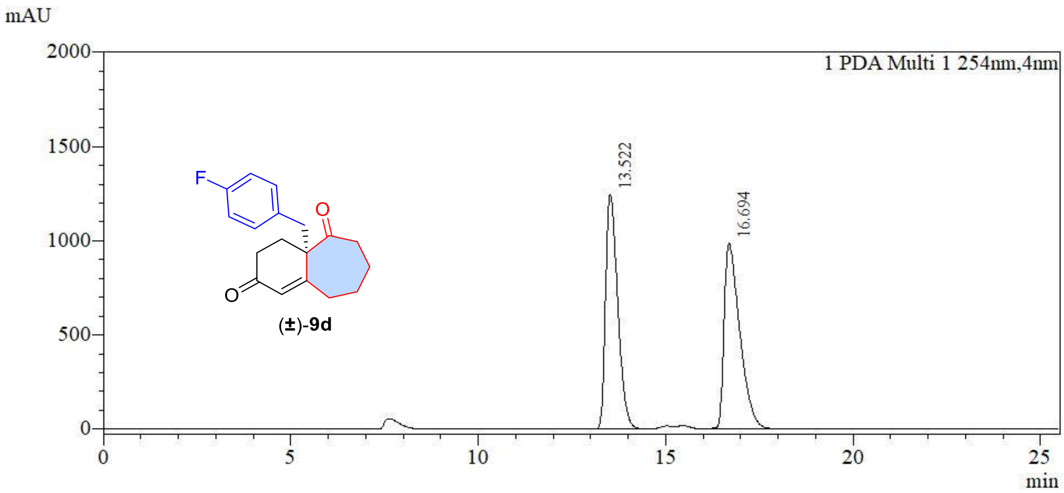


Figure 33: ^{1}H NMR and ^{13}C NMR spectrum of product **9d**.

Racemic **(±)-9d**:



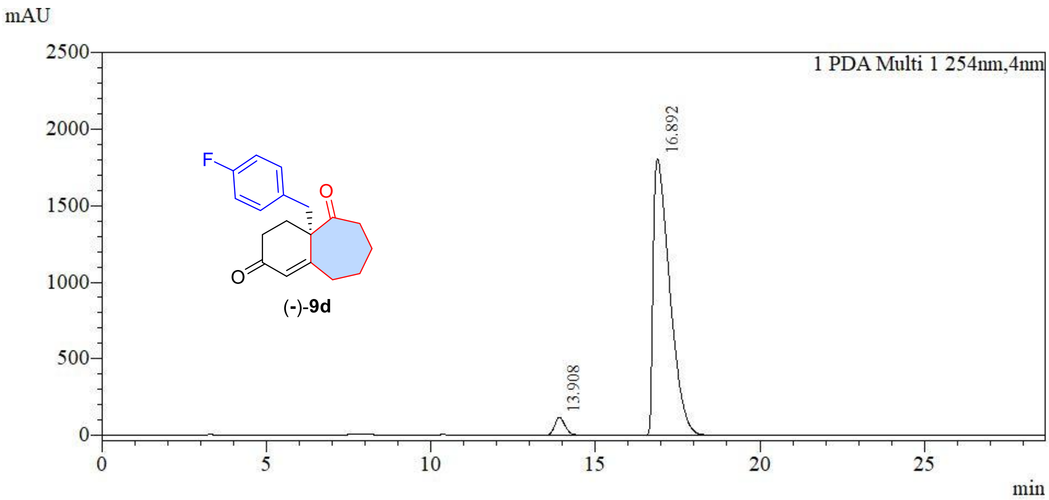
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:13.522	13.522	28109069	1247011	49.480	55.853
2	RT:16.694	16.694	28700073	985660	50.520	44.147
Total			56809142	2232671	100.000	100.000

Chiral **(-)-9d** (92% *ee*):



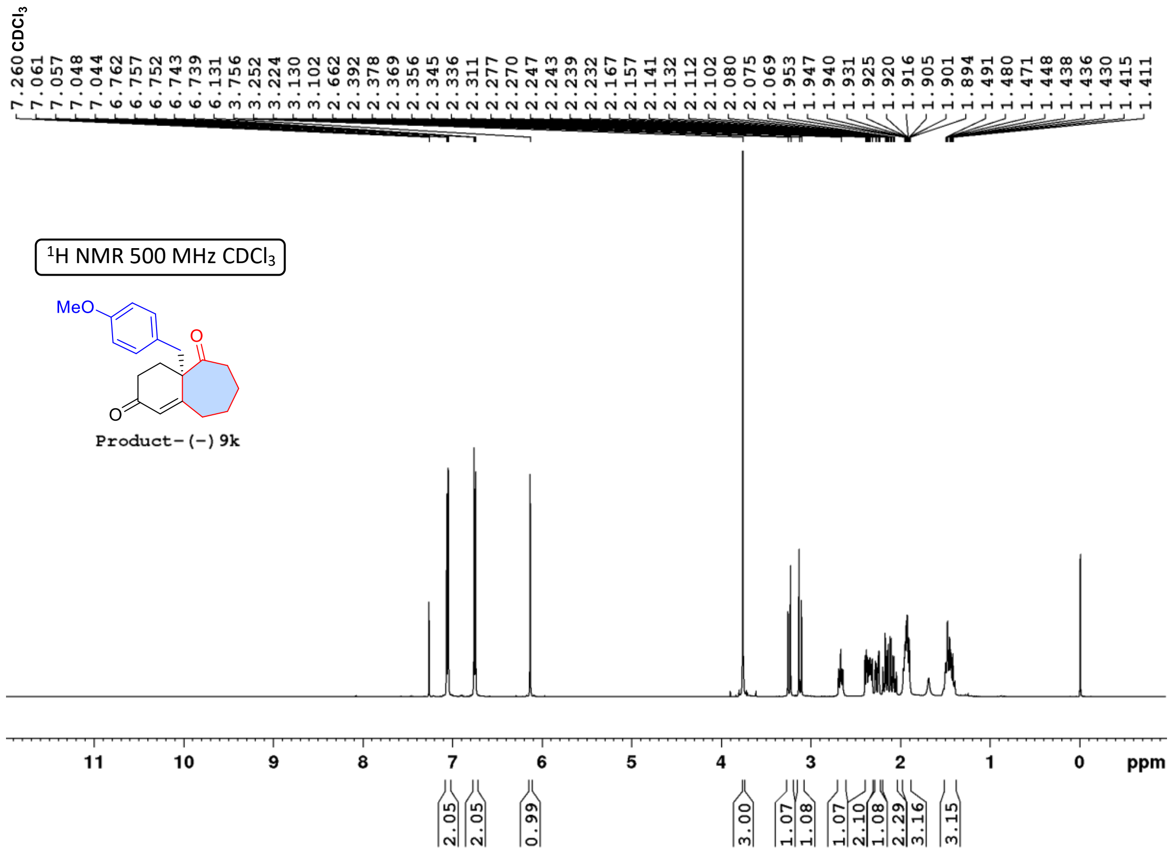
Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:13.908	13.908	2548123	117535	3.887	6.111
2	RT:16.892	16.892	63014469	1805875	96.113	93.889
Total			65562593	1923410	100.000	100.000

Figure 34: HPLC spectra of the product **9d**.



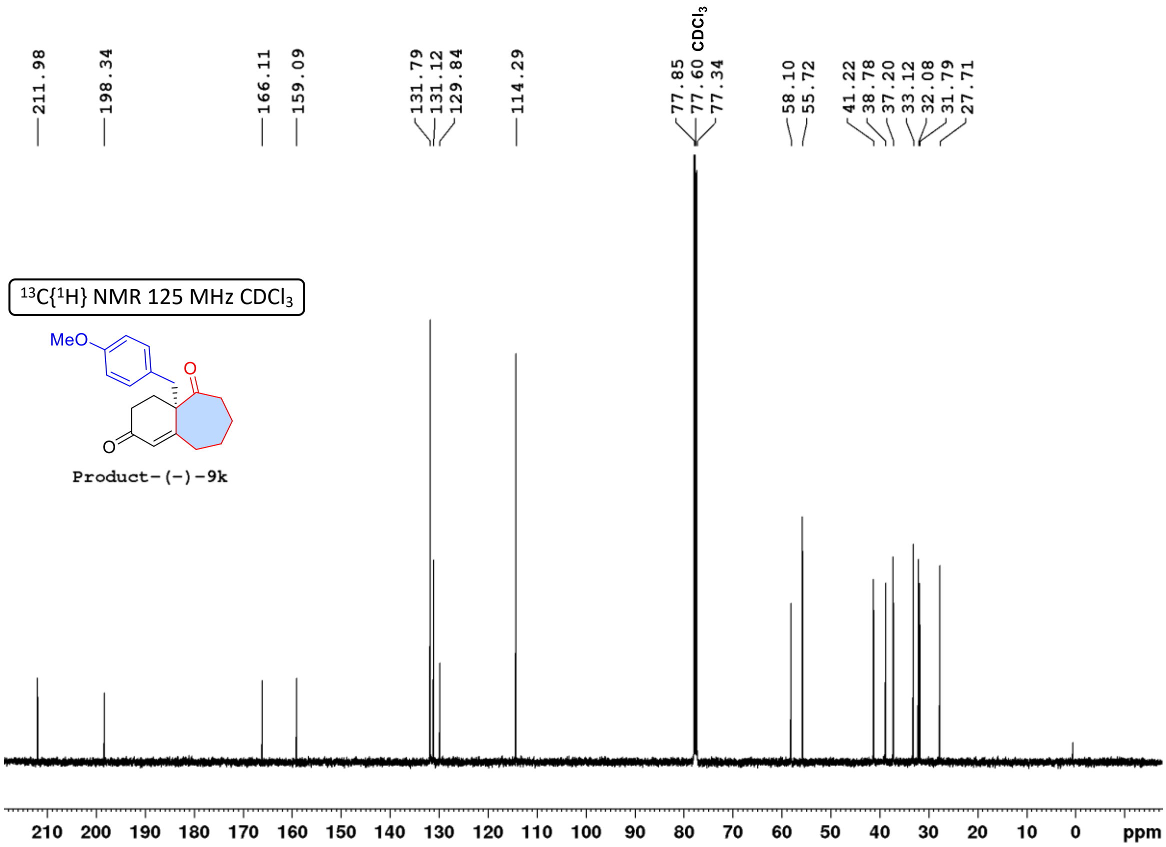
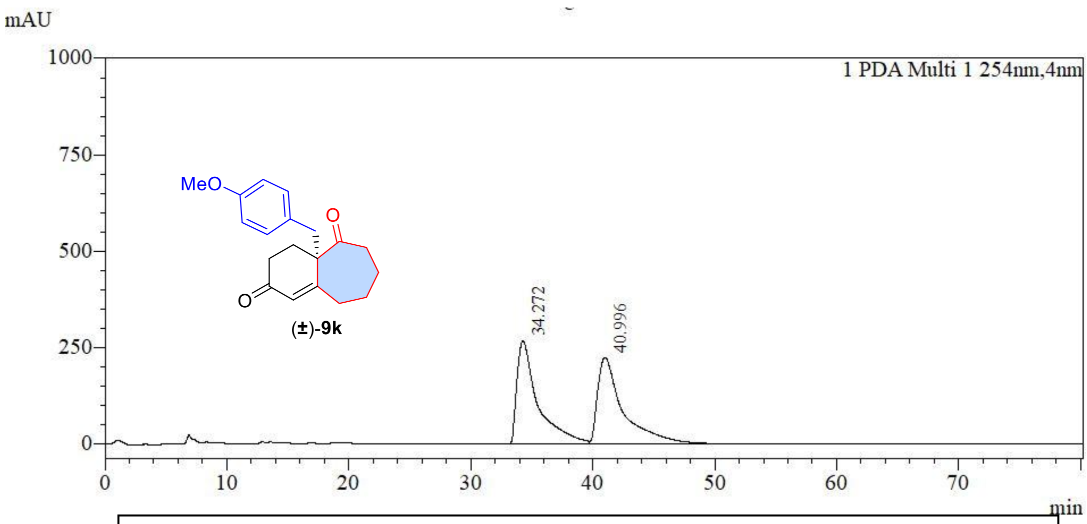


Figure 35: ^{1}H NMR and ^{13}C NMR spectrum of product **9k**.

Racemic **(±)-9k**:



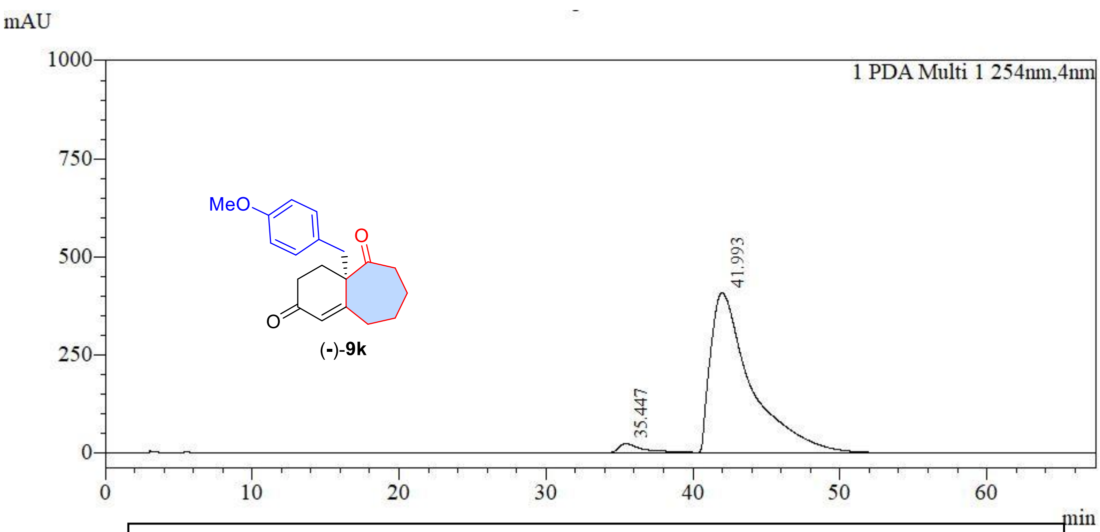
Chiralpak IC-3, Hexane/*i*-PrOH = 80:20, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:34.272	34.272	31568414	267321	49.568	54.411
2	RT:40.996	40.996	32118257	223983	50.432	45.589
Total			63686671	491304	100.000	100.000

Chiral **(-)-9k** (93% *ee*):



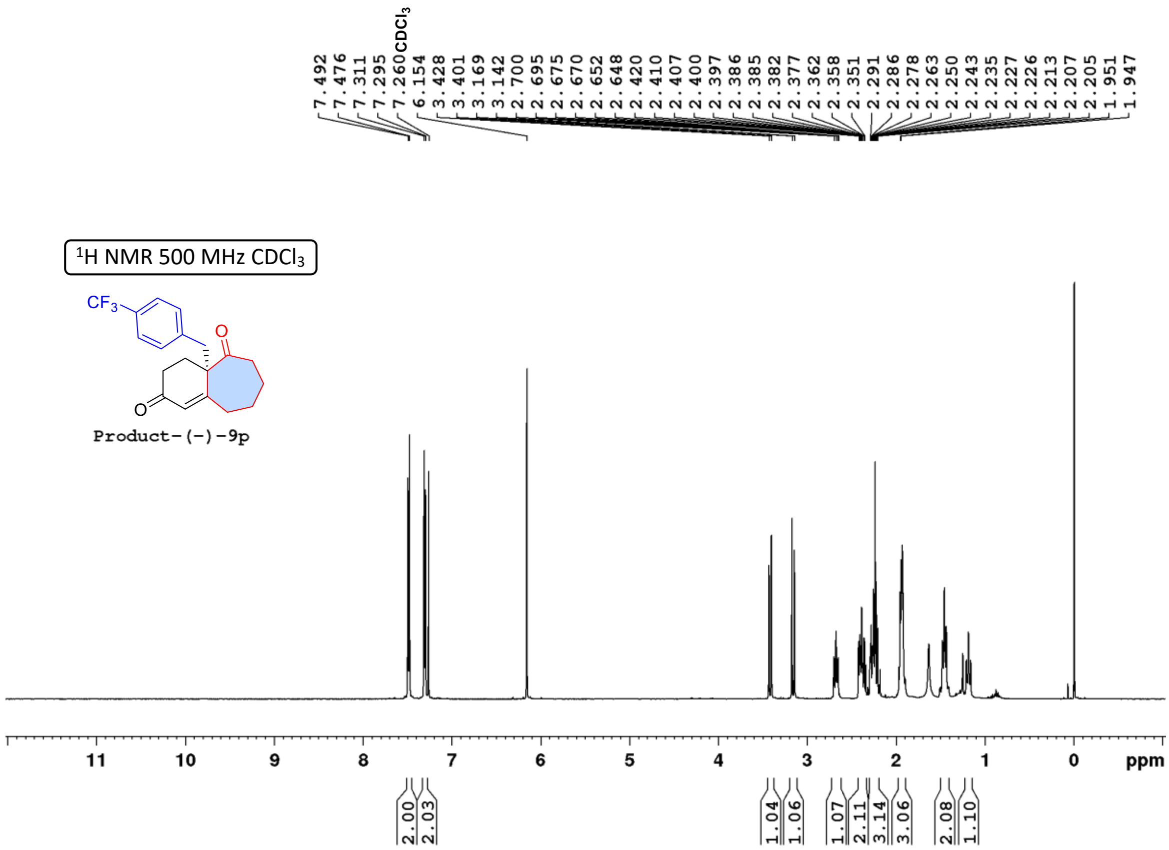
Chiralpak IC-3, Hexane/*i*-PrOH = 80:20, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:35.447	35.447	2782627	23278	3.414	5.404
2	RT:41.993	41.993	78716444	407479	96.586	94.596
Total			81499070	430757	100.000	100.000

Figure 36: HPLC spectra of the product **9k**.



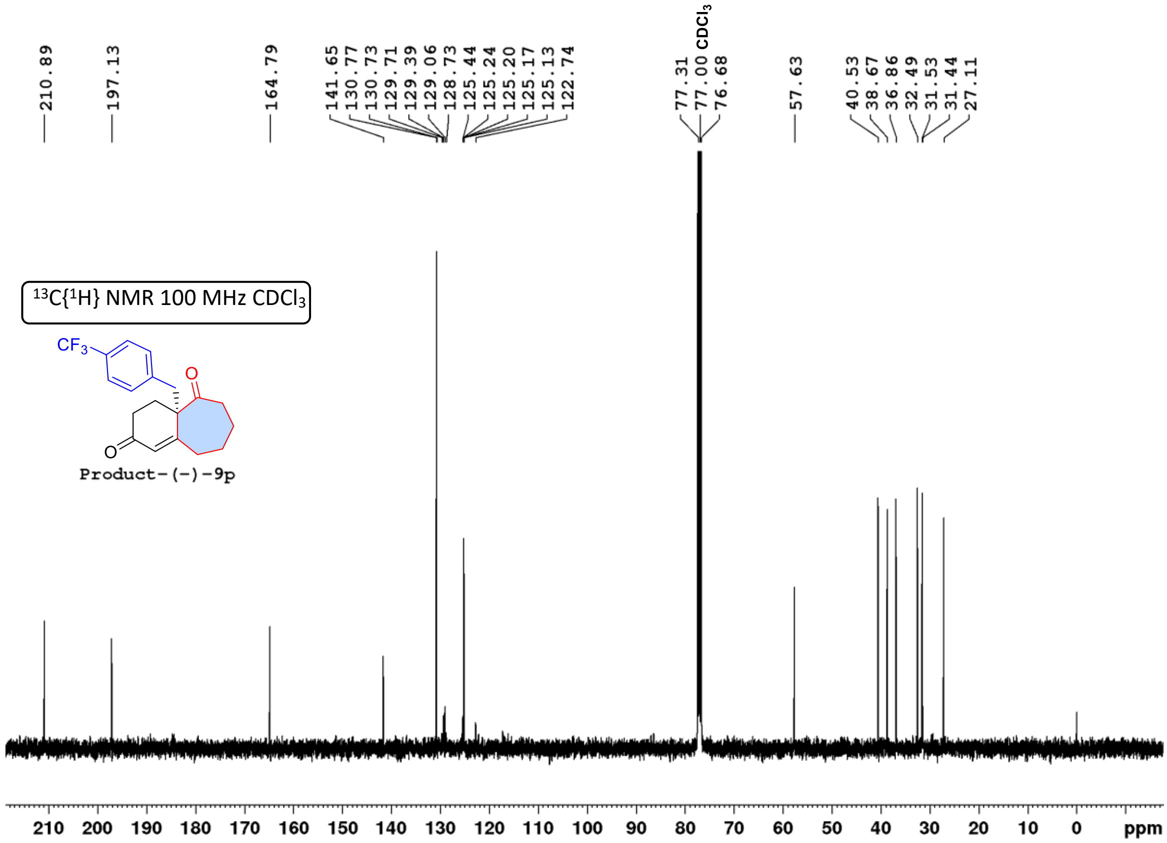
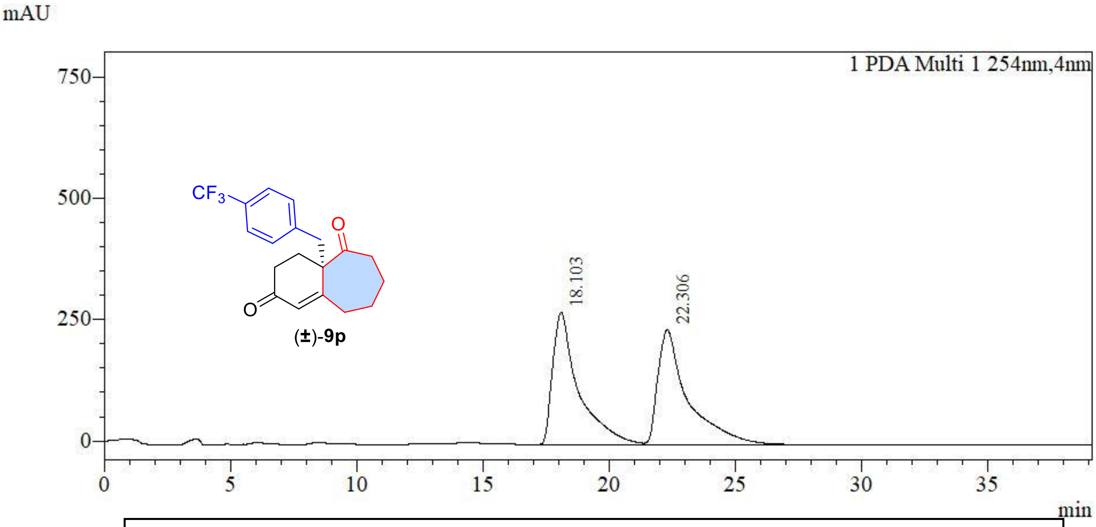


Figure 37: ^{1}H NMR and ^{13}C NMR spectrum of product **9p**.

Racemic **(±)-9p**:



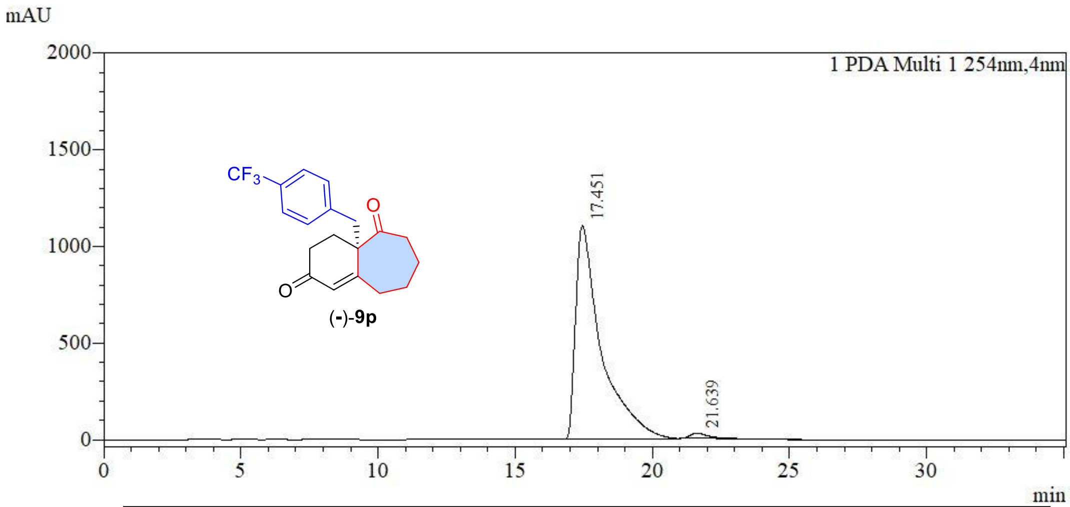
Chiralpak IC-3, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:18.103	18.103	19372333	272329	49.887	53.538
2	RT:22.306	22.306	19459930	236338	50.113	46.462
Total			38832263	508667	100.000	100.000

Chiral **(-)-9p** (96% *ee*):



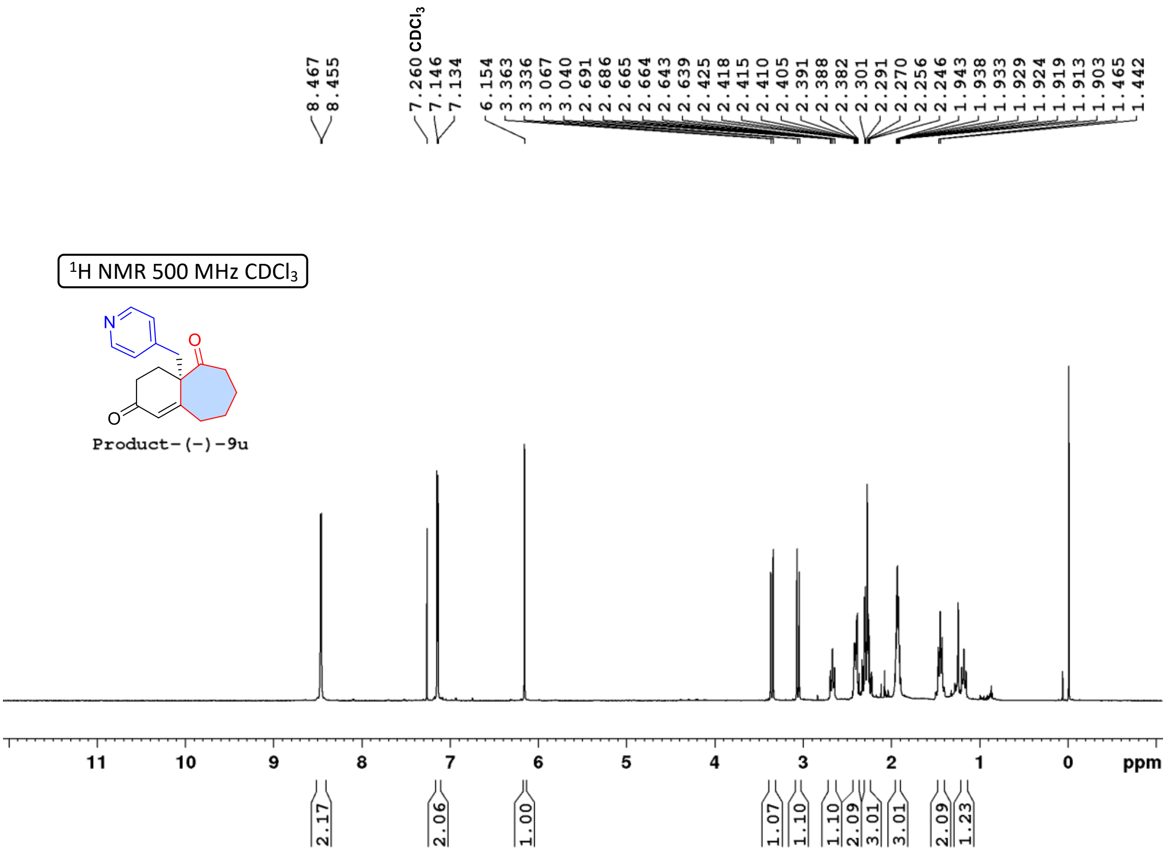
Chiralpak IC-3, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:17.451	17.451	72112855	1105872	97.845	97.515
2	RT:21.639	21.639	1588420	28187	2.155	2.485
Total			73701275	1134059	100.000	100.000

Figure 38: HPLC spectra of the product **9p**.



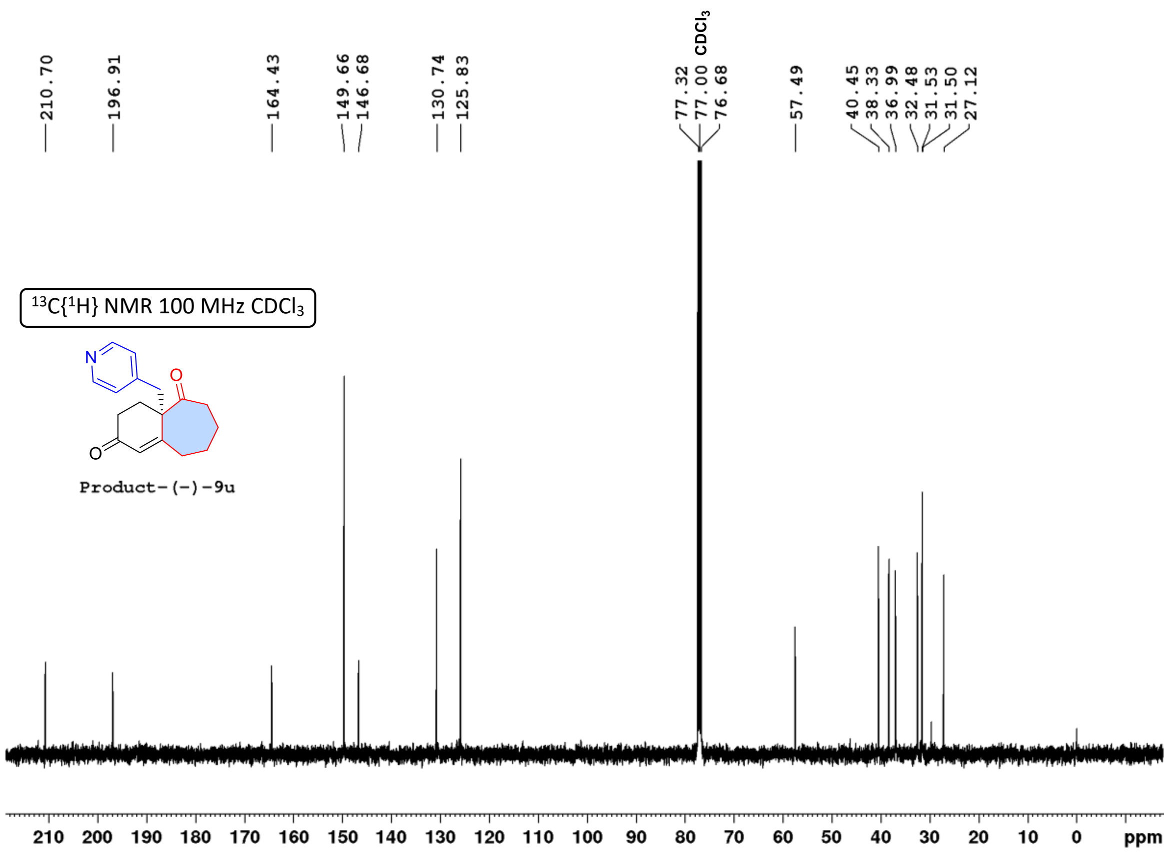
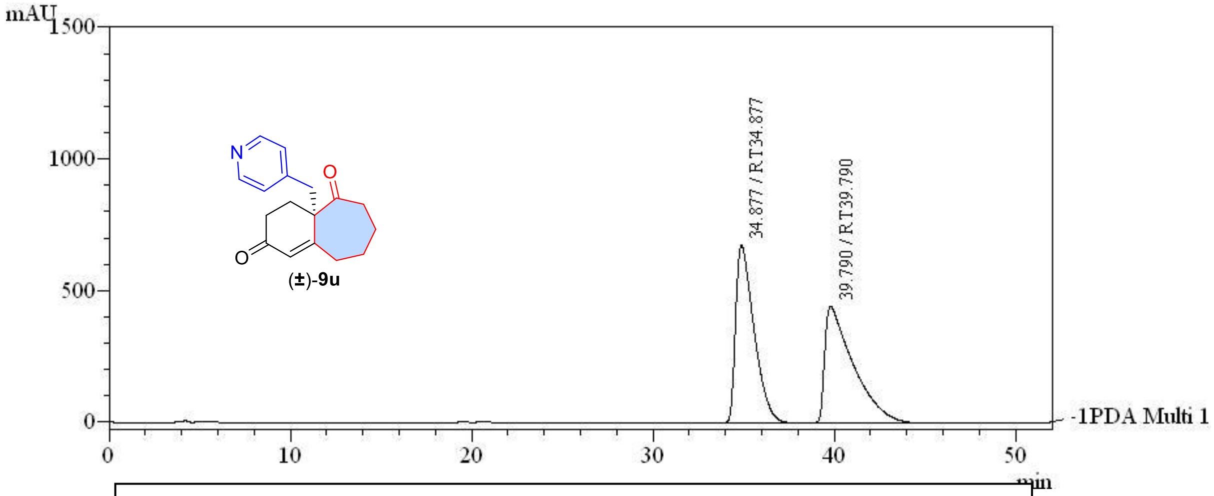


Figure 39: ^{1}H NMR and ^{13}C NMR spectrum of product **9u**.

Racemic **(±)-9u**:



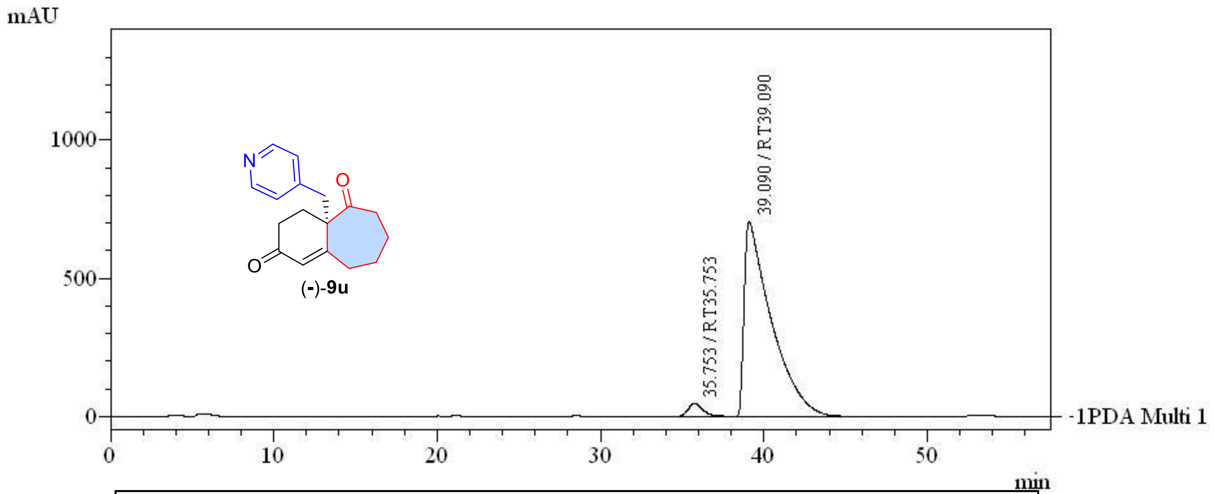
Chiralpak IG, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT34.877	34.877	47678484	675287	49.692	60.430
2	RT39.790	39.790	48269863	442181	50.308	39.570
Total			95948346	1117467	100.000	100.000

Chiral **(-)-9u** (93% *ee*):



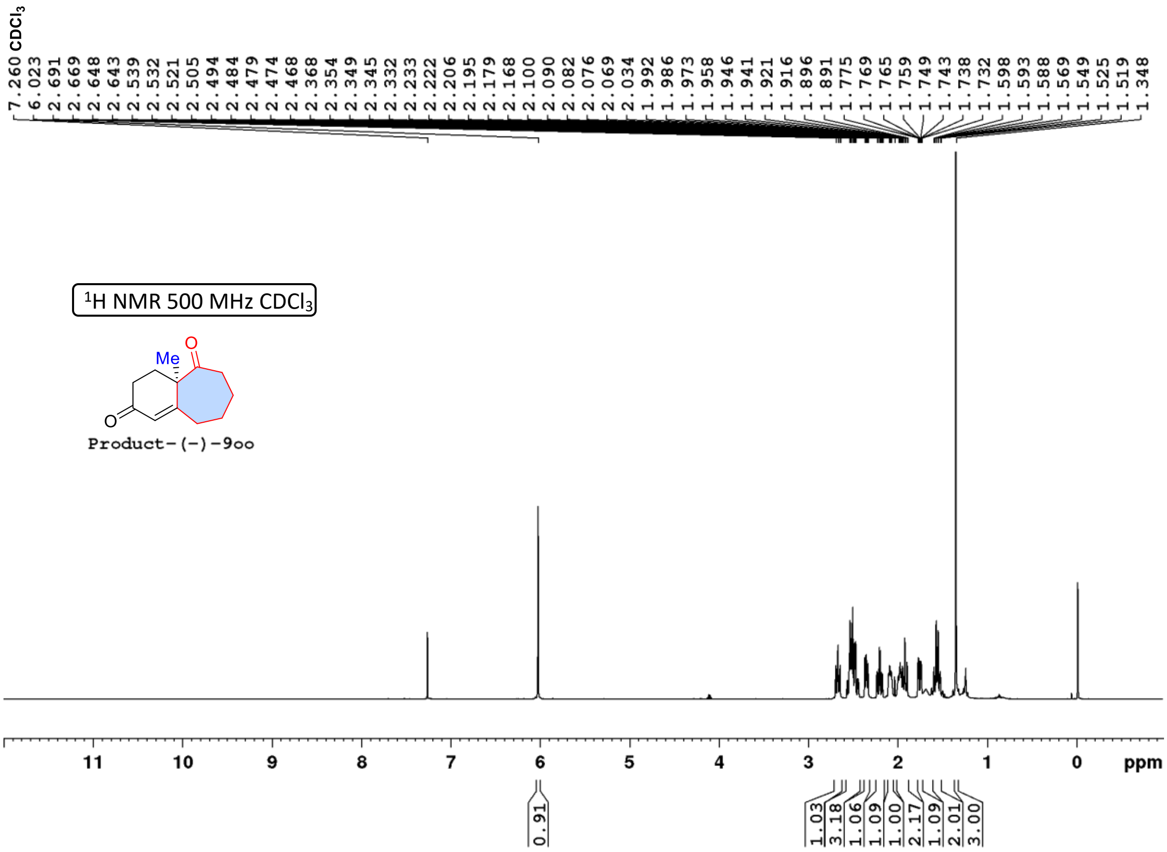
Chiralpak IG, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT35.753	35.753	2976790	47076	3.532	6.269
2	RT39.090	39.090	81293073	703832	96.468	93.731
Total			84269863	750909	100.000	100.000

Figure 40: HPLC spectra of the product **9u**.



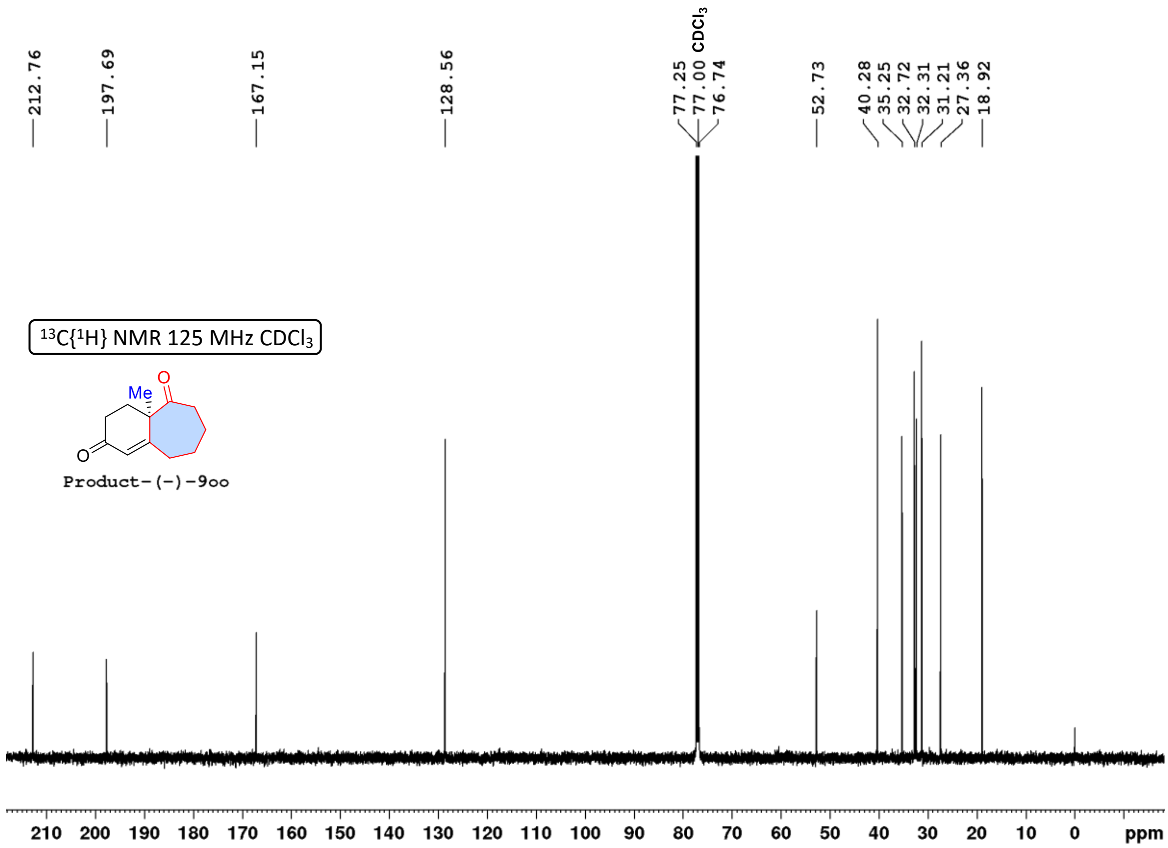
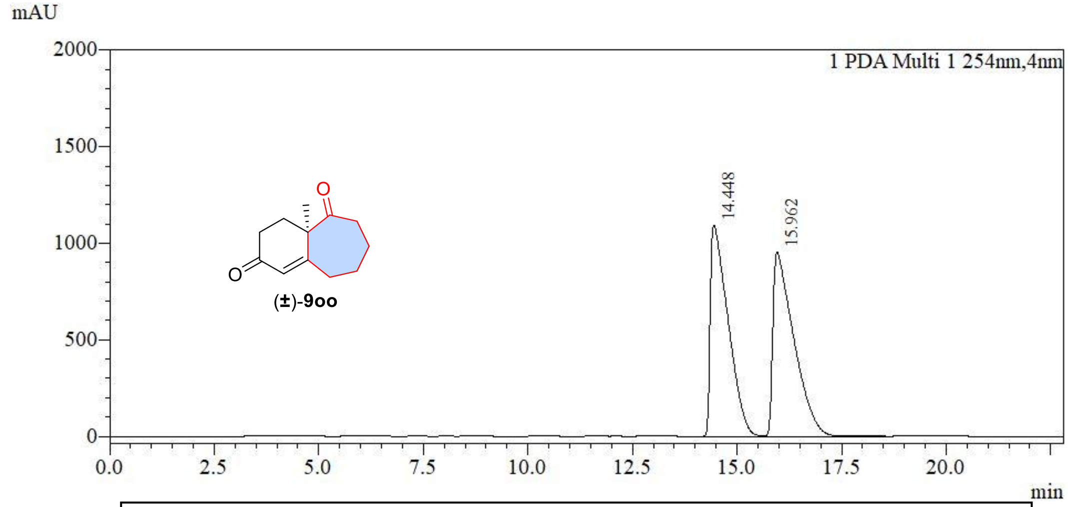


Figure 41: ^1H NMR and ^{13}C NMR spectrum of product **9oo**.

Racemic **(±)-9oo**:



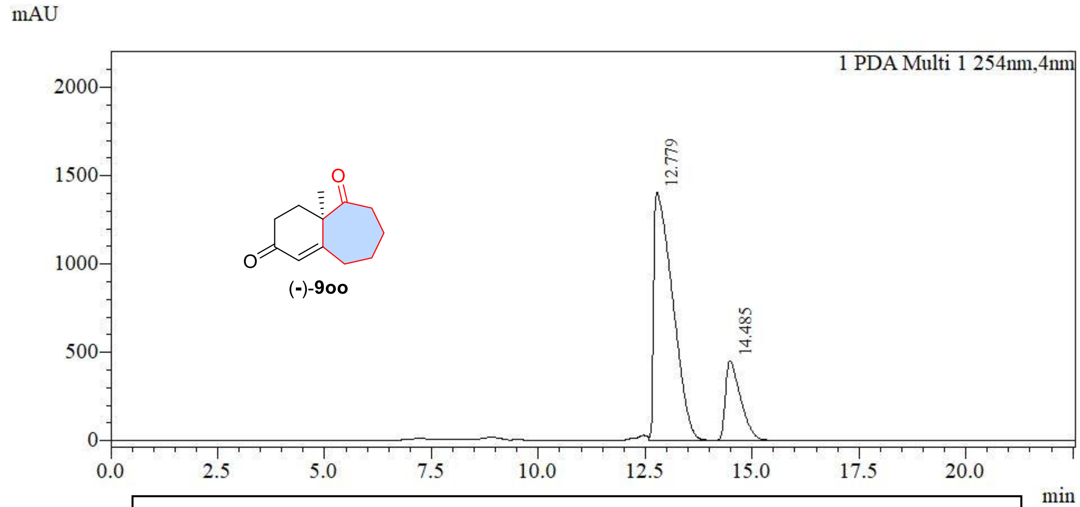
Chiralpak ID, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:14.448	14.448	32431820	1094791	49.304	53.502
2	RT:15.962	15.962	33347605	951467	50.696	46.498
Total			65779425	2046258	100.000	100.000

Chiral **(-)-9oo** (59% *ee*):



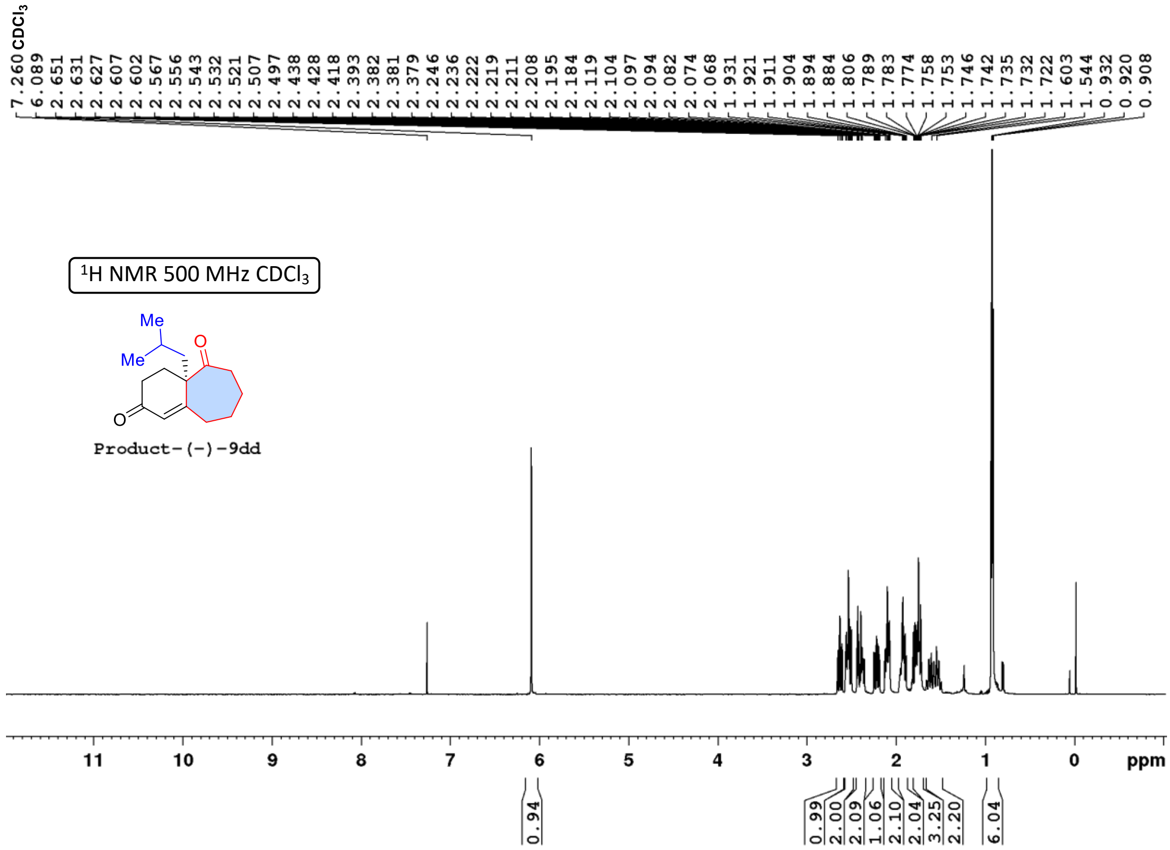
Chiralpak ID, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:12.779	12.779	43585722	1406369	79.434	75.679
2	RT:14.485	14.485	11284423	451975	20.566	24.321
Total			54870145	1858344	100.000	100.000

Figure 42: HPLC spectra of the product **9oo.**



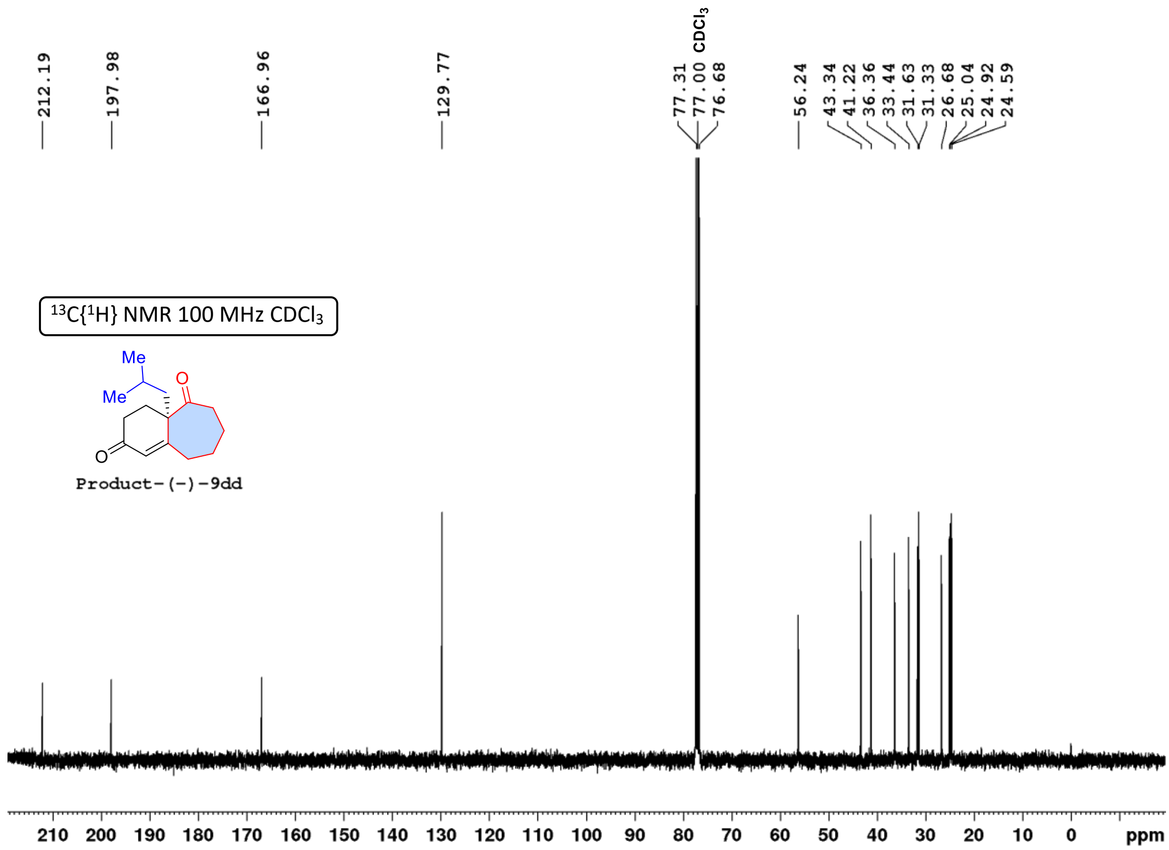
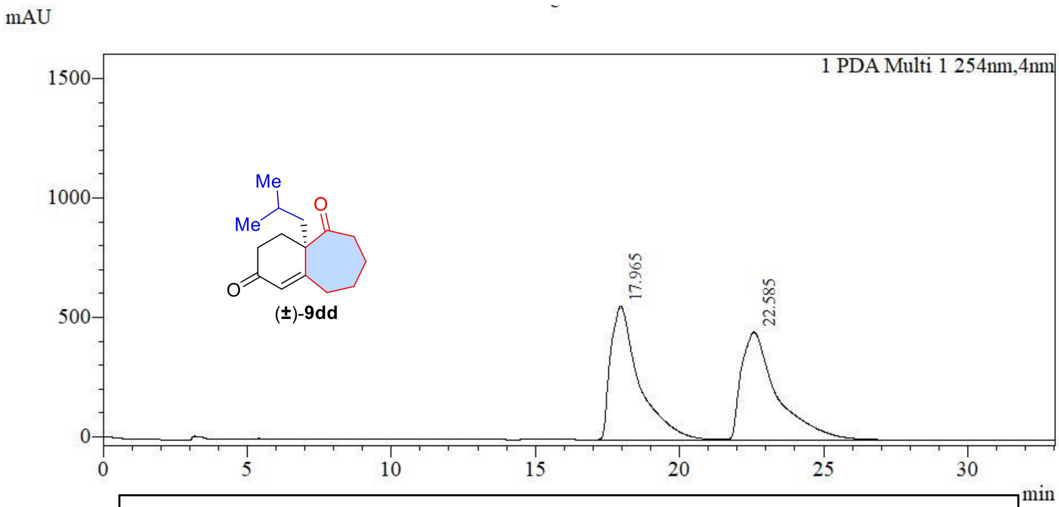


Figure 43: ^{1}H NMR and ^{13}C NMR spectrum of product **9dd**.

Racemic **(±)-9dd**:



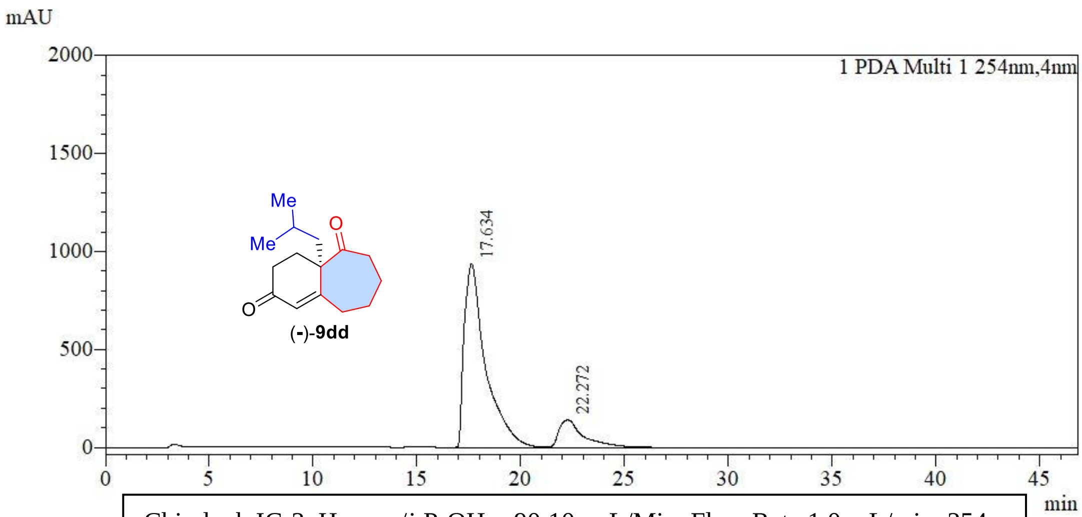
Chiralpak IC-3, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:17.965	17.965	38627409	558297	49.945	55.364
2	RT:22.585	22.585	38712861	450108	50.055	44.636
Total			77340269	1008404	100.000	100.000

Chiral **(-)-9dd** (71% *ee*):



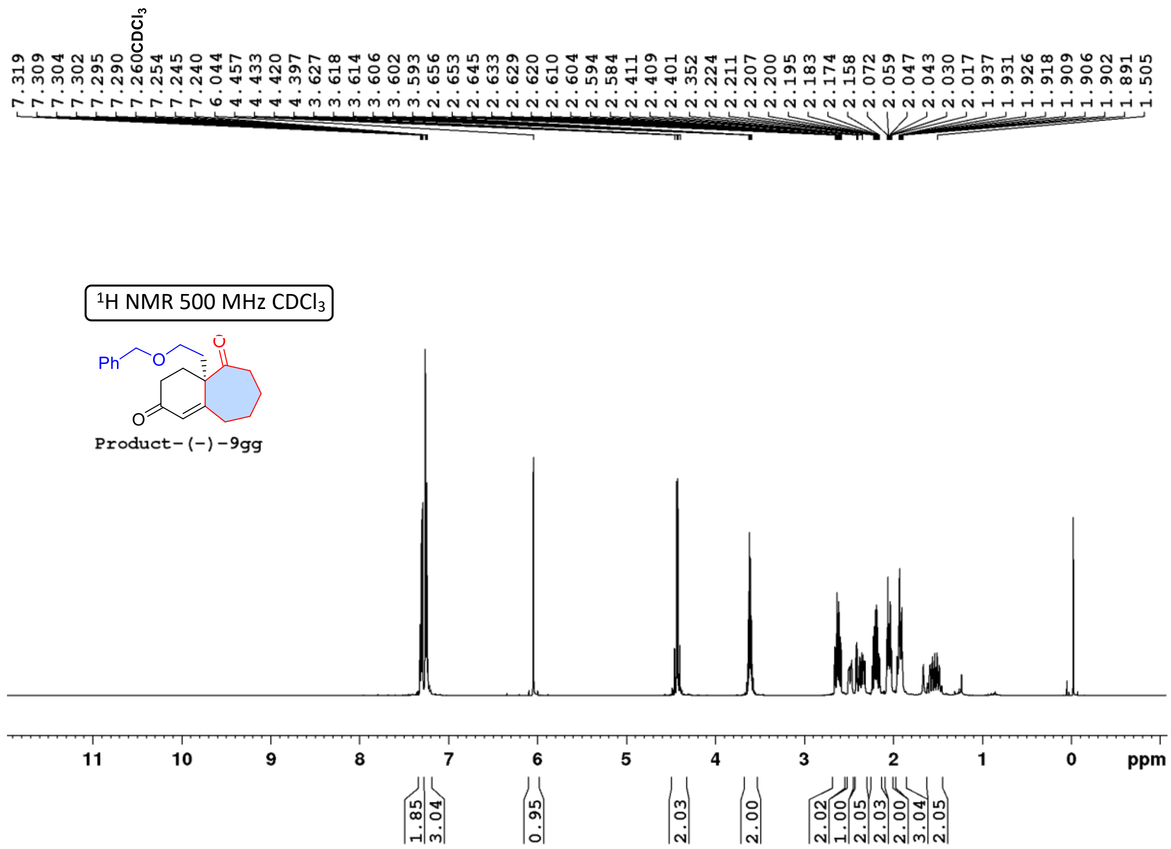
Chiralpak IC-3, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:17.634	17.634	67256576	938511	85.464	87.053
2	RT:22.272	22.272	11438822	139584	14.536	12.947
Total			78695398	1078095	100.000	100.000

Figure 44: HPLC spectra of the product **9dd.**



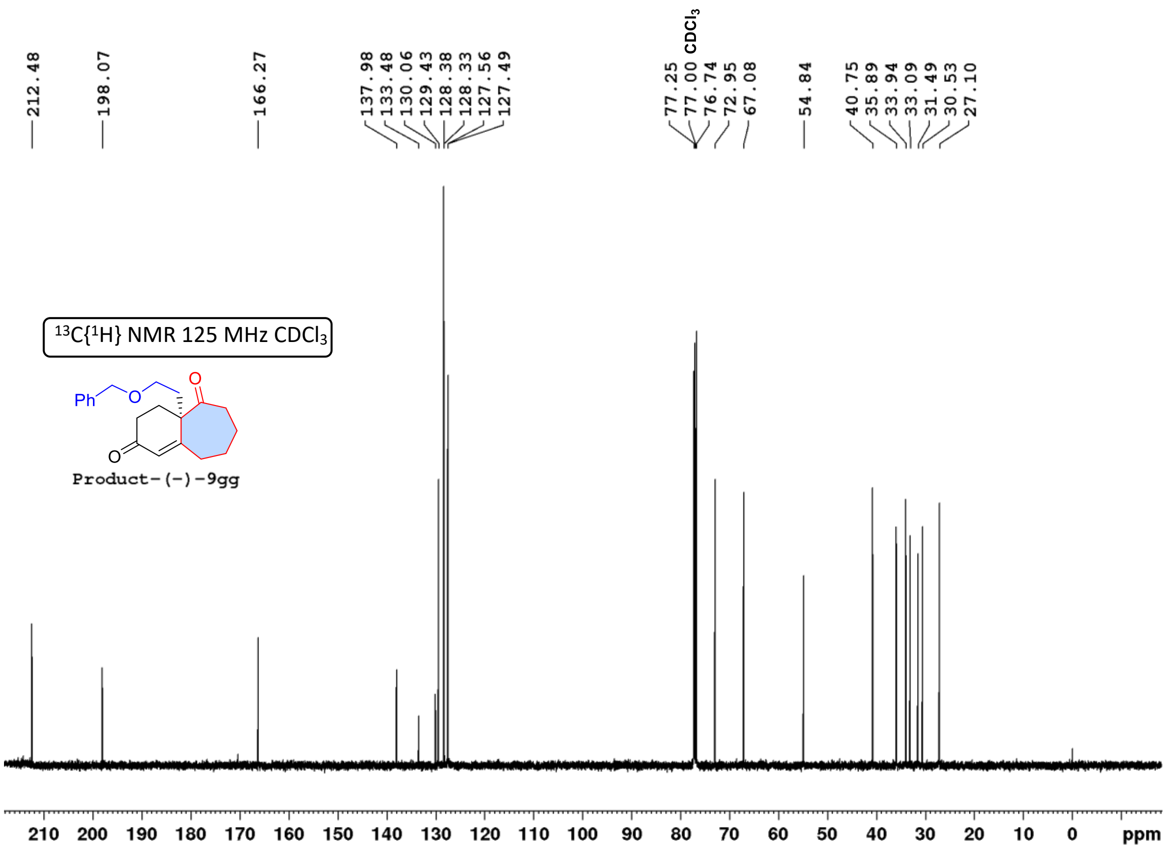
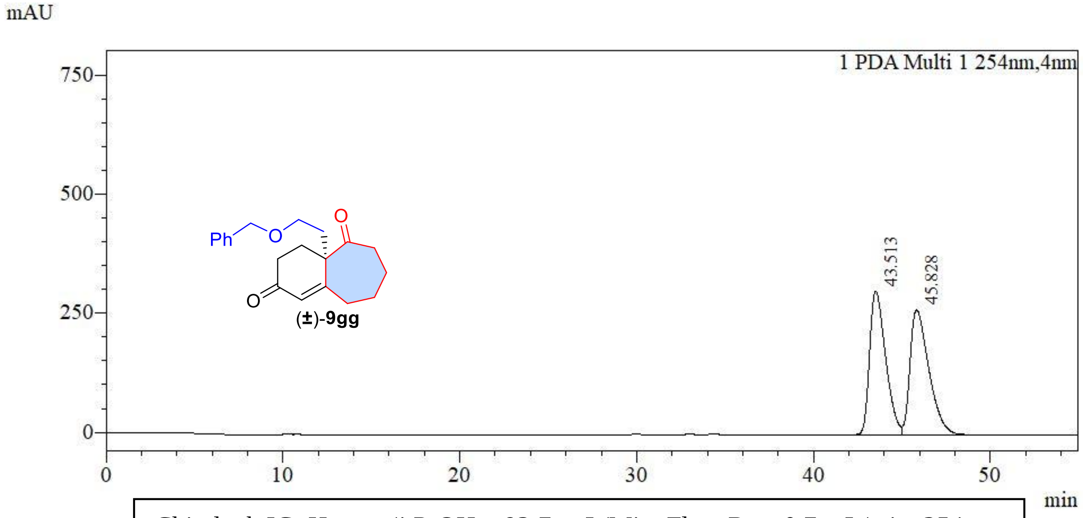


Figure 45: ^{1}H NMR and ^{13}C NMR spectrum of product **9gg**.

Racemic **(±)-9gg**:



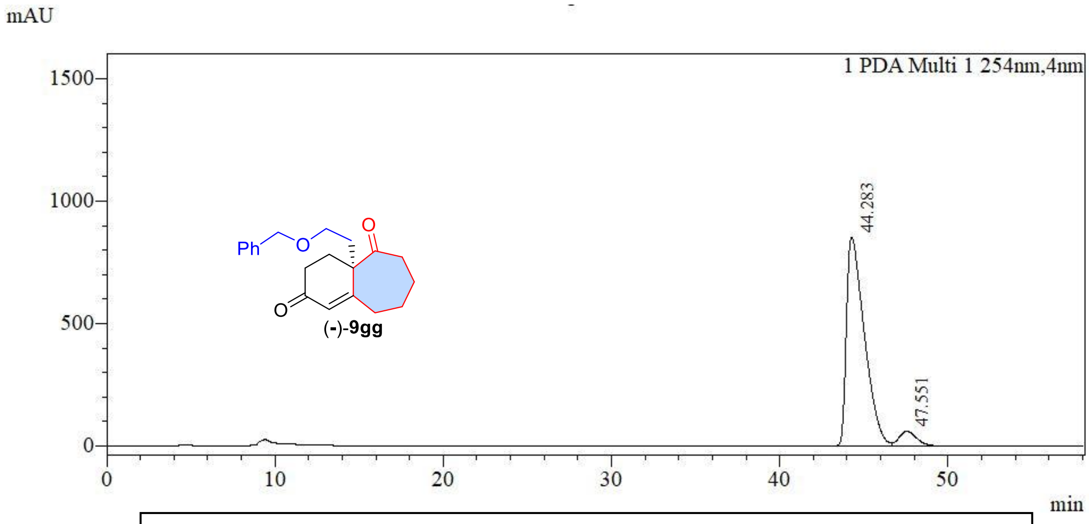
Chiralpak IG, Hexane/*i*-PrOH = 93:7, mL/Min, Flow Rate 0.7 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:43.513	43.513	19009236	301361	49.689	53.512
2	RT:45.828	45.828	19246972	261805	50.311	46.488
Total			38256208	563166	100.000	100.000

Chiral **(-)-9gg** (87% *ee*):



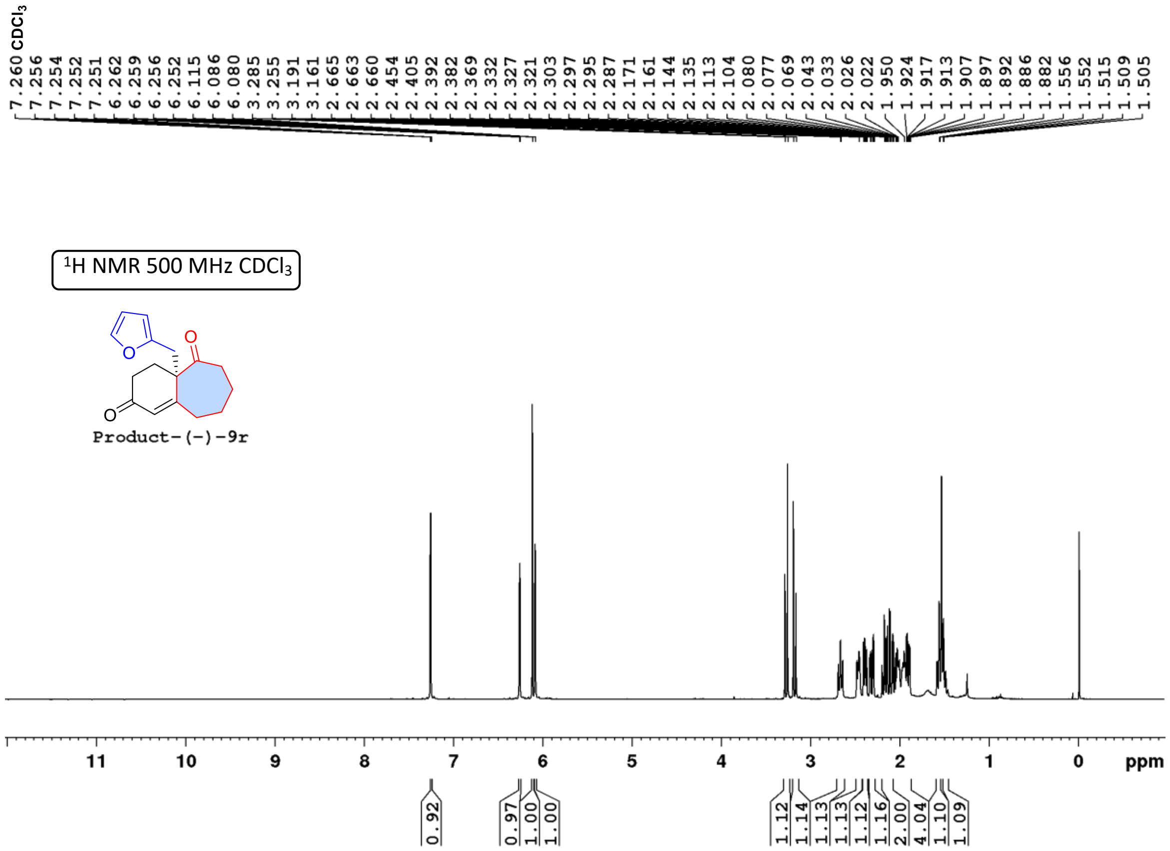
Chiralpak IG, Hexane/*i*-PrOH = 93:7, mL/Min, Flow Rate 0.7 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:44.283	44.283	63190445	853864	93.557	93.417
2	RT:47.551	47.551	4351469	60170	6.443	6.583
Total			67541913	914034	100.000	100.000

Figure 46: HPLC spectra of the product **9gg.**



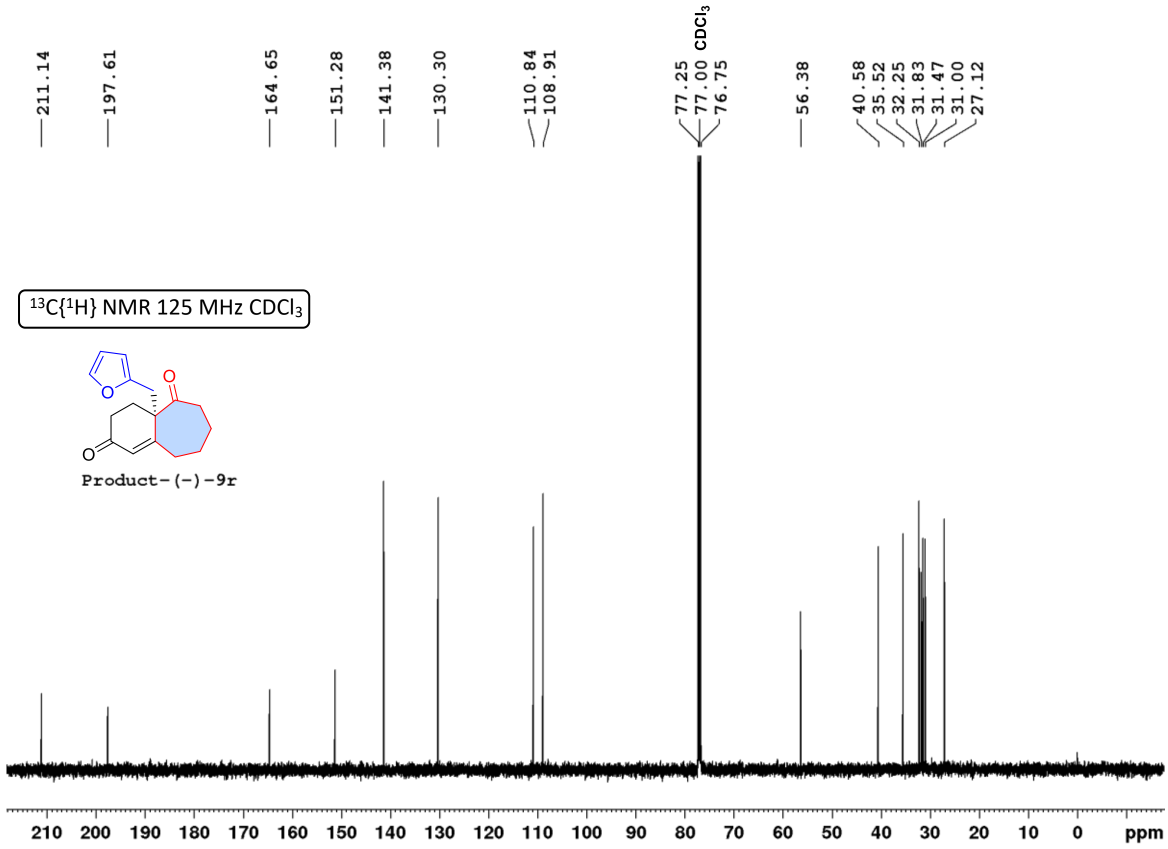
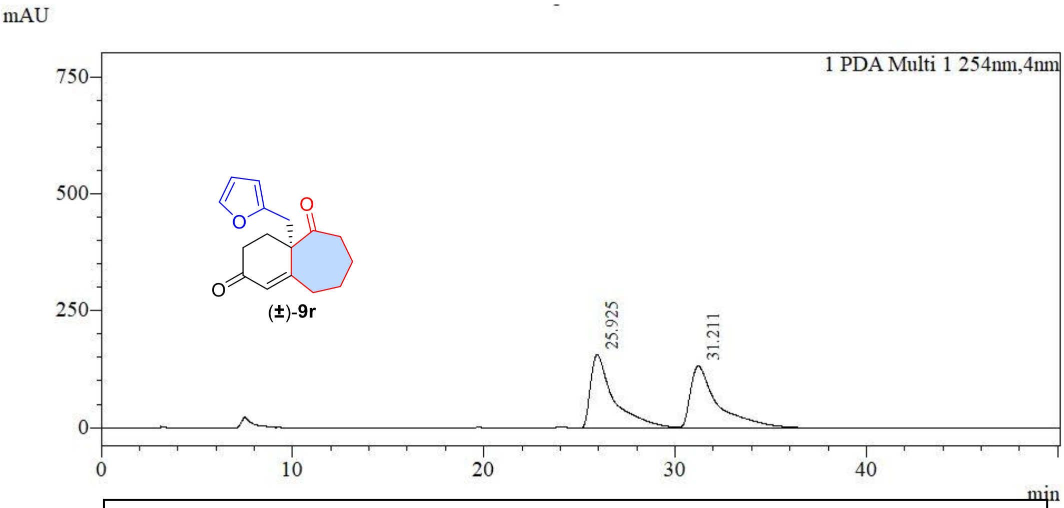


Figure 47: ^{1}H NMR and ^{13}C NMR spectrum of product **9r**.

Racemic **(±)-9r**:



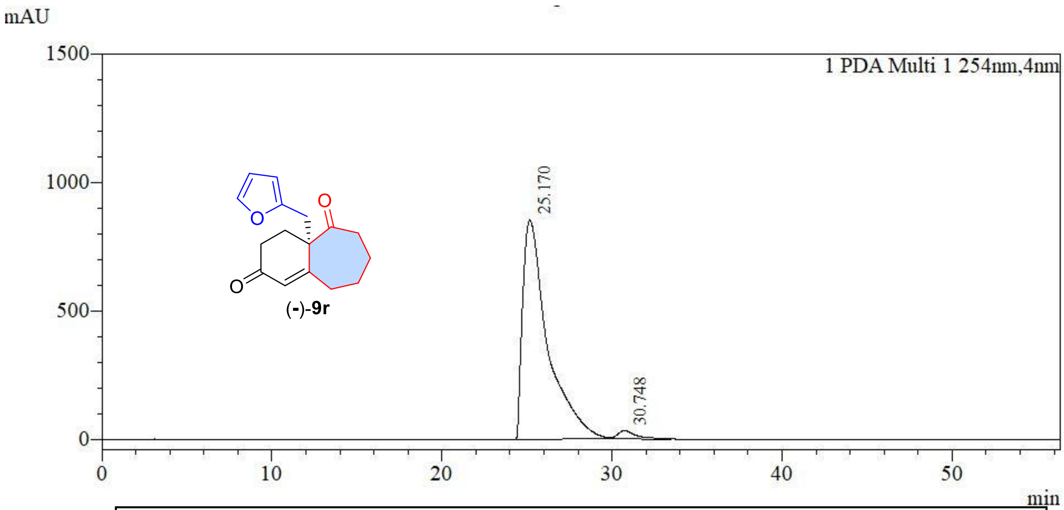
Chiralpak IC-3, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:25.925	25.925	13233611	156198	50.018	54.108
2	RT:31.211	31.211	13224114	132481	49.982	45.892
Total			26457725	288679	100.000	100.000

Chiral **(-)-9r** (95% *ee*):



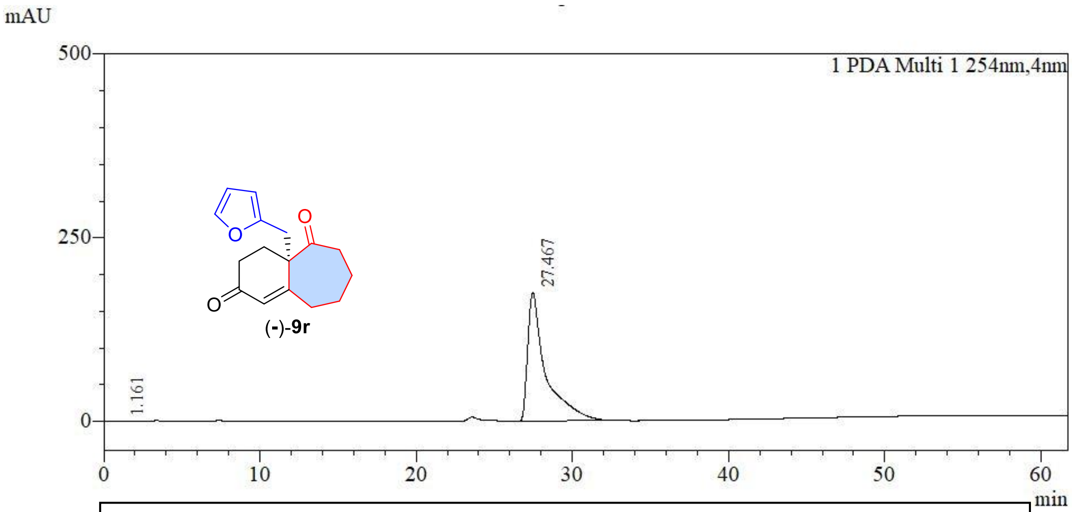
Chiralpak IC-3, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:25.170	25.170	87273352	854342	97.325	96.471
2	RT:30.748	30.748	2398404	31255	2.675	3.529
Total			89671756	885597	100.000	100.000

Chiral **(-)-9r** (>99% *ee*) (crystal):



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

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1		1.161	-37	4	-0.000	0.003
2	RT:27.467	27.467	14073218	174961	100.000	99.997
Total			14073181	174966	100.000	100.000

Figure 48: HPLC spectra of the product **9r**.

The absolute structure of compound (-)-**9r** was again confirmed by X-ray crystallography (Figure 49).[7]

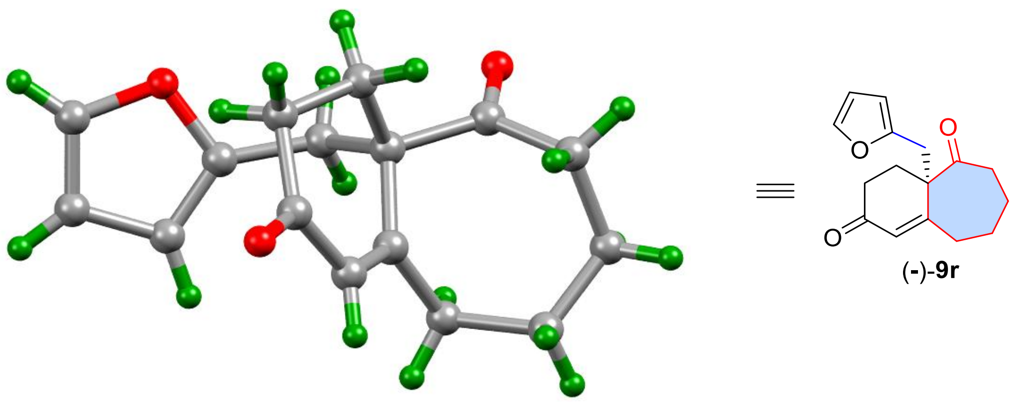
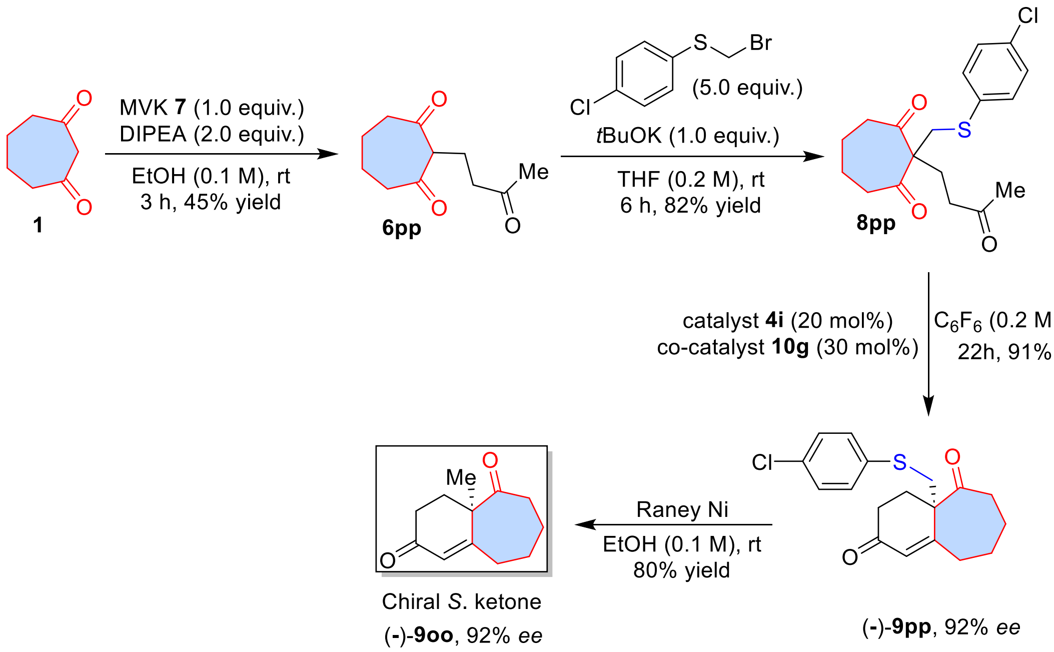


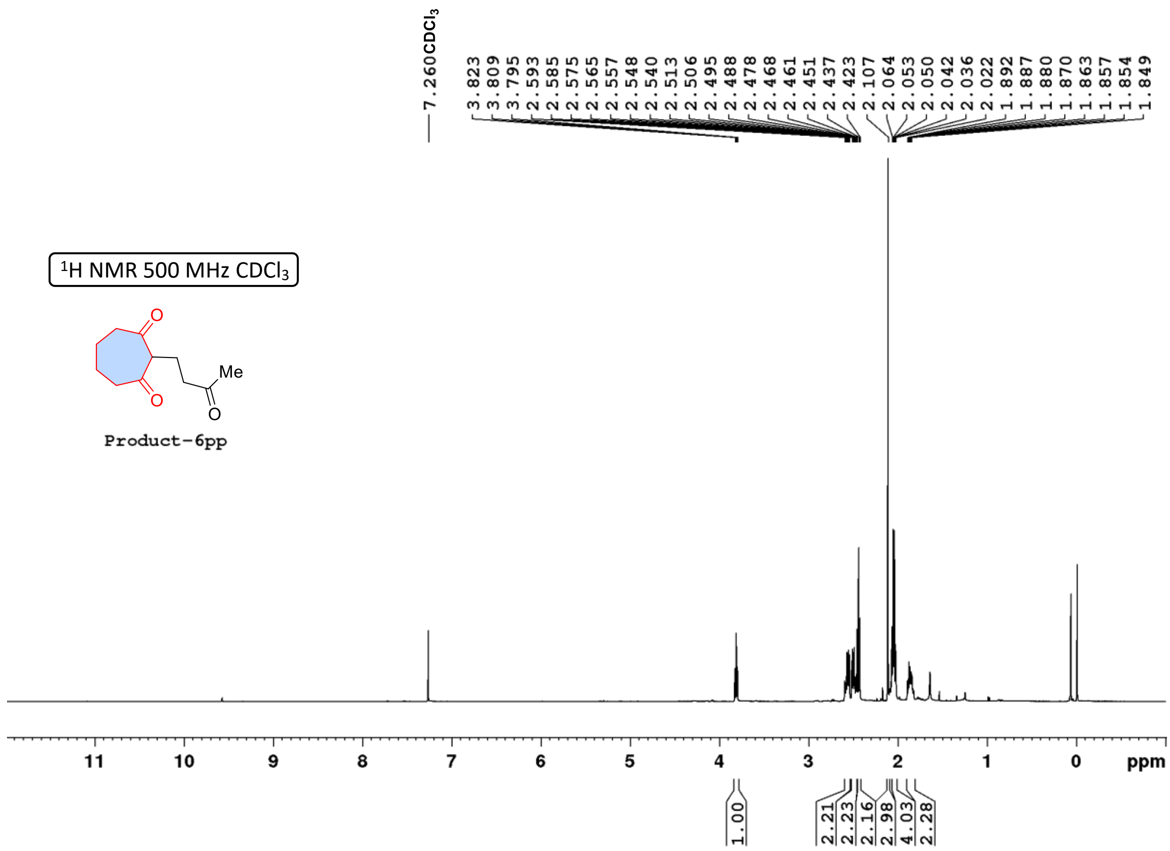
Figure 49: X-Ray crystal structure of (*S*)-4a-(furan-2-ylmethyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione (-)-**9r**.

5.2.5.3 New synthetic route to access high enantioselective chiral S. ketone (-)-9oo

Disappointed with the low *ee* (59%) of chiral S. ketone (-)-**9oo**, herein, we proposed a new synthetic route for improving its enantioselectivity by controlling conformational flexibility of triketone **8oo** in the **4i**/**10g**-catalysed *pre*-transition state through increasing steric hindrance of substitution at the *C*-2 carbon. With the understanding of steric effects on enantioselectivity, we designed a special triketone **8pp** having the methyl masked with 4-chlorophenylthio group in order to induce the steric hindrance at *C*-2 position (Scheme 2). Firstly, we reacted cycloheptane-1,3-dione **1** with 1.0 equiv. of methyl vinyl ketone **7** in the presence of DIPEA (2.0 equiv.) in ethanol (0.1 M) at room temperature for 3 h affording the corresponding 2-alkylated cycloheptane-1,3-dione **6pp** with 45% yield (Scheme 2) (for NMR, see Figure 50). Next, when the compound **6pp** was reacted with 5.0 equiv. of (bromomethyl)(4-chlorophenyl)sulfane in the presence of *t*BuOK (1.0 equiv.) in THF (0.2 M) at room temperature for 6 h, it furnished the corresponding triketone **8pp** with 82% yield (Scheme 2) (for NMR, see Figure 51). Next, we applied optimized asymmetric reaction conditions of intramolecular aldol condensation through asymmetric desymmetrization on the **8pp**. The reaction of triketone **8pp** in the presence of 20 mol% **4i** and 30 mol% **10g** in C_6F_6 (0.2 M) at 60 °C for 22 h afforded the corresponding chiral S. ketone analogue (-)-**9pp** with a yield of 91% and excellent enantioselectivity of 92% (Scheme 2) (for NMR and HPLC analysis, see Figure 52-23). Finally, the desulfurization of (-)-**9pp** with an excess of Raney nickel (one small tea spoon, 200 mg) in ethanol (0.1 M) at room temperature for 1 h furnished the chiral S. ketone (-)-**9oo** in 80% yield with 92% *ee* (Scheme 2) which was confirmed by the HPLC analysis (Figure 54). Using this four-step strategy from **1**, we can easily achieve chiral S. ketone in 27% overall yield with 92% *ee* (Scheme 2).



Scheme 2: An efficient synthetic route to access high enantioselective chiral S. ketone (-)-**9oo**.



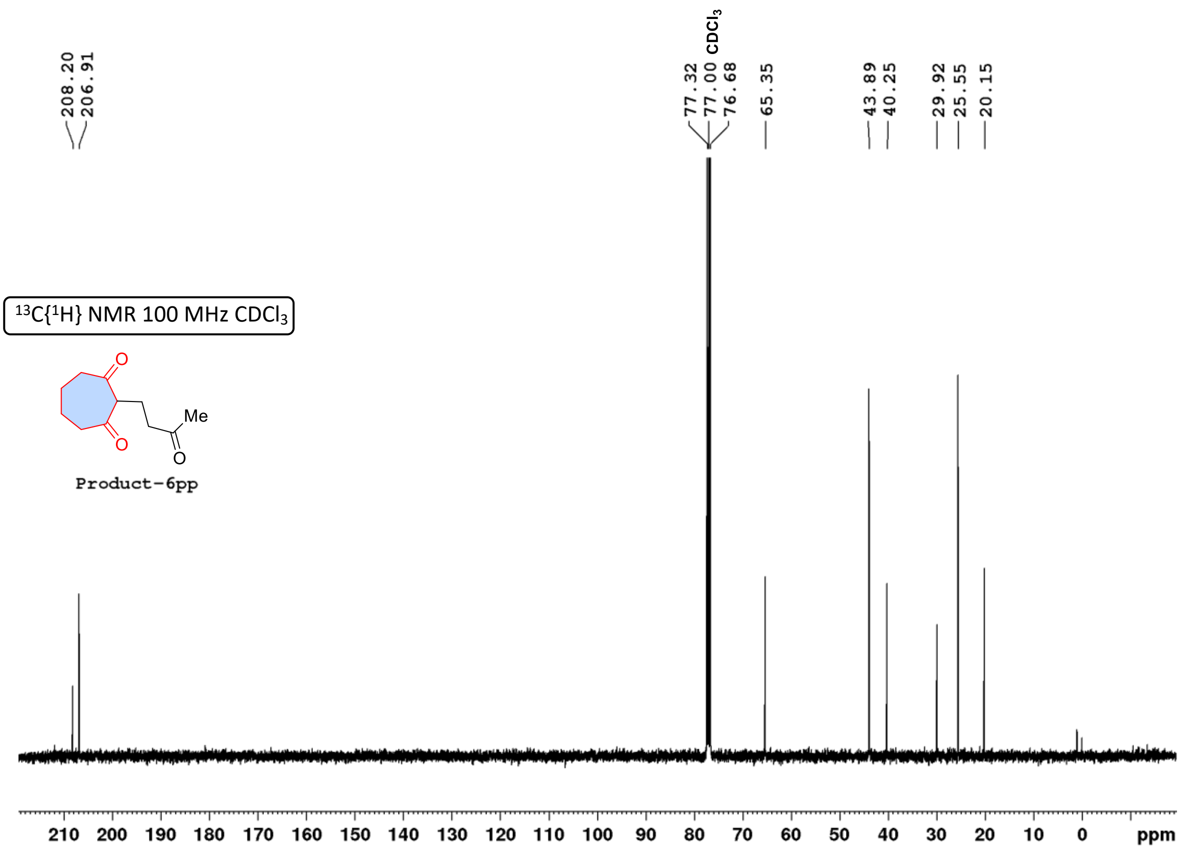
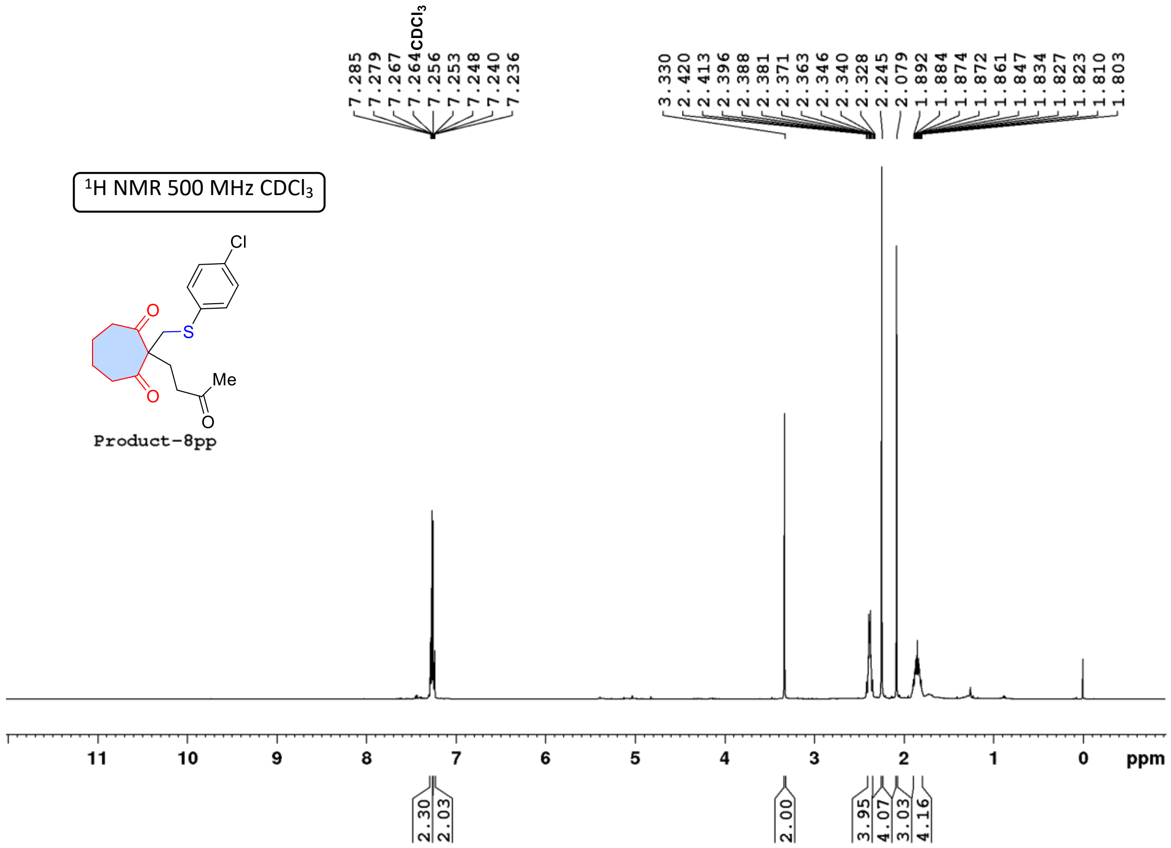


Figure 50: ^{1}H NMR and ^{13}C NMR spectrum of product **6pp**.



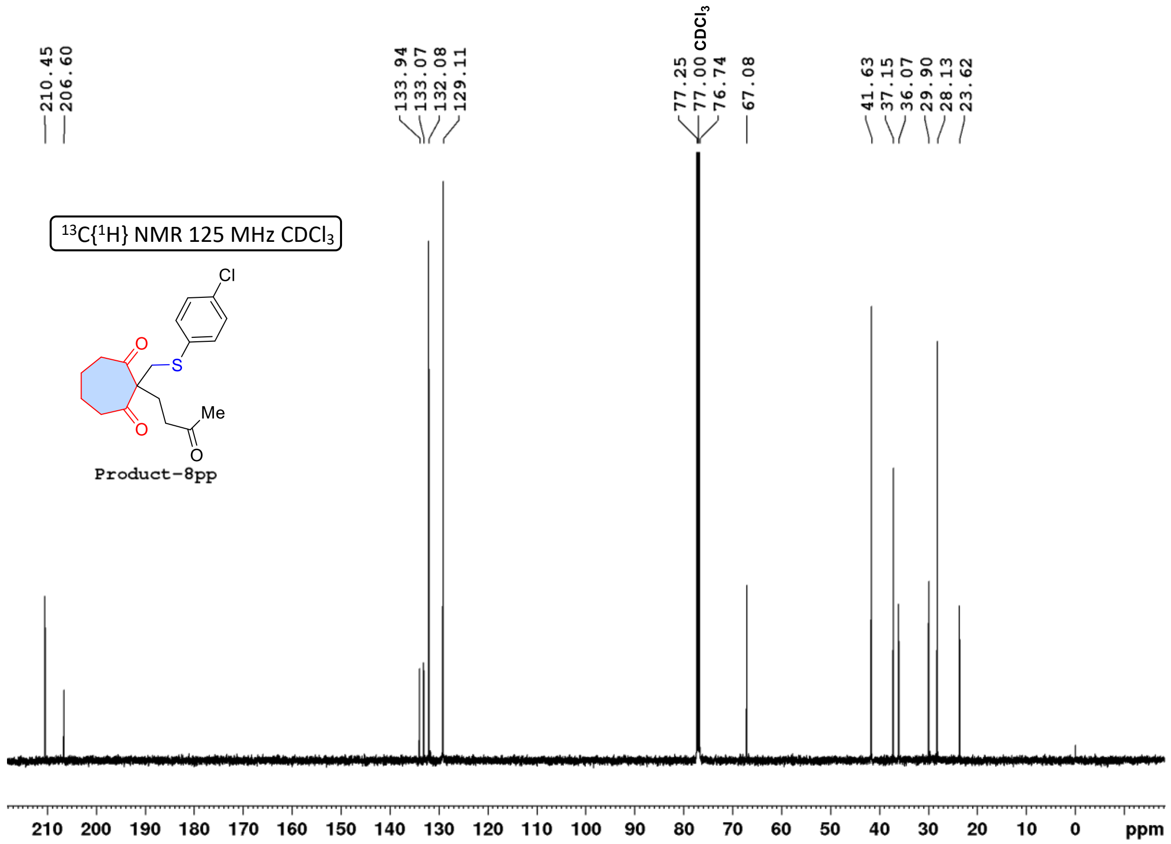
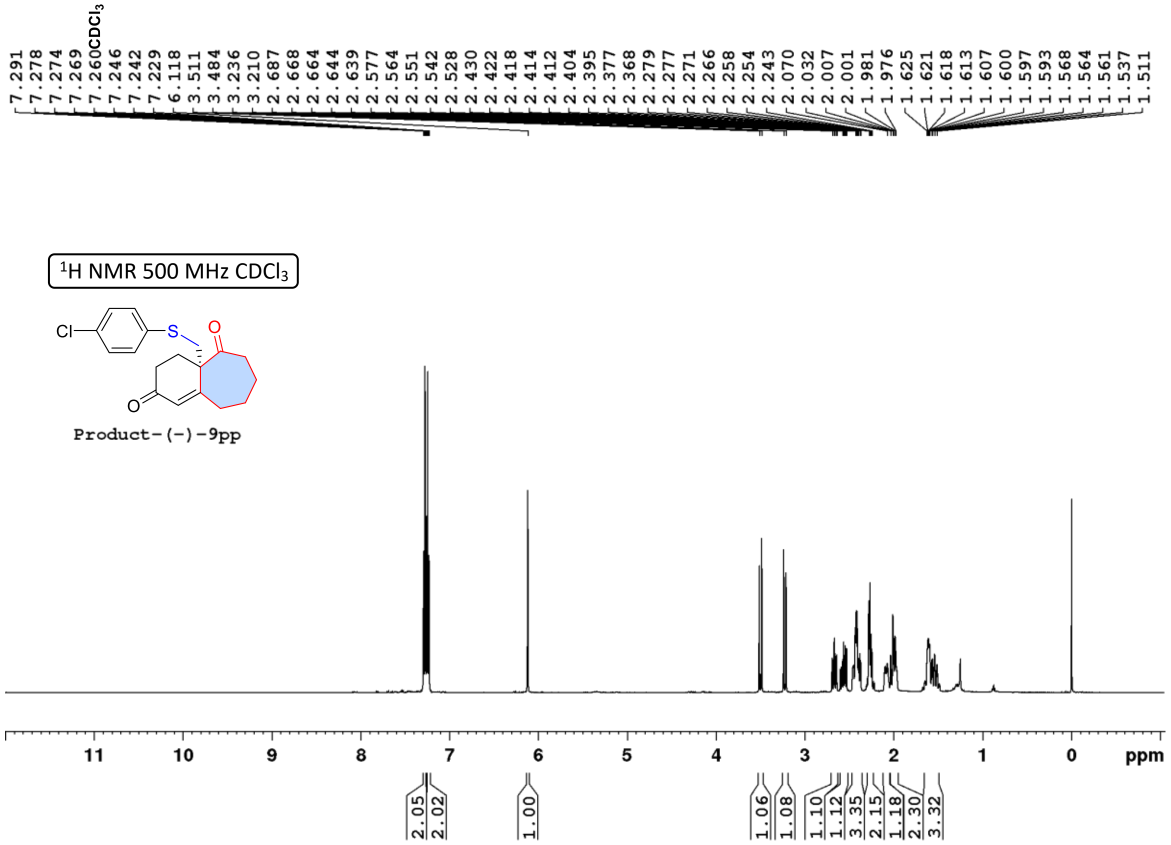


Figure 51: ^{1}H NMR and ^{13}C NMR spectrum of product **8pp**.



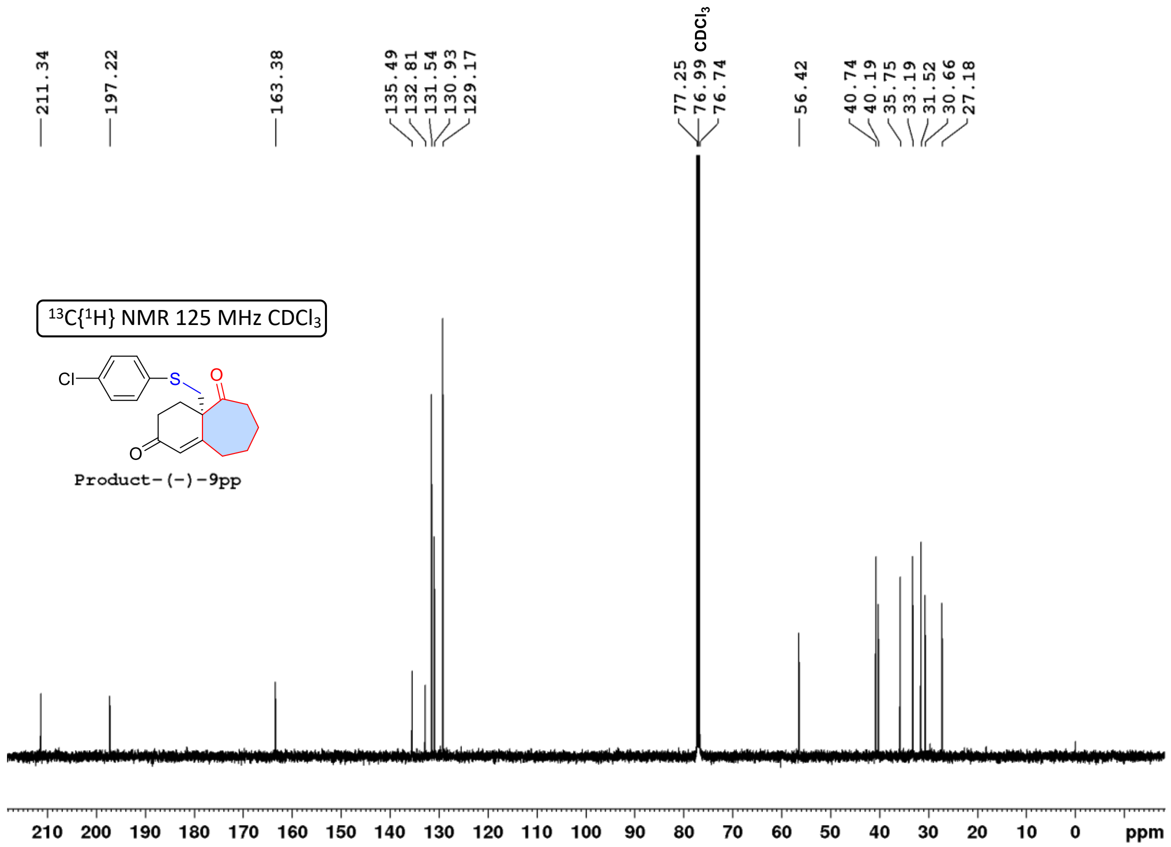
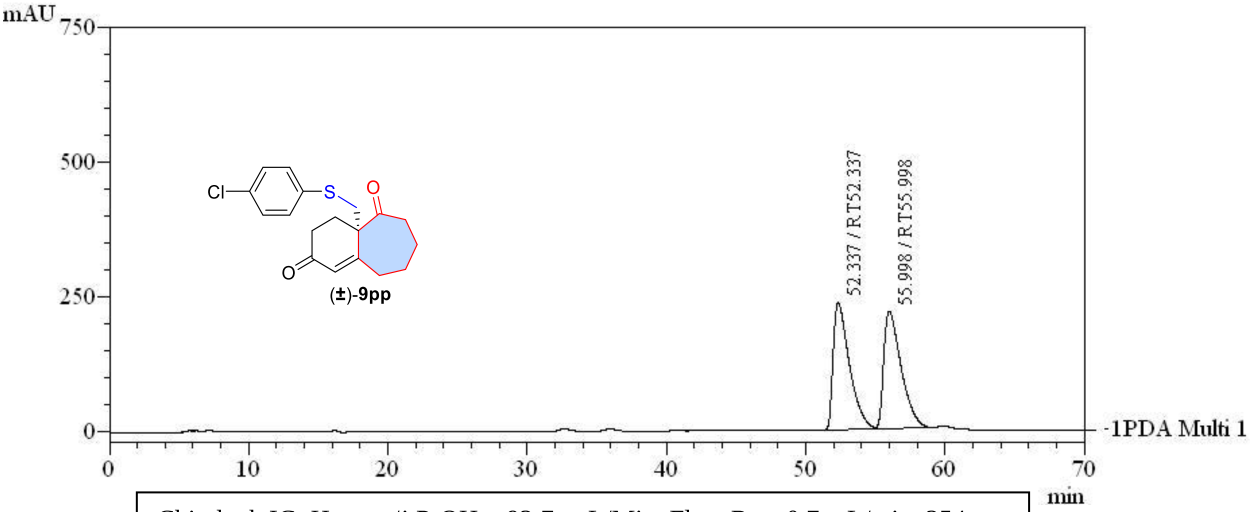


Figure 52: ^{1}H NMR and ^{13}C NMR spectrum of product **9pp**.

Racemic **(±)-9pp**:



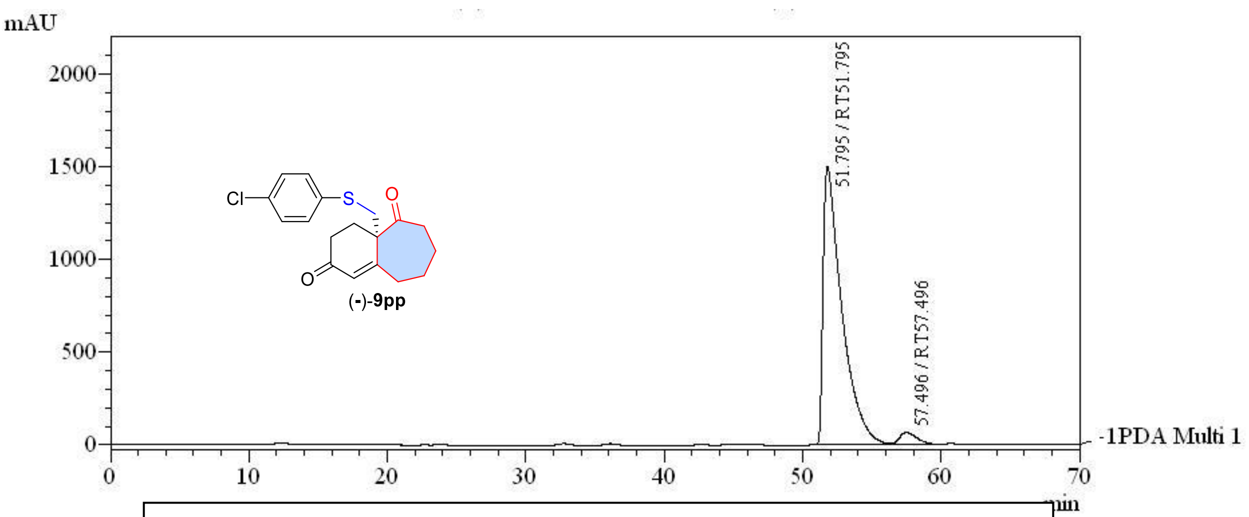
Chiralpak IG, Hexane/*i*-PrOH = 93:7, mL/Min, Flow Rate 0.7 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT52.337	52.337	19256715	236522	50.320	51.981
2	RT55.998	55.998	19011717	218490	49.680	48.019
Total			38268432	455013	100.000	100.000

Chiral **(-)-9pp** (92% *ee*)



Chiralpak IG, Hexane/*i*-PrOH = 93:7, mL/Min, Flow Rate 0.7 mL/min, 254 nm

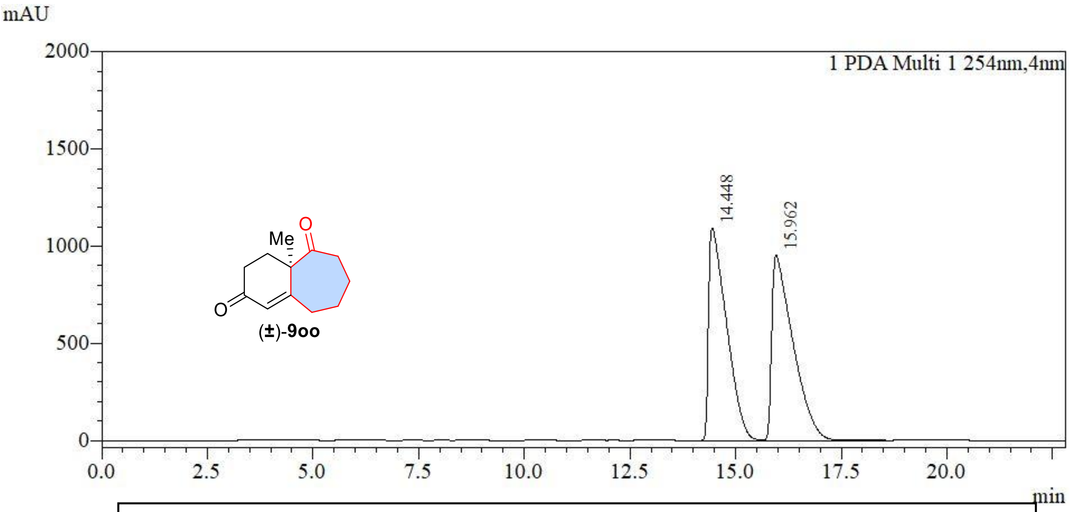
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT51.795	51.795	140768619	1498966	96.351	95.991
2	RT57.496	57.496	5331269	62599	3.649	4.009
Total			146099888	1561565	100.000	100.000

Figure 53: HPLC spectra of the product **9pp.**

Racemic **(±)-9oo**:



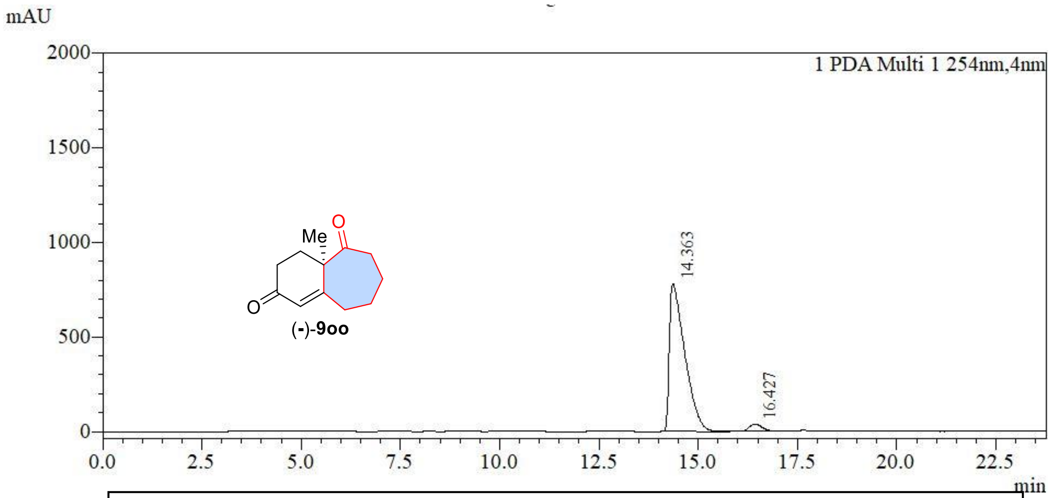
Chiralpak ID, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:14.448	14.448	32431820	1094791	49.304	53.502
2	RT:15.962	15.962	33347605	951467	50.696	46.498
Total			65779425	2046258	100.000	100.000

Chiral **(-)-9oo** (92% *ee*)



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

Peak Table

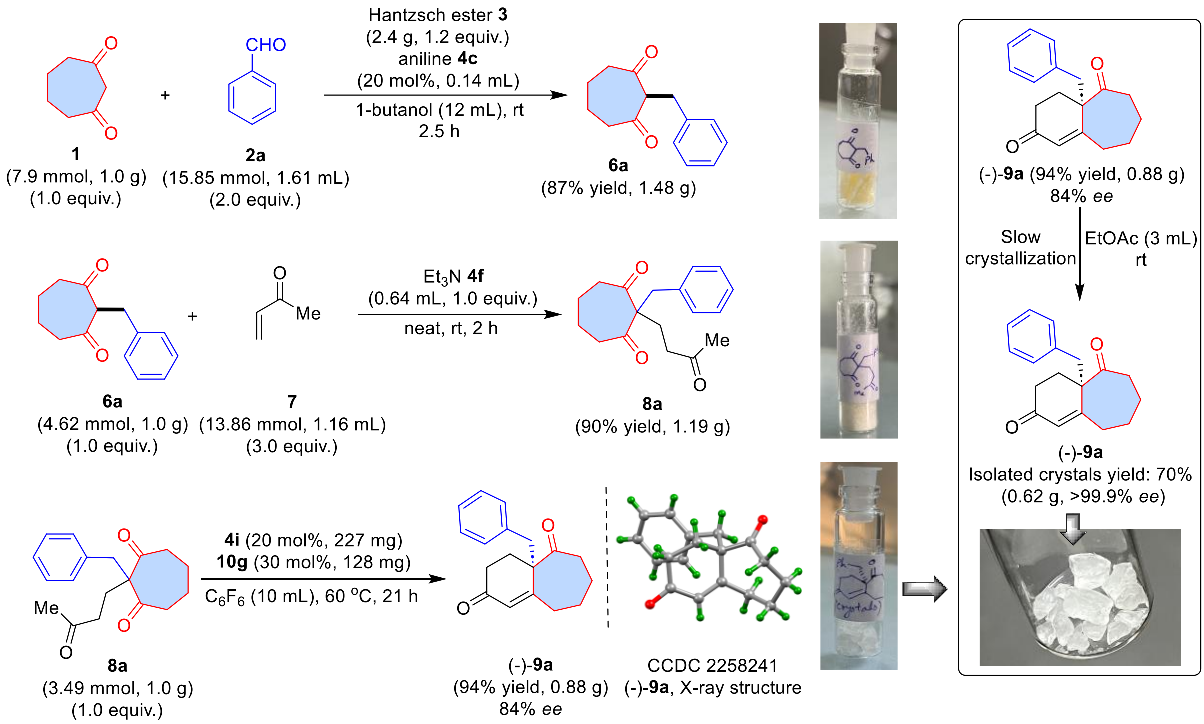
PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:14.363	14.363	21232006	782667	96.111	95.427
2	RT:16.427	16.427	859196	37507	3.889	4.573
Total			22091202	820174	100.000	100.000

Figure 54: HPLC spectra of the product **9oo.**

5.2.6 Gram-scale Reactions and Crystallization Technique to Access Enantiomerically Pure Chiral S. Ketone Analogue (-)-9a

In order to prove the sustainability of the developed synthetic methods, we have performed the gram-scale reactions of organocatalytic reductive coupling, Michael addition, and intramolecular asymmetric aldol condensation (Scheme 3). The organocatalytic reductive coupling of cycloheptane-1,3-dione **1** (1.0 g) with 2.0 equiv. of benzaldehyde **2a** (1.61 mL) in the presence of 1.2 equiv. of Hantzsch ester **3** (2.4 g) and 20 mol% of aniline **4c** (0.14 mL) in 1-butanol (12 mL) at room temperature for 2.5 h furnished the 2-benzylcycloheptane-1,3-dione **6a** with an excellent yield of 87% (1.48 g) (Scheme 3). The Michael addition of 2-benylcycloheptane-1,3-dione **6a** (1.0 g) with 3.0 equiv. of methyl vinyl ketone **7** (1.16 mL) in the presence of 1.0 equiv. of Et_3N **4f** (0.64 mL) at room temperature for 3 h furnished the 2-benzyltriketone **8a** with 90% yield (1.19 g) (Scheme 3).

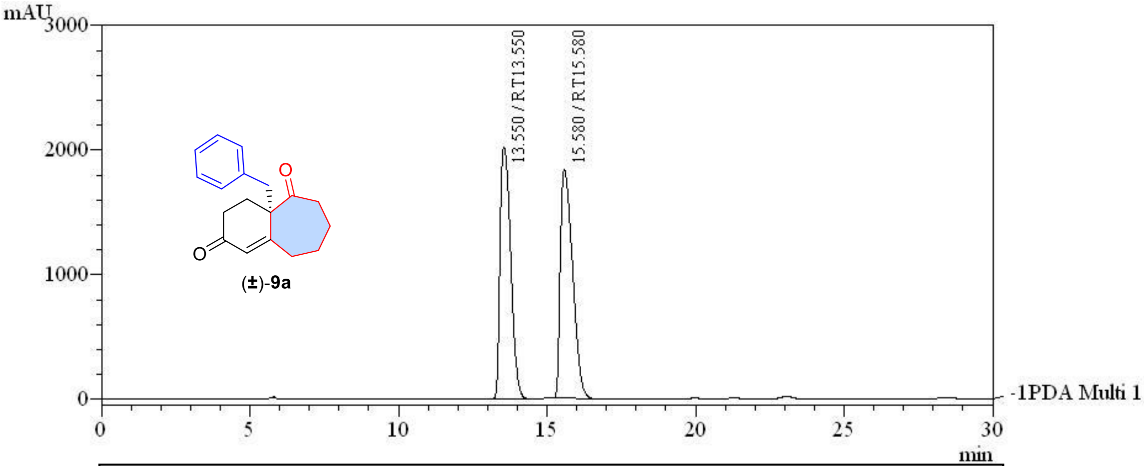


Scheme 3: Gram-scale reactions and crystallization technique for achieving >99.9% enantiomerically pure S. ketone analogue (-)-**9a**.

Finally, the intramolecular aldol condensation of **8a** (1.0 g) *via* asymmetric desymmetrization in the presence of 20 mol% of catalyst **4i** (0.23 g) and 30 mol% of co-catalyst **10g** (0.13 g) in

C_6F_6 (10 mL) at 60 °C afforded the chiral S. ketone analogue (-)-**9a** with 94% yield (0.88 g) and 84% *ee* in 21 h (Scheme 3).

Racemic **(±)-9a**:



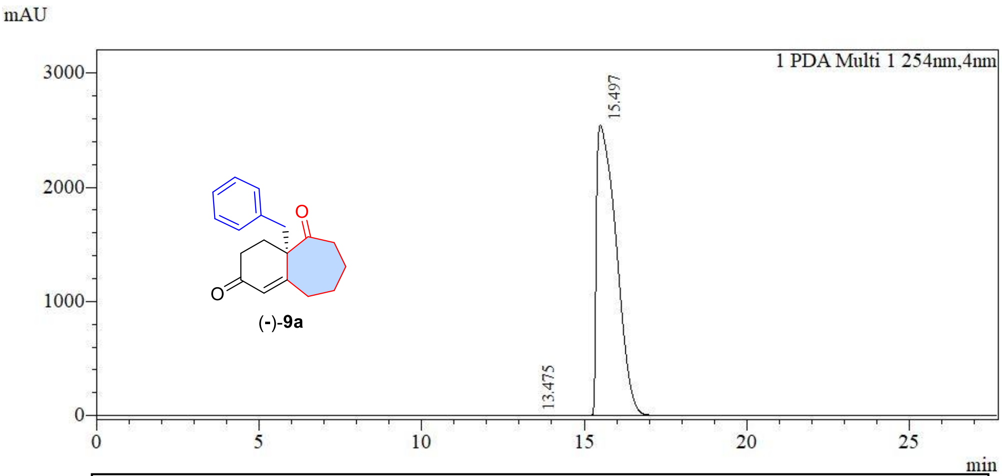
Chiralpak IG, Hexane/*i*-PrOH = 90:10, mL/Min, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT13.550	13.550	50568890	2022666	48.892	52.378
2	RT15.580	15.580	52861884	1838985	51.108	47.622
Total			103430774	3861651	100.000	100.000

Chiral **(-)-9a** (Crystals after slow crystallization) (>99% *ee*)



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

Peak Table

PDA Ch1 254nm

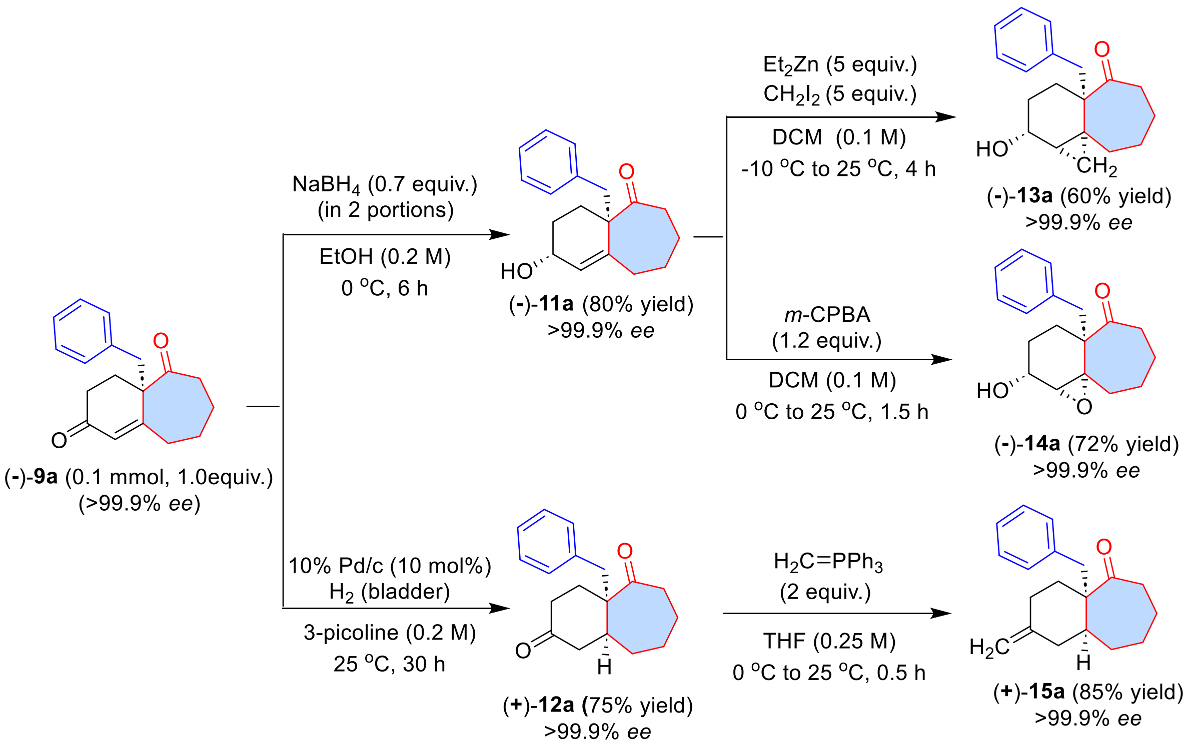
Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:13.475	13.475	31967	1619	0.030	0.064
2	RT:15.497	15.497	106550113	2547063	99.970	99.936
Total			106582080	2548682	100.000	100.000

Figure 55: HPLC spectra of the product **9a.**

Interestingly, the slow crystallization of the chiral S. ketone (-)-**9a** (0.88 g, 84% *ee*) in 3.0 mL of EtOAc at 25 °C for 12 h yielded the single enantiomer of (-)-**9a** as a white crystals in 70% yield (0.62 g) with >99.9% *ee* (Scheme 3, Figure 56) which was confirmed by HPLC analysis (Figure 55) and filtrate (0.26 g) in 30% yield with 43% *ee*.

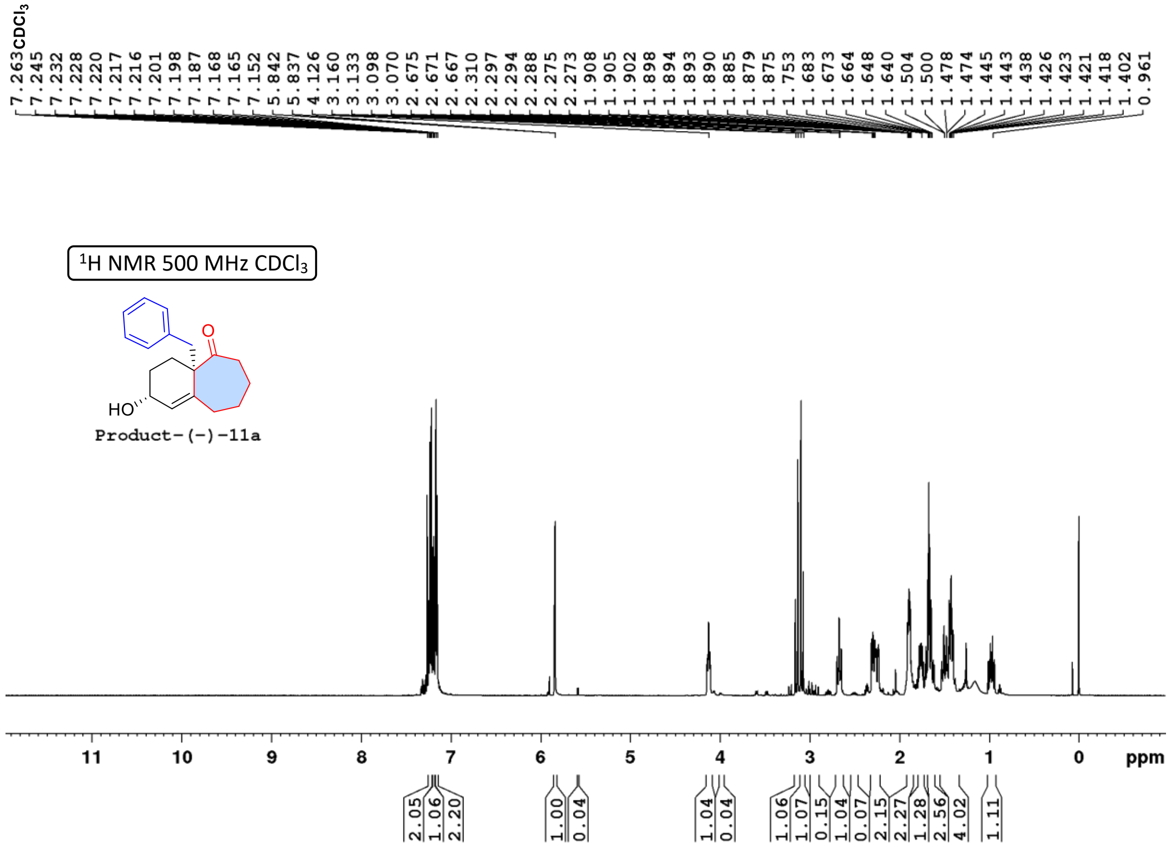
5.2.7 Synthetic Transformations on Enantiomerically Pure Chiral S. Ketone Analogue (-)-9a

We have then performed few synthetic transformations on the enantiomerically pure (-)-**9a** to prove its synthetic utility. When the compound (-)-**9a** (>99.9% *ee*) was reacted with two portions of 0.7 equiv. $NaBH_4$ in ethanol at 0 °C for 6 h, the reaction afforded the regio-/chemo-selectively reduced single isomer of (-)-**11a** in 80% yield with >25:1 *dr* and >99% *ee* (Scheme 4). The Simmons-Smith reaction of (-)-**11a** (>99.9% *ee*) with diethylzinc (5.0 equiv.) and diiodomethane (5.0 equiv.) in DCM (0.1 M) at -10 °C to 25 °C for 4 h furnished the corresponding cyclopropane bearing chiral S. ketone analogue (-)-**13a** (>99.9% *ee*) in 60% yield with >25:1 *dr* (Scheme 4).



Scheme 4: Synthetic transformations on enantiomerically pure (-)-**9a**.

Similarly, the epoxidation of (-)-**11a** (>99.9% *ee*) using 1.2 equiv. of *m*-CPBA in DCM (0.1 M) at 0 °C to 25 °C for 1.5 h afforded the corresponding epoxide bearing chiral S. ketone analogue (-)-**14a** (>99.9%) in 72% yield with >25:1 *dr* (Scheme 4). The α,β-unsaturated double bond of (-)-**9a** (>99.9% *ee*) was readily reduced by hydrogen gas in the presence of 10% Pd/C (10 mol%) in 3-picoline (0.2 M) at 25 °C for 30 h to furnish the reduced product (+)-**12a** (>99.9% *ee*) in 75% yield with >25:1 *dr* (Scheme 4). Interestingly, when the olefin reduced double-carbonyl containing (+)-**12a** was reacted with methylenetriphenylphosphorane (2.0 equiv.) in THF (0.25 M) at 0 °C to 25 °C for 0.5 h furnished the regioselectively Wittig olefination product (+)-**15a** (>99.9% *ee*) in 85% yield (Scheme 4). These different reactions on the chiral S. ketone (-)-**9a** highlighting the importance of bicyclo[5.4.0]undecane system to produce stereoselective transformations, which are going to inspire many chemists to study in biological and natural products synthesis. The structures of (-)-**11a**, (+)-**12a**, (-)-**13a**, (-)-**14a**, and (+)-**15a** were further confirmed by NMR spectroscopy (Figures 56-60).



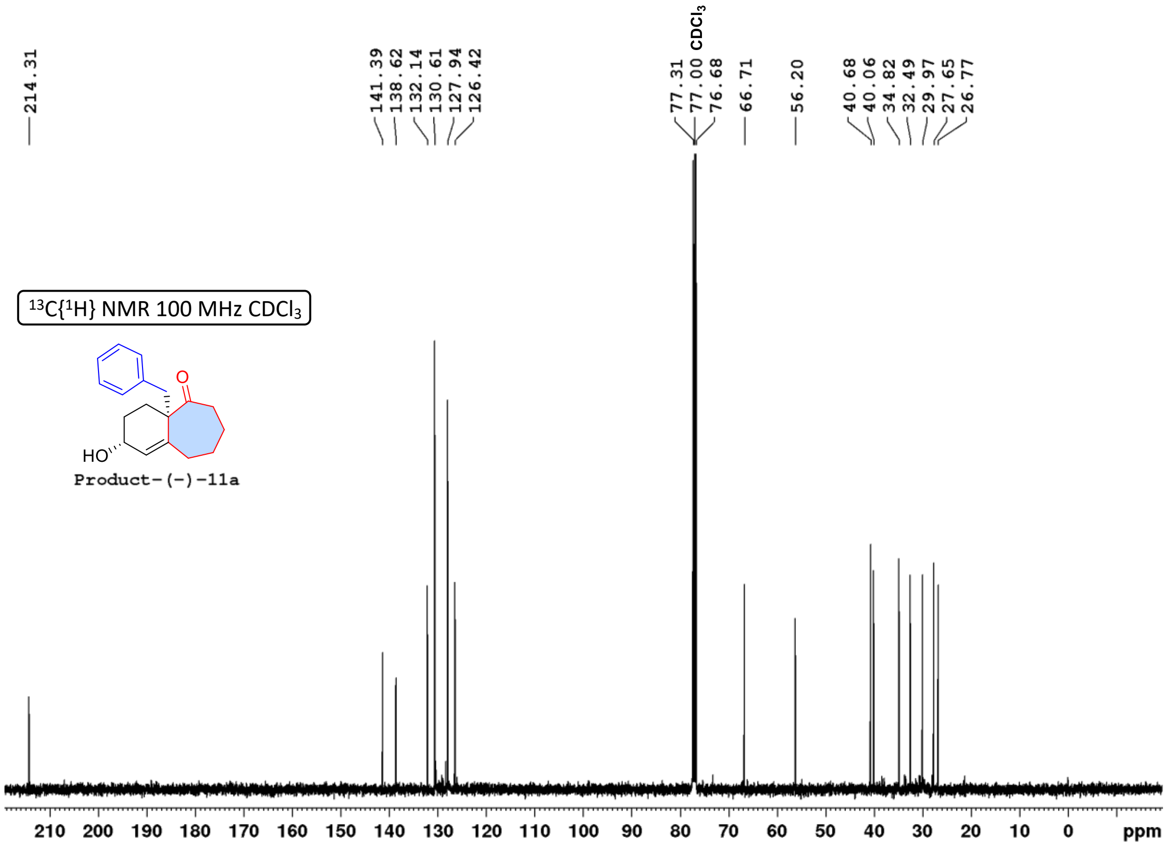


Figure 56: ^{1}H NMR and ^{13}C NMR spectrum of product **11a**.

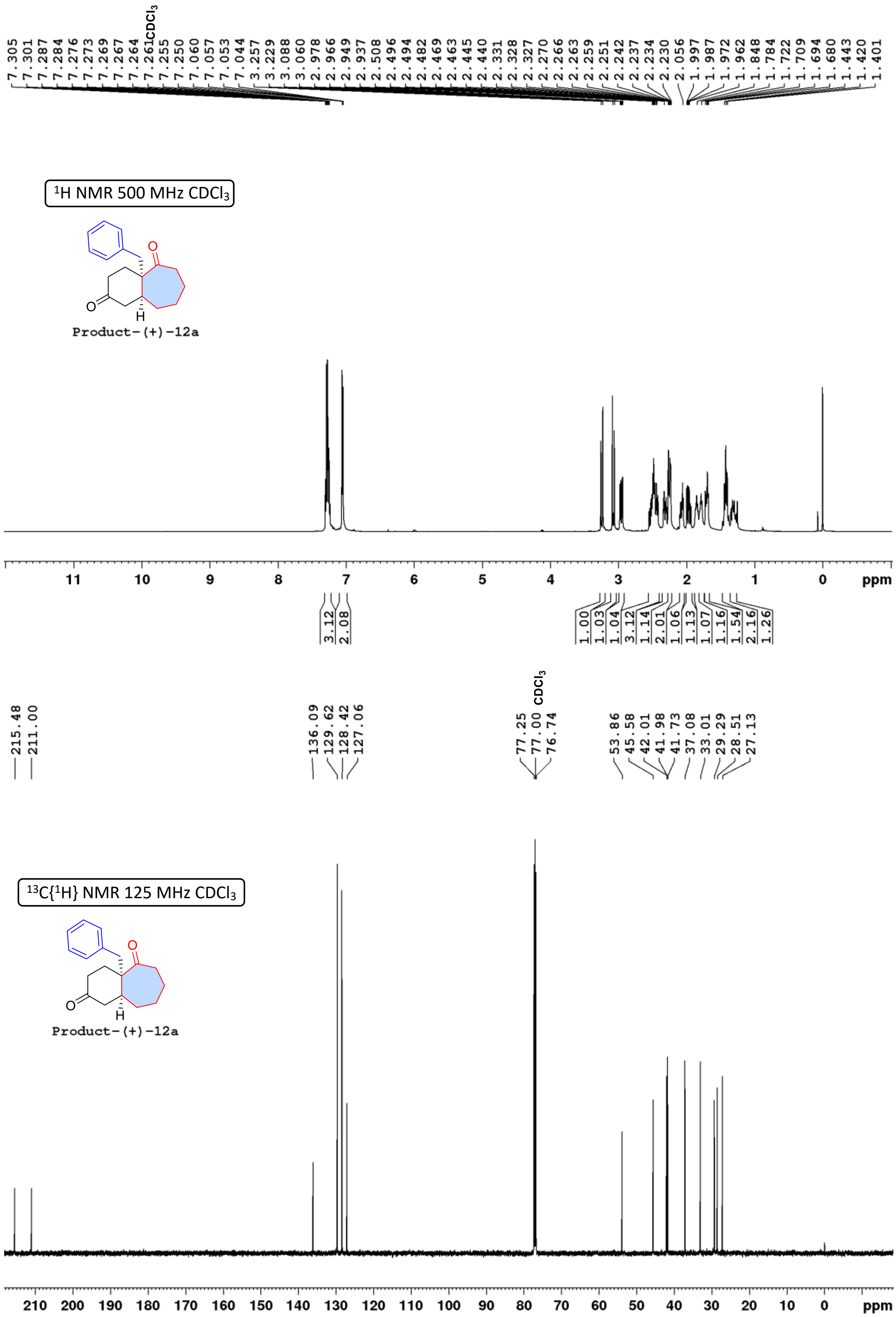
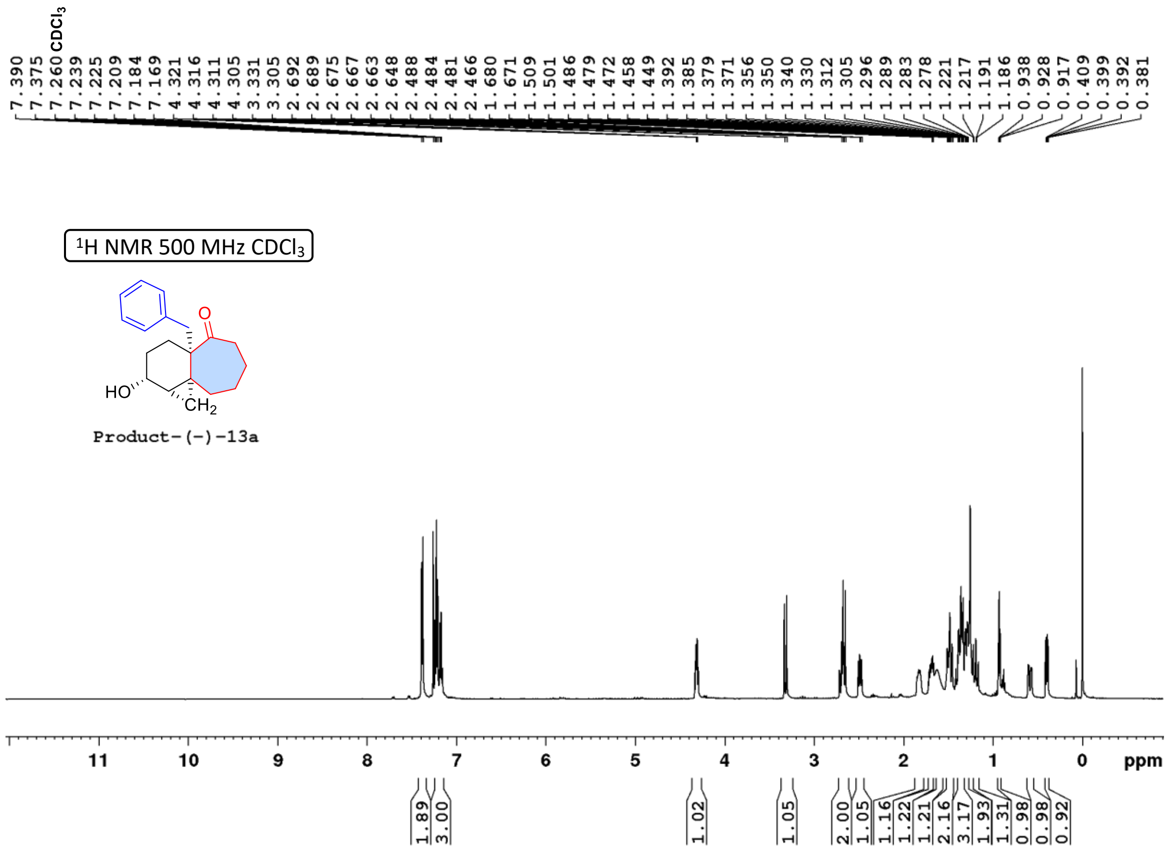


Figure 57: ^{1}H NMR and ^{13}C NMR spectrum of product **12a**.



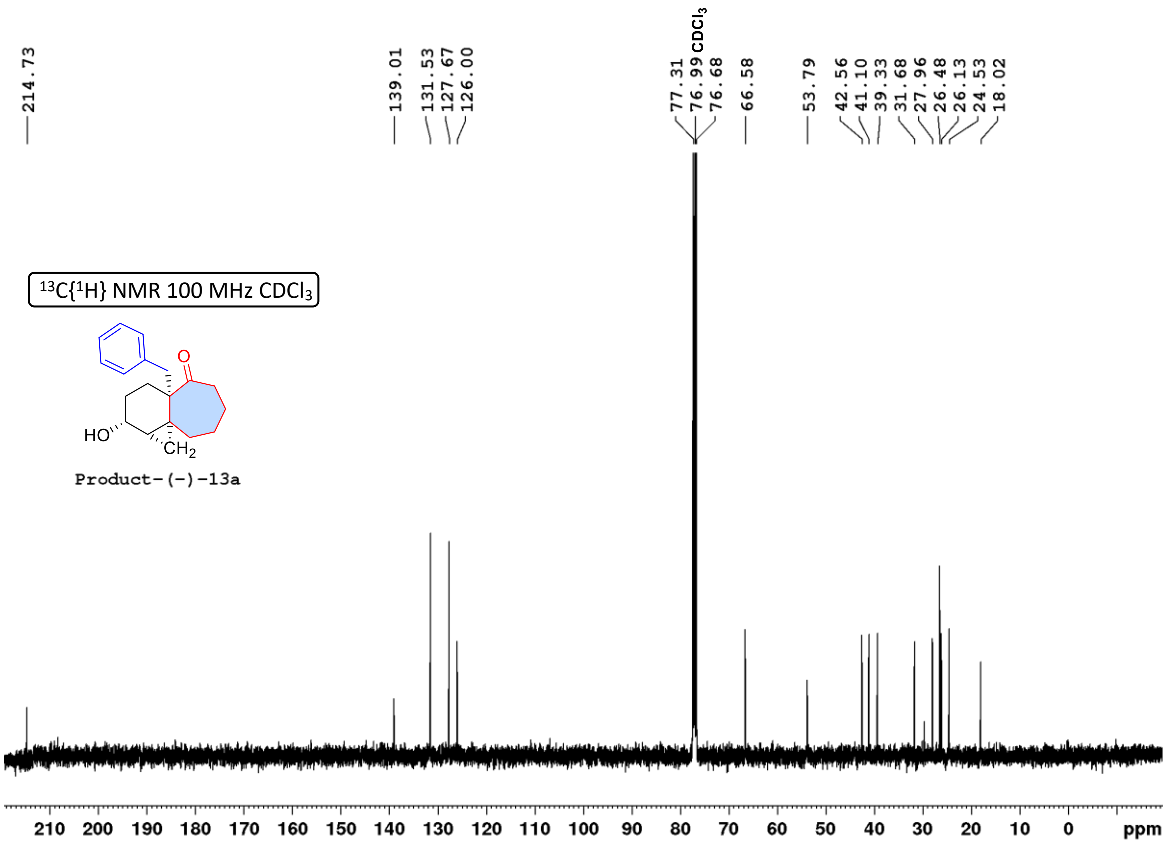
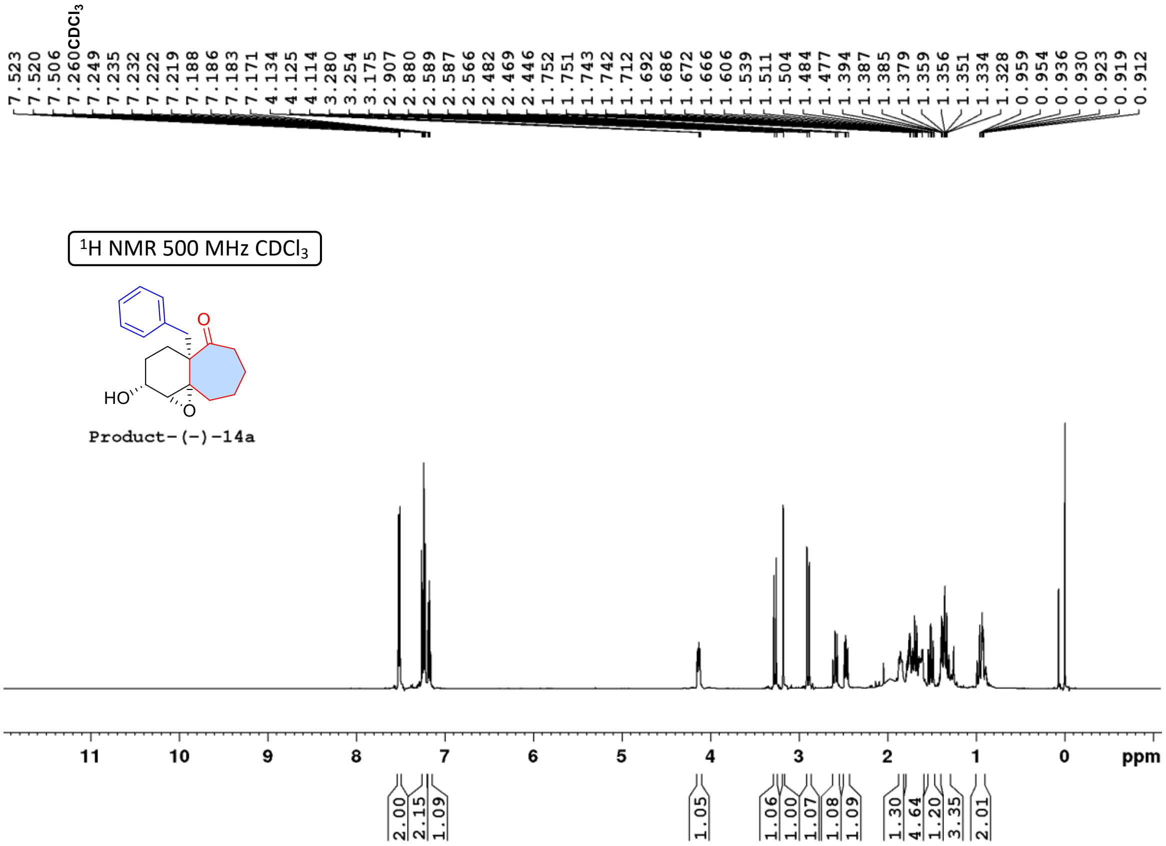


Figure 58: ^{1}H NMR and ^{13}C NMR spectrum of product **13a**.



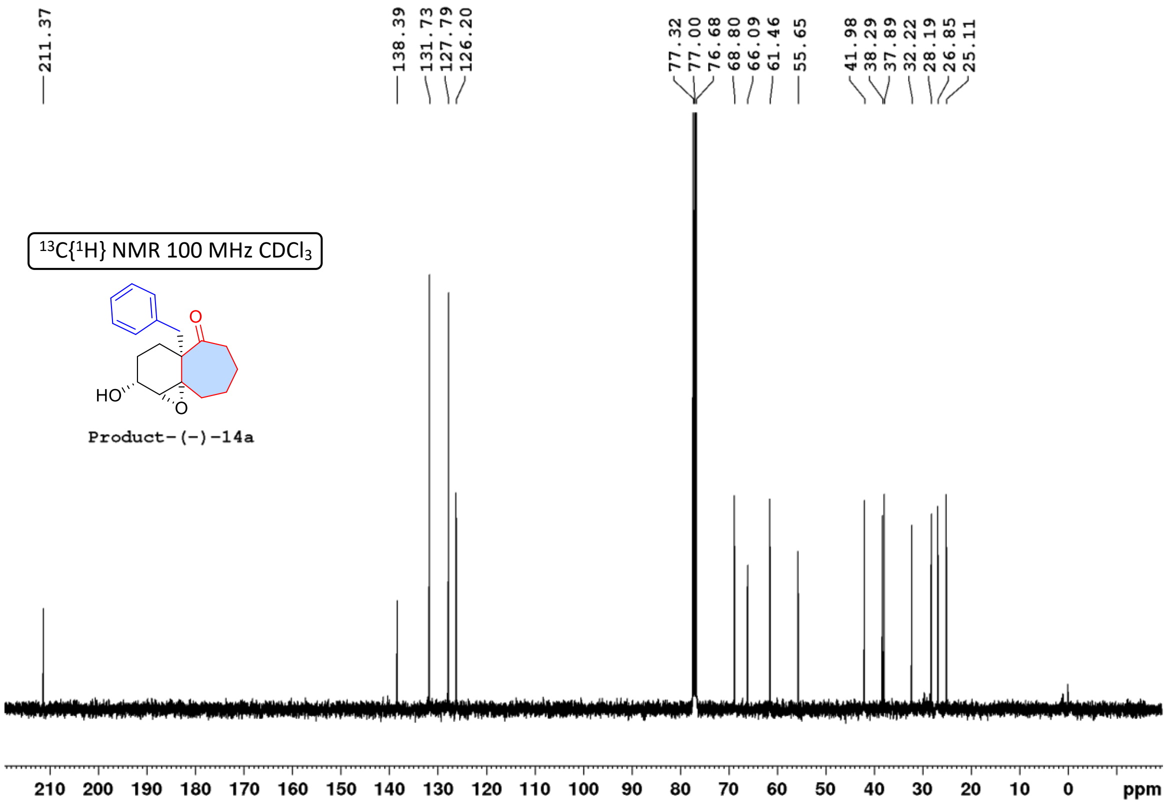
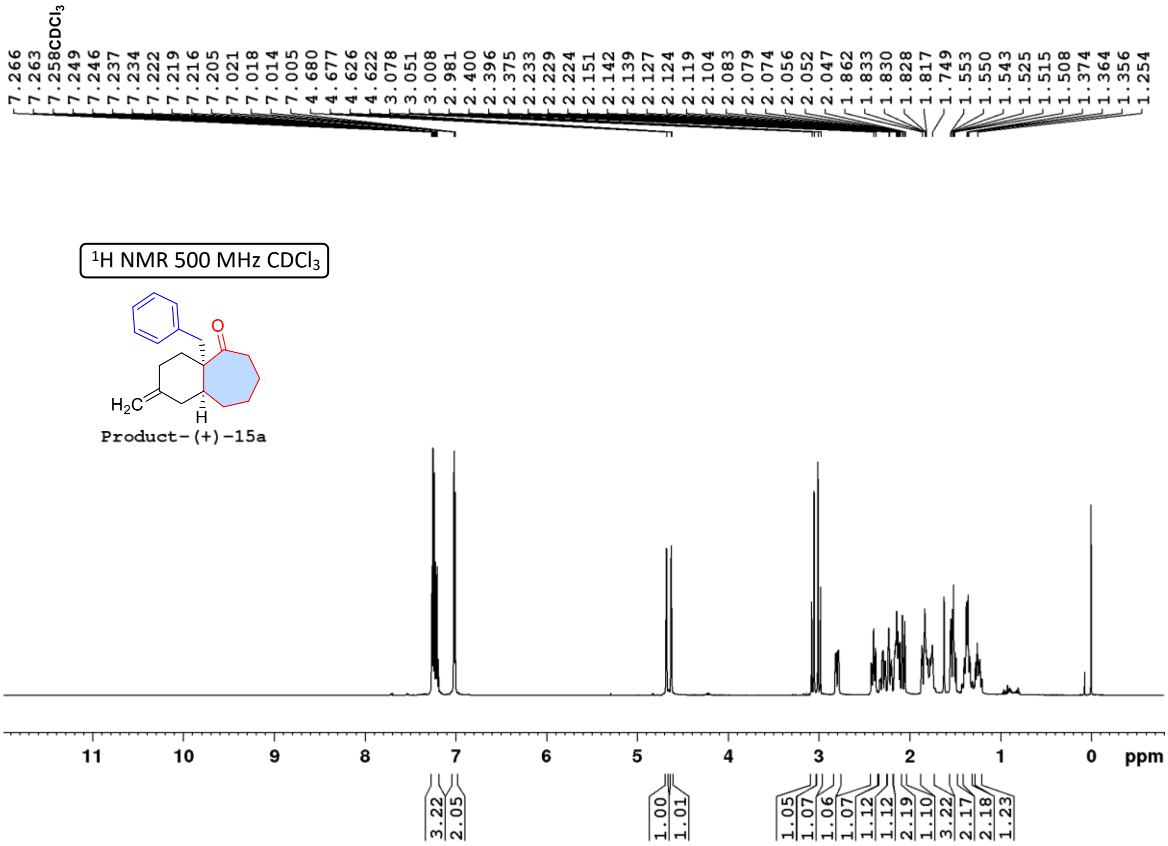


Figure 59: ^{1}H NMR and ^{13}C NMR spectrum of product **14a**.



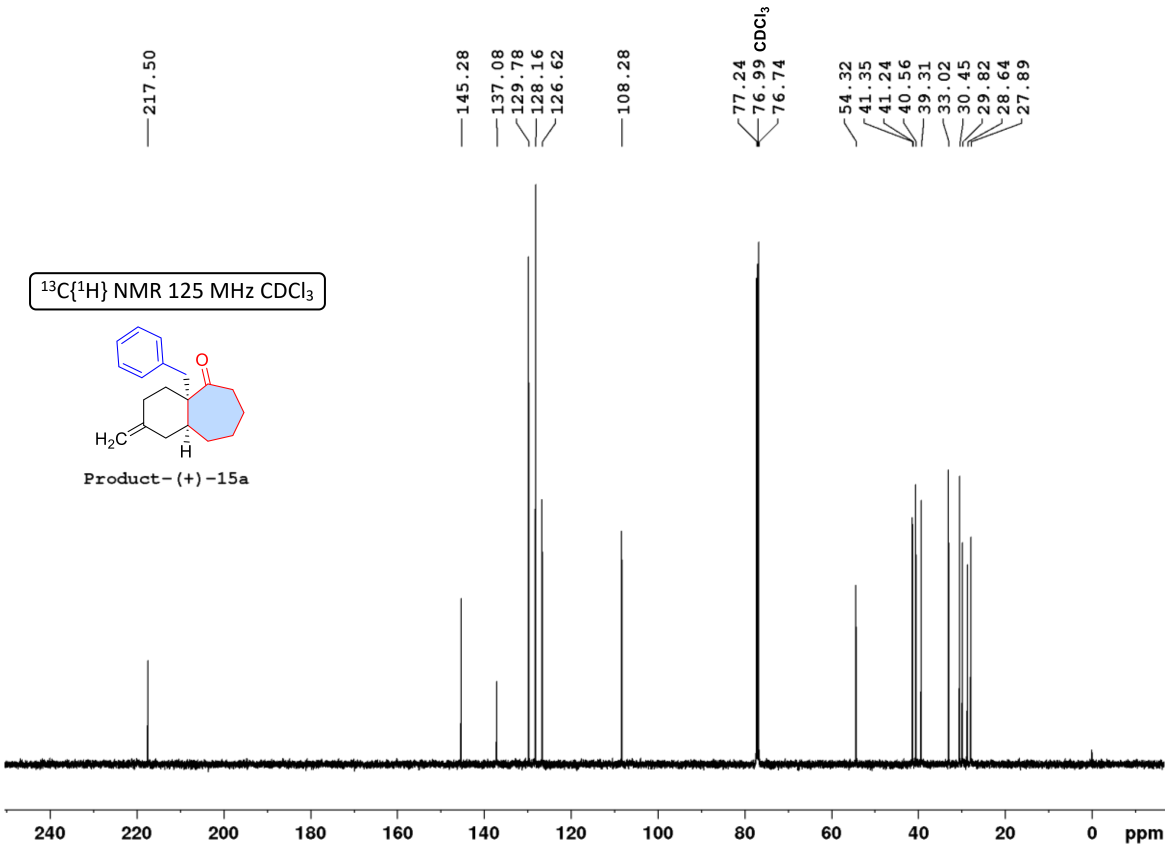
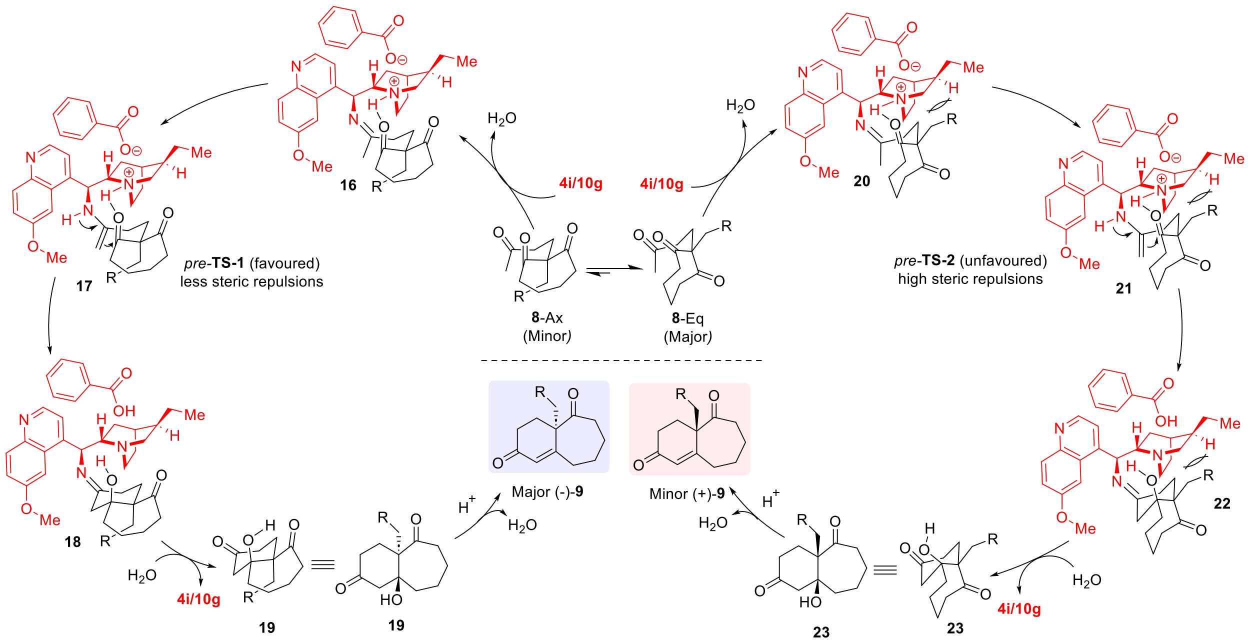


Figure 60: ^{1}H NMR and ^{13}C NMR spectrum of product **15a**.

5.2.8 Mechanistic Insights

After successful catalytic asymmetric synthesis of chiral S. ketones (-)-**9**, herein, we have proposed the most possible reaction mechanism for the substitution-induced conformation-controlled intramolecular aldol condensation of (±)-**8** through **4i/10g**-catalysed asymmetric desymmetrization (Scheme 5). Due to the conformational flexibility of the seven membered ring **8**,[10] the alkyl group of triketone **8** can exist in both axial (**8**-Ax) and equatorial (**8**-Eq) forms. At room temperature, the triketone **8** preferably exists in **8**-Eq form since it is thermodynamically more stable. When **8**-Eq was reacted under the catalysis of dihydroquinine-NH_2 **4i**/benzoic acid **10g**, an imine **20** forms with high steric repulsions between alkyl group of triketone **8** and the bicyclic component of catalyst **4i** making it less favourable for the reaction. This can be justified by the sluggish reactivity of **8** under amine catalysis at room temperature. Then, the increase in reaction temperature to 60 °C induced a conformational interconversion of triketone **8** from thermodynamically stable **8**-Eq to kinetically stable **8**-Ax.



Scheme 5: Proposed mechanism for the conformation-controlled intramolecular aldol reaction *via* asymmetric desymmetrization.

The triketone **8**-Ax then forms the imine **16** under **4i**/**10g**-catalysis with minimum steric repulsions making it more favourable for the aldol reaction. The *in situ* formed imine **16** further isomerizes to an enamine **17**. Meanwhile, components of catalyst **4i**/co-catalyst **10g** anchors or activate the intermediate molecule **17** through intramolecular hydrogen bonding of bicyclic N-H with carbonyl oxygen to orient itself in the most kinetically favoured way as shown in *pre*-**TS-1** for the enantioselective intramolecular aldol reaction (Scheme 4). The *in situ* formed enamine **17** undergoes selective intramolecular aldol reaction furnishing imine **18** which upon *in situ* hydrolysis with H_2O afforded bicyclic-alcohol **19**, regenerating the catalyst **4i/10g**. Soon after the formation of bicyclic-alcohol **19**, under acidic medium, it undergoes a rapid dehydration forming chiral S. ketone analogue (-)-**9** as a single major product. On the other hand, the sterically hindered minor imine **20** will also generates an enamine **21** *in situ* as shown in *pre*-**TS-2** which undergoes intramolecular aldol reaction furnishing sterically hindered imine **22**. This imine **22** upon *in situ* hydrolysis with H_2O afforded bicyclic-alcohol **23**, regenerating the catalyst **4i/10g**. As usual, the formed bicyclic-alcohol **23** undergoes a rapid dehydration forming chiral S. ketone analogue (+)-**9** in minor.

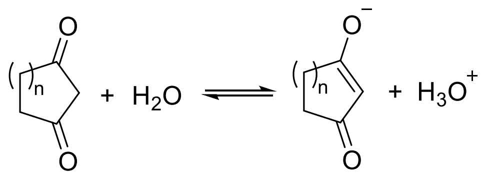
This *pre*-**TS** model validated the low enantioselectivities of the chiral S. ketone and analogues (-)-**9** bearing less bulky alkyl groups, for example, **8oo** furnished (-)-**9oo** with just 59% *ee*, when R = H. This means **4i/10g**-catalysed high asymmetric induction of intramolecular aldol reaction through desymmetrization of **8** is fully controlled by substitution-induced conformation-control for interconversion.

5.3 Conclusions

In conclusion, we have successfully achieved the target of synthesizing chiral S. ketone and analogues (-)-**9** in a catalytic asymmetric fashion. The preliminary kinetic and DFT studies inspired to perform a systematic investigation of selective reductive alkylation on cycloheptane-1,3-dione. For which, initially, we developed a general protocol for organocatalytic reductive coupling of conformationally flexible cycloheptane-1,3-dione **1** with various aromatic, heteroaromatic, aliphatic and chiral aldehydes **2** and Hantzsch ester **3** for generating a huge library of 2-alkylcycloheptane-1,3-diones **6** through *in situ* olefins **5**; which has a plenty of synthetic applications. Basic treatment of these alkylation compounds **6** with methyl vinyl ketone **7** furnished various functionally diverse triketones **8** as Michael adducts in very good yields, which are synthons for S. ketones **9**. For the first time, an efficient dihydroquinine-NH_2/benzoic acid-catalyzed asymmetric tool for the intramolecular aldol condensation of functionally rich triketones **8** through conformation-controlled asymmetric desymmetrization was successfully discovered to construct the chiral S. ketone and analogues (-)-**9** with excellent enantioselectivities. We performed the gram-scale synthesis of synthons **6a**, **8a** and final target (-)-**9a** in high yields without compromising on the rate and selectivity. One of the chiral S. ketones (-)-**9a** (88% *ee*) was enriched to single enantiomer by a quick high-yielding crystallization technique. The chiral S. ketone (-)-**9a** (>99% *ee*) was explored with different synthetic transformations such as chemo- and diastereoselective carbonyl reduction, cyclopropanation, epoxidation, olefin reduction, and Wittig reactions. All these selective transformations on (-)-**9a** furnished functionally rich optically pure single isomer of drug-like bicyclo[5.4.0]undecane systems **11a-15a**. Further utilization of these synthons **5**, **6**, **8** and chiral S. ketone analogues (-)-**9** in the total synthesis is underway.

5.4 Annexure

5.4.1 Theory behind the determination of pK_a using potentiometry



The dissociation constant of the acid K_a is given by the following equation:

$$K_a = \frac{[H_3O^+]\,[A^-]}{[A]}$$

$$[H_3O^+] = \frac{K_a\,[A]}{[A^-]}$$

Taking -log on both sides

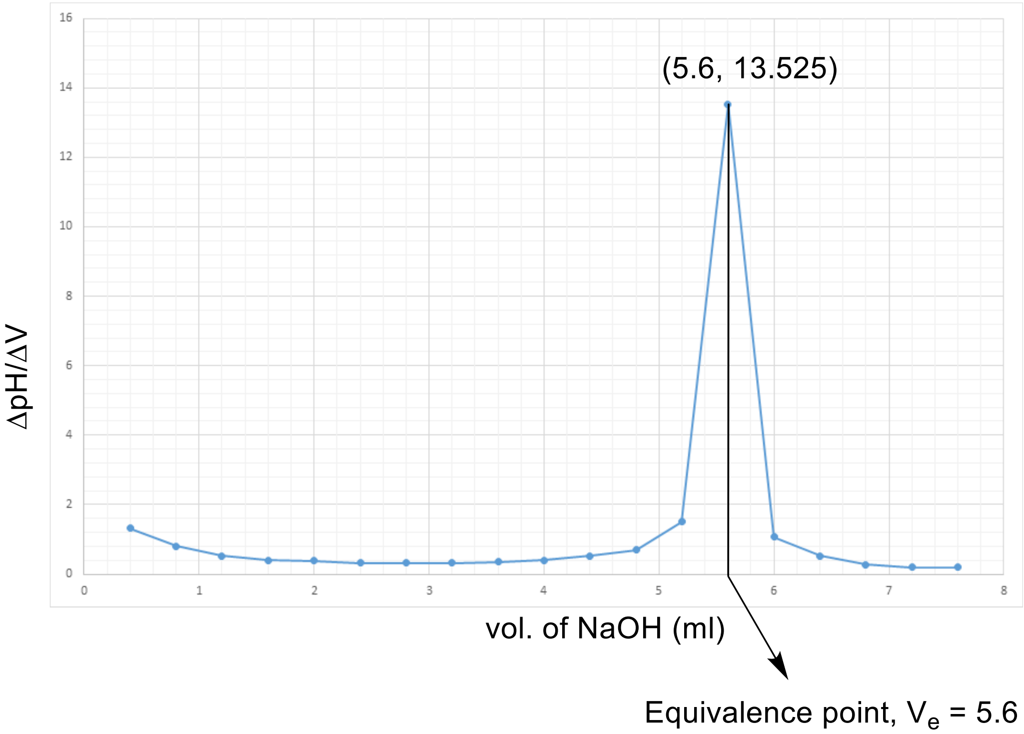
$$-\log[H_3O^+] = -\log K_a + \log\frac{[A^-]}{[A]}$$

$$pH = pK_a + \log\frac{[A^-]}{[A]}$$

When the weak acid **A** is titrated against NaOH solution, pH of the titrant solution increases since the concentration of **A**$^-$ increases and the concentration of **A** decreases

When A is exactly half titrated, $[A^-] = [A]$

Thus, pK_a = pH at the half equivalance point.



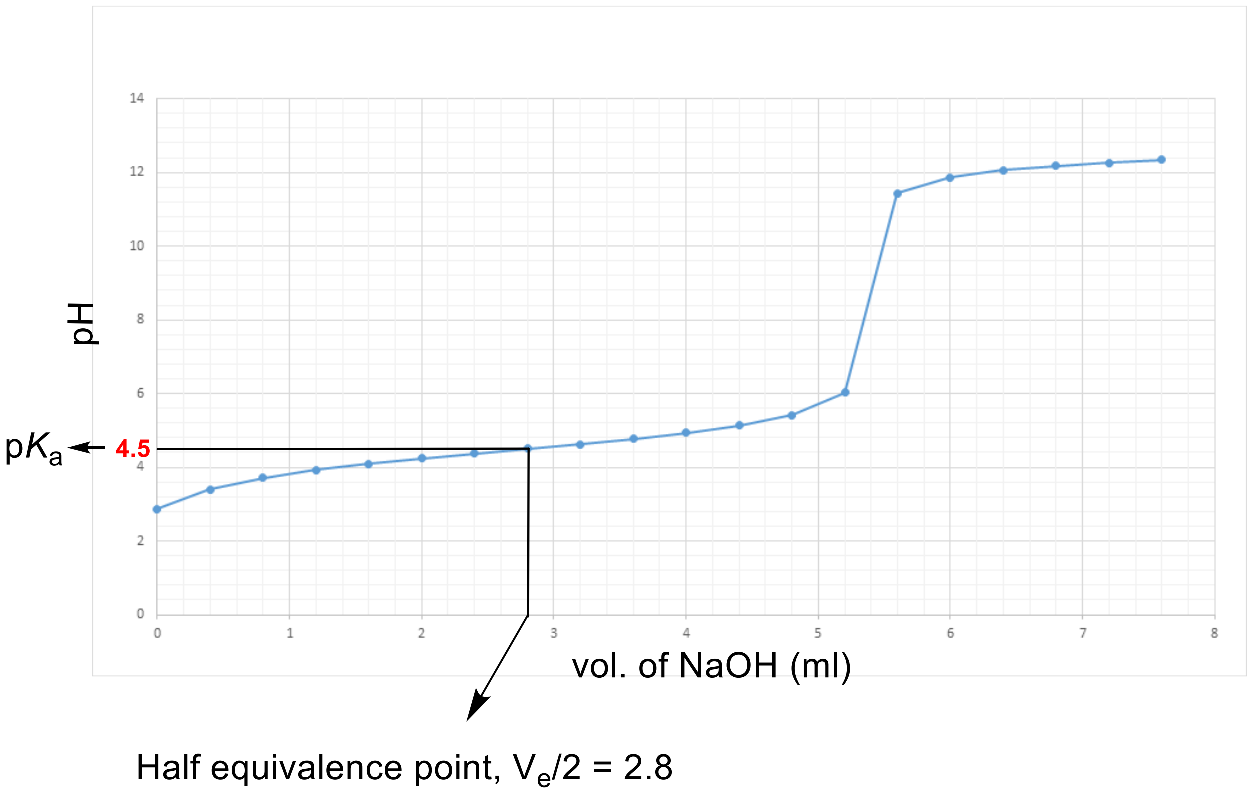
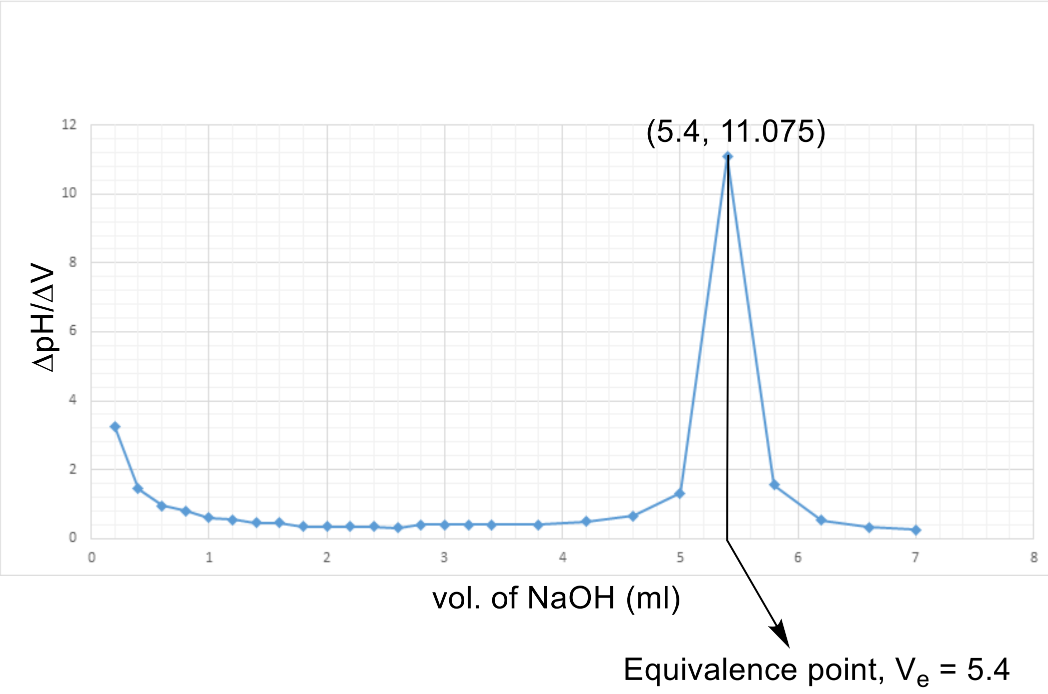


Figure 61: Graphs for the determination of pK_a of cyclopentane-1,3-dione.



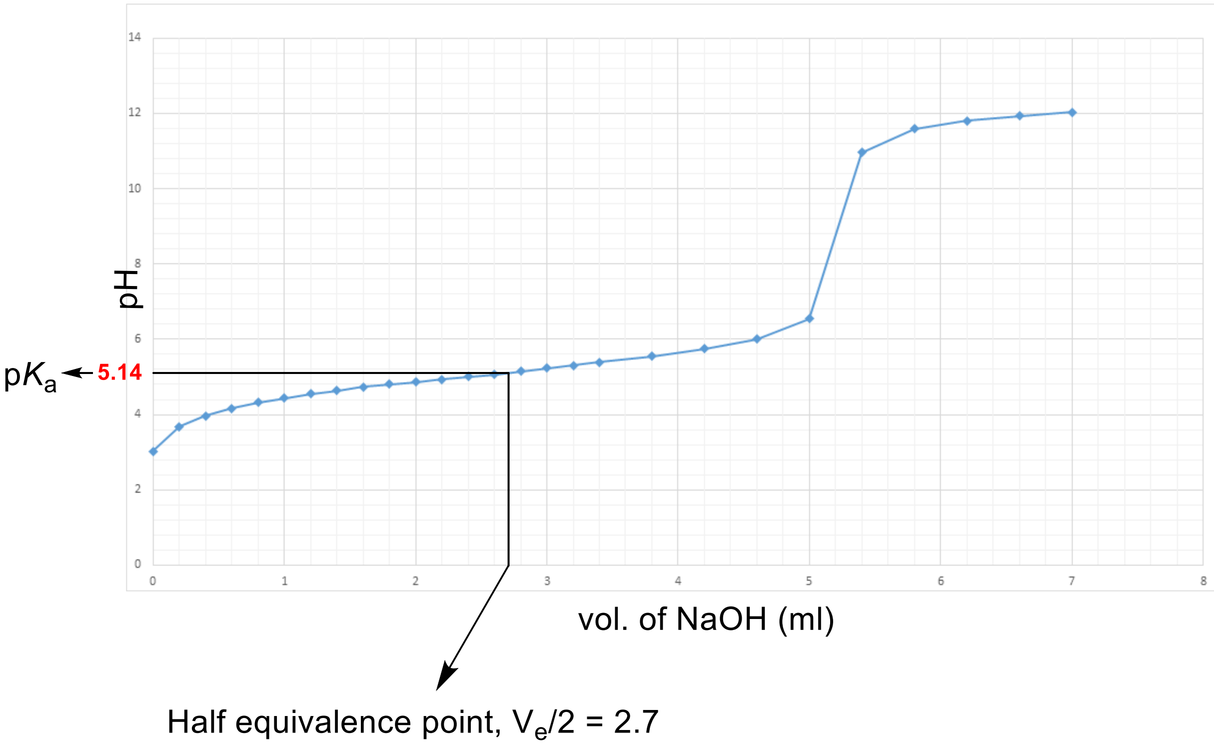


Figure 62: Graphs for the determination of pK_a of cyclohexane-1,3-dione.

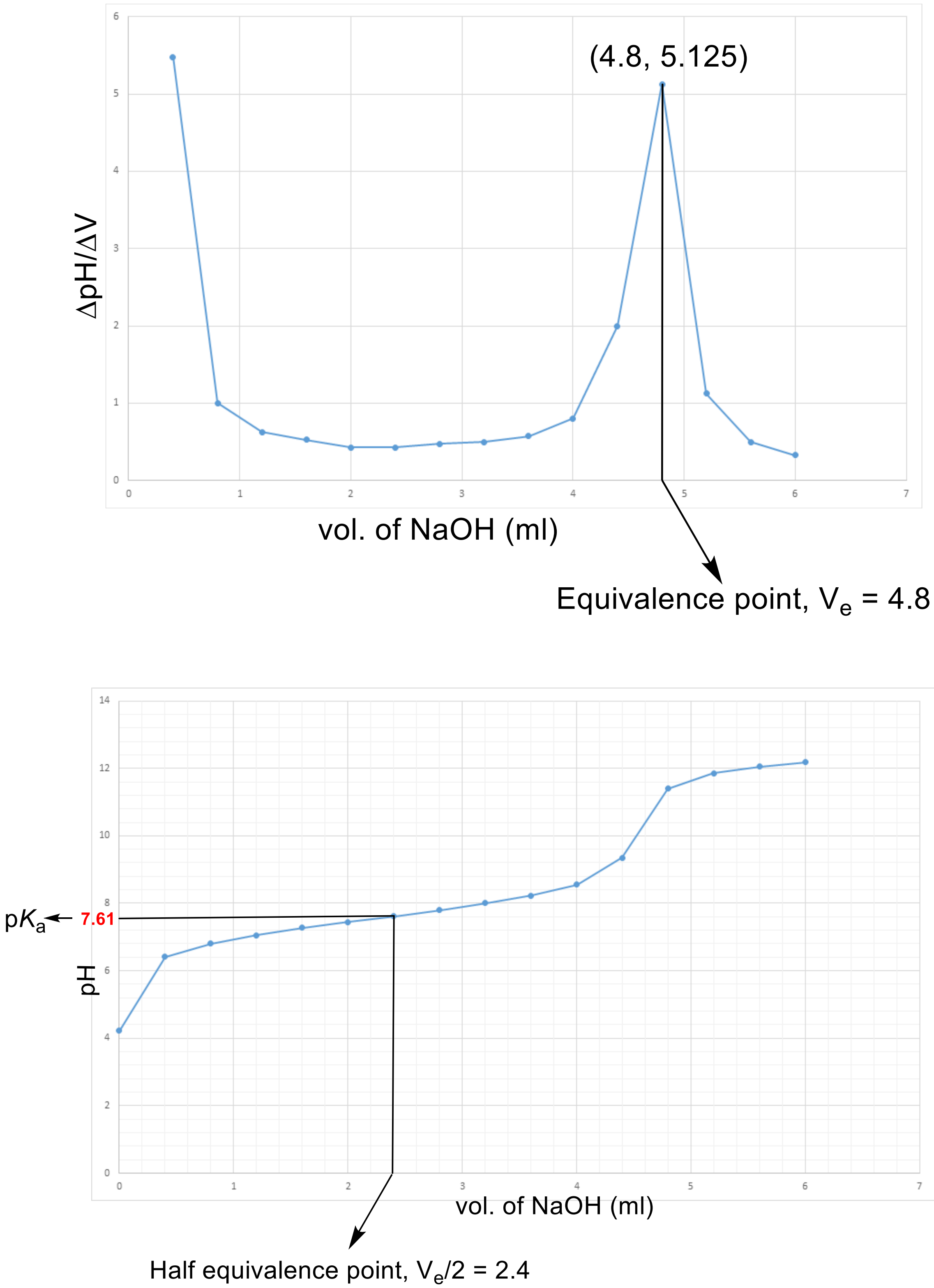
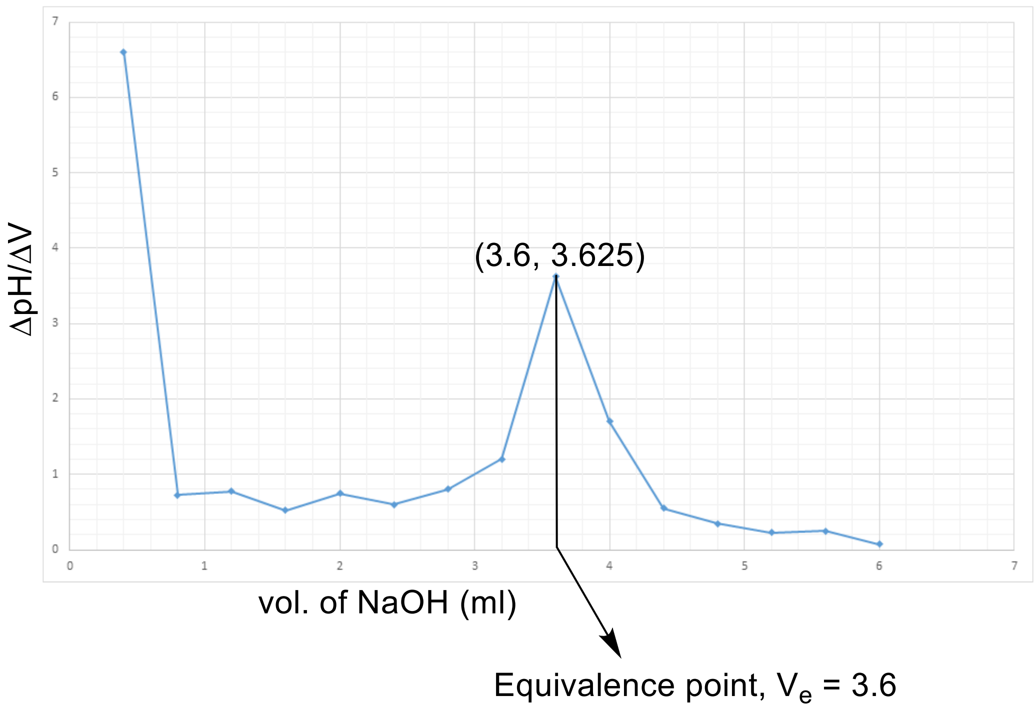


Figure 63: Graphs for the determination of pK_a of cycloheptane-1,3-dione.



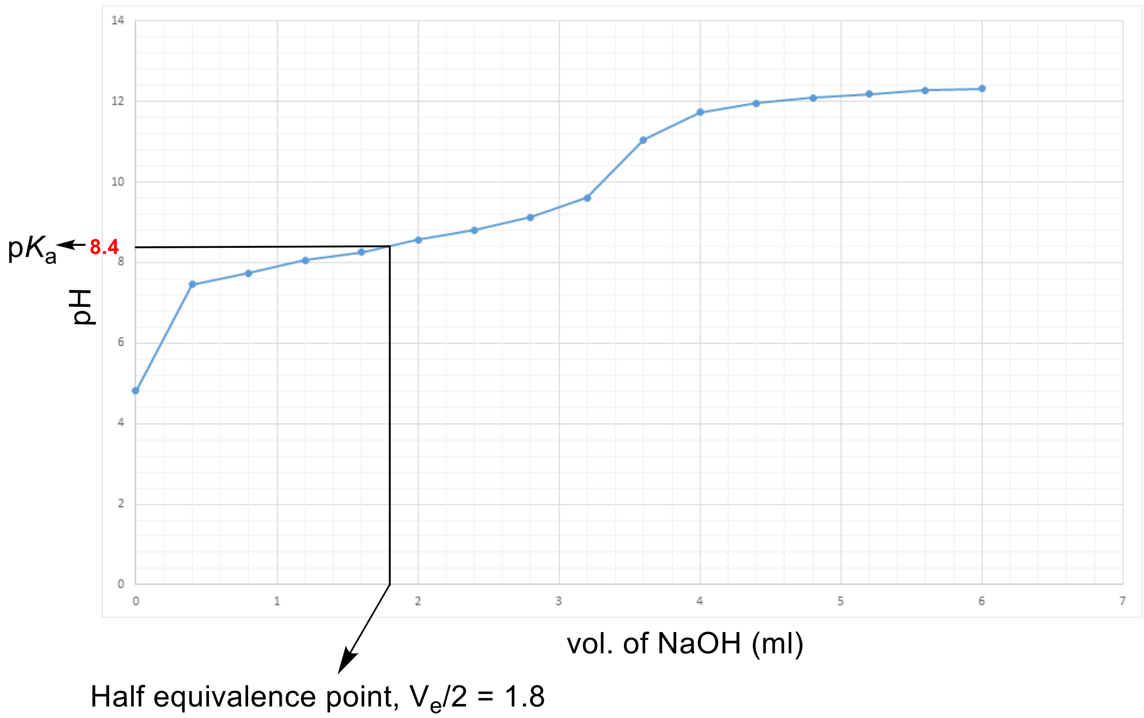


Figure 64: Graphs for the determination of pK_a of cyclooctane-1,3-dione.

5.4.2 DFT-Calculations for HOMO-LUMO Energy Gap

The molecules (**B1**), (**B2**), (**B3**), and (**B4**) were optimized using CAM-B3LYP[11a-b] method with 6-311++g*[12] basis set in the Gaussian 09 suite of program.[13] Using the obtained orbital energies from the current calculations, a pictorial representation is shown below. The picture of energy difference between the HOMO **3** (Hantzsch ester) and LUMO of (**B1**), (**B2**), (**B3**) and (**B4**) shows a visible trend of increase in the HOMO-LUMO energy gap which benefits in explaining the experimental studies.

The cartesian coordinates of the optimized geometries of molecules (**B1**), (**B2**), (**B3**), (**B4**) and Hantzsch ester **3** are shown below, respectively.

2-benzylidenecyclopentane-1,3-dione (**B1**):

Input orientation:

Atomic Number	Coordinates (Angstroms) X	Y	Z
1	1.196409	0.144380	0.356637
6	0.579403	0.052949	1.244326
6	-0.995975	-0.177024	3.508976
6	0.308766	-1.199561	1.763741
6	0.068959	1.214880	1.846860
6	-0.727926	1.080077	2.993724
6	-0.481957	-1.315829	2.900499
1	0.712039	-2.084450	1.284911
1	-1.128239	1.964703	3.468005
1	-0.697950	-2.295633	3.312340
1	-1.613138	-0.268953	4.395554
6	0.418032	2.473246	1.216717
1	1.041471	2.354343	0.329870
6	0.154450	3.777136	1.468168
6	0.723225	4.795393	0.543699
6	0.300376	6.183309	0.996496
6	-0.517112	5.982683	2.272728
6	-0.612957	4.479971	2.515752
1	1.193824	6.793864	1.139048
1	-0.268334	6.649485	0.189051
1	-1.529711	6.385504	2.211910
1	-0.057186	6.435976	3.153515
8	-1.233556	4.005812	3.441051
8	1.412176	4.567808	-0.421552

2-benzylidenecyclohexane-1,3-dione (**B2**):

Input orientation:

Atomic Number	Coordinates (Angstroms) X	Y	Z
1	1.512888	2.943233	4.599033
6	0.842960	2.183937	4.209595
6	-0.883746	0.262675	3.231832
6	0.371865	1.196229	5.054781
6	0.480411	2.223190	2.851446
6	-0.406542	1.245272	2.378701
6	-0.495787	0.228427	4.564514
1	0.673689	1.184985	6.095925
1	-0.723687	1.273052	1.348901
1	-0.876216	-0.544933	5.222936
1	-1.572590	-0.482386	2.849624
6	1.074199	3.314259	2.086901
1	1.535278	4.054243	2.737594
6	1.270591	3.629338	0.781761
6	1.615220	3.071704	-1.691173
6	2.650614	5.162362	-0.804018
6	1.853347	4.555002	-1.948145
6	2.066601	4.892461	0.566792
6	0.847320	2.843740	-0.406987
1	2.579200	2.554140	-1.605849
1	3.661767	4.735136	-0.793589
1	0.893353	5.070376	-2.054906
1	1.057005	2.592045	-2.494876
1	2.772376	6.241627	-0.900481
1	2.384824	4.693609	-2.891959
8	2.269041	5.673240	1.470743
8	-0.078308	2.058982	-0.388526

2-benzylidenecycloheptane-1,3-dione (**B3**):

Input orientation:

Atomic Number	Coordinates (Angstroms) X	Y	Z
6	-1.291001	3.259725	3.075981
1	-2.096429	3.874189	2.679740
6	-0.262289	4.060107	3.737695
6	1.604881	5.822210	4.863388

6	-0.271212	5.429115	3.423209
6	0.689906	3.599812	4.656241
6	1.609428	4.478005	5.209589
6	0.657848	6.298552	3.965437
1	-1.016886	5.807548	2.731806
1	0.694455	2.559360	4.939527
1	2.335291	4.105363	5.923783
1	0.637552	7.348632	3.696516
1	2.329668	6.500153	5.300833
6	-1.455382	1.955747	2.758158
6	-0.406036	-0.221159	1.936268
6	-1.355760	-1.363985	2.325321
6	-2.716953	1.654053	1.979369
6	-0.467511	0.866108	2.988466
1	-0.674616	0.179431	0.955461
1	0.622605	-0.578365	1.882116
1	-0.896387	-1.961392	3.115953
1	-1.485442	-2.024360	1.462995
6	-3.291237	0.242199	1.894455
1	-4.357966	0.373998	2.089229
1	-3.231244	-0.058173	0.842030
6	-2.712631	-0.842496	2.797908
1	-3.421331	-1.672386	2.852469
1	-2.628511	-0.460978	3.820900
8	0.256002	0.808172	3.960240
8	-3.338988	2.545089	1.442963

2-benzylidenecyclooctane-1,3-dione (**B4**):

Input orientation:

Atomic Number	Coordinates (Angstroms) X	Y	Z
6	-1.759601	0.814172	0.287568
6	-1.911968	0.567326	1.752297
6	-2.763046	0.201831	-0.676075
1	-3.236221	1.056998	-1.168255
1	-3.554766	-0.335861	-0.151798
6	-0.945851	-2.063631	0.136609
1	-0.358608	-2.980782	0.211405
6	-1.910526	-2.036086	1.346157
1	-1.736528	-2.896369	1.991721
1	-2.944270	-2.136825	0.998077
6	-1.879250	-0.843047	2.285222
1	-0.210137	-1.255964	0.196787
6	-2.075260	-0.669246	-1.733186

1	-2.744789	-0.795758	-2.587910
1	-1.209292	-0.113138	-2.101064
6	-1.637694	-2.047134	-1.232229
1	-0.966327	-2.481128	-1.978744
1	-2.503887	-2.717464	-1.188965
8	-0.868593	1.509957	-0.147766
8	-1.849332	-1.037603	3.480508
6	-2.140819	1.534418	2.658653
1	-2.301752	1.151812	3.664047
6	-2.309054	2.986633	2.541445
6	-2.769716	5.748829	2.493124
6	-3.178666	3.590804	3.459569
6	-1.647021	3.802612	1.617359
6	-1.879607	5.170132	1.598951
6	-3.419947	4.953508	3.428208
1	-3.677109	2.974718	4.200902
1	-0.933343	3.367447	0.933638
1	-1.351033	5.789603	0.882898
1	-4.106365	5.397440	4.140512
1	-2.945859	6.818694	2.471611

Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Hantzsch ester) (**3**):

Input orientation:

Atomic Number		Coordinates (Angstroms) X	Y	Z
N	7	-1.241526	-0.009127	3.859133
C	6	-0.402479	-1.277878	2.062037
C	6	-0.390002	1.242884	2.056126
C	6	-1.021436	1.214860	3.246591
C	6	-1.033711	-1.238077	3.252282
H	1	-1.746001	-0.004526	4.728424
C	6	-0.136634	-2.498998	1.292245
O	8	-0.675389	-3.631773	1.796802
C	6	-0.112144	2.457725	1.280658
O	8	-0.641250	3.597826	1.778900
O	8	0.537389	2.451486	0.261008
O	8	0.511744	-2.503716	0.271848
C	6	0.146076	-0.021668	1.422186
H	1	1.242336	-0.027005	1.458282
H	1	-0.081395	-0.023065	0.355408
C	6	-0.372808	4.791587	1.027683
H	1	0.707536	4.930351	0.960314
H	1	-0.748264	4.659880	0.011689
C	6	-1.048694	5.940279	1.736474

H	1	-0.662746	6.061496	2.750329
H	1	-2.127685	5.786679	1.796066
H	1	-0.868858	6.870361	1.193173
C	6	-0.418855	-4.831637	1.051178
H	1	0.660089	-4.980504	0.982973
H	1	-0.794600	-4.701628	0.035068
C	6	-1.104076	-5.970597	1.766685
H	1	-0.717758	-6.090209	2.780588
H	1	-0.933469	-6.904982	1.227813
H	1	-2.181541	-5.806914	1.827042
C	6	-1.576918	-2.391283	4.048603
H	1	-0.839633	-3.181192	4.163140
H	1	-2.441938	-2.835403	3.556056
H	1	-1.883148	-2.060556	5.043517
C	6	-1.553050	2.377056	4.037633
H	1	-0.809095	3.161558	4.145665
H	1	-1.859339	2.054528	5.035224
H	1	-2.415777	2.825343	3.544757

5.5 Experimental Section

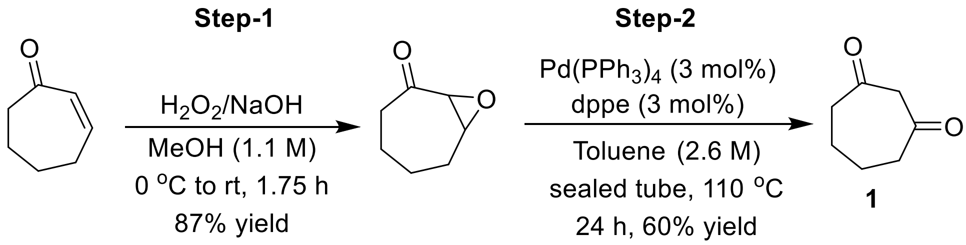
General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS (δ = 0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR. *In the ^{13}C NMR spectra, the nature of 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. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-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.

Procedure A: **General procedure for determination of pK_a using potentiometry**:

In order to determine the pK_a of the cyclic-1,3-diones **A** (with ring size varying from five to eight), the cyclic-1,3-diones were titrated against aqueous NaOH. For this, 0.1 M solution of **A** in H_2O was prepared and was taken in a beaker which is fitted with pH meter having glass-calomel electrode. Apart from this, 0.1 M solution of aqueous NaOH was prepared and used for titration. Initially, the pH of the solution **A** was recorded before the addition of NaOH. Then, the pH readings were continuously recorded with the consecutive addition of 0.4 ml of NaOH using burette. Make sure that the solution is mixed well after the addition of each 0.4 ml of NaOH before recording the pH. Collect the values until a sudden rise in pH is observed. Continue to collect another 4-5 readings after that. Now, the equivalence point $\mathbf{V_e}$ can be easily determined by plotting ΔpH/ΔV against the volume of NaOH as shown in the above Figures S7-S10. Then, another graph was made by plotting pH against volume of NaOH. From these two graphs, we can easily determine the pK_a of the cyclic-1,3-diones **A** since the pK_a will become equal to pH at the half-equivalence point $\mathbf{V_e}/2$.

Procedure B: **Modified procedure for the synthesis of cycloheptane-1,3-dione 1:**[14]



Step-1: To a solution of cyclohept-2-enone (2.0 g, 18.16 mmol, 1.0 equiv.) in methanol (13.5 mL) was added 30% H_2O_2 (4.53 mL, 2.6 equiv.) at -4 °C, followed by 10% aq. NaOH (2.3 mL). The resulting mixture was stirred at 0 °C for 40 min followed by 1.0 h at room temperature. Then, the reaction mixture was diluted with brine solution (100 mL) and extracted with DCM, dried with Na_2SO_4 and evapourated under vacuum to afford pure epoxide (colourless oil) which can be directly used in the next step without further purification. Yield: 87% (2.0 g); IR (Neat): ν_{max} 2931, 2859, 1699, 1448, 1355, 1252, 1180, 933, 839 and 733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.39-3.35 (2H, m), 2.65-2.60 (1H, m), 2.46-2.42 (1H, m), 2.31-2.28 (1H, m), 1.83-1.65 (4H, m), 1.03-0.95 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 210.3 (C, *C*=O), 59.3 (CH), 55.0 (CH), 40.4 (CH_2), 27.3 (CH_2), 23.4 (CH_2), 22.9 (CH_2); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_7H_{10}O_2Na$ 149.0578; Found 149.0579.

Step-2: To the above obtained epoxide (2.0 g, 15.85 mmol, 1.0 equiv.) in dry toluene (6.0 mL) was added $Pd(PPh_3)_4$ (550 mg, 0.47 mmol, 3 mol%) and 1,2-bis(diphenylphosphino)ethane (189.5 mg, 0.47 mmol, 3 mol%). The reaction was bubbled with N_2 for 10 min, sealed in a 15 mL pressure tube and heated at 110 °C for 24 h. The reaction was cooled to room temperature and the solid was filtered off. The filterate was collected, concentrated and purified by coloumn chromatography using ethyl acetate:hexanes (12:88) to afford pure cyclohept-1,3-dione **1**. Yield: 60% (1.2 g); IR (Neat): ν_{max} 2936, 1715, 1691, 1452, 1327, 1204, 1132 and 922 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.59 (2H, s), 2.59-2.56 (4H, m), 1.99-1.96 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 204.9 (2 x C, 2 x *C*=O), 59.7 (CH_2), 44.0 (2 x CH_2), 25.0 (2 x CH_2); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_7H_{10}O_2Na$ 149.0578; Found 149.0578.

Procedure C: **General procedure for organocatalytic three-component reductive coupling**: In an oven dried reaction vial equipped with a magnetic stirring bar at rt was taken cycloheptane-1,3-dione **1 (**0.3 mmol, 1.0 equiv.), to which catalyst **4a**/**c** (0.06 mmol, 20 mol%), Hantzsch ester **3** (0.36 mmol, 1.2 equiv.) and 1.0 mL of 1-butanol was added and stirred for 20 seconds followed by the addition of aldehyde **2** (0.6 mmol, 2.0 equiv.) and allowed to stir for respective reaction times. After the completion of reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, mixture of hexanes/ethyl acetate) to afford pure 2-alkyl-cycloheptane-1,3-diones **6**.

Procedure D: **General procedure for the Michael addition of MVK to 6**: In an oven dried reaction vial equipped with a magnetic stirring bar at rt was taken *C*-alkylated cycloheptane-1,3-dione **6** (0.2 mmol, 1.0 equiv.) and methyl vinyl ketone **7** (0.6 mmol, 3.0 equiv.) to which catalyst Et_3N **4f** (0.2 mmol, 1.0 equiv.) was added and stirred at room temperature for respective reaction times. After the completion of reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, mixture of hexanes/ethyl acetate) to afford pure Michael adducts **8**.

Procedure E: **General procedure for the preparation of racemic S. Ketones** (±)-**9**: In an oven dried glass vial was taken Michael adduct **8** (0.1 mmol, 1.0 equiv.) to which catalyst pyrrolidine **4e** (0.1 mmol, 1.0 equiv.) and co-catalyst acetic acid **10i** (0.1 mmol, 1.0 equiv.) were added in THF (0.5 mL, 0.2 M) and allowed to stir at room temperature for respective reaction times. After the completion of reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, mixture of hexanes/ethyl acetate) to afford pure racemic Swaminathan ketones (±)-**9**.

Procedure F: **General procedure for the preparation of chiral S. ketones** (-)-**9**: In an oven dried glass vial was taken Michael adduct **8** (0.1 mmol, 1.0 equiv.) to which catalyst dihydroquinine-NH_2 **4i** (0.02 mmol, 20 mol%) and co-catalyst benzoic acid **10g** (0.03 mmol, 30 mol%) were added in C_6F_6 (0.5 mL, 0.2 M) and allowed to stir for respective reaction times at 60 □C on a hot plate. After the completion of reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, mixture of hexanes/ethyl acetate) to afford pure chiral S. ketones (-)-**9**.

Procedure G: **General procedure for the synthesis of Michael adduct 6pp**: In an oven dried round bottomed flask equipped with a magnetic stirring bar was taken methyl vinyl ketone **7** (0.4 mmol, 1.0 equiv.) and diisopropylethylamine (0.8 mmol, 2.0 equiv.) in EtOH (2.0 ml) and stirred at room temperature for 5 minutes. To this, the solution of cycloheptane-1,3-dione (0.4 mmol, 1.0 equiv.) in EtOH (2.0 ml) was added dropwise. Allowed the reaction mixture to stir at room temperature for 2.5 hours. Then, the reaction mixture was concentrated under vacuum and purified by coloumn chromatography (silica gel, mixture of hexanes/ethyl acetate) to afford pure compound **6pp**.

Procedure H: **General procedure for the synthesis of alkylation product 8pp**: In an oven dried round bottomed flask equipped with a magnetic stirring bar was taken compound **6pp** (0.2 mmol, 1.0 equiv.) in dry THF (1.0 ml). To this, *t*BuOK (0.2 mmol, 1.0 equiv.) was added under inert atmosphere and allowed to stir for 5 minutes. Then, corresponding alkyl bromide, (bromomethyl)(4-chlorophenyl)sulfane (1.0 mmol, 5.0 equiv.) was added and allowed to stir at room temperature for 6 h. Then, the reaction mixture was concentrated under vacuum and purified by coloumn chromatography (silica gel, mixture of hexanes/ethyl acetate) to afford pure alkylation compound **8pp**.

Procedure I: **General procedure for the desulfurization of** (-)-**9pp to S. Ketone** (-)-**9oo**: In an oven dried round bottomed flask equipped with a magnetic stirring bar was taken compound (-)-**9pp** (0.2 mmol, 1.0 equiv.) and dissolved in EtOH (2.0 mL). To this one small full table spoon of Raney nickel (200 mg) was added and allowed to stir at room temperature for 1.0 hour. After the completion of reaction, the reaction mixture was carefully filtered through a pack of celiete and washed with ethanol thrice. The collected filterate was concentrated under vacuum and purified using coloumn chromatography to afford pure S. ketone product (-)-**9oo**.

Procedure J: **General procedure for the regioselective reduction of** (-)-**9a**: In an oven dried round bottomed flask equipped with a magnetic stirring bar was taken chiral S. ketone (-)-**9a** (0.1 mmol, 1.0 equiv.) in 0.5 mL EtOH (0.2 M) and stirred at 0 °C for 5 min after which half portion of $NaBH_4$ (0.035 mmol, 0.35 equiv.) was added and allowed to stir at same temperature for 3.0 h. Then, added another half portion of $NaBH_4$ (0.035 mmol, 0.35 equiv.) to the reaction mixture and allowed to stir for another 3 h at the same temperature. After completion of reaction, 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) and concentrated. Pure chiral product (-)-**11a** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure K: **General procedure for the olefin reduction of** (-)-**9a**: In an oven dried round bottomed flask equipped with a magnetic stirring bar was taken chiral S. ketone (-)-**9a** (0.1 mmol, 1.0 equiv.) in 0.5 mL 3-picoline (0.2 M) and 10% Pd/C (10 mol%) was added and stirred at room temperature for 30 h under hydrogen atmosphere (hydrogen bladder). After the completion of reaction, the reaction mixture was diluted with EtOAc (5.0 mL) and washed five times with 4% aq. HCl (5 mL) inorder to remove 3-picoline from the reaction mixture, and the organic layer was concentrated under reduced pressure and purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to afford pure reduced product (+)-**12a**.

Procedure L: **General procedure for the Simmons-Smith reaction of** (-)-**11a**: In an oven dried round bottomed flask equipped with a magnetic stirring bar was taken compound (-)-

11a (0.1 mmol, 1.0 equiv.) in 1.0 mL anhydrous DCM (0.1 M) and stirred at -10 °C for 5 min. To this, diethyl zinc (1.5 M in toluene, 0.5 mmol, 5.0 equiv.) was added dropwise followed by diiodomethane (0.5 mmol, 5.0 equiv.). The cooling bath was allowed to warm to room temperature in over 3.0 h and the reaction was stirred for an additional 1.0 h, after which the TLC showed complete consumption of (-)-**11a**. To the reaction mixture, a saturated NH_4Cl (5 mL) was added and was diluted with EtOAc (10 mL) and 10% aq. HCl (5 mL). The layers were separated and the organic layer was then successively washed with saturated aq. Na_2SO_3 (5 mL), saturated aq. $NaHCO_3$ (5 mL) and saturated NaCl (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give crude product, and purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to afford pure chiral tricyclic compound (-)-**13a**.

Procedure M: **General procedure for the epoxidation of** (-)-**11a**: In an oven dried round bottomed flask, *m*-CPBA (0.12 mmol, 1.2 equiv.) was added to a stirred solution of allylic alcohol (-)-**11a** (0.1 mmol, 1.0 equiv.) in 0.5 mL anhydrous DCM (0.2 M) at 0 °C and allowed to warm to room temperature and stirred for 1.5 h. After the completion of reaction, the reaction mixture was diluted with DCM, washed with 10% aq. K_2CO_3 (5 mL), brine solution (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give crude product, and purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to afford pure chiral epoxide (-)-**14a**.

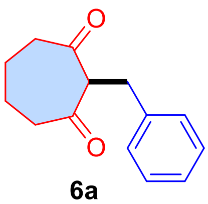
Procedure N: **General procedure for the regioselective Wittig reaction of** (+)-**12a**:

Step-1: <u>Preparation of 1.0 M methylenetriphenylphosphorane solution</u>: In an oven dried round bottomed flask equipped with a magnetic stirring bar was taken methyltriphenylphosphonium bromide (1.0 mmol, 1.0 equiv.) in 1.0 mL dry THF (1.0 M) and cooled to 0 °C. To this *n*-BuLi (1.0 mmol, 1.0 equiv.) was added drop wise at the same temperature. Then, the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 30 min. during which dark yellow colour develops and sustains upon the formation of ylide. This is the 1.0 M ylide stock solution.

Step-2: In a seperate oven dried round bottomed flask equipped with a magnetic stirring bar was taken compound (+)-**12a** (0.1 mmol, 1.0 equiv.) in 0.5 mL dry THF (0.2 M) and cooled to 0 °C. To this, 0.2 mL of freshly prepared 1.0 M ylide solution (0.2 mmol, 2.0 equiv.) was added dropwise allowed to stir for 35 min. After the completion of reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to afford pure compound (+)-**15a**.

Procedure O: General procedure for the preparation of 2-(4-nitrobenzylidene)cycloheptane-1,3-dione (5n): In an oven dried reaction vial equipped with a magnetic stirring bar at rt was taken cycloheptane-1,3-dione **1** (0.3 mmol, 1.0 equiv.), to which catalyst **4a** (0.06 mmol, 20 mol%), and 1.0 mL of 1-butanol was added and stirred for 20 seconds followed by the addition of *p*-nitrobenzaldehyde **2n** (0.6 mmol, 2.0 equiv.) and allowed to stir for 2.0 h. After the completion of reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to afford pure 2-(4-nitrobenzylidene)cycloheptane-1,3-dione (**5n**).

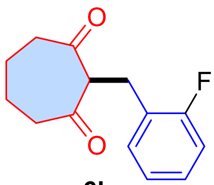
2-Benzylcycloheptane-1,3-dione (6a): Prepared by following the procedure **C** and purified



6a

by column chromatography using EtOAc/hexane (3:97) and isolated as light yellow solid. Yield: 90% (58 mg); Mp.: 48-50 °C; IR (Neat): ν_{max} 3305, 1703, 1453, 1275, 1261, 1075, 750 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25-7.22 (2H, m), 7.18-7.13 (3H, m), 4.21 (1H, t, *J* = 7.0 Hz), 3.15 (2H, d, *J* = 6.5 Hz), 2.55 (2H, ddd, *J* = 13.7, 8.7, 4.5 Hz), 2.46 (2H, ddd, *J* = 13.7, 9.5, 3.5 Hz), 2.12-2.05 (2H, m), 1.88-1.82 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.5 (2 x C, 2 x *C*=O), 139.1 (C), 129.0 (2 x CH), 128.4 (2 x CH), 126.3 (CH), 68.4 (CH), 44.3 (2 x CH_2), 31.9 (CH_2), 25.1 (2 x CH_2); HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{14}H_{17}O_2$ 217.1229; Found 217.1231.

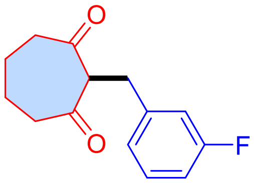
2-(2-Fluorobenzyl)cycloheptane-1,3-dione (6b): Prepared by following the procedure **C**



6b

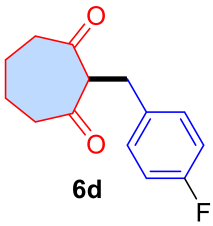
and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 80% (56 mg). IR (Neat): ν_{max} 2924, 2853, 1721, 1695, 1583, 1491, 1453, 1321, 1228, 1113, 1093, 910, 797 and 756 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21-7.14 (2H, m), 7.03-6.95 (2H, m), 4.29 (1H, t, *J* = 7.0 Hz), 3.16 (2H, d, *J* = 7.0 Hz), 2.58 (2H, ddd, *J* = 14.1, 8.7, 4.5 Hz), 2.50 (2H, ddd, *J* = 14.5, 8.5, 4.0 Hz), 2.15-2.07 (2H, m), 1.89-1.84 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.1 (2 x C, 2 x *C*=O), 161.1 (C, d, *J* = 243.7 Hz, *C*-F), 131.9 (CH, d, *J* = 5.0 Hz), 128.2 (CH, d, *J* = 7.5 Hz), 125.7 (C, d, *J* = 16.2 Hz), 124.0 (CH, d, *J* = 3.7 Hz), 115.1 (CH, d, *J* = 22.5 Hz), 66.6 (CH), 44.2 (2 x CH_2), 25.78 (CH_2), 25.77 (2 x CH_2). ^{19}F NMR ($CDCl_3$, 375 MHz): δ -117.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}FO_2$ 235.1134; Found 235.1128.

2-(3-Fluorobenzyl)cycloheptane-1,3-dione (6c): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as light yellow solid. Mp.: 108-110 °C. Yield: 84% (59 mg). IR (Neat): ν_{max} 3013, 2968, 1738, 1431, 1396, 1228, 1215, 1040, 922 and 718 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21-7.17 (1H, m), 6.91 (1H, d, J = 7.5 Hz), 6.88-6.84 (2H, m), 4.21 (1H, t, J = 7.0 Hz), 3.13 (2H, d, J = 7.0 Hz), 2.57 (2H, ddd, J = 14.2, 8.5, 4.0 Hz), 2.47 (2H, ddd, J = 14.5, 8.7, 4.0 Hz), 2.14-2.06 (2H, m), 1.89-1.81 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.0 (2 x C, 2 x *C*=O), 162.7 (C, d, J = 243.7 Hz, *C*-F), 141.6 (C, d, J = 7.5 Hz), 129.8 (CH, d, J = 8.7 Hz), 124.6 (CH, d, J = 2.5 Hz), 115.8 (CH, d, J = 21.2 Hz), 113.2 (CH, d, J = 21.2 Hz), 68.0 (CH), 44.4 (2 x CH_2), 31.5 (CH_2, d, J = 2.5 Hz), 24.9 (2 x CH_2). ^{19}F NMR ($CDCl_3$, 375 MHz): δ -113.3; HRMS (ESI-TOF) *m/z*: $[M + K]^+$ Calcd for $C_{14}H_{15}FO_2K$ 273.0693; Found 273.0696.

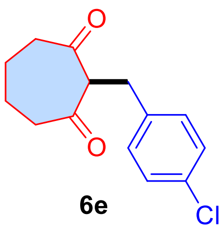


6c

2-(4-Fluorobenzyl)cycloheptane-1,3-dione (6d): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as yellow solid. Mp.: 62-64 °C. Yield: 85% (60 mg). IR (Neat): ν_{max} 2937, 1720, 1694, 1601, 1508, 1452, 1347, 1275, 1260, 1158, 1135, 750 and 544 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12-7.10 (2H, m), 6.95-6.90 (2H, m), 4.16 (1H, t, J = 7.0 Hz), 3.11 (2H, d, J = 6.5 Hz), 2.55 (2H, ddd, J = 14.4, 9.7, 3.5 Hz), 2.46 (2H, ddd, J = 14.2, 8.5, 4.0 Hz), 2.13-2.05 (2H, m), 1.89-1.81 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 205.3 (2 x C, 2 x *C*=O), 161.5 (C, d, J = 244 Hz, *C*-F), 134.7 (C), 130.4 (2 x CH, d, J = 7.0 Hz), 115.2 (2 x CH, d, J = 22.0 Hz), 68.4 (CH), 44.3 (2 x CH_2), 31.0 (CH_2), 25.0 (2 x CH_2). ^{19}F NMR ($CDCl_3$, 375 MHz): δ -116.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}FO_2$ 235.1134; Found 235.1129.



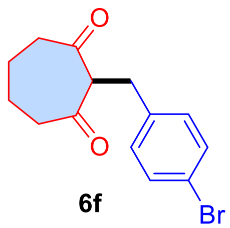
6d



6e

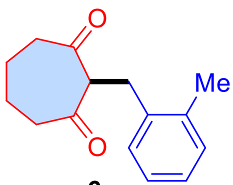
2-(4-Chlorobenzyl)cycloheptane-1,3-dione (6e): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as light yellow solid. Mp.: 95-97 °C. Yield: 80% (60 mg). IR (Neat): ν_{max} 2943, 1719, 1693, 1490, 1450, 1407, 1317, 1264, 1219, 1128, 1091, 1049 and 1013 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.19 (2H, td, J = 8.0, 4.0 Hz), 7.07 (2H, br d, J = 8.5 Hz), 4.16 (1H, t, J = 6.5 Hz), 3.09 (2H, d, J = 6.5 Hz), 2.54 (2H, ddd, J = 14.0, 8.7, 4.0 Hz), 2.45 (2H, ddd, J = 14.0, 9.5, 4.0 Hz), 2.12-2.05 (2H, m), 1.87-1.83 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 205.1 (2 x C, 2 x *C*=O), 137.6 (C), 132.1 (C), 130.4 (2 x CH), 128.5 (2 x CH), 68.2 (CH), 44.3 (2 x CH_2), 31.1 (CH_2), 24.9 (2 x CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{16}ClO_2$ 251.0839; Found 251.0842.

2-(4-Bromobenzyl)cycloheptane-1,3-dione (6f): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as white solid. Mp.: 69-71 °C. Yield: 82% (73 mg). IR (Neat): ν_{max} 2937, 2860, 1718, 1693, 1487, 1456, 1401, 1315, 1209, 1070, 1054, 915 and 814 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35 (2H, td, J = 8.5, 2.5 Hz), 7.02 (2H, br d, J = 8.5 Hz), 4.16 (1H, t, J = 6.5 Hz), 3.08 (2H, d, J = 6.5 Hz), 2.55 (2H, ddd, J = 14.2, 8.7, 4.5 Hz), 2.46 (2H, ddd, J = 13.8, 9.5, 3.5 Hz), 2.12-2.05 (2H, m) 1.88-1.82 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.1 (2 x C, 2 x *C*=O), 138.1 (C), 130.8 (2 x CH), 131.5 (2 x CH), 120.2 (C), 68.1 (CH), 44.4 (2 x CH_2), 31.2 (CH_2), 25.0 (2 x CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{16}O_2Br$ 295.0334; Found 295.0330.



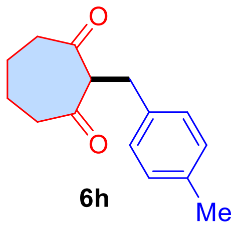
6f

2-(2-Methylbenzyl)cycloheptane-1,3-dione (6g): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 90% (62 mg). IR (Neat): ν_{max} 2935, 1721, 1694, 1452, 1321, 1208, 1120, 1097, 910 and 741 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.13-7.09 (2H, m), 7.08-7.02 (2H, m), 4.15 (1H, t, J = 6.5 Hz), 3.16 (2H, d, J = 7.0 Hz), 2.58 (2H, ddd, J = 14.1, 8.5, 4.0 Hz), 2.51 (2H, ddd, J = 14.1, 8.5, 4.0 Hz), 2.30 (3H, s, Ar-CH_3), 2.13-2.06 (2H, m), 1.91-1.83 (2H. m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 205.7 (2 x C, 2 x *C*=O), 137.2 (C), 136.2 (C), 130.4 (CH), 129.2 (CH), 126.5 (CH), 125.9 (CH), 67.0 (CH), 44.2 (2 x CH_2), 28.9 (CH_2), 25.3 (2 x CH_2), 19.5 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{15}H_{18}O_2Na$ 253.1204; Found : 253.1209.



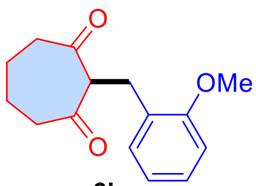
6g

2-(4-Methylbenzyl)cycloheptane-1,3-dione (6h): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as yellow oil. Yield: 94% (65 mg). IR (Neat): ν_{max} 2928, 2154, 1720, 1694, 1514, 1450, 1321, 1218, 1186, 909, 809, 730 and 544 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.06-7.02 (4H, m), 4.16 (1H, t, J = 7.0 Hz), 3.11 (2H, d, J = 6.5 Hz), 2.55 (2H, ddd, J = 13.8, 8.7, 3.5 Hz), 2.46 (2H, ddd, J = 14.1, 8.7, 3.5 Hz), 2.29 (3H, s, Ar-CH_3), 2.12-2.04 (2H, m), 1.88-1.81 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 205.7 (2 x C, 2 x C=O), 135.9 (C), 135.8 (C), 129.1 (2 x CH), 128.8 (2 x CH), 68.5 (CH), 44.3 (2 x CH_2), 31.4 (CH_2), 25.1 (2 x CH_2), 21.0 (CH_3). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{15}H_{18}O_2Na$ 253.1204; Found 253.1208.



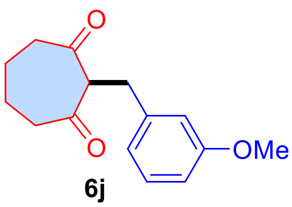
6h

2-(2-Methoxybenzyl)cycloheptane-1,3-dione (6i): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as yellow oil. Yield: 86% (63 mg). IR (Neat): ν_{max} 2921, 2851, 2359, 1721, 1695, 1600, 1493, 1460, 1322, 1243, 1119, 1290, 1259, 1211, 1153, 1046, 909, 780 and 693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17 (1H, dt, J = 8.0, 1.5 Hz), 7.12 (1H, dd, J = 7.5, 1.5 Hz), 6.84 (1H, dt, J = 7.5, 1.0 Hz), 6.80 (1H, br d, J = 8.5 Hz), 4.15 (1H, t, J = 6.5 Hz), 3.78 (3H, s, OCH_3), 3.14 (2H, d, J = 6.5 Hz), 2.57-2.47 (4H, m), 2.08-2.02 (2H, m), 1.88-1.81 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 206.4 (2 x C, 2 x C=O), 157.3 (C), 131.1 (CH), 127.7 (CH), 127.1 (C), 120.5 (CH), 110.1 (CH), 66.8 (CH), 55.0 (CH_3, OCH_3), 43.9 (2 x CH_2), 27.4 (CH_2), 25.6 (2 x CH_2). HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{19}O_3$ 247.1334; Found 247.1339.



6i

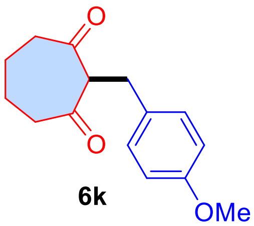
2-(3-Methoxybenzyl)cycloheptane-1,3-dione (6j): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 90% (66 mg). IR (Neat): ν_{max} 2937, 2031, 1721, 1694, 1599, 1583, 1488, 1452, 1316, 1290, 1259, 1211, 1153, 1046, 909, 780 and 693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 (1H, t, J = 7.5 Hz), 6.73-6.69 (3H, m), 4.21 (1H, t, J = 6.5 Hz), 3.77 (3H, s, OCH_3), 3.13 (2H, d, J = 6.5 Hz), 2.56 (2H, ddd, J = 14.0, 8.5, 4.0 Hz), 2.47 (2H, ddd, J = 14.0, 9.7, 3.5 Hz), 2.11-2.06 (2H, m) 1.87-1.82 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 205.4 (2 x C, 2 x C=O), 159.6 (C), 140.7 (C),



6j

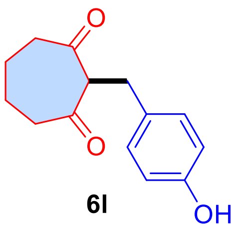
129.4 (CH), 121.2 (CH), 114.7 (CH), 111.7 (CH), 68.3 (CH), 55.1 (CH_3, OCH_3), 44.3 (2 x CH_2), 31.8 (CH_2), 25.0 (2 x CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{18}O_3Na$ 269.1154; Found 269.1154.

2-(4-Methoxybenzyl)cycloheptane-1,3-dione (6k): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 93% (69 mg). IR (Neat): ν_{max} 2934, 1986, 1720, 1694, 1610, 1610, 1582, 1511, 1453, 1299, 1245, 1178, 1114, and 1033 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.06 (2H, d, J = 8.5 Hz), 6.78 (2H, d, J = 8.0 Hz), 4.12 (1H, t, J = 7.0 Hz), 3.76 (3H, s, OCH_3), 3.09 (2H, d, J = 6.5 Hz), 2.53 (2H, ddd, J = 13.8, 8.7, 4.0 Hz), 2.45 (2H, ddd, J = 13.5, 9.5, 3.5 Hz), 2.08-2.03 (2H, m) 1.87-1.83 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.8 (2 x C, 2 x *C*=O), 158.1 (C), 131.0 (C), 129.9 (2 x CH), 113.8 (2 x CH), 68.7 (CH), 55.2 (CH_3, OCH_3), 44.3 (2 x CH_2), 31.0 (CH_2), 25.2 (2 x CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{19}O_3$ 247.1334; Found 247.1335.



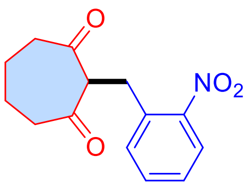
6k

2-(4-Hydroxybenzyl)cycloheptane-1,3-dione (6l): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.2:8.8) and isolated as light yellow solid. Mp.: 83-85 °C. Yield: 85% (59 mg). IR (Neat): ν_{max} 3335, 2929, 2857, 1711, 1678, 1614, 1596, 1394, 1263, 1094, 973 and 739 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.00 (2H, td, J = 8.5, 3.0 Hz), 6.89 (2H, td, J = 8.5, 3.0 Hz), 5.20 (1H, br s, O*H*), 4.12 (1H, t, J = 7.0 Hz), 3.07 (2H, d, J = 6.5 Hz), 2.54 (2H, ddd, J = 13.8, 8.5, 4.5 Hz), 2.46 (2H, ddd, J = 13.7, 9.5, 3.5 Hz), 2.11-2.03 (2H, m), 1.88-1.81 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 206.2 (2 x C, 2 x *C*=O), 154.2 (C), 130.9 (C), 130.2 (2 x CH), 115.3 (2 x CH), 68.7 (CH), 44.3 (2 x CH_2), 31.1 (CH_2), 25.2 (2 x CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{16}O_3Na$ 255.0997; Found 255.0998.



6l

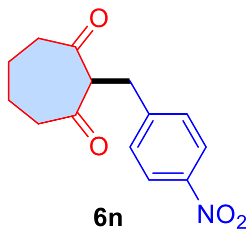
2-(2-Nitrobenzyl)cycloheptane-1,3-dione (6m): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.2:8.8) and isolated as white solid. Mp.: 67-69 °C. Yield: 95% (74 mg). IR (Neat): ν_{max} 2952, 2863, 1710, 1688, 1608, 1574, 1519, 1449, 1231, 1357, 1313, 1265, 1051, 1033, 959 and 738 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.95 (1H, dd, J = 8.2, 1.5 Hz), 7.49 (1H, dt, J = 7.5, 1.5 Hz),



6m

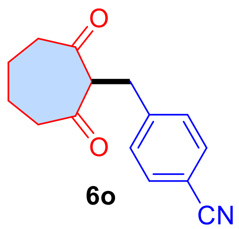
7.43 (1H, dd, J = 7.5, 1.5 Hz), 7.36 (1H, dt, J = 7.0, 1.5 Hz), 4.52 (1H, t, J = 6.5 Hz), 3.40 (2H, d, J = 6.0 Hz), 2.64 (2H, ddd, J = 14.8, 8.7, 4.0 Hz), 2.52 (2H, ddd, J = 14.8, 8.7, 4.0 Hz), 2.17-2.09 (2H, m), 1.89-1.83 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 204.3 (2 x C, 2 x *C*=O), 149.1 (C), 134.7 (C), 133.9 (CH), 133.2 (CH), 127.8 (CH), 125.0 (CH), 67.2 (CH), 44.4 (2 x CH_2), 29.4 (CH_2), 24.7 (2 x CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{14}H_{15}NO_4Na$ 284.0899; Found 284.0897.

2-(4-Nitrobenzyl)cycloheptane-1,3-dione (6n): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.2:8.8) and isolated as white solid. Mp.: 115-117 °C. Yield: 93% (73 mg). IR (Neat): ν_{max} 2929, 2874, 1716, 1691, 1594, 1507, 1456, 1433, 1342, 1210, 1111, 910, 856 and 751 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.09 (2H, m), 7.32 (2H, d, J = 8.5 Hz), 4.26 (1H, t, J = 7.0 Hz), 3.22 (2H, d, J = 7.0 Hz), 5.16 (2H, ddd, J = 14.2, 8.7, 4.5 Hz), 4.98 (2H, ddd, J = 14.0, 9.7, 3.5 Hz), 2.15-2.08 (2H, m), 1.90-1.83 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 204.4 (2 x C, 2 x *C*=O), 147.1 (C), 146.6 (C), 129.9 (2 x CH), 123.6 (2 x CH), 67.7 (CH), 44.4 (2 x CH_2), 31.6 (CH_2), 24.8 (2 x CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_4$ 262.1079; Found 262.1077.



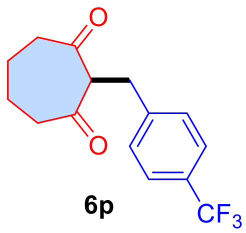
6n

2-(4-Cyanobenzyl)cycloheptane-1,3-dione (6o): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.2:8.8) and isolated as white solid. Mp.: 69-71 °C. Yield: 97% (70 mg). IR (Neat): ν_{max} 2935, 1714, 1689, 1433, 1215, 1113 and 825 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (2H, br d, J = 8.0 Hz), 7.27 (2H, br d, J = 7.5 Hz), 4.20 (1H, t, J =7.0 Hz), 3.19 (2H, d, J = 7.0 Hz), 2.58 (2H, ddd, J = 14.3, 8.5, 4.0 Hz), 2.49 (2H, ddd, J = 14.0, 9.7, 4.0 Hz), 2.15-2.01 (2H, m), 1.91-1.83 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 204.5 (2 x C, 2 x C=O), 144.9 (C), 132.1 (2 x CH), 129.8 (2 x CH), 118.8 (C), 110.3 (C), 67.6 (CH), 44.3 (2 x CH_2), 31.8 (CH_2), 24.8 (2 x CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{15}H_{15}NNaO_2$ 264.1000; Found 264.1010.



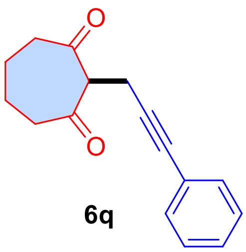
6o

2-(4-(Trifluoromethyl)cycloheptane-1,3-dione (6p): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.2:8.8) and isolated as white solid. Mp.: 67-69 °C. Yield: 89% (76 mg). IR (Neat): ν_{max} 2922, 2054, 1716, 1689, 1617, 1453, 1371, 1286, 1157, 1102, 1049, 969 and 748 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50 (2H, d, J = 8.0 Hz), 7.28 (2H, d, J = 8.0 Hz), 4.23 (1H, t, J = 7.0 Hz), 3.19 (2H, d, J = 6.5 Hz), 2.58 (2H, ddd, J = 14.5, 8.5, 4.0 Hz), 2.49 (2H, ddd, J = 14.6, 8.7, 3.5 Hz), 2.15-2.07 (2H, m), 1.90-1.83 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 204.8 (2 x C, 2 x *C*=O), 143.3 (C), 129.4 (2 x CH), 128.7 (C, q, J = 32.5 Hz), 125.3 (2 x CH, q, J = 3.75 Hz), 124.2 (C, q, J = 270 Hz, *C*F_3), 68.0 (CH), 44.4 (2 x CH_2), 31.6 (CH_2), 24.9 (2 x CH_2). ^{19}F NMR ($CDCl_3$, 375 MHz): δ -62.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{16}F_3O_2$ 285.1102; Found 285.1101.



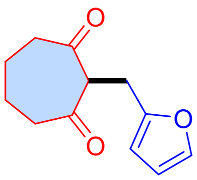
6p

2-(3-Phenylprop-2-yn-1-yl)cycloheptane-1,3-dione (6q): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.5:9.5 to 0.7:9.3) and isolated as yellow oil. Yield: 83% (60 mg). IR (Neat): ν_{max} 2927, 2631, 2334, 1722, 1697, 1597, 1490, 1442, 1416, 1316, 1245, 1193, 1129 and 1070 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.33 (2H, m), 7.26-7.25 (3H, m), 4.24 (1H, t, J = 6.5 Hz), 2.91 (2H, d, J = 6.5 Hz), 2.69 (2H, ddd, J = 14.6, 8.5, 3.5 Hz), 2.56 (2H, ddd, J = 14.6, 8.5, 3.5 Hz), 2.18-2.11 (2H, m), 1.91-1.87 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 204.0 (2 x C, 2 x *C*=O), 131.5 (2 x CH), 128.1 (2 x CH), 127.8 (CH), 123.3 (C), 86.7 (C), 81.5 (C), 65.4 (CH), 44.2 (2 x CH_2), 24.7 (2 x CH_2), 16.4 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{16}O_2Na$ 263.1048; Found 263.1053.



6q

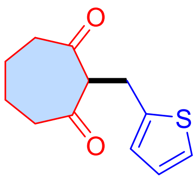
2-(Furan-2-ylmethyl)cycloheptane-1,3-dione (6r): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as yellow oil. Yield: 94% (58 mg). IR (Neat): ν_{max} 2935, 1721, 1694, 1595, 1506, 1452, 1354, 1215, 1163, 1072, 1010, 910, 805, 733 and 595 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (1H, t, J = 2.0 Hz), 6.23 (1H, t, J = 2.0 Hz), 5.99 (1H, d, J = 3.5 Hz), 4.36 (1H, t, J = 6.5 Hz), 3.17 (2H, d, J = 6.5 Hz), 2.64 (2H, ddd, J = 14.6, 9.0, 4.0 Hz), 2.49 (2H, ddd, J = 14.5, 9.0, 4.0 Hz), 2.17-2.10 (2H, m), 1.88-1.85 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 204.5 (2 x C, 2 x *C*=O), 152.6 (C), 141.2 (CH), 110.3 (CH), 106.4 (CH), 65.0 (CH), 44.2 (2



6r

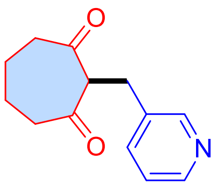
x CH_2), 24.8 (2 x CH_2), 24.4 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{14}O_3Na$ 229.0841; Found 229.0839.

2-(Thiophen-2-ylmethyl)cycloheptane-1,3-dione (6s): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as brown oil. Yield: 95% (63 mg). IR (Neat): ν_{max} 2929, 1719, 1693, 1430, 1209, 909 and 696 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.09 (1H, dd, J = 5.25, 1.5 Hz), 6.87 (1H, dd, J = 5.25, 3.5 Hz), 6.77 (1H, dd, J = 3.5, 1.0 Hz), 4.30 (1H, t, J = 6.5 Hz), 3.37 (2H, d, J = 7.0 Hz), 2.62 (2H, ddd, J = 14.5, 8.7, 4.5 Hz), 2.49 (2H, ddd, J = 14.6, 8.7, 3.5 Hz), 2.17-2.09 (2H, m), 1.89-1.82 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 204.6 (2 x C, 2 x *C*=O), 141.2 (C), 126.8 (CH), 125.9 (CH), 123.8 (CH), 68.4 (CH), 44.5 (2 x CH_2), 26.1 (CH_2), 24.7 (2 x CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{15}O_2S$ 223.0793; Found 223.0790.



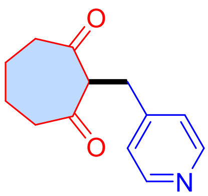
6s

2-(Pyridin-3-ylmethyl)cycloheptane-1,3-dione (6t): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (3.0:7.0 to 3.2:6.8) and isolated as yellow oil. Yield: 81% (53 mg). IR (Neat): ν_{max} 2931, 2865, 1718, 1696, 1596, 1479, 1425, 1373, 1320, 1185, 1129, 1048, 912 and 866 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.41 (2H, br s), 7.50 (1H, d, J = 8.0 Hz), 7.17 (1H, t, J = 6.5 Hz), 4.22 (1H, t, J = 7.0 Hz), 3.12 (2H, d, J = 7.0 Hz), 2.59-2.54 (2H, m), 2.49-2.45 (2H, m), 2.10-2.06 (2H, m), 1.88-1.81 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 204.6 (2 x C, 2 x *C*=O), 150.0 (CH), 147.6 (CH), 136.9 (CH), 134.7 (C), 123.3 (CH), 67.8 (CH), 44.4 (2 x CH_2), 29.0 (CH_2), 24.8 (2 x CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1181; Found 218.1178.



6t

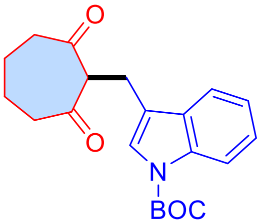
2-(Pyridin-4-ylmethyl)cycloheptane-1,3-dione (6u): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (3.0:7.0 to 3.2:6.8) and isolated as yellow oil. Yield: 89% (58 mg). IR (Neat): ν_{max} 3033, 2928, 2863, 1720, 1696, 1602, 1558, 1416, 1373, 1252, 1216, 1134, 1068 and 1042 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.46 (2H, dd, J = 4.5, 1.5 Hz), 7.09 (2H, dd, J = 4.5, 1.5 Hz), 4.24 (1H, t, J = 7.0 Hz), 3.13 (2H, d, J = 7.0 Hz), 2.59 (2H, ddd, J = 14.5, 8.7, 4.5 Hz), 2.49 (2H, ddd, J = 14.6, 9.0, 2.0 Hz), 2.16-2.08 (2H, m), 1.94-1.86 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 204.4 (2 x



6u

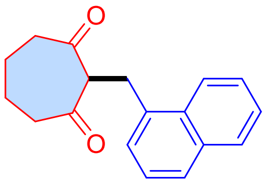
C, 2 x *C*=O), 149.7 (2 x CH), 148.4 (C), 124.4 (2 x CH), 67.2 (CH), 44.4 (2 x CH_2), 31.1 (CH_2), 24.8 (2 x CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1181; Found 218.1180.

***tert*-Butyl-3-((2,7-dioxocycloheptyl)methyl)-1*H*-indole-1-carboxylate (6v):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as orange solid. Mp.: 110-112 °C. Yield: 70% (75 mg). IR (Neat): ν_{max} 2921, 2851, 1963, 1724, 1608, 1452, 1370, 1308, 1254, 1222, 1156, 1082, 1017, 909, 765, 747 and 589 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.10 (1H, br s), 7.50 (1H, d, J = 7.5 Hz), 7.33-7.28 (2H, m), 7.25-7.22 (1H, m), 4.31 (1H, t, J = 7.0 Hz), 3.24 (2H, dd, J = 6.0, 1.0 Hz), 2.60 (2H, ddd, J = 13.8, 9.0, 4.0 Hz), 2.51 (2H, ddd, J = 14.0, 9.5, 4.0 Hz), 2.14-2.06 (2H, m), 1.90-1.82 (2H, m), 1.65 (9H, s). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.4 (2 x C, 2 x *C*=O), 149.6 (C, O-*C*=O), 135.4 (C), 130.2 (C), 124.3 (CH), 123.6 (CH), 122.4 (CH), 118.8 (CH), 117.6 (C), 115.2 (CH), 83.5 (C), 66.4 (CH), 44.3 (2 x CH_2), 28.2 (3 x CH_3), 25.0 (2 x CH_2), 21.2 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + NH_4]^+$ Calcd for $C_{21}H_{29}N_2O_4$ 373.2127; Found 373.2129.

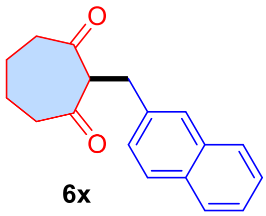


6v

2-(Naphthalen-1-ylmethyl)cycloheptane-1,3-dione (6w): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.6:9.4 to 0.8:9.2) and isolated as yellow oil. Yield: 83% (66 mg). IR (Neat): ν_{max} 3045, 2935, 1720, 1694, 1596, 1509, 1540, 1344, 1323, 1263, 1206, 1134, 1018, 909 and 778 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.97 (1H, d, J = 8.5 Hz), 7.85 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 7.5 Hz), 7.52 (1H, br dt, J = 8.0, 1.5 Hz), 7.47 (1H, br dt, J = 8.0, 1.5 Hz), 7.35 (1H, t, J = 7.5 Hz), 7.32 (1H, d, J = 7.5 Hz), 4.32 (1H, t, J = 6.5 Hz), 3.65 (2H, d, J = 6.5 Hz), 2.56-2.52 (4H, m), 2.09-2.01 (2H, m), 1.90-1.83 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.7 (2 x C, 2 x *C*=O), 135.0 (C), 133.9 (C), 131.5 (C), 129.0 (CH), 127.4 (CH), 127.2 (CH), 126.2 (CH), 125.5 (CH), 125.4 (CH), 123.2 (CH), 67.3 (CH), 44.2 (2 x CH_2), 28.7 (CH_2), 25.1 (2 x CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + NH_4]^+$ Calcd for $C_{18}H_{22}NO_2$ 284.1651; Found 284.1651.



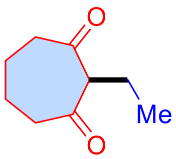
6w



6x

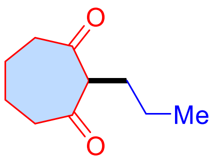
2-(Naphthalen-2-ylmethyl)cycloheptane-1,3-dione (6x): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.6:9.4 to 0.8:9.2) and isolated as white solid. Mp.: 69-71 °C. Yield: 91% (73 mg). IR (Neat): ν_{max} 2923, 2853, 1719, 1693, 1631, 1599, 1507, 345, 1207, 1168, 1126, 1106, 1038, 961, 816 and 748 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.79-7.73 (3H, m), 7.61 (1H, br s), 7.43 (2H, m), 7.29 (1H, dd, J = 8.5, 1.5 Hz), 4.32 (1H, t, J = 7.0 Hz), 3.32 (2H, d, J = 7.0 Hz), 2.56 (2H, ddd, J = 14.0, 8.5, 4.0 Hz), 2.47 (2H, ddd, J = 13.8, 9.5, 3.5 Hz), 2.13-2.05 (2H, m), 1.88-1.81 (2H, m). ^{13}C NMR (CDCl$_3$, DEPT-135, 100 MHz): δ 205.4 (2 x C, 2 x C=O), 136.6 (C), 133.4 (C), 132.1 (C), 128.0 (CH), 127.5 (CH), 127.5 (CH), 127.4 (CH), 127.4 (CH), 126.0 (CH), 125.4 (CH), 68.4 (CH), 44.4 (2 x CH$_2$), 32.0 (CH$_2$), 25.0 (2 x CH$_2$). HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{18}H_{19}O_2$ 267.1385; Found 267.1386.

2-Ethylcycloheptane-1,3-dione (6y): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 80% (37 mg). IR (Neat): ν_{max} 2918, 1687, 1406, 1273, 1189, 921, 734 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.56 (1H, t, J = 7.0 Hz), 2.57-2.45 (4H, m), 2.08-2.00 (2H, m), 1.90-1.80 (4H, m), 0.85 (3H, t, J = 7.5 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135, 125 MHz): δ 207.6 (2 x C, 2 x C=O), 68.4 (CH), 43.7 (2 x CH$_2$), 25.8 (2 x CH$_2$), 19.7 (CH$_2$), 11.6 (CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_9H_{15}O_2$ 155.1072; Found 155.1076.



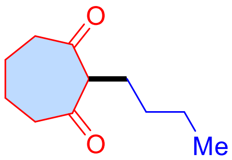
6y

2-Propylcycloheptane-1,3-dione (6z): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 86% (43 mg). IR (Neat): ν_{max} 2931, 2359, 1694, 1454, 1209 and 911 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.63 (1H, t, J = 7.0 Hz), 2.56-2.45 (4H, m), 2.06-1.99 (2H, m), 1.89-1.81 (2H, m), 1.79-1.74 (2H, m), 1.26-1.19 (2H, m), 0.88 (3H, t, J = 7.5 Hz). ^{13}C NMR (CDCl$_3$, DEPT-135, 125 MHz): δ 207.7 (2 x C, 2 x C=O), 66.6 (CH), 43.6 (2 x CH$_2$), 28.4 (CH$_2$), 25.9 (2 x CH$_2$), 20.3 (CH$_2$), 13.8 (CH$_3$). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{10}H_{16}O_2Na$ 191.1048; Found 191.1041.



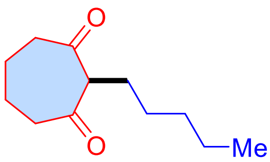
6z

2-Butylcycloheptane-1,3-dione (6aa): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 94% (51 mg). IR (Neat): ν_{max} 2930, 2867, 1721, 1696, 1453, 1204, 1142, 757 and 576 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.64 (1H, t, J = 7.0 Hz), 2.58-2.47 (4H, m), 2.09-2.01 (2H, m), 1.91-1.83 (2H, m), 1.82-1.78 (2H, m), 1.34-1.25 (2H, m), 1.22-1.16 (2H, m) 0.88 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 207.7 (2 x C, 2 x *C*=O), 66.9 (CH), 43.7 (2 x CH_2), 29.3 (CH_2), 26.1 (CH_2), 25.9 (2 x CH_2), 22.6 (CH_2) 13.8 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{19}O_2$ 183.1385; Found 183.1381.



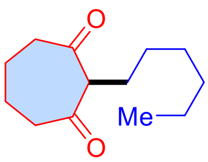
6aa

2-Pentylcycloheptane-1,3-dione (6bb): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 92% (54 mg). IR (Neat): ν_{max} 2924, 2855, 2361, 2339, 1723, 1694, 1454, 1217, 1125, 670 and 587 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.63 (1H, t, J = 7.0 Hz), 2.58-2.47 (4H, m), 2.09-2.00 (2H, m), 1.92-1.84 (2H, m), 1.82-1.77 (2H, m), 1.32-1.17 (6H, m), 0.87 (3H, t, J =7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 207.7 (2 x C, 2 x *C*=O), 66.9 (CH), 43.7 (2 x CH_2), 31.6 (CH_2), 26.8 (CH_2), 26.3 (CH_2), 25.9 (2 x CH_2), 22.3 (CH_2), 13.9 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{21}O_2$ 197.1542; Found 197.1547.



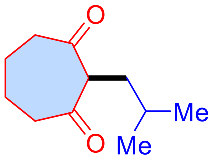
6bb

2-Hexylcycloheptane-1,3-dione (6cc): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 83% (52 mg). IR (Neat): ν_{max} 2927, 2858, 1702, 1454, 1173, 1142, 734 and 600 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.63 (1H, t, J = 7.0 Hz), 2.58-2.47 (4H, m), 2.09- 2.01 (2H, m), 1.91-1.84 (2H, m), 1.82-1.78 (2H, m), 1.30-1.17 (8H, m), 0.87 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 207.7 (2 x C, 2 x *C*=O), 66.9 (CH), 43.7 (2 x CH_2), 31.5 (CH_2), 29.1 (CH_2), 27.0 (CH_2), 26.3 (CH_2), 25.9 (2 x CH_2), 22.5 (CH_2), 14.0 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{23}O_2$ 211.1698; Found 211.1693.



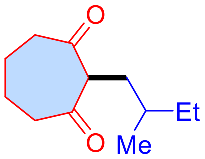
6cc

2-Isobutylcycloheptane-1,3-dione (6dd): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 70% (38 mg). IR (Neat): ν_{max} 2953, 2868, 1722, 1695, 1454, 1211, 1175, 683 and 576 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.73 (1H, t, J = 7.0 Hz), 2.58-2.46 (4H, m), 2.08-2.01 (2H, m), 1.90-1.82 (2H, m), 1.70 (2H, t, J = 7.0 Hz), 1.53-1.42 (1H, m), 0.86 (6H, d, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 207.8 (2 x C, 2 x *C*=O), 65.0 (CH), 43.6 (2 x CH_2), 35.0 (CH_2), 26.0 (2 x CH_2), 25.8 (CH), 22.4 (2 x CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{11}H_{18}O_2Na$ 205.1204; Found 205.1205.



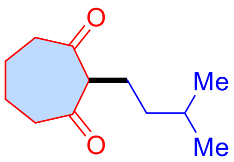
6dd

2-(2-Methylbutyl)cycloheptane-1,3-dione (6ee): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 85% (50 mg). IR (Neat): ν_{max} 2957, 2929, 1694, 1456, 1202, 1141, 909 and 549 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.75 (1H, t, J = 6.5 Hz), 2.60-2.49 (4H, m), 2.09-2.01 (2H, m), 1.91-1.83 (3H, m), 1.64-1.58 (1H, m), 1.37-1.21 (2H, m), 1.17-1.09 (1H, m), 0.87-0.82 (6H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 207.9 (C, *C*=O), 207.8 (C, *C*=O), 64.9 (CH), 43.7 (CH_2), 43.5 (CH_2), 33.0 (CH_2), 32.0 (CH), 29.4 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 18.9 (CH_3), 11.1 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{21}O_2$ 197. 1542; Found 197. 1546.



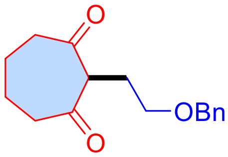
6ee

2-Isopentylcycloheptane-1,3-dione (6ff): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as colourless oil. Yield: 90% (53 mg). IR (Neat): ν_{max} 2953, 2359, 1723, 1695, 1454, 1205, 1125, 685 and 575 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.60 (1H, t, J = 7.0 Hz), 2.56-2.47 (4H, m), 2.07-2.00 (2H, m), 1.90-1.83 (2H, m), 1.81-1.76 (2H, m), 1.53-1.47 (1H, m), 1.09-1.04 (2H, m), 0.85 (6H, d, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 207.6 (2 x C, 2 x *C*=O), 67.1 (CH), 43.7 (2 x CH_2), 36.2 (CH_2), 28.0 (CH), 25.8 (2 x CH_2), 24.3 (CH_2), 22.3 (2 x CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{20}O_2Na$ 219.1361; Found 219.1359.



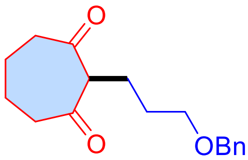
6ff

2-(2-(Benzyloxy)ethyl)cycloheptane-1,3-dione (6gg): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.6:9.4 to 0.8:9.2) and isolated as colourless oil. Yield: 75% (59 mg). IR (Neat): ν_{max} 2939, 1720, 1365, 1216, 1070, 909 and 715 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.32 (2H, m), 7.29-7.26 (3H, m), 4.42 (2H, s), 4.09 (1H, t, J = 7.0 Hz), 3.45 (2H, t, J = 6.0 Hz), 2.60-2.55 (2H, m), 2.49-2.44 (2H, m), 2.14 (2H, q, J = 7.0 Hz), 2.11-2.05 (2H, m), 1.87-1.81 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 206.2 (2 x C, 2 x C=O), 138.2 (C), 128.3 (2 x CH), 127.7 (2 x CH), 127.6 (CH), 72.8 (CH_2), 67.4 (CH_2), 63.4 (CH), 44.1 (2 x CH_2), 26.3 (CH_2), 25.2 (2 x CH_2). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}O_3$ 261.1491; Found 261.1493.



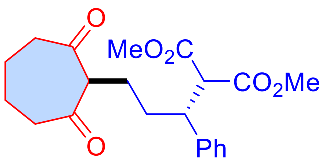
6gg

2-(3-(Benzyloxy)propyl)cycloheptane-1,3-dione (6hh): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.6:9.4 to 0.8:9.2) and isolated as colourless oil. Yield: 78% (64 mg). IR (Neat): ν_{max} 3012, 2969, 1738, 1367, 1232, 1216 and 718 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.31 (4H, m), 7.29-7.26 (1H, m), 4.46 (2H, s), 3.82 (1H, t, J = 7.0 Hz), 3.46 (2H, t, J = 6 Hz), 2.56-2.51 (2H, m), 2.49-2.43 (2H, m), 2.06-2.00 (2H, m), 1.93-1.89 (2H, m), 1.87-1.79 (2H, m), 1.58-1.53 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 207.0 (2 x C, 2 x C=O), 138.4 (C), 128.3 (2 x CH), 127.7 (2 x CH), 127.5 (CH), 72.9 (CH_2), 70.1 (CH_2), 66.3 (CH), 43.9 (2 x CH_2), 27.1 (CH_2), 25.5 (2 x CH_2), 23.3 (CH_2). HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{17}H_{26}NO_3$ 292.1913; Found 292.1916.



6hh

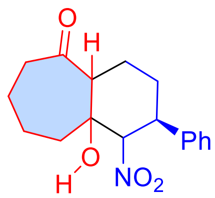
Dimethyl (*R*)-2-(3-(2,7-dioxocycloheptyl)-1-phenylpropyl)malonate [(+)-6ii]: Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.6:9.4 to 0.9:8.9) and isolated as yellow oil. Yield: 96% (108 mg). $[\alpha]_D^{25}$ = +10.0º [c = 0.1, $CHCl_3$]; IR (Neat): ν_{max} 2923, 2853, 1725, 1694, 1434, 1249, 1155 and 702 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.27 (2H, m), 7.21 (1H, tt, J = 7.5, 1.0 Hz), 7.18-7.16 (2H, m), 3.75 (3H, s, OCH_3), 3.64-3.61 (2H, m), 3.41 (3H, s, OCH_3), 3.34-3.29 (1H, m), 2.53-2.44 (2H, m), 2.42-2.36 (2H, m), 2.03-1.96 (2H, m), 1.84-1.76 (2H, m), 1.68-1.57 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 207.0 (C, C=O), 206.7 (C, C=O), 168.7 (C, O-C=O), 168.0 (C, O-C=O), 140.0 (C), 128.5 (2 x CH), 128.2 (2 x CH), 127.2 (CH), 66.1 (CH), 58.4 (CH), 52.6 (CH_3, OCH_3), 52.2 (CH_3, OCH_3), 45.5 (CH), 43.73



(+)-6ii

(CH_2), 43.71 (CH_2), 30.9 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 23.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{26}NaO_6$ 397.1627; Found 397.1633.

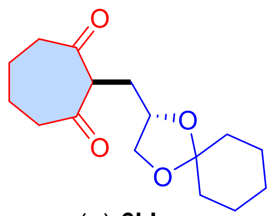
(2*S*)-9a-Hydroxy-1-nitro-2-phenyldecahydro-5*H*-benzo[7]annulen-5-one [(-)-6'jj]:



(-)-**6'jj**

Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.2:8.8) and isolated as white solid. Mp.: 141-143 °C. Yield: 92% (84 mg). $[\alpha]_D^{25}$ = -127.0° [*c* = 0.1, $CHCl_3$]; IR (Neat): ν_{max} 3523, 2941, 1693, 1542, 1334, 1249, 698 and 544 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, single isomer): δ 7.32-7.30 (2H, m), 7.26-7.23 (1H, m), 7.20-7.18 (2H, m), 4.63 (1H, d, *J* = 12.0 Hz), 3.58 (1H, dt, *J* = 12.7, 4.0 Hz), 3.18 (1H, br d, *J* = 1.5 Hz), 2.81-2.75 (1H, m), 2.65 (1H, br dd, *J* = 12.6, 1.8 Hz), 2.59-2.55 (1H, m), 2.28 (1H, dq, *J* = 13.0, 4.1 Hz), 2.08-1.99 (1H, m), 2.03-1.98 (1H, m), 1.89-1.85 (1H, m), 1.81-1.76 (1H, m), 1.75-1.71 (1H, m), 1.70-1.67 (1H, m), 1.66-1.62 (3H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz, single isomer): δ 210.8 (C, *C*=O), 139.2 (C), 128.9 (2 x CH), 127.8 (CH), 127.2 (2 x CH), 98.5 (CH), 71.5 (C), 55.9 (CH), 43.7 (CH), 43.6 (CH_2), 40.2 (CH_2), 31.5 (CH_2), 23.9 (CH_2), 23.4 (CH_2), 22.2 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{17}H_{25}N_2O_4$ 321.1814; Found 321.1813.

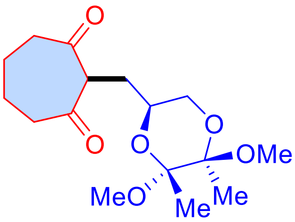
(*S*)-2-((1,4-Dioxaspiro[4.5]decan-2-yl)methyl)cycloheptane-1,3-dione (+)-(6kk): Prepared



(+)-**6kk**

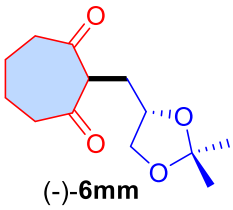
by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as yellow oil. Yield: 77% (65 mg). $[\alpha]_D^{25}$ = +14.0° [*c* = 0.1, $CHCl_3$]; IR (Neat): ν_{max} 2932, 2859, 1722, 1695, 1445, 1203, 1099, 1039, 928 and 910 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 4.14 (1H, dd, *J* = 10.0, 5.0 Hz), 4.01-3.98 (2H, m), 3.50-3.46 (1H, m), 2.68-2.62 (2H, m), 2.52-2.44 (2H, m), 2.17 (1H, dq, *J* = 6.0, 3.5 Hz), 2.15-2.07 (2H, m), 1.89-1.81 (3H, m), 1.53-1.49 (10H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.9 (C, *C*=O), 205.8 (C, *C*=O), 109.5 (C), 73.0 (CH), 69.0 (CH_2), 63.1 (CH), 44.4 (CH_2), 44.0 (CH_2), 36.5 (CH_2), 35.0 (CH_2), 30.2 (CH_2), 25.1 (CH_2), 25. (CH_2), 25.01 (CH_2), 24.0 (CH_2), 23.8 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{24}O_4Na$ 303.1572; Found 303.1570.

2-(((2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)cycloheptane-1,3-dione (-)-(6ll): Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as yellow oil. Yield: 72% (68 mg). $[\alpha]_D^{25}$ = -135.5° [*c* = 0.1, $CHCl_3$]; IR (Neat): ν_{max} 2932, 1725, 1695, 1449, 1361, 1117, 1036, and 956 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 4.25 (1H, dd, *J* = 9.5, 4.5 Hz), 3.80 (1H, tt, *J* = 10.5, 3.0 Hz), 3.47 (1H, t, *J* = 11.0 Hz), 3.40-3.37 (1H, m), 3.22 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 2.64-2.58 (2H, m), 2.52-2.44 (2H, m), 2.13-2.01 (3H, m), 1.88-1.77 (2H, m), 1.73-1.68 (1H, m), 1.23 (3H, s, CH_3), 1.22 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.6 (C, *C*=O), 205.5 (C, *C*=O), 99.0 (C), 97.9 (C), 64.5 (CH), 63.4 (CH_2), 61.9 (CH), 47.95 (CH_3, OCH_3), 47.92 (CH_3, OCH_3), 44.4 (CH_2), 43.8 (CH_2), 27.3 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 17.8 (CH_3), 17.5 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + NH_4]^+$ Calcd for $C_{16}H_{30}NO_6$ 332.2073; Found 332.2079.



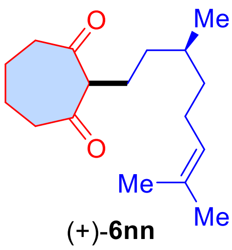
(-)-**6ll**

(*S*)-2-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)cycloheptane-1,3-dione [(-)-6mm]: Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as yellow oil. Yield: 76% (55 mg). $[\alpha]_D^{25}$ = -21.0° [*c* = 0.1, $CHCl_3$]; IR (Neat): ν_{max} 2932, 1721, 1694, 1453, 1370, 1211, 1155, 1061, 972, 910, 840 and 470 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 4.17 (1H, dd, *J* = 9.0, 4.0 Hz), 4.03-3.99 (2H, m), 3.52-3.49 (1H, m), 2.70-2.60 (2H, m), 2.54-2.45 (2H, m), 2.21 (1H, m), 2.16-2.06 (2H, m), 1.90-1.80 (3H, m), 1.35 (3H, s, CH_3), 1.28 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 205.9 (C, *C*=O), 205.7 (C, *C*=O), 109.0 (C), 73.4 (CH), 69.3 (CH_2), 63.0 (CH), 44.4 (CH_2), 44.0 (CH_2), 30.2 (CH_2), 26.8 (CH_3), 25.5 (CH_3), 25.1 (CH_2), 24.9 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_{20}O_4Na$ 263.1259; Found 263.1262.



(-)-**6mm**

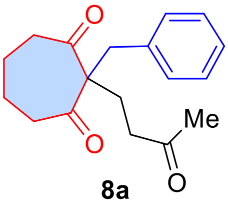
(*S*)-2-(3,7-Dimethyloct-6-en-1-yl)cycloheptane-1,3-dione [(+)-6nn]: Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3:9.7 to 0.5:9.5) and isolated as yellow oil. Yield: 82% (65 mg). $[\alpha]_D^{25}$ = +8.0° [*c* = 0.1, $CHCl_3$]; IR (Neat): ν_{max} 2922, 2854, 1722, 1697, 1455, 1378, 1180 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.06 (1H, tt, *J* = 7.0, 3.5 Hz), 5.60 (1H, t, *J* = 7.0 Hz), 2.56-2.48 (4H, m), 2.06-2.00 (2H, m), 1.97-1.72 (6H, m), 1.66 (3H, s, CH_3), 1.58 (3H, s, CH_3),



(+)-**6nn**

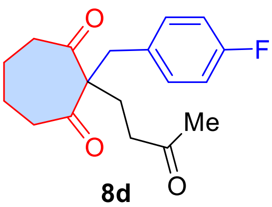
1.41-1.27 (2H, m), 1.24-0.98 (3H, m), 0.85 (3H, d, J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 207.68 (C, C=O), 207.66 (C, C=O), 131.1 (C), 124.7 (CH), 67.2 (CH), 43.7 (2 x CH_2), 36.7 (CH_2), 34.2 (CH_2), 32.4 (CH), 25.9 (CH_2), 25.8 (CH_2), 25.7 (CH_3), 25.4 (CH_2), 23.9 (CH_2), 19.3 (CH_3), 17.6 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{29}O_2$ 265.2168; Found 265.2166.

2-Benzyl-2-(3-oxobutyl)cycloheptane-1,3-dione (8a): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 95-97 °C. Yield: 93% (53 mg). IR (Neat): ν_{max} 2951, 2867, 1707, 1689, 1448, 1356, 1170, 1130, 1083 and 750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23-7.17 (3H, m), 6.97 (2H, br d, J = 7.0 Hz), 3.09 (2H, s), 2.44-2.41 (2H, m), 2.36-2.30 (4H, m), 2.10 (3H, s, CH_3), 2.03 (2H, t, J = 7.5 Hz), 1.86-1.77 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.6 (2 x C, 2 x C=O), 206.7 (C, C=O), 135.8 (C), 129.9 (2 x CH), 128.4 (2 x CH), 126.9 (CH), 68.8 (C), 42.5 (2 x CH_2), 37.4 (CH_2), 36.9 (CH_2), 30.0 (CH_3), 27.8 (2 x CH_2), 24.8 (CH_2). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}O_3$ 287.1647; Found 287.1649.

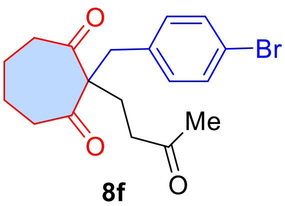


8a

2-(4-Fluorobenzyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8d): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 100-102 °C. Yield: 94% (57 mg). IR (Neat): ν_{max} 2937, 2867, 1705, 1689, 1601, 1509, 1448, 1359, 1265, 1133, 1094, 974, 851 and 784 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.97-6.89 (4H, m), 3.05 (2H, s), 2.44-2.40 (2H, m), 2.35-2.27 (4H, m), 2.11 (3H, s, CH_3), 2.04 (2H, t, J = 7.5 Hz), 1.86-1.80 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.6 (2 x C, 2 x C=O), 206.6 (C, C=O), 161.9 (C, d, J = 248.7 Hz, C-F), 131.5 (C, d, J = 2.5 Hz), 131.4 (2 x CH, d, J = 7.5 Hz), 115.3 (2 x CH, d, J = 21.2 Hz), 68.7 (C), 42.6 (2 x CH_2), 37.4 (CH_2), 36.3 (CH_2), 30.0 (CH_3), 27.7 (2 x CH_2), 25.0 (CH_2); ^{19}F NMR ($CDCl_3$, 375 MHz): δ -115.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{21}FO_3Na$ 327.1372; Found 327.1376.



8d

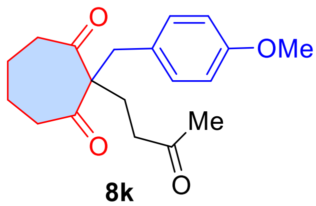


8f

2-(4-Bromobenzyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8f): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 107-109 °C. Yield: 93% (68 mg). IR (Neat): ν_{max}

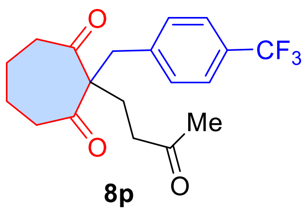
2935, 1714, 1688, 1695, 1477, 1458, 1327, 1178, 1127, 1067, 1016, 800 and 727 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37 (2H, td, J = 8.5, 3.0 Hz), 6.89 (2H, br d, J = 8.5 Hz), 3.05 (2H, s), 2.47-2.42 (2H, m), 2.37-2.32 (4H, m), 2.13 (3H, s, CH_3), 2.06 (2H, t, J = 8.0 Hz), 1.91-1.80 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.5 (2 x C, 2 x C=O), 206.6 (C, C=O), 134.9 (C), 131.65 (2 x CH), 131.56 (2 x CH), 121.1 (C), 68.6 (C), 42.6 (2 x CH_2), 37.3 (CH_2), 36.5 (CH_2), 30.1 (CH_3), 27.8 (2 x CH_2), 25.0 (CH_2). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{18}H_{21}BrO_3Na$ 387.0572; Found 387.0573.

2-(4-Methoxybenzyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8k): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 105-107 °C. Yield: 94% (59 mg). IR (Neat): ν_{max} 2936, 2202, 2008, 1715, 1686, 1610, 1511, 1439, 1371, 1318, 1250, 1174, 1033, 813, 779 and 712 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.88 (2H, td, J = 9.0, 2.0 Hz), 6.75 (2H, td, J = 8.5, 2.0 Hz), 3.75 (3H, s, OCH_3), 3.03 (2H, s), 2.44-2.39 (2H, m), 2.35-2.29 (4H, m), 2.10 (3H, s, CH_3), 2.03 (2H, t, J = 4.0 Hz), 1.87-1.76 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.9 (2 x C, 2 x C=O), 206.9 (C, C=O), 158.5 (C), 130.9 (2 x CH), 127.6 (C), 113.8 (2 x CH), 68.9 (C), 55.2 (CH_3, OCH_3), 42.6 (2 x CH_2), 37.5 (CH_2), 36.2 (CH_2), 30.0 (CH_3), 27.8 (2 x CH_2), 24.9 (CH_2). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{24}O_4Na$ 339.1572; Found 339.1572.



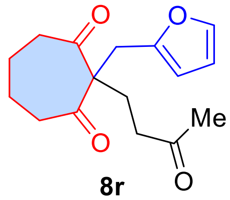
8k

2-(4-(Trifluoromethyl)benzyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8p): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 85-87 °C. Yield: 91% (64 mg). IR (Neat): ν_{max} 2922, 1721, 1688, 1623, 1464, 1426, 1322, 1161,1109, 1067, 1032, and 857 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.50 (2H, d. J = 8 Hz), 7.13 (2H, d, J = 8 Hz), 3.15 (2H, s), 2.49-2.44 (2H, m), 2.39-2.31 (4H, m), 2.14 (3H, s, CH_3), 2.07 (2H, t, J = 7.5 Hz), 1.91-1.81 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.3 (2 x C, 2 x C=O), 206.5 (C, C=O), 140.1 (C), 130.3 (2 x CH), 129.4 (C, q, J = 32.5 Hz), 125.3 (2 x CH, q, J = 3.75 Hz), 124.0 (C, q, J = 275.0 Hz, CF_3), 68.7 (C), 42.6 (2 x CH_2), 37.4 (CH_2), 36.8 (CH_2), 30.1 (CH_3), 27.8 (2 x CH_2), 25.0 (CH_2). ^{19}F NMR ($CDCl_3$, 375 MHz): δ -62.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{19}H_{22}F_3O_3$ 355.1521; Found 355.1514.



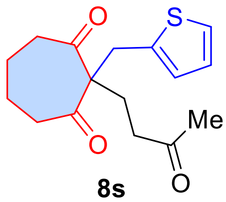
8p

2-(Furan-2-ylmethyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8r): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 78-80 °C. Yield: 92% (51 mg). IR (Neat): ν_{max} 2937, 2359, 2160, 1709, 1696, 1501, 1439, 1324, 1124, 1170, 1012, 925, 738, 530 and 477 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24-7.23 (1H, m), 6.24-6.23 (1H, m), 5.99 (1H, d, J = 3.0 Hz), 3.13 (2H, s), 2.51-2.47 (2H, m), 2.43-2.38 (2H, m), 2.34 (2H, t, J = 7.5 Hz), 2.10 (3H, s, CH_3), 2.04 (2H, t, J = 4.0 Hz), 1.88-1.83 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.2 (2 x C, 2 x C=O), 207.0 (C, C=O), 149.9 (C), 141.9 (CH), 110.4 (CH), 108.4 (CH), 67.2 (C), 41.7 (2 x CH_2), 37.4 (CH_2), 30.0 (CH_3), 29.4 (CH_2), 28.0 (2 x CH_2), 24.2 (CH_2). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}O_4Na$ 299.1259; Found 299.1261.



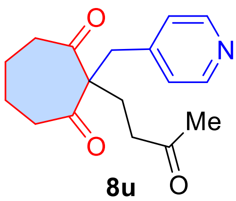
8r

2-(3-oxobutyl)-2-(thiophen-2-ylmethyl)cycloheptane-1,3-dione (8s): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as off-white solid. Mp.: 77-79 °C. Yield: 75% (44 mg). IR (Neat): ν_{max} 2969, 1738, 1367, 1216, 1119, 896, 722 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13 (1H, dd, J = 5.2, 1.5 Hz), 6.88 (1H, dd, J = 5.2, 3.0 Hz), 6.66 (1H, br d, J = 3.5 Hz), 3.31 (2H, s), 2.49-2.45 (2H, m), 2.38-2.33 (4H, m), 2.12 (2H, t, J = 8.5 Hz), 2.12 (3H, s, CH_3), 1.91-1.82 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 211.4 (2 x C, 2 x C=O), 206.7 (C, C=O), 137.1 (C), 127.3 (CH), 127.0 (CH), 124.8 (CH), 68.5 (C), 42.3 (2 x CH_2), 37.4 (CH_2), 31.3 (CH_2), 30.0 (CH_3), 27.8 (2 x CH_2), 24.7 (CH_2). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}O_3SNa$ 315.1031; Found 315.1033.



8s

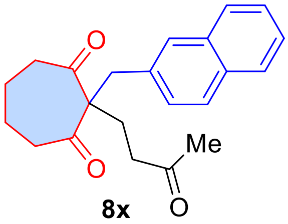
2-(3-Oxobutyl)-2-(pyridin-4-ylmethyl)cycloheptane-1,3-dione (8u): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 83-85 °C. Yield: 91% (52 mg). IR (Neat): ν_{max} 2928, 2857, 1713, 1691, 1600, 1448, 1325, 1168, 1130, 1070, and 518 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.47 (2H, s), 6.94 (2H, d, J = 5.0 Hz), 3.05 (2H, s), 2.47-2.43 (2H, m), 2.35-2.28 (4H, m), 2.11 (3H, s, CH_3), 2.06 (2H, t, J = 7.5 Hz), 1.89-1.77 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 210.6 (2 x C, 2 x C=O), 205.9 (C, C=O), 149.9 (2 x CH), 145.2 (C), 125.3 (2 x CH), 69.0 (C), 42.6 (2 x CH_2), 37.4 (CH_2), 36.8 (CH_2),



8u

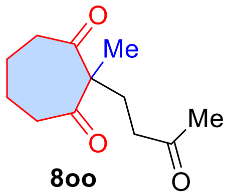
29.8 (CH_3), 27.5 (2 x CH_2), 25.7 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{22}NO_3$ 288.1600; Found 288.1597.

2-(Naphthalen-2-ylmethyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8x): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 79-81 °C. Yield: 85% (57 mg). IR (Neat): ν_{max} 2948, 1713, 1688, 1695, 1454, 1330, 1372, 1264, 1175, 1130, 1070, 956, 895, and 734 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.78-7.76 (1H, m), 7.74 (1H, dd, J = 6.2, 3.0 Hz), 7.70 (1H, d, J = 8.5 Hz), 7.48 (1H, br s), 7.45-7.42 (2H, m), 7.10 (1H, dd, J = 7.5, 2.0 Hz), 3.26 (2H, s), 2.46-2.40 (4H, m), 2.34-2.30 (2H, m), 2.13 (3H, s, CH_3), 2.11-2.08 (2H, m), 1.90-1.75 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.8 (2 x C, 2 x C=O), 206.9 (C, C=O), 133.4 (C), 133.3 (C), 132.3 (C), 128.8 (CH), 128.04 (CH), 128.03 (CH), 127.63 (CH), 127.60 (CH), 126.2 (CH), 125.8 (CH), 69.0 (C), 42.7 (2 x CH_2), 37.5 (CH_2), 37.2 (CH_2), 30.0 (CH_3), 28.0 (2 x CH_2), 25.2 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}O_3$ 337.1804; Found 337.1805.



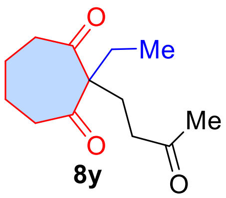
8x

2-Methyl-2-(3-oxobutyl)cycloheptane-1,3-dione (8oo): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 95% (40 mg). IR (Neat): ν_{max} 2937, 2864, 1714, 1690, 1446, 1369, 1324, 1165, 1088, 1054, 950 and 898 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.48-2.39 (4H, m), 2.31 (2H, t, J = 7.5 Hz), 2.09 (3H, s, CH_3), 2.04 (2H, t, J = 7.5 Hz), 1.85 (4H, t, J = 2.5 Hz), 1.15 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 212.3 (2 x C, 2 x C=O), 207.1 (C, C=O), 63.5 (C), 41.3 (2 x CH_2), 37.6 (CH_2), 29.9 (CH_3), 27.9 (2 x CH_2), 26.7 (CH_2), 17.7 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{19}O_3$ 211.1334; Found 211.1337.



8oo

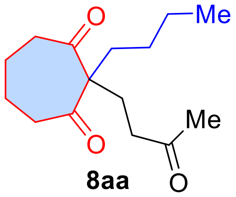
2-Ethyl-2-(3-oxobutyl)cycloheptane-1,3-dione (8y): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 80% (36 mg). IR (Neat): ν_{max} 2969, 1738, 1366, 1216, 1093 and 898 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.46-2.42 (4H, m), 2.22 (2H, t, J = 8.0 Hz), 2.10 (3H, s, CH_3), 2.09-2.05 (2H, m), 1.88-1.85 (4H, m), 1.83-1.79 (2H, m), 0.68 (3H, t, J = 8.0 Hz). ^{13}C NMR



8y

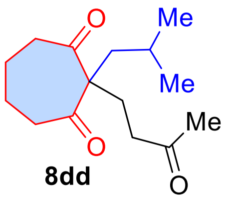
($CDCl_3$, DEPT-135, 100 MHz): δ 211.8 (2 x C, 2 x *C*=O), 206.5 (C, *C*=O), 67.7 (C), 41.8 (2 x CH_2), 37.4 (CH_2), 29.8 (CH_3), 27.8 (2 x CH_2), 23.2 (2 x CH_2), 7.7 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{20}O_3Na$ 247.1310; Found 247.1311.

2-Butyl-2-(3-oxobutyl)cycloheptane-1,3-dione (8aa): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 90% (45 mg). IR (Neat): ν_{max} 2934, 1689, 1446, 1326, 1171, 963 and 727 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.44-2.41 (4H, m), 2.21 (2H, t, J = 7.0 Hz), 2.08 (3H, s, C*H*$_3$), 2.06 (2H, br t, J = 8.5 Hz), 1.87-1.83 (4H, m), 1.75-1.71 (2H, m), 1.30-1.22 (2H, m), 0.95-0.90 (2H, m), 0.85 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 212.4 (2 x C, 2 x *C*=O), 207.1 (C, *C*=O), 67.2 (C), 41.7 (2 x CH_2), 37.3 (CH_2), 30.0 (CH_3), 29.7 (CH_2), 28.1 (2 x CH_2), 25.4 (CH_2), 23.1 (CH_2), 23.0 (CH_2), 12.8 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{25}O_3$ 253.1804; Found 253.1803.



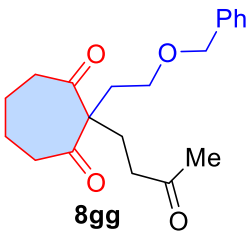
8aa

2-Isobutyl-2-(3-oxobutyl)cycloheptane-1,3-dione (8dd): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 91% (46 mg). IR (Neat): ν_{max} 2942, 1689, 1446, 1322, 1171, 1103, 898 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.46-2.43 (4H, m), 2.23-2.19 (2H, m), 2.15-2.13 (2H, m), 2.10 (3H, s, C*H*$_3$), 1.91-1.83 (4H, m), 1.77 (2H, d, J = 6.2 Hz), 1.50-1.40 (1H, m), 0.82 (6H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 212.4 (2 x C, 2 x *C*=O), 206.6 (C, *C*=O), 67.4 (C), 41.8 (2 x CH_2), 39.3 (CH_2), 37.7 (CH_2), 29.8 (CH_3), 28.2 (2 x CH_2), 24.2 (2 x CH_3), 23.8 (CH), 23.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{25}O_3$ 253.1804; Found 253.1804.



8dd

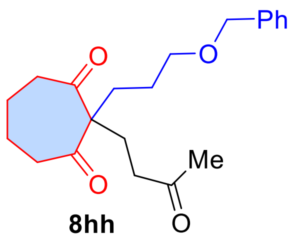
2-(2-(Benzyloxy)ethyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8gg): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as colourless oil. Yield: 90% (59 mg). IR (Neat): ν_{max} 2929, 2860, 2359, 2340, 1715, 1690, 1448, 1364, 1325, 1265, 1089, 1027 and 773 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.31-7.24 (5H, m), 4.32 (2H, s), 3.35 (2H, t, J = 6.0 Hz), 2.41 (4H, t, J = 6.0 Hz), 2.22-2.18 (2H, m), 2.11 (4H, m), 2.05 (3H, s, C*H*$_3$), 1.87-1.78 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.9 (2 x C, 2 x *C*=O), 207.0 (C,



8gg

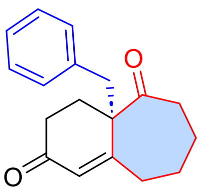
C=O), 137.8 (C), 128.3 (2 x CH), 127.7 (2 x CH), 127.6 (CH), 73.1 (CH_2), 65.7 (C), 65.3 (CH_2), 41.7 (2 x CH_2), 37.5 (CH_2), 30.8 (CH_2), 29.9 (CH_3), 28.1 (2 x CH_2), 23.5 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{26}O_4Na$ 353.1729; Found 353.1731.

2-(3-(Benzyloxy)propyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8hh): Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as colourless oil. Yield: 90% (62 mg). IR (Neat): ν_{max} 2936, 2861, 2355, 2169, 1714, 1688, 1452, 1362, 1326, 1094, 898, 738 and 699 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.27 (5H, m), 4.46 (2H, s), 3.42 (2H, t, J = 6.0 Hz), 2.44 (4H, m), 2.23 (2H, t, J = 8.0 Hz), 2.08 (2H, t, J = 8.0 Hz), 2.06 (3H, s, CH_3), 1.89-1.85 (6H, m), 1.32-1.26 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 212.1 (2 x C, 2 x *C*=O), 207.1 (C, *C*=O), 138.3 (C), 128.3 (2 x CH), 127.5 (3 x CH), 72.9 (CH_2), 69.8 (CH_2), 66.8 (C), 41.6 (2 x CH_2), 37.2 (CH_2), 30.0 (CH_3), 28.0 (2 x CH_2), 26.5 (CH_2), 23.6 (CH_2), 22.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{21}H_{32}NO_4$ 362.2331; Found 362.2336.



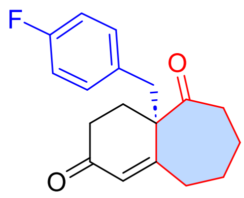
8hh

(*S*)-4a-Benzyl-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-9a]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 96-98 °C. Yield: 93% (25 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak IG column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 15.65 min (major), t_R = 13.41 min (minor); $[\alpha]_D^{25}$ = -178.0° [c = 0.1, $CHCl_3$, >99.9% *ee*]; IR (Neat): ν_{max} 2929, 2859, 1703, 1664, 1616, 1493, 1450, 1333, 1242, 1115, 1080, 867, 730 and 701 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.21-7.19 (3H, m), 7.15-7.13 (2H, m), 6.13 (1H, s, olefinic-*H*), 3.29 (1H, d, J = 13.5 Hz), 3.17 (1H, d, J = 13.5 Hz), 2.70-2.65 (1H, m), 2.40-2.33 (2H, m), 2.23-2.14 (2H, m), 2.06-1.99 (1H, m), 1.96-1.91 (3H, m), 1.53-1.38 (3H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.2 (C, *C*=O), 197.6 (C, *C*=O), 165.1 (C), 137.3 (C), 130.6 (CH), 130.3 (2 x CH), 128.3 (2 x CH), 126.8 (CH), 57.5 (C), 40.5 (CH_2), 39.0 (CH_2), 36.5 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 31.2 (CH_2), 27.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{21}O_2$ 269.1542; Found 269.1542.



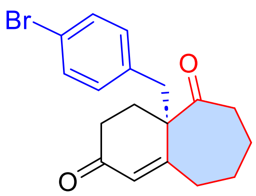
(-)-**9a**

(*S*)-4a-(4-Fluorobenzyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-**9d**]**:** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 75-77 °C. Yield: 91% (26 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 = 16.89 min (major), t_R = 13.91 min (minor); $[\alpha]_D^{25}$ = -170.0° [*c* = 0.1, $CHCl_3$, 92% *ee*]; IR (Neat): ν_{max} 2934, 2861, 1706, 1668, 1616, 1508, 1451, 1358, 1220, 1156, 1120, 1097 and 838 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.16-7.13 (2H, m), 6.96-6.92 (2H, m), 6.17 (1H, s, olefinic-*H*), 3.33 (1H, d, *J* = 13.5 Hz), 3.13 (1H, d, *J* = 13.5 Hz), 2.72-2.66 (1H, m), 2.43-2.39 (1H, m), 2.36-2.32 (2H, m), 2.23-2.13 (2H, m), 1.98-1.92 (3H, m), 1.47 (2H, br t, *J* = 3.0 Hz), 1.30 (1H, dt, *J* = 12.7, 2.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.1 (C, *C*=O), 197.4 (C, *C*=O), 165.2 (C), 161.9 (C, d, *J* = 243.7 Hz, *C*-F), 133.1 (C, d, *J* = 3.7 Hz), 131.8 (2 x CH, d, *J* = 7.5 Hz), 130.6 (CH), 115.2 (2 x CH, d, *J* = 21.2 Hz), 57.5 (C), 40.6 (CH_2), 38.1 (CH_2), 36.8 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 31.3 (CH_2), 27.1 (CH_2). ^{19}F NMR ($CDCl_3$, 375 MHz): δ -115.7. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{20}FO_2$ 287.1447; Found 287.1446.



(-)-**9d**

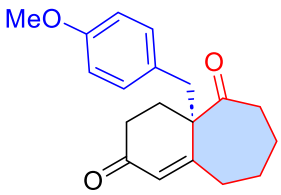
(*S*)-4a-(4-Bromobenzyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-**9f**]**:** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 103-105 °C. Yield: 92% (32 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak IG column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.93 min (major), t_R = 15.78 min (minor); $[\alpha]_D^{25}$ = -150.0° [*c* = 0.1, $CHCl_3$, 91% *ee*]; IR (Neat): ν_{max} 2933, 1706, 1666, 1616, 1487, 1072, and 842 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (2H, td, *J* = 8.0, 1.5 Hz), 7.05 (2H, br d, *J* = 8.0 Hz), 6.14 (1H, s, olefinic-*H*), 3.30 (1H, d, *J* = 13.5 Hz), 3.07 (1H, d, *J* = 13.5 Hz), 2.69-2.64 (1H, m), 2.41-2.27 (3H, m), 2.24-2.18 (2H, m), 1.94-1.90 (3H, m), 1.47-1.43 (2H, m), 1.25 (1H, dt, *J* = 12.5, 2.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 211.0 (C, *C*=O), 197.3 (C, *C*=O), 165.0 (C), 136.4 (C), 132.1 (2 x CH), 131.4 (2 x CH), 130.6 (CH), 120.9 (C), 57.5 (C), 40.5 (CH_2), 38.3 (CH_2), 36.9 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 31.4



(-)-**9f**

(CH_2), 27.1 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{20}BrO_2$ 347.0647; Found 347.0646.

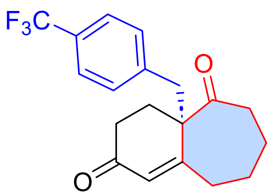
(*S*)-4a-(4-Methoxybenzyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione



(-)-**9k**

[(-)-9k]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 112-114 °C. Yield: 90% (27 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak IC-3 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 41.99 min (major), t_R = 35.45 min (minor); $[\alpha]_D^{25}$ = -159.0° [c = 0.1, $CHCl_3$, 93% *ee*]; IR (Neat): ν_{max} 2926, 2857, 1704, 1665, 1610, 1510, 1449, 1247, 1177, 1032 and 832 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.05 (2H, td, J = 8.5, 2.0 Hz), 6.75 (2H, td, J = 9.0, 2.0 Hz), 6.13 (1H, s, olefinic-*H*), 3.76 (3H, s, OCH_3), 3.24 (1H, d, J = 14.0 Hz), 3.12 (1H, d, J = 14.0 Hz), 2.69-2.64 (1H, m), 2.38-2.31 (2H, m), 2.28-2.23 (1H, m), 2.19-2.04 (2H, m), 1.96-1.89 (3H, m), 1.49-1.39 (3H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 212.0 (C, *C*=O), 198.3 (C, *C*=O), 166.1 (C), 159.1 (C), 131.8 (2 x CH), 131.1 (CH), 129.8 (C), 114.3 (2 x CH), 58.1 (C), 55.7 (CH_3, OCH_3), 41.2 (CH_2), 38.8 (CH_2), 37.2 (CH_2), 33.1 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 27.7 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{23}O_3$ 299.1647; Found: 299.1644.

(*S*)-4a-(4-(Trifluoromethyl)benzyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione

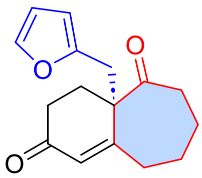


(-)-**9p**

[(-)-9p]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 84-86 °C. Yield: 90% (30 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 = 17.45 min (major), t_R = 21.64 min (minor); $[\alpha]_D^{25}$ = -154.0° [c = 0.1, $CHCl_3$, 96% *ee*]; IR (Neat): ν_{max} 2933, 2863, 1708, 1671, 1617, 1452, 1324, 1162, 1113, 1067 and 860 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.48 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 6.15 (1H, s, olefinic-*H*), 3.41 (1H, d, J = 13.5 Hz), 3.15 (1H, d, J = 13.5 Hz), 2.70-2.65 (1H, m), 2.42-2.38 (2H, m), 2.28-2.20 (3H, m), 1.95-1.92 (3H, m), 1.48-1.43 (2H, m), 1.18 (1H, dt, J = 12.5, 2.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 210.9 (C, *C*=O), 197.1 (C, *C*=O), 164.8 (C), 141.6 (C), 130.8 (2 x CH), 130.7 (CH), 129.2 (C, q, J = 33.0 Hz), 125.2 (2 x CH, q, J = 3.0 Hz), 124.1 (C, q, J =

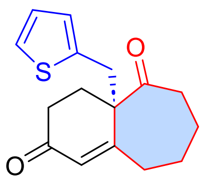
270.0 Hz, CF_3), 57.6 (C), 40.5 (CH_2), 38.7 (CH_2), 36.9 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 27.1 (CH_2). ^{19}F NMR ($CDCl_3$, 375 MHz): δ -62.4. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{20}F_3O_2$ 337.1415; Found 337.1417.

(*S*)-4a-(Furan-2-ylmethyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione


(-)-**9r**

[(-)-9r]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 68-70 °C. Yield: 91% (23 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 = 25.17 min (major), t_R = 30.75 min (minor); $[\alpha]_D^{25}$ = -109.0° [*c* = 0.1, $CHCl_3$, 95% *ee*]; IR (Neat): ν_{max} 2933, 1705, 1668, 1260, 1150, 1009 and 741 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25 (1H, dd, *J* = 2.0, 1.0 Hz), 6.26 (1H, dd, *J* = 3.0, 1.5 Hz), 6.11 (1H, s, olefinic-*H*), 6.08 (1H, d, *J* = 3.0 Hz), 3.27 (1H, d, *J* = 15.0 Hz), 3.18 (1H, d, *J* = 15.0 Hz), 2.69-2.64 (1H, m), 2.48-2.45 (1H, m), 2.40-2.37 (1H, m), 2.33-2.29 (1H, m), 2.20-2.08 (2H, m), 2.07-1.90 (4H, m), 1.58-1.55 (1H, m), 1.51-1.48 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.1 (C, *C*=O), 197.6 (C, *C*=O), 164.6 (C), 151.3 (C), 141.4 (CH), 130.3 (CH), 110.8 (CH), 108.9 (CH), 56.4 (C), 40.6 (CH_2), 35.5 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 31.5 (CH_2), 31.0 (CH_2), 27.1 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{19}O_3$ 259.1334; Found 259.1336.

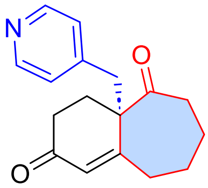
(*S*)-4a-(Thiophene-2-ylmethyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione


(-)-**9s**

[(-)-9s]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 79-81 °C. Yield: 88% (24 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 = 25.72 min (major), t_R = 33.03 min (minor); $[\alpha]_D^{25}$ = -171.0° [*c* = 0.1, $CHCl_3$, 92% *ee*]; IR (Neat): ν_{max} 2925, 2856, 1704, 1664, 1616, 1448, 1537, 1232, 1119, 1079, 867, 707 and 551 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.14 (1H, dd, *J* = 5.5, 1.5 Hz), 6.88 (1H, dd, *J* = 5.0, 3.5 Hz), 6.80 (1H, br d, *J* = 3.5 Hz), 6.14 (1H, s, olefinic-*H*), 3.42 (2H, br s), 2.70-2.64 (1H, m), 2.44-2.33 (3H, m), 2.31-2.17 (2H, m), 2.00-1.91 (3H, m), 1.56-1.46 (3H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 211.4 (C, *C*=O), 197.5 (C, *C*=O), 165.2 (C), 139.1 (C), 130.5 (CH), 127.6 (CH), 126.7 (CH), 125.2 (CH), 57.4 (C), 40.7

(CH_2), 36.3 (CH_2), 33.9 (CH_2), 32.6 (CH_2), 31.6 (CH_2), 31.1 (CH_2), 27.0 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{16}H_{18}O_2SNa$ 297.0925; Found 297.0925.

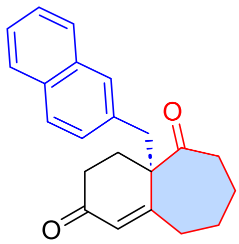
(*S*)-4a-(Pyridin-4-ylmethyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione



(-)-**9u**

[(-)-9u]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as yellow oil. Yield: 92% (25 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak IG column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 39.09 min (major), t_R = 35.75 min (minor); $[\alpha]_D^{25}$ = -137.0° [*c* = 0.1, $CHCl_3$, 93% *ee*]; IR (Neat): ν_{max} 2931, 2860, 1705, 1664, 1600, 1416, 1360, 1224, 1122, and 826 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.46 (2H, d, *J* = 6.0 Hz), 7.14 (2H, d, *J* = 6.0 Hz), 6.15 (1H, s, olefinic-*H*), 3.35 (1H, d, *J* =13.5 Hz), 3.05 (1H, d, *J* = 13.5 Hz), 2.69-2.64 (1H, m), 2.42-2.38 (2H, m), 2.30-2.25 (3H, m), 1.94-1.90 (3H, m), 1.47-1.42 (2H, m), 1.20-1.15 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 210.7 (C, *C*=O), 196.9 (C, *C*=O), 164.4 (C), 149.7 (2 x CH), 146.7 (C), 130.7 (CH), 125.8 (2 x CH), 57.5 (C), 40.4 (CH_2), 38.3 (CH_2), 37.0 (CH_2), 32.5 (CH_2), 31.53 (CH_2), 31.50 (CH_2), 27.1 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{20}NO_2$ 270.1494; Found 270.1493.

(*S*)-4a-(Naphthalen-2-ylmethyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione

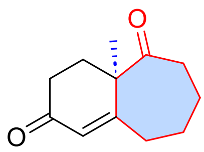


(-)-**9x**

[(-)-9x]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as white solid. Mp.: 125-127 °C. Yield: 92% (29 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak IG column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.00 min (major), t_R = 18.26 min (minor); $[\alpha]_D^{25}$ = -288.0° [*c* = 0.1, $CHCl_3$, 91% *ee*]; IR (Neat): ν_{max} 2924, 2854, 1705, 1668, 1617, 1450, 1151, 1120, and 754 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79-7.74 (2H, m), 7.70 (1H, d, *J* = 8.5 Hz), 7.64 (1H, s), 7.47-7.41 (2H, m), 7.29 (1H, dd, *J* = 6.5, 2.0 Hz), 6.16 (1H, s, olefinic-*H*), 3.53 (1H, d, *J* = 13.5 Hz), 3.30 (1H, d, *J* = 13.5 Hz), 2.71-2.66 (1H, m), 2.43-2.39 (1H, m), 2.33-2.18 (4H, m), 2.02-1.99 (1H, m), 1.93-1.87 (2H, m), 1.51-1.39 (2H, m), 1.30 (1H, td, *J* = 10.0, 2.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 211.3 (C, *C*=O), 197.6 (C, *C*=O), 165.6 (C), 135.0 (C), 133.3 (C), 132.2 (C), 130.6 (CH), 129.0 (CH), 128.6 (CH), 127.82 (CH), 127.62 (CH), 127.58 (CH), 126.1 (CH), 125.7 (CH), 57.8

(C), 40.6 (CH_2), 39.1 (CH_2), 36.8 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 31.5 (CH_2), 27.1 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{22}H_{23}O_2$ 319.1698; Found 319.1694.

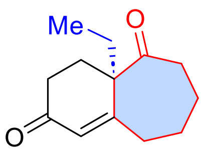
(*R*)-4a-Methyl-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-9oo]:



(-)-**9oo**

Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 90% (17 mg). The enantiomeric excess (*ee*) was determined by chira stationary phase HPLC using a Daicel chiralpak ID column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.78 min (major), t_R = 14.48 min (minor); $[\alpha]_D^{25}$ = -3.4° [*c* = 0.1, $CHCl_3$, 59% *ee*]; IR (Neat): ν_{max} 2931, 1706, 1668, 1448, 1333, 1234, 1155 and 865 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.02 (1H, s, olefinic-*H*), 2.70-2.64 (1H, m), 2.57-2.43 (3H, m), 2.37-2.33 (1H, m), 2.20 (1H, dt, *J* = 13.5, 5.5 Hz), 2.10-2.03 (1H, m), 2.00-1.89 (2H, m), 1.75 (1H, qd, *J* = 13.2, 3.0 Hz), 1.60-1.52 (2H, m), 1.35 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 212.8 (C, *C*=O), 197.7 (C, *C*=O), 167.1 (C), 128.6 (CH), 52.7 (C), 40.3 (CH_2), 35.2 (CH_2), 32.7 (CH_2), 32.3 (CH_2), 31.2 (CH_2), 27.4 (CH_2), 18.9 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{12}H_{17}O_2$ 193.1229; Found 193.1230.

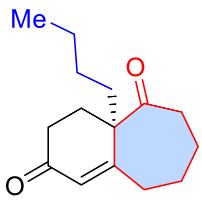
(*R*)-4a-Ethyl-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-9y]:



(-)-**9y**

Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 90% (19 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 = 24.10 min (major), t_R = 29.61 min (minor); $[\alpha]_D^{25}$ = -42.0° [*c* = 0.1, $CHCl_3$, 88% *ee*]; IR (Neat): ν_{max} 2928, 1738, 1671, 1365, 1216 and 864 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.09 (1H, s, olefinic-*H*), 2.63 (1H, dt, *J* = 12.5, 2.5 Hz), 2.56-2.52 (1H, m), 2.51-2.46 (1H, m), 2.43-2.37 (2H, m), 2.26-2.20 (1H, m), 2.12-2.04 (2H, m), 1.98-1.92 (3H, m), 1.85-1.79 (1H, m), 1.64-1.53 (2H, m), 0.98 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 212.5 (C, *C*=O), 198.0 (C, *C*=O), 166.7 (C), 129.6 (CH), 55.9 (C), 41.6 (CH_2), 36.0 (CH_2), 33.4 (CH_2), 31.6 (CH_2), 30.5 (CH_2), 27.8 (CH_2), 26.8 (CH_2), 10.1 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{19}O_2$ 207.1385; Found 207.1385.

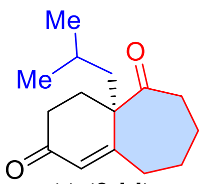
(*R*)-4a-Butyl-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-9aa]:



(-)-(**9aa**)

Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 90% (21 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 = 19.45 min (major), t_R = 23.45 min (minor); $[\alpha]_D^{25}$ = -63.0º [*c* = 0.1, $CHCl_3$, 86% *ee*]; IR (Neat): ν_{max} 2931, 2861, 1667, 1450, 1616, 1333, 1152, 864 and 729 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.07 (1H, s, olefinic-*H*), 2.62 (1H, dt, *J* = 12.5, 2.5 Hz), 2.54-2.46 (2H, m), 2.42-2.35 (2H, m), 2.25-2.18 (1H, m), 2.11-2.02 (2H, m), 1.96-1.83 (3H, m), 1.75-1.69 (1H, m), 1.64-1.51 (2H, m), 1.41-1.19 (4H, m), 0.89 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 212.5 (C, *C*=O), 198.0 (C, *C*=O), 166.9 (C), 129.4 (CH), 55.8 (C), 41.5 (CH_2), 36.0 (CH_2), 34.8 (CH_2), 33.4 (CH_2), 31.6 (CH_2), 30.9 (CH_2), 27.7 (CH_2), 26.8 (CH_2), 23.5 (CH_2), 13.9 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{23}O_2$ 235.1698; Found 235.1693.

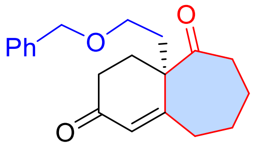
(*S*)-4a-Isobutyl-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-9dd]:



(-)-(**9dd**)

Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 90% (21 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 = 17.63 min (major), t_R = 22.27 min (minor); $[\alpha]_D^{25}$ = -49.0º [*c* = 0.1, $CHCl_3$, 71% *ee*]; IR (Neat): ν_{max} 2931, 2864, 1668, 1614, 1449, 1334, 1257, 1152, 1081, 916 and 867 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.09 (1H, s, olefinic-*H*), 2.63 (1H, dt, *J* = 12.2, 2.5 Hz), 2.57-2.50 (2H, m), 2.44-2.35 (2H, m), 2.25-2.18 (1H, m), 2.12-2.07 (2H, m), 1.96-1.88 (2H, m), 1.81-1.71 (3H, m), 1.63-1.51 (2H, m), 0.92 (3H, d, *J* = 6.0 Hz), 0.91 (3H, d, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 212.2 (C, *C*=O), 198.0 (C, *C*=O), 167.0 (C), 129.8 (CH), 56.2 (C), 43.3 (CH_2), 41.2 (CH_2), 36.4 (CH_2), 33.4 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 26.7 (CH_2), 25.0 (CH), 24.9 (CH_3), 24.6 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{23}O_2$ 235.1698; Found 235.1696.

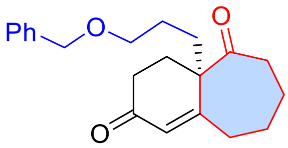
(*S*)-4a-(2-(Benzyloxy)ethyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione



(-)-(**9gg**)

[(-)-9gg]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as colourless oil. Yield: 85% (27 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak IG column (hexane/2-propanol = 93:7, flow rate 0.7 mL/min, λ = 254 nm), t_R = 44.28 min (major), t_R = 47.55 min (minor); $[\alpha]_D^{25}$ = -72.0º [*c* = 0.1, $CHCl_3$, 87% *ee*]; IR (Neat): ν_{max} 3024, 2930, 2859, 1738, 1668, 1365, 1216, 1093 and 739 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.29 (2H, m), 7.25-7.24 (3H, m), 6.04 (1H, s, olefinic-*H*), 4.43 (2H, ABq, *J* = 12.0 Hz, OCH_2Ph), 3.65-3.57 (2H, m), 2.66-2.60 (2H, m), 2.50-2.47 (1H, m), 2.42-2.32 (2H, m), 2.24-2.15 (2H, m), 2.07-2.02 (2H, m), 1.96-1.89 (3H, m), 1.62-1.45 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 212.4 (C, *C*=O), 197.9 (C, *C*=O), 166.1 (C), 138.0 (C), 129.5 (CH), 128.3 (2 x CH), 127.6 (CH), 127.5 (2 x CH), 73.0 (CH_2), 67.1 (CH_2), 54.9 (C), 40.8 (CH_2), 35.9 (CH_2), 34.0 (CH_2), 33.1 (CH_2), 31.5 (CH_2), 30.6 (CH_2), 27.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{24}O_3Na$ 335.1623; Found 335.1618.

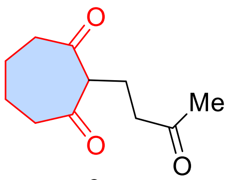
(*R*)-4a-(3-(Benzyloxy)propyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione



(-)-(**9hh**)

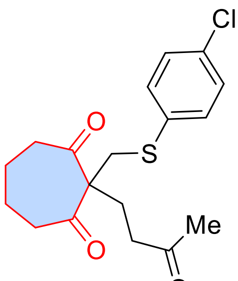
[(-)-9hh]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as colourless oil. Yield: 86% (28 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak IG column (hexane/2-propanol = 93:7, flow rate 0.7 mL/min, λ = 254 nm), t_R = 42.77 min (major), t_R = 41.32 min (minor); $[\alpha]_D^{25}$ = -56.0º [*c* = 0.1, $CHCl_3$, 82% *ee*]; IR (Neat): ν_{max} 2935, 2858, 1738, 1450, 1667, 1364, 1228, 1098 739 and 698 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.30 (4H, m), 7.29-7.27 (1H, m), 6.07 (1H, s, olefinic-*H*), 4.50 (2H, s, OCH_2Ph), 3.49-3.46 (2H, m), 2.63 (1H, dt, *J* = 12.0, 2.5 Hz), 2.53-2.47 (2H, m), 2.43-2.37 (2H, m), 2.27-2.21 (1H, m), 2.10-2.02 (2H, m), 1.97-1.91 (3H, m), 1.83 (1H, dt, *J* = 13.2, 3.5 Hz), 1.79-1.73 (1H, m), 1.67-1.51 (3H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 212.4 (C, *C*=O), 197.9 (C, *C*=O), 166.5 (C), 138.3 (C), 129.6 (CH), 128.3 (2 x CH), 127.6 (2 x CH), 127.5 (CH), 72.9 (CH_2), 70.4 (CH_2), 55.4 (C), 41.4 (CH_2), 36.0 (CH_2), 33.3 (CH_2), 31.6 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 26.8 (CH_2), 25.9 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{27}O_3$ 327.1960; Found 327.1965.

2-(3-Oxobutyl)cycloheptane-1,3-dione (6pp): Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane (2.5:7.5 to 2.8:7.2) and isolated as colourless oil. Yield: 45% (35 mg); IR (Neat): ν_{max} 2937, 2176, 1711, 1691, 1443, 1164 and 909 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.81 (1H, t, J = 7.0 Hz), 2.59-2.54 (2H, m), 2.51-2.46 (2H, m), 2.44 (2H, t, J =7.0 Hz), 2.11 (3H, s, CH_3), 2.06-2.02 (4H, m), 1.89-1.81 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 208.2 (C, C=O), 206.9 (2 x C, 2 x C=O), 65.3 (CH), 43.9 (2 x CH_2), 40.2 (CH_2), 29.9 (CH_3), 25.5 (2 x CH_2), 20.1 (CH_2). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{17}O_3$ 197.1178; Found 197.1173.



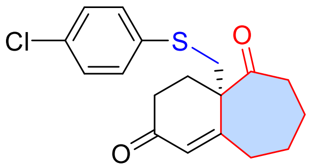
6pp

2-(((4-Chlorophenyl)thio)methyl)-2-(3-oxobutyl)cycloheptane-1,3-dione (8pp): Prepared by following the procedure **H** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as yellow oil. Yield: 82% (58 mg); IR (Neat): ν_{max} 2929, 2147, 1715, 1692, 1475, 1446, 1092, 1010, 817 and 739 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28-7.26 (2H, m), 7.26-7.24 (2H, m), 3.33 (2H, s), 2.40-2.36 (4H, m), 2.24 (4H, s), 2.08 (3H, s, CH_3), 1.89-1.80 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 210.4 (2 x C, 2 x C=O), 206.6 (C, C=O), 133.9 (C), 133.1 (C), 132.1 (2 x CH), 129.1 (2 x CH), 67.1 (C), 41.6 (2 x CH_2), 37.1 (CH_2), 36.1 (CH_2), 29.9 (CH_3), 28.1 (2 x CH_2), 23.6 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}ClO_3S$ 353.0978; Found 353.0981.



8pp

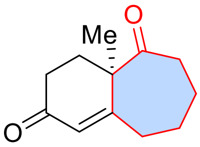
(*S*)-4a-(((4-Chlorophenyl)thio)methyl)-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-9pp]: Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as yellow oil. Yield: 91% (35 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak IG column (hexane/2-propanol = 93:7, flow rate 0.7 mL/min, λ = 254 nm), t_R = 51.79 min (major), t_R = 57.50 min (minor); $[\alpha]_D^{25}$ = -142.0^o [c = 0.1, $CHCl_3$, 93% *ee*]; IR (Neat): ν_{max} 2928, 2856, 2358, 1706, 1668, 1475, 1449, 1274, 1260, 1151, 1094, 817 and 750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (2H, m), 7.23 (2H, m), 6.11 (1H, s, olefinic-H), 3.49 (1H, d, J =13.5 Hz), 3.22 (1H, d, J



(-)-(9pp)

= 13.5 Hz), 2.66 (1H, dt, J = 12.2, 2.5 Hz), 2.60-2.52 (1H, m), 2.45-2.36 (3H, m), 2.28-2.24 (2H, m), 2.09-2.06 (1H, m), 2.03-1.96 (2H, m), 1.65-1.48 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 211.3 (C, C=O), 197.2 (C, C=O), 163.4 (C), 135.5 (C), 132.8 (C), 131.5 (2 x CH), 130.9 (CH), 129.2 (2 x CH), 56.4 (C), 40.7 (CH_2), 40.2 (CH_2), 35.7 (CH_2), 33.2 (CH_2), 31.5 (CH_2), 30.7 (CH_2), 27.2 (CH_2). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}ClO_2S$ 335.0873; Found 335.0874.

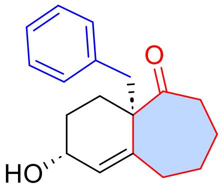
(*R*)-4a-methyl-4,4a,6,7,8,9-hexahydro-2*H*-benzo[7]annulene-2,5(3*H*)-dione [(-)-9oo]:



(-)-(**9oo**)

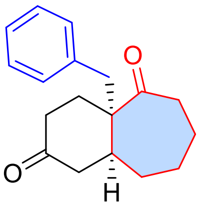
Prepared by following the procedure **I** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.6:8.4) and isolated as colourless oil. Yield: 80% (31 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak ID column (hexane/2-propanol = 90:10, flow rate 0.7 mL/min, λ = 254 nm), t_R = 14.36 min (major), t_R = 16.43 min (minor); $[\alpha]_D^{25}$ = -30.0º [c = 0.1, $CHCl_3$, 92% *ee*].

(2*R*,4a*S*)-4a-Benzyl-2-hydroxy-2,3,4,4a,6,7,8,9-octahydro-5*H*-benzo[7]annulen-5-one [(-)-11a]:



(-)-**11a**

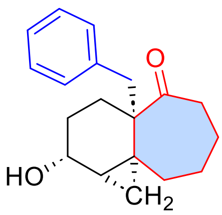
Prepared by following the procedure **J** and purified by column chromatography using EtOAc/hexane (1.7:8.3 to 2.0:8.0) and isolated as colourless oil. Yield: 80% (22 mg); $[\alpha]_D^{25}$ = -67.0º [c = 0.1, $CHCl_3$, >99% *ee*, >20:1 *dr*]; IR (Neat): ν_{max} 3360, 2930, 1703, 1695, 1616, 1448, 1450, 1009, 729 and 701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24-7.22 (2H, m), 7.20-7.19 (1H, m), 7.17-7.15 (2H, m), 5.84 (1H, d, J = 2.5 Hz, olefinic-H), 4.14-4.11 (1H, m), 3.15 (1H, d, J = 13.5 Hz), 3.08 (1H, d, J = 14.0 Hz), 2.70-2.64 (1H, m), 2.31-2.23 (2H, m), 1.91-1.88 (2H, m), 1.78-1.73 (1H, m), 1.68-1.61 (2H, m), 1.53-1.40 (4H, m), 1.01-0.94 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 214.3 (C, C=O), 141.4 (C), 138.6 (C), 132.1 (CH), 130.6 (2 x CH), 127.9 (2 x CH), 126.4 (CH), 66.7 (CH), 56.2 (C), 40.7 (CH_2), 40.1 (CH_2), 34.8 (CH_2), 32.5 (CH_2), 30.0 (CH_2), 27.7 (CH_2), 26.8 (CH_2). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}O_2$ 271.1696; Found 271.1698.



(+)-**12a**

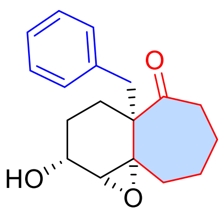
(4a*S*,9a*S*)-4a-Benzyloctahydro-1*H*-benzo[7]annulene-2,5-dione [(+)-12a]: Prepared by following the procedure **K** and purified by column chromatography using EtOAc/hexane (0.5:9.5 to 0.6:9.4) and isolated as colourless oil. Yield: 75% (20 mg); $[\alpha]_D^{25}$ = +42.0º [c = 0.1, $CHCl_3$, >99% *ee* and >30:1 *dr*]; IR (Neat): ν_{max} 2924, 2855, 1699, 1451, 1318, 1175, 1071, 961, 770, 731, 701 and 541 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.23 (3H, m), 7.06-7.04 (2H, m), 3.24 (1H, d, J = 14.0 Hz), 3.07 (1H, d, J = 14.0 Hz), 2.96 (1H, dd, J = 14.5, 6.0 Hz), 2.55-2.44 (3H, m), 2.34-2.29 (1H, m), 2.27-2.23 (2H, m), 2.10-2.04 (1H, m), 2.00-1.93 (1H, m), 1.86-1.83 (1H, m), 1.83-1.77 (1H, m), 1.72-1.68 (1H, m), 1.44-1.38 (2H, m) 1.35-1.25 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 215.5 (C, *C*=O), 211.0 (C, *C*=O), 136.1 (C), 129.6 (2 x CH), 128.4 (2 x CH), 127.1 (CH), 55.9 (C), 45.6 (CH_2), 42.03 (CH_2), 41.99 (CH), 41.7 (CH_2), 37.1 (CH_2), 33.0 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 27.1 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{23}O_2$ 271.1698; Found 271.1694.

(1a*S*,2*R*,4a*S*,9a*R*)-4a-Benzyl-2-hydroxydecahydro-5*H*-cyclopropa[1,6]benzo[1,2][7]annulen-5-one [**(-)-13a**]**:** Prepared by following the procedure **L** and purified by column chromatography using EtOAc/hexane (1.7:8.3 to 2.0:8.0) and isolated as colourless oil. Yield: 60% (17 mg); $[\alpha]_D^{25}$ = -59.0° [*c* = 0.1, $CHCl_3$, >99% *ee* and >30:1 *dr*]; IR (Neat): ν_{max} 3432, 2925, 1697, 1452, 1026, 701 and 586 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.38 (2H, d, J = 7.5 Hz), 7.24-7.17 (3H, m), 4.33-4.29 (1H, m), 3.32 (1H, d, J = 13.0 Hz), 2.71-2.65 (2H, m), 2.50-2.47 (1H, m), 1.85-1.80 (1H, m), 1.71-1.63 (1H, m), 1.62 (1H, br s), 1.51-1.45 (2H, m), 1.40-1.33 (3H, m), 1.31-1.28 (2H, m), 1.22-1.16 (1H, m), 0.93 (1H, t, J = 5.0 Hz), 0.60-0.56 (1H, m), 0.39 (1H, dd, J = 8.7, 5.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 214.7 (C, *C*=O), 139.0 (C), 131.5 (2 x CH), 127.7 (2 x CH), 126.0 (CH), 66.6 (CH), 53.8 (C), 42.5 (CH_2), 41.1 (CH_2), 39.3 (CH_2), 31.7 (CH_2), 28.0 (CH_2), 26.5 (CH_2), 26.48 (C), 26.1 (CH_2), 24.5 (CH), 18.0 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{24}NaO_2$ 307.1674; Found 307.1671.



(-)-**13a**

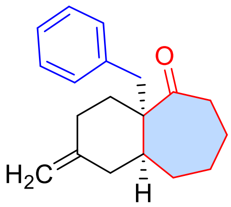
(1a*R*,2*R*,4a*S*,9a*S*)-4a-Benzyl-2-hydroxyoctahydrocyclohepta[1,6]benzo[1,2-b]oxiren-5(1a*H*)-one [**(-)-14a**]**:** Prepared by following the procedure **M** and purified by column chromatography using EtOAc/hexane (1.6:8.4 to 1.7:8.3) and isolated as colourless oil. Yield: 72% (21 mg); $[\alpha]_D^{25}$ = -7.9° [*c* = 0.1, $CHCl_3$, >99% *ee* and >30:1 *dr*]; IR (Neat): ν_{max} 3385, 2932, 1702, 1450, 1616, 1012, 873, 702 and 571 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (2H, br d, J = 7.0 Hz), 7.25-7.22 (2H, m), 7.19-7.17 (1H, m), 4.13 (1H, dd, J = 10.0, 5.5 Hz), 3.27 (1H, d, J = 13.0 Hz), 3.17 (1H, s), 2.89 (1H, d, J = 13.5 Hz), 2.61-2.56 (1H, m), 2.48-2.46 (1H, m), 1.86-1.84 (1H, m), 1.77-1.60 (4H, m), 1.51 (1H, dt, J = 13.5, 3.5 Hz), 1.39-1.30 (3H, m), 0.96-0.91 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 211.4



(-)-(**14a**)

(C, *C*=O), 138.4 (C), 131.7 (2 x CH), 127.8 (2 x CH), 126.2 (CH), 68.8 (CH), 66.1 (C), 61.5 (CH), 55.7 (C), 42.0 (CH_2), 38.3 (CH_2), 37.9 (CH_2), 32.2 (CH_2), 28.2 (CH_2), 26.8 (CH_2), 25.1 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{23}O_3$ 287.1647; Found 287.1648.

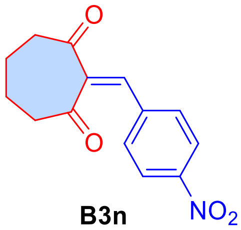
(4a*S*,9a*S*)-4a-Benzyl-2-methylenedecahydro-5*H*-benzo[7]annulen-5-one [(+)-15a]:



(+)-**15a**

Prepared by following the procedure **N** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.2:8.8) and isolated as colourless oil. Yield: 85% (23 mg); $[\alpha]_D^{25}$ = +5.9° [*c* = 0.1, $CHCl_3$, >99% *ee* and >30:1 *dr*]; IR (Neat): ν_{max} 2925, 2360, 1695, 1450, 1132, 884, 726, 699 and 564 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.20 (3H, m), 7.02-7.01 (2H, m), 4.68 (1H, br d, *J* = 1.5 Hz, olefinic-*H*), 4.62 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 3.06 (1H, d, *J* = 13.5 Hz), 3.00 (1H, d, *J* = 13.5 Hz), 2.80 (1H, br td, *J* = 13.5, 2.0 Hz), 2.42-2.37 (1H, m), 2.33-2.26 (1H, m), 2.24-2.19 (1H, m), 2.16-2.10 (2H, m), 2.06 (1H, td, *J* = 13.5, 2.0 Hz), 1.85-1.74 (3H, m), 1.55-1.49 (2H, m), 1.40-1.33 (2H, m), 1.28-1.22 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 217.5 (C, *C*=O), 145.3 (C), 137.1 (C), 129.8 (2 x CH), 128.2 (2 x CH), 126.6 (CH), 108.3 (CH_2), 54.3 (C), 41.3 (CH_2), 41.2 (CH_2), 40.6 (CH), 39.3 (CH_2), 33.0 (CH_2), 30.4 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 27.9 (CH_2). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{25}O$ 269.1905; Found 269.1896.

2-(4-nitrobenzylidene)cycloheptane-1,3-dione (5n): The title compound was prepared



B3n

following the procedure **O** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.2 : 8.8), and isolated as a white solid. Mp.: 125-127 °C. Yield: 82% (63.7 mg). IR (Neat): ν_{max} 2958, 1700, 1677, 1512, 1340, 1258, 1103, 1009, 797, 695 and 501 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.19 (2H, td, *J* = 8.5, 2.5 Hz), 7.62 (1H, s, olefinic-*H*), 7.59 (2H, td, *J* = 8.5, 2.5 Hz), 2.80-2.77 (2H, m), 2.68-2.65 (2H, m), 2.08-2.00 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 207.8 (C, *C*=O), 195.7 (C, *C*=O), 148.4 (C), 143.4 (C), 139.4 (C), 137.7 (CH), 130.9 (2 x CH), 123.8 (2 x CH), 43.9 (CH_2), 41.7 (CH_2), 24.8 (CH_2), 24.5 (CH_2). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}NO_4$ 260.0923; Found 260.0921.

5.5 References

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❖ The research work described in this thesis has been included in the following publications:

1. Organocatalytic Asymmetric Formal [3+3]-Cycloaddition to Access 2,3-Diazaspiro[4.5]deca-3,6-dien-1-ones. A. V. Krishna, G. S. Reddy, B. Gorachand, D. B. Ramachary*, *Eur. J. Org. Chem*. **2020**, *2020*, 6623-6628.
2. The seven-step, one-pot regioselective synthesis of biologically important 3-aryllawsones: scope and applications. A. V. Krishna, D. B. Ramachary*, *Org. Biomol. Chem*. **2022**, *20*, 3948-3954.
3. Conformation-Controlled Catalytic Asymmetric Synthesis of Swaminathan Ketones. A. V. Krishna, S. D. Sanwal, S. Rath, P. R. Lakshmi, D. B. Ramachary* (Manuscript submitted).

❖ Other publications as a co-author during the PhD tenure:

1. Catalytic [3 + 3]-Cycloaddition for Regioselective Preparation of Tricyclic Oxadiazines. T. P. Reddy, A. V. Krishna, D. B. Ramachary*, *Org. Lett.* **2018**, *20*, 6979-6983.
2. Organocatalytic Reductive Propargylation: Scope and Applications. M. A. Pasha, A. V. Krishna, E. Ashok, D. B. Ramachary*, *J. Org. Chem.* **2019**, *84*, 15399-15416.
3. Direct Organocatalytic Reductive Alkylation of Syncarpic Acid: Scope and Applications. P. Roy, A. V. Krishna, D. B. Ramachary*, *J. Org. Chem.* **2022**, *87*, 16026-16038.

❖ Presentations and conferences attended:

1. "**Best Oral Presentation Award**" in ChemFest 2022. (National Level) (Sponsered by Royal Society of Chemistry). Title of the talk: *Organocatalytic Asymmetric Synthesis of Biologically Important Chiral Molecules.*
2. Poster Presentation in **CHEMFEST 2022** with the title "Organocatalytic Asymmetric Synthesis of Biologically Important Chiral Molecules" organized by the School of Chemistry, University of Hyderabad.
3. "**Best Oral Presentation Award**" in International Conference on Chemistry and Allied Sciences (**ICCAS-2022**) (International Level) (Sponsered by DST-SERB, CSIR and TSCHE). Title of the talk: *Organocatalytic Asymmetric Synthesis of Biologically important Functionally Rich 2,3-Diazasopiro[4.5]deca-3,6-dien-1-ones and 3-Aryllawsones*.
4. Attended Nobel Symposium 2021 organized by the University of Hyderabad.
5. Attended CHEMFEST 2018, 2019, 2021, 2022 and 2023 organized by the School of Chemistry, University of Hyderabad.
6. Attended Prof. A. Srikrishna memorial Lecture Series in 2019, 2021 and 2023 at the University of Hyderabad.

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