Discovery of Parts-per-Million Level, Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules

A

Thesis

Submitted for the Degree of

Doctor of Philosophy

By

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November 2023

Dedicated to……..

My father **Etikala Rajaiah**

and mother **Etikala Rama**

&

All the Teachers in my life

DECLARATION

I hereby declare that the matter embodied in the thesis entitled "*Discovery of Parts-per-Million Level, 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 "*Discovery of Parts-per-Million Level, Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules*" has been carried out by Mr. Etikala Ashok 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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CONTENTS

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PREFACE

Organocatalysis commenced over the past two decades and numerous approaches have been developed to make organocatalysis a reliable replacement for stoichiometric procedures and non-catalytic reactions. This prevalence of asymmetric organocatalysis is brought about by the accessibility and extensive use of diverse activation modalities. Chiral organic molecules effectiveness as catalysts can be linked to a number of factors, including their simple availability from natural resources and comparative cost to metal or enzyme catalysis. Many factors, including the ease with which chiral organic molecules can be obtained from natural resources and their comparative affordability to metal or enzyme catalysis, contribute to the effectiveness of using them as catalysts. In recognition, David MacMillan and Benjamin List shared the 2021 Nobel Prize for their enormous contribution in asymmetric organocatalysis. In spite of these advantages there are some problems that we need to overcome using excess amount of catalyst loading in the range of 5-30 mol% of catalyst, this inefficiency is one of the major disadvantages of organocatalysis compared to transition metal or enzyme catalysis.

As of today, very few publications are listed on ppm level. The development of organocatalytic reactions with an extremely low catalyst loading, such as ppm or ppb level is highly desirable. Thus, organocatalytic asymmetric reactions with low catalyst loading are in urgent demand. The present thesis entitled "***Discovery of Parts-per-Million Level, Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules***" is an honest attempt to develop a novel strategies to synthesize bicyclo[3.2.1]octanes using organocatalysis. A large library of methanobenzo[7]annulens have been synthesized using these protocols which opens up large prospects for their further biological or material studies. 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.

The first chapter illustrates a synthetic methodology for the preparation of chiral methanobenzo[7]annulenes. In this protocol, 3-alkyllawsones are selectively reacted with α-alkylnitroethylenes under 500 parts-per-million (ppm) quinine-*NH*-thiourea-catalysis to furnish the chiral methanobenzo[7]annulenes in up to >99% *ee* with >20:1 *dr* and up to 1820 TONs through tandem Michael/Henry [3+2]-annulations. These asymmetric ppm-level, catalytic tandem [3+2]-annulations would be highly inspirational to design many more ppm-

level organocatalytic reactions, and at the same time these final molecules are basic skeletons of antibiotics.

In the second chapter, we described the synthesis of bicyclo[3.2.1]octanes in very good yields with excellent enantio and diastereoselectivities through organaocatalytic formal [3+2] cycloaddition from hydroxy-*p*-quinone and nitroethylene. The bicyclo[3.2.1]octane unit is present in both natural and synthetic compounds which possess various biological activities. These bicyclo[3.2.1]octane core moiety acts as a reactive intermediate in various stereoselective synthetic transformations. These systems form a fundamental building block for biologically significant active molecules such as sesquiterpenoids, lignans, and alkaloids. Some of them include enaimeone, liliflodione and vitisinol D which have antibacterial activity and antithrombic activity highlighting the importance of chiral bicyclo[3.2.1]octane core moiety.

In the third chapter, we developed an unprecedented protocol to synthesize natural products such as embelin, rapanone, irisoquins from three-component reductive alkylation method in excellent yields. These natural products exhibit various biological activities and pharmacological effects including antihelmintic, analgesic, antifertility, antitumor and antioxidant properties.

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	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

Discovery of Parts-per-Million Level, Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug-Like Molecules

1. Abstract:

The first chapter illustrates a synthetic methodology for the preparation of chiral methanobenzo[7]annulenes. In this protocol, 3-alkyllawsones are selectively reacted with *α*-alkyl nitroethylenes under 500 parts-per-million (ppm) quinine-*NH*-thiourea-catalysis to furnish the chiral methanobenzo[7]annulenes in up to >99% *ee* with >20:1 *dr* and up to 1820 TONs through tandem Michael/Henry [3+2]-annulations. These asymmetric ppm-level, catalytic tandem [3+2]-annulations would be highly inspirational to design many more ppm-level organocatalytic reactions, and at the same time these final molecules are basic skeletons of antibiotics.

In the second chapter, we have described the synthesis of bicyclo[3.2.1]octanes in very good yields with excellent enantio and diastereoselectivities through organocatalytic [3+2]-annulations from hydroxy-*p*-quinone and nitroethylene. The bicyclo[3.2.1]octane unit is present in both natural and synthetic compounds that possess various biological activities. This bicyclo[3.2.1]octane core moiety acts as a reactive intermediate in various stereoselective synthetic transformations. These systems form a fundamental building block for biologically significant active molecules such as sesquiterpenoids, lignans, and alkaloids.

In the third chapter, we have developed an unprecedented protocol for the synthesis of various natural products such as embelin, rapanone, irisoquins, from three-component reductive alkylation method, which we have been working on over the past two decades. These natural products exhibit various pharmacological and wide range of biological activities including antihelmintic, analgesic, antitumor and antioxidant properties.

2. Introduction

In the early era of organocatalysis, it was very predominant to find catalytic loadings of up to 20-30 mol%, which is quite disappointing for many chemists who are accustomed to use metals or enzymes as catalysts at ppm/ppb-level loading. Employing higher catalyst loading is inappreciable due to its failure to find applicability in large-scale asymmetric synthesis, because of a lack of cost effectiveness. This is particularly when true expensive catalysts are to

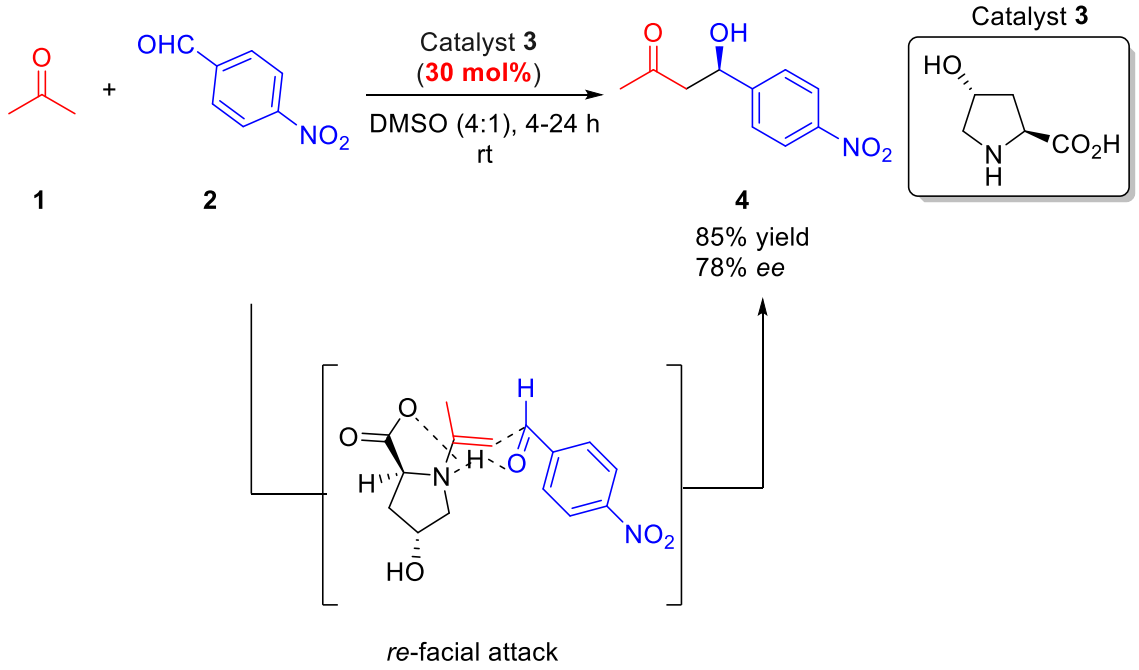
be used in numerous synthetic steps. Hence it became necessary to develop low catalytic loading systems and accomplishing such an endeavor is considered highly noteworthy.

Over the last two decades, few research groups have been paying attention in discovering many active organic catalysts that can promote asymmetric chemical transformations with low catalyst loading. To develop a reaction with high enantioselectivity, good turnover number (TON) and turnover frequency (TOF) a powerful catalyst is has to be discovered. Therefore, the main aim of catalysis is to offer an infinite turnover number (TON) for a desired chemical transformation by regenerating the catalyst without altering its molecular level structure and physicochemical properties. However, limitations arise from different deactivation mechanisms such as catalyst poisoning by chemical impurities and side products, thus lowering the lifetime of catalytically active species.

Organocatalysis employs small organic molecules as a catalyst which are comparable to transition-metal catalysts owing to their noble activation modes and excellent selectivity. However, further application of these organocatalysts in industry is often hampered by their relatively low turnover efficiency compared to the corresponding homogeneous or heterogeneous metal-catalyzed reactions. Despite many efforts, the current limit of catalyst loading for asymmetric organocatalysis is usually in the range of 0.1-1 mol% and achieving the synthesis of compounds with high turnover number at ppm level loading is considered a formidable challenge.

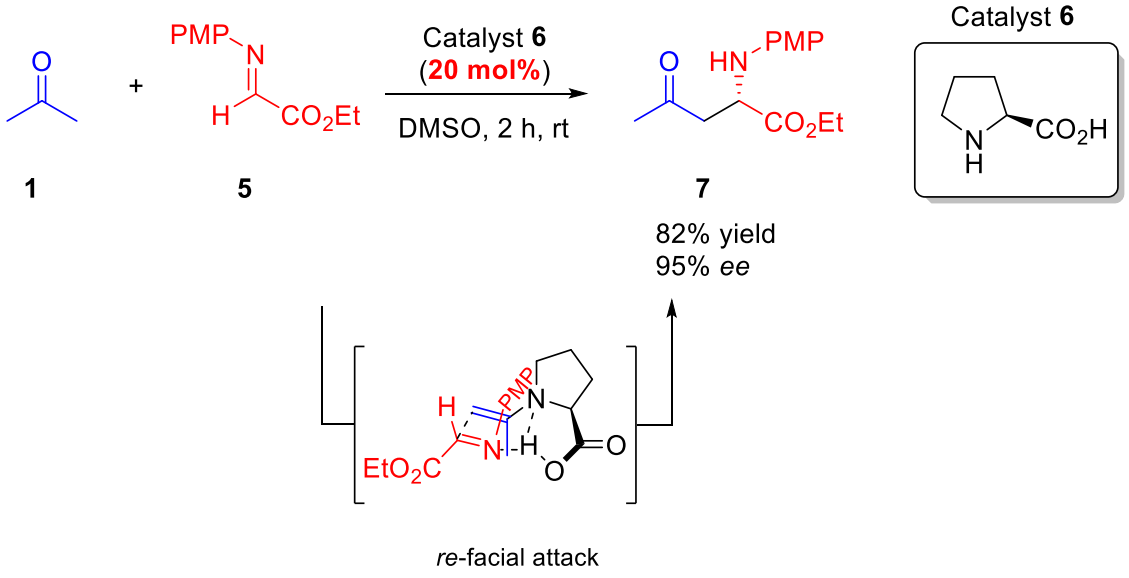
A comprehensive list of some novel organocatalytic reactions is represented by taking a few novel examples from literature to depict the evolution of organocatalysis from using high catalytic loading to perform the reactions at the ppm level catalyst loading.

Likewise, in 2001, C. F. Barbas et al. suggested a protocol to construct C-C bond through asymmetric aldol reaction under 4-hydroxy-L-proline **3** catalysis that reacts with ketone **1** through an enamine intermediate that further reacts with an aldehyde **2** via Zimmerman-Traxler transition to furnish aldol product **4** with high enantioselectivity, regioselectivity and diastereoselectivity. Herein, acetone **1** (1.0 mL) is treated with 4-nitrobenzaldehyde **2** (0.5 mmol) in the presence of **3** (30 mol%) in DMSO (4.0 mL) solvent at room temperature to give the desired asymmetric aldol product **4** with 85% yield and 78% *ee*. In addition, this reaction tolerates even trace amount of water (< 4 vol %) and is also very convenient to perform at room temperature in various solvents (Scheme 1).[1]



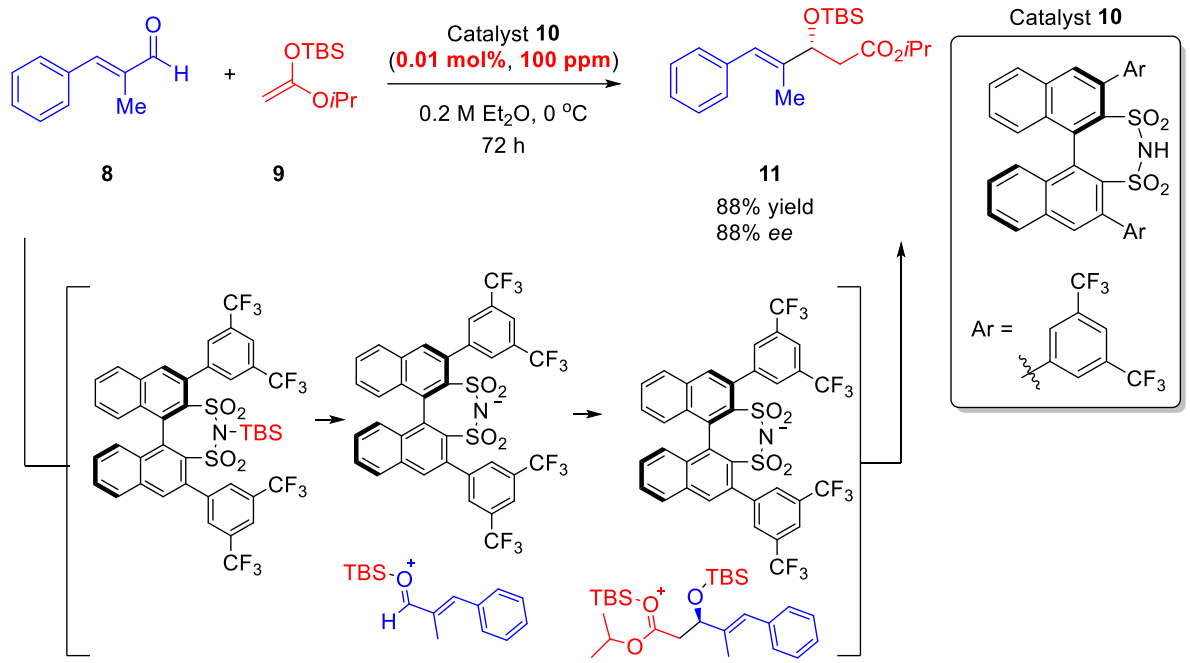
Scheme 1. Barbas's approach for asymmetric aldol reaction by using 30 mol% of substituted proline **3**.

Similarly in the year 2002, Barbas developed a strategy for the synthesis of functionalized α-amino acids using 20 mol% of L-proline **6**. They treated α-imino ethyl glyoxylate **5** and acetone **1** (1.0 mL) in the presence of catalyst **6** in DMSO (4.0 mL) at rt, to afford the corresponding protected α-amino acid **7** in 2 h with 82% yield and 95% *ee* (Scheme 2).[2]



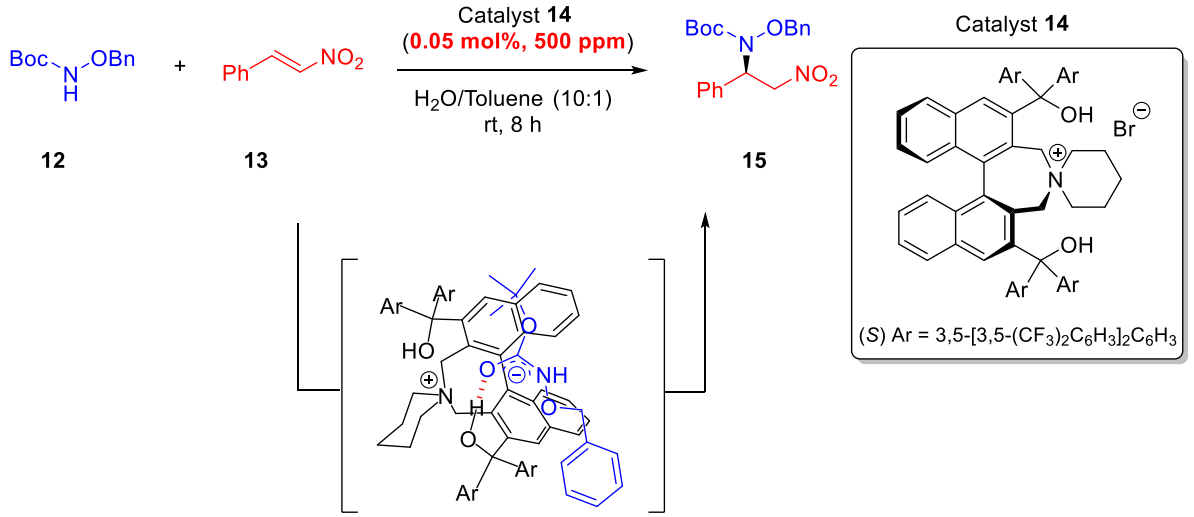
Scheme 2. Barbas's approach for asymmetric Mannich reaction using 20 mol% of L-proline **6**.

Furthermore, B. List et al. in 2009 described a new phenomenon to synthesize Mukaiyama aldol product **11** in the presence of disulfonimide **10** catalyst *via* ppm-level loading. Herein, catalyst **10** activates the α, β–unsaturated aldehyde **8**, resulting in the formation of oxonium ion *via O*-silylation. The disulfonimide anion and oxonium ion further reacts with acetal **9** to give the desired Mukaiyama aldol product **11** in 88% yield and 88% *ee* with TON up to 8800 which is considered as remarkable in the field of asymmetric organocatalysis (Scheme 3).[3]



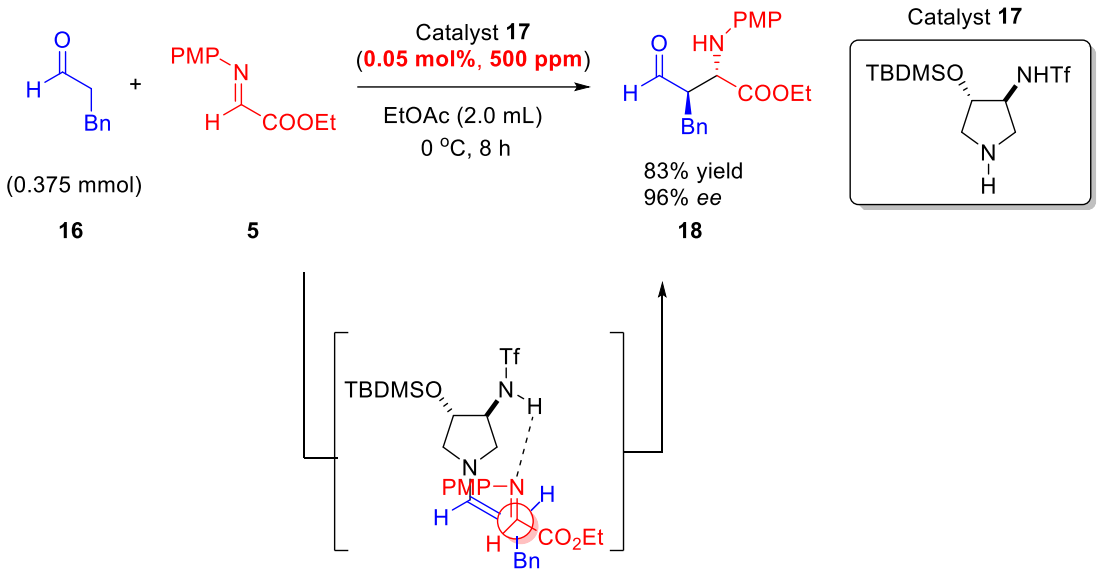
Scheme 3. B. List's protocol for Mukaiyama aldol reaction using 100 ppm of disulfonimide organocatalyst **10**.

In addition, Maruoka and co-workers in 2011 reported an efficient catalytic method for the enantioselective amination of nitroolefins. Initially, 0.05 mol% of tetraalkylammonium bromide salt **14** interacts with tertiary butoxy carbamate **12** in 2 ml of H_2O/toluene (10:1) through hydrogen bonding to generate amide anion. This generated anion attacks on nitrostyrene **13** to furnish the desired product **15** with 91% yield and 90% *ee*. Moreover, they also demonstrated the reaction utilizing 0.01 mol% of catalyst to give product **15** in 76% yield with TON of 7600 and an excellent enantioselectivity of 91% *ee* with a prolonged reaction time of 72 h (Scheme 4).[4]



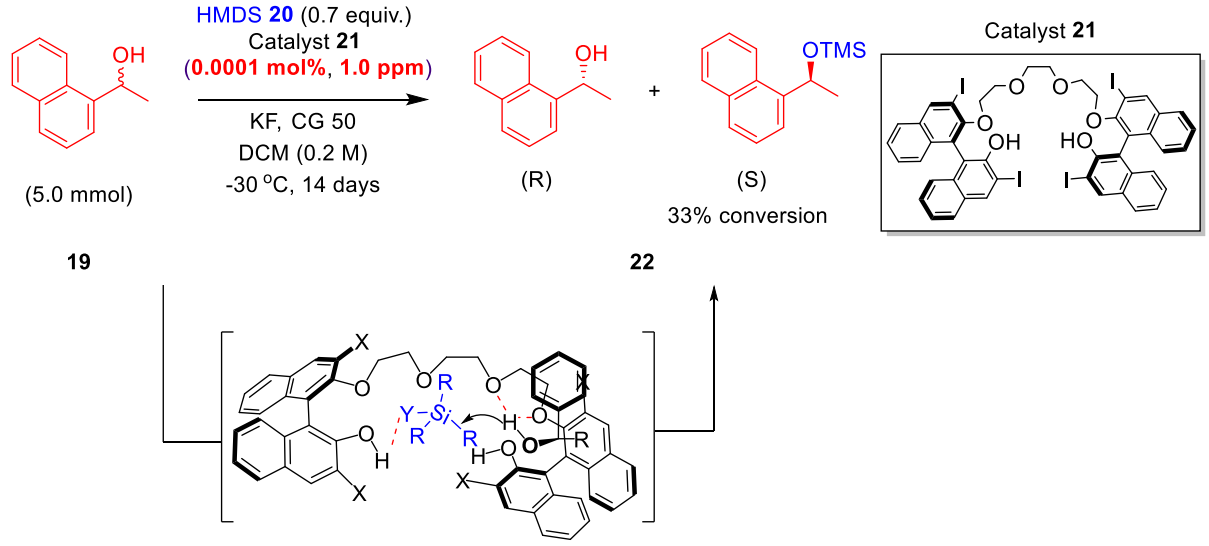
Scheme 4. K. Maruoka's protocol for enantioselective amination using 500 ppm of catalyst **14**.

In 2011, M. A. Pericas et al. reported an anti-type Mannich reaction which is highly uncommon. Here, they reacted aldehyde **16** (0.375 mmol) with imine **5** under pyrrolidine **17** (0.05 mol%) catalysis in EtOAc (2.0 mL) solvent at 0 □C to give product **18** in 83% yield with 96% *ee* in 8 h. Herein, C4 substituent on pyrrolidine **17** ring plays a major role in enhancing the activity of the catalyst and controlling the diastereoselectivity and simultaneously C4 substituent assists in H-bonding with catalyst **17** and imine **5** leading to the formation of *anti*-type Mannich product **18** (Scheme 5).[5]



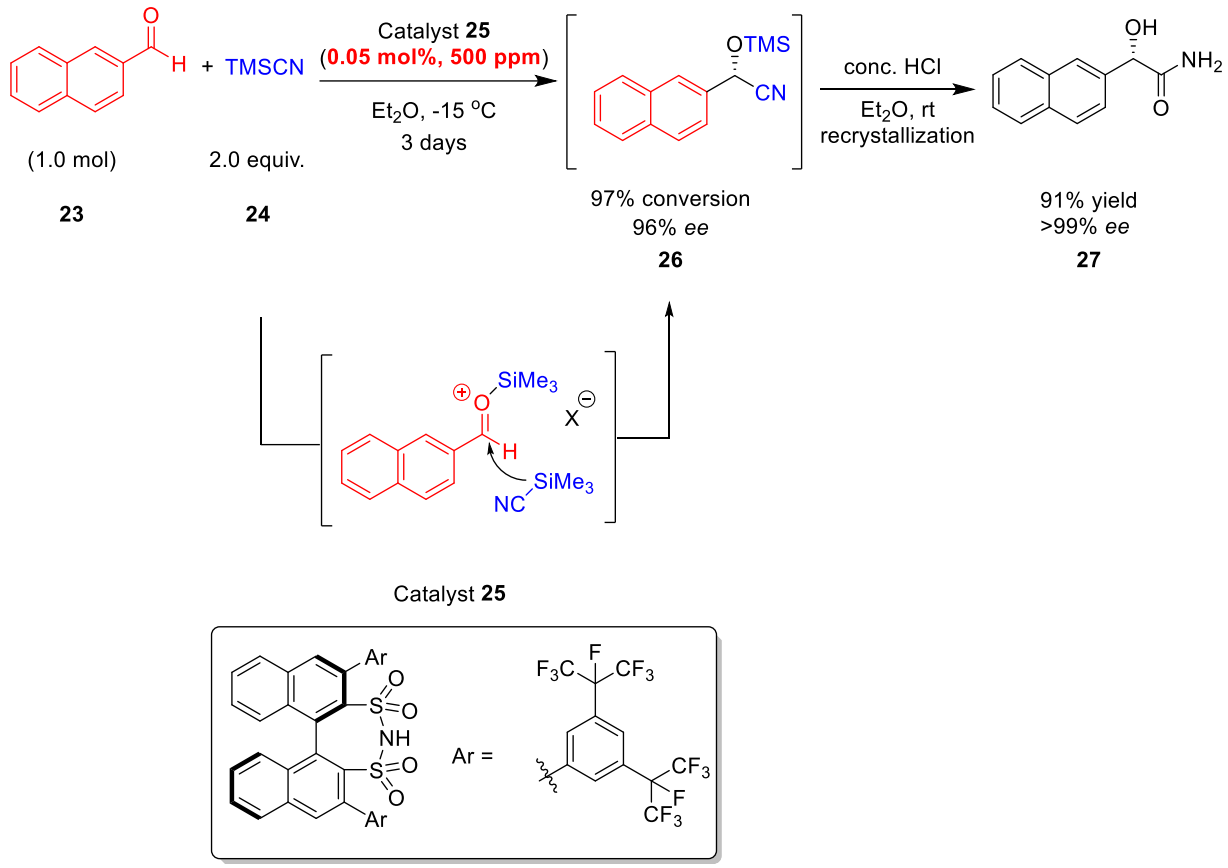
Scheme 5. Pericas approach for *anti*-type Mannich reaction using 500 ppm of catalyst **17**.

In 2015, C. E. Song and co-workers postulated a synthetic method for the synthesis of highly enantiomeric pure secondary alcohols. They treated racemic secondary alcohol **19** (5.0 mmol) with HMDS **20** (0.7 equiv.) in the presence of 1,10-bi-2-naphthol-based polyether catalyst **21** (1.0 ppm loading) and KF, CG-50 additives in DCM solvent (0.2 M) at -30 □C to furnish the desired TMS-protected secondary alcohols **22** in 14 days with 33% conversion. Acidic protons in catalyst **21** interact with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) **20** by hydrogen bonding interactions which enhances the electrophilicity of Si accounting for high enantioselectivity (Scheme 6).[6]



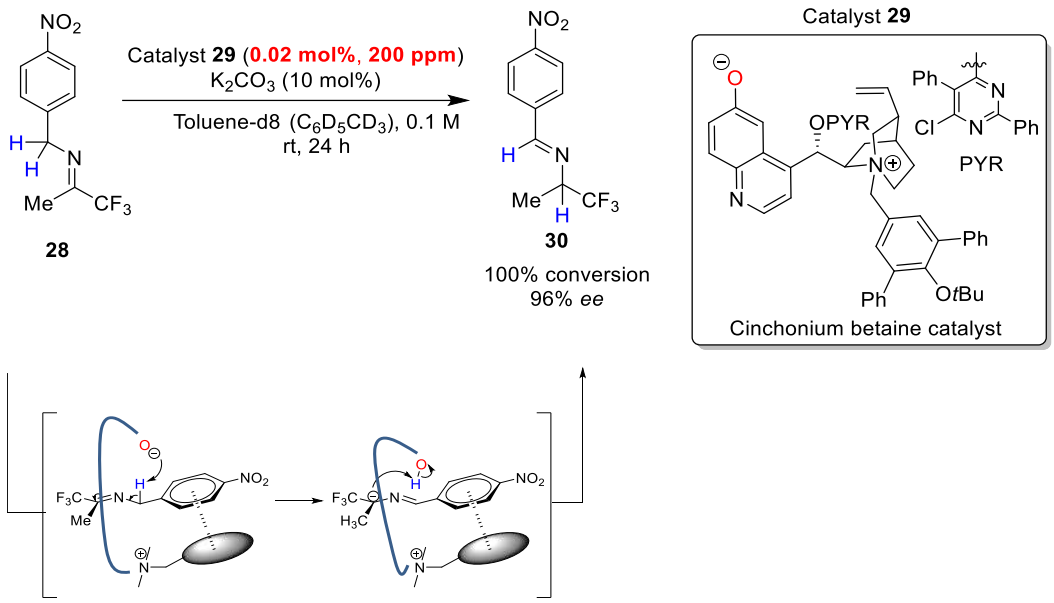
Scheme 6. Song's approach for the synthesis of high enantioselective silylated alcohol using 1.0 ppm of catalyst **21**.

Moreover, in 2016, B. List et al. reported the asymmetric synthesis of cyanohydrin **26** under disulfonimide **25** catalysis. Herein, 2-napthaldehyde **23** (1.0 mol) is treated with TMSCN **24** (2.0 mmol) utilizing 500 ppm of catalyst **25** in Et_2O solvent (2.0 mL) at -15 □C for 3 days furnishing the desired product **26** with 97% conversion and 96% *ee* with a TON 18400. Initially, pre-catalyst chiral disulfonimide **25** activates by reacting with either TMSCN **24** or silyl ketene acetal in dormant period which is further neutralized by H_2O or silanol (Scheme 7).[7]



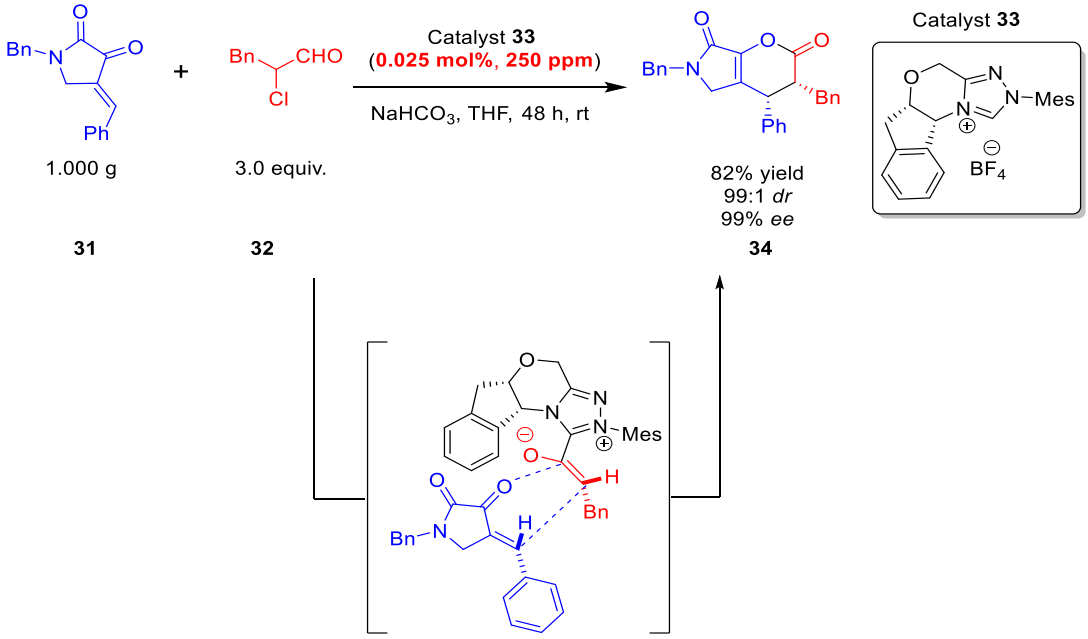
Scheme 7. B. List protocol for the synthesis of cyanohydrin **26** with high enantioselectivity using 500 ppm of catalyst **25**.

Furthermore, in 2016 Deng et al. demonstrated the enantioselective isomerization of trifluoromethyl imines **28** by using cinchonium betaine catalyst **29**. They reacted imine **28** (0.025 mmol) with 0.02 mol% of catalyst **29** utilizing 10 mol% of K_2CO_3 as a base, in deuterated toluene solvent (0.1 M) at room temperature to give the corresponding trifluoro methylated amine **30** with 100% conversion and 96% *ee*. Initially, catalyst **29** reacts with K_2CO_3 generating alkoxide anion having π-π interactions that helps to bind the imine **28** with catalyst **29** leading to the deprotonation and protonation in an intramolecular fashion to afford the desired trifluoro methylated amines **30** (Scheme 8).[8]



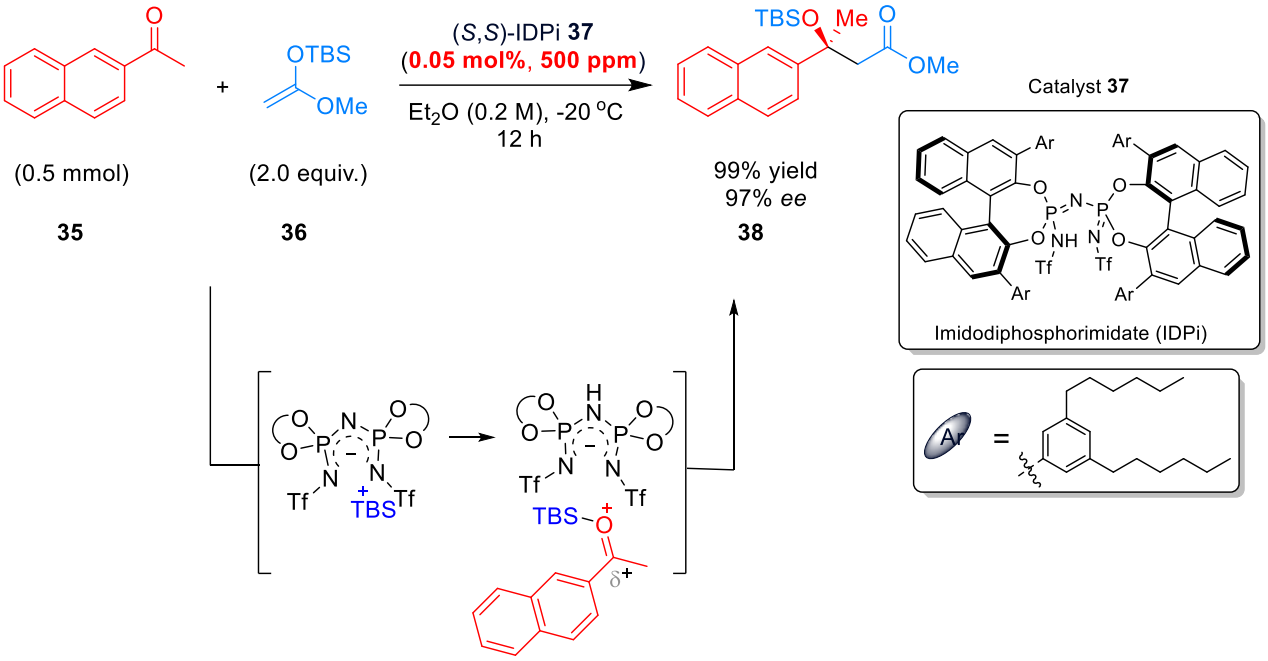
Scheme 8. Deng's approach for enantioselective isomerization reaction using 200 ppm of catalyst **29**.

Next immediately in 2017, B. Han and X. D. Shene et al. disclosed an elegant piece of work showing the enantioselective synthesis of dihydropyranone **34** under NHC catalysis. They reacted cyclic dienones **31** with α-halo aldehyde **32** in the presence of NHC catalyst **33** (0.025 mol%) in THF solvent (8.0 mL) under inert atmosphere at rt for 48 h to get the expected product **34** in 82% yield with >99:1 *dr* and 99% *ee* (Scheme 9).[9]



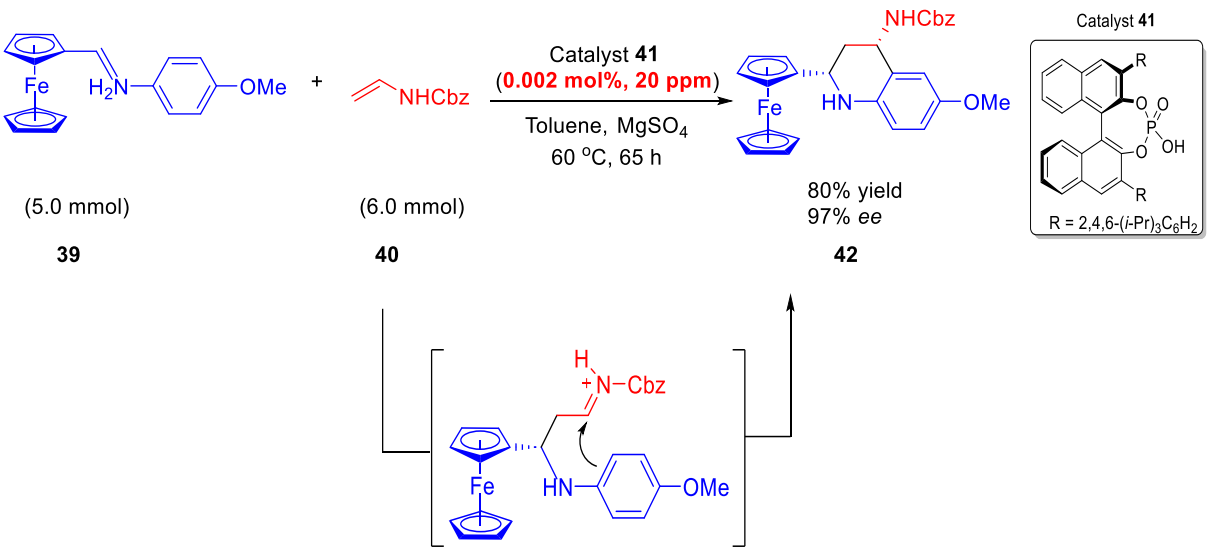
Scheme 9. Han's and Shen's approach for the synthesis of enantioselective dihydropyranone using 250 ppm of catalyst **33**.

With the same spirit in 2018, B. List et al. disclosed a protocol to synthesize chiral tertiary aldol product **38** by using IDPi catalyst **37**. They reacted 2-acetonapthone **35** (0.5 mmol) with acetal **36** (2.0 equiv.) in the presence of catalyst at 500 ppm. Primarily, catalyst **37** gets activated upon treatment with silyl ketene acetal **36** which attacks the ketone **35** producing oxocarbenium ion pair that further reacts with another equivalent of acetal **36** followed by deprotonation of oxocarbonium ion to give the desired tertiary aldol product **38**. They have successfully developed a protocol to synthesize the chiral tertiary aldol product **38** in 12 h with 97% *ee* and 99% yield (Scheme 10).[10]



Scheme 10. B. List's protocol for synthesis of chiral tertiary aldol product using 500 ppm of catalyst **37**.

In 2018, M. Fochi and L. Bernadi et al. postulated the synthesis of 2-ferrocenyl-1,2,3,4-tetrahydroquinoline **42** under phosphoric acid **41** catalysis. They treated the imine **39** (5.0 mmol) with *N*-vinyl carbamate **40** (6.0 mmol) in the presence of chiral phosphoric acid **41** (0.002 mol%) and $MgSO_4$ as additives in anhydrous toluene (20 mL) at 60 □C in 65 h to afforded the corresponding tetrahydroquinoline **42** with 80% yield and 97% *ee* (Scheme 11).[11]



Scheme 11. L. Bernadi's approach for the synthesis of 2-ferrocenyl-1,2,3,4-tetrahydroquinoline using 20 ppm of catalyst **41**.

2.1 References

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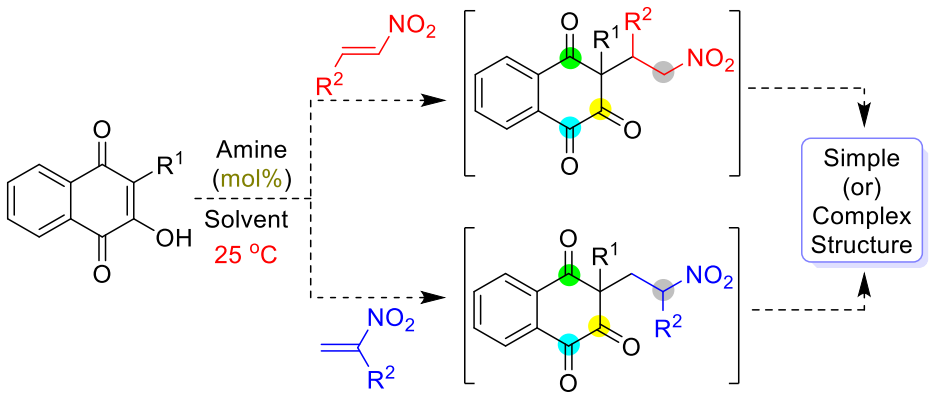
3. Parts-per-Million-Level, Catalytic [3+2]-Annulations for the Asymmetric Synthesis of Methanobenzo[7]annulenes

3.1 Introduction

Since time immemorial, enzymes and antibodies, and recently artificially-evolved enzymes have been found to catalyze chemical transformations very effectively with excellent selectivity, most importantly, even when they are used in miniscule quantities.[1] As we always continuously strive for improvising efficacy, countless endeavors were made to mimic this extraordinary quality of catalytic activity in other catalyst types. As a result, some closely comparable, metal-catalyzed reactions with low catalyst loadings emerged as observed in asymmetric hydrogenations and cross□coupling reactions.[2]

On the other hand, though, asymmetric organocatalysis has flourished complimentary to enzyme- and metal-catalysis in the last two decades, it has not yet proven its full potential. The shortcoming is that it is not as efficient as metal- or enzyme-catalysis at low parts-per-million (ppm)-level catalyst loadings and the organocatalysts are usually required in higher quantities (up to 30 mol%).[3] Asymmetric organocatalyzed reactions with extremely low catalyst loadings is one step higher up in its evolution and is the need of the hour, as it would be highly appreciable in pharmaceutical industries. General challenges associated with developing low ppm-level organocatalyzed reactions include requirement of very high reaction rates, preventing catalyst poisoning from impurities/byproducts, rapidity of catalyst regeneration, catalyst stability, and product stability under the reaction conditions. Recently, a few research groups have elegantly reported their breakthroughs on the exploration of low ppm catalyzed reactions in the field of asymmetric organocatalysis.[4]

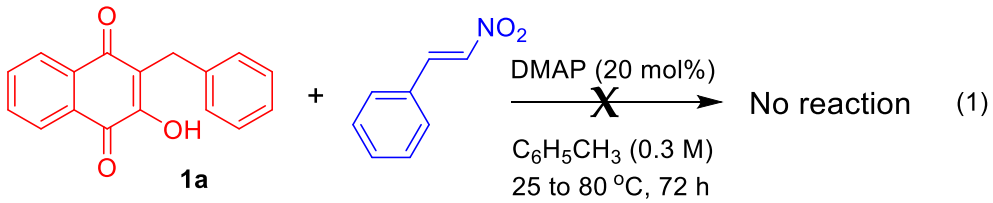
We wondered if we plan a reaction between the 3-alkyl-lawsones and *β*-nitro styrenes or *α*-alkyl-nitroethylenes, would it help us to bring about a low ppm-level catalyst loading reaction (Scheme 1). There are two underlying reasons for this motivation. One is our expertise in utilizing the reactivity of 3-alkyl-lawsones in asymmetric organocatalysis[3h-j] and the second is our fascination toward developing asymmetric organocatalytic tandem one-pot reactions which function under very low catalyst loadings at ppm-level. Consequently, we begin on the journey to try our hands on the low ppm-level catalyst loading for tandem reaction.



Scheme 1: Reaction layout for the ppm-level tandem organocatalysis.

1.2 Results and Discussions

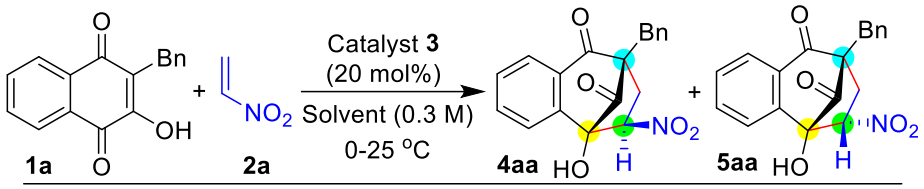
Despite the initial disappointment from the reaction between 3-benzyl-lawsone **1a** and *β*-nitrostyrene, as the reaction did not furnish any product under the catalysis of DMAP or quinine-N*H*-thiourea at the 25 to 80 °C for 72 h (Eq. 1). we stayed on track and advanced further with simple yet extremely reactive nitroethylene **2a**. Nitroethylene **2a**, a less stable liquid at 25 °C, was prepared, stored as a 1.0 M solution in toluene in the refrigerator and used.[5]



When we first executed the reaction between **1a** and **2a** in toluene at 0 to 25 °C, in the absence of catalyst for 24 h, there was no product formation (Table 1, entry 1). Next, on conducting the reaction with 20 mol% of DBU **3a** in toluene at 0 to 25 °C for 24 h, it was very encouraging to obtain the product bicyclo[3.2.1]octane **4aa**/**5aa** out of many possibilities, nevertheless only in 30% yield with 4.0:1 *dr* (Table 1, entry 2). Both the catalysts DABCO **3b** and Ph_3P **3c** performed the reaction between **1a** and **2a**, moderately better than DBU **3a**, to furnish **4aa**/**5aa** in each 50% yield with 4.5:1/4.6:1 *dr* respectively (Table 1, entries 3-4). With Et_3N **3d** as catalyst, the reaction rate drastically increased and the reaction completed within 9 h to furnish **4aa**/**5aa** in 70% yield with 4.7:1 *dr* (Table 1, entry 5). Same trend followed for catalyst TBD **(**1,5,7-triazabicyclo[4.4.0]dec-5-ene) **3e**, with further amplification in reaction rate and yield and the reaction was over in 4 h to furnish **4aa**/**5aa** in 80% yield with 4.0:1 *dr* (Table 1, entry 6). Ultimately, catalyst DMAP **3f**, was found to be superior under identical

reaction conditions and generated the product **4aa**/**5aa** within 2 h, in 85% yield with 5.2:1 *dr* (Table 1, entry 7). By diminishing the catalyst **3f** quantity to 15, 10 and 5 mol%, not only the reaction took longer than 2 h for completion, but also suffered slightly in yield and *dr* (Table 1, entries 8-10). Surprisingly, ^{1}H NMR analysis of the **3f**-catalysed crude product of **4aa**/**5aa** gave 14:1 *dr*, which after purification through column chromatography decreased due to the epimerization α to the *tert*-hydroxyl group. Despite the fact that it does not make much sense in performing the reaction in other solvents, as there is always 0.9 ml of toluene coming from nitroethylene solution for external 0.1ml solvent, the reaction was performed in chloroform and THF. As anticipated, the solvent change did not seem to have any perceptible effect on the reaction due to its insignificant proportion (Table 1, entries 11-12).

Table 1: Preliminary investigation of the proposed reaction. [a]

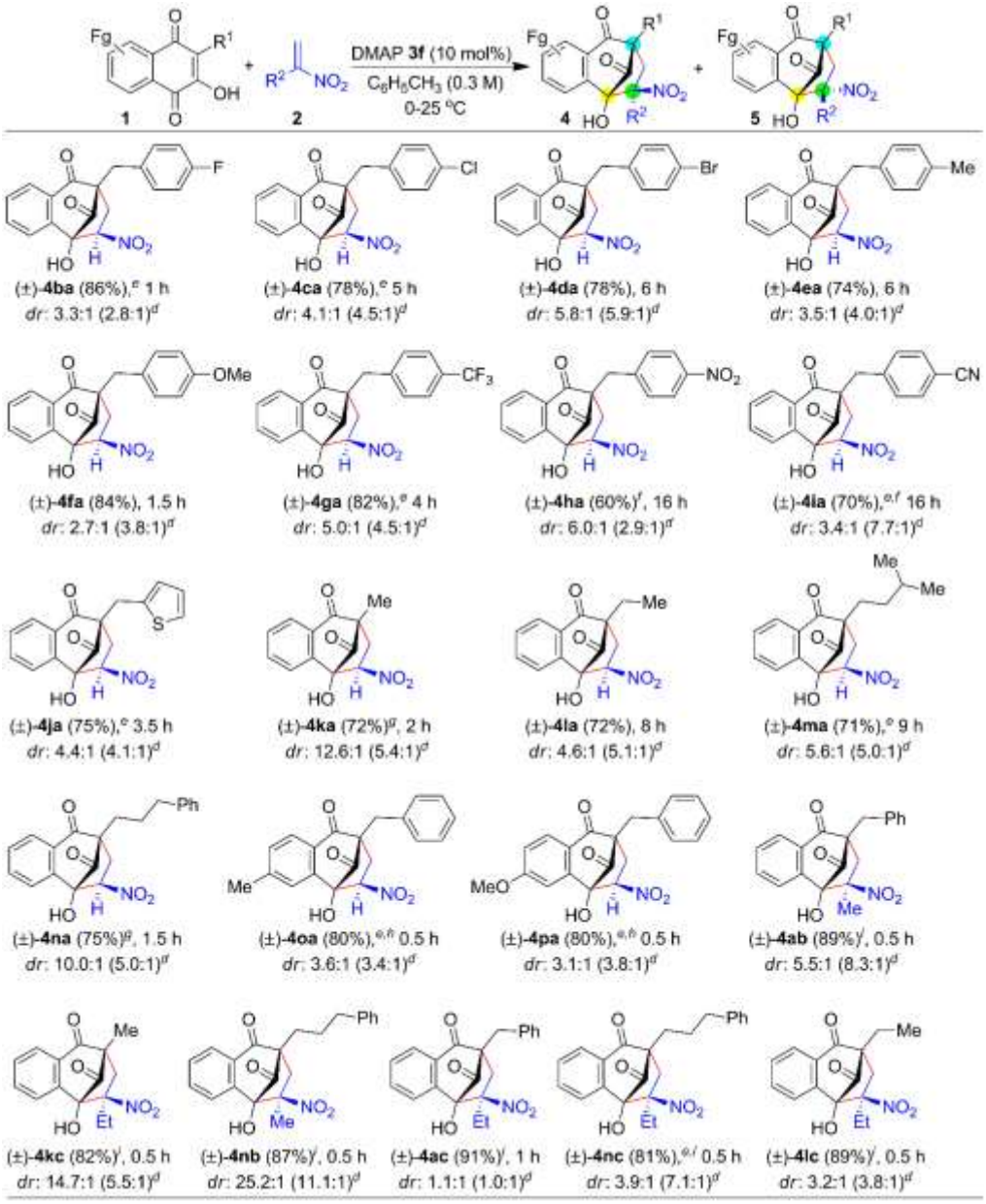


Entry	Catalyst **3** [20 mol%]	Solvent [0.3 M]	Time [h]	Yield [%][b] [**4aa** + **5aa**]	*dr*[c] [**4aa**/**5aa**]
1	-	$C_6H_5CH_3$	24	-	-
2	DBU **3a**	$C_6H_5CH_3$	24	30	4.0:1
3	DABCO **3b**	$C_6H_5CH_3$	24	50	4.5:1
4	PPh_3 **3c**	$C_6H_5CH_3$	24	50	4.6:1
5	Et_3N **3d**	$C_6H_5CH_3$	9	70	4.7:1
6	TBD **3e**	$C_6H_5CH_3$	4	80	4.0:1
7	DMAP **3f**	$C_6H_5CH_3$	2	85	5.2:1
8[d]	DMAP **3f**	$C_6H_5CH_3$	2.5	85	3.4:1
9[e]	DMAP **3f**	$C_6H_5CH_3$	3	85	3.8:1
10[f]	DMAP **3f**	$C_6H_5CH_3$	4	82	4.0:1
11[e]	DMAP **3f**	$CHCl_3$	3	80	3.3:1
12[e]	DMAP **3f**	THF	3	78	4.3:1

[a] Reactions were carried out in solvent (0.1 mL) with 3.0 equiv. of **2a** (0.9 mL, 1.0 M in toluene) relative to the **1a** (0.3 mmol) in the presence of 20 mol% of catalyst **3** at 0 °C for 0.5 h and rest of time at 25 °C. [b] Yield refers to the column-purified product of **4aa**+**5aa**. [c] Determined by ^{1}H NMR analysis of the column-purified product of **4aa**+**5aa**. [d] 15 mol% of **3f** was used. [e] 10 mol% of **3f** was used. [f] 5 mol% of **3f** was used. Note: ^{1}H NMR analysis of the crude product **4aa**/**5aa** was determined to be >14:1 *dr* and during this reaction optimization, we are not observed Michael or *retro*-Henry product **4'aa**.

Further, we have synthesized a library of racemic tandem products **4ba**/**5ba** to **4lc**/**5lc** by reacting 3-alkyllawsones **1** with nitroethylenes **2** in the presence of 10 mol% of DMAP **3f** in 0.3 M toluene at 0-25 ºC for 0.5 to 5 h. We successfully furnished all the racemic tandem products **4/5** with very good yields and moderate *dr* as shown in the Table 2.

Table 2: Synthesis of Racemic Tandem Michael/Henry [3+2]-Annulation Products.[a,b,c]



[a] Reactions were carried out in $C_6H_5CH_3$ (0.1 mL) with 3.0 equiv. of **2** (0.9 mL, 1.0 M in toluene) relative to the **1** (0.3 mmol) in the presence of DMAP **3f** (10 mol%) at 0 °C for 0.5 h and rest of time at 25 °C. [b] Yield refers to the column-purified product of **4**+**5**. [c] *dr* was determined by CSP-HPLC analysis. [d] *dr* values in parenthesis determined by ^{1}H NMR analysis of column-purified products. [e] Retro-Henry product **4'** was *in situ* generated during CSP-HPLC analysis in the 1-15%. [f] Reaction performed in DCM (0.1 mL). [g] Reaction performed with 10 mol-% of quinine/quinidine (1:1) as catalyst. [h] Reaction performed at 0 °C. [i] Reaction performed at 25 °C.

After preliminary understanding of the reaction rate/selectivity/products importance,[6] further emphasis was on screening chiral catalysts for asymmetric induction. The chiral catalysts chosen for the purpose are quinine/quinidine based thiourea/squaramides **3g** to **3k** (Table 3).[3] The reaction of **1a** with **2a** was performed in the presence of 5 mol% of **3g** in toluene at 0 °C for 0.5 h and the product (+)-**4aa**/**5aa** was obtained magnificently in 90% yield with 4.3:1 *dr* and 91/98% *ee* in just 18 turnover number (Table 3, entry 1). On reducing **3g** loading to 2.5 mol% and then to 1 mol%, fortunately, the reaction completed within 0.5 h at 0 °C, the yield maintained constant and the *ee* of the major isomer increased marginally, while the *dr* fluctuated a little (Table 3, entries 2-3). When the catalyst **3h** (1 mol%) was used, the opposite enantiomer (-)-**4aa**/**5aa** was produced in 90% yield with 5.4:1 *dr* and 93/86% *ee* in 0.5 h (Table 3, entry 4). With **3i**, **3j** or **3k** as the catalyst, even though the reaction yield and *dr* were equivalent to that of **3g** and **3h**, the *ee*'s were very poor (Table 3, entries 5-7).

Further decreasing of the catalyst **3g** loading from 1 mol% to 0.5 mol%, providentially resulted in reaction completion within 0.5 h even at -10 °C, to give (+)-**4aa**/**5aa** in 90% yield with 4.1:1 *dr* and 92/97% *ee* (Table 3, entry 8). The same reaction performed at 0 °C, gave 90% yield with slightly better 5.0:1 *dr* and 93/95% *ee* (Table 3, entry 9). With the catalyst **3g** loading of 0.4 mol%, the reaction completed within 1 h at -10 °C, to produce (+)-**4aa**/**5aa** in 88% yield with 6.3:1 *dr* and 92/98% *ee* (Table 3, entry 10). Encouraged with this persistent reaction rate/yield/*dr*/*ee*, we were motivated to examine the reaction with even less catalytic loading. Consequently, with little change in reaction temperature and time, we were able to shrink the catalyst loading size progressively and fruitfully up to 0.05 mol% (500 ppm), with the observation of only little erosion in yield, slight oscillation in *dr* and almost sustained and increased *ee* (Table 3, entries 11-17).

In the presence of 0.05 mol% (500 ppm) **3g** catalyst loading, the reaction took 12 h for completion, resulting in a little fall in the yield (82%), with amplified 11.4:1 *dr* and enhanced 99/99% *ee* (Table 3, entry 17). The same reaction when performed at 25 °C for the whole time, produced less yield (68%) and diminished *dr* and faintly dwindled *ee* (Table 3, entry 18). From this optimization study, the ideal reaction condition was observed to be entry 17, with the most appreciable low catalyst loading of 500 ppm. The turnover number (TON) for this optimized reaction was calculated to be 1640. As per our initial expectation and to our delight, the high reactivity of the reactants **1a** and **2a**, actually ended up with a high reaction rate, thereby launching the reaction into the most desired low catalyst loading zone. For the opposite enantiomer (-)-**4aa**/**5aa**, the optimized condition was implemented on the substrates **1a** and **2a**

using the catalyst **3h** in the place of **3g** and the reaction took 15 h to deliver 76% yield, 6.3:1 *dr* and 88/88% *ee* (Table 3, entry 19). The performance of the reaction in toluene:trifluorotoluene (9:1) was found to be deleterious for the reaction yield, *dr* and *ee* (Table 3, entry 20). As similar to Table-1, ^{1}H NMR analysis of the **3g**-catalysed crude product of (+)-**4aa/5aa** was furnished with >16:1 *dr*, which after quick purification through silica gel column chromatography decreased their *dr* as shown in the Table-3. The structure of the compound (+)-**4aa** was further confirmed by X-Ray crystallography (Figure 1).

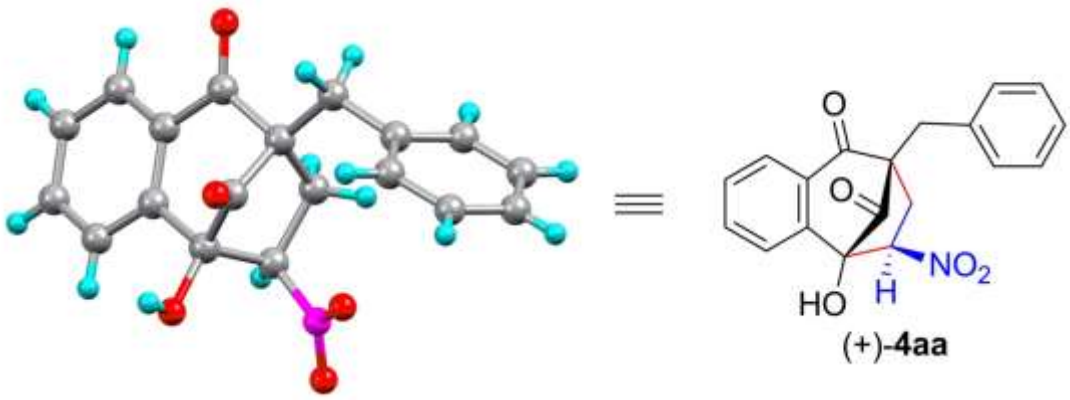
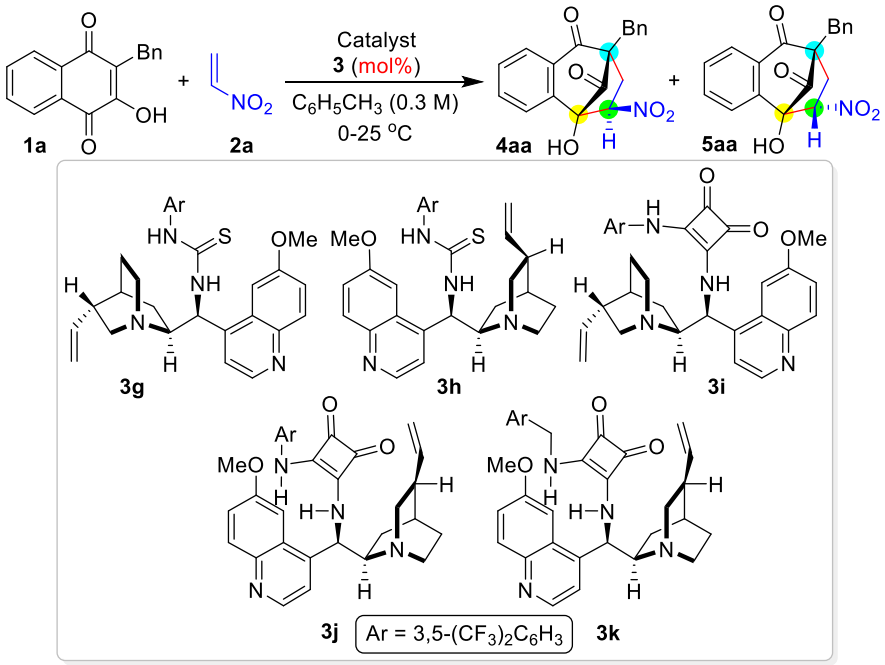


Figure 1: X-Ray crystal structure of (5*R*,6*R*,8*S*)-8-benzyl-5-hydroxy-6-nitro-5,6,7,8-tetrahydro-9H-5,8-methanobenzo[7]annulene-9,10-dione (+)-**4aa**.

Table 3: Investigation of the proposed ppm-level asymmetric reaction. [a]



Entry	Catalyst **3** [mol%]	Time [h]	Yield [%][b] [**4aa**+**5aa**]	*dr*[c] [**4aa**:**5aa**]	*ee* [%][d] **4aa**(**5aa**)	TON
1[e]	**3g** (5.0)	0.5	90	4.3:1	91 (98)	18
2[e]	**3g** (2.5)	0.5	90	5.0:1	91 (93)	36
3[e]	**3g** (1.0)	0.5	90	4.2:1	93 (96)	90
4[e,f]	**3h** (1.0)	0.5	90	5.4:1	93 (86)	90
5[e]	**3i** (1.0)	0.5	90	4.4:1	62 (64)	90
6[e,f]	**3j** (1.0)	0.5	90	3.8:1	62 (65)	90
7[e,f]	**3k** (1.0)	0.5	90	4.0:1	66 (74)	90
8[g]	**3g** (0.5)	0.5	90	4.1:1	92 (97)	180
9[e]	**3g** (0.5)	0.5	90	5.0:1	93 (95)	180
10[g]	**3g** (0.4)	1	88	6.3:1	92 (98)	220
11[h]	**3g** (0.3)	2	87	5.3:1	90 (93)	290
12	**3g** (0.3)	2	88	5.7:1	93 (98)	293
13[g]	**3g** (0.1 = 1000 ppm)	10	86	4.4:1	95 (98)	860
14[e]	**3g** (0.1 = 1000 ppm)	8	85	4.5:1	94 (98)	850
15	**3g** (0.1 = 1000 ppm)	8	85	5.1:1	92 (97)	850
16[i]	**3g** (0.1 = 1000 ppm)	1	85	6.5:1	92 (93)	850
17	**3g** (0.05 = 500 ppm)	12	82	11.4:1	99 (99)	1640
18[i]	**3g** (0.05 = 500 ppm)	3	68	4.6:1	94 (97)	1360
19[f]	**3h** (0.05 = 500 ppm)	15	76	6.3:1	88 (88)	1520
20[j]	**3g** (0.05 = 500 ppm)	12	70	7.2:1	93 (96)	1400

[a] Reactions were carried out in toluene (0.1 mL) with 3.0 equiv. of **2a** (0.9 mL, 1.0 M in toluene) relative to the **1a** (0.3 mmol) in the presence of catalyst **3** (mol%) at 0 °C for 0.5 h and rest of time at 25 °C. [b] Yield refers to the column-purified product of **4aa**+**5aa**. [c] Determined by CSP-HPLC analysis of the column-purified product of **4aa**+**5aa**. [d] Determined by CSP-HPLC analysis and values in parenthesis represent for minor diastereomer **5**aa. [e] Reaction performed at 0 °C. [f] Opposite enantiomer observed. [g] Reaction performed at -10 °C. [h] Reaction performed at -10 to 25 °C. [i] Reaction performed at 25 °C. [j] Reaction performed in trifluorotoluene (0.1 mL). Note: ^{1}H NMR analysis of the crude product **4aa**/**5aa** was determined to be >16:1 *dr* and during this reaction optimization, we are not observed Michael or *retro*-Henry product **4'aa**. TON: Turnover number.

^{1}H, ^{13}C NMR and HPLC spectra of **4aa** from optimization Table 3 depicted in Figures 2-3.

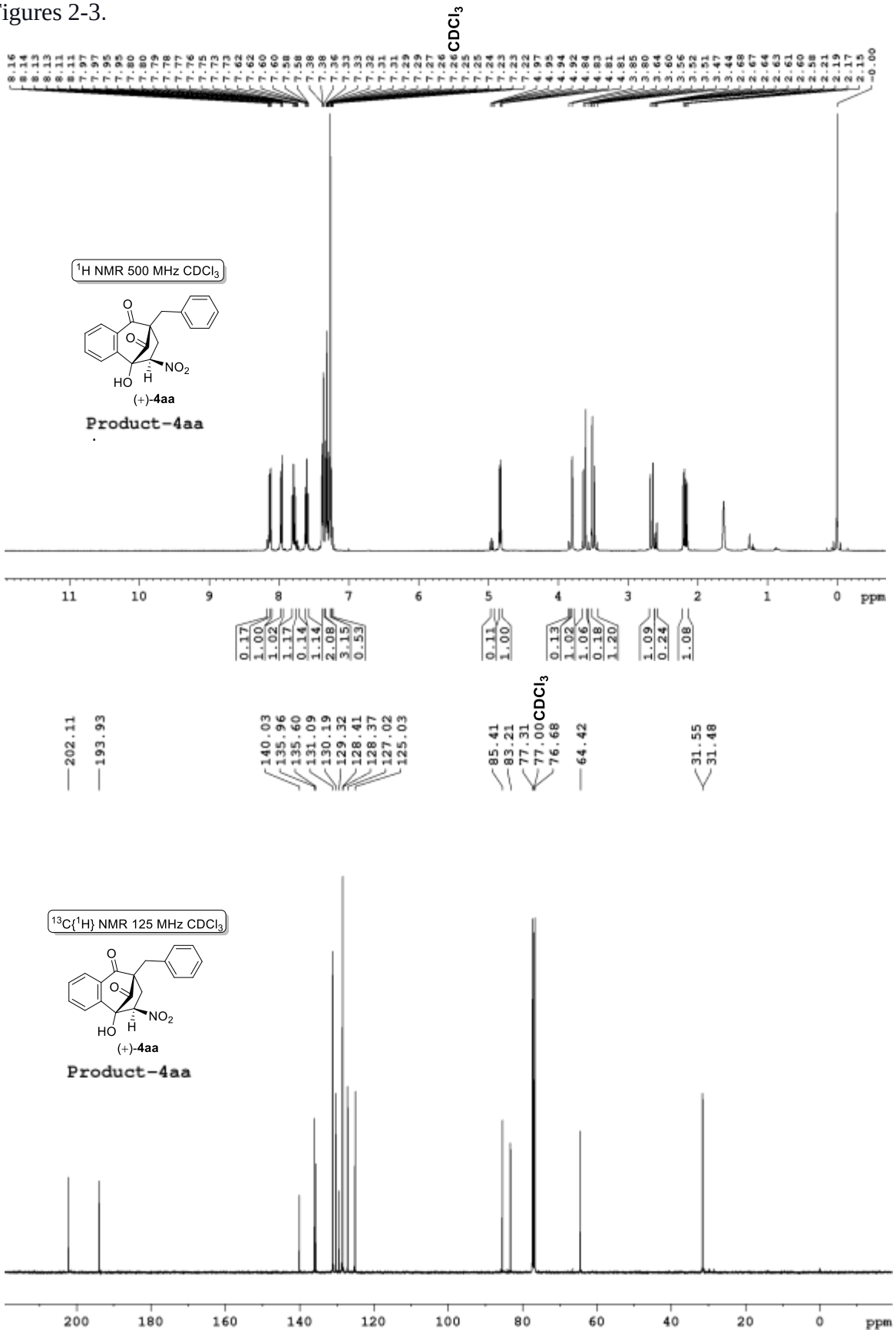
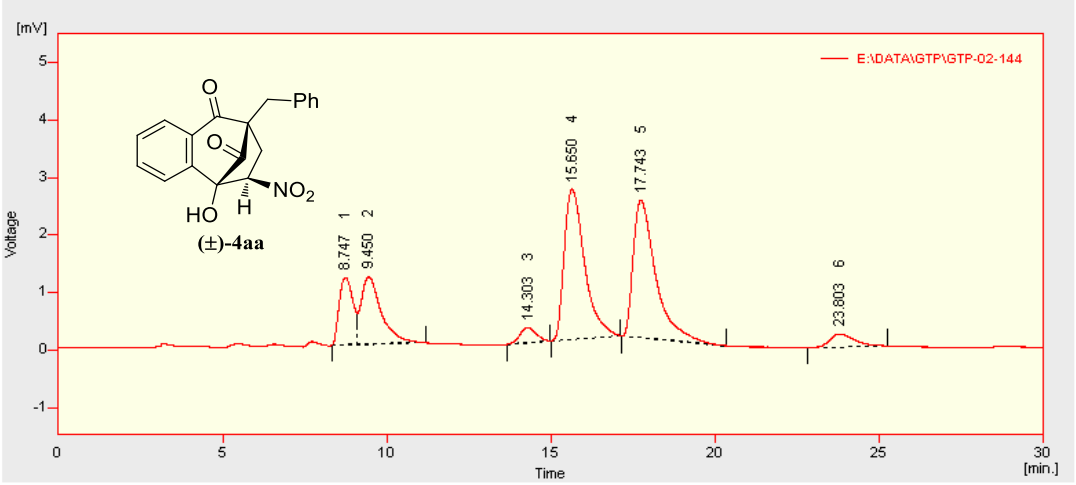


Figure 2: ^{1}H NMR and ^{13}C NMR spectrum of product **4aa**.

Racemic (±)-4aa:

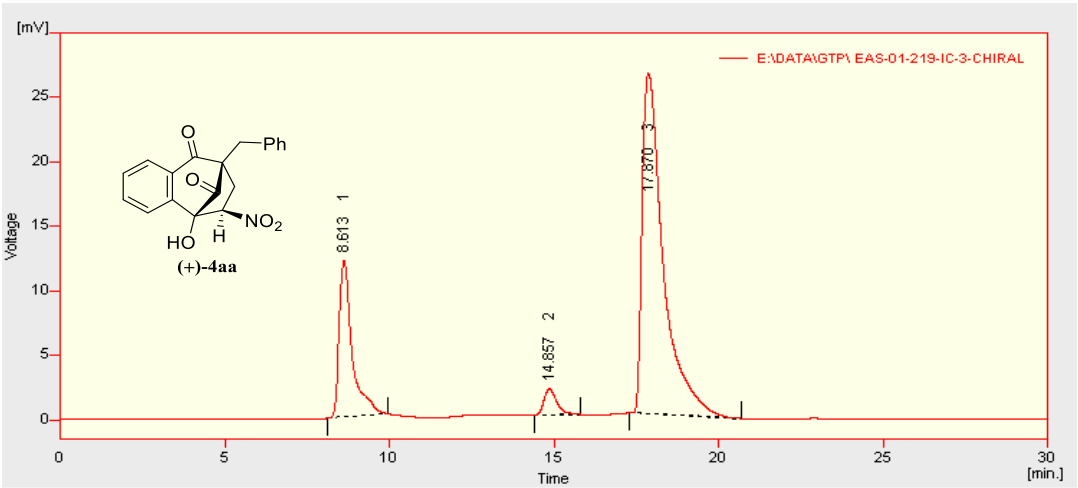


Daicel Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254

Result Table (Uncal - E:\DATA\GTP\GTP-02-144)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	8.747	33.089	1.165	9.9	14.9	0.54
2	9.450	51.329	1.165	15.4	14.9	0.66
3	14.303	9.186	0.266	2.8	3.4	0.56
4	15.650	113.135	2.608	34.0	33.4	0.65
5	17.743	114.804	2.389	34.5	30.6	0.68
6	23.803	11.634	0.221	3.5	2.8	0.82
	Total	333.177	7.813	100.0	100.0	

Chiral-(+)-4aa [Major: >99% *ee;* Minor: >99% *ee*; *retro*-Henry product: 21% (>99% *ee*)]:



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

Result Table (Uncal - E:\DATA\GTP\EAS-01-219-IC-3-CHIRAL)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	8.613	336.862	12.101	21.4	29.9	0.37
2	14.857	55.812	2.066	3.5	5.1	0.41
3	17.870	1182.572	26.355	75.1	65.0	0.61
	Total	1575.245	40.522	100.0	100.0	

Figure 3: HPLC spectra of product **4aa**.

3.2.1 Substrate scope of alkyl lawsones:

Mesmerized with this ppm-level catalyzed reaction, next, we organized to investigate the extendibility of the reaction to create a library of differently substituted bicyclo[3.2.1]octanes **4**/**5**. Diversely functionalized benzyls, hetero-aryls, and alkyl groups at the 3rd-position in the lawsone **1b** to **1p** were generously suitable for the tandem reaction with **2a** under the 500 ppm-catalysis. The halogen containing benzyl groups in lawsone **1b** to **1d** furnished the tandem products (+)-**4ba**/**5ba** to (+)-**4da**/**5da** in 88%, 80% and 80% yields with 94 to 96% *ee* and good *dr*'s in 12 to 15 h (Table 4). Reaction of the lawsones **1e** to **1g** possessing Me, OMe and CF_3 substituted benzyl groups furnished the tandem products (+)-**4ea**/**5ea** to (+)-**4ga**/**5ga**, in each 81% yield with 94 to >99% *ee* and good *dr*'s in 10 to 13 h (Table 4). The lawsones **1h**/**1i** with NO_2 and CN substituents on the benzyl groups generated the tandem products (+)-**4ha**/**5ha** and (+)-**4ia**/**5ia**, in 60 to 74% yields with >99% *ee* and moderate *dr*'s in 16 h (Table 3). In these two reactions, due to solubility issues, 0.1 mL of dichloromethane was used. The hetero-cycle containing lawsone **1j** underwent the reaction to give the product (+)-**4ja**/**5ja** in 78% yield with 3.7:1 *dr* and 86/91% *ee* in 18 h (Table 4). The lawsones **1k** to **1n** possessing different alkyl groups resulted in the tandem products (+)-**4ka/5ka** to (+)-**4na/5na**, in 70 to 80% yields with 80 to 94% *ee* and good *dr*'s in 10 to 18 h (Table 4). The benzyl containing lawsones **1o**/**1p** possessing Me and OMe on the phenyl group of the naphthoquinone moiety, took part in the tandem reaction with **2a** to furnish the products (+)-**4oa**/**5oa** and (+)-**4pa**/**5pa** in each 90% yields with 91 to >99% *ee* and good *dr*'s within 1 h (Table 4). Surprisingly, the products (+)-**4aa**, and (+)-**4ga** to (+)-**4ja** exhibited the in situ formation of the corresponding retro-Henry or Michael products, varying from 20 to 99%, with the highest percentage for (+)-**4ia**, exclusively under the high pressure experienced during the CSP-HPLC analysis. These results were additional support to the observation of epimerization during the column purification (Tables 1-4). The turnover numbers (TON) calculated for all the entries were found to be in the range of 1200 to 1800 (Table 4). The structure of the compound **4ha** was further confirmed by X-Ray crystallography (Figure 4).

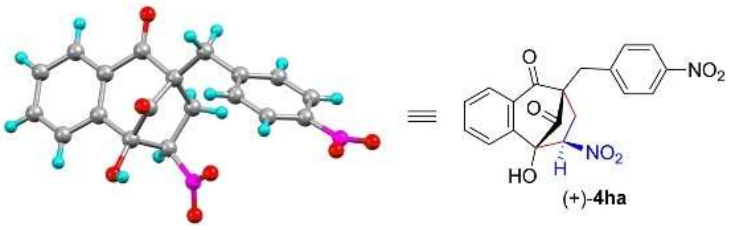
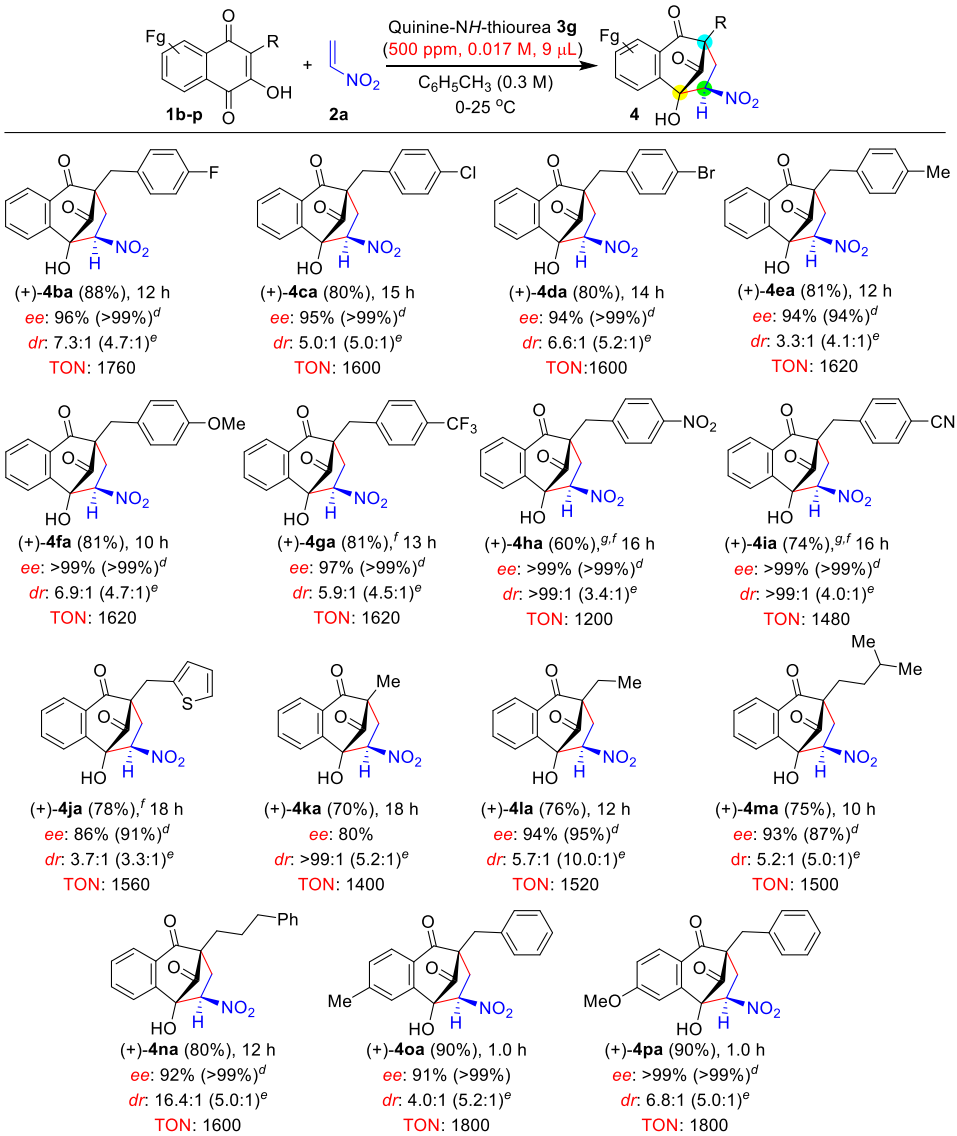


Figure 4: X-Ray crystal structure of (5*R*,6*R*,8*S*)-5-hydroxy-6-nitro-8-(4-nitrobenzyl)-5,6,7,8-tetrahydro-9H-5,8-methanobenzo[7]annulene-9,10-dione (+)-**4ha**.

Table 4: 3-Alkyl-lawsones scope.[a-c]



[a] Reactions were carried out in toluene (0.1 mL) with 3.0 equiv. of **2a** (0.9 mL, 1.0 M in toluene) relative to the **1a** to **1p** (0.3 mmol) in the presence of catalyst **3g** (500 ppm) at 0 °C for 0.5 h and rest of time at 25 °C. [b] Yield refers to the column-purified product. [c] *Ee* and *dr* were determined by CSP-HPLC analysis of the column-purified products. [d] In parenthesis values refer to minor *ee*. [e] In parenthesis values determined by ^{1}H NMR analysis of the column-purified products. [f] *retro*-Henry or Michael product **4'** (15-90%) was observed *in situ* during the CSP-HPLC analysis. [g] Reaction performed in DCM (0.1 mL).

^{1}H, ^{13}C NMR and HPLC spectra of few compounds from Table 4 have depicted in Figure 5-10.

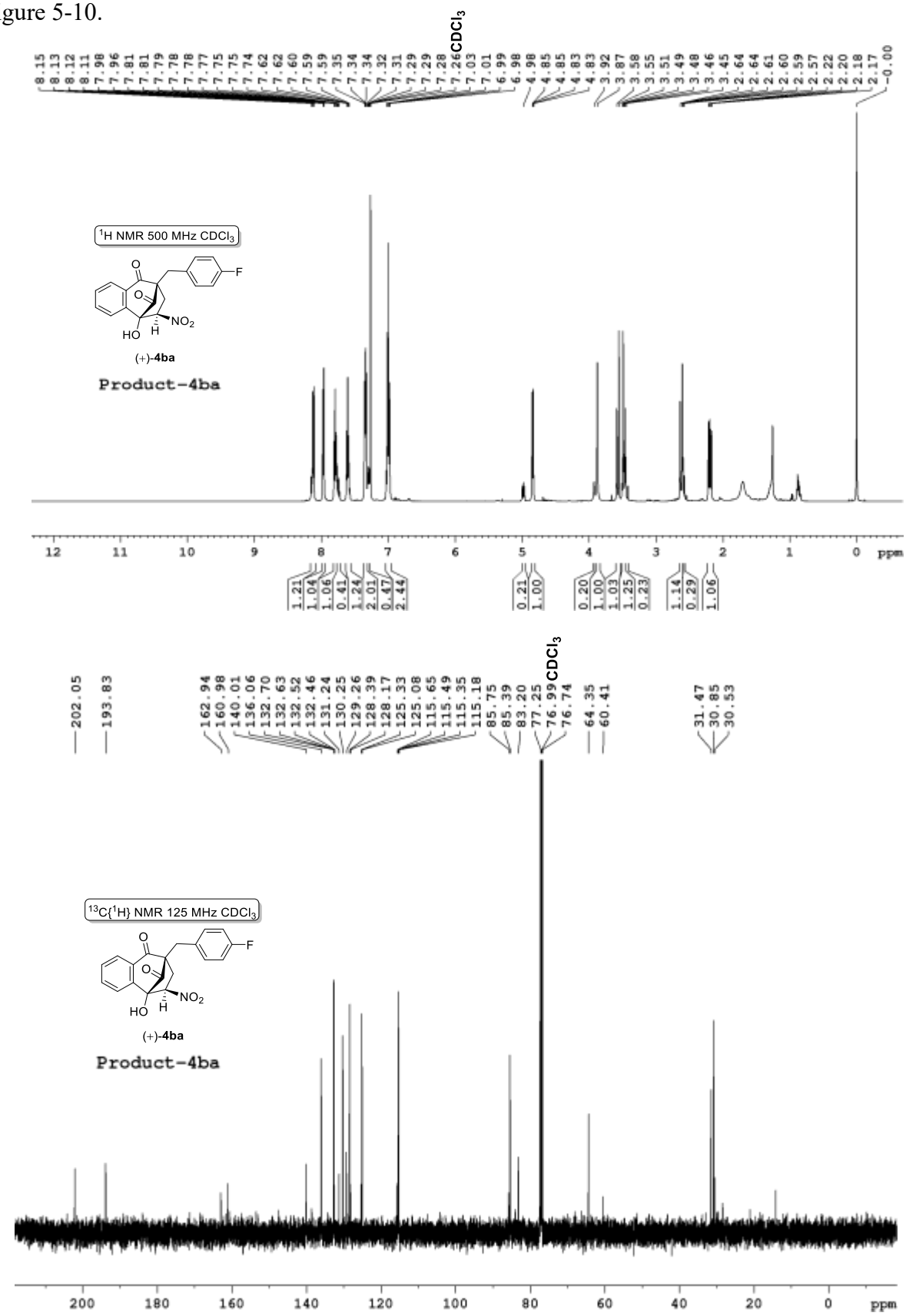
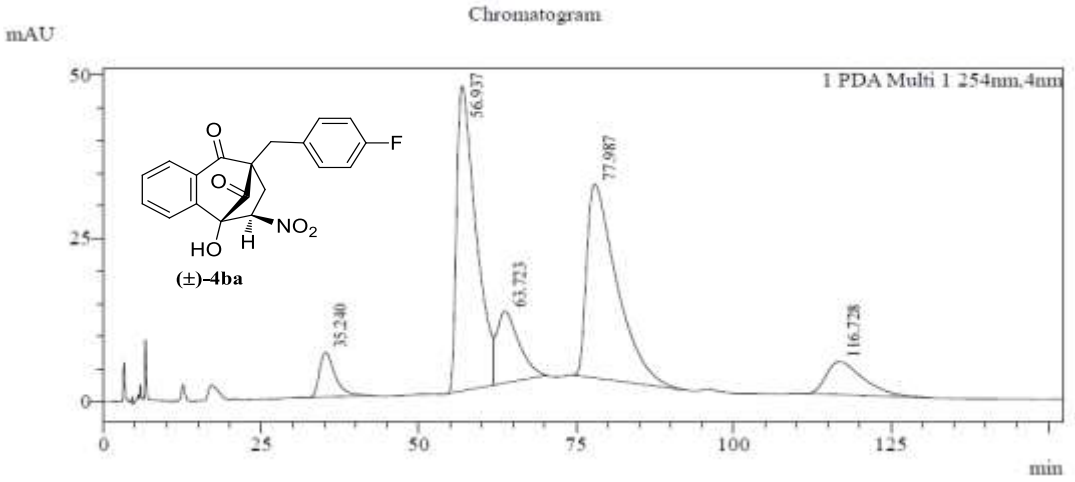


Figure 5: ^{1}H NMR and ^{13}C NMR spectrum of product **4ba**.

Racemic (±)-**4ba**:



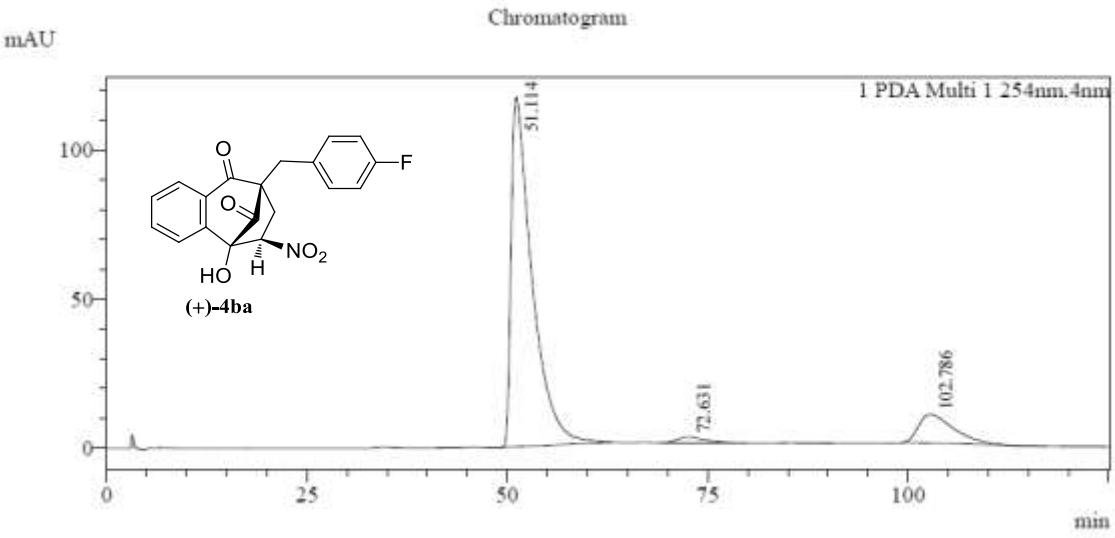
Daicel Chiralcel OJ-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:35.240	35.240	1182850	6842	4.585	6.898
2	RT:56.937	56.937	9930741	46666	38.498	47.051
3	RT:63.723	63.723	2694727	10979	10.446	11.070
4	RT:77.987	77.987	9908839	29653	38.413	29.897
5	RT:116.728	116.728	2078500	5042	8.058	5.083
Total			25795657	99182	100.000	100.000

Chiral-(+)-4ba (Major: 96% *ee;* Minor: >99% *ee*):



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

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:51.114	51.114	21359853	117283	86.305	91.058
2	RT:72.631	72.631	424843	1863	1.717	1.447
3	RT:102.786	102.786	2964672	9655	11.979	7.496
Total			24749368	128801	100.000	100.000

Figure 6: HPLC spectra of product **4ba**.

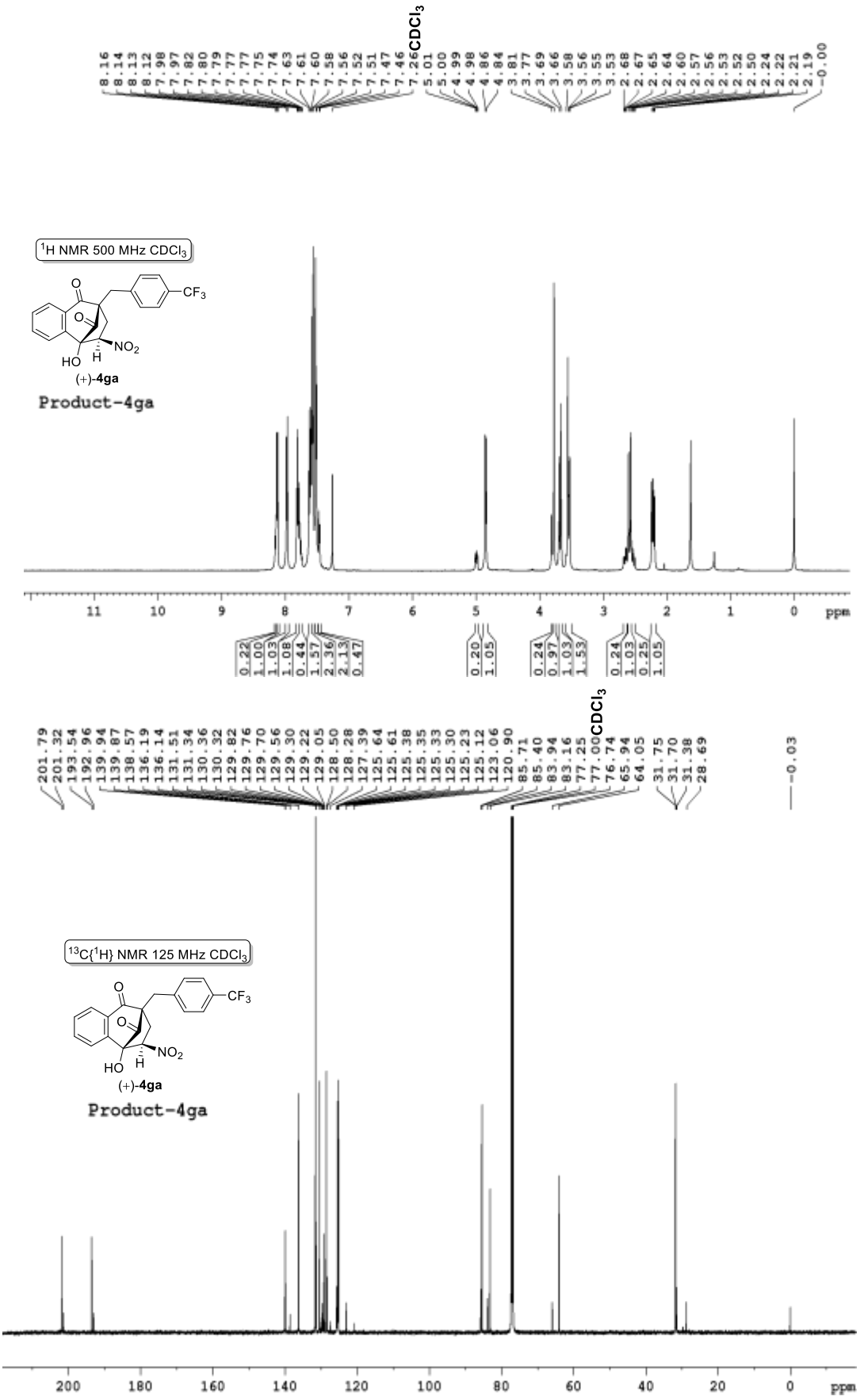
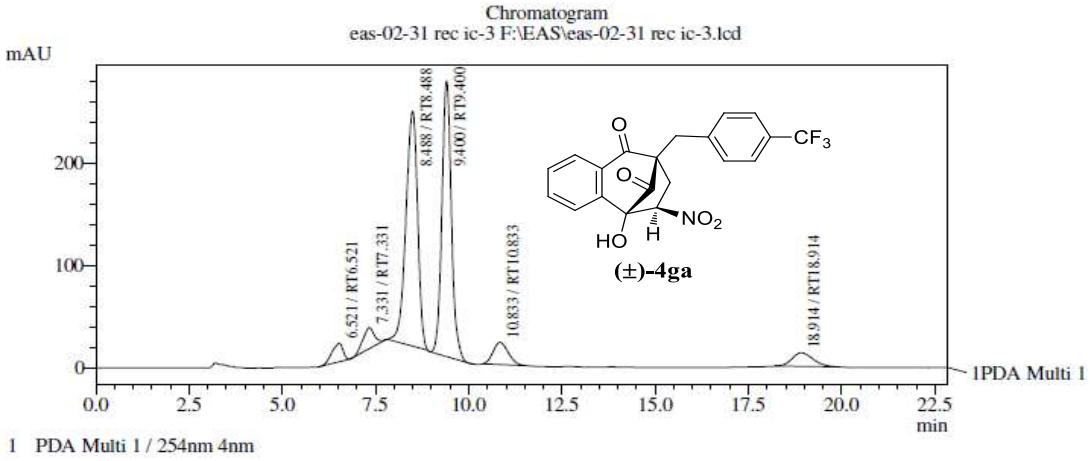


Figure 7: ^{1}H NMR and ^{13}C NMR spectrum of product **4ga**.

Racemic (±)-**4ga**:



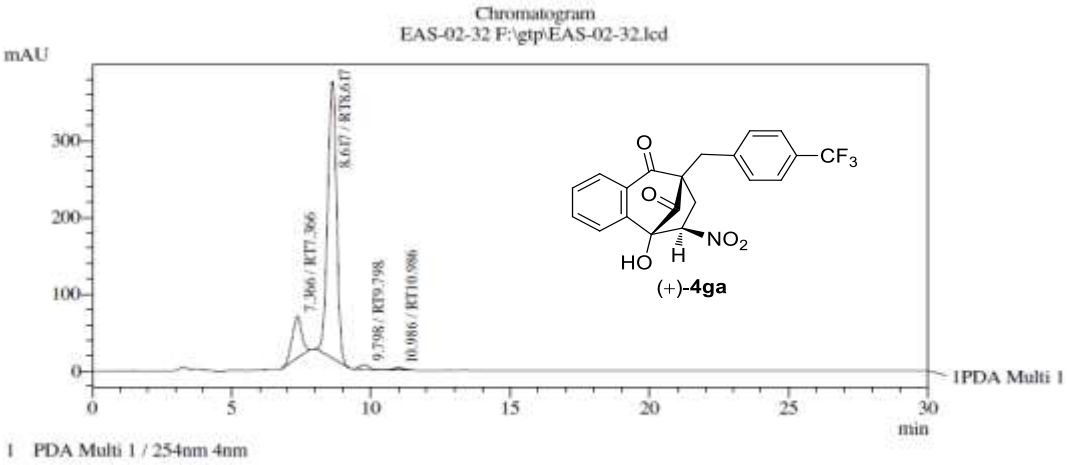
Daicel Chiralpak IC-3, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT6.521	6.521	381655	18320	3.241	3.193
2	RT7.331	7.331	444777	20584	3.777	3.587
3	RT8.488	8.488	5043841	229855	42.828	40.060
4	RT9.400	9.400	4768308	270004	40.488	47.057
5	RT10.833	10.833	615474	21768	5.226	3.794
6	RT18.914	18.914	522984	13247	4.441	2.309
Total			11777038	573779	100.000	100.000

Chiral-(+)-4ga [Major: 97% *ee;* Minor: >99% *ee*; *retro*-Henry product: 13% (>99% *ee*)]:



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

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT7.366	7.366	1299450	54247	13.591	12.783
2	RT8.617	8.617	8048277	361318	84.177	85.140
3	RT9.798	9.798	128601	5685	1.345	1.340
4	RT10.986	10.986	84833	3132	0.887	0.738
Total			9561161	424382	100.000	100.000

Figure 8: HPLC spectra of product **4ga**.

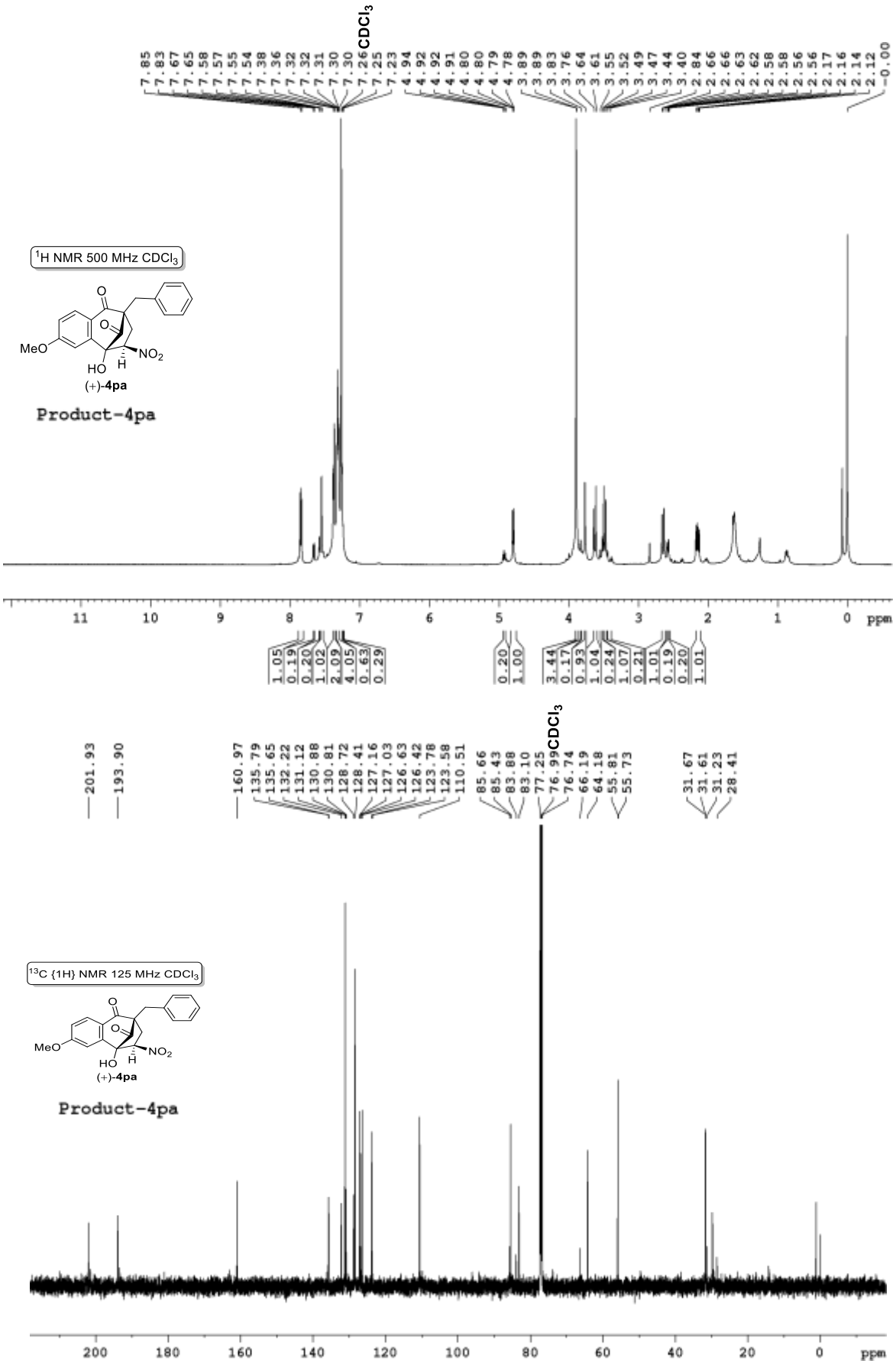
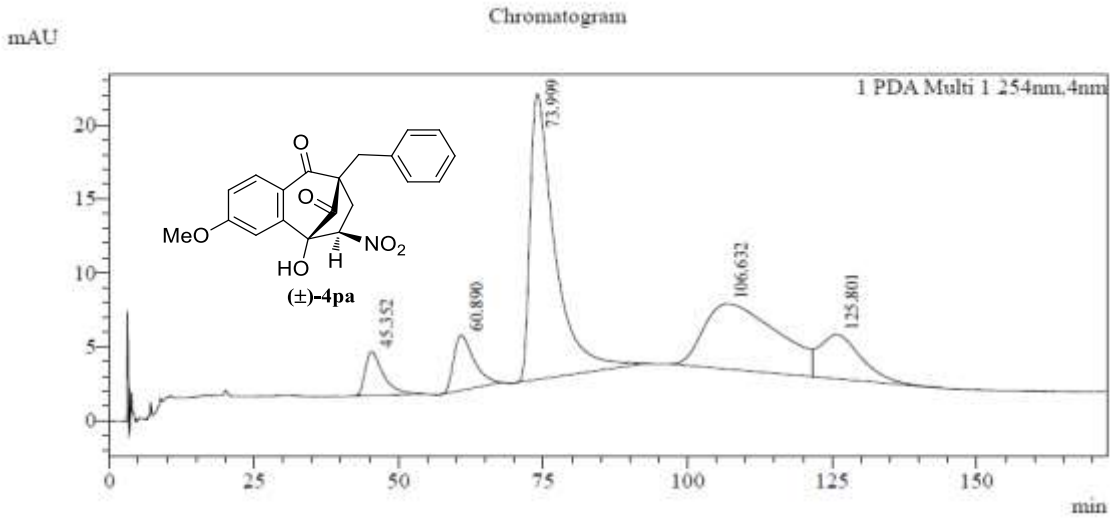


Figure 9: ^{1}H NMR and ^{13}C NMR spectrum of product **4pa**.

Racemic (±)-**4pa**:



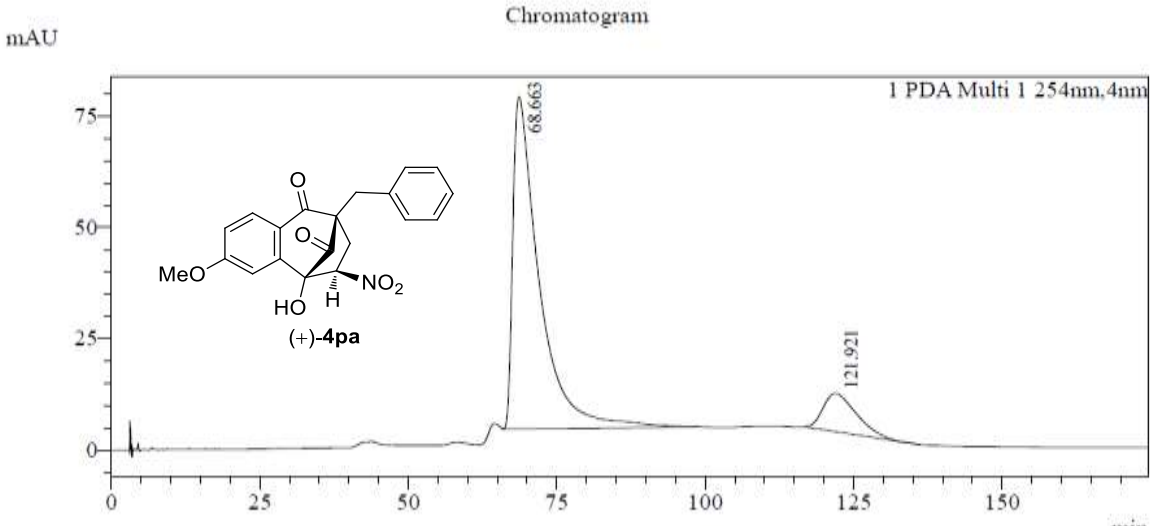
Daicel Chiralcel OJ-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:45.352	45.352	641919	2963	5.007	8.873
2	RT:60.890	60.890	910136	3722	7.098	11.146
3	RT:73.999	73.999	5765772	19318	44.969	57.852
4	RT:106.632	106.632	3980076	4396	31.042	13.164
5	RT:125.801	125.801	1523722	2994	11.884	8.966
Total			12821625	33393	100.000	100.000

Chiral-(+)-4pa (Major: >99% *ee*; Minor: >99% *ee*):



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

Peak Table

PDA Ch1 254nm

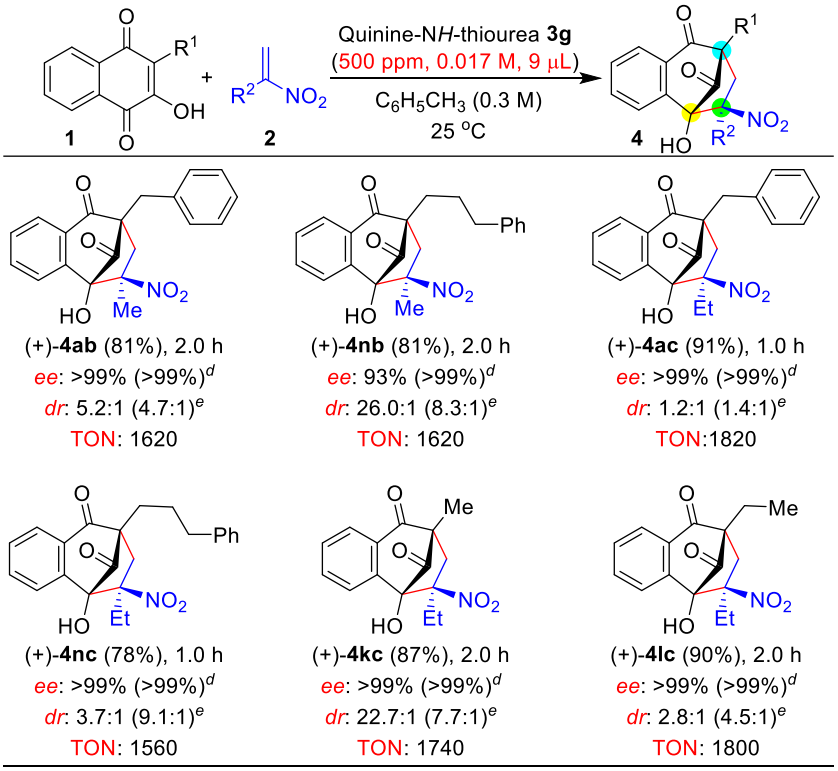
Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:68.663	68.663	23076736	74573	87.241	89.685
2	RT:121.921	121.921	3375037	8577	12.759	10.315
Total			26451773	83150	100.000	100.000

Figure 10: HPLC spectra of product **4pa**.

3.2.2 Substrate scope of nitroethylenes

In order to broaden the ppm-level catalyzed tandem reaction, α-methyl and α-ethyl substituted nitroethylenes **2b**/**2c** were prepared and utilized in the reaction with the lawsones to study their reactivity/selectivity (Table 5). Gratifyingly, the nitroethylenes **2b**/**2c** reacted very comfortably with the lawsones **1a**, **1k**, **1l** and **1n** under the optimal catalytic conditions to furnish the tandem products (+)-**4ab/5ab** & (+)-**4nb/5nb**, (+)-**4ac/5ac** & (+)-**4nc/5nc** and (+)-**4kc/5kc** & (+)-**4lc/5lc** correspondingly, in 78 to 91% yields with 93 to >99% *ee* and moderate to very good *dr*'s with 1560 to 1820 as TONs (Table 5). Surprisingly, ppm-level catalytic tandem reactions of **2b**/**2c** with **1a** to **1n** completed within 2 h, compared to **2a** may be due to the high stability/purity. The discrepancies in the *dr* values determined from HPLC and ^{1}H NMR of pure compounds are due to the in-situ formation of retro-Henry or Michael product and epimerization during the silica gel-mediated purification or high pressure HPLC analysis on chiral stationary phase.

Table 5: Nitroethylenes scope.[a-c]



[a] Reactions were carried out in toluene (0.1 mL) with 3.0 equiv. of **2** (0.9 mL, 1.0 M in toluene) relative to the **1** (0.3 mmol) in the presence of catalyst **3g** (500 ppm) at 25 °C. [b] Yield refers to the column-purified product. [c] *Ee* and *dr* were determined by CSP-HPLC analysis of the column-purified products. [d] In parenthesis values refer to minor *ee*. [e] In parenthesis values determined by ^{1}H NMR analysis of the column-purified products.

^{1}H, ^{13}C NMR and HPLC spectra of few compounds from Table 5 have depicted in Figure 11-14.

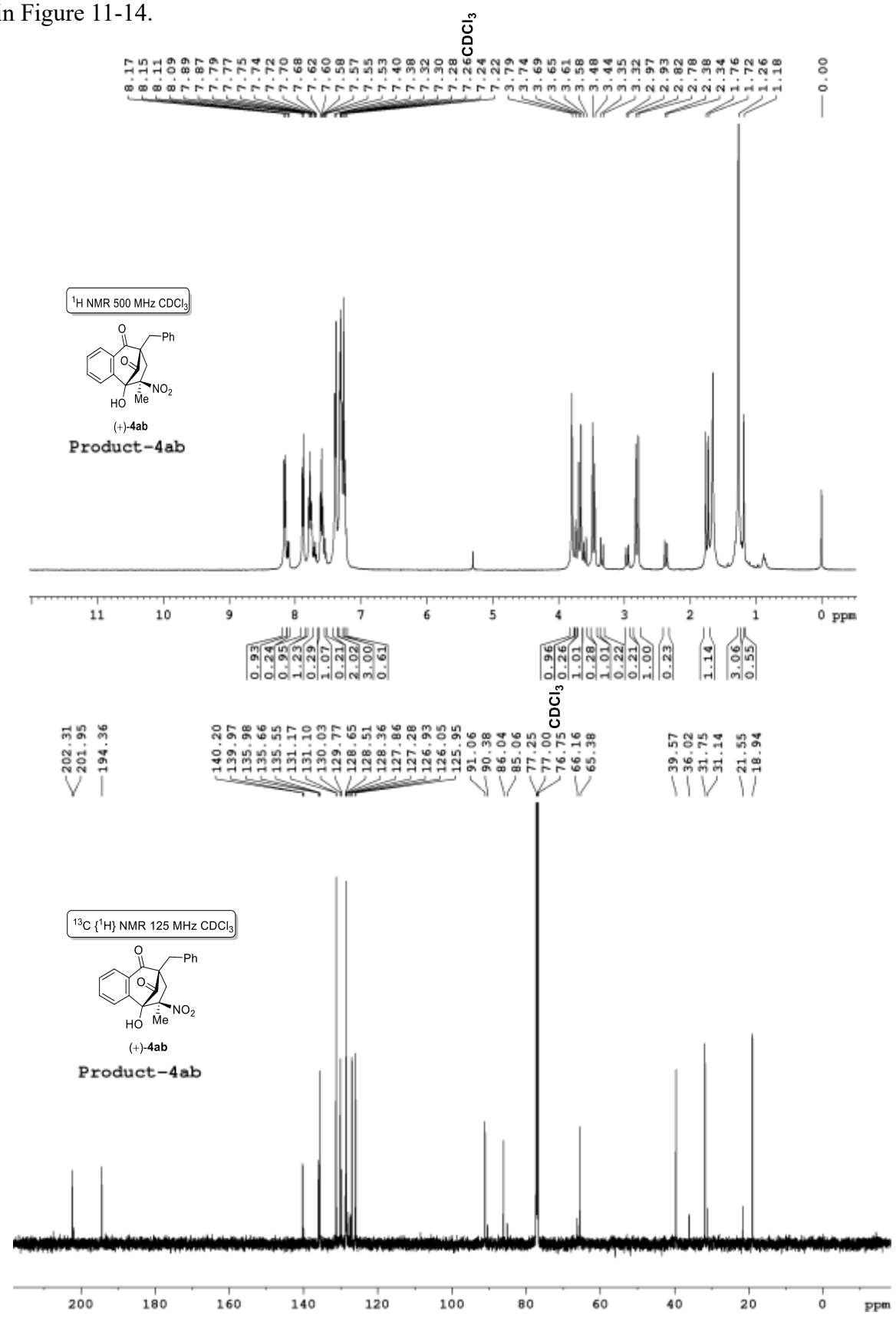
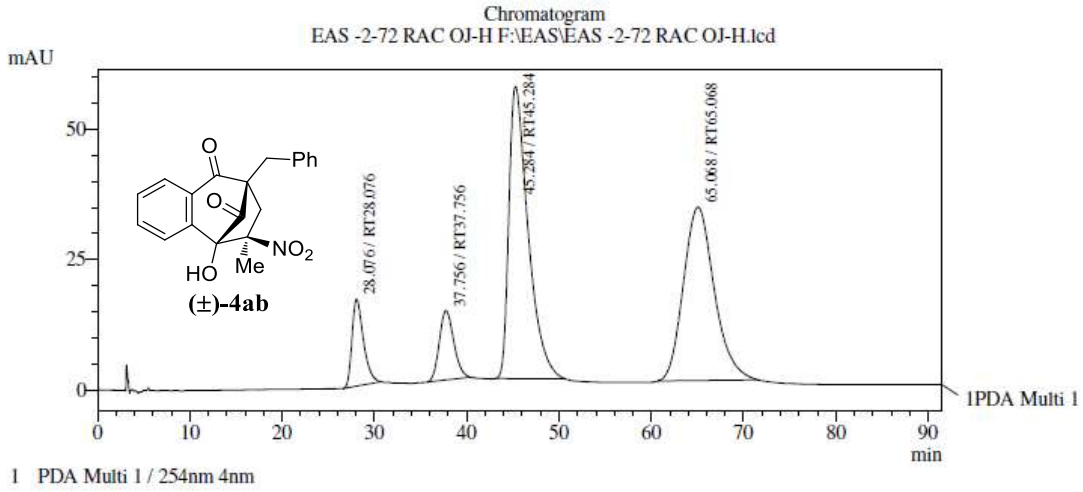


Figure 11: ^{1}H NMR and ^{13}C NMR spectrum of product **4ab**.

Racemic (±)-**4ab**:



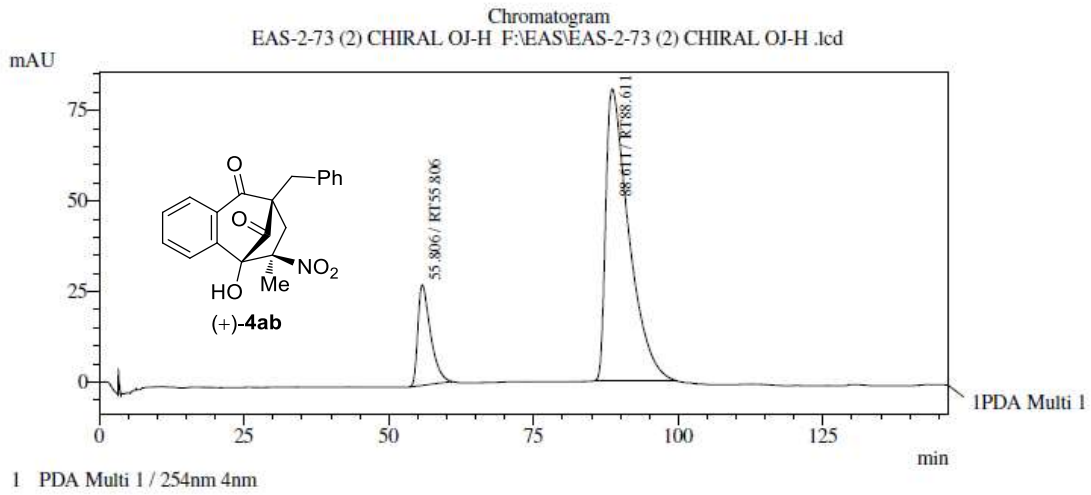
Daicel Chiralcel OJ-H, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT28.076	28.076	1438331	16684	7.680	13.996
2	RT37.756	37.756	1453278	13289	7.759	11.148
3	RT45.284	45.284	8109348	56011	43.298	46.986
4	RT65.068	65.068	7728240	33222	41.263	27.869
Total			18729197	119207	100.000	100.000

Chiral-(+)-4ab (Major: >99% *ee*; Minor: >99% *ee*):



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

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT55.806	55.806	4212991	27708	15.877	25.595
2	RT88.611	88.611	22321740	80545	84.123	74.405
Total			26534731	108253	100.000	100.000

Figure 12: HPLC spectra of product **4ab**.

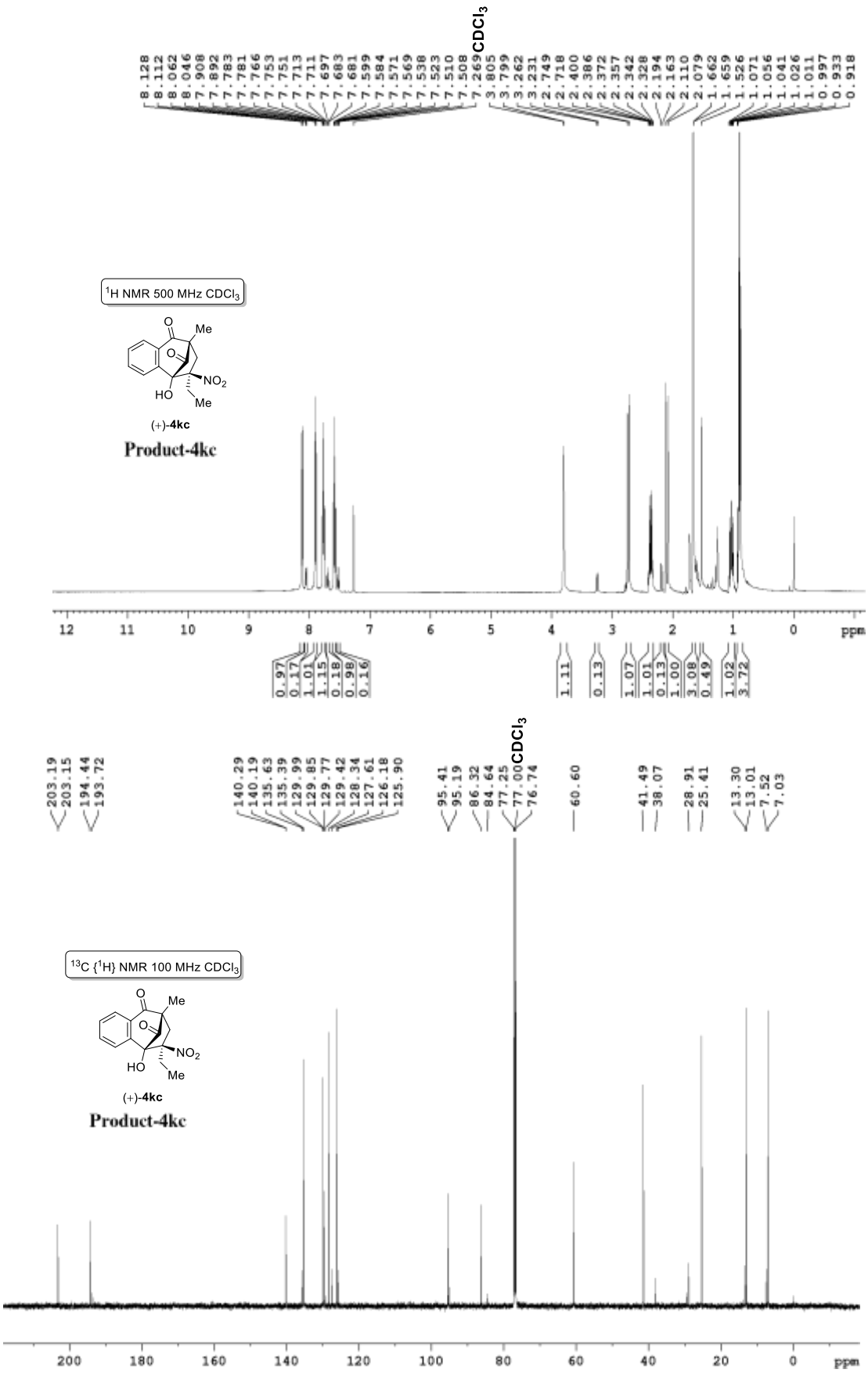
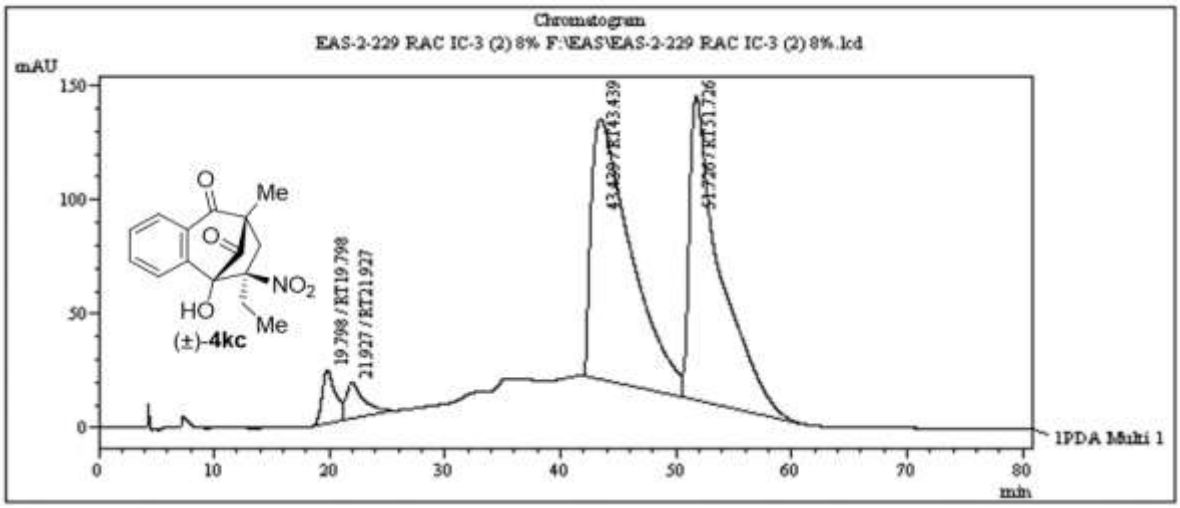


Figure 13: ^{1}H NMR and ^{13}C NMR spectrum of product **4kc**.

Racemic (±)-**4kc**:



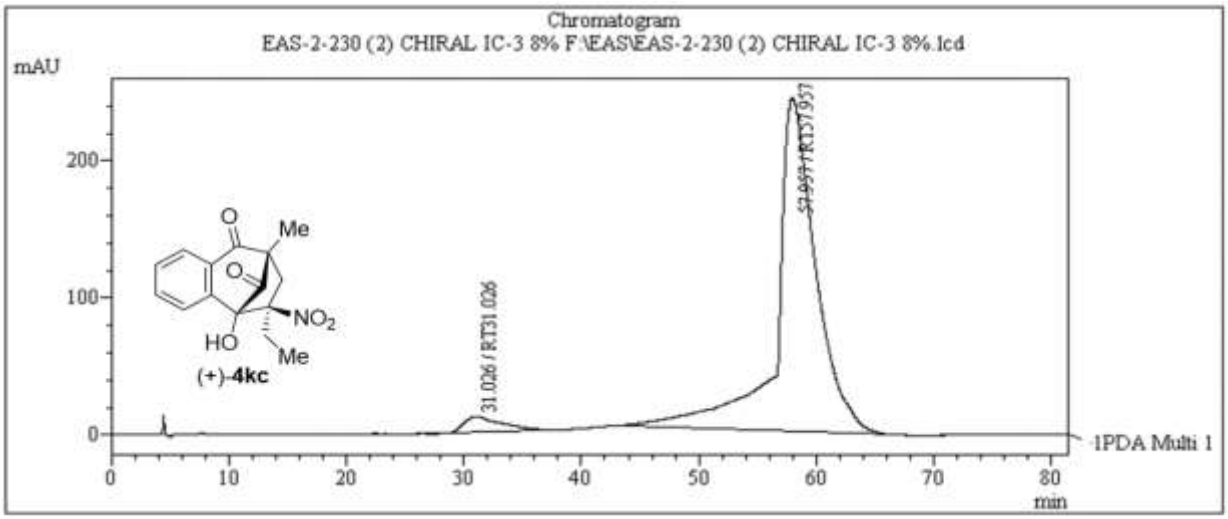
Daicel Chiralpak IC-3, Hexane/ *i*-PrOH = 92:8, Flow Rate 0.8 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT19.798	19.798	1873995	23829	3.362	8.289
2	RT21.927	21.927	1660711	15826	2.980	5.505
3	RT43.439	43.439	27518079	114365	49.373	39.783
4	RT51.726	51.726	24682320	133451	44.285	46.423

Chiral-(+)-4kc (Major: >99% *ee*; Minor: >99% *ee*):



Daicel Chiralpak IC-3, Hexane/ *i*-PrOH = 92:8, Flow Rate 0.8 mL/Min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

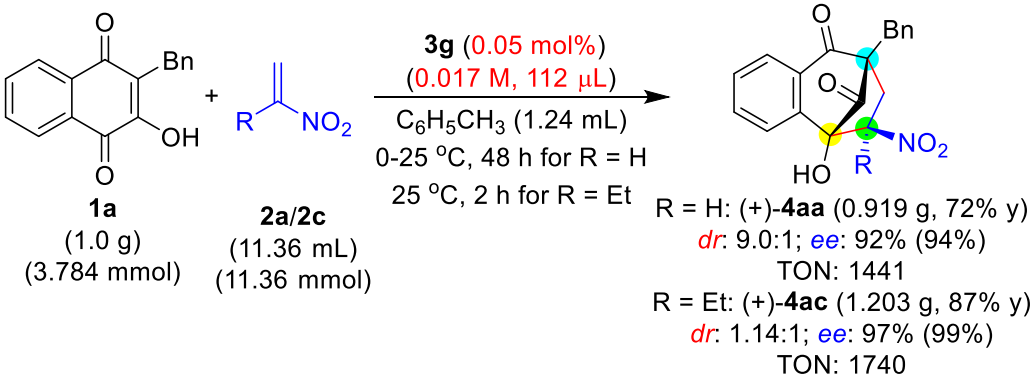
Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT31.026	31.026	2531429	11791	4.214	4.628
2	RT57.957	57.957	57547503	242965	95.786	95.372
Total			60078932	254756	100.000	100.000

Figure 14: HPLC spectra of product **4kc**.

3.2.3 Gram scale synthesis and synthetic transformations

Applicability of this low catalyst **3g** loaded (500 ppm-level) reaction between **1a** (1.0 g) and **2a/2c** (11.36 mL, 1.0 M) on gram-scale quantities was studied and found to be sustained with respect to yield/*ee*/*dr*/rate as 0.919 g (72% yield), 9.0:1 *dr* and 92/94% *ee* with 1441 TON for the tandem product (+)-**4aa/5aa**; 1.203 g (87% yield), 1.14:1 *dr* and 97/99% *ee* with 1740 TON for the tandem product (+)-**4ac/5ac** were obtained (Scheme 2). For exemplifying the significance and applications of the tandem products **4**/**5**, a few synthetic transformations were executed. Interestingly, treatment of (+)-**4aa/5aa** with zinc and ammonium chloride in ethanol at 25 °C for 5 h generated the oxazinol (+)-**6aa** in 44% yield with 99:1 *dr* through the sequence of retro-Henry/nitro-reduction/ketalization. Alternatively, reaction of (+)-**4aa/5aa** and (+)-**4ca/5ca** with Et_3SiH in the presence of $BF_3.OEt_2$ in DCM at 0 to 25 °C for 24 h, resulted in the formation of the tetrahydrofuran-4(2*H*)-ones (+)-**7aa** and (-)-**7ca** in 42% and 44% yields with >99:1 *dr* respectively through the sequence of retro-Henry/carbonyl-reduction/alkylation (Scheme 2). These two reactions first initiated by retro-Henry, which is confirming once again sensitive nature of tandem products **4/5**. Fused-ring tetrahydrofuran **7** and oxazinol **6** analogous found in a number of natural products possess antibiotic and anti-HIV activity and also versatile building blocks in the organic synthesis, which is highlighting the importance of tandem products **4/5**.[7] To control the epimerization *α*-to the *tert*-OH group, we protected (+)-**4aa** [>16:1 *dr* and 99% *ee*] with acetyl chloride under the 30 mol% of H_2SO_4 at 25 °C for 1.5 h to furnish the (+)-**8aa** in 70% yield with >20:1 *dr* and 96.6% *ee* (Scheme 2). We have done five more tandem products **4** *tert*-OH protection to prevent the isomerization through *in situ* retro-Henry/Henry reaction. After OH-protection, we did not observe the epimerization or retro-Henry during the column purification or HPLC analysis of the products (+)-**8.** In a further application, carbonyl reduction of (+)-**8aa** (>20:1 *dr* and 90% *ee*) with 1.3 equiv. of $NaBH_4$ in dry methanol at 0 °C for 4 h gave selectively mono-hydroxyl product (+)-**9aa** in 40% yield with >25:1 *dr* and 89% *ee* along with unreacted starting material (+)-**8aa** in 50% recovery (Scheme 2). We established the structure and absolute stereochemistry of the tandem products **4/5/6/7/8/9** by IR/NMR/mass/2D-NMR analysis and also finally confirmed by X-ray structure analysis on (+)-**4aa**, (+)-**4ha** and (+)-**5ac** as shown in Figures **1** and **4**.

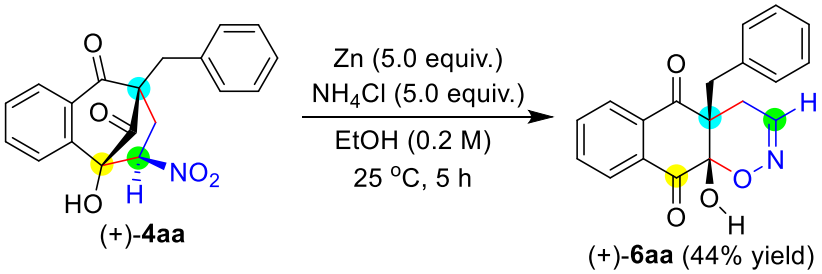
Gram-scale synthesis *via* 500 ppm-level catalysis:



1a
(1.0 g)
(3.784 mmol)

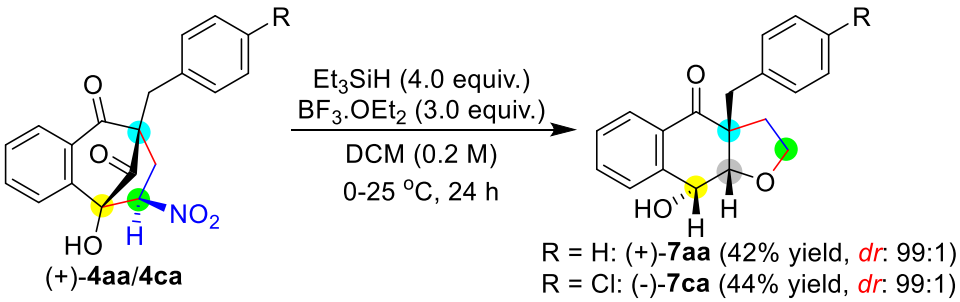
2a/2c
(11.36 mL)
(11.36 mmol)

R = H: (+)-**4aa** (0.919 g, 72% y)
dr: 9.0:1; *ee*: 92% (94%)
TON: 1441
R = Et: (+)-**4ac** (1.203 g, 87% y)
dr: 1.14:1; *ee*: 97% (99%)
TON: 1740



(+)-**4aa**

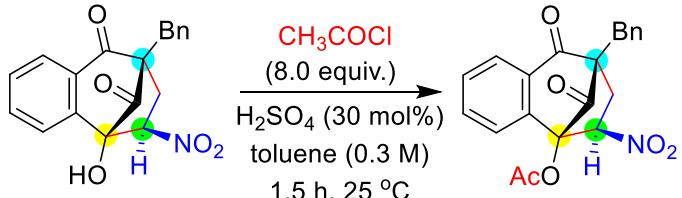
(+)-**6aa** (44% yield)



(+)-**4aa/4ca**

R = H: (+)-**7aa** (42% yield, *dr*: 99:1)
R = Cl: (-)-**7ca** (44% yield, *dr*: 99:1)

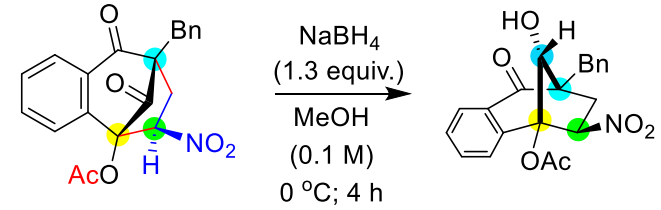
Controlling the epimerization through OH protection:



(+)-**4aa** (0.3 mmol)
dr: >16:1; *ee*: 99%

(+)-**8aa** (70% yield)
dr: >20:1; *ee*: 96.6%

Selective carbonyl reduction:



(+)-**8aa** 90% *ee*
>20:1 *dr*

(+)-**9aa**: 40% yield
89% *ee*; >25:1 *dr*

Scheme 2: Synthetic applications of chiral bicyclo[3.2.1]octanes.

^{1}H, ^{13}C NMR, Hetero-COSY, NOESY and HPLC spectra of few compounds from scheme 2 have depicted in Figure 15-22.

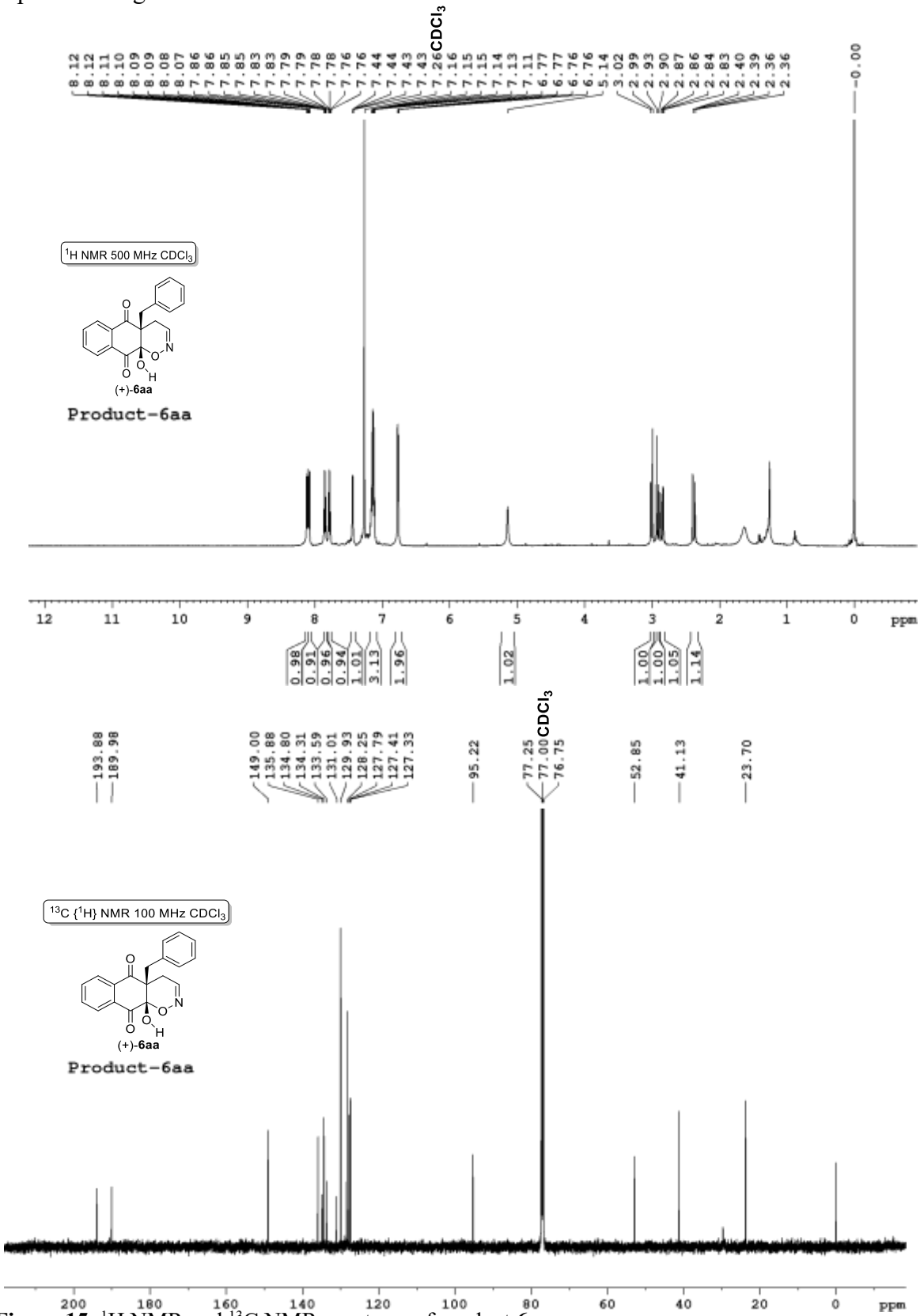


Figure 15: ^{1}H NMR and ^{13}C NMR spectrum of product **6aa**.

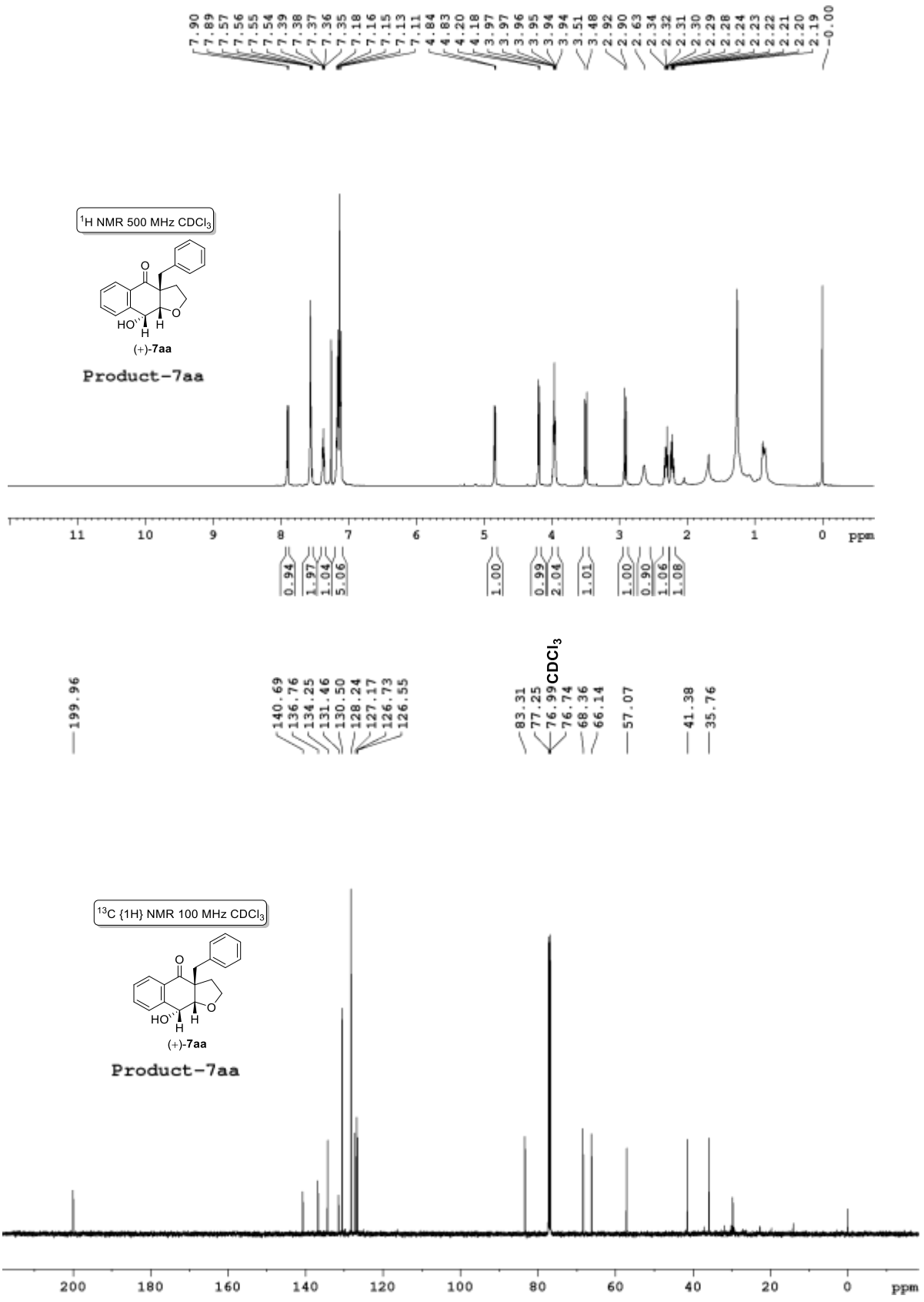


Figure 16: ^{1}H NMR and ^{13}C NMR spectrum of product **7aa**.

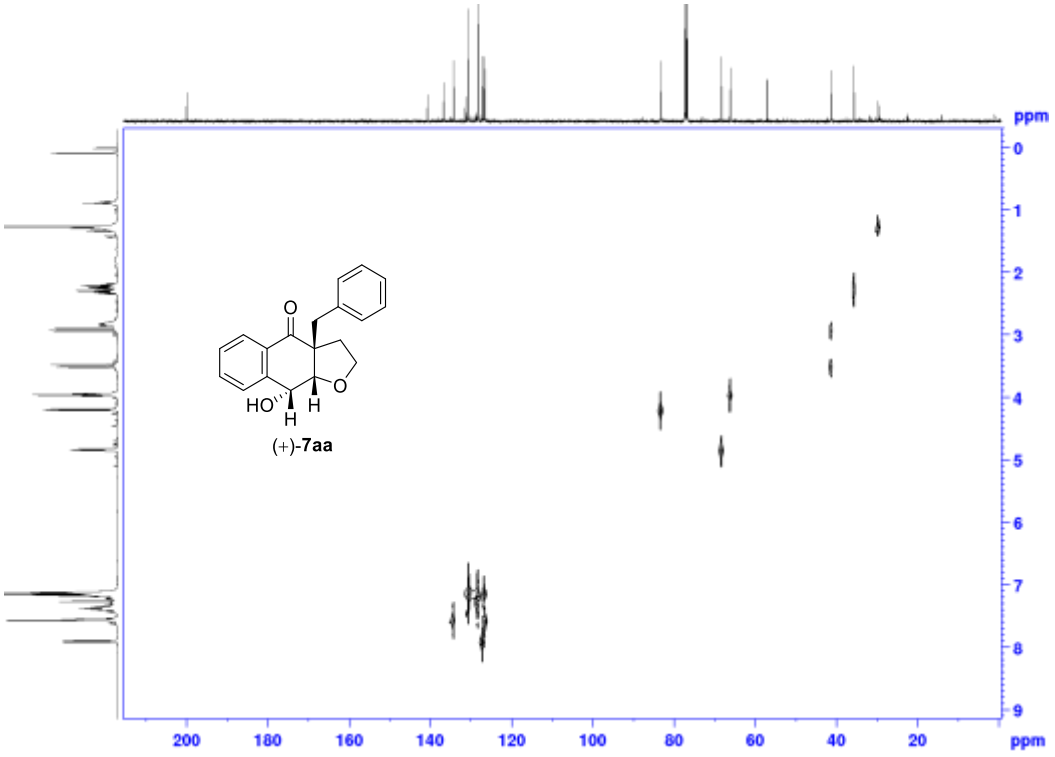


Figure 17: Hetero-COSY spectrum of compound (+)-**7aa** (500 MHz, $CDCl_3$ at 25 °C).

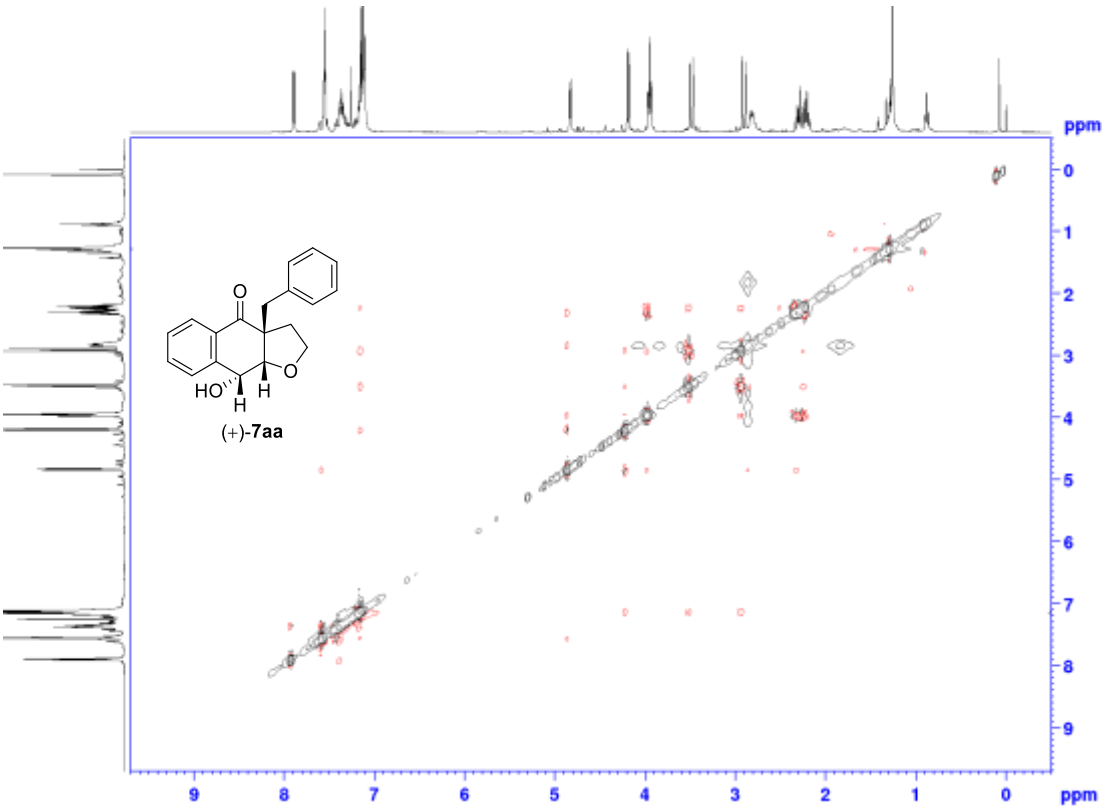


Figure 18: NOESY spectrum of compound (+)-**7aa** (500 MHz, $CDCl_3$ at 25 °C).

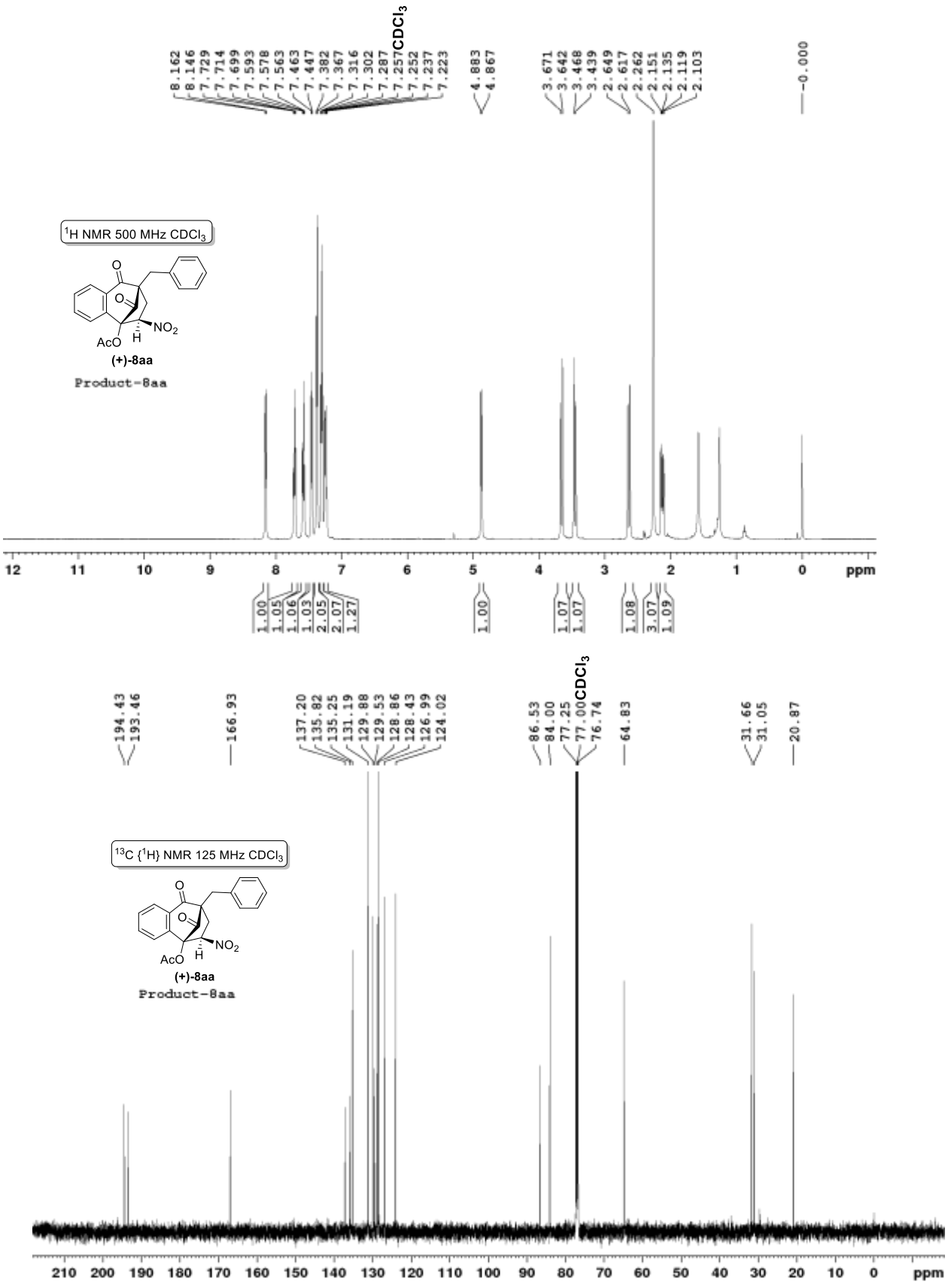
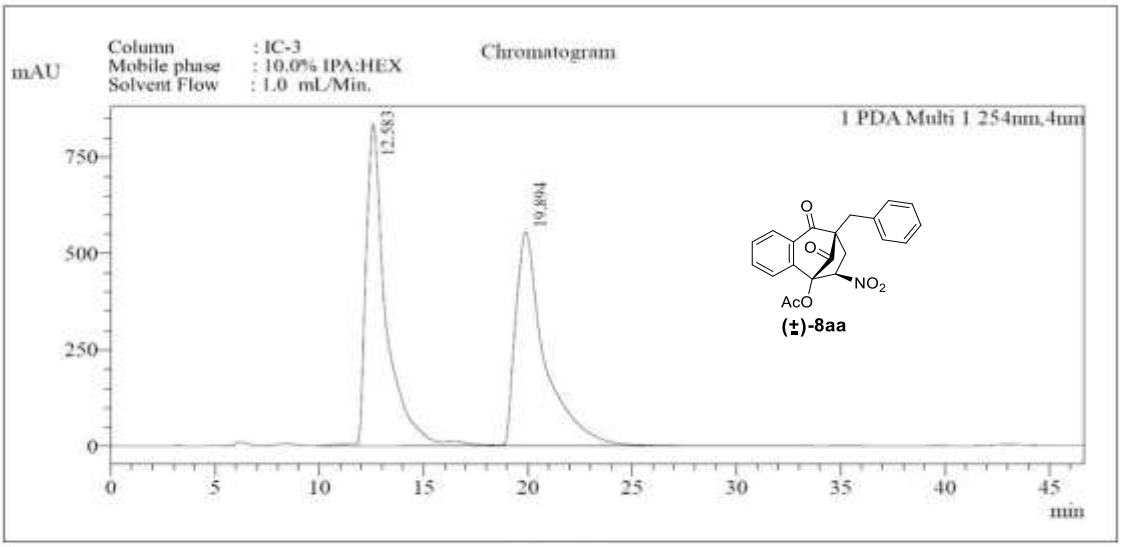


Figure 19: ^{1}H NMR and ^{13}C NMR spectrum of product **8aa**.

Racemic (±)-8aa:

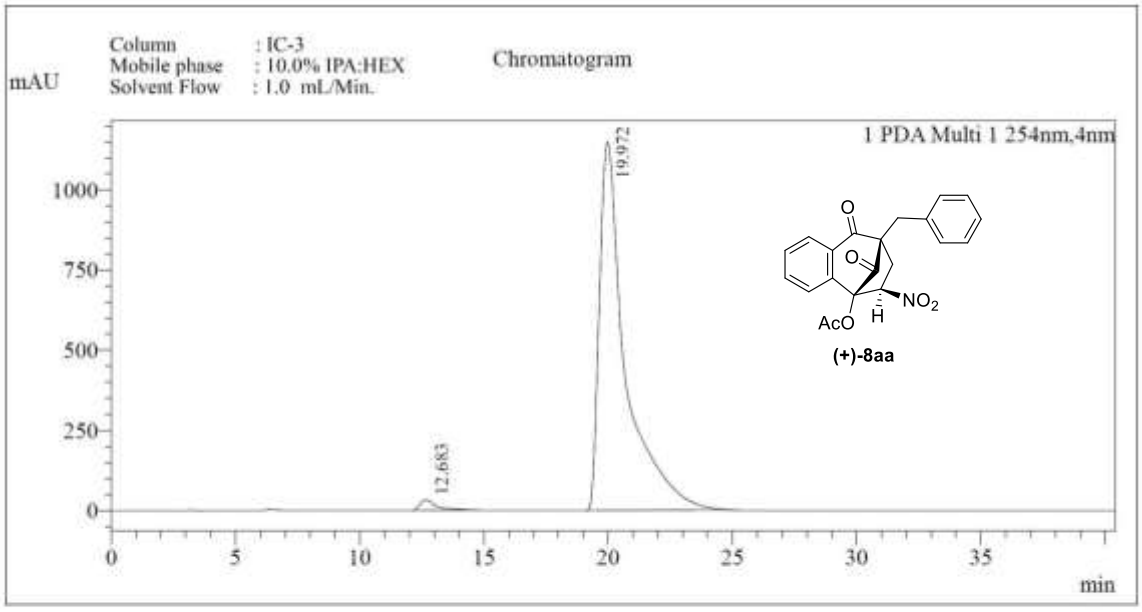


Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:12.583	12.583	56154120	835258	50.993	60.034
2	RT:19.894	19.894	53966685	556040	49.007	39.966
Total			110120805	1391298	100.000	100.000

Chiral-(+)-8aa (Major: 96.6% *ee*):



Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:12.683	12.683	1457120	31995	1.707	2.709
2	RT:19.972	19.972	83894821	1149226	98.293	97.291
Total			85351942	1181221	100.000	100.000

Figure 20: HPLC spectra of product **8aa**.

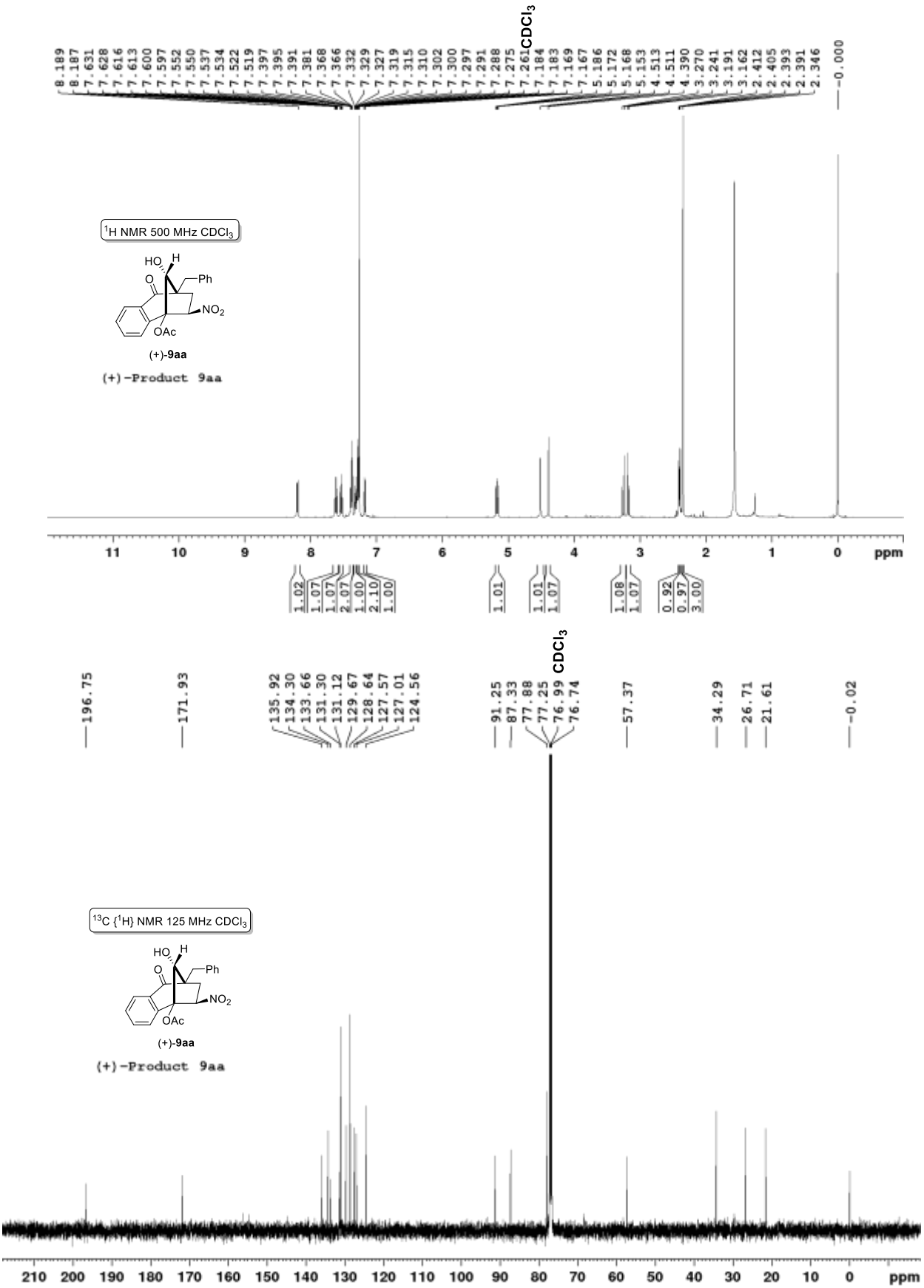
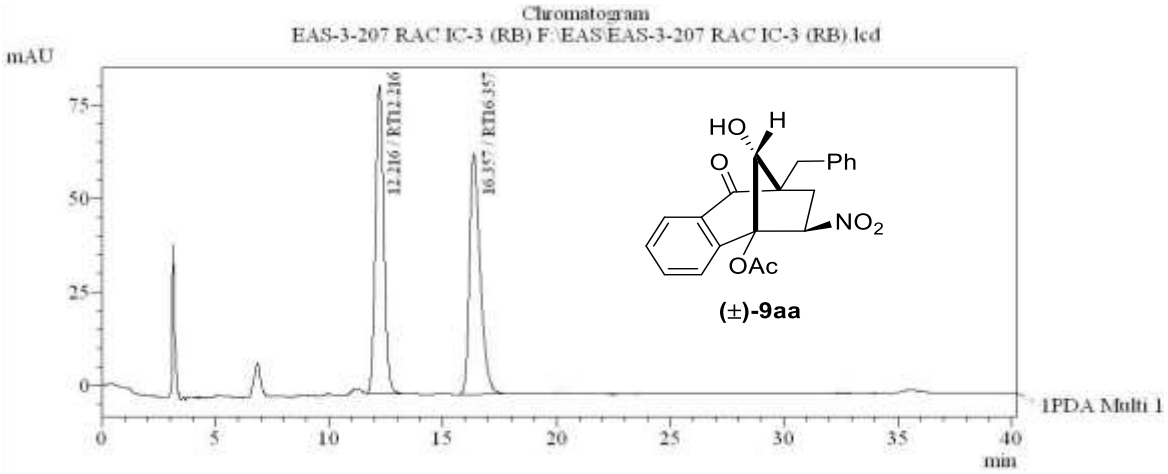


Figure 21: ^{1}H NMR and ^{13}C NMR spectrum of product **9aa**.

Racemic (±)-**9aa**:



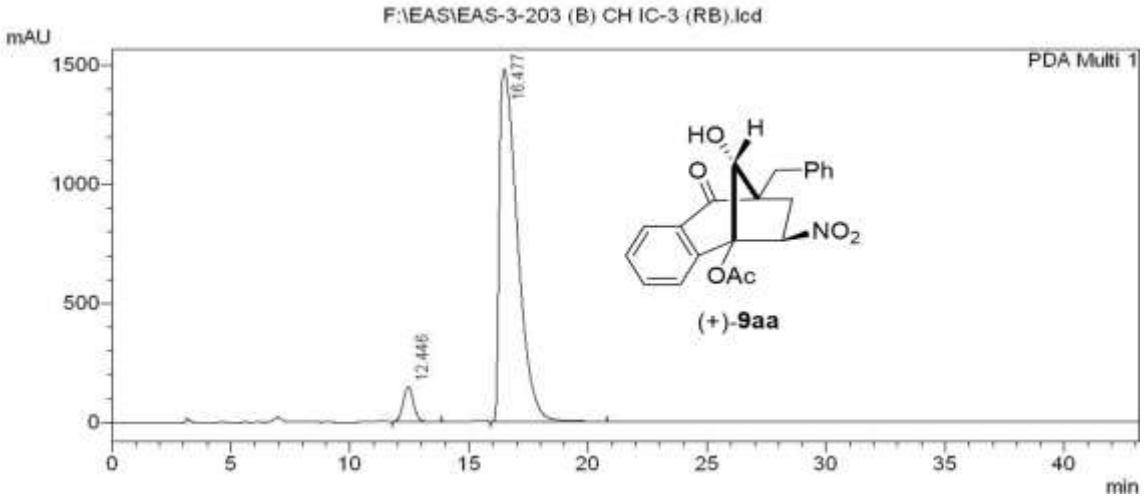
Daicel Chiralpak IC-3, Hexane/i-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT12.216	12.216	2079242	82220	49.755	56.126
2	RT16.357	16.357	2099732	64271	50.245	43.874
Total			4178974	146491	100.000	100.000

Chiral (+)-9aa (89% *ee*) obtained from the selective reduction of (+)-8aa (90% *ee*):



PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT12.446	12.446	4479689	146085	5.433	8.984
2	RT16.477	16.477	77978189	1480013	94.567	91.016
Total			82457878	1626098	100.000	100.000

Figure 22: HPLC spectra of product **9aa**.

3.2.4 Mechanistic Insights

Even though further studies are necessary for illuminating the mechanism of the tandem Michael/Henry [3+2]-annulation[9,10] through ppm-level **3g**-catalysis, most probably, the annulation reaction might be proceeding in a stepwise manner between the *in situ* generated lawsone-enolates **1'** and nitroethylenes **2** (Figure 23). The observed high *ee* for major diastereomers (+)-**4aa** to (+)-**4lc** could be explained on the consideration of X-ray crystal structure studies, through a favourable *pre*-transition state, where the *si*-face of *in situ* generated lawsone-enolate **1'** approaches the *si*-face of the nitroethylene **2** owing to the strong double hydrogen-bonding and less steric hindrance between the catalyst **3g** and substrates **1/2** as shown in the **TS-1**. The model **TS-2** having a smaller number of hydrogen-bonding interactions between the catalyst **3g** and substrates **1/2** might explain the unfavourable situation for generation of the minor enantiomer of the minor diastereomers (+)-**5aa** to (+)-**5lc** (Figure 23). This might be the reason to get high *ee* for many of the minor diastereomers (+)-**5aa** to (+)-**5lc** (Tables 3-4).

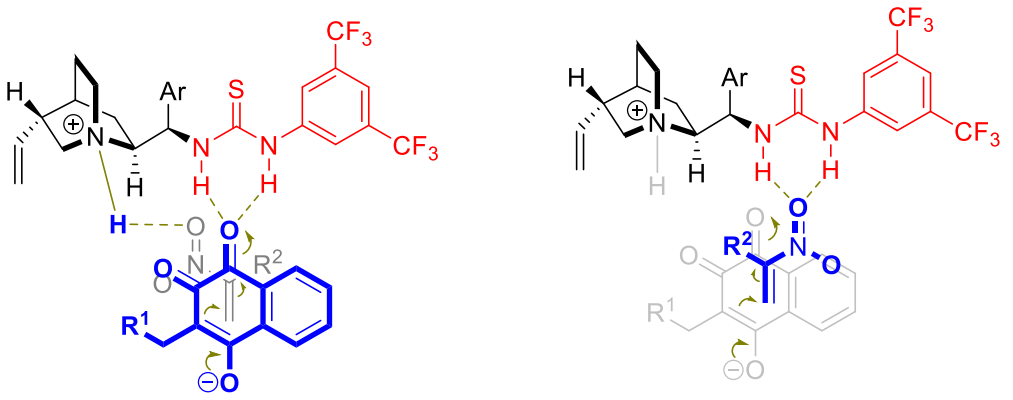


Figure 23: Proposed reaction mechanism.

3.3 Conclusion

we have demonstrated the ppm-level asymmetric organocatalysis for the high-yielding synthesis of chiral methanobenzo[7]annulenes in excellent *ee* and *dr* through the tandem Michael/Henry [3+2]-annulation of 3-alkyl-lawsones **1** with nitroethylenes **2** under 500 ppm catalyst loading of quinine-thiourea **3g**. Sustainability of the ppm-level asymmetric organocatalysis was confirmed by developing a library of chiral tandem methanobenzo[7]annulenes in very good yields/*ee*/*dr*, and was further demonstrated in grams-

scale synthesis also. We have shown the applicability of annulation products **4/5** in a few synthetic transformations, which would be useful in natural and pharmaceutical chemistry. Further work in this line of exploring the ppm-level into ppb-level catalysis by choosing perfect pair of chiral organocatalysts with unmodified reactive substrates is in progress.

3.4 Experimental section:

General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 500, 400, 125 and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) 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. 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 CAD_4 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. 2-Hydroxy-3-alkyl-1,4-naphthoquinones **1a** to **1p** and nitro-olefins **2a** to **2c** were prepared according to the literature procedures.[10, 11]

Procedure A: Preparation of Racemic Tandem Michael/Henry Annulation Products 4/5. In an oven-dried round bottom flask equipped with a magnetic stirring bar, to 2-hydroxy-3-alkyl-1,4-naphthoquinones **1a** to **1p** (0.3 mmol) and 4-dimethylaminopyridine **3f** (10 mol%) in 0.1 mL of toluene at 0 °C, added 0.9 mmol (0.9 mL, 1.0 M in toluene) of nitro-olefins **2a** to **2c**. The reaction mixture was stirred 0 °C for 0.5 h and the rest of time at 25 °C as shown in Table-S1. After completion of the reaction, diluted with H_2O (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Pure racemic

tandem annulation products **4** and **5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure B: **Preparation of Chiral Tandem Michael/Henry Annulation Products 4/5**: In an oven-dried round bottom flask equipped with a magnetic stirring bar, to 2-hydroxy-3-alkyl-1,4-naphthoquinones **1a** to **1p** (0.3 mmol) and chiral quinine-N*H*-thiourea **3g** (0.05 mol% or 500 ppm) in 0.1 mL of toluene at 0 °C, added 0.9 mmol (0.9 mL, 1.0 M in toluene) of nitro-olefins **2a** to **2c**. The reaction mixture was stirred 0 °C for 0.5 h and the rest of time at 25 °C. After completion of the reaction, the crude reaction mixture was directly loaded onto silica gel for column chromatography without aqueous workup. Pure chiral annulation products **4/5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure C: **General Procedure for the Synthesis of (4a*S*,10a*S*)-4a-Benzyl-10a-hydroxy-4a,10a-dihydro-4*H*-naphtho[2,3-e][1,2]oxazine-5,10-dione 6aa**: In an oven-dried round bottom flask equipped with a magnetic stirring bar, to the compound (+)-**4aa** (0.2 mmol) in EtOH (1.0 mL), Zn (1.0 mmol) and NH_4Cl (1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 5 h. The crude reaction mixture filtered, the filtrate was treated with water and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Pure product (+)-**6aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

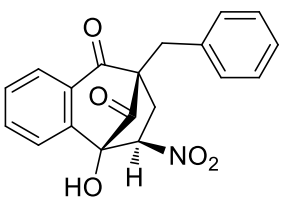
Procedure D: **General Procedure for the Reduction of (+)-4aa/(+)-4ca**: In an oven-dried round bottom flask equipped with a magnetic stirring bar, to a solution of (+)-**4aa**/(+)-**4ca** (0.2 mmol) in dry DCM (1.0 mL) at 0 °C, added triethyl silane (0.8 mmol) followed by boron trifluoride etherate (0.6 mmol). Slowly reaction mixture was brought to room temperature and stirred for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Pure chiral products (+)-**7aa**/(-)-**7ca** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure E: **General Procedure for the Synthesis of 8-Benzyl-6-nitro-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-5-yl acetates (8)**: In an oven dried 10 mL round bottom flask equipped with a magnetic stirring bar, to the crude compound **4** (0.3 mmol), which is obtained after the quick flash filtration of the reactions mixture obtained by Procedure **A** or **B**, in dry toluene (1.0 mL), acetyl chloride (2.4 mmol, 8.0 equiv., 0.17 mL) and H_2SO_4 (0.09 mmol, 30.0 mol%, 4.82 µl) were added. The reaction mixture was stirred at 25 °C for 0.5

to 2.0 h. Pure products **8** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

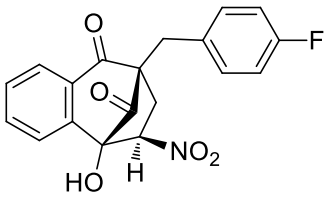
Procedure F: **General Procedure for the Reduction of (5*R*,6*R*,8*S*)-8-Benzyl-6-nitro-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-5-yl acetate 8aa**: In a 10 mL round-bottom flask equipped with a magnetic stirring bar, compound (+)-**8aa** (0.3 mmol, 113.81 mg) was dissolved in dry MeOH (3.0 mL) and then cooled to ice temperature, followed by addition of $NaBH_4$ (14.75 mg, 0.39 mmol, 1.3 equiv.) under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 4.0 h. The crude reaction mixture was worked up with water, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product **(+)-9aa** (45.7 mg, 40% yield) was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(5*R*,6*R*,8*S*)-8-Benzyl-5-hydroxy-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (**4aa**): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as off-white solid; Yield: 82% (83 mg); Mp: 260-262 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 92:8, flow rate 0.8 mL/min, λ = 254 nm), t_R = 78.96 min (major), t_R = 71.69 min (minor) [For retro-Henry]; t_R = 97.95 min (minor), t_R = 130.12 min (major) [For major isomer]; t_R = 111.69 min (major), t_R = 151.67 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +56.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 99% major *ee*, >99% minor *ee* and 11.4:1 *dr*)**; IR (Neat): ν_{max} 3385, 2922, 1773, 1679, 1555, 1495, 1362, 1287, 1060, 977, 834 and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 9.1:1 *dr*, major isomer) δ 8.12 (1H, dd, *J* = 8.0, 0.8 Hz), 7.96 (1H, dd, *J* = 8.0, 0.8 Hz), 7.78 (1H, dt, *J* = 7.6, 1.6 Hz), 7.60 (1H, dt, *J* = 7.6, 1.2 Hz), 7.38-7.36 (2H, m), 7.33-7.26 (3H, m), 4.82 (1H, dd, *J* = 8.0, 1.2 Hz), 3.80 (1H, br s, *OH*), 3.62 (1H, d, *J* = 14.8 Hz), 3.49 (1H, d, *J* = 14.4 Hz), 2.66 (1H, dd, *J* = 16.0, 1.6 Hz), 2.18 (1H, dd, *J* = 16.0, 8.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 9.1:1 *dr*, major isomer) δ 202.1 (C, *C*=O), 193.9 (C, *C*=O), 140.0 (C), 136.0 (CH), 135.6 (C), 131.1 (2 x CH), 130.2 (CH), 129.3 (C), 128.41 (2 x CH), 128.37 (CH), 127.0 (CH), 125.0 (CH), 85.4 (CH), 83.2 (C), 64.4 (C), 31.55 (CH_2), 31.48 (CH_2); LCMS m/z 338.25 ($M + H^+$), calcd for $C_{19}H_{16}NO_5H$ 338.1028; Anal.calcd for $C_{19}H_{15}NO_5$ (337.0950): C, 67.65; H, 4.48; N, 4.15. Found: C, 67.58; H, 4.52; N, 4.18%.



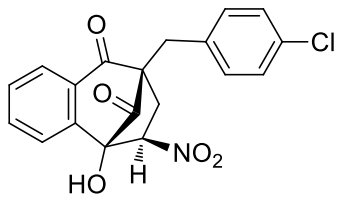
(+)-**4aa**

(5*R*,6*R*,8*S*)-8-(4-Fluorobenzyl)-5-hydroxy-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (**4ba**): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.0:8.0) and isolated as off-white solid; Yield: 88% (93.80 mg); Mp.: 104-106 °C; The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 51.11 min (major), t_R = 72.63 min (minor) [For major isomer]; t_R = 102.78 min (major), t_R = 63.72 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +52.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 96% major *ee*, >99% minor *ee* and 7.3:1 *dr*)**; IR (Neat): ν_{max} 3447, 2924, 1772, 1692, 1556, 1454, 1368, 1220, 1156, 1060, 926, 851, 755 and 610 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.7:1 *dr*, major isomer) δ 8.12 (1H, d, *J* = 8.0 Hz), 7.97 (1H, d, *J* = 8.0 Hz), 7.79 (1H, dt, *J* = 7.5, 1.0 Hz),7.60 (1H, dt, *J* = 7.5, 1.0 Hz), 7.35-7.32 (2H, m), 7.03-6.97 (2H, m), 4.84 (1H, dd, *J* = 8.0, 1.0 Hz), 3.87 (1H, br s O*H*), 3.57 (1H, d, *J* = 15.0 Hz), 3.47 (1H, d, *J* = 15.0 Hz), 2.62 (1H, dd, *J* = 16.0, 1.0 Hz), 2.19 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 4.7:1 *dr*, major isomer) δ 202.0 (C, *C*=O), 193.8 (C, *C*=O), 162.0 (C, d, *J* = 245.0 Hz, *C*-F), 140.0 (C), 136.1 (CH), 132.7 (2 x CH, d, *J* = 8.7 Hz), 131.2 (C), 130.2 (CH), 129.3 (C), 128.4 (CH), 125.1 (CH), 115.3 (2 x CH, d, *J* = 21.2 Hz), 85.4 (CH), 83.2 (C), 64.3 (C), 31.5 (CH_2), 30.8 (CH_2); ^{19}F NMR ($CDCl_3$, 470 MHz): δ = -115.6; HRMS (ESI-TOF) m/z 378.0754 (M + Na^+), calcd for $C_{19}H_{14}FNO_5Na$ 378.0754.



(+)-**4ba**

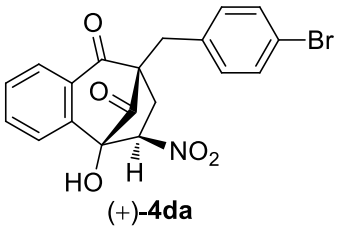
(5*R*,6*R*,8*S*)-8-(4-Chlorobenzyl)-5-hydroxy-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4ca): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as off-white solid; Yield: 80% (89.22 mg); Mp.:118-120 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 50.63 min (major), t_R = 85.73 min (minor) [For major isomer]; t_R = 114.79 min (major), t_R = 70.94 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +38.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 95% major *ee*, >99% minor *ee* and 5.0:1 *dr*);** IR (Neat): ν_{max} 3450, 2923, 1772, 1692, 1556, 1490, 1366, 1266, 1088, 1015, 928, 845 and 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 5.0:1 *dr*, major isomer) δ 8.11 (1H, dd, *J* = 7.6, 0.8 Hz), 7.96 (1H, d, *J* = 7.6 Hz), 7.79 (1H, dt, *J* = 7.6, 1.6 Hz), 7.60 (1H, dt, *J* = 7.6, 0.8 Hz), 7.32 - 7.26 (4H, m), 4.83 (1H, dd,



(+)-**4ca**

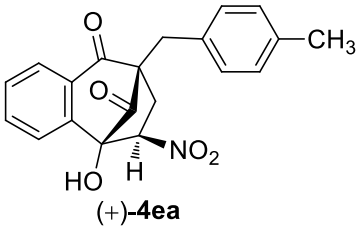
J = 8.4, 1.2 Hz), 3.85 (1H, br s, O*H*), 3.57 (1H, d, *J* = 14.4 Hz), 3.45 (1H, d, *J* = 14.4 Hz), 2.60 (1H, dd, *J* = 16.0, 1.2 Hz), 2.19 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 5.0:1 *dr*, major isomer) δ 202.0 (C, *C*=O), 193.7 (C, *C*=O), 140.0 (C), 136.1 (CH), 134.1 (C), 133.0 (C), 132.5 (2 x CH), 130.3 (CH), 129.2 (C), 128.6 (2 x CH), 128.4 (CH), 125.1 (CH), 85.4 (CH), 83.2 (C), 64.2 (C), 31.6 (CH_2), 31.1 (CH_2); LCMS m/z 370.80 ($M + H^+$), calcd for $C_{19}H_{13}ClNO_5$ 370.0482; Anal. calcd for $C_{19}H_{14}ClNO_5$ (371.0561): C, 61.38; H, 3.80; N, 3.77. Found: C, 61.45; H, 3.76; N, 3.81%.

(5*R*,6*R*,8*S*)-8-(4-Bromobenzyl)-5-hydroxy-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4da): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as off-white solid; Yield: 80% (99.89 mg); Mp.: 219-221 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 62.70 min (major), t_R = 104.48 min (minor) [For major isomer]; t_R = 146.55 min (major), t_R = 84.31 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +51.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 94% major *ee*, >99% minor *ee* and 6.6:1 *dr*);** IR (Neat): ν_{max} 3455, 1774, 1695, 1559, 1488, 1368, 1071, 930, 845 and 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 5.2:1 *dr*, major isomer) δ 8.09 (1H, d, *J* = 7.6 Hz), 7.96 (1H, d, *J* = 8.0 Hz), 7.79 (1H, t, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 7.6 Hz), 7.41 (2H, d, *J* = 8.4 Hz), 7.24 (2H, d, *J* = 8.4 Hz), 4.84 (1H, d, *J* = 8.0 Hz), 3.98 (1H, br s, O*H*), 3.54 (1H, d, *J* = 14.8 Hz), 3.41 (1H, d, *J* = 14.8 Hz), 2.59 (1H, d, *J* = 15.6 Hz), 2.18 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 5.2:1 *dr*, major isomer) δ 202.0 (C, *C*=O), 193.7 (C, *C*=O), 140.0 (C), 136.1 (CH), 134.6 (C), 132.8 (2 x CH), 131.5 (2 x CH), 130.3 (CH), 129.2 (C), 128.4 (CH), 125.0 (CH), 121.1 (C), 85.4 (CH), 83.2 (C), 64.1 (C), 31.5 (CH_2), 31.1 (CH_2); LCMS m/z 415.25 (M^+), calcd for $C_{19}H_{14}BrNO_5$ 415.0055; Anal. calcd for $C_{19}H_{14}BrNO_5$ (415.0055): C, 54.83; H, 3.39; N, 3.37. Found: C, 54.75; H, 3.42; N, 3.34%.



(+)-**4da**

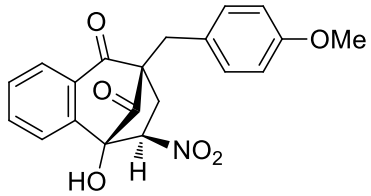
(5*R*,6*R*,8*S*)-5-Hydroxy-8-(4-methylbenzyl)-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4ea): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as off-white solid; Yield: 81% (85.38 mg); Mp.:234-236 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H



(+)-**4ea**

column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 41.24 min (major), t_R = 101.90 min (minor) [For major isomer]; t_R = 68.83 min (major), t_R = 61.73 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +35.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 94% major *ee*, 94% minor *ee* and 3.3:1 *dr*);** IR (Neat): ν_{max} 3397, 2916, 1782, 1679, 1554, 1452, 1363, 1286, 1153, 1074, 936, 799 and 723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.1:1 *dr*, major isomer) δ 8.11 (1H, d, *J* = 7.5 Hz), 7.96 (1H, d, *J* = 7.5 Hz), 7.78 (1H, dt, *J* = 7.5, 1.0 Hz), 7.59 (1H, t, *J* = 7.5 Hz), 7.24 (2H, d, *J* = 8.0 Hz), 7.11 (2H, d, *J* = 7.5 Hz), 4.83 (1H, d, *J* = 8.0 Hz), 3.81 (1H, br s, O*H*), 3.58 (1H, d, *J* = 14.5 Hz), 3.44 (1H, d, *J* = 15.0 Hz), 2.66 (1H, dd, *J* = 16.0, 1.0 Hz), 2.31 (3H, s, C*H*$_3$), 2.16 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 4.1:1 *dr*, major isomer) δ 202.2 (C, *C*=O), 194.0 (C, *C*=O), 140.1 (C), 136.6 (C), 135.9 (CH), 132.5 (C), 131.0 (2 x CH), 130.2 (CH), 129.4 (C), 129.1 (2 x CH), 128.4 (CH), 125.0 (CH), 85.5 (CH), 83.2 (C), 64.5 (C), 31.6 (CH_2), 31.1 (CH_2), 21.0 (CH_3); LCMS m/z 352.10 ($M + H^+$), calcd for $C_{20}H_{17}NO_5H$ 352.1185; Anal. calcd for $C_{20}H_{17}NO_5$ (351.1107): C, 68.37; H, 4.88; N, 3.99. Found: C, 68.26; H, 4.85; N, 3.92%.

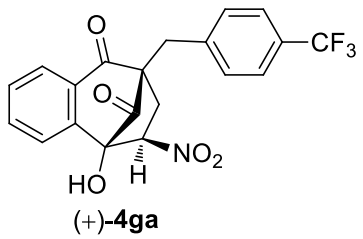
(5*R*,6*R*,8*S*)-5-Hydroxy-8-(4-methoxybenzyl)-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4fa): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.3:8.7 to 1.8:8.2) and isolated as off-white solid; Yield: 81% (89.26 mg); Mp.: 100-102 °C; The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 59.29 min (major), t_R = 39.15 min (minor) [For major isomer]; t_R = 53.80 min (major), t_R = 25.80 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +47.0° (*c* = 0.1 g/100 mL, $CHCl_3$, >99% major *ee*, >99% minor *ee* and 6.9:1 *dr*)**; IR (Neat): ν_{max} 3444, 2918, 2847, 1774, 1676, 1557, 1453, 1369, 1245, 1180, 981, 758 and 616 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.7:1 *dr*, major isomer) δ 8.11 (1H, d, *J* = 8.0 Hz), 7.96 (1H, d, *J* = 8.0 Hz), 7.78 (1H, t, *J* = 8.0 Hz), 7.59 (1H, t, *J* = 8.0 Hz), 7.28 (2H, d, *J* = 8.5 Hz), 6.84 (2H, d, *J* = 8.0 Hz), 4.83 (1H, d, *J* = 8.0 Hz), 3.96 (1H, br s, O*H*), 3.78 (3H, s, OC*H*$_3$), 3.56 (1H, d, *J* = 14.5 Hz), 3.43 (1H, d, *J* = 14.5 Hz), 2.66 (1H, d, *J* = 16.0 Hz), 2.16 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 4.7:1 *dr*, major isomer) δ 202.3 (C, *C*=O), 194.1 (C, *C*=O), 158.6 (C), 140.0 (C), 135.9 (CH), 132.1 (2 x CH), 130.2 (CH), 129.4 (C), 128.3 (CH), 127.5 (C), 125.0 (CH), 113.8 (2 x CH), 85.4 (CH), 83.2 (C), 64.6 (C), 55.2 (CH_3, O*C*H$_3$), 31.5 (CH_2), 30.7 (CH_2); LCMS m/z 368.10 [$M + H^+$], calculated for $C_{20}H_{17}NO_6H$ 368.1134; HRMS (ESI-TOF)



(+)-**4fa**

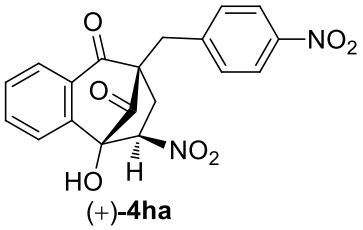
m/z 390.0956 (M + Na^+), calcd for $C_{20}H_{17}NO_6Na$ 390.0954; Anal. Calcd for $C_{20}H_{17}NO_6$ (367.1056); C, 65.39; H, 4.66; N, 3.81. Found: C, 65.48; H, 4.62; N, 3.85%.

(5*R*,6*R*,8*S*)-5-Hydroxy-6-nitro-8-(4-(trifluoromethyl)benzyl)-7,8-dihydro-5*H*-5,8-methanobenzo [7]annulene-9,10(6*H*)-dione (4ga): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.0:8.0) and isolated as off-white solid; Yield: 81% (98.49 mg); Mp.:160-162 °C; The enanantiomeric 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 = 7.36 min (major), t_R = 6.52 min (minor) [For retro-Henry]; t_R = 8.62 min (major), t_R = 9.80 min (minor) [For major isomer]; t_R = 10.98 min (major), t_R = 18.91 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +54.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 97% major *ee*, >99% minor *ee* and 5.9:1 *dr*)**; IR (Neat): ν_{max} 3433, 2925, 1782, 1683, 1556, 1422, 1323, 1288, 1115, 1065, 937, 841, 755 and 599 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.5:1 *dr*, major isomer) δ 8.13 (1H, d, *J* = 8.0 Hz), 7.97 (1H, d, *J* = 8.0 Hz), 7.80 (1H, t, *J* = 8.0 Hz), 7.61 (1H, t, *J* = 8.0 Hz), 7.57 (2H, d, *J* = 8.5 Hz), 7.51 (2H, d, *J* = 8.0 Hz), 4.85 (1H, d, *J* = 8.0 Hz), 3.77 (1H, br s, O*H*), 3.68 (1H, d, *J* = 14.5 Hz), 3.55 (1H, d, *J* = 14.5 Hz), 2.59 (1H, d, *J* = 16.0 Hz), 2.21 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 4.5:1 *dr*, major isomer) δ 201.8 (C, *C*=O), 193.5 (C, *C*=O), 139.94 (C), 139.90 (C), 136.2 (CH), 131.5 (2 x CH), 130.4 (CH), 129.4 (C, q, *J* = 32.5 Hz), 129.2 (C), 128.5 (CH), 125.3 (2 x CH, q, *J* = 3.7 Hz), 125.1 (CH), 124.1 (C, q, *J* = 270.0 Hz, *C*F_3), 85.4 (CH), 83.2 (C), 64.0 (C), 31.75 (CH_2), 31.70 (CH_2); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -62.5; HRMS (ESI-TOF) m/z 444.0465 (M + K^+), calcd for $C_{20}H_{14}F_3NO_5K$ 444.0461.



(+)-**4ga**

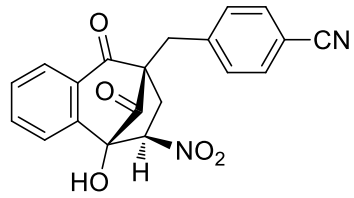
(5*R*,6*R*,8*S*)-5-Hydroxy-6-nitro-8-(4-nitrobenzyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene 9,10(6*H*)-dione (4ha): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as off-white solid; Yield: 60% (68.82 mg); Mp.: 332-334 °C; 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 = 47.40 min (major), t_R = 62.47 min (minor) [For retro-Henry]; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/ min, λ = 254 nm), t_R =



(+)-**4ha**

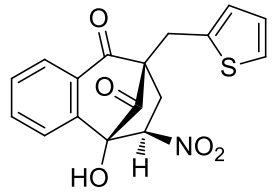
50.30 min (major), t_R = 60.61 min (minor) [For major isomer]; t_R = 70.30 min (major), t_R = 98.59 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +44.0° (*c* = 0.1 g/100 mL, $CHCl_3$, >99% major *ee*, >99% minor *ee*, >99% *ee* for *retro*-Henry and >99:1 *dr*)**; IR (Neat): ν_{max} 3409, 2920, 2851, 1778, 1693, 1553, 1455, 1343, 1261, 1176, 1061, 978, 854 and 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, >99:1 *dr* after crystallization) δ 8.18 (2H, d, *J* = 8.8 Hz), 8.13 (1H, d, *J* = 7.6 Hz), 7.98 (1H, d, *J* = 7.6 Hz), 7.82 (1H, t, *J* = 7.2 Hz), 7.63 (1H, t, *J* = 7.2 Hz), 7.58 (2H, d, *J* = 8.4 Hz), 4.85 (1H, d, *J* = 8.0 Hz), 3.72 (1H, br s, O*H*), 3.69 (1H, d, *J* = 14.4 Hz), 3.62 (1H, d, *J* = 14.4 Hz), 2.57 (1H, d, *J* = 16.0 Hz), 2.27 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$ + DMSO-D_6, DEPT-135, >99:1 *dr* after crystallization) δ 201.0 (C, *C*=O), 192.6 (C, *C*=O), 145.2 (C), 143.0 (C), 140.1 (C), 134.2 (CH), 130.8 (2 x CH), 128.5 (CH), 128.0 (C), 126.5 (CH), 124.0 (CH), 121.64 (CH), 121.61 (CH), 84.5 (CH), 82.9 (C), 62.9 (C), 30.6 (CH_2), 29.6 (CH_2); LCMS m/z 383.35 ($M + H^+$), calcd for $C_{19}H_{14}N_2O_7H$ 383.0879; Anal. calcd for $C_{19}H_{14}N_2O_7$ (382.0801): C, 59.69; H, 3.69; N, 7.33. Found: C, 59.75; H, 3.63; N, 7.38%.

4-(((5*R*,6*R*,8*S*)-5-Hydroxy-6-nitro-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen 8-yl)methyl)benzonitrile (4ia): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as off-white solid; Yield: 74 % (80.44 mg); Mp.: 286-288 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA-3 column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 29.64 min (major), t_R = 25.14 min (minor) [For *retro*-Henry]; **$[\alpha]_D^{25}$ = +56.0° (*c* = 0.1 g/100 mL, $CHCl_3$, >99% *ee*)**; IR (Neat): ν_{max} 3400, 2922, 2851, 2228, 1775, 1696, 1558, 1455, 1367, 1287, 1064, 930, 854 and 758 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, >99:1 *dr* after crystallization) δ 8.13 (1H, dd, *J* = 8.0, 0.8 Hz), 7.98 (1H, dd, *J* = 8.0, 0.8 Hz), 7.81 (1H, dt, *J* = 7.6, 1.6 Hz), 7.64-7.60 (3H, m), 7.53-7.51 (2H, m), 4.85 (1H, dd, *J* = 8.0, 1.2 Hz), 3.68 (1H, br s, O*H*), 3.65 (1H, d, *J* = 14.4 Hz), 3.57 (1H, d, *J* = 14.8 Hz), 2.55 (1H, dd, *J* = 16.0, 1.2 Hz), 2.24 (1H, dd, *J* = 16.0, 8.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, >99:1 *dr* after crystallization) δ 201.6 (C, *C*=O), 193.3 (C, *C*=O), 141.3 (C), 139.9 (C), 136.3 (CH), 132.2 (2 x CH), 132.0 (2 x CH), 130.4 (CH), 129.1 (C), 128.5 (CH), 125.2 (CH), 118.7 (C), 111.2 (C), 85.3 (CH), 83.1 (C), 63.9 (C), 32.1 (CH_2), 31.7 (CH_2); LCMS m/z 363.20 ($M + H^+$), calcd for $C_{20}H_{14}N_2O_5H$ 363.0981; Anal. calcd for $C_{20}H_{14}N_2O_5$ (362.0903): C, 66.30; H, 3.89; N, 7.73. Found: C, 66.25; H, 3.83; N, 7.78%.



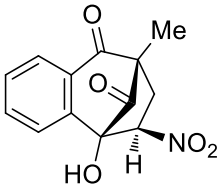
(+)-**4ia**

(5*R*,6*R*,8*R*)-5-Hydroxy-6-nitro-8-(thiophen-2-ylmethyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7] annulene-9,10(6*H*)-dione (4ja): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.0:8.0) and isolated as off-white solid; Yield: 78% (80.34 mg); Mp.: 136-138 °C; 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 = 9.82 min (major), t_R = 11.44 min (minor) [For *retro*-Henry]; t_R = 23.22 min (major), t_R = 17.41 min (minor) [For major isomer]; **$[\alpha]_D^{25}$ = +70.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 86% major *ee*, 91% minor *ee* and 3.7:1 *dr*);** IR (Neat): ν_{max} 3383, 2916, 1774, 1680, 1554, 1453, 1366, 1288, 1193, 1065, 924, 807, 757 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 3.3:1 *dr*, major isomer) δ 8.12 (1H, d, *J* = 8.0 Hz), 7.97 (1H, d, *J* = 8.0 Hz), 7.79 (1H, t, *J* = 8.0 Hz), 7.60 (1H, t, *J* = 7.5 Hz), 7.19 (1H, d, *J* = 5.0 Hz), 7.00-6.94 (2H, m), 4.86 (1H, d, *J* = 8.0 Hz), 3.87 (1H, s), 3.81 (1H, d, *J* = 15.5 Hz), 3.60 (1H, d, *J* = 15.5 Hz), 2.76 (1H, d, *J* = 16.0 Hz), 2.25 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 3.3:1 *dr*, major isomer): δ 201.6 (C, *C*=O), 193.8 (C, *C*=O), 140.0 (C), 137.0 (C), 136.1 (CH), 130.3 (CH), 129.3 (C), 128.9 (CH), 128.4 (CH), 126.9 (CH), 125.6 (CH), 125.1 (CH), 85.4 (CH), 83.3 (C), 64.1 (C), 31.9 (CH_2), 26.6 (CH_2); ^1H NMR ($CDCl_3$, 500 MHz, 3.3:1 *dr*, minor isomer) δ 8.14 (1H, d, *J* = 9.0 Hz), 7.78 (1H, d, *J* = 8.0 Hz), 7.74 (1H, t, *J* = 7.5 Hz), 7.58 (1H, t, *J* = 7.5 Hz), 7.19 (1H, d, *J* = 5.0 Hz), 7.00-6.94 (2H, m), 5.06 (1H, dd, *J* = 10.0, 7.0 Hz), 3.94 (1H, br s, O*H*), 3.70 (1H, d, *J* = 15.5 Hz), 3.63 (1H, d, *J* = 16.5 Hz), 2.70-2.58 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 3.3:1 *dr*, minor isomer): δ 201.2 (C, *C*=O), 193.1 (C, *C*=O), 138.7 (C), 137.3 (C), 136.1 (CH), 130.3 (CH), 129.8 (C), 128.8 (CH), 128.2 (CH), 127.2 (CH), 125.6 (CH), 125.5 (CH), 85.8 (CH), 84.1 (C), 66.4 (C), 28.7 (CH_2), 26.0 (CH_2); HRMS (ESI-TOF) m/z 344.0596 ($M + H^+$), calcd for $C_{17}H_{13}NO_5SH$ 344.0593.



(+)-**4ja**

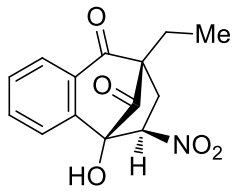
(5*R*,6*R*,8*S*)-5-Hydroxy-8-methyl-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4ka): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.0:8.0) and isolated as off-white semi solid; Yield: 70% (54.85 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 92:8, flow rate 0.8 mL/min, λ = 254 nm), t_R = 36.26 min (major), t_R = 32.19 min (minor) [For major isomer]; **$[\alpha]_D^{25}$ = +57.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 80% major *ee* and >99:1 *dr*)**; IR (Neat): ν_{max} 3455,



(+)-**4ka**

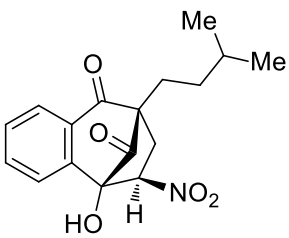
2923, 2853, 1776, 1695, 1557, 1454, 1371, 1276, 1085, 965, 863, 758 and 666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 5.2:1 *dr*, major isomer) δ 8.10 (1H, d, *J* = 8.0 Hz), 7.99 (1H, d, *J* = 7.6 Hz), 7.79 (1H, t, *J* = 7.6 Hz), 7.59 (1H, t, *J* = 7.6 Hz), 4.92 (1H, d, *J* = 6.4 Hz), 3.83 (1H, br s, O*H*), 2.58-2.44 (2H, m), 1.65 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135, 5.2:1 *dr*, major isomer) δ 202.6 (C, *C*=O), 194.0 (C, *C*=O), 140.1 (C), 135.9 (CH), 130.2 (CH), 129.4 (C), 128.2 (CH), 125.2 (CH), 85.6 (CH), 83.1 (C), 59.7 (C), 36.2 (CH_2), 13.1 (CH_3); HRMS (ESI-TOF) m/z 262.0711 ($M + H^+$), calcd for $C_{13}H_{11}NO_5H$ 262.0715.

(5*R*,6*R*,8*S*)-8-Ethyl-5-hydroxy-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4la): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.4:8.6 to 1.9:8.1) and isolated as off-white semi solid; Yield: 76% (62.76 mg). The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 92:8 flow rate 0.8 mL/min, λ = 254 nm), t_R = 93.88 min (major), t_R = 159.70 min (minor) [For major isomer]; t_R = 108.94 min (major), t_R = 88.91 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +27.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 94% major *ee*, 95% minor *ee* and 5.7:1 *dr*);** IR (Neat): ν_{max} 3446, 2923, 2853, 1770, 1693, 1558, 1456, 1369, 1266, 1187, 1056, 940, 896 and 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 10.0:1 *dr*, major isomer) δ 8.08 (1H, d, *J* = 8.0 Hz), 7.97 (1H, d, *J* = 8.0 Hz), 7.78 (1H, dt, *J* = 8.0, 0.8 Hz), 7.58 (1H, t, *J* = 7.6 Hz), 4.93 (1H, dd, *J* = 8.0, 0.8 Hz), 3.87 (1H, br s, O*H*), 2.75 (1H, d, *J* = 16.0, Hz), 2.34 (1H, dd, *J* = 16.0, 8.0 Hz), 2.18 (2H, dq, *J* = 7.6, 3.2 Hz), 1.17 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 10.0:1 *dr*, major isomer) δ 202.5 (C, *C*=O), 194.4 (C, *C*=O), 140.1 (C), 135.8 (CH), 130.1 (CH), 129.5 (C), 128.1 (CH), 125.0 (CH), 85.5 (CH), 83.0 (C), 63.5 (C), 32.3 (CH_2), 20.0 (CH_2), 8.1 (CH_3); LCMS m/z 276.15 [$M + H^+$], calculated for $C_{14}H_{13}NO_5H$ 276.0872; HRMS (ESI-TOF) m/z 298.0693 ($M + Na^+$), calcd for $C_{14}H_{13}NO_5Na$ 298.0691; Anal. Calcd for $C_{14}H_{13}NO_5$ (275.0794): C, 61.09; H, 4.76; N, 5.09. Found: C, 61.22; H, 4.71; N, 5.15%.



(+)-**4la**

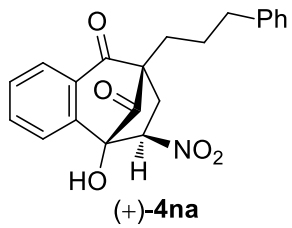
(5*R*,6*R*,8*S*)-5-Hydroxy-8-isopentyl-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4ma): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.2:8.8 to 1.7:8.3) and isolated as off-white semi solid; Yield: 75% (71.40 mg) The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R



(+)-**4ma**

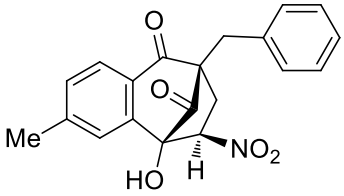
= 17.11 min (major), t_R = 28.10 min (minor) [For major isomer]; t_R = 25.75 min (major), t_R = 23.76 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +23.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 93% major *ee*, 87% minor *ee* and 5.2:1 *dr*);** IR (Neat): ν_{max} 3449, 2954, 2869, 1773, 1692, 1558, 1454, 1367, 1266, 1063, 934, 867 and 757 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 5.0:1 *dr*, major isomer) δ 8.08 (1H, d, *J* = 8.0 Hz), 7.97 (1H, d, *J* = 7.5 Hz), 7.78 (1H, dt, *J* = 8.0, 1.0 Hz), 7.58 (1H, dt, *J* = 8.0, 1.0 Hz), 4.92 (1H, d, *J* = 8.0 Hz), 3.82 (1H, br s O*H*), 2.74 (1H, d, *J* = 16.0 Hz), 2.36 (1H, dd, *J* = 16.0, 8.0 Hz), 2.16-2.07 (2H, m), 1.67 (1H, septet, *J* = 7.0 Hz), 1.52-1.45 (1H, m), 1.44-1.37 (1H, m), 0.98 (6H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 5.0:1 *dr*, major isomer) δ 202.5 (C, *C*=O), 194.4 (C, *C*=O), 140.1 (C), 135.8 (CH), 130.1 (CH), 129.5 (C), 128.1 (CH), 125.0 (CH), 85.6 (CH), 83.0 (C), 63.2 (C), 32.8 (CH_2), 32.2 (CH_2), 28.7 (CH), 25.1 (CH_2), 22.5 (CH_3), 22.4 (CH_3); HRMS (ESI-TOF) m/z 340.1161 ($M + Na^+$), calcd for $C_{17}H_{19}NO_5Na$ 340.1161.

(5*R*,6*R*,8*S*)-5-Hydroxy-6-nitro-8-(3-phenylpropyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4na): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.2:8.8 to 1.7:8.3) and isolated as off-white semi solid; Yield: 80% (87.69 mg). The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 34.46 min (major), t_R = 16.43 min (minor) [For major isomer]; t_R = 28.43 min (major), t_R = 67.67 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +53.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 92 % major *ee*, >99% minor *ee* and 16.4:1 *dr*);** IR (Neat): ν_{max} 3455, 2922, 1772, 1692, 1557, 1453, 1368, 1286, 1061, 923, 870 and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 5.0:1 *dr*, major isomer) δ 8.05 (1H, dd, *J* = 8.0, 1.0 Hz), 7.94 (1H, d, *J* = 7.5 Hz), 7.77-7.73 (1H, m), 7.58-7.52 (1H, m), 7.30-7.17 (5H, m), 4.89 (1H, dd, *J* = 8.0, 1.0 Hz), 3.88 (1H, s), 2.78 -2.64 (3H, m), 2.31 (1H, dd, *J* =16.0, 8.0 Hz), 2.17-2.10 (2H, m), 1.98-1.86 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 5.0:1 *dr*, major isomer) δ 202.4 (C, *C*=O), 194.2 (C, *C*=O), 141.7 (C), 140.0 (C), 135.9 (CH), 130.1 (CH), 129.4 (C) 128.4 (2 x CH), 128.3 (2 x CH), 128.1 (CH), 125.8 (CH), 125.0 (CH), 85.5 (CH), 83.0 (C), 63.0 (C), 36.3 (CH_2), 32.9 (CH_2), 26.9 (CH_2), 25.1 (CH_2); HRMS (ESI-TOF) m/z 388.1164 ($M + Na^+$), calcd for $C_{21}H_{19}NO_5Na$ 388.1161.



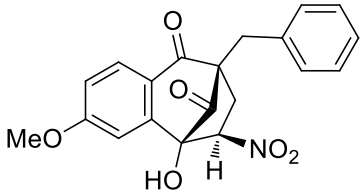
(+)-**4na**

(5*R*,6*R*,8*S*)-8-Benzyl-5-hydroxy-3-methyl-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4oa): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as off-white solid; Yield: 90% (94.86 mg); Mp.: 242-244 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 38.33 min (major), t_R = 66.19 min (minor) [For minor isomer]; t_R = 33.51 min (major), t_R = 96.69 min (minor) [For major isomer]; **$[\alpha]_D^{25}$ = +83.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 91% major *ee*, >99% *ee* for minor** and **4.0:1 *dr*);** IR (Neat): ν_{max} 3456, 3029, 2923, 1773, 1691, 1603, 1559, 1436, 1368, 1257, 932, 838 and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 5.2:1 *dr*, major isomer) δ 8.00 (1H, d, *J* = 8.0 Hz), 7.75 (1H, s), 7.40-7.35 (3H, m), 7.32-7.28 (3H, m), 4.81 (1H, dd, *J* = 8.0, 1.2 Hz), 3.76 (1H, br s, O*H*), 3.60 (1H, d, *J* = 14.4 Hz), 3.47 (1H, d, *J* = 14.4 Hz), 2.63 (1H, dd, *J* = 16.0, 1.2 Hz), 2.50 (3H, s, CH_3), 2.16 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 5.2:1 *dr*, major isomer) δ 202.3 (C, *C*=O), 193.6 (C, *C*=O), 147.7 (C), 140.0 (C), 135.7 (C), 131.2 (CH), 131.1 (2 x CH), 128.5 (CH), 128.4 (2 x CH), 127.1 (C), 127.0 (CH), 125.3 (CH), 85.5 (CH), 83.1 (C), 64.2 (C), 31.8 (CH_2), 31.5 (CH_2), 22.1 (CH_3); LCMS m/z 352.10 ($M + H^+$), calcd for $C_{20}H_{17}NO_5H$ 352.1185; Anal. calcd for $C_{20}H_{17}NO_5$ (351.1107): C, 68.37; H, 4.88; N, 3.99. Found: C, 68.45; H, 4.85; N, 3.92%.



(+)-**4oa**

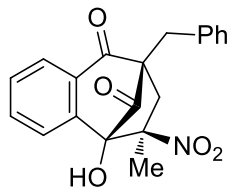
(5*R*,6*R*,8*S*)-8-Benzyl-5-hydroxy-3-methoxy-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4pa): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as off-white semi solid; Yield: 90% (99.18 mg); Mp.: 130-132 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 68.66 min (major), t_R = 106.6 min (minor) [For major isomer]; t_R = 121.92 min (major), t_R = 60.89 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +55.0° (*c* = 0.1 g/100 mL, $CHCl_3$, >99% major *ee*, >99% minor *ee*** and **6.8:1 *dr*)**; IR (Neat): ν_{max} 3438, 2923, 2851, 1774, 1694, 1557, 1486, 1368, 1279, 1029, 838 and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 5.0:1 *dr*, major isomer) δ 7.84 (1H, d, *J* = 8.5 Hz), 7.54 (1H, d, *J* = 3.0 Hz), 7.37 (2H, d, *J* = 7.5 Hz), 7.32-7.30 (4H, m), 4.79 (1H, dd, *J* = 8.5, 1.0 Hz), 3.89 (3H, s, OCH_3),



(+)-**4pa**

3.76 (1H, br s, O*H*), 3.62 (1H, d, *J* = 14.5 Hz), 3.48 (1H, d, *J* = 14.0 Hz), 2.64 (1H, dd, *J* = 16.0, 0.5 Hz), 2.15 (1H, dd, *J* = 16.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 5.0:1 *dr*, major isomer) δ 201.9 (C, *C*=O), 193.9 (C, *C*=O), 161.0 (C), 135.6 (C), 132.2 (C), 131.1 (2 x CH), 130.8 (C), 128.4 (2 x CH), 127.0 (CH), 126.4 (CH), 123.8 (CH), 110.5 (CH), 85.4 (CH), 83.1 (C), 64.2 (C), 55.8 (CH_3, O*C*H_3), 31.7 (CH_2), 31.6 (CH_2); LCMS m/z 368.10 (M + H^+), calcd for $C_{20}H_{17}NO_6H$ 368.1134; Anal. calcd for $C_{20}H_{17}NO_6$ (367.1056): C, 65.39; H, 4.66; N, 3.81. Found: C, 65.28; H, 4.62; N, 3.86%.

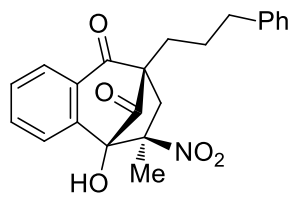
(5*R*,6*R*,8*S*)-8-Benzyl-5-hydroxy-6-methyl-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4ab): Prepared by following the procedure **B**



(+)-**4ab**

and purified by column chromatography using EtOAc/hexane (1.4:8.6 to 1.9:8.1) and isolated as off-white solid; Yield: 81% (85.38 mg); Mp.: 158-160 °C; The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 88.61 min (major), t_R = 45.28 min (minor) [For major isomer]; t_R = 55.80 min (major), t_R = 28.07 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +88.0° (*c* = 0.1 g/100 mL, $CHCl_3$, >99% major *ee*, >99% minor *ee* and 5.2:1 *dr*)**; IR (Neat): ν_{max} 3496, 2922, 2852, 1775, 1686, 1543, 1451, 1289, 1150, 1033, 986, 851 and 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 4.7:1, *dr*, major isomer) δ 8.16 (1H, d, *J* = 7.6 Hz), 7.88 (1H, d, *J* = 7.6 Hz), 7.77 (1H, t, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 7.6 Hz), 7.39 (2H, d, *J* = 7.2 Hz), 7.32-7.28 (3H, m), 3.79 (1H, br s, O*H*), 3.67 (1H, d, *J* = 14.4 Hz), 3.46 (1H, d, *J* = 14.8 Hz), 2.80 (1H, d, *J* = 15.6 Hz), 1.74 (1H, d, *J* = 16.0 Hz), 1.26 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 4.7:1 *dr*, major isomer) δ 202.3 (C, *C*=O), 194.4 (C, *C*=O), 140.2 (C), 136.0 (C), 135.5 (CH), 131.2 (2 x CH), 130.0 (CH), 129.8 (C), 128.5 (CH), 128.4 (2 x CH), 126.9 (CH), 125.9 (CH), 91.1 (C), 86.0 (C), 65.4 (C), 39.6 (CH_2), 31.7 (CH_2), 18.9 (CH_3); LCMS m/z 352.10 (M + H^+), calcd for $C_{20}H_{17}NO_5H$ 352.1185; HRMS (ESI-TOF) m/z 374.1005 (M + Na^+), calcd for $C_{20}H_{17}NO_5Na$ 374.1004; Anal. calcd for $C_{20}H_{17}NO_5$ (351.1107): C, 68.37; H, 4.88; N, 3.99. Found: C, 68.15; H, 4.82; N, 3.91%.

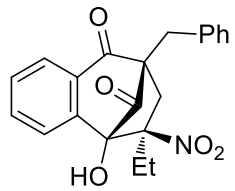
(5*R*,6*R*,8*S*)-5-Hydroxy-6-methyl-6-nitro-8-(3-phenylpropyl)-7,8-dihydro-5*H*-5,8-methanobenzo [7]annulene-9,10(6*H*)-dione (4nb): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.3:8.7 to 1.8:8.2) and isolated as off-white semi solid; Yield: 81% (91.19 mg); The enanantiomeric excess (*ee*)



(+)-**4nb**

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 = 34.92 min (major), t_R = 32.21 min (minor) [For major isomer]; t_R= 19.37 min (major), t_R = 16.64 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +68.0° (*c* = 0.1 g/100 mL, $CHCl_3$, 93% major *ee*, >99% minor *ee*** and **26.0:1 *dr*);** IR (Neat): ν_{max} 3447, 2922, 2853, 1771, 1692, 1549, 1452, 1348, 1266, 1081, 991, 856, 763 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 8.3:1 *dr*, major isomer) δ 8.10 (1H, d, *J* = 8.0 Hz), 7.87 (1H, d, *J* = 7.5 Hz), 7.75 (1H, dt, *J* = 7.5, 1.0 Hz), 7.57 (1H, dt, *J* = 8.0, 1.0 Hz), 7.29 (2H, t, *J* = 7.5 Hz), 7.25 (2H, d, *J* = 7.0 Hz), 7.18 (1H, t, *J* = 7.0 Hz), 3.70 (1H, br s, O*H*), 2.85 (1H, d, *J* = 15.5 Hz), 2.78-2.74 (2H, m), 2.18-2.15 (2H, m), 2.04-1.95 (1H, m), 1.90 (2H, d, *J* = 16.0 Hz), 1.32 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 8.3:1 *dr*, major isomer) δ 202.9 (C, *C*=O), 194.6 (C, *C*=O), 141.8 (C), 140.1 (C), 135.5 (CH), 129.9 (CH), 129.7 (C), 128.4 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 125.84 (CH), 125.77 (CH), 91.0 (C), 85.8 (C), 64.0 (C), 40.9 (CH_2), 36.3 (CH_2), 27.2 (CH_2), 25.1 (CH_2), 19.0 (CH_3); LCMS m/z 380.25 [M + H^+], calcd for $C_{22}H_{21}NO_5H$ 380.1498; HRMS (ESI-TOF) m/z 402.1318 (M + Na^+), calcd for $C_{22}H_{21}NO_5Na$ 402.1317; Anal. calcd for $C_{22}H_{21}NO_5$ (379.1420): C, 69.64; H, 5.58; N, 3.69. Found: C, 69.48; H, 5.51; N, 3.72%.

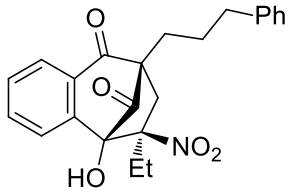
(5*R*,6*R*,8*S*)-8-Benzyl-6-ethyl-5-hydroxy-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4ac): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.4:8.6 to 1.9:8.1) and isolated as off-white solid; Yield: 91% (99.75 mg); Mp.: 116-118 °C. The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 13.39 min (major), t_R = 25.83 min (minor) [For major isomer]; t_R = 53.36 min (major), t_R = 68.65 (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +15.0° (*c* = 0.1 g/100 mL, $CHCl_3$, >99% major *ee*, >99% minor *ee*** and **1.2:1 *dr*);** IR (Neat): ν_{max} 3463, 2925, 1770, 1693, 1543, 1453, 1355, 1218, 1182, 1020, 926 and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 1.4:1 *dr*, major isomer) δ 8.15 (1H, dd, *J* = 8.0, 1.0 Hz), 7.89 (1H, d, *J* = 7.5 Hz), 7.76 (1H, dt, *J* = 8.0, 1.0 Hz), 7.59 (1H, dt, *J* = 7.5, 1.0 Hz), 7.41 (2H, d, *J* = 7.0 Hz), 7.33-7.23 (3H, m), 3.76 (1H, br s, O*H*), 3.67 (1H, d, *J* = 14.5 Hz), 3.45 (1H, d, *J* = 14.5 Hz), 2.81 (1H, d, *J* = 16.0 Hz), 2.14 (1H, sextet, *J* = 7.5 Hz), 1.78 (1H, d, *J* = 16.0 Hz), 1.05 (1H, sextet, *J* = 7.5 Hz), 0.83 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.4:1 *dr*, major isomer) δ 202.5 (C, *C*=O), 194.4 (C, *C*=O), 140.1 (C), 136.0 (C), 135.5 (CH), 131.2 (2 x CH), 130.0 (CH), 129.8 (C), 128.5 (CH), 128.3 (2 x CH), 126.9 (CH), 126.0



(+)-**4ac**

(CH), 95.0 (C), 86.4 (C), 65.0 (C), 37.1 (CH_2), 31.8 (CH_2), 25.7 (CH_2), 7.2 (CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz, 1.4:1 *dr*, minor isomer) δ: 8.10 (1H, dd, *J* = 8.0, 1.0 Hz), 7.73-7.67 (2H, m), 7.54 (1H, dt, *J* = 8.0, 1.5 Hz), 7.33-7.23 (2H, m), 7.28-7.25 (3H, m), 3.68 (1H, br s O*H*), 3.60 (1H, d, *J* = 14.5 Hz), 3.33 (1H, d, *J* = 14.0 Hz), 2.81 (1H, d, *J* = 16.0 Hz), 2.47 (1H, d, *J* = 15.5 Hz), 2.45-2.39 (1H, m), 0.64 (1H, sextet, *J* = 7.5 Hz), 0.34 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.4:1 *dr*, minor isomer) δ 202.2 (C, *C*=O), 193.4 (C, *C*=O), 140.0 (C), 135.8 (C), 135.7 (CH), 131.0 (2 x CH), 129.9 (CH), 129.5 (C), 128.6 (2 x CH), 127.8 (CH), 127.3 (CH), 125.9 (CH), 94.3 (C), 85.1 (C), 66.2 (C), 31.4 (CH_2), 31.0 (CH_2), 26.7 (CH_2), 6.95 (CH_3); LCMS m/z 366.15 [M + H^+], calculated for $C_{21}H_{19}NO_5H$ 366.1341; HRMS (ESI-TOF) m/z (M + Na^+) 388.1163, calcd for $C_{21}H_{19}NO_5Na$ 388.1161. Anal. calcd for $C_{21}H_{19}NO_5$ (365.1263); C, 69.03; H, 5.24; N, 3.83. Found: C, 69.12; H, 5.19; N, 3.80%.

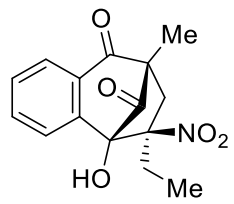
(5*R*,6*R*,8*S*)-6-Ethyl-5-hydroxy-6-nitro-8-(3-phenylpropyl)-7,8-dihydro-5*H*-5,8-methanobenzo[7] annulene-9,10(6*H*)-dione (4nc): Prepared by following the procedure **B**



(+)-**4nc**

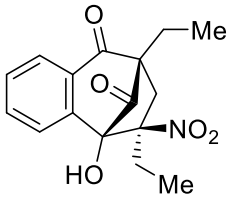
and purified by column chromatography using EtOAc/hexane (1.3:8.7 to 1.8:8.2) and isolated as off-white solid; Yield: 78% (92.06 mg); Mp.:140-142 °C; The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 53.03 min (major), t_R = 31.50 min (minor) [For major isomer]; t_R = 26.38 min (major), t_R = 82.72 min (minor) [For minor isomer]; **$[\alpha]_D^{25}$ = +99.0° (*c* = 0.1 g/100 mL, $CHCl_3$, >99% major *ee*, >99% minor *ee* and 3.7:1 *dr*);** IR (Neat): ν_{max}, 3449, 2921, 2852, 1771, 1691, 1547, 1454, 1351, 1289, 1192, 1010, 945, 736 and 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 9.1:1 *dr*, major isomer) δ 8.10 (1H, d, *J* = 7.5 Hz), 7.88 (1H, d, *J* = 8.0 Hz), 7.75 (1H, t, *J* = 7.5 Hz), 7.57 (1H, t, *J* = 8.0 Hz), 7.31-7.25 (4H, m), 7.19 (1H, t, *J* = 7.0 Hz), 3.71-3.69 (1H, m), 2.86 (1H, d, *J* = 15.5 Hz), 2.77 (2H, t, *J* = 7.5 Hz), 2.29-2.13 (3H, m), 2.09-1.99 (1H, m), 1.94 (1H, d, *J* = 15.5 Hz), 1.91-1.85 (1H, m), 1.03 (1H, sextet, *J* = 7.5 Hz), 0.89 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 9.1:1 *dr*, major isomer) δ 202.9 (C, *C*=O), 194.5 (C, *C*=O), 141.9 (C), 140.1 (C), 135.4 (CH), 129.9 (CH), 129.8 (C), 128.4 (3 x CH), 128.3 (2 x CH), 126.0 (CH), 125.8 (CH), 95.2 (C), 86.1 (C), 63.7 (C), 38.6 (CH_2), 36.4 (CH_2), 27.4 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 7.1 (CH_3); LCMS m/z 394.40 [M + H^+], calculated for $C_{23}H_{23}NO_5H$ 394.1654; HRMS (ESI-TOF) m/z 411.1925 (M + NH_4^+), calcd for $C_{23}H_{23}NO_5NH_4$ 411.1920; Anal. Calcd for $C_{23}H_{23}NO_5$ (393.1576); C, 70.21; H, 5.89; N, 3.56. Found: C, 70.32; H, 5.82; N, 3.61%.

(5*R*,6*R*,8*S*)-6-Ethyl-5-hydroxy-8-methyl-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4kc): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.4:8.6 to 1.9:8.1) and isolated as solid; Yield: 87% (75.5 mg). The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IC-3 column (hexane/2-propanol = 92:8, flow rate 0.8 mL/min, λ = 254 nm), t_R = 57.95 min (major), t_R = 43.43 min (minor) [for major isomer]; t_R = 31.02 min (major), t_R = 19.79 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = +109.0° [*c* = 0.1 g/100 mL, $CHCl_3$, >99% major *ee*, >99% minor *ee*);** IR (Neat): ν_{max} 3328, 2924, 2853, 1773, 1678, 1542, 1380, 1299, 1089, 985, 846, 747 and 682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 7.7:1 *dr*, major isomer) δ 8.12 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 8.0 Hz), 7.80 (1H, dt, *J* = 8.5, 1.0 Hz), 7.60 (1H, dt, *J* = 7.5, 1.0 Hz), 3.80 (1H, br s, O*H*), 2.73 (1H, d, *J* = 15.5 Hz), 2.36 (1H, qd, *J* = 7.5 Hz), 2.10 (1H, d, *J* = 15.5 Hz), 1.66 (3H, s, CH_3), 1.03 (1H, qd, *J* = 7.5 Hz), 0.89 (3H, t, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 7.7:1 *dr*, major isomer) δ 203.1 (C, *C*=O), 194.4 (C, *C*=O), 140.3 (C), 135.4 (CH), 130.0 (CH), 129.8 (C), 128.8 (CH), 126.2 (CH), 95.4 (C), 86.3 (C), 60.6 (C), 41.5 (CH_2), 25.4 (CH_2), 13.0 (CH_3), 7.0 (CH_3); HRMS (ESI-TOF) m/z: 312.0847 ($M + Na^+$), calcd for $C_{15}H_{15}NO_5Na$ 312.0848.



(+)-**4kc**

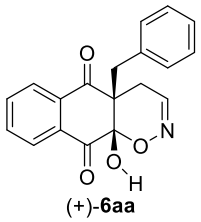
(5*R*,6*R*,8*S*)-6,8-Diethyl-5-hydroxy-6-nitro-7,8-dihydro-5*H*-5,8-methanobenzo[7]annulene-9,10(6*H*)-dione (4lc): Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.3:8.7 to 1.8:8.2) and isolated as solid; Yield: 90% (81.8 mg). The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 24.84 min (minor), t_R = 25.93 min (major) [for major isomer]; t_R = 17.13 min (major), t_R = 22.72 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = +123.0° [*c* = 0.1 g/100 mL, $CHCl_3$, 99% major *ee*, >99% minor *ee*);** IR (Neat): ν_{max} 3480, 3320, 2976, 2882, 1777, 1757, 1694, 1672, 1594, 1539, 1453, 1294, 936, 806, 749 and 682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 4.5:1 *dr*, major isomer) δ 8.11 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 7.5 Hz), 7.76 (1H, dt, *J* = 7.0, 1.0 Hz), 7.58 (1H, t, *J* = 8.0 Hz), 3.77 (1H, s, O*H*), 2.90 (1H, d, *J* = 16.0 Hz), 2.20 (4H, m), 1.95 (1H, d, *J* = 16.0 Hz), 1.20 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.92 (3H, t, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 4.5:1 *dr*, major isomer) δ 203.0 (C, *C*=O), 194.7 (C, *C*=O), 140.2 (C), 135.4 (CH), 129.95 (C), 129.92 (CH), 128.8 (CH),



(+)-**4lc**

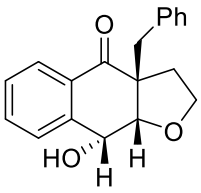
126.0 (CH), 95.2 (C), 86.2 (C), 64.1 (C), 38.2 (CH_2), 25.9 (CH_2), 20.5 (CH_2), 8.3 (CH_3), 7.2 (CH_3); HRMS (ESI-TOF) m/z: 326.1004 ($M + Na^+$), calcd for $C_{16}H_{17}NO_5Na$ 326.1004.

(4a*S*,10a*S*)-4a-Benzyl-10a-hydroxy-4a,10a-dihydro-4*H*-naphtho[2,3-e][1,2]oxazine-5,10-dione (**6aa**): Prepared following the procedure **C** and purified by column chromatography


(+)-**6aa**

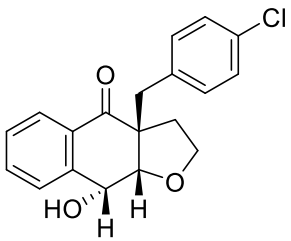
using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as colourless oily liquid. Yield: 44% (28.27 mg); **$[\alpha]_D^{25}$ = +72.0° (*c* = 0.1 g/100 mL, $CHCl_3$);** IR (Neat): ν_{max} 3428, 2921, 2851, 1703, 1593, 1455, 1364, 1274, 1067, 974, 853 and 752 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, dd, *J* = 7.5, 1.0 Hz), 8.08 (1H, dd, *J* = 7.5, 1.0 Hz), 7.85 (1H, dt, *J* = 7.5, 1.5 Hz), 7.78 (1H, dt, *J* = 7.5, 1.0 Hz), 7.43 (1H, dd, *J* = 4.5, 1.0 Hz), 7.16-7.11 (3H, m), 6.76 (2H, dd, *J* = 8.0, 1.5 Hz), 5.14 (1H, br s, O*H*), 2.96 (1H, d, *J* = 13.5 Hz), 2.92 (1H, d, *J* = 14.0 Hz), 2.85 (1H, dd, *J* = 18.5, 4.5 Hz), 2.38 (1H, dd, *J* = 18.0, 1.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.9 (C, *C*=O), 190.0 (C, *C*=O), 149.0 (CH), 135.9 (CH), 134.8 (C), 134.3 (CH), 133.6 (C), 131.0 (C), 129.9 (2 x CH), 128.2 (2 x CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 95.2 (C), 52.8 (C), 41.1 (CH_2), 23.7 (CH_2); LCMS m/z 322.35 ($M + H^+$), calcd for $C_{19}H_{15}NO_4H$ 322.1079; HRMS (ESI-TOF) m/z: 344.0899 ($M + Na^+$), calcd for $C_{19}H_{15}NO_4Na$ 344.0899; Anal. calcd for $C_{19}H_{15}NO_4$ (321.1001): C, 71.02; H, 4.71; N, 4.36. Found: C, 71.12; H, 4.68; N, 4.41%.

(3a*R*,9*R*,9a*S*)-3a-Benzyl-9-hydroxy-3,3a,9,9a-tetrahydronaphtho[2,3-b]furan-4(2*H*)-one


(+)-**7aa**

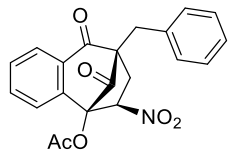
(7aa): Prepared following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as oily liquid. Yield: 42% (24.72 mg); **$[\alpha]_D^{25}$ = +14.0° (*c* = 0.1 g/100mL, $CHCl_3$);** IR (Neat): ν_{max} 3408, 2925, 1678, 1600, 1454, 1366, 1273, 1038, 983, 847, 701 and 633 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.90 (1H, d, *J* = 8.0 Hz), 7.57-7.53 (2H, m), 7.39-7.35 (1H, m), 7.18-7.11 (5H, m), 4.84 (1H, d, *J* = 6.5 Hz), 4.19 (1H, d, *J* = 7.0 Hz), 3.97-3.94 (2H, m), 3.49 (1H, d, *J* = 13.5 Hz), 2.91 (1H, d, *J* = 13.5 Hz), 2.63 (1H, br s, O*H*), 2.33-2.28 (1H, m), 2.24-2.19 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 200.0 (C, *C*=O), 140.7 (C), 136.8 (C), 134.2 (CH), 131.5 (C), 130.5 (2 x CH), 128.2 (3 x CH), 127.2 (CH), 126.7 (CH), 126.5 (CH), 83.3 (CH), 68.4 (CH), 66.1 (CH_2), 57.1 (C), 41.4 (CH_2), 35.8 (CH_2); LCMS m/z 293.20 ($M - H^+$), calcd for $C_{19}H_{17}O_3$ 293.1178; HRMS (ESI-TOF) m/z: 295.1331 ($M + H^+$), calcd for $C_{19}H_{18}O_3H$ 295.1334; Anal. calcd for $C_{19}H_{18}O_3$ (294.1256): C, 77.53; H, 6.16. Found: C, 77.45; H, 6.19%.

(3a*R*,9*R*,9a*S*)-3a-(4-chlorobenzyl)-9-hydroxy-3,3a,9,9a-tetrahydronaphtho[2,3-b]furan-4(2*H*)-one (7ca): Prepared following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 1.8:8.2) and isolated as oily liquid. Yield: 44% (28.93 mg); **$[\alpha]_D^{25}$ = +11.0° (*c* = 0.1 g/100mL, $CHCl_3$);** IR (Neat): ν_{max} 3420, 2924, 2853, 1677, 1600, 1491, 1368, 1291, 1089, 985, 846, 747 and 682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.90 (1H, d, *J* = 8.0 Hz), 7.60-7.59 (2H, m), 7.41-7.38 (1H, m), 7.14 (2H, d, *J* = 8.5 Hz), 7.06 (2H, d, *J* = 8.5 Hz), 4.85 (1H, d, *J* = 7.0 Hz), 4.13 (1H, d, *J* = 7.0 Hz), 4.00-3.97 (2H, m), 3.46 (1H, d, *J* = 13.5 Hz), 2.88 (1H, d, *J* = 13.5 Hz), 2.55 (1H, br s, O*H*), 2.33-2.28 (1H, m), 2.21-2.16 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 199.6 (C, *C*=O), 140.6 (C), 135.2 (C), 134.5 (CH), 132.7 (C), 131.8 (2 x CH), 131.2 (C), 128.39 (2 x CH), 128.38 (CH), 127.2 (CH), 126.5 (CH), 83.2 (CH), 68.3 (CH), 66.1 (CH_2), 56.9 (C), 40.4 (CH_2), 35.5 (CH_2); LCMS m/z 328.30 (M^+), calcd for $C_{19}H_{17}ClO_3$ 328.0866; HRMS (ESI-TOF) m/z: 351.0767 (M + Na^+), calcd for $C_{19}H_{17}ClO_3Na$ 351.0764; Anal. calcd for $C_{19}H_{17}ClO_3$ (328.0866): C, 69.41; H, 5.21. Found: C, 69.48; H, 5.25%.



(–)-**7ca**

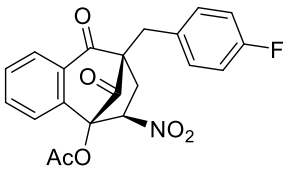
(5*R*,6*R*,8*S*)-8-Benzyl-6-nitro-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-5-yl acetate (8aa): Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.2:7.8) and isolated as off-white solid; Yield: 70% (80.8 mg). Mp.: 186-188 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 19.97 min (major), t_R = 12.68 min (minor); **$[\alpha]_D^{25}$ = +99.0° [*c* = 0.1 g/100 mL, $CHCl_3$, 96.6% *ee*]**; IR (Neat): ν_{max} 3025, 2926, 1788, 1758, 1686, 1596, 1557, 1494, 1437, 1367, 1284, 1197, 1147, 1039, 928, 853, 829, 779, 700, 620 and 588 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.15 (1H, d, *J* = 8.0 Hz), 7.71 (1H, t, *J* = 7.5 Hz), 7.58 (1H, t, *J* = 7.5 Hz), 7.45 (1H, d, *J* = 8.0 Hz), 7.37 (2H, d, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 7.24 (1H, t, *J* = 7.5 Hz), 4.87 (1H, d, *J* = 8.0 Hz), 3.65 (1H, d, *J* = 14.5 Hz), 3.45 (1H, d, *J* = 14.5 Hz), 2.63 (1H, d, *J* = 16.0 Hz), 2.26 (3H, s, O-CO-C*H*$_3$), 2.13 (1H, dd, *J* = 8.0, 16.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.4 (C, *C*=O), 193.4 (C, *C*=O), 166.9 (C, O-C=O), 137.2 (C), 135.8 (C), 135.2 (CH), 131.2 (2 x CH), 129.9 (CH), 129.5 (C), 128.8 (CH), 128.4 (2 x CH), 127.0 (CH), 124.0 (CH), 86.5 (C), 84.0 (CH), 64.8 (C), 31.7 (CH_2), 31.0 (CH_2), 20.9



(+)-**8aa**

(CH_3, O-CO-*C*H_3); HRMS (ESI-TOF) m/z 418.0694 (M + K), calcd for $C_{21}H_{17}NO_6K$ 418.0693.

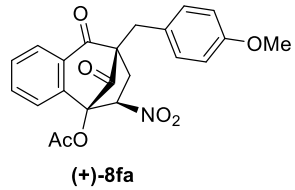
(5*R*,6*R*,8*S*)-8-(4-Fluorobenzyl)-6-nitro-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-5-yl acetate (8ba): Prepared by following the procedure **E** and



(+)-8ba

purified by column chromatography using EtOAc/hexane (1.6:8.4 to 2.3:7.7) and isolated as off-white solid; Yield: 88% (100 mg). Mp.: 157-159 °C. The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 68.97 min (major), t_R = 89.05 min (minor); **$[\alpha]_D^{25}$ = +96.0° [*c* = 0.1 g/100 mL, $CHCl_3$, 92% *ee*]**; IR (Neat): ν_{max} 3027, 2921, 1786, 1759, 1686, 1596, 1557, 1508, 1436, 1366, 1284, 1195, 1150, 1041, 926, 847, 745, 656, 592, 566, 525 and 495 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.14 (1H, d, *J* = 7.5 Hz), 7.72 (1H, t, *J* = 7.0 Hz), 7.60 (1H, t, *J* = 7.5 Hz), 7.46 (1H, d, *J* = 8.0 Hz), 7.35 (2H, t, *J* = 7.0 Hz), 7.0 (2H, t, *J* = 8.5 Hz), 4.88 (1H, d, *J* = 7.5 Hz), 3.59 (1H, d, *J* = 14.5 Hz), 3.44 (1H, d, *J* = 14.5 Hz), 2.60 (1H, d, *J* = 16.0 Hz), 2.26 (3H, s, COC*H*$_3$), 2.14 (1H, q, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.4 (C, *C*=O), 193.4 (C, *C*=O), 166.9 (C, O-C=O), 161.9 (C, d, J_{C-F} = 243.75 Hz, *C*-F), 137.2 (C), 135.3 (CH), 132.74 (2 x CH, d, J_{C-F} = 7.5 Hz), 131.3 (C, d, J_{C-F} = 3.75 Hz), 129.9 (CH), 129.4 (C), 128.0 (CH), 124.0 (CH), 115.2 (2 x CH, d, J_{C-F} = 21.25 Hz), 86.4 (C), 83.9 (CH), 64.7 (C), 30.96 (CH_2), 30.94 (CH_2), 20.8 (CH_3, CO*C*H_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −115.7; HRMS (ESI-TOF) m/z 420.0859 (M + Na^+), calcd for $C_{21}H_{16}FNO_6Na$ 420.0859.

(5*R*,6*R*,8*S*)-8-(4-Methoxybenzyl)-6-nitro-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-5-yl acetate (8fa): Prepared by following the procedure **E** and

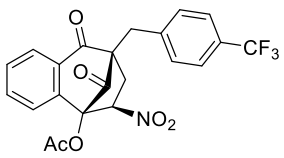


(+)-8fa

purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.2:7.8) and isolated as off-white solid; Yield: 86% (105.5 mg). Mp.: 138-140 °C. The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IC-3 column (hexane/2-propanol = 95:05 flow rate 0.7 mL/min, λ = 254 nm), t_R = 96.68 min (major), t_R = 120.31 min (minor); **$[\alpha]_D^{25}$ = +9.6° [*c* = 0.125 g/100 mL, $CHCl_3$, 96% *ee*]**; IR (Neat): ν_{max} 3030, 2838, 1782, 1759, 1691, 1556, 1510, 1302, 1195, 923, 840, and 656 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.15 (1H, dd, *J* = 7.5, 1.0 Hz), 7.71 (1H, dt, *J* = 8.0, 1.5 Hz), 7.59 (1H, dt, *J* = 7.5, 1.0 Hz), 7.45 (1H, d, *J* = 7.5 Hz), 7.29 (2H, d, *J* = 8.5 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 4.88 (1H, dd, *J* = 8.0, 1.0 Hz), 3.80 (3H, s, OC*H*$_3$), 3.59 (1H, d, *J* = 14.5 Hz), 3.40 (1H, d, *J* =

15.0 Hz), 2.64 (1H, dd, *J* = 16.0, 1.0 Hz), 2.27 (3H, s, COC*H*$_3$), 2.11 (1H, q, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.6 (C, *C*=O), 193.6 (C, *C*=O), 166.9 (C, O-C=O), 158.5 (C), 137.2 (C), 135.2 (CH), 132.2 (2 x CH), 129.9 (CH), 129.5 (C), 128.8 (CH), 127.7 (C), 124.0 (CH), 113.8 (2 x CH), 86.5 (C), 84.0 (CH), 65.0 (C), 55.2 (CH_3, O*C*H$_3$), 31.0 (CH_2), 30.8 (CH_2), 20.9 (CH_3, CO*C*H$_3$); HRMS (ESI-TOF) m/z 410.1242 (M + H$^+$), calcd for $C_{22}H_{19}NO_7H$ 410.1240.

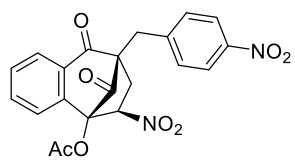
(5*R*,6*R*,8*S*)-6-Nitro-9,10-dioxo-8-(4-(trifluoromethyl)benzyl)-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-5-yl acetate (8ga): Prepared by following the procedure **E** and



(+)-8ga

purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.2:7.8) and isolated as off-white solid; Yield: 91% (122.1 mg). Mp.: 116-118 °C. The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IC-3 column (hexane/2-propanol = 95:05 flow rate 0.7 mL/min, λ = 254 nm), t_R = 23.18 min (major), t_R = 15.04 min (minor); **[α]$_D^{25}$ = +98.0° [*c* = 0.15 g/100 mL, $CHCl_3$, 94% *ee*]**; IR (Neat): ν_{max} 2916, 2848, 1776, 1743, 1690, 1617, 1555, 1369, 1111, 933, 754, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (1H, dd, *J* = 8.0, 1.5 Hz), 7.73 (1H, dt, *J* = 7.5, 1.5 Hz), 7.60 (1H, dt, *J* = 8.0,1.5 Hz), 7.56 (2H, d, *J* = 8.5 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 7.47 (1H, dd, *J* = 7.5, 0.5 Hz), 4.86 (1H, dd, *J* = 8.0, 2.5 Hz), 3.70 (1H, d, *J* = 15.0 Hz), 3.51 (1H, d, *J* = 14.5 Hz), 2.57 (1H, dd, *J* = 16.0, 1.0 Hz), 2.27 (3H, s, COC*H*$_3$), 2.16 (1H, q, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.2 (C, *C*=O), 193.1 (C, *C*=O), 166.8 (C, O-C=O), 140.0 (C), 137.1 (C), 135.5 (CH), 131.6 (2 x CH), 130.0 (CH), 129.4 (C, q, *J* = 32.5 Hz), 129.3 (C), 128.9 (CH), 125.3 (2 x CH, q, *J* = 3.75 Hz), 124.0 (CH), 124.1 (C, q, *J* = 270.0 Hz, *C*F$_3$), 86.4 (C), 83.9 (CH), 64.4 (C), 31.8 (CH_2), 31.2 (CH_2), 20.8 (CH_3, CO*C*H$_3$); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −62.5; HRMS (ESI-TOF) m/z 470.0823 (M + Na$^+$), calcd for $C_{22}H_{16}F_3NO_6Na$ 470.0822.

(5*R*,6*R*,8*S*)-6-Nitro-8-(4-nitrobenzyl)-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methano benzo[7]annulen-5-yl acetate (8ha): Prepared by following the procedure **E** and purified by

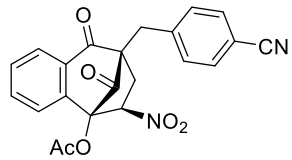


(+)-8ha

column chromatography using EtOAc/hexane (2.5:7.5 to 3.0:7.0) and isolated as off-white solid; Yield: 83% (105.6 mg). Mp.: 171-173 °C. The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IA-3 column (hexane/2-propanol = 95:05 flow rate 0.7 mL/min, λ = 254 nm), t_R = 133.17 min (major), t_R = 102.93 min (minor); **[α]$_D^{25}$ = +59.0° [*c* = 0.1 g/100 mL, $CHCl_3$, 92.7% *ee*]**; IR (Neat): ν_{max} 2922, 2852, 1769, 1788, 1695, 1560, 1366, 851, 754, and 590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500

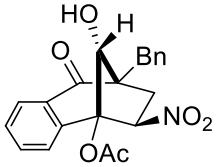
MHz) δ 8.16 (3H, m), 7.75 (1H, dt, *J* = 8.0, 1.5 Hz), 7.60 (3H, m), 7.48 (1H, d, *J* = 8.0 Hz), 4.90 (1H, dd, *J* = 8.0, 1.0 Hz), 3.70 (1H, d, *J* = 14.5 Hz), 3.60 (1H, d, *J* = 14.5 Hz), 2.55 (1H, dd, *J* = 16.0, 1.0 Hz), 2.27 (3H, s, COC*H*$_3$), 2.20 (1H, q, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.0 (C, *C*=O), 192.8 (C, *C*=O), 166.8 (C, O-C=O), 147.1 (C), 143.6 (C), 137.0 (C), 135.6 (CH), 132.2 (2 x CH), 130.1 (CH), 129.2 (C), 129.0 (CH), 124.1 (CH), 123.5 (2 x CH), 86.3 (C), 83.9 (CH), 64.3 (C), 31.9 (CH_2), 31.1 (CH_2), 20.8 (CH_3, CO*C*H$_3$); HRMS (ESI-TOF) m/z 425.0985 (M + Na$^+$), calcd for $C_{21}H_{16}N_2O_8Na$ 425.0985.

(5*R*,6*R*,8*S*)-8-(4-Cyanobenzyl)-6-nitro-9,10-dioxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-5-yl acetate (8ia): Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.2:7.8) and isolated as off-white solid; Yield: 88% (110.5 mg). Mp.: 146-148 °C. The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IA-3 column (hexane/2-propanol = 95:05 flow rate 0.7 mL/min, λ = 254 nm), t_R = 126.34 min (major), t_R = 96.88 min (minor); **[α]$_D^{25}$ = +45.0° [*c* = 0.1 g/100 mL, $CHCl_3$, 97.6% *ee*]**; IR (Neat): ν_{max} 2921, 2851, 2228, 1784, 1763, 1687, 1561, 1199, 979, 752 and 623 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (1H, d, *J* = 8.0 Hz), 7.74 (1H, t, *J* = 7.0 Hz), 7.75 (3H, m), 7.52 (2H, d, *J* = 8.0 Hz), 7.47 (1H, d, *J* = 8.0 Hz), 4.89 (1H, d, *J* = 7.5 Hz), 3.65 (1H, d, *J* = 14.5 Hz), 3.53 (1H, d, *J* = 15.0 Hz), 2.53 (1H, d, *J* = 16.0 Hz), 2.27 (3H, s, COC*H*$_3$), 2.20 (1H, q, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.1 (C, *C*=O), 192.9 (C, *C*=O), 166.8 (C, O-C=O), 141.4 (C), 137.0 (C), 135.6 (CH), 132.1 (2 x CH), 132.0 (2 x CH), 130.0 (CH), 129.2 (C), 128.9 (CH), 124.0 (CH), 118.7 (C), 111.0 (C), 86.3 (C), 83.8 (CH), 64.3 (C), 32.1 (CH_2), 31.1 (CH_2), 20.8 (CH_3, CO*C*H$_3$); HRMS (ESI-TOF) m/z 427.0901 (M + Na$^+$), calcd for $C_{22}H_{16}N_2O_6Na$ 427.0906.



(+)-8ia

(6*R*,8*R*,10*R*)-8-Benzyl-10-hydroxy-6-nitro-9-oxo-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzo[7]annulen-5-yl acetate (9aa): Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (1.5:8.5 to 3:7) and isolated as an oil; Yield: 40% (45.7 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.47 min (major), t_R = 12.44 min (minor); **[α]$_D^{25}$ = +17.8° [*c* = 0.1 g/100 mL, $CHCl_3$, >25:1 *dr*, 89% *ee*]**; IR (Neat): ν_{max} 3429 (OH), 2959, 2924, 1727, 1696, 1599, 1554, 1367, 1238, 1052, 755, and 706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (1H, dd, *J* = 7.5, 1.0



(+)-9aa

Hz), 7.61 (1H, dt, *J* = 7.5, 1.5 Hz), 7.53 (1H, dt, *J* = 7.5, 1.5 Hz), 7.38 (2H, br t, *J* = 8.0 Hz), 7.33 (1H, br t, *J* = 7.5 Hz), 7.29 (2H, br d, *J* = 7.5 Hz), 7.17 (1H, dd, *J* = 7.5, 1.0 Hz), 5.17 (1H, dd, *J* = 9.0, 7.0 Hz), 4.51 (1H, O-*H*), 4.39 (1H, C*H*OH), 3.25 (1H, d, *J* = 14.5 Hz), 3.17 (1H, d, *J* = 14.5 Hz), 2.41-2.39 (2H, m), 2.34 (3H, s, O-CO-CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.7 (C, *C*=O), 171.9 (C, O-C=O), 135.9 (C), 134.3 (CH), 133.6 (C), 131.3 (C), 131.1 (2 x CH), 129.7 (CH), 128.6 (2 x CH), 127.6 (CH), 127.0 (CH), 124.5 (CH), 91.2 (C), 87.3 (CH), 77.9 (CH), 57.4 (C), 34.3 (CH_2), 26.7 (CH_2), 21.6 (CH_3, O-CO-*C*H_3); HRMS (ESI-TOF) m/z 404.1110 (M + Na^+), calcd for $C_{21}H_{19}NO_6Na$ 404.1115.

3.5 References:

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4. Chiral Bicyclo[3.2.1]octanes Construction *via* Low-catalyst Loading Asymmetric Tandem Michael/Henry Reactions

4.1 Introduction

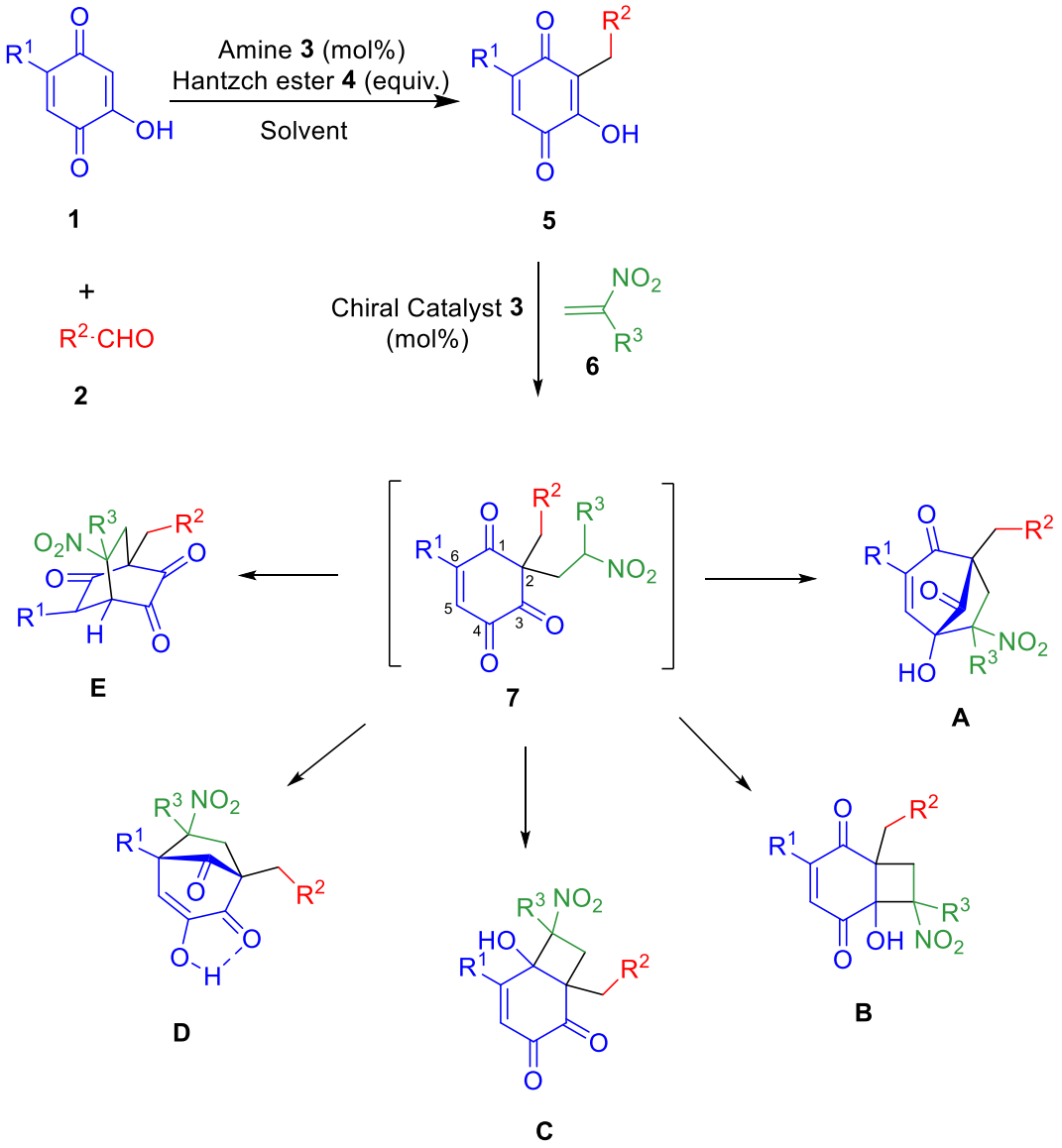
Organocatalysis aims to develop sustainable approaches in organic transformations by minimizing the consumption of time, money, energy and simultaneously limiting the utilization of resources.[1] Over the past two decades, several strategies have been designed to make organocatalysis a resilient substitute for stoichiometric methods and non-catalytic circumstances. This predominance of asymmetric organocatalysis is due to the accessibility of various activation modes and their widespread adoption. Numerous factors account for the successful usage of chiral organic molecules as catalysts, such as the ability to conveniently access them from natural resources and cost-effectiveness relative to metal or enzyme catalysis.

After recognizing the contributions of asymmetric organocatalysis with a Nobel Prize in the year 2021, there is a sharp surge in the cultivation of these strategies for developing novel reactions. However, specific challenges like the catalyst reproducibility and the inability to limit the loading of the catalyst obstruct in satisfying the exquisite principles of green chemistry. In principle, catalysts with low turnover numbers fail to find applicability in the industry, and this predicament arises due to catalyst poisoning, resulting in fewer active catalytic cycles. Thus, renewing the catalyst without modifying its physicochemical characteristics becomes necessary to achieve high turnover numbers (TON) for the envisioned asymmetric chemical transformations.

Recently, scientists have been focusing on developing low or ppm-level loading catalysed reactions to devise novel reactions with high turnover numbers[2]. To obtain this objective, the interaction between the substrate and catalyst must be very rapid. Therefore, the species involved in the reaction should be highly reactive, thus making the catalyst's active site accessible for multiple cycles, accounting for limited catalyst loading. Recently, our group published an article on ppm-level organocatalyzed asymmetric [3+2]-annulation for synthesizing chiral methanobenzo[*7*]annulenes. Therein, we have chosen highly reactive, ambident nitroethylene species as an electrophilic partner and lawsone as a nucleophilic partner owing to its abundant reactive sites for the synthesis of methanobenzo[*7*]annulenes with excellent enantioselectivity and diastereoselectivity and high yields. Furthermore, to gain insight into low catalyst loading reactions, we have chosen α-substituted nitroethylenes, which

are often less explored in the literature.[3] Thus, it would be very fascinating to study its reactivity.

We chose hydroxy-*p*-quinones as nucleophilic partners, as they possess interesting molecular architecture with multiple reactive centers and could be accessed easily from their corresponding phenols. They also portray an exciting array of photo-physical properties and act as interesting pharmacophores, hence grabbing consideration from the pharmaceutical arena.



Scheme 1: Reaction design for the exploring nitroethylenes reactivity.

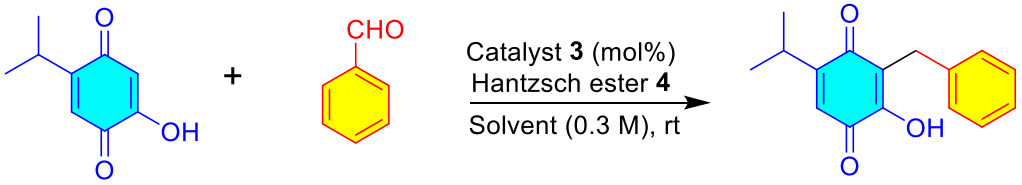
To understand the reactivity of α-substituted nitroethylenes, we have designed the reaction between nitroethylenes and hydroxy-*p*-quinones. To accomplish this objective, we envisioned utilizing the scope of TCRA reaction to synthesize reductive alkylated product **5** using suitable

amine **3**, as a catalyst. The reaction of the TCRA product **5** with substituted nitroethylenes **6** in the presence of chiral catalyst **3** generates intermediate **7**, which has multiple reactive sites owing to its ambident nature, thus opening a possibility for the formation of various bicyclic products. For instance, intermediate **7** can undergo a Henry reaction with the adjacent carbonyl groups (C4, C3, C1), forming bicyclic compounds **A**, **B**, and **C**, respectively. Similarly, intermediate **7** can also undergo Michael addition at (C5, C6), resulting in Michael adducts **D** and **E**. This plausibility for formation of various products **A** to **E** motivates us to move forward with the reaction design and investigate its reactivity in terms of regioselectivity, diastereoselectivity, and enantioselectivity (Scheme 1).

4.2 Results and Discussions

4.2.1 Reaction Optimization: Initially, we synthesized **1a** from *p*-isopropylphenol and then treated it with commercially available benzaldehyde **2a** to give us the corresponding reductive alkylated product **5aa**. In this reaction, we have utilized *L*-proline **3a** as the catalyst in DCM solvent at room temperature and obtained **5aa** in 28% yield (Table 1, entry 1). The desired product was obtained when we performed reactions using benzylamine **3b** as a catalyst, but there is no considerable increase in the yield with the increase in loading of **3b**, moreover, stirring the reaction for a longer time i.e., more than 1 h has decreased the yield as multiple spots appeared. (Table 1, entry 2, 3, 4). A reaction was then carried out using aniline **3c** as the catalyst and to our delight, the yield slightly improved to 56% (Table 1, entry 5). When the equivalence of **3c** was changed from 0.2 to 0.05, the reaction took longer hours with decreased product formation of **5aa** (Table 1, entries 5-7). Screening of solvents such as THF, *n*-butanol, methanol, isopropanol, DCE, and CH_3CN, has proved that only DCM and DCE are efficient, establishing them as the most suitable solvents in this reaction (Table 1, entries 8-14). Upon increasing the loading of **3c** from 0.5 equiv. to 1.0 equiv, the yield of **5aa** enhanced from 58% to 70% within 0.5 h, thus indicating it as the optimized condition for the reaction (Table 1, entries 15-16).

Table 1: Investigation of Reductive Coupling Reaction on the Hydroxy-*p*-quinones **1a**. [a]



1a **2a** **5aa**

Entry	Catalyst **3** (mol%)	**2a** (equiv.)	**4** (equiv.)	Solvent [0.3 M]	Time [h]	Yield [%][b]
1	Proline **3a** (20)	2.0	1.1	DCM	11 h	28
2	Benzylamine **3b** (5)	2.0	1.1	DCM	1 h	15
3	Benzylamine **3b** (10)	2.0	1.1	DCM	0.25 h	36
4	Benzylamine **3b** (20)	2.0	1.1	DCM	0.25 h	42
5	Aniline **3c** (20)	2.0	1.1	DCM	3 h	56
6	Aniline **3c** (10)	2.0	1.1	DCM	3 h	53
7	Aniline **3c** (5.0)	2.0	1.1	DCM	16 h	50
8	Aniline **3c** (20)	2.0	1.1	THF	3 h	45
9	Aniline **3c** (20)	2.0	1.1	n-butanol	3 h	56
10	Aniline **3c** (20)	2.0	1.1	DMSO	3 h	25
11	Aniline **3c** (20)	2.0	1.1	MeOH	3 h	20
12	Aniline **3c** (20)	2.0	1.1	*i*-PrOH	3 h	45
13	Aniline **3c** (20)	2.0	1.1	DCE	1 h	58
14	Aniline **3c** (20)	2.0	1.1	CH_3CN	6 h	33
15	Aniline **3c** (50)	2.0	2.0	DCM	1 h	60
16	Aniline **3c** (1.0 equiv.)	2.0	2.0	DCM	0.5 h	70

[a] Reactions were carried out in solvent (0.3 M) with 2.0 equiv. of **2a** and 2.0 equiv. of **4** relative to hydroxy-*p*-quinone **1a** (0.3 mmol) in the presence of catalyst **3c**. [b] Yield refers to the column-purified product.

^{1}H, ^{13}C NMR spectra of **5aa** from optimization Table 1 depicted in Figure 1

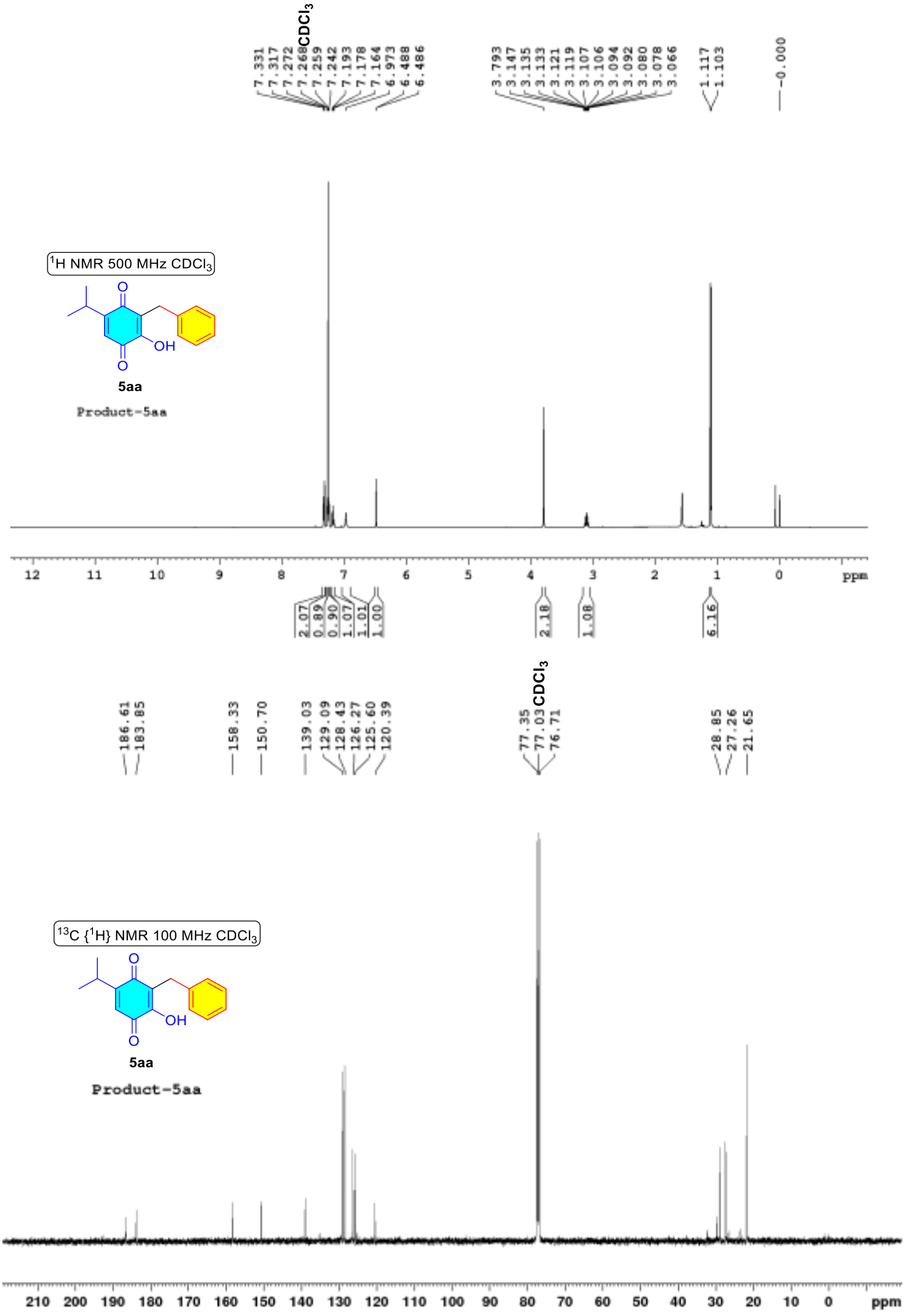
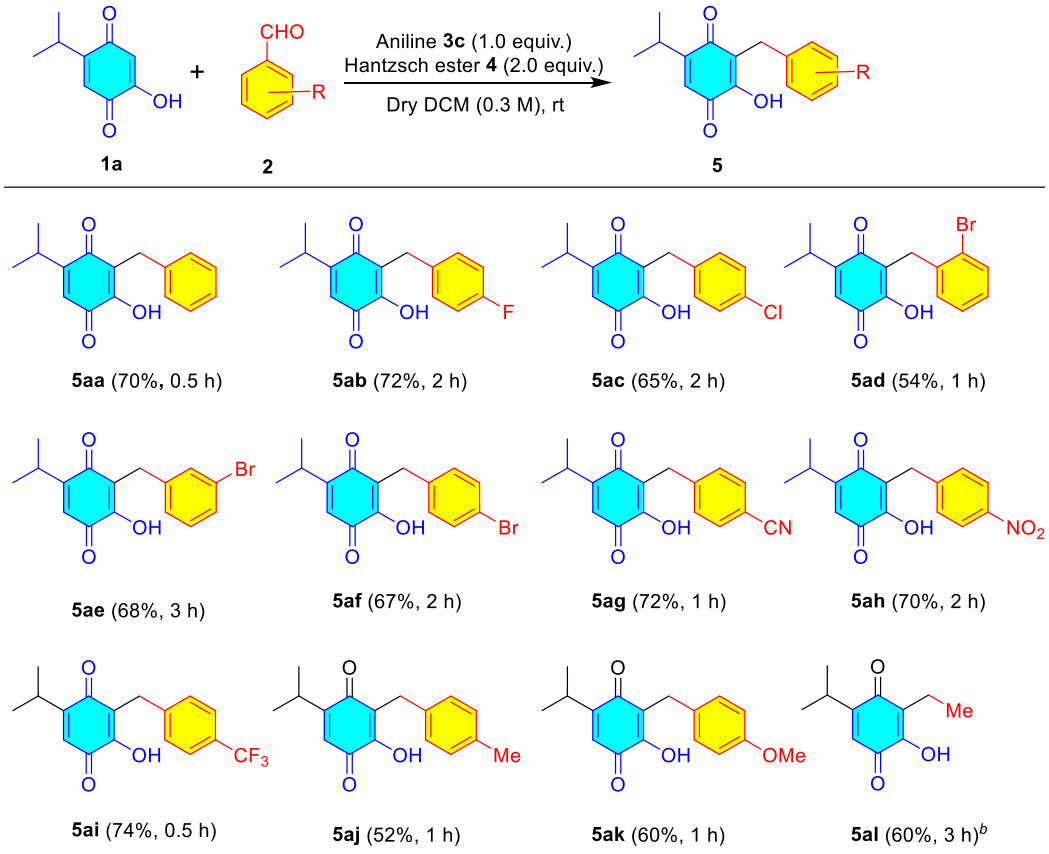


Figure 1: ^{1}H NMR and ^{13}C NMR spectrum of product **5aa**.

4.2.2 A Study for Understanding the Scope of the Reaction:

With the established optimized reaction conditions in hand, we investigated various substituent effects governing the reaction. We initially performed the reaction between **1a** and various aldehydes **2b-l** to furnish products **5ab-5al**. The reaction of 4-fluoro and 4-chlorobenzaldehydes, **2b** and **2c** gave **5b** and **5c** in 2 h with 72% and 65% yields respectively (Table 2). The reaction of **1a** with **2d-2f** went smoothly to give **5ad-5af** in moderate yields (54%, 68%, 67%) in less than 3 h, stating that steric factors govern the reaction (Table 2). Reactions were carried out with electron-withdrawing groups 4-CN, 4-NO_2, and 4-CF_3 to give products **5ag-5ai** in good yields, i.e., 72%, 70%, 74%, respectively and also with electron-donating groups 4-methyl and 4-methoxy **2j** and **2k** to give **5aj** and **5ak** in 1 h with moderate yields of 52% and 60% respectively (Table 2). The reaction went smoothly with 5.0 equiv. of acetaldehyde **2l** at 0 °C to give **5al** in 3 h with 60% yield (Table 2).

Table 2: Reaction Scope of Hydroxy-*p*-quinone **1a** with Various Aldehydes **2**. [a]



[a] Reactions were performed with 1.0 equiv. (0.3 mmol) of hydroxy-*p*-quinone **1a** and 2.0 equiv. (0.6 mmol) of aldehyde **2** in the presence of 1.0 equiv. of Aniline **3c** and 2.0 equiv. of Hantzsch ester **4** in DCM (0.3 M) at room temperature. [b] Reaction was performed with 5.0 equiv. of **2l** at 0 °C.

^{1}H, ^{13}C NMR spectra of few compounds from Table 2 depicted in Figure 2-4.

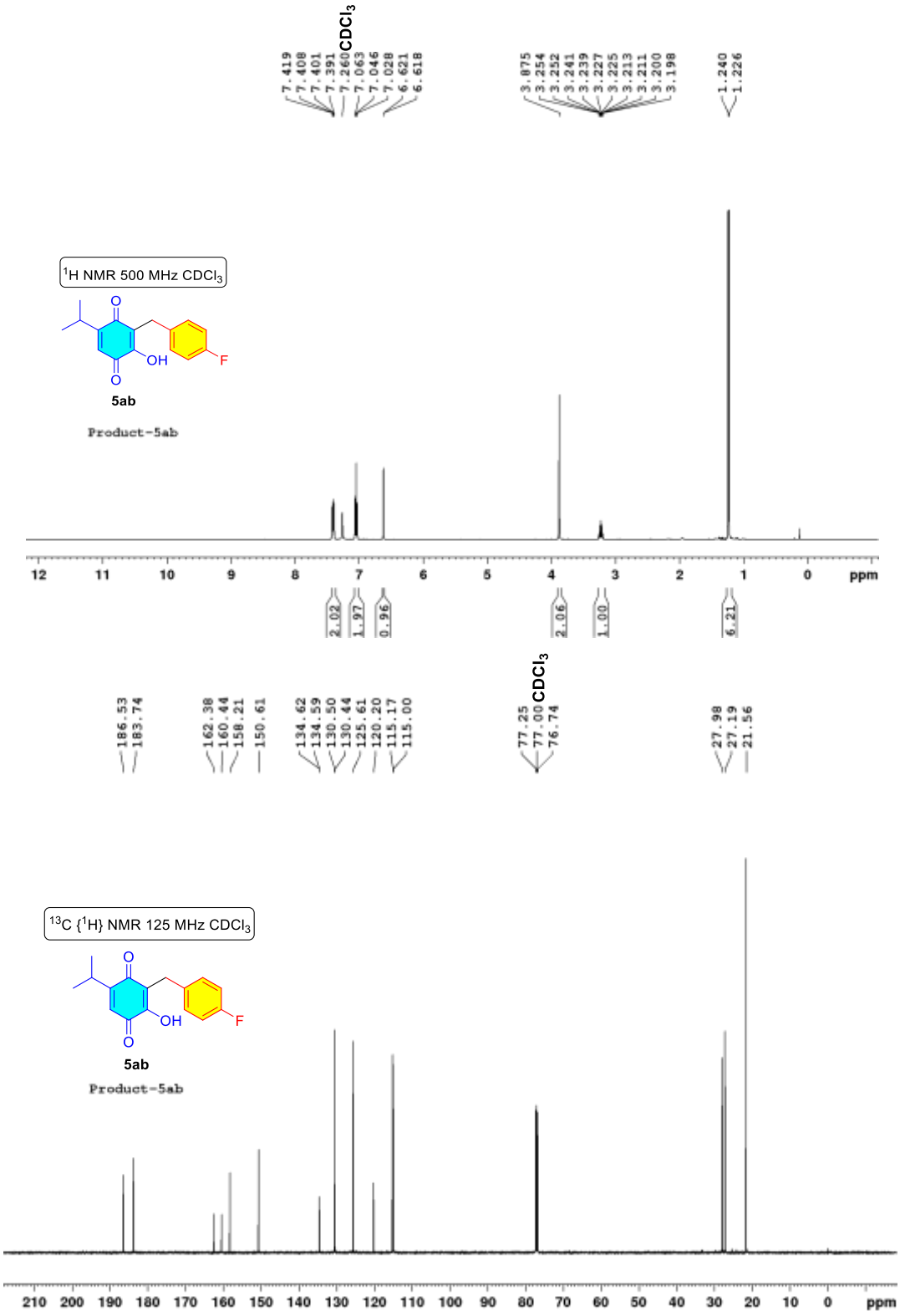


Figure 2: ^{1}H NMR and ^{13}C NMR spectrum of product-**5ab**.

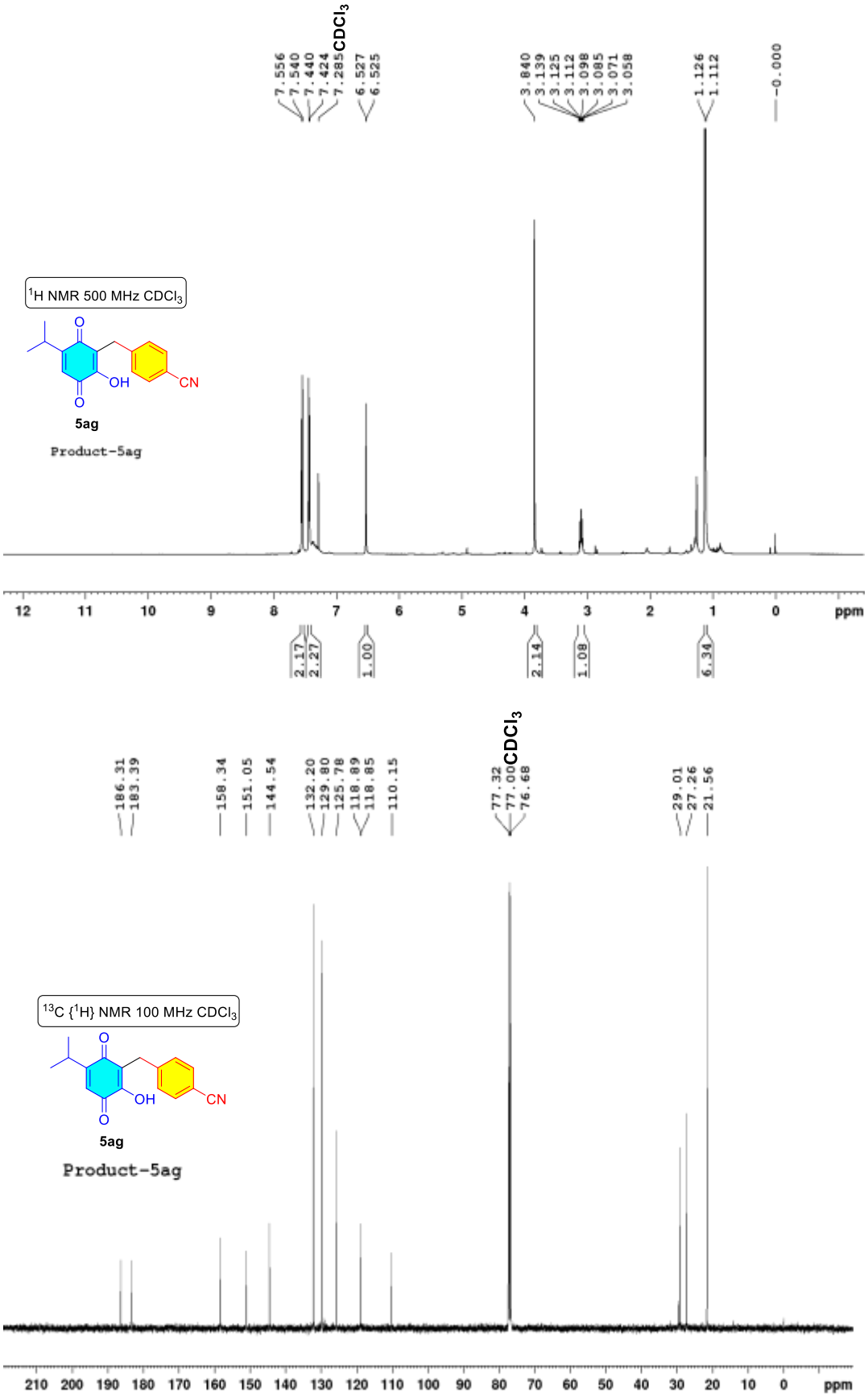


Figure 3: ^{1}H NMR and ^{13}C NMR spectrum of product-**5ag**.

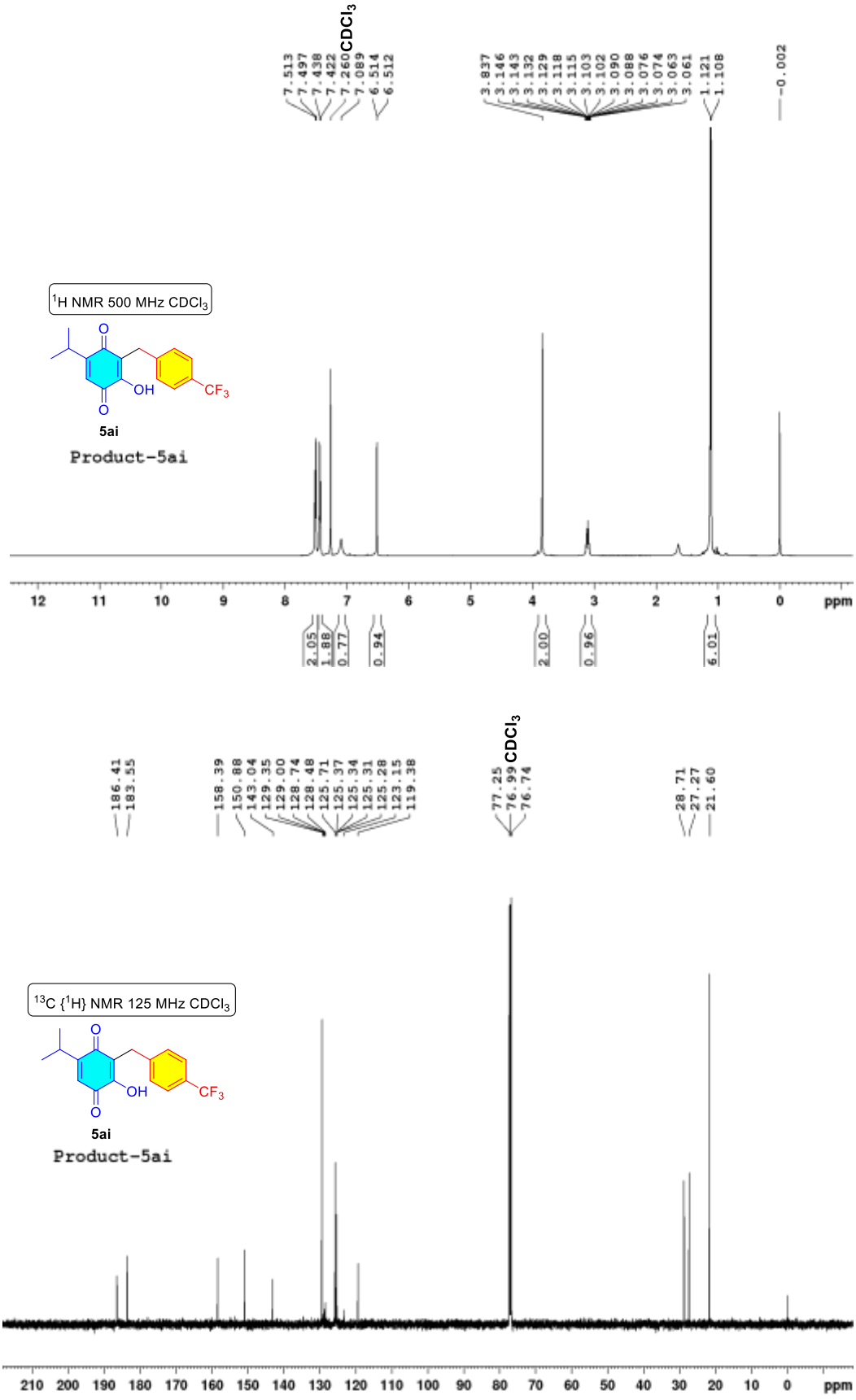
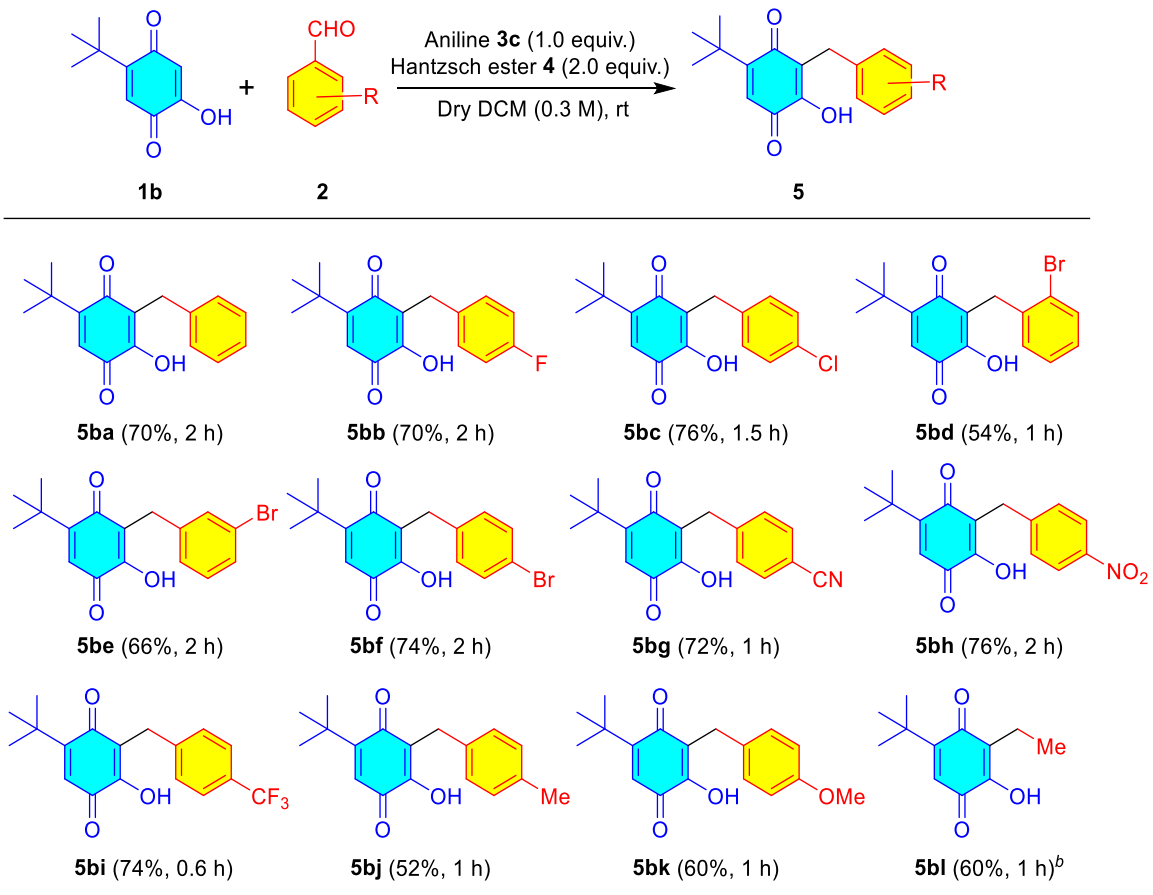


Figure 4: ^{1}H NMR and ^{13}C NMR spectrum of product-**5ai**.

We went onto investigate the reaction scope for 2-(*tert*-butyl)-5-hydroxycyclohexa-2,5-diene-1,4-dione **1b** with various aldehydes **2** following the optimized reaction conditions to give products **5ba-5bl** (Table 3). The reaction of **1b** with aldehydes **2a-2c** resulted in the formation of products **5ba-5bc** with moderate yields of 70% and 76% in 2 h or less than 2 h respectively (Table 3). Treatment of **1b** with aldehydes **2d-2f** gave products **5bd-5bf** with 54%, 66%, 74% yields respectively, which can be attributed to steric factors (Table 3). Electron withdrawing groups such as 4-CN, 4-NO_2, and 4-CF_3, gave the products **5bg-5bi** in less than 2 h with good yields and electron-donating groups such as 4-Me and 4-OMe gave products **5bj-5bk** in 1 h with yields of 52% and 60% (Table 3). A reaction was also carried out with 5.0 equiv. of **2l** at 0 °C to give **5bl** in 60% yield (Table 3).

Table 3: Reaction Scope of **1b** with Various Aldehydes **2**.[a]



[a] Reaction was performed with 1.0 equiv. (0.3 mmol) of hydroxy-*p*-quinone **1b** and 2.0 equiv. (0.6 mmol) of aldehyde **2** in presence of 1.0 equiv. of Aniline **3c** and 2.0 equiv. of Hantzsch ester **4** in DCM (0.3 M) at room temperature. [b] Reaction was performed with 5.0 equiv. of **2l** at 0 °C.

^{1}H and ^{13}C NMR spectra of few compounds from Table 3 depicted in Figure 5-7.

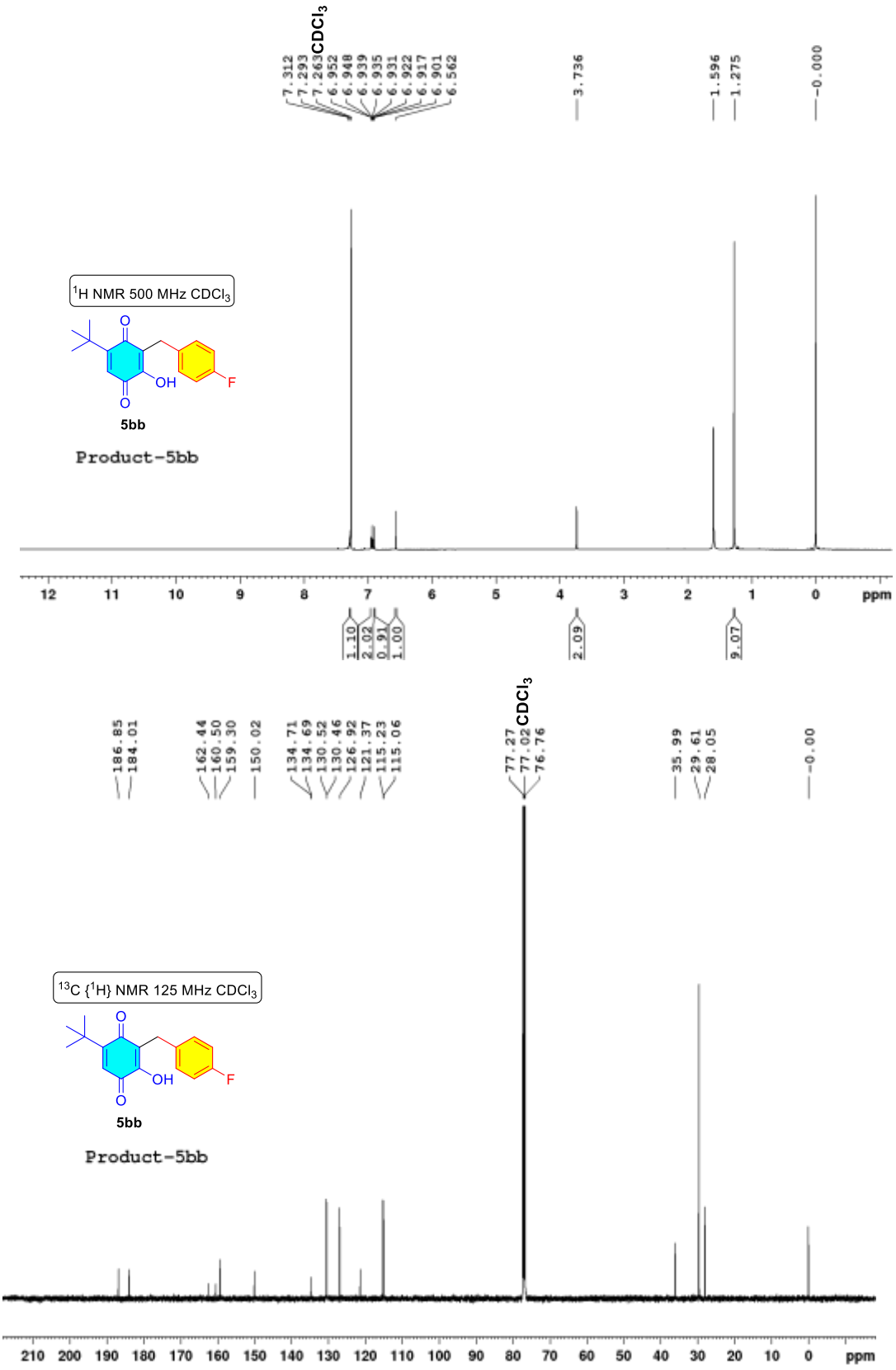


Figure 5: ^{1}H NMR and ^{13}C NMR spectrum of product-**5bb**.

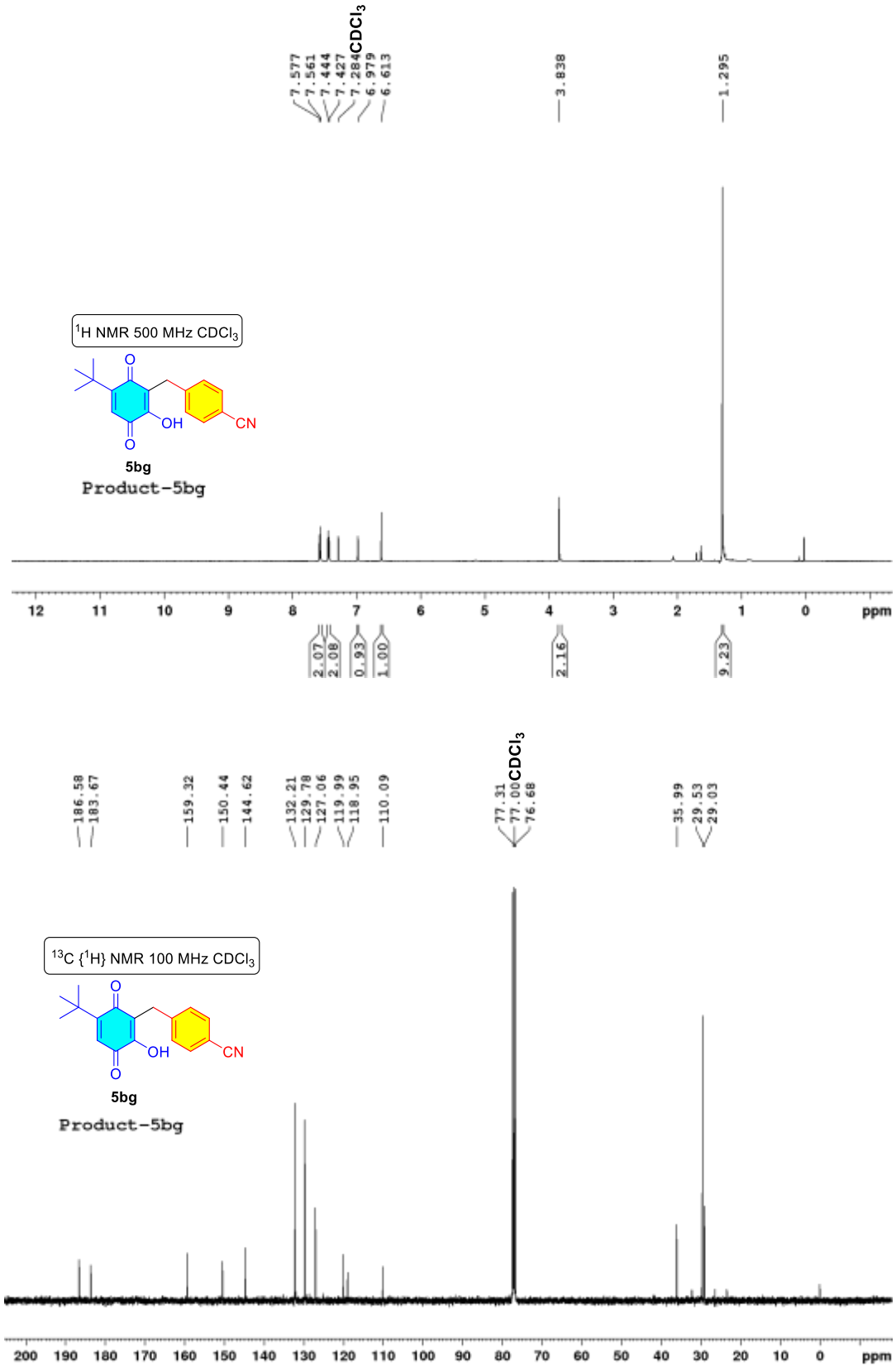


Figure 6: ^{1}H NMR and ^{13}C NMR spectrum of product-**5bg**.

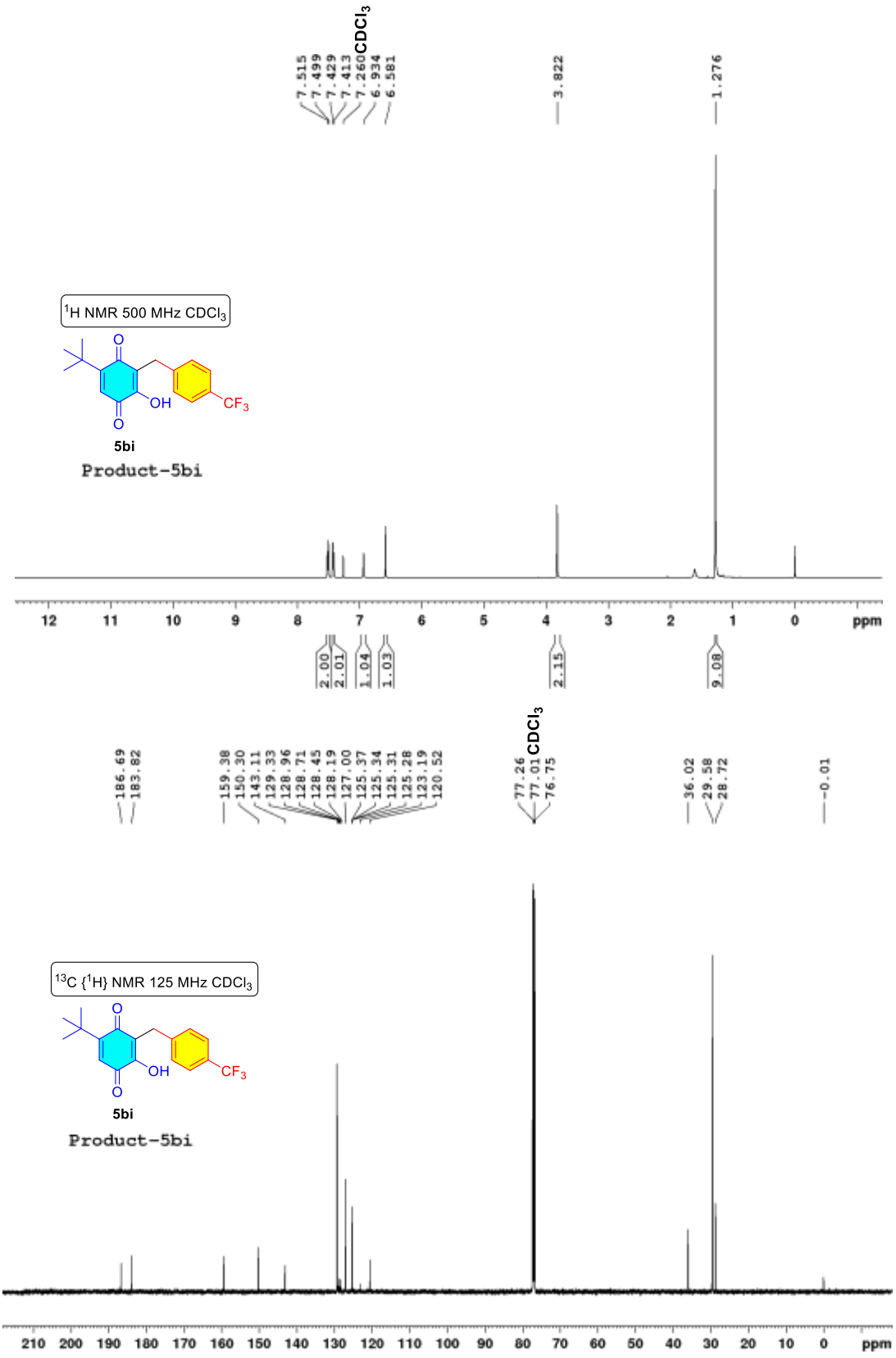
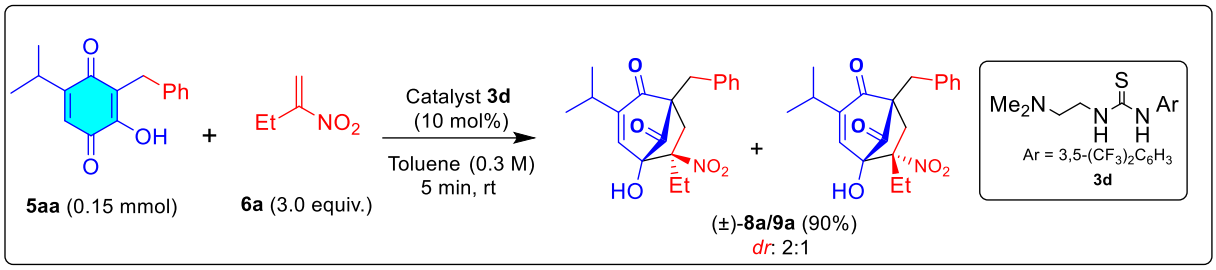


Figure 7: ^{1}H NMR and ^{13}C NMR spectrum of product-**5bi**.

Following the synthesis of a library of TCRA products, **5ab-5al** and **5ba-5bl**, we then moved forward with the investigation of the reactivity of **5** and **6**, and we were fascinated to probe its selectivity despite possessing interesting possibilities, as evident from the reaction design.

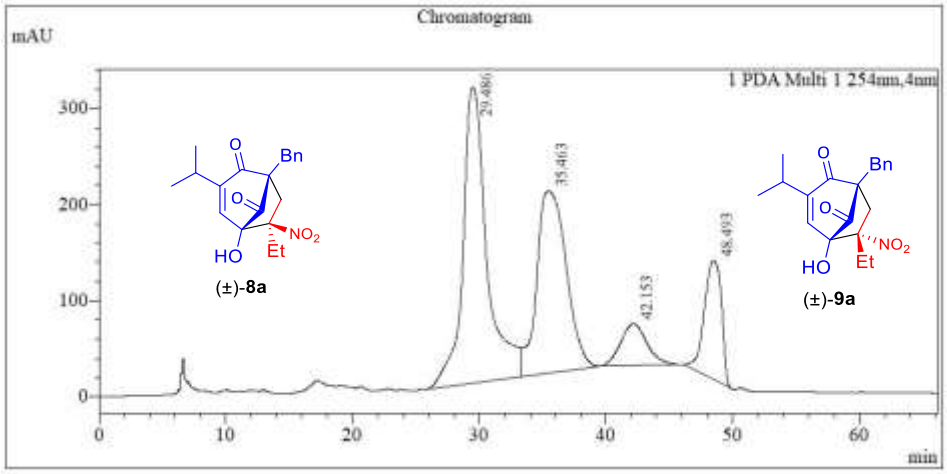
Initially, we took **5aa** and **6a** in the presence of achiral thiourea catalyst **3d** (10 mol%) in toluene that gave (±)-**8a** and (±)-**9a**, with a *dr* of 1.5:1 for the crude reaction mixture and a *dr* of 2:1 for the column purified products in 90% yield (Scheme 2).



Scheme 2: Initial investigation of the proposed catalytic tandem reaction.

The NMR analysis of (±)-**8a/9a** did not help to predict the accurate diastereomeric ratio, as it showed varying *dr* values in the crude reaction mixture and column purified product of (±)-**8a** and (±)-**9a.** There is no significant separation of (±)-**8a** and (±)-**9a** in HPLC, and the prediction of *dr* was inaccurate from the HPLC data, and this can be due to retro Henry reaction and epimerization of *a-tert*-hydroxy group (Figure 8).

Racemic tandem Michael/Henry products (±)-**8a/9a**:



Chiralpak IG, Hexane/ *i*-PrOH = 97:3, Flow Rate 0.5 mL/min 254 nm

Peak Table

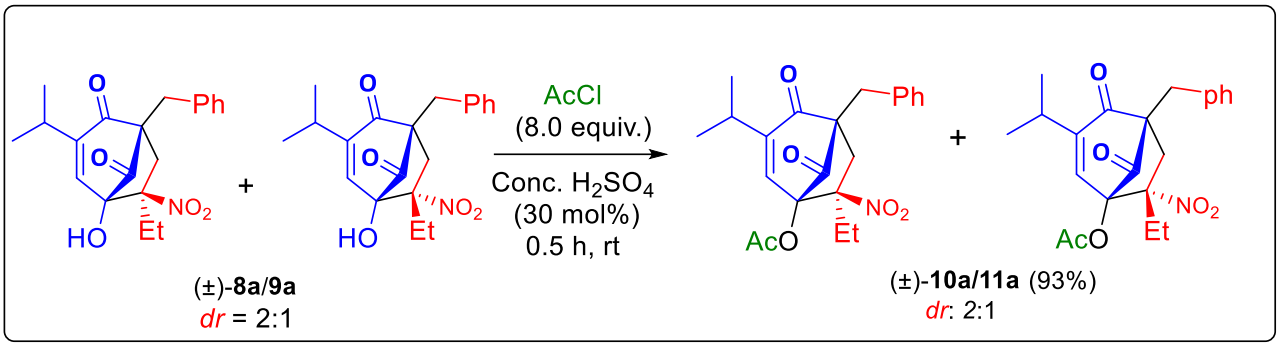
PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:29.486	29.486	40732504	308228	45.620	46.367
2	RT:35.463	35.463	30611512	189329	34.285	28.481
3	RT:42.153	42.153	6296059	43396	7.052	6.528
4	RT:48.493	48.493	11646150	123800	13.044	18.623

Figure 8: HPLC spectra of the racemic tandem products (±)-**8a/9a**.

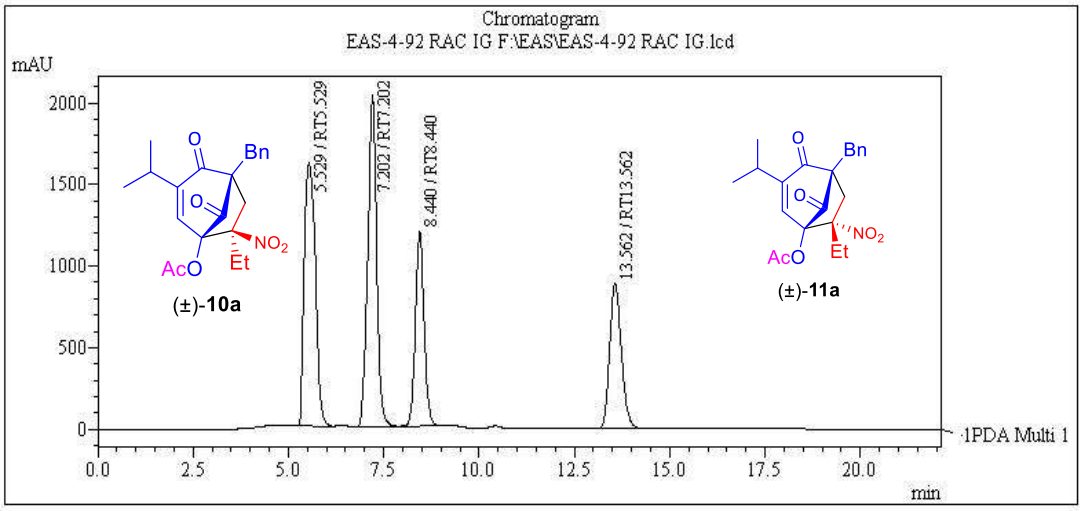
To prevent (±)-**8a** and (±)-**9a** diastereomers from undergoing epimerization, we protected the hydroxy group with CH_3COCl (8.0 equiv.) in the presence of conc.H_2SO_4 (30 mol%) as a catalyst to give (±)-**10a** and (±)-**11a**, as diastereomers. (Scheme 3). As predicted, the separation

of (±)-**10a** and (±)-**11a** was achieved with sharp peaks, thus helping us in analyzing the accurate *dr*, following the protection of the hydroxy group (Figure 9).



Scheme 3: Initial investigation for the protection of *tert*-hydroxyl group.

Racemic *tert*-hydroxyl group protected tandem Michael/Henry products (±)-**10a/11a**:



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

PeakTable

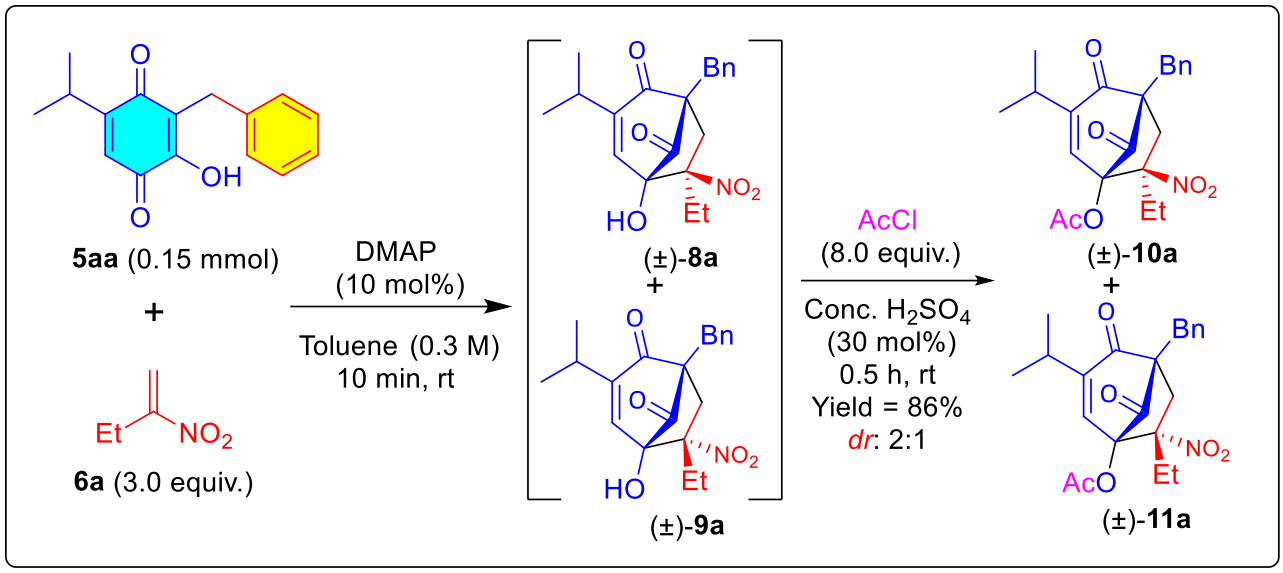
PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT5.529	5.529	32886777	1614223	31.652	28.173
2	RT7.202	7.202	33016150	2031520	31.776	35.456
3	RT8.440	8.440	18979177	1194414	18.266	20.846
4	RT13.562	13.562	19020056	889597	18.306	15.526

Figure 9: HPLC spectra of the racemic products (±)-**10a/11a**.

We have further tried 10 mol% of DMAP in the place of catalyst **3d**, expecting to get a better *dr* and yield. As isolation of (±)-**8a** and (±)-**9a** and further protection is cumbersome, as evident from our previous experience, we adopted an alternative one-pot method as a substitute for step-by-step synthesis. To our delight, the first step of the reaction was completed in just 10 min and then subsequently, the protection with CH_3COCl was done in the same pot to give (±)-

10a and (±)-**11a** in 30 min, with no change in *dr*, instead a reduced yield of 86% was obtained, thus establishing **3d** as the best catalyst for the reaction. (Scheme 4).



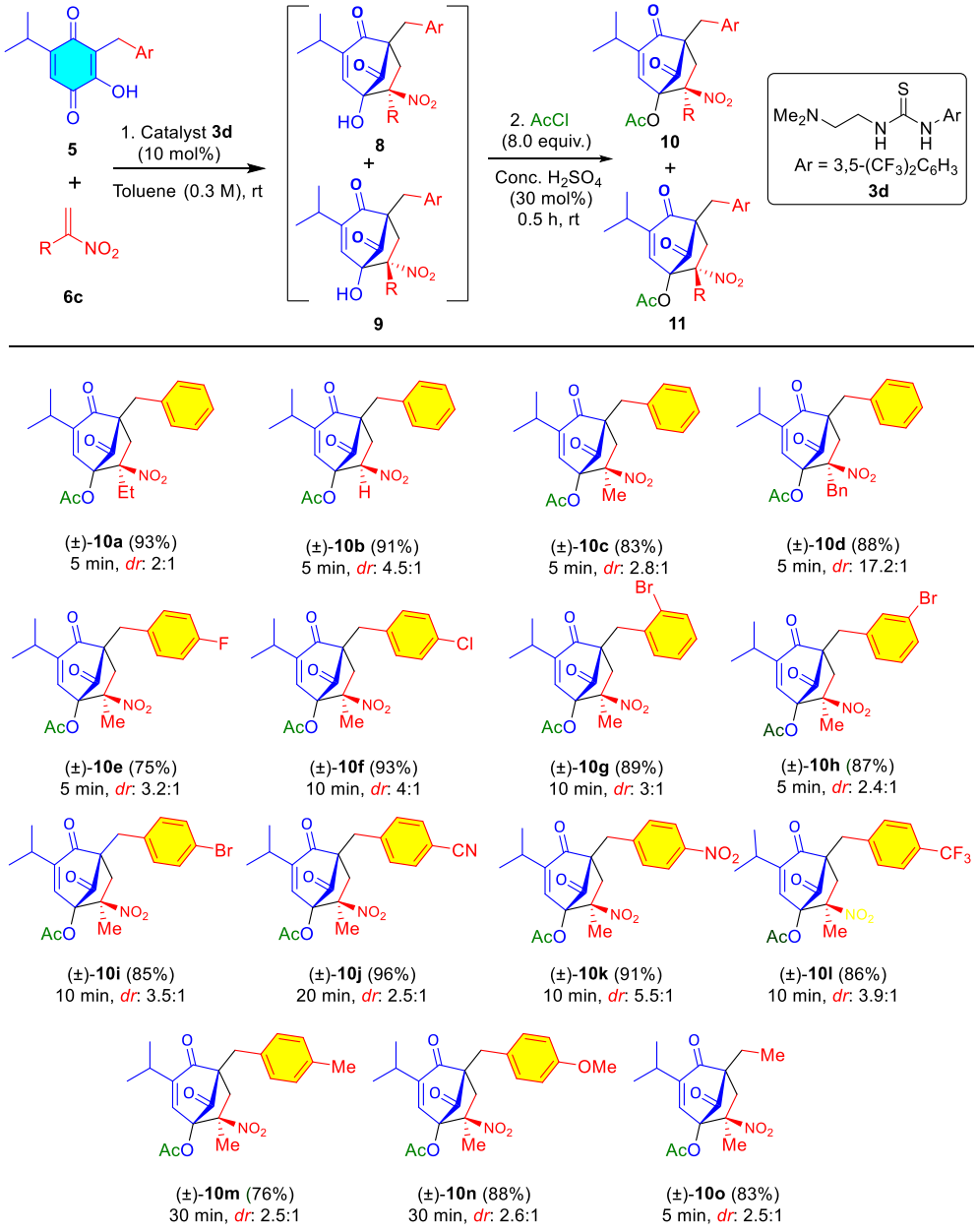
Scheme 4: One-pot synthesis of (±)-**10a/11a** under the DMAP-catalysis.

4.2.3 Substrate scope for racemic synthesis

Then, we went on to synthesize a library of compounds (±)-**10a** to **10o**, considering all the electronic factors and steric factors into account, and using **3d** as the catalyst. The reaction of **5aa** with different substituted nitroethylenes **6b**, **6c,** and **6d** gave the products (±)-**10b**, (±)-**10c** and (±)-**10d** respectively, in 5 min, which itself highlights the reactivity of nitroethylenes. The reactions of **6b** and **6c** gave excellent yields of 91% and 83% and a *dr* of 4.5:1 and 2.8:1 respectively (Table 4). The same reaction with **6d** gave excellent diastereoselectivity of 17.2 :1 with 88% yield which can be attributed to the inherent nature of the benzyl group to participate in epimerization (Table 4). The reaction of **5ab** and **5ac** with **6c** gave products (±)-**10e** and (±)-**10f** with 75% and 93% yield with a *dr* of 3.2:1 and 4:1 in 5 and 10 min respectively (Table 4). The products (±)-**10g**, (±)-**10h**, and (±)-**10i** were also synthesized in good yields with no remarkable change in yield, diastereoselectivity, and reaction time, stating its conditions to be independent of the steric factors (Table 4). The reaction with electron-withdrawing groups such as 4-CN, 4-NO_2, and 4-CF_3 as in the case of **5ag-5ai** reacted without any hassle in less than 20 min with excellent yields and a *dr* of 2.5:1, 5.5:1, and 3.9:1 to give (±)-**10j**, (±)-**10k** and (±)-**10l** respectively (Table 4). Electron donating groups such as 4-Me and 4-OMe gave (±)-**10m** and (±)-**10n** in 30 min with yields of 76% and 88% and a *dr* of 2.5:1 and 2.6:1 respectively (Table 4). Reaction with **5al** gave (±)-**10o** in 5 min and *dr* of 2.5:1 with 83% yield

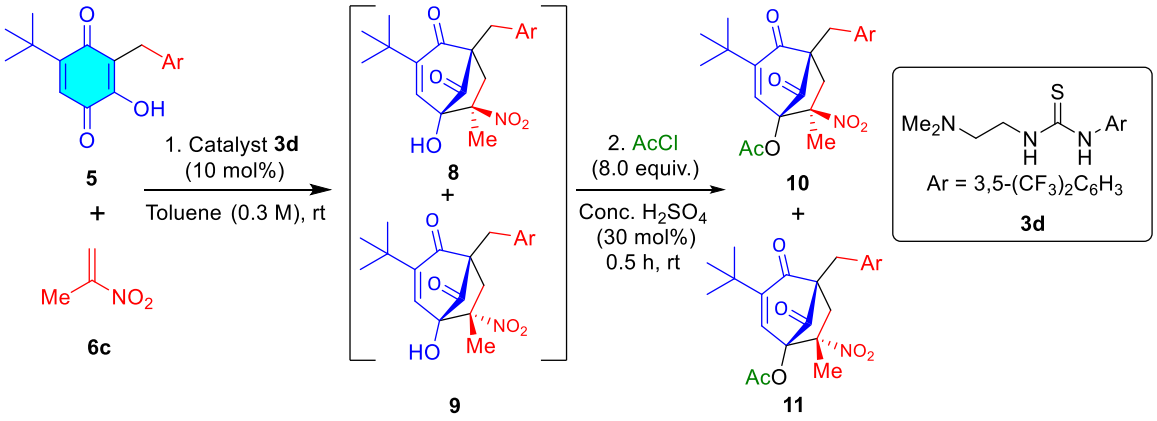
ascertaining that the reaction conditions are independent of the reactant's aliphatic and aromatic nature (Table 4).

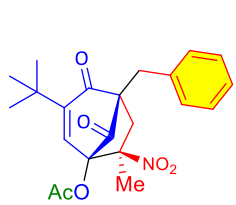
Table 4: Catalytic One-pot Racemic Synthesis of Bicyclo[3.2.1]octanes **10**/**11**. [a-c]



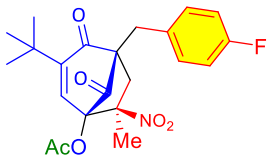
[a] Reactions were carried out in toluene (0.05 mL) with 3.0 equiv. of **6** (0.45 mL, 1.0 M in toluene) relative to **5** (0.15 mmol) in the presence of catalyst **3d** (10 mol%) at room temperature for time indicated followed by *tert*-hydroxy group protection with 8.0 equiv. of acetyl chloride in the presence of 0.3 equiv. of conc.H_2SO_4 at room temp for 0.5 h. [b] Yield refers to the column-purified product (**10**+**11**). [c] *dr* was determined by CSP-HPLC analysis of the column-purified products.

Table 5: Catalytic Racemic Synthesis of Bicyclo[3.2.1]octanes **10**/**11**. [a-c]

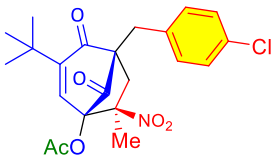




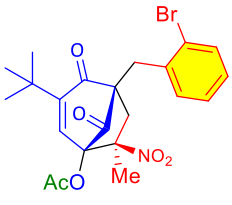
(±)-**10p** (95%)
30 min, *dr*: 4.5:1



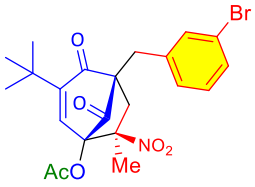
(±)-**10q** (95%)
20 min, *dr*: 3:1



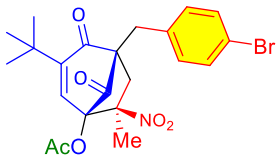
(±)-**10r** (90%)
20 min, *dr*: 3.1:1



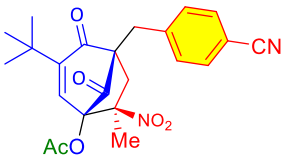
(±)-**10s** (83%)
20 min, *dr*: 3.1:1



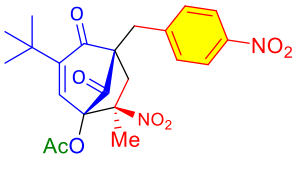
(±)-**10t** (80%)
20 min, *dr*: 2.6:1



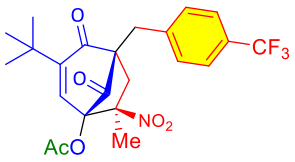
(±)-**10u** (87%)
20 min, *dr*: 2.9:1



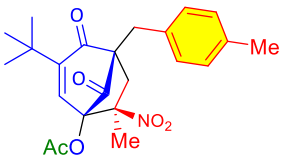
(±)-**10v** (82%)
20 min, *dr*: >20:1



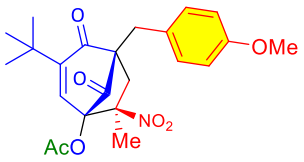
(±)-**10w** (82%)
20 min, *dr*: 11:1



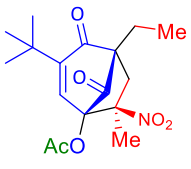
(±)-**10x** (94%)
20 min, *dr*: 4.0:1



(±)-**10y** (82%)
20 min, *dr*: 1.5:1



(±)-**10z** (60%)
20 min, *dr*: >20:1



(±)-**10aa** (80%)
20 min, *dr*: >20:1

[a] Reactions were carried out in toluene (0.05 mL) with 3.0 equiv. of **6c** (0.45 mL, 1.0 M in toluene) relative to **5** (0.15 mmol) in the presence of catalyst **3d** (10 mol%) at room temperature for time indicated followed by *tert*-hydroxy group protection with 8.0 equiv. of acetyl chloride in the presence of 0.3 equiv. of conc.H_2SO_4. [b] Yield refers to the column-purified product **10**+**11**. [c] *dr* was determined by CSP-HPLC analysis of the column-purified products.

After accomplishing the synthesis of a library of compounds with **5a** and **6c**, we wanted to investigate the reaction scope of **5b** with **6c**. We performed the reaction with **5ba**, **5bb** and **5bc** to give (±)-**10p**, (±)-**10q**, and (±)-**10r** in excellent yields in less than 30 min with *dr* of 4.5:1, 3:1 and 3.1:1 respectively (Table 5). The investigation of steric factors concerning the reaction

was performed using **5bd-5bf** to furnish products (±)-**10s-10u** within 20 min, with no drastic difference in yields and *dr*. The reaction went smoothly with electron-withdrawing groups **5bg-5bi** with excellent diastereoselectivity to furnish (±)-**10v** and (±)-**10w** both in 82% yield and (±)-**10x** in 94% yield within 20 min (Table 5). The reaction with electron-donating groups **5bj** and **5bk** gave **10y** and (±)-**10z** with *dr* of 1.5:1 and 20:1 with 82% and 60% yield respectively, and low yield with **5bk** can be attributed to the electronic factors related to the methoxy group (Table 5). Aliphatic group **5bl** with **6c** furnished (±)-**10aa** in 20 min with 80% yield and a *dr* of > 20:1 (Table 5).

We can infer from the aforementioned sentences that we have effectively synthesized compounds (±)-**10a-10aa**, comprising a bicyclo[3.2.1]octane core moiety. These bicyclo[3.2.1] core moiety acts as a reactive intermediate in various stereoselective synthetic transformations. These systems form a fundamental building block for biologically significant active molecules such as sesquiterpenoids, lignans, and alkaloids. Some of them include enaimeone, liliflodione and vitisinol D which have antibacterial activity and antithrombic activity and many others which cannot be listed due to their sheer abundance[4] (Figure 10).

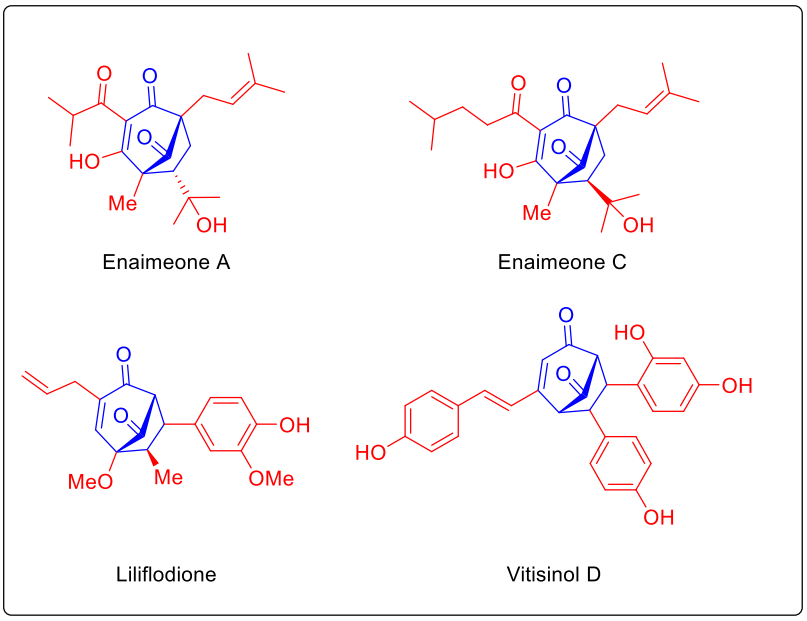


Figure 10: Natural products containing bicyclo[3.2.1]octane.

Although several stereoselective methods have been reported earlier for the synthesis of bicyclo[3.2.1]octanes, their ubiquitous nature and medicinal importance still make it pertinent to devise a new strategy for the construction of bicyclo[3.2.1]octanes. Motivated by this, we envisioned to develop a chiral version in order to get a solid grasp of its reactivity pattern. For

this purpose, we have synthesized various chiral catalysts **3e-3k** and chose to investigate the optimization studies using them (Figure 11).

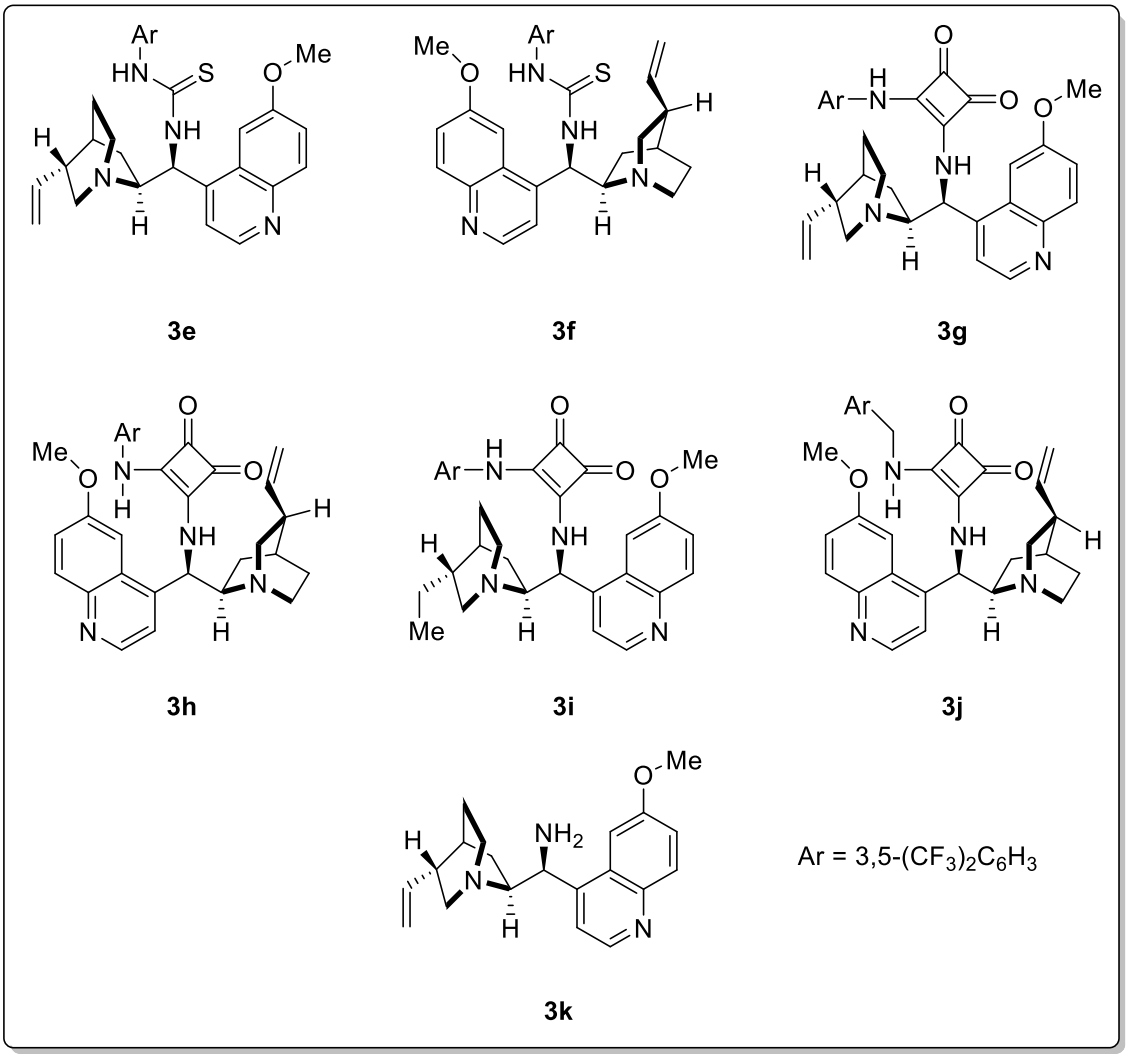


Figure 11: Chiral catalysts screened for the proposed asymmetric reaction.

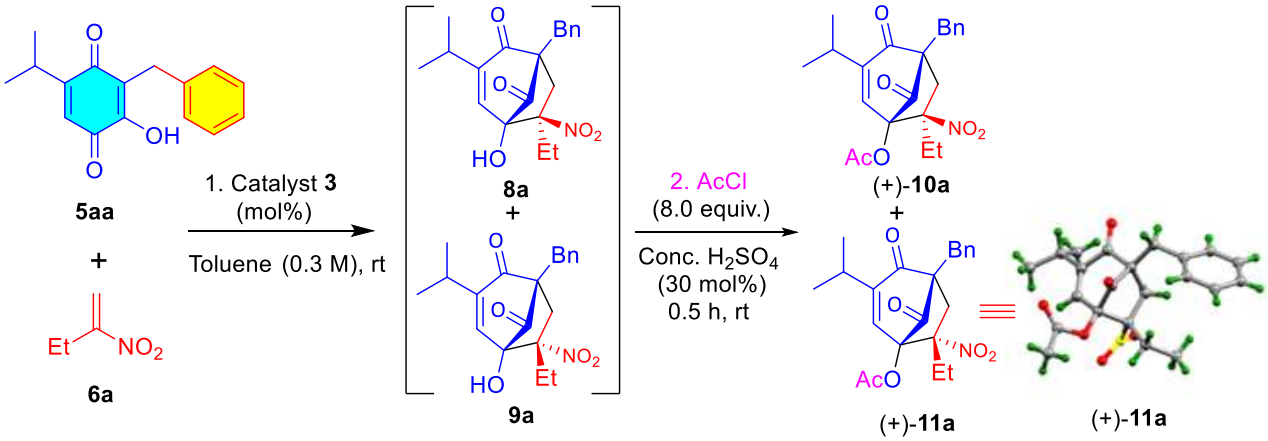
4.2.4 Preliminary Investigation of Reaction Conditions

Initially, we took **5aa** and 3.0 equiv. of **6a** in the presence of 10 mol% of catalyst **3e**, to our delight, the reaction was completed in 5 min with an overall yield of 97% and 86% *ee* corresponding to the major isomer and 83% *ee* corresponding to that of minor isomer and a *dr* of 1.5:1 (Table 6, entry 1). Varying the catalyst from **3e** to 10 mol % of **3f** doesn't seem to have any remarkable changes in the yield and reaction time, but there is a slight improvement in the *dr* with 1.9:1 and a drastic fall in the *ee* of both major and minor enantiomers (Table 6, entry 2). Upholding the catalyst loading constant, we altered the catalyst from **3f** to **3g** although it doesn't seem to have any considerable changes on the reaction time, but there was an

enhancement in *ee* of product to 91%/92% with slight fall in *dr* (Table 6, entry 3). There was a trivial increment in *dr* from 1.5:1 to 1.9:1 and a drastic fall in the *ee* of (+)-**10a/11a** to 80%/80% with **3h** and vice versa with **3i** and **3j** with an increment in *ee* and slight fall in *dr* to 1.4:1 (Table 6, entries 4-6). The same reaction when examined with 10 mol% of **3k**, the reaction completed within 15 min with 92% yield and a *dr* of 2:1 but there was a severe drop in the *ee* of (+)-**10a/11a** to 18%/14% (Table 6, entry 7). We may conclude that out of all the chiral catalysts from **3e**-**3k**, **3e** and **3g** proved to be the best catalysts for continuing the reaction scope further.

In order to thrive for a better *dr* and *ee*, **6a** was added gradually to the reaction mixture for 15 min which was carried out in 0.15 M of solvent followed by a separate reaction in which **6a** was added slowly for 30 min (Table 6, entries 8-9). There was not much improvement in reaction conditions as there was only a slight plunge in *ee* and no significant change in *dr* and *ee*. Our interest in limited catalyst loading prompted us to further examine the reaction conditions with low loading of the catalyst. We decreased the catalyst loading of **3e** from 10 mol% to 7 mol% which showed an improvement in the *ee* from 86%/83% to 91%/74% and a very minute change in *dr* and a similar yield of 97% and reaction time of 5 min. (Table 6, entry 10). This encouraged us to gradually decrease the catalyst loading of **3e** from 7 mol% to 5 mol%, 2 mol% and lastly, 500 ppm or 0.05 mol%, and all these reactions were carried out in 0.15 M of toluene (Table 6, entries 11-14). The reaction took longer time to complete when performed with 2 mol% and 0.05 mol% with a drastic drop in *ee* to 62%/40% and 77%/76% and insignificant *dr* change to 1.8:1 and 2.5:1. To avoid immediate discouragement from these results, we performed a reaction by altering the catalyst from **3e** to **3g** as the results with **3g** were also promising. When we carried out the reaction with 1 mol% of **3g**, it took 1 h to complete the first step of the reaction with a promising yield of 93% and excellent *ee* of 99%/86% and a *dr* of (+)-**10a**:**11a** is 1.4:1 motivating us to move forward with the reaction (Table 6, entry 15). We also performed a blank reaction without a catalyst and observed that there is considerable product formation of (+)-**10a** and (+)-**11a** which emphasizes the effectiveness of reaction design and chiral catalyst in achieving higher enantioselectivity (Table 6, entry 16).

Table 6: Preliminary Investigation of Reaction Conditions with **5aa**.[a]



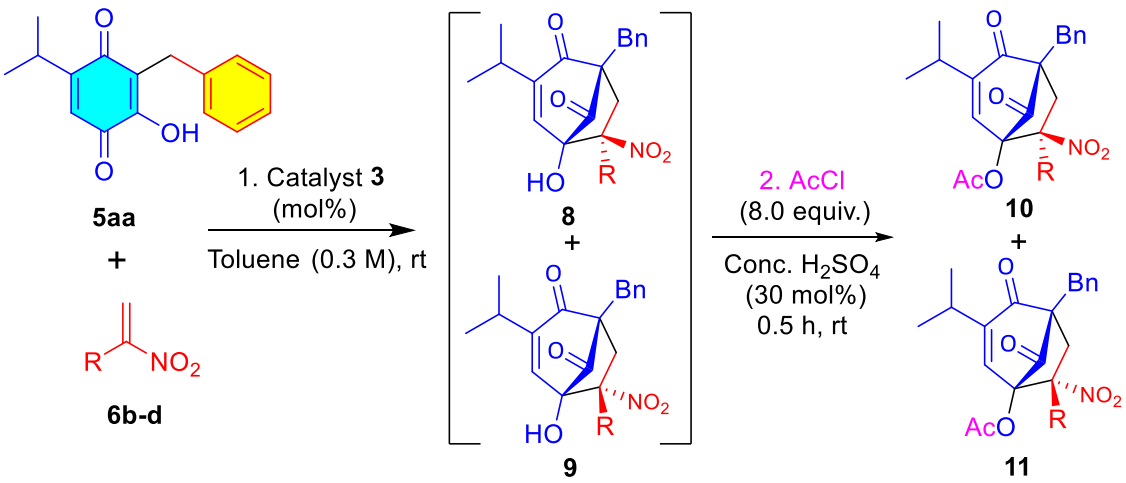
Entry	Catalyst (mol%)	Time (min/h)	Yield [%][b] (**10a+11a**)	*ee* [%][c] **10a** (**11a**)	*dr*[d] **10a**:**11a**
1	**3e** (10)	5 min	97	86 (83)	1.5:1
2	**3f** (10)	5 min	97	73 (72)	1.9:1
3	**3g** (10)	5 min	93	91 (92)	1.5:1
4	**3h** (10)	5 min	93	80 (80)	1.9:1
5	**3i** (10)	5 min	90	88 (90)	1.4:1
6	**3j** (10)	5 min	95	82 (84)	1.4:1
7	**3k** (10)	15 min	92	18 (14)	2:1
8[e,f]	**3e** (10)	15 min	97	84 (84)	1.6:1
9[g]	**3e** (10)	30 min	97	80 (80)	1.7:1
10[e]	**3e** (7.0)	5 min	97	91 (74)	1.4:1
11[e]	**3e** (5.0)	5 min	97	81 (83)	1.8:1
12[f]	**3e** (5.0)	15 min	97	78 (80)	1.6:1
13[e,h]	**3e** (2.0)	3 h	97	62 (40)	1.8:1
14[e]	**3e** (0.05)	9 h	97	77 (76)	2.5:1
15	**3g** (1.0)	1 h	93	99 (86)	1.4:1
16[i]	-	12 h	20	nd	nd

[a] Reactions were carried out in toluene (0.05 mL) with 3.0 equiv. of **6a** (0.45 mL, 1.0 M in toluene) relative to the **5aa** (0.15 mmol) in the presence of catalyst **3** and protected with 8.0 equiv. of acetyl chloride in the presence of 0.3 equiv. of conc.H_2SO_4. [b] Yield refers to the column-purified product of **10a+11a**. [c] Determined by CSP-HPLC analysis and values in parenthesis represents minor diastereomer. [d] Determined by CSP-HPLC analysis of the column-purified product of **10a+11a**. [e] Reactions were performed in (0.15 M) solvent. [f] **6a** was added dropwise to the reaction mixture for 15 min. [g] **6a** was added dropwise to the reaction mixture for 0.5 h. [h] Reaction performed at -10 °C. [i] Reaction performed without catalyst.

Even though there are some prominent changes in catalyst loading/yield/*ee* the yearn for a better *dr* motivated us to approach it in a different way.

We prepared **6b**, **6c**, and **6d** from the reported literature and then went on to react with **5aa** by varying the catalyst. Initially, **5aa** was treated with **6b** in the presence of 2 mol% of **3e** at 0 °C the reaction was completed in 5 min with 70% yield of (+)-**10b** with 60% *ee*, and no minor isomer was detected (Table 7, entry 1). The same reaction was performed at 0 °C with 10 mol% and 1 mol% of **3g** resulting in a slight increase in *ee* to 62% and 70% and a similar *dr* of >50:1 was observed. (Table 7, entries 2-3). We performed the reaction with **6c** while gradually decreasing the catalyst loading of **3g** from 10 mol% to 0.1 mol% showing a remarkable increase in the *dr* to >20:1 of products (+)-**10c/11c.** (Table 7, entries 4-5). The reaction when performed with 1 mol% of the catalyst gave 91% yield within 3 h and *ee* of 93%/92% with an appreciable *dr* of 14:1. The same reaction when performed with 0.1 mol% of **3g** catalyst took 24 h to complete with excellent yield and *dr* of >20:1. Stock solutions of **3g** catalyst was prepared individually in toluene and DCM solvent while utilising 1000 ppm of it and *ee* dropped to 88%/79% and 87%/66% respectively, which can be accounted for poor solubility of catalyst in both solvents (Table 7, entries 6-7). Reaction of **5aa** with **6d** in the presence of 10 mol% of **3g** catalyst resulted in a *dr* of 9.2:1 and *ee* of 83%/82% with 90% yield (Table 7, entry 8). After a detailed study of the optimization conditions, reaction with **6c** in the presence of 1 mol% of **3g** in 0.3 M toluene and further protection with 8.0 equiv. of CH_3COCl is regarded as the ideal condition (Table 7, entry 5).

Table 7: Preliminary Investigation of Reaction Conditions with **5aa**.[a]



Entry	Catalyst (mol%)	R (**6**)	Time (min/h)	Yield [%][b]	*ee* [%][c] **10** (**11**)	*dr*[d]
1[e]	**3e** (2.0)	H (**6b**)	5 min	70 (**10b+11b**)	60 (-)	>50:1
2[e]	**3g** (10.0)	H (**6b**)	5 min	72 (**10b+11b**)	62 (-)	>50:1
3[e]	**3g** (1.0)	H (**6b**)	30 min	81 (**10b+11b**)	70 (-)	>50:1
4	**3g** (10.0)	Me (**6c**)	5 min	91 (**10c+11c**)	90 (80)	8.6:1
5	**3g** (1.0)	Me (**6c**)	3 h	91 (**10c+11c**)	93 (92)	14:1
6[f]	**3g** (0.1)	Me (**6c**)	24 h	86 (**10c+11c**)	88 (79)	>20:1
7[g]	**3g** (0.1)	Me (**6c**)	24 h	84 (**10c+11c**)	87 (66)	>20:1
8	**3g** (10.0)	Bn (**6d**)	5 min	90 (**10d+11d**)	83 (82)	9.2:1

[a] Reactions were carried out in toluene (0.05 mL) with 3.0 equiv. of **6** (0.45 mL, 1.0 M in toluene) relative to **5aa** (0.15 mmol) in the presence of catalyst **3** (mol%) at room temp and protected with 8.0 equiv. of acetyl chloride in the presence of 0.3 equiv. of Conc.H_2SO_4. [b] Yield refers to the column-purified product **10+11**. [c] Determined by CSP-HPLC analysis and values in parenthesis represent minor diastereomer **11**. [d] Determined by CSP-HPLC analysis of the column-purified product of **10+11**. [e] Reaction performed at 0 °C. [f] Prepared stock solution in toluene. [g] Prepared stock solution in DCM.

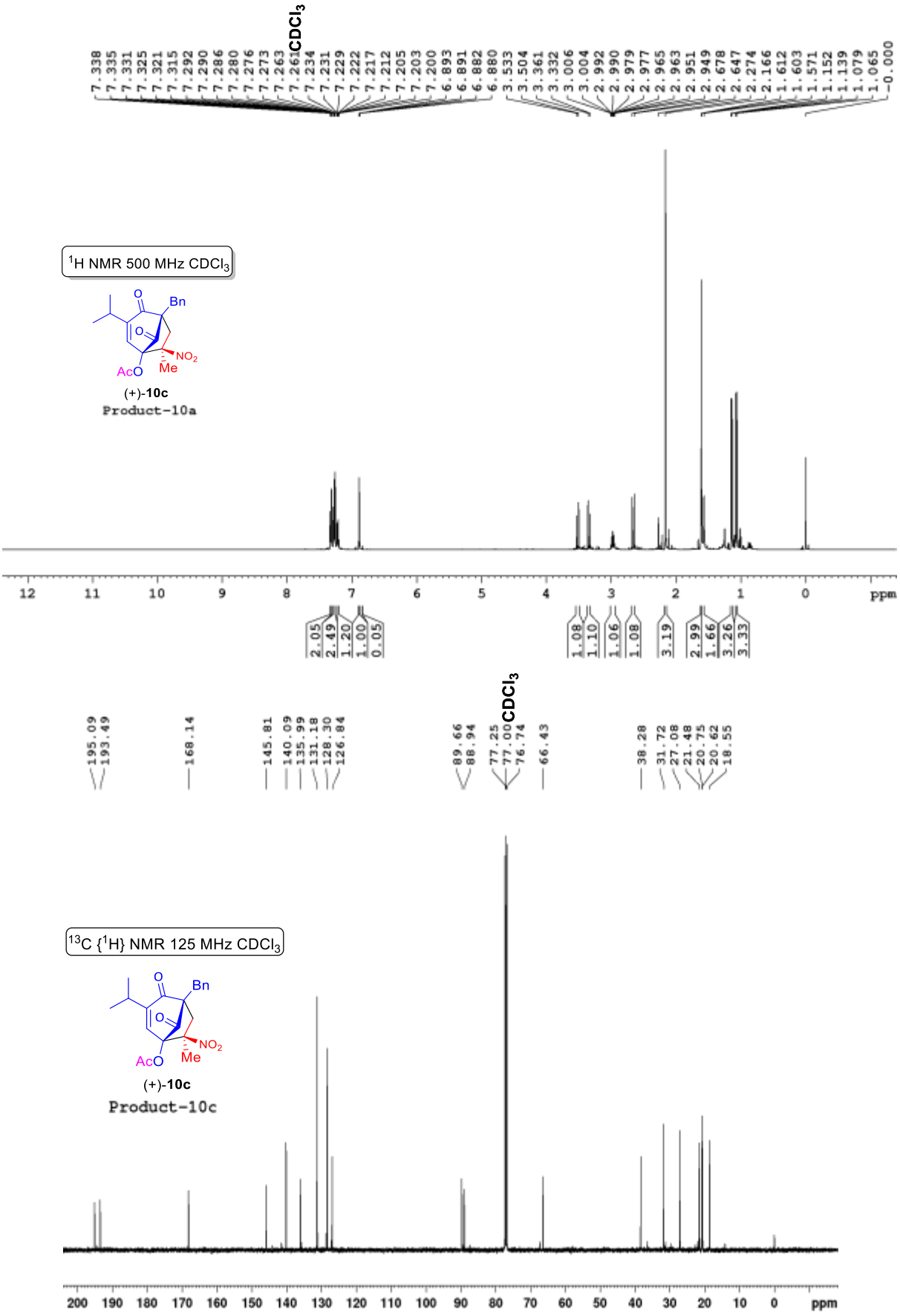
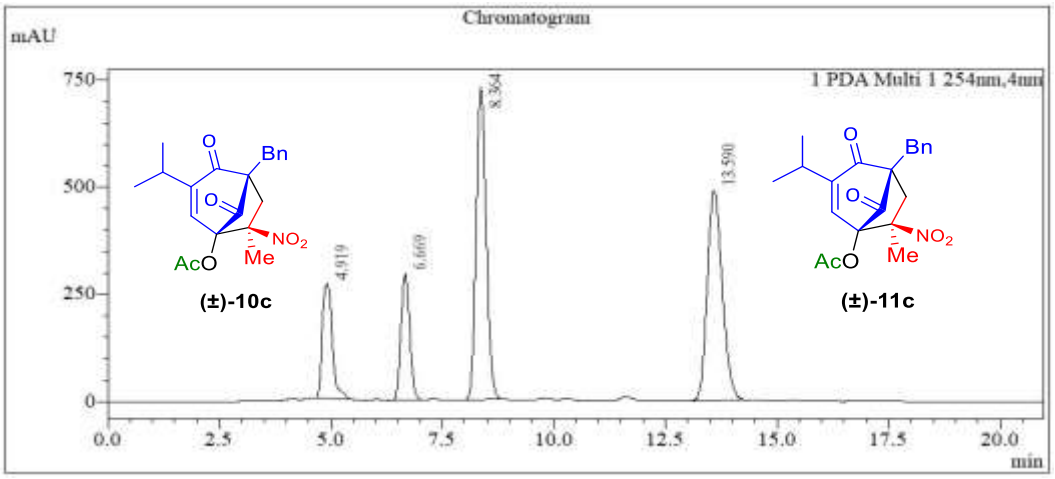


Figure 12: ^{1}H NMR and ^{13}C NMR spectrum of product-**10c**.

Racemic (±)-**10c**+**11c**:



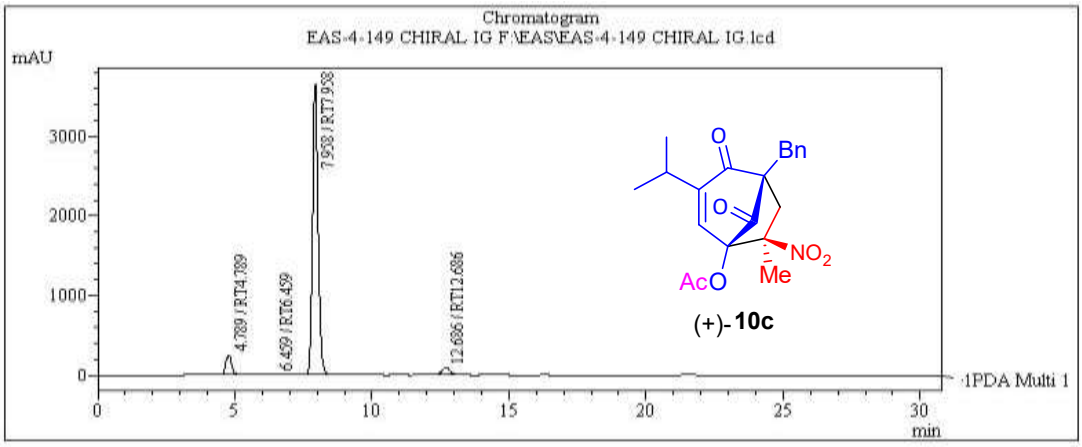
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm.

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:4.919	4.919	4186286	267457	13.450	15.022
2	RT:6.669	6.669	4046350	294111	13.000	16.519
3	RT:8.364	8.364	11469469	729471	36.849	40.973
4	RT:13.590	13.590	11423194	489350	36.701	27.486

Chiral (+)-**10c**:



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

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT4.789	4.789	3550242	242519	6.296	6.101
2	RT6.459	6.459	137611	9702	0.244	0.244
3	RT7.958	7.958	50965611	3635957	90.388	91.473
4	RT12.686	12.686	1731925	86709	3.072	2.181

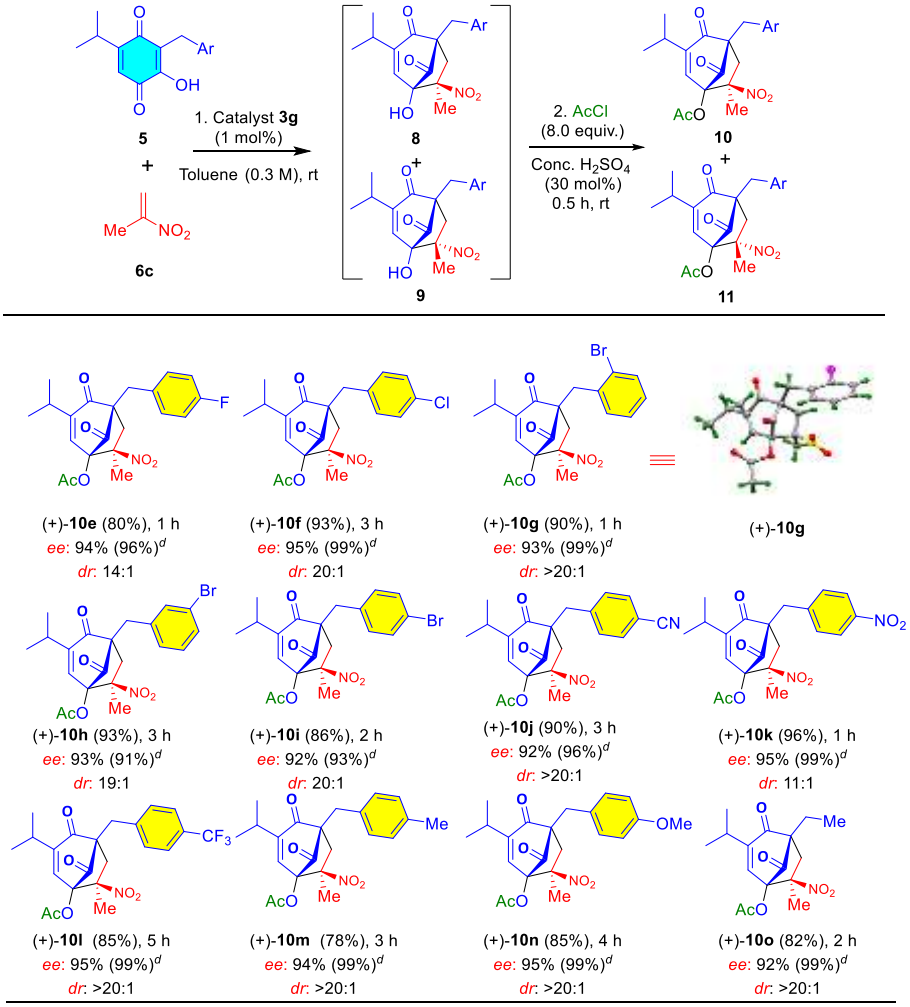
Figure 13: HPLC spectrum of product-**10c/11c**.

4.2.5 Substrate scope utilizing chiral catalyst

With optimized conditions in hand, we further tried to investigate the sustainability of the reaction to synthesize a library of bicyclo[3.2.1]octanes. Initially, **5ab** and **5ac** were treated with **6c** to give (+)-**10e** and (+)-**10f** with 80% and 93% yield in 1 h and 3 h and an *ee* of

94%/96% and 95%/99% and a *dr* of 14:1 and 20:1 respectively (Table 8). (+)-**10g/11g**, (+)-**10h/11h** and (+)-**10i/11i** were obtained using **5ad**, **5ae** and **5af** and gave excellent yields within 1-3 h with *dr* of almost 20:1 and *ee* of 93%/99%, 93%/91% and 92%/93% respectively (Table 8). The same reaction of **5ag** and **5ah** having electron-withdrawing groups, 4-CN, 4-NO_2 gave excellent yields of 90% and 96% with >92% *ee* and a *dr* of >20:1 and 11:1 in 3 h and 1 h respectively (Table 8). The reaction of **5ai** with **6c** took 5 h and gave 85% yield of (+)-**10l/11l** with 95%/99% *ee* and a *dr* of > 20:1. The same reaction employing **5aj**, **5ak**, **5al** as substrates gave good yields with a *dr* of >20:1 in 2-4 h and with *ee* of 92-95% affirming that even aliphatic groups doesn't exhibit any interference with the reaction design (Table 8).

Table 8: Synthesis of Substrates Employing Chiral Catalyst **3g**. [a-c]



[a] Reactions were carried out in toluene (0.05 mL) with 3.0 equiv. of **6c** (0.45 mL, 1.0 M in toluene) relative to **5** (0.15 mmol) in presence of catalyst **3g** (1 mol%) at room temp and protected with 8.0 equiv. of acetyl chloride in the presence of 0.3 equiv. of Conc.H_2SO_4. [b] Yield refers to the column-purified product **10+11**. [c] *ee* and *dr* were determined by CSP-HPLC analysis of the column-purified products. [d] In parenthesis values refer to minor *ee*.

^{1}H, ^{13}C NMR and HPLC spectra of few compounds from Table 8 have depicted in Figure 14-21.

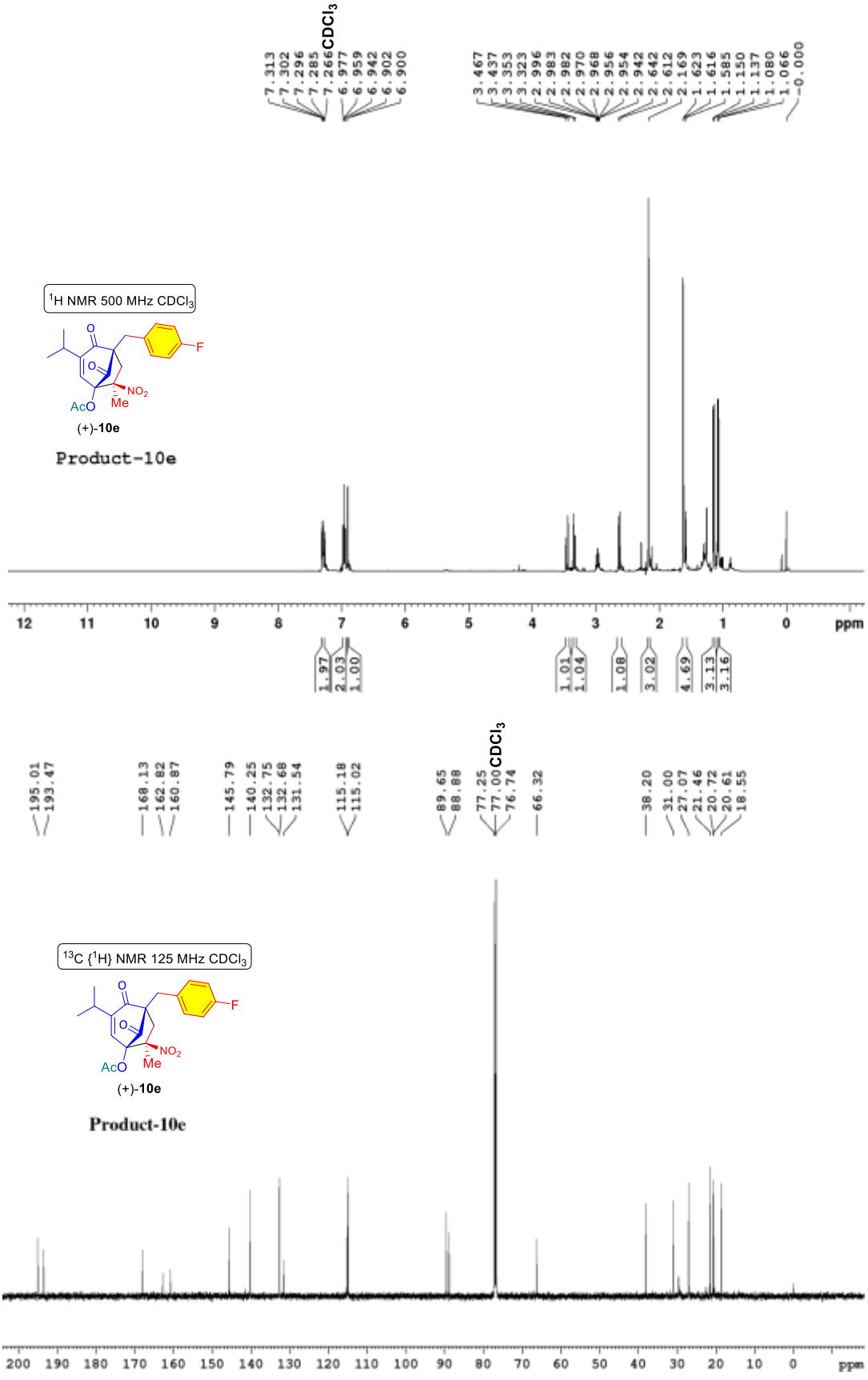
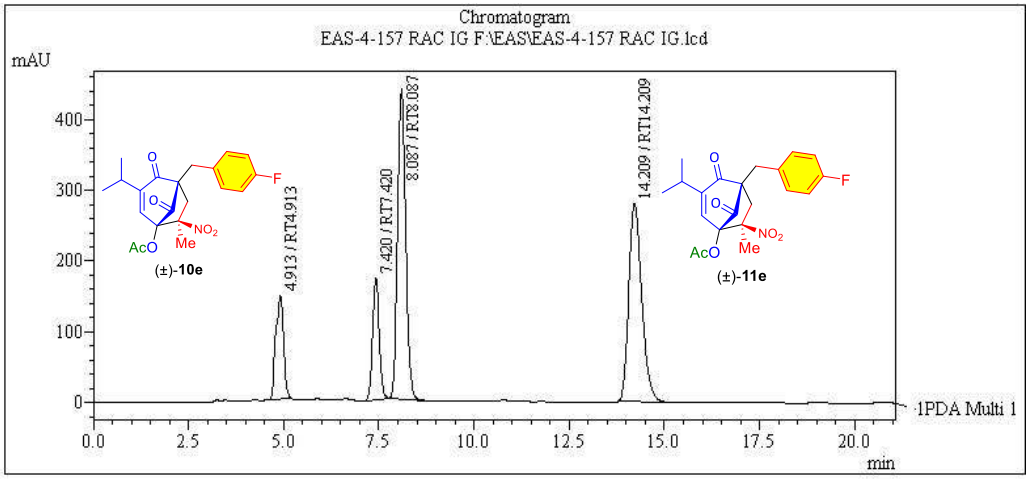


Figure 14: ^{1}H NMR and ^{13}C NMR spectrum of product-**10e**.

Racemic (±)-**10e**+**11e**:



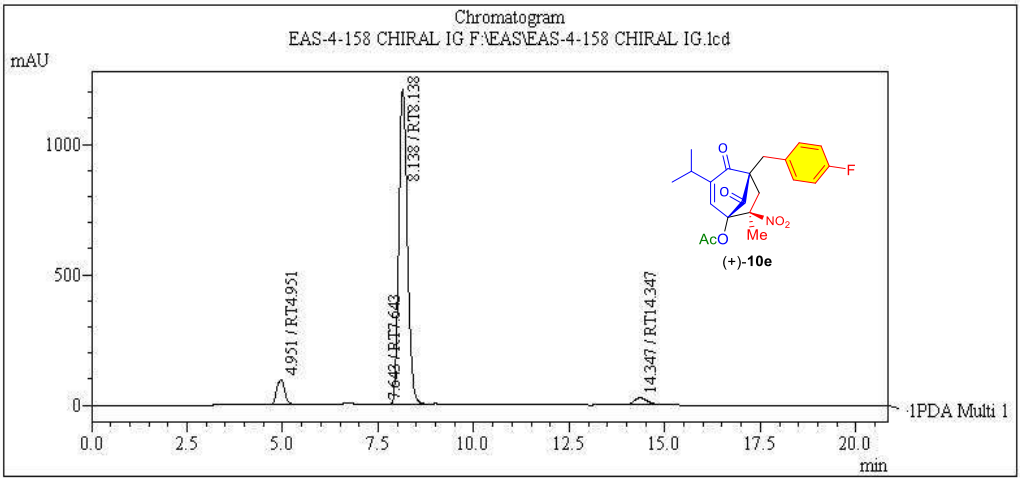
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 0.8 mL/min, 254 nm.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT4.913	4.913	2076062	146093	12.029	14.131
2	RT7.420	7.420	2048758	170661	11.871	16.508
3	RT8.087	8.087	6489541	436975	37.602	42.267
4	RT14.209	14.209	6643933	280106	38.497	27.094

Chiral (+)-**10e**:



Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 0.8 mL/min, 254 nm.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT4.951	4.951	1350479	93573	6.486	7.054
2	RT7.643	7.643	27542	1929	0.132	0.145
3	RT8.138	8.138	18892460	1205934	90.733	90.913
4	RT14.347	14.347	551538	25034	2.649	1.887

Figure 15: HPLC spectrum of product-**10e**.

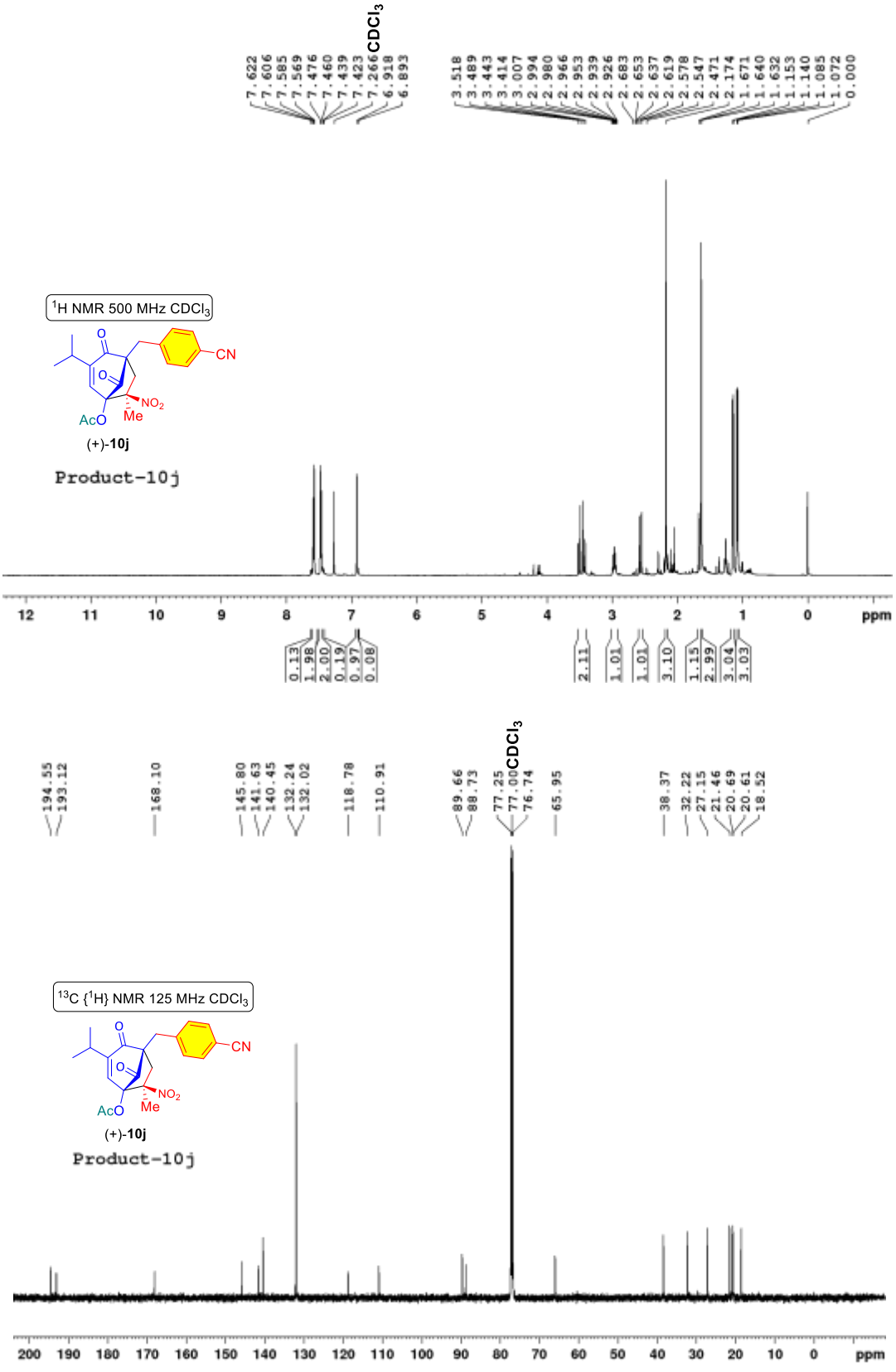
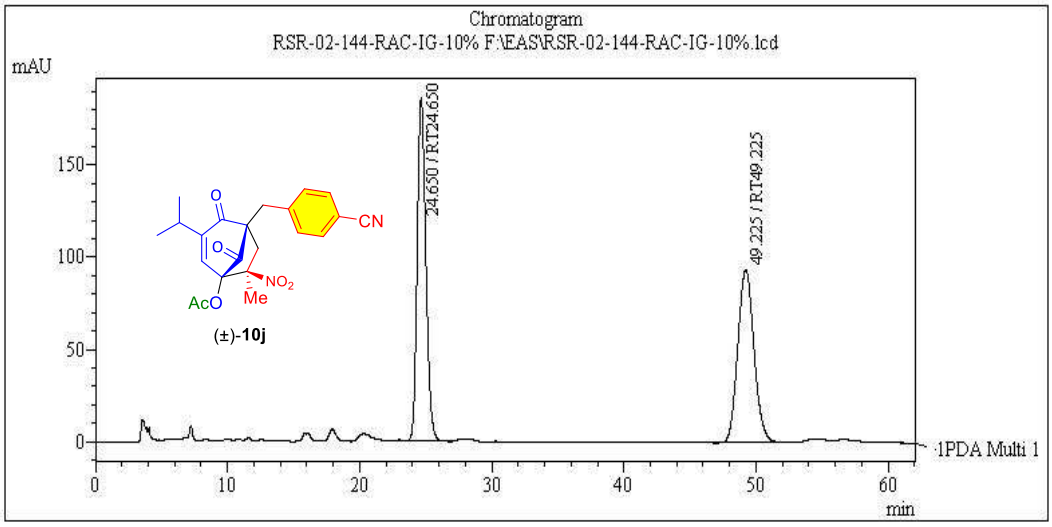


Figure 16: ^{1}H NMR and ^{13}C NMR spectrum of product-**10j**.

Racemic (±)-**10j**:



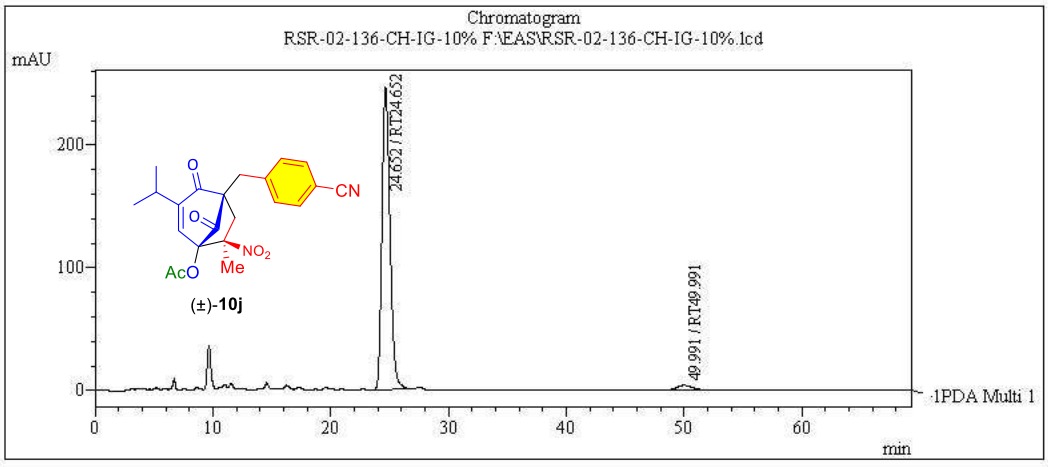
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 0.8 mL/min, 254 nm.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT24.650	24.650	8457256	185873	51.293	66.446
2	RT49.225	49.225	8030779	93864	48.707	33.554
Total			16488035	279737	100.000	100.000

Chiral (+)-**10j**:



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

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT24.652	24.652	11693863	246396	97.318	98.504
2	RT49.991	49.991	322233	3742	2.682	1.496
Total			12016096	250138	100.000	100.000

Figure 17: HPLC spectrum of product-**10j**.

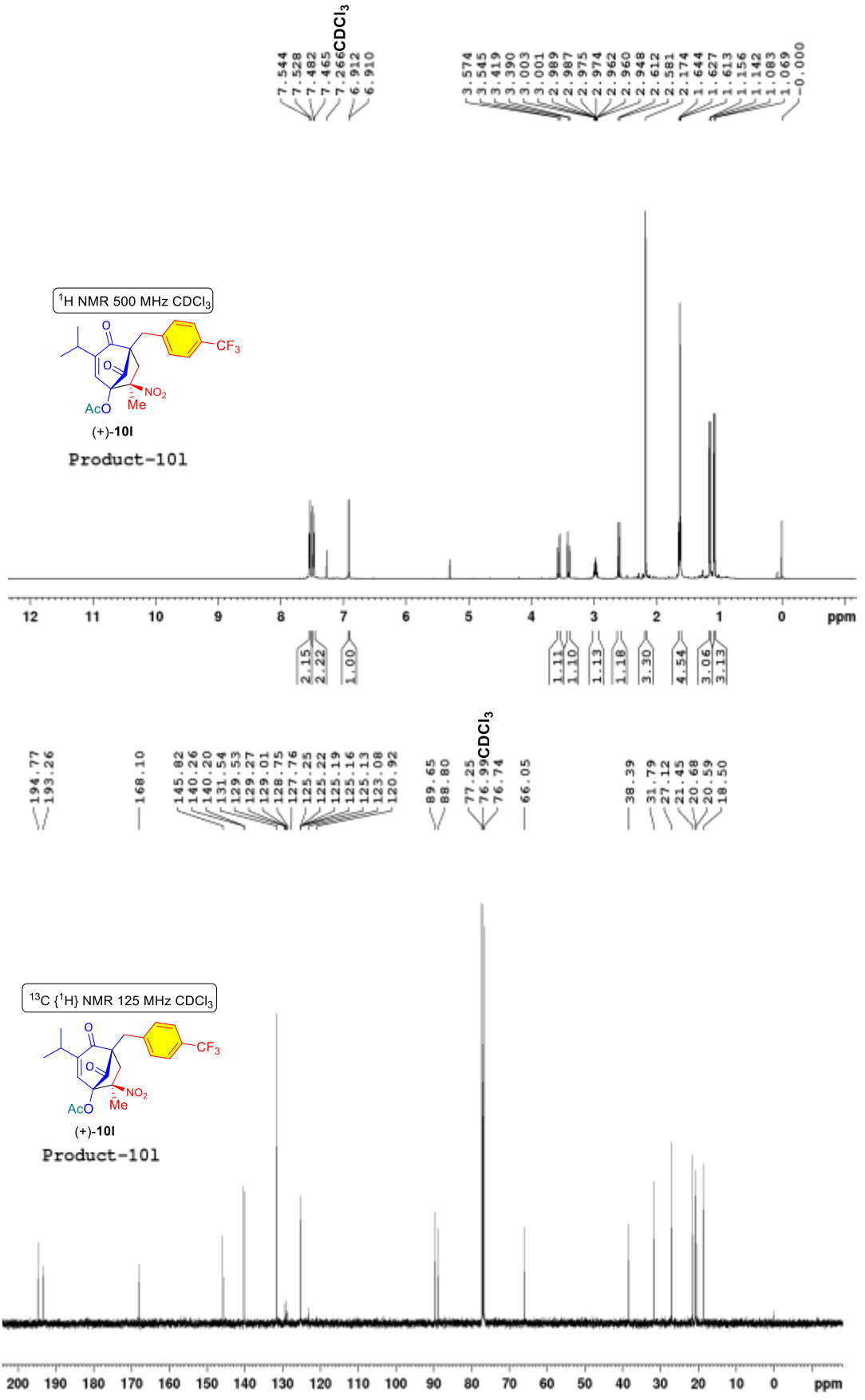
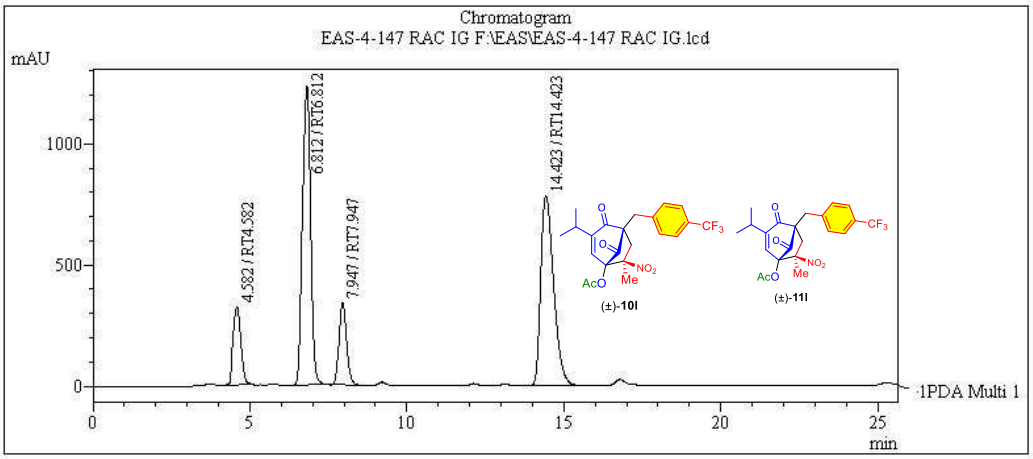


Figure 18: ^{1}H NMR and ^{13}C NMR spectrum of product-**10l**.

Racemic (±)-**10l**+**11l**:



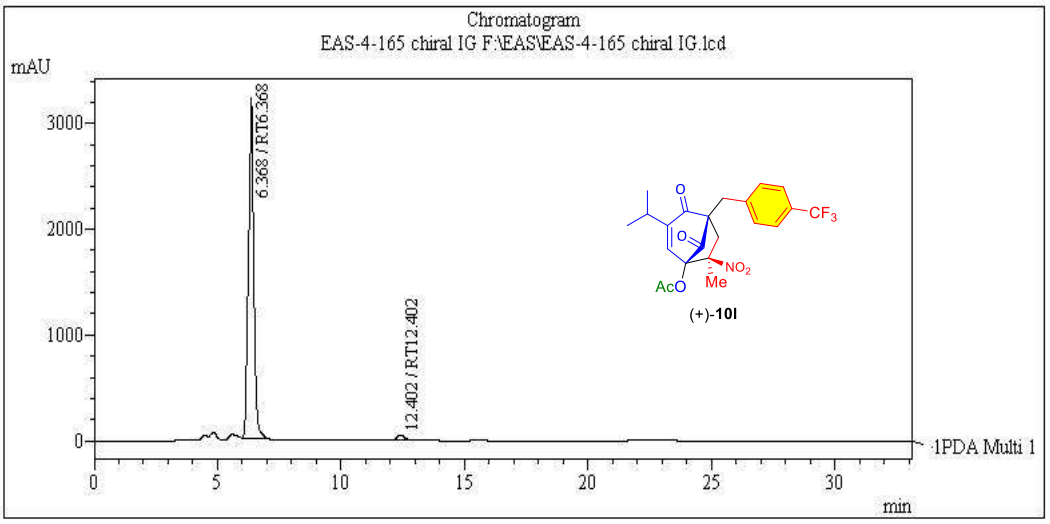
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT4.582	4.582	5594773	322572	10.050	12.065
2	RT6.812	6.812	22168494	1229055	39.823	45.968
3	RT7.947	7.947	5673312	338772	10.191	12.670
4	RT14.423	14.423	22231437	783313	39.936	29.297

Chiral (+)-**10l**:



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

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT6.368	6.368	47001103	3208372	97.770	98.451
2	RT12.402	12.402	1072104	50468	2.230	1.549
Total			48073206	3258840	100.000	100.000

Figure 19: HPLC spectrum of product-**10l**.

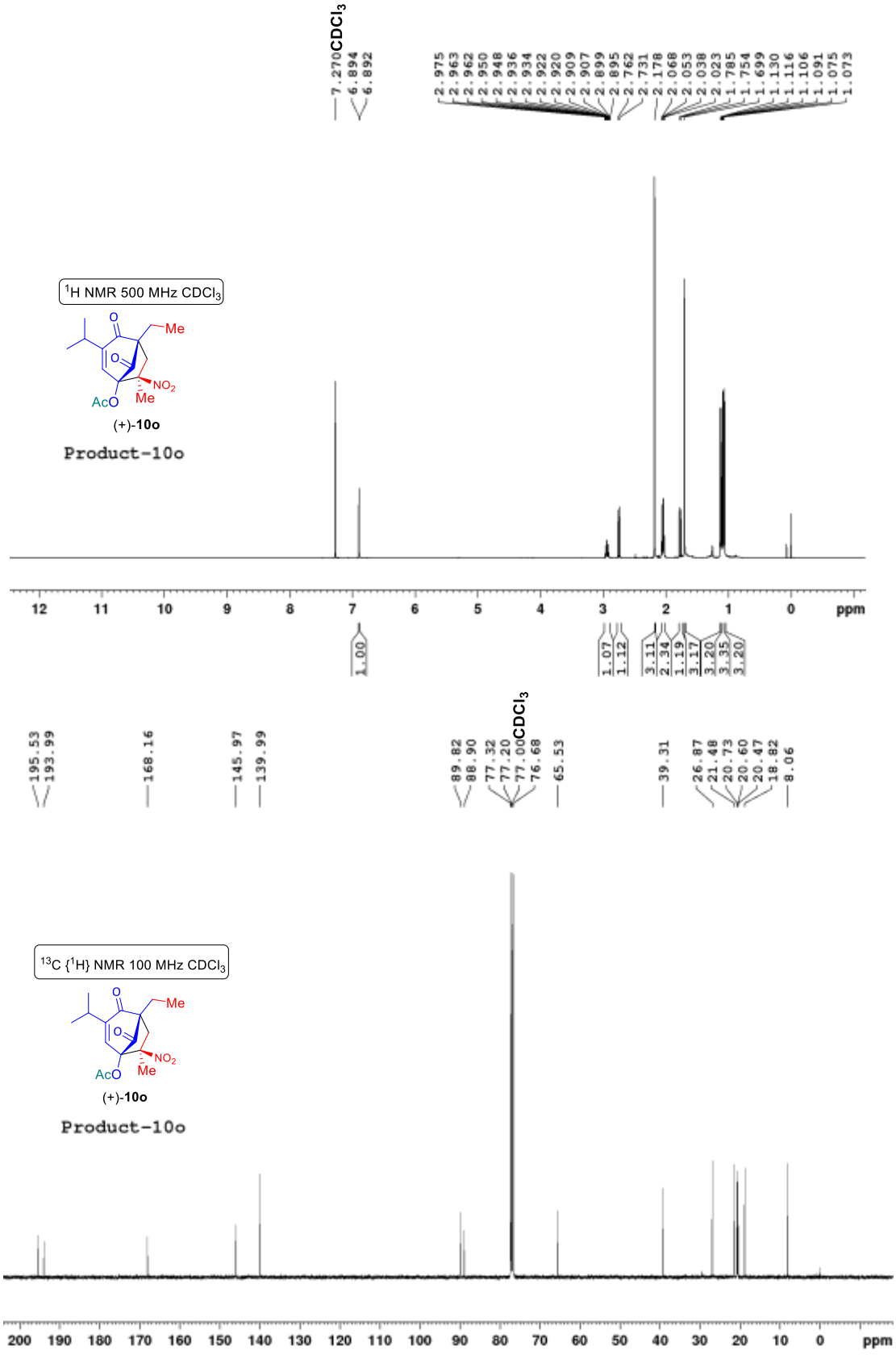
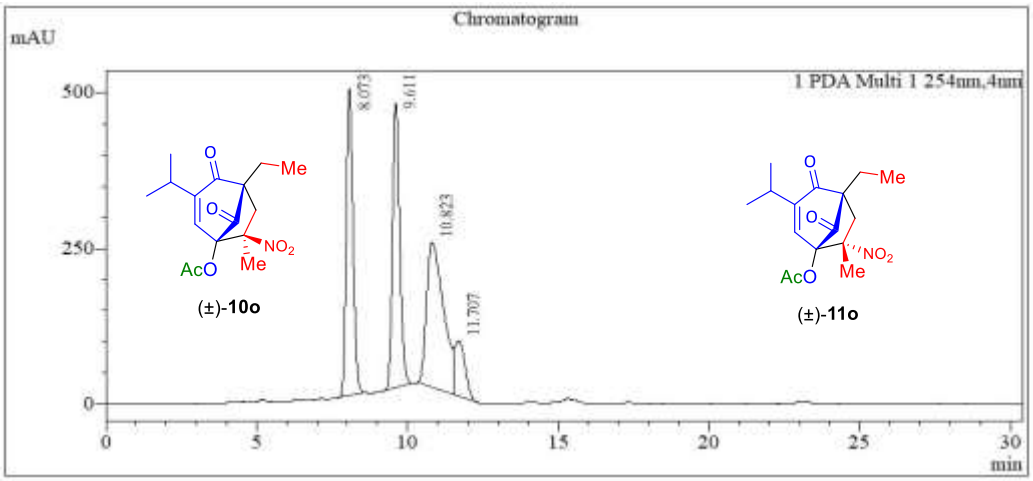


Figure 20: ^{1}H NMR and ^{13}C NMR spectrum of product-**10o**.

Racemic (±)-**10o**+**11o**:



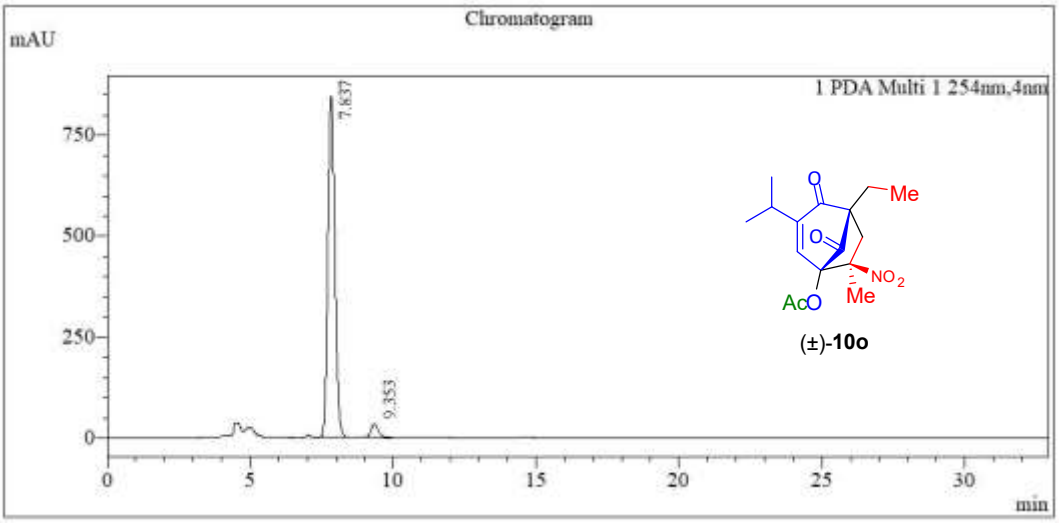
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm.

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:8.073	8.073	7574120	492881	28.632	38.781
2	RT:9.611	9.611	7591160	456693	28.697	35.933
3	RT:10.823	10.823	9126721	232530	34.502	18.296
4	RT:11.707	11.707	2160881	88839	8.169	6.990

Chiral (+)-**10o**:



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

Peak Table

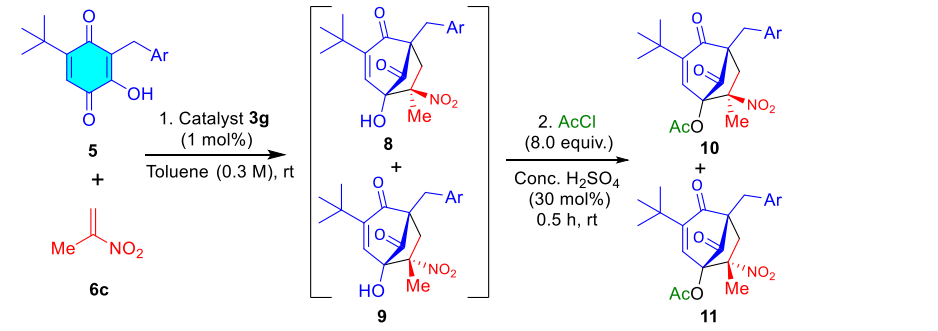
PDA Ch1 254nm

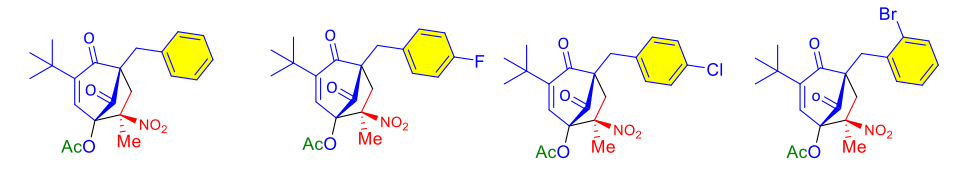
Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:7.837	7.837	14380123	845269	95.888	96.208
2	RT:9.353	9.353	616643	33313	4.112	3.792
Total			14996767	878582	100.000	100.000

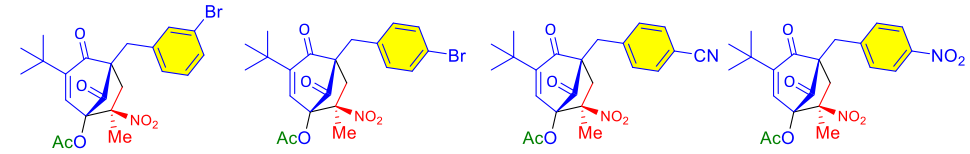
Figure 21: HPLC spectrum of product-**10o**.

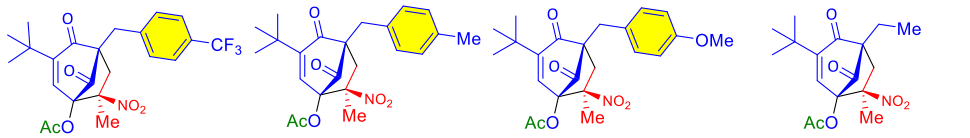
We then further checked the scope of the reaction with hydroxy-*p*-quinone **5ba** with **6c** in the presence of **3g** to give 93% of (+)-**10p/11p** with 95%/99% *ee* and *dr* of 8.7:1 within 2 h (Table 9). Reaction of **5bb** and **5bc** with **6c** gave (+)-**10q/11q** and (+)-**10r/11r** with excellent yields and *ee* of >90% and good *dr*s (Table 9). The same reaction of **5bd-5bf** with **6c** gave good yield with excellent enantioselectivity and *dr's* of 7:1, 20:1 and 9.9:1 respectively within 3-4 h (Table 9). The formation of (+)-**10v/11v** and (+)-**10w/11w** proceeded within 4 h with excellent enantioselectivity and good yields and good *dr*s (Table 9). Reaction of **5bi-5bl** with **6c** furnished good yield with excellent enantioselectivity and outstanding *dr* of >20:1 within 1- 4 h to give (+)-**10x/11x** to (+)-**10aa/11aa** (Table 9).

Table 9: Synthesis of Chiral Substrates with Catalyst **3g**. [a-c]









[a] Reactions were carried out in toluene (0.05 mL) with 3.0 equiv. of **6c** (0.45 mL, 1.0 M in toluene) relative to **5** (0.15 mmol) in the presence of catalyst **3g** (1 mol%) at room temp protected with 8.0 equiv. of acetyl chloride in the presence of 0.3 equiv. of conc.H_2SO_4 [b] Yield refers to the column-purified product **10+11**. [c] *ee* and *dr* were determined by CSP-HPLC analysis of the column-purified products. [d] In parenthesis values refer to minor *ee*.

^{1}H, ^{13}C NMR and HPLC spectra of few compounds from Table 9 have depicted in Figure 22-29.

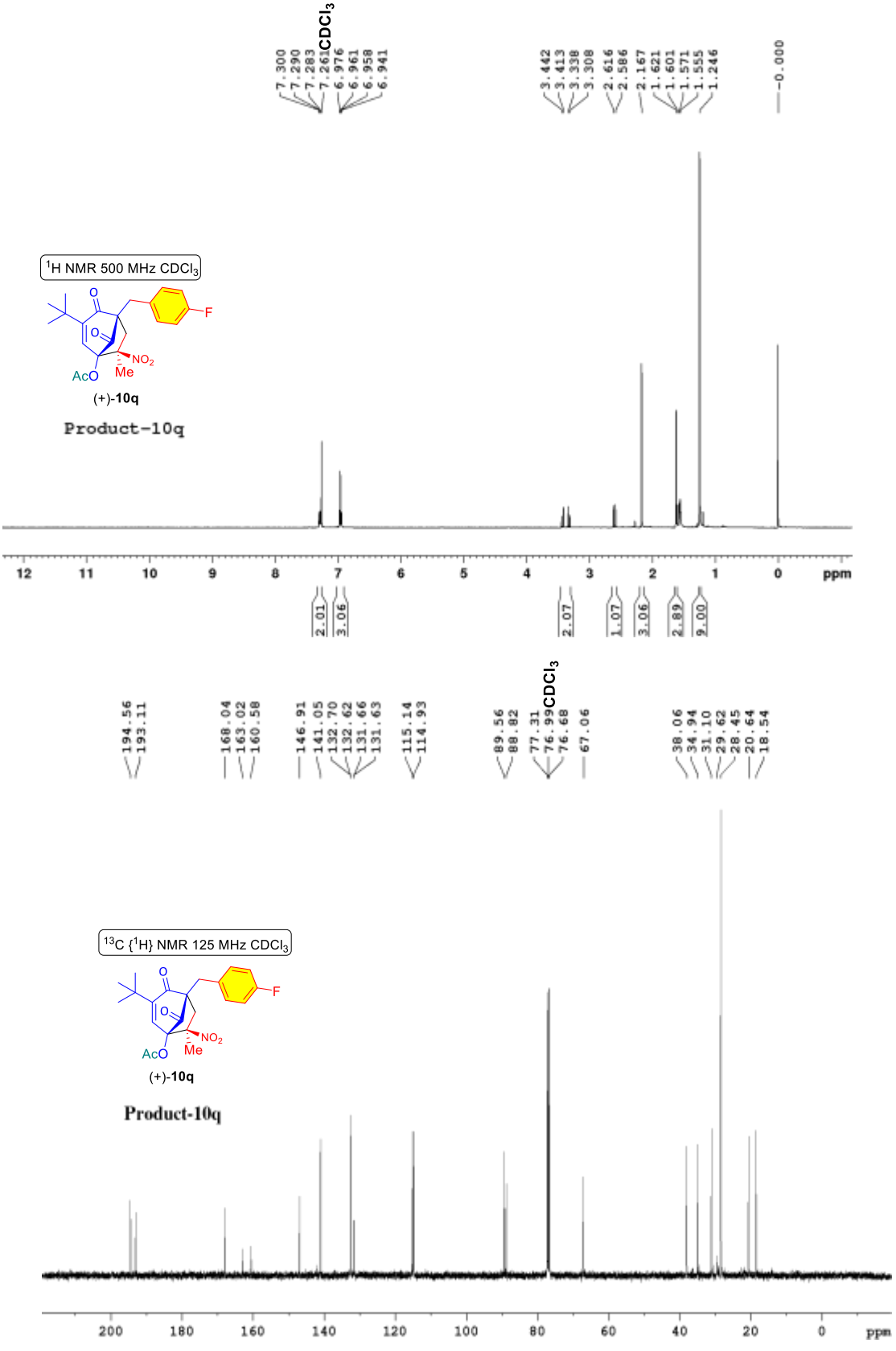
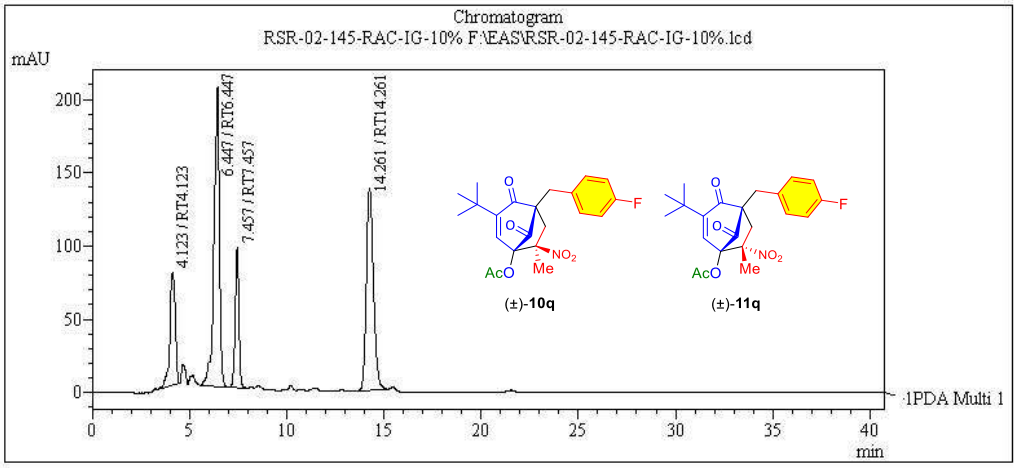


Figure 22: ^{1}H NMR and ^{13}C NMR spectrum of product-**10q**.

Racemic (±)-**10q**+**11q**:



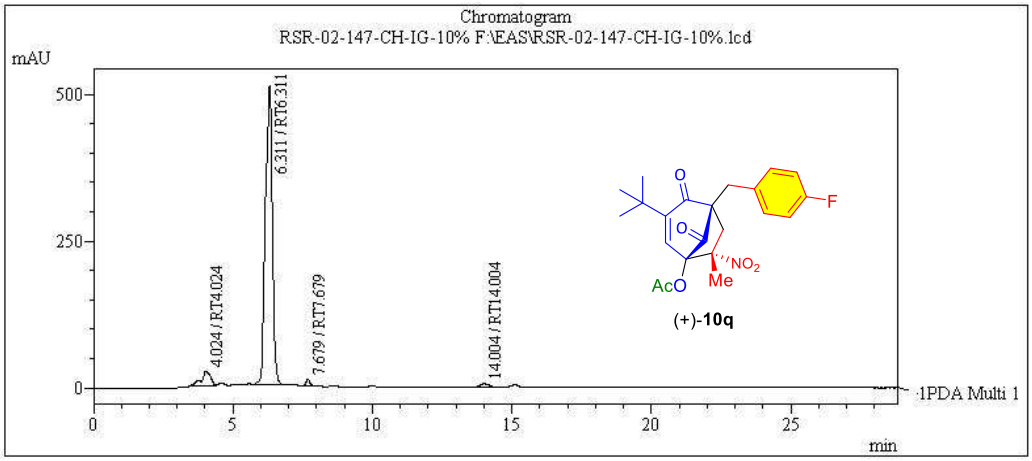
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT4.123	4.123	1514417	76739	14.791	14.907
2	RT6.447	6.447	3941586	204208	38.496	39.668
3	RT7.457	7.457	1265836	95825	12.363	18.614
4	RT14.261	14.261	3517173	138018	34.351	26.811

Chiral (+)-**10q**:



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

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT4.024	4.024	550592	23922	5.759	4.363
2	RT6.311	6.311	8787840	508070	91.922	92.657
3	RT7.679	7.679	98959	10822	1.035	1.974
4	RT14.004	14.004	122673	5523	1.283	1.007

Figure 23: HPLC spectrum of product-**10q**.

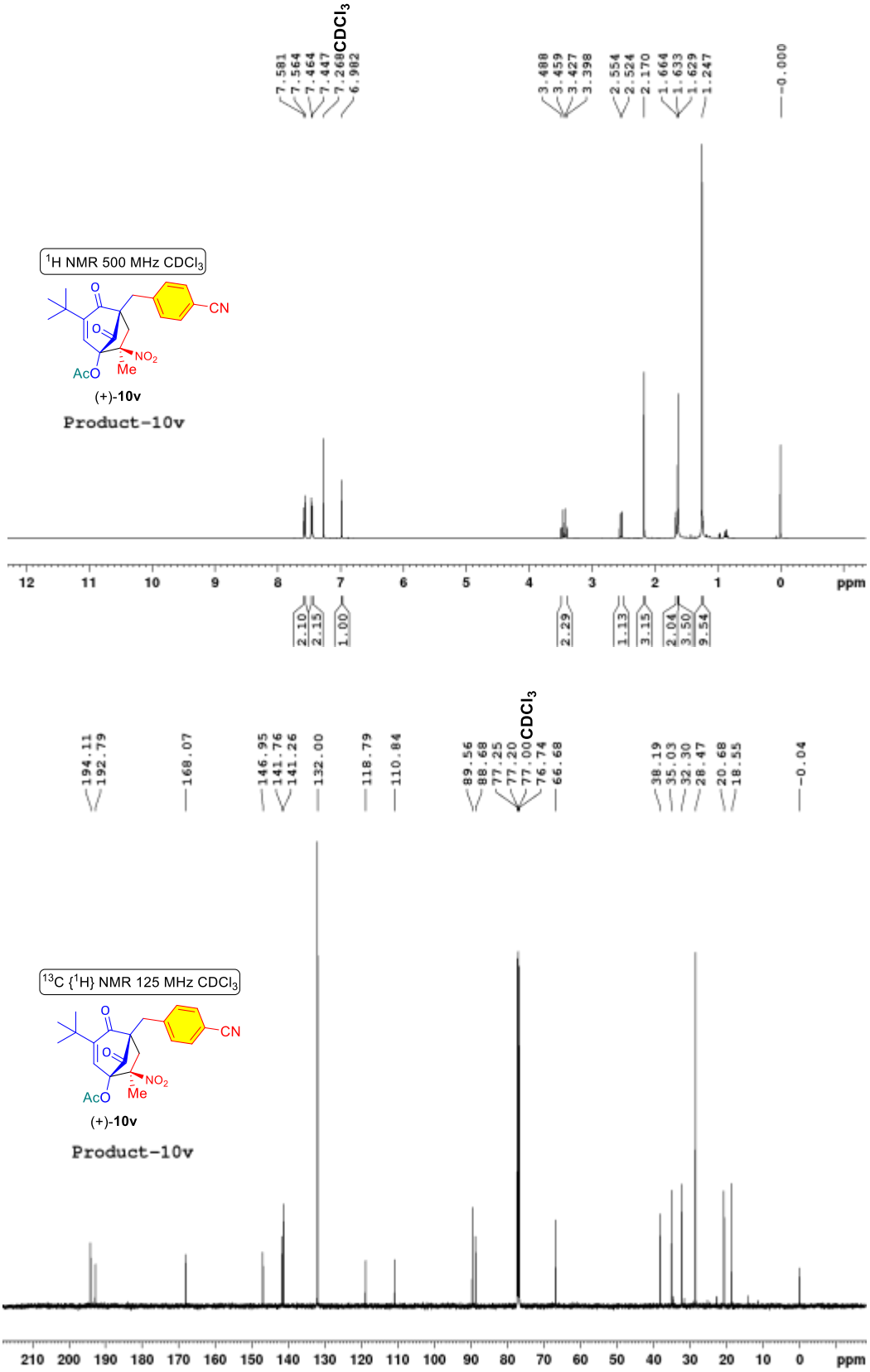
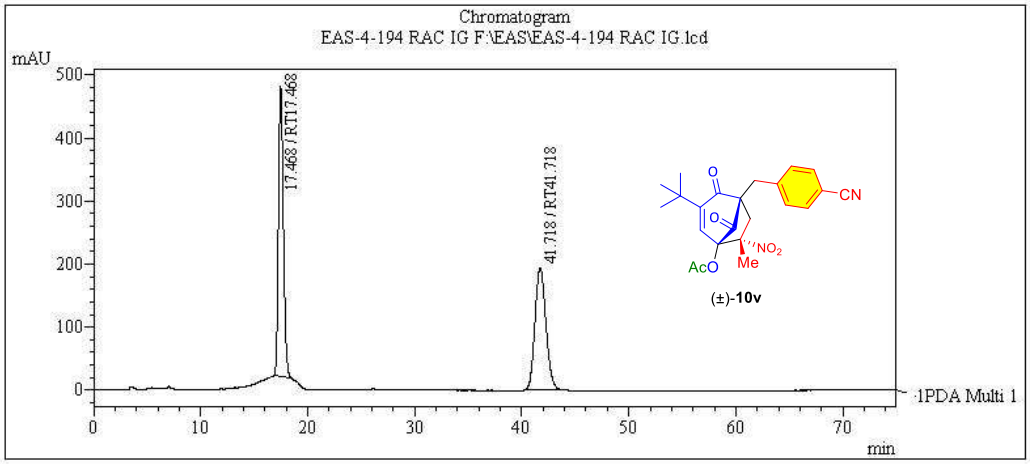


Figure 24: ^{1}H NMR and ^{13}C NMR spectrum of product-**10v**.

Racemic (±)-**10v**:



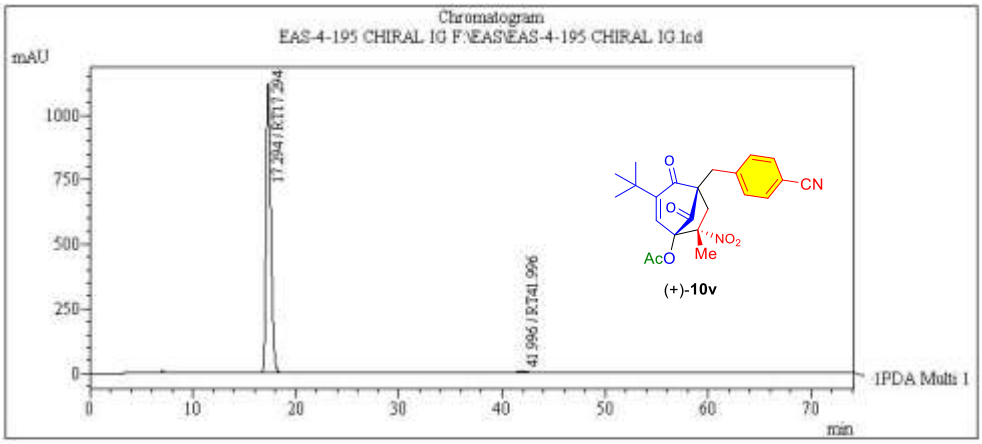
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT17.468	17.468	14752755	460181	51.636	70.284
2	RT41.718	41.718	13817782	194561	48.364	29.716
Total			28570538	654742	100.000	100.000

Chiral (+)-**10v**:



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

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT17.294	17.294	35929211	1118272	98.599	99.289
2	RT41.996	41.996	510435	8006	1.401	0.711
Total			36439646	1126278	100.000	100.000

Figure 25: HPLC spectrum of product-**10v**.

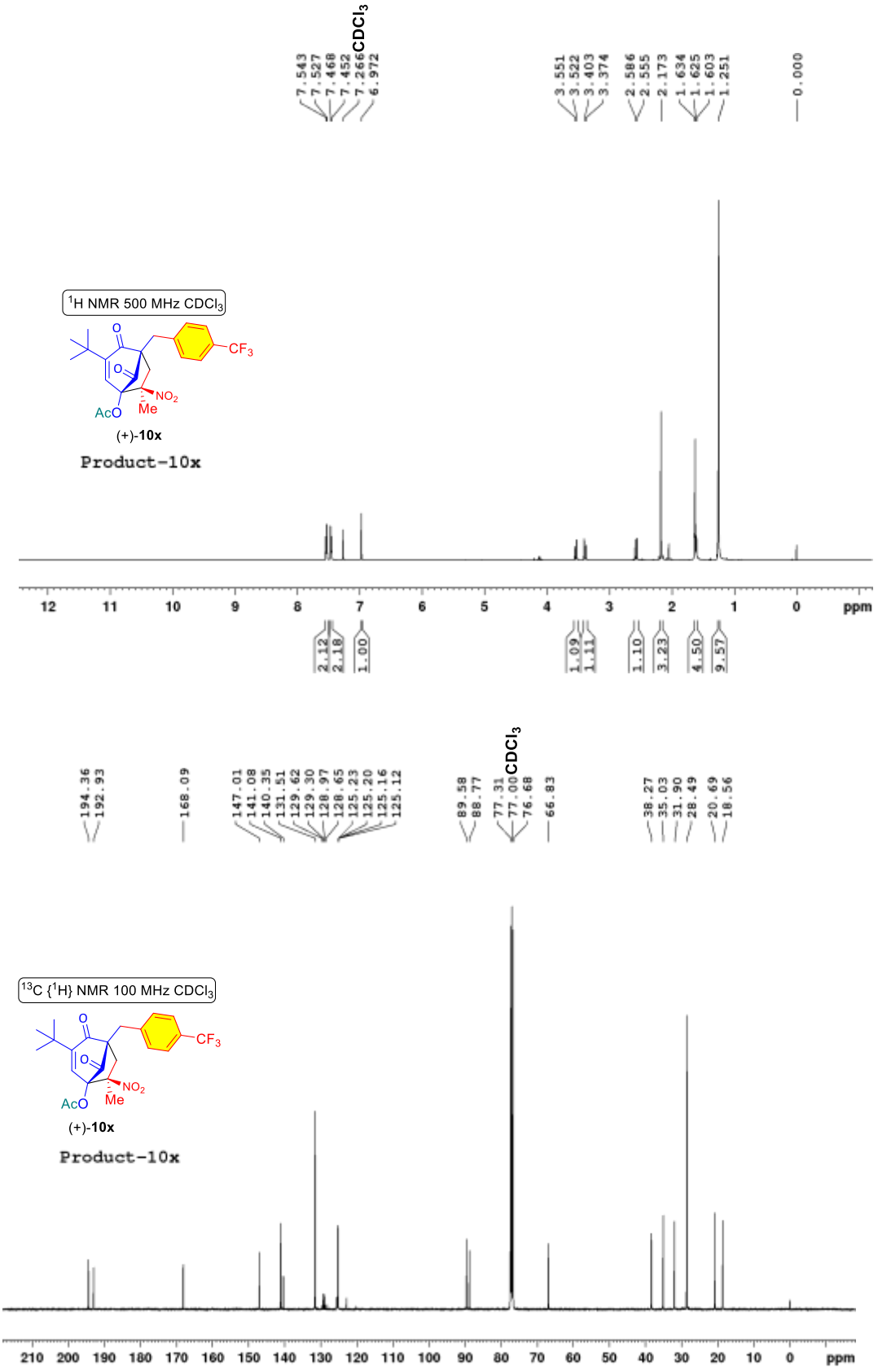
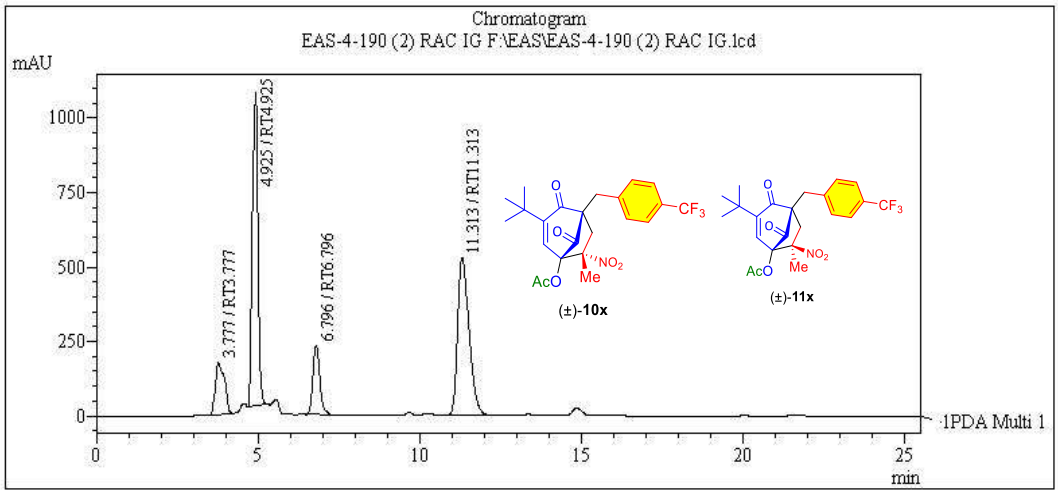


Figure 26: ^{1}H NMR and ^{13}C NMR spectrum of product-**10x**.

Racemic (±)-**10x**+**11x**:



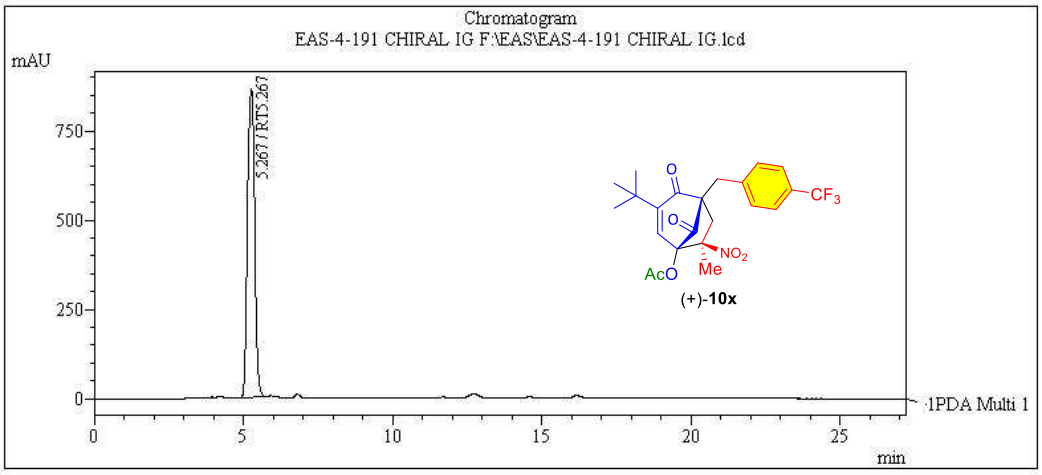
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT3.777	3.777	3374001	174643	10.331	8.802
2	RT4.925	4.925	12917690	1050372	39.553	52.936
3	RT6.796	6.796	3345749	231166	10.244	11.650
4	RT11.313	11.313	13021705	528057	39.872	26.613

Chiral (+)-**10x**:



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

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT5.267	5.267	14410267	860982	100.000	100.000
Total			14410267	860982	100.000	100.000

Figure 27: HPLC spectrum of product -**10x**.

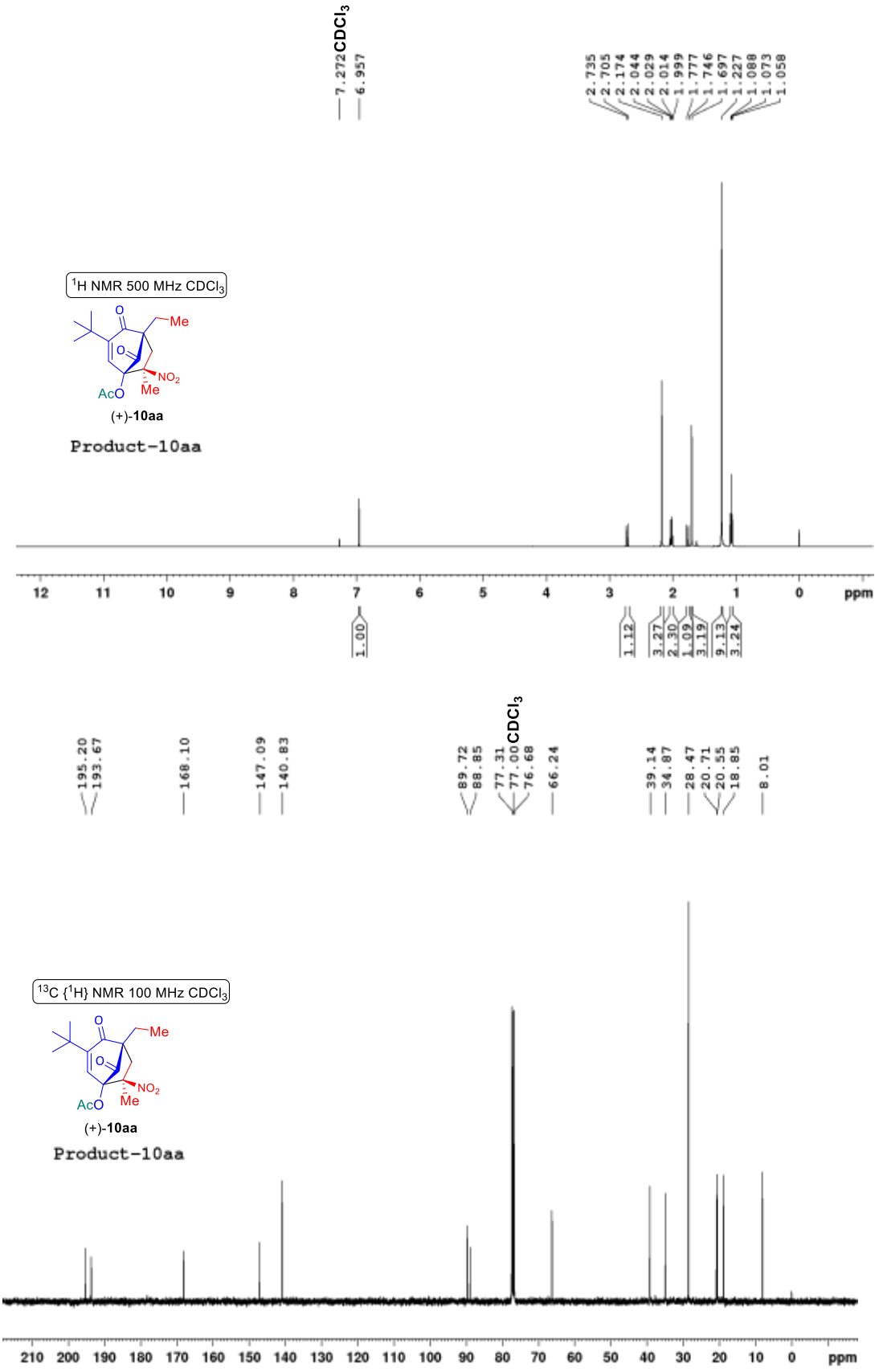
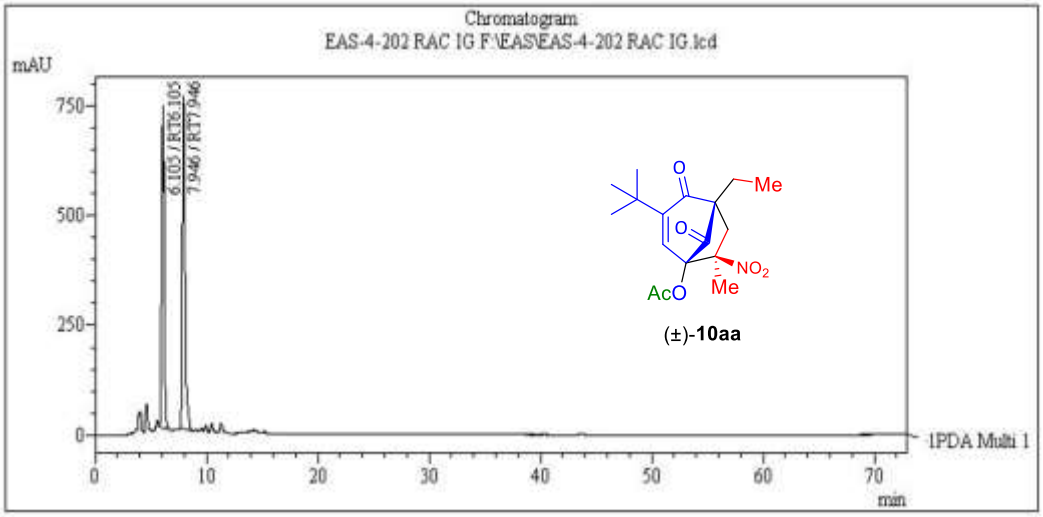


Figure 28: ^{1}H NMR and ^{13}C NMR spectrum of product-**10aa**.

Racemic (±)-**10aa**:



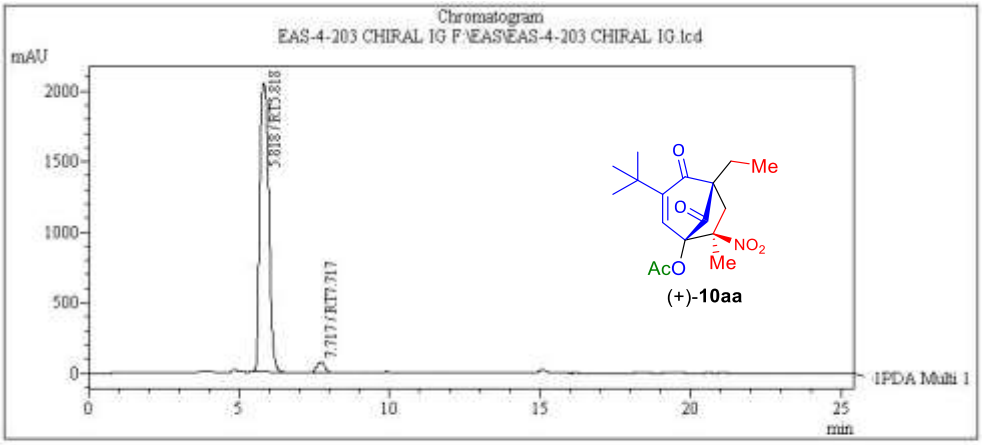
Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT6.105	6.105	11388600	735087	47.212	49.167
2	RT7.946	7.946	12733808	760003	52.788	50.833
Total			24122408	1495090	100.000	100.000

Chiral (+)-**10aa**:



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

PeakTable

PDA Ch1 254nm 4nm

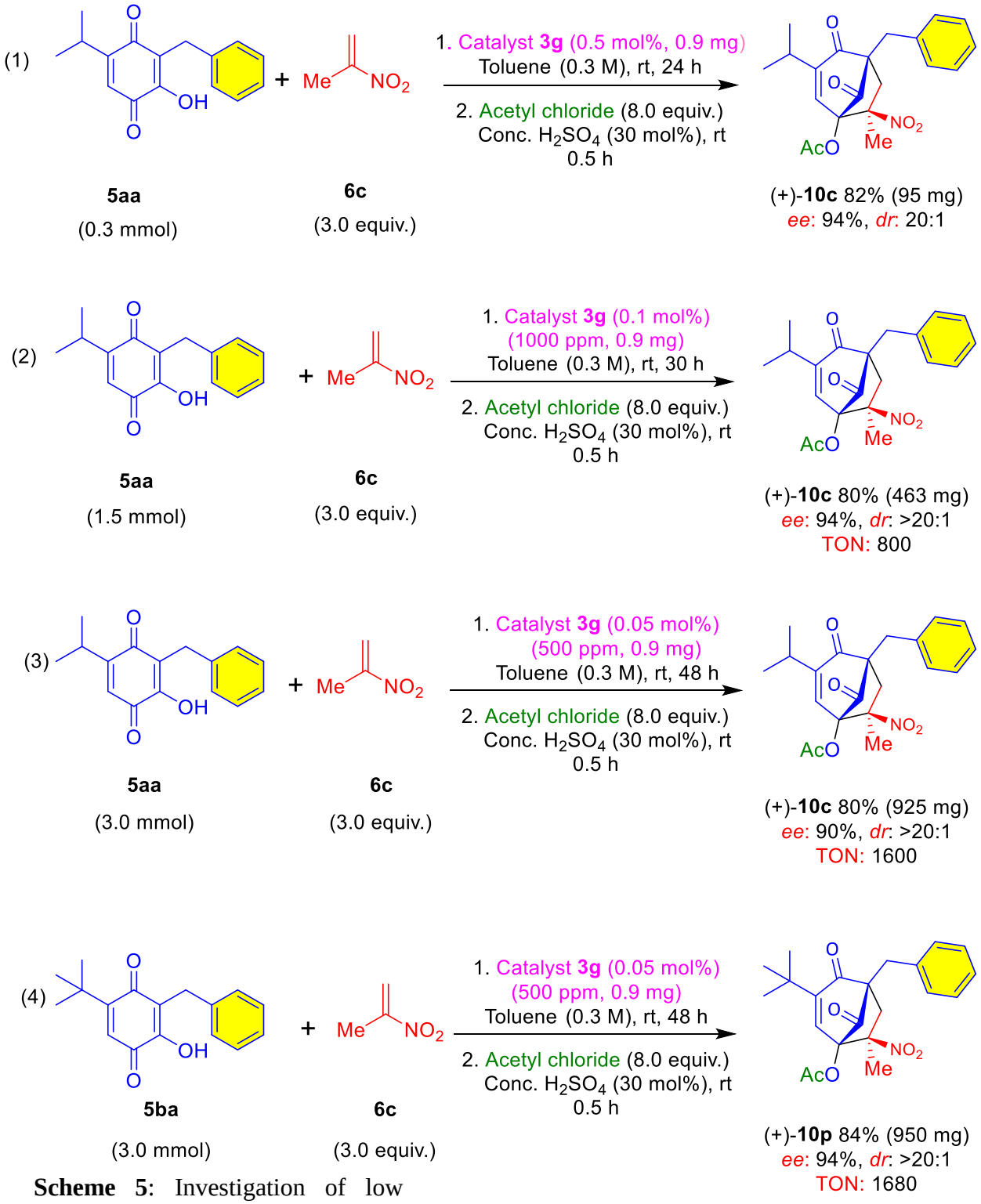
Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT5.818	5.818	42364681	2042047	97.137	96.680
2	RT7.717	7.717	1248436	70128	2.863	3.320
Total			43613117	2112175	100.000	100.000

Figure 29: HPLC spectrum of product **-10aa**.

In spite of the fact that we have successfully accomplished our objective of low-catalyst loading reaction as proposed and considered numerous reaction parameters concerning the reaction design which established to be a fruitful methodology, still our quest for ppm-level catalyst loading reactions made us further indulge into its reactivity.

4.2.6 Investigation for low catalyst loading of asymmetric [3+2]-annulation reactions

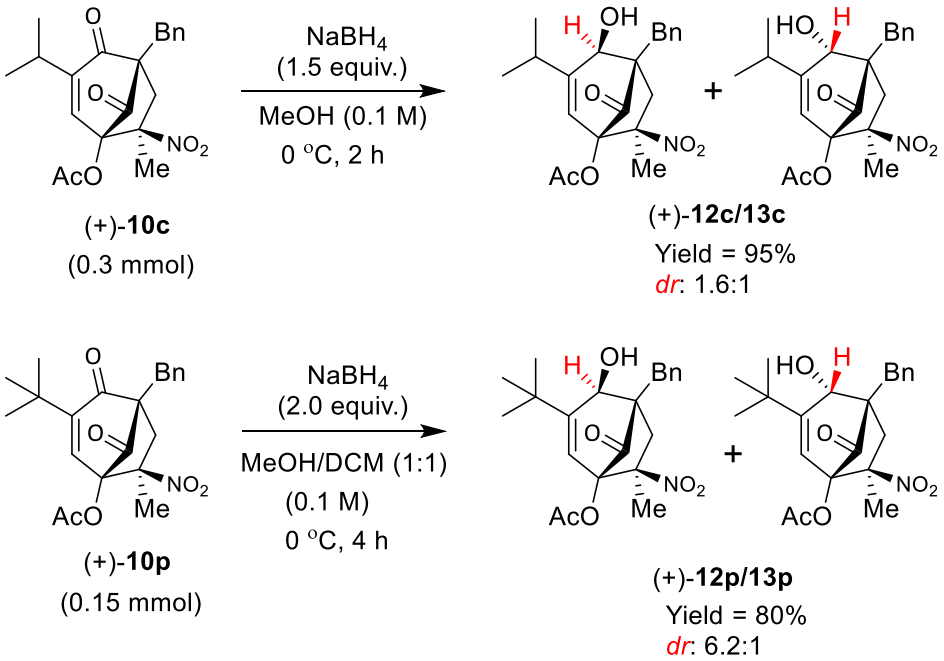
In the optimization studies, we have tried to investigate the reactions with 0.1 mol% or 1000 ppm of **3g** catalyst. The poor solubility of quinine squaramide catalyst **3g** in toluene, resisted us to perform the reactions at a small scale. Though we dissolved **3g** in DCM and treated it with **6c**, there was a fall in the *ee* of (+)-**10c/11c**. We therefore performed reactions in large scale so that there wouldn't be any problem associated with the solubility and accuracy in measurement of the catalyst. We took **5aa** with **6c** and performed the reaction on 0.3 mmol scale and decreased the catalyst loading from 1 mol% to 0.5 mol% and synthesised (+)-**10c** in 82% yield (Scheme 5, eq 1). We utilized only 0.9 mg of the catalyst in first step of the reaction and it took 24 h to complete, later we protected it with acetyl chloride which gave (+)-**10c** in 0.5 h with an *ee* of 94% and excellent *dr* of 20:1. These results prompted us to further decreased the loading of catalyst to 0.1 mol% and hence performed the reaction with 1.5 mmol scale of **5aa** to give (+)-**10c** with 80% yield and *ee* of 94% with *dr* of >20:1 and TON of 800 (Scheme 5, eq 2). we further decreased the loading of the catalyst to 0.05 mol% or 500 ppm and increased the scale of the reaction to 3.0 mmol and we got (+)-**10c** in 80% yield within 48 h and *ee* of 90% and *dr* of >20:1 with a TON of 1600 (Scheme 5, eq 3). We have also studied the electronics involved by modifying the sidechain of the reaction, by treating **5ba** with **6c** in 0.05 mol% of the catalyst to synthesize (+)-**10p** with 84% yield *i.e.*, 950 mg in 48 h with 94% *ee* and *dr* of >20:1 and TON of 1680 (Scheme 5, eq 4). These outstanding results conclude that scale-up reactions can be performed via ppm-level catalyst loading without any hassle and achieve excellent enantioselectivity and diastereoselectivity, thus accomplishing our foremost objective.



Scheme 5: Investigation of low catalyst loading for asymmetric [3+2]-annulation reactions.

4.2.7 Synthetic transformations

Subsequently, functional group transformations have been carried out to exemplify the synthetic efficacy of the reaction. Treatment of (+)-**10c** with 1.5 equiv. of $NaBH_4$ in 0.1 M MeOH at 0 °C gave (+)-**12c/13c** with 95% yield and a *dr* of 1.6:1 within 2 h. In the general scenario, reduction of the bridged carbonyl group occurs, but the unusual transformation of the carbonyl group adjacent to the double bond takes place in the case of (+)-**10c**. This can be due to the steric hindrance caused by the -Me and $-NO_2$ groups present closer to the bridged carbonyl, making it impossible for the nucleophile to approach it, which resulted in the formation of (+)-**12c/13c**. The structure of (+)-**12c/13c** was further confirmed by IR/NMR/mass/2D NMR analysis. For further confirmation, we treated (+)-**10p** with 2.0 equiv. of $NaBH_4$ in a 1:1 ratio of MeOH/DCM solvent at 0 °C for 4 h to give (+)-**12p/13p** in 80% yield with 6.2:1. Almost equimolar ratio of DCM was used due to the solubility of (+)-**10p** in MeOH and the structure of (+)-**12p/13p** was further confirmed by 2D NMR technique (Scheme 6). We have attempted a few classical reactions on our structural motif, such as epoxidation, and Pd/C mediated hydrogenation for making further functional group transformations, but those reactions failed which can be attributed to the complex nature of the skeleton.



Scheme 6: Synthetic transformations of Bicyclo[3.2.1]octanes.

^{1}H, ^{13}C NMR and NOESY spectra of (+)-**12p/13p** from scheme 6 have depicted in Figure

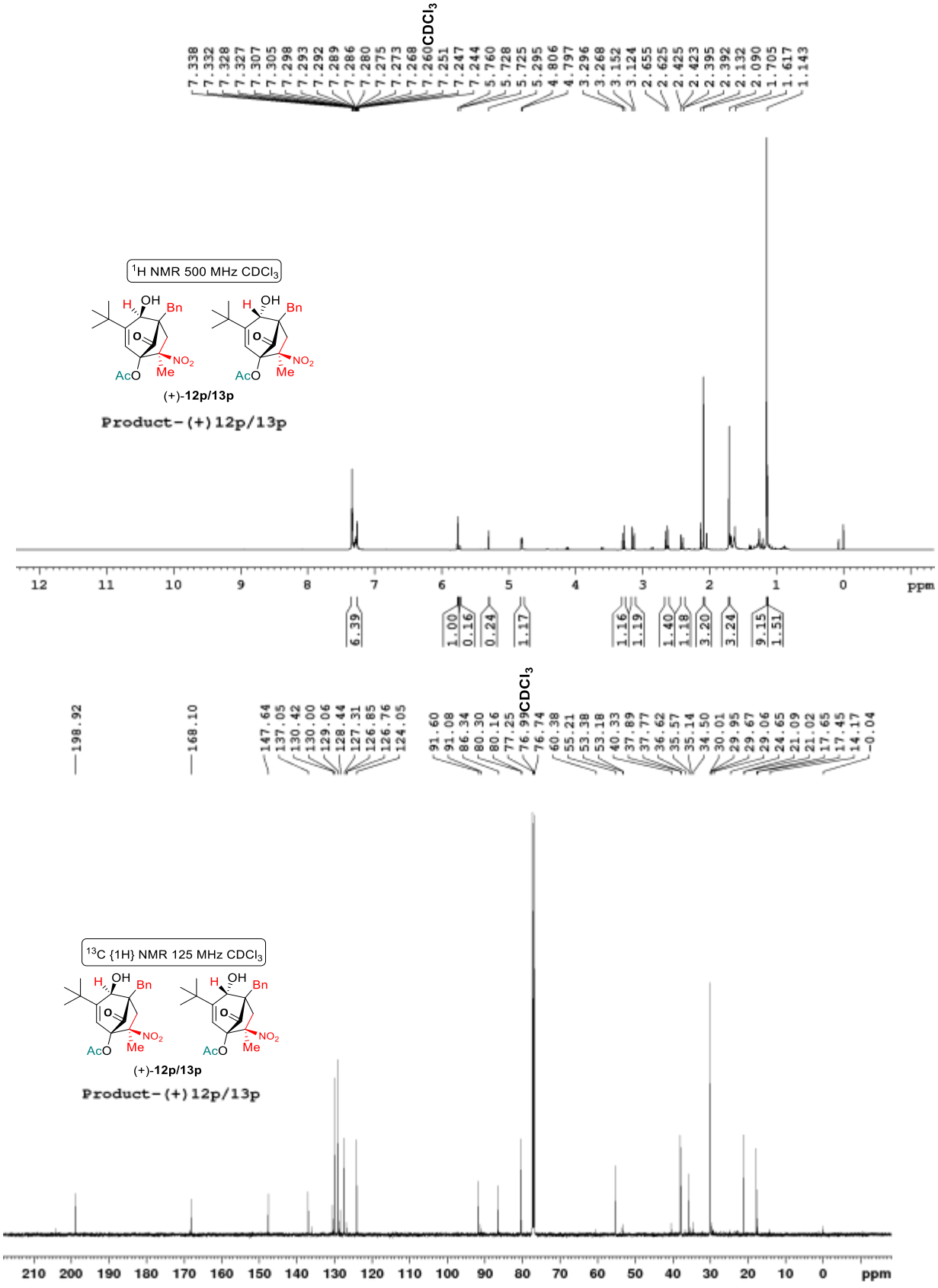


Figure 30: ^{1}H NMR and ^{13}C NMR spectrum of product-**12p/13p**.

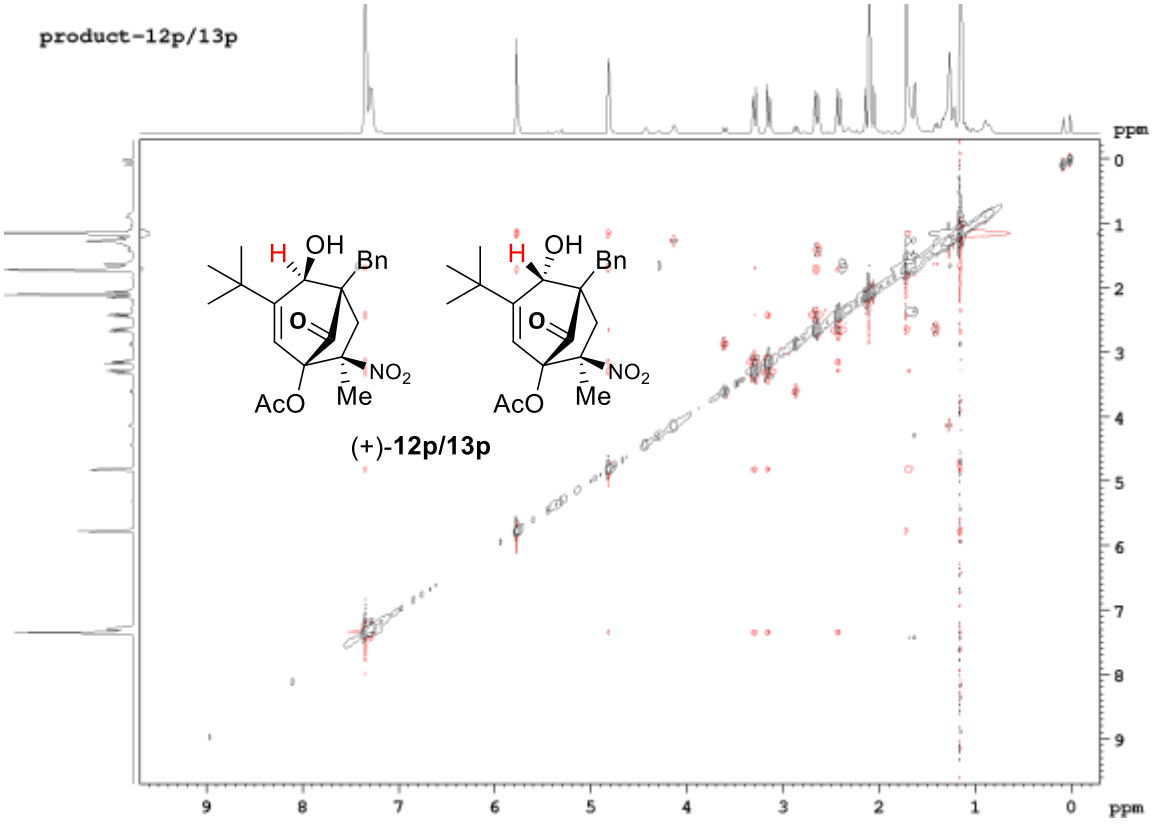
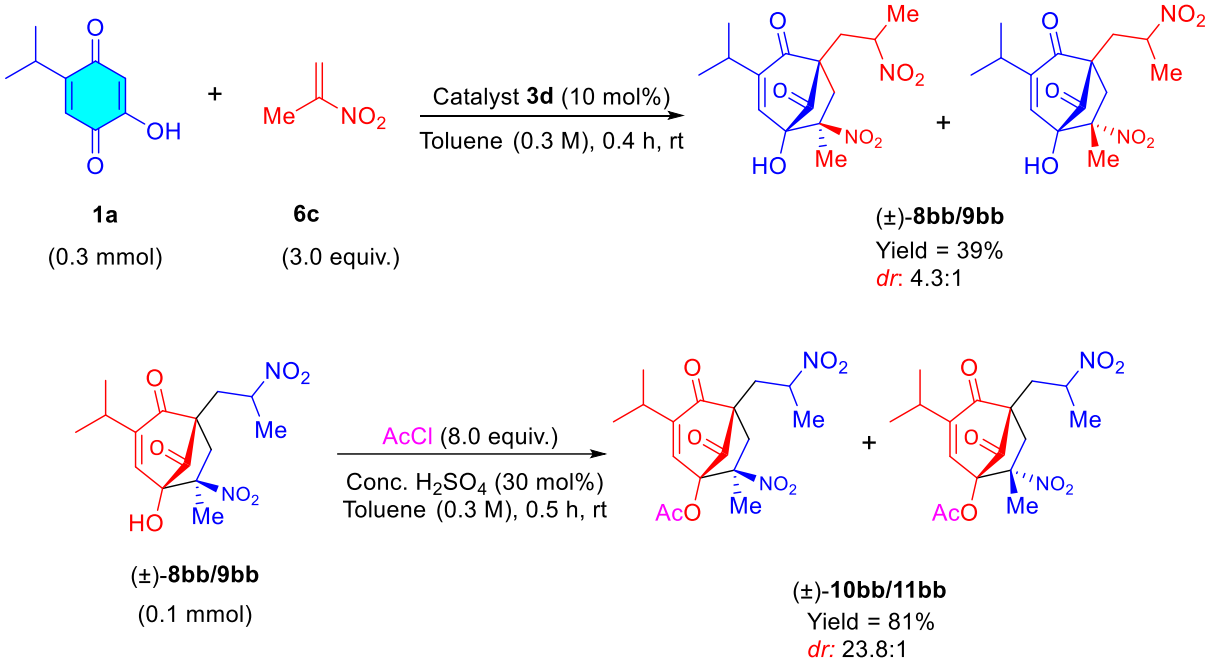
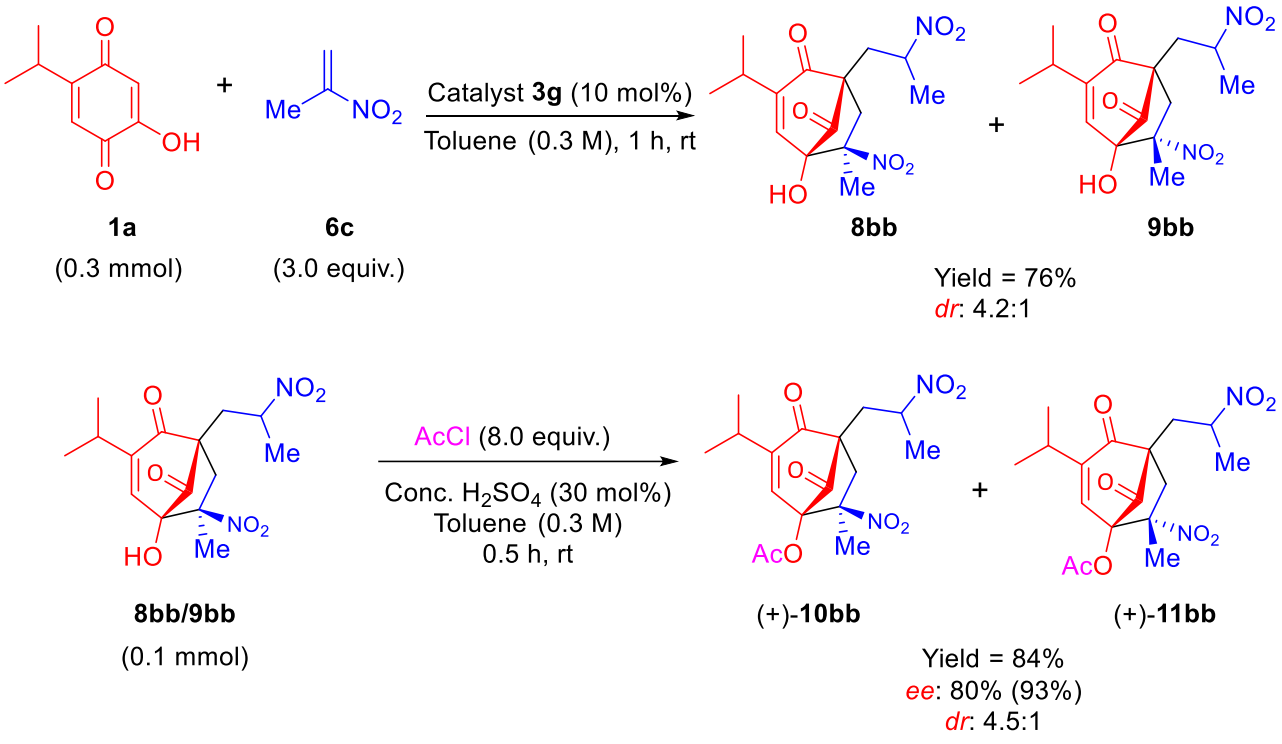


Figure 31: NOESY spectrum of compound (±)-**12p/13p** (500 MHz, $CDCl_3$ at 25 °C).

In order to further understand the reactivity of **1a**, it was treated with **6c** using 10 mol% of **3d** in 0.3 M toluene solvent within 20 min it gave (±)-**8bb** and (±)-**9bb** in 39% yield which gave a complex diastereomeric ratio. (±)-**8bb/9bb** was isolated and then protected with acetyl chloride to give (±)-**10bb/11bb** in 81% yield (Scheme 7). Developing a chiral version will also give us a better understanding of the nature of **1a**. Treatment of **1a** with **6c** in the presence of 10 mol% of **3g** gave **8bb/9bb** in 76% yield in 1 h which was isolated, unlike other previous reaction **8bb/9bb** on protection with acetyl chloride in 30 min gave 84% yield of (+)-**10bb/11bb** with 80%/93% *ee* and *dr* of 4:1 (Scheme 8). This reaction also signifies the essentiality of TCRA reaction on **1a** prior to the reaction with **6** for a better analysis of the synthesized products.



Scheme 7: Investigation of further reactivity of **1a** with catalyst **3d**.



Scheme 8: Investigation of reactivity of **1a** with chiral catalyst **3g**.

^{1}H, ^{13}C NMR and HPLC spectra of (+)-**10bb/11bb** from scheme 8 have depicted in Figure 32-33.

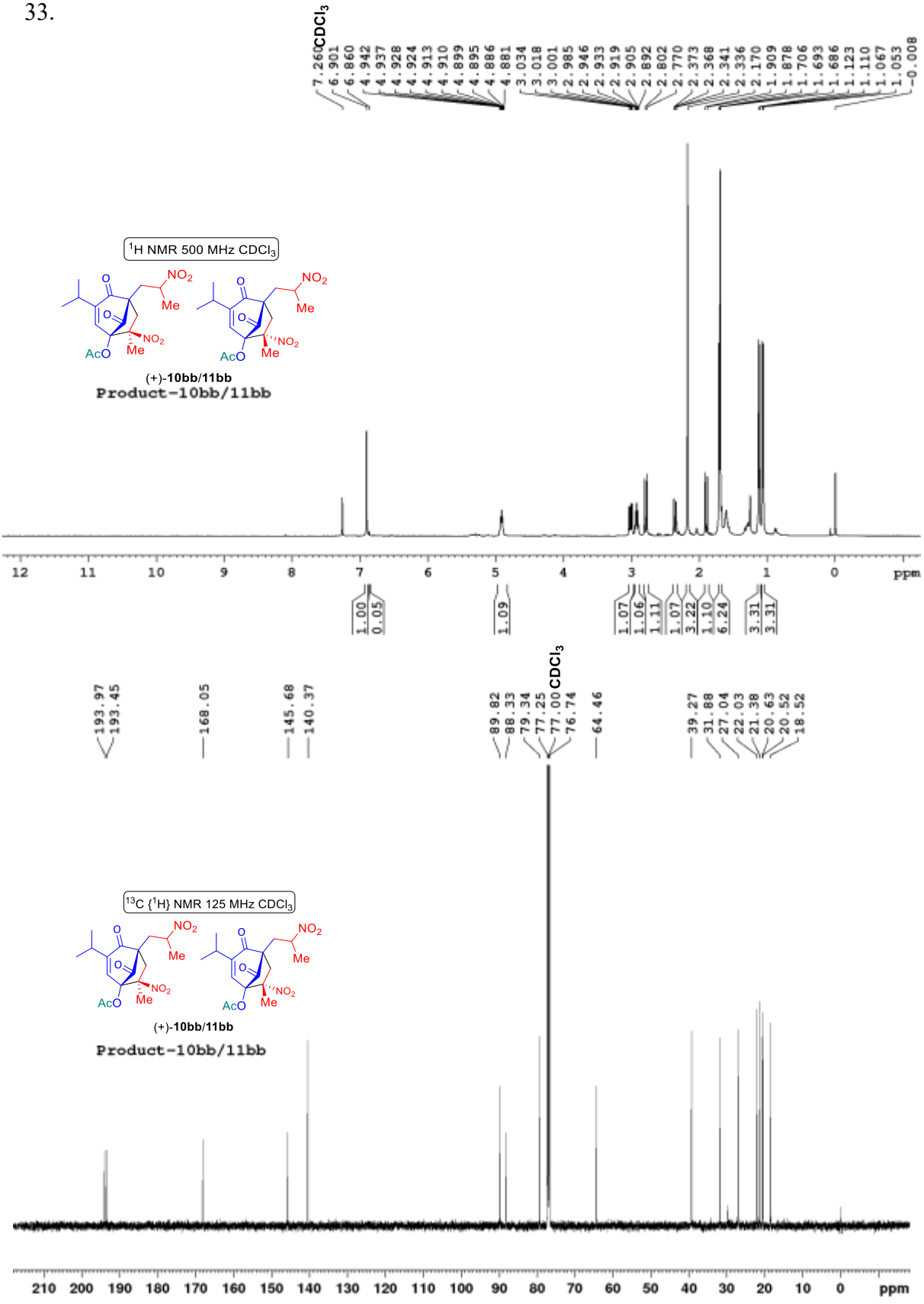
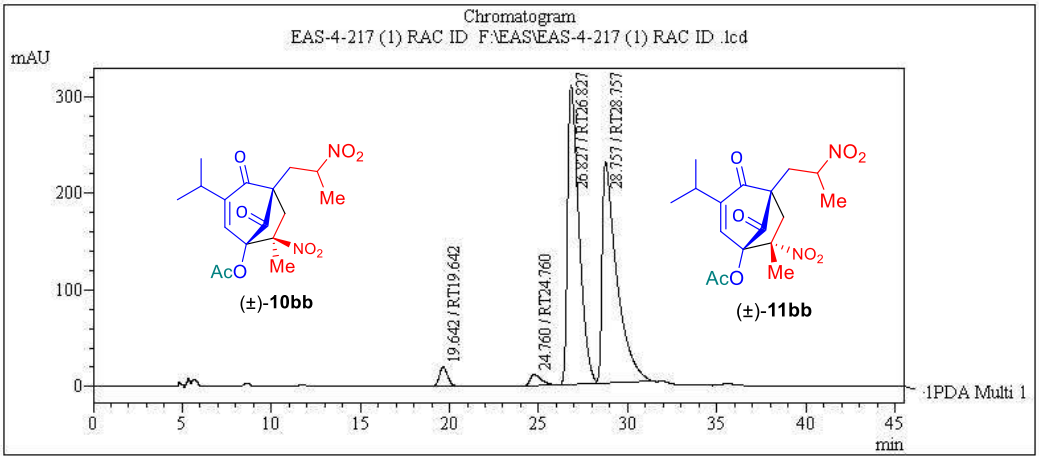


Figure 32: ^{1}H NMR and ^{13}C NMR spectrum of product-**10**

Racemic (±)-**10bb**+**11bb**:

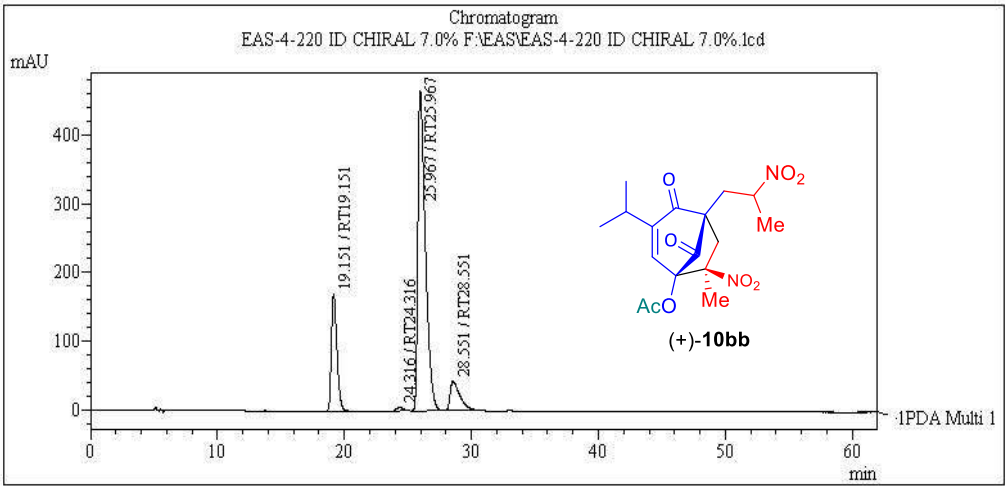


PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT19.642	19.642	625361	19780	2.226	3.474
2	RT24.760	24.760	505163	11276	1.798	1.980
3	RT26.827	26.827	13782207	309367	49.056	54.338
4	RT28.757	28.757	13182231	228919	46.920	40.208

Chiral (+)-**10bb**:



Daicel Chiralpak ID, Hexane/ *i*-PrOH = 90:10 Flow Rate 0.7 mL/min, 254 nm.

PeakTable

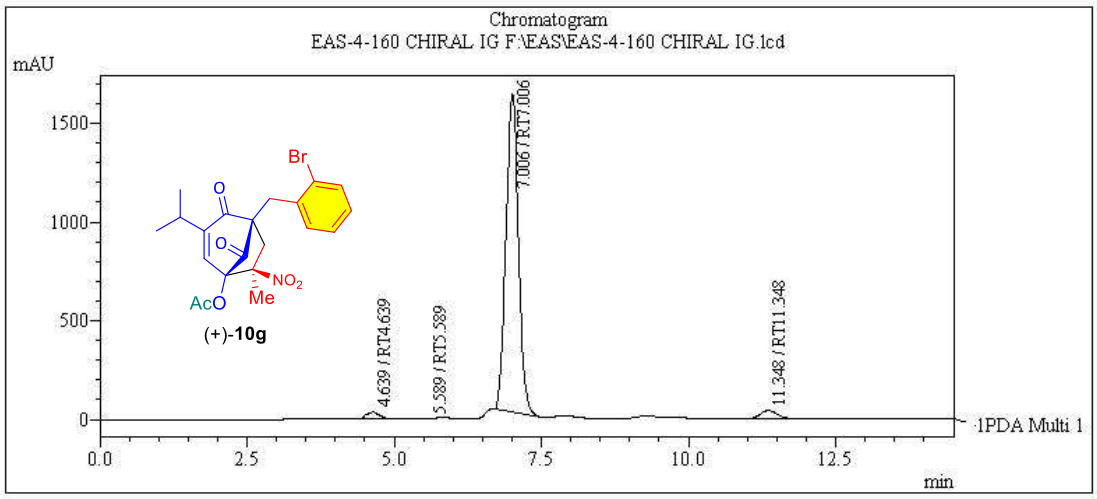
PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT19.151	19.151	5191438	170231	19.441	25.009
2	RT24.316	24.316	195742	4997	0.733	0.734
3	RT25.967	25.967	19121626	463689	71.608	68.121
4	RT28.551	28.551	2194223	41764	8.217	6.136

Figure 33: HPLC spectrum of product -**10bb/11bb**.

The data obtained from single crystal X-ray diffraction studies of (+)-**11a** and (+)-**10g** played a prominent role in identifying the major and minor diastereomer. The diffracted crystal obtained from (+)-**10g** was subsequently injected into the HPLC to identify the major and minor isomer and also determine the absolute stereochemistry taking reference from the HPLC of (+)-**10g** (Figure 34). we got the major isomer with >99% *ee* thus confirming (+)-**10g** to be the major isomer and (+)-**11g** to be the minor isomer (Figure 35).

Chiral-(+)-**10g** (Major: 93% *ee*; Minor: 99% *ee*):



Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 0.8 mL/min 254 nm.

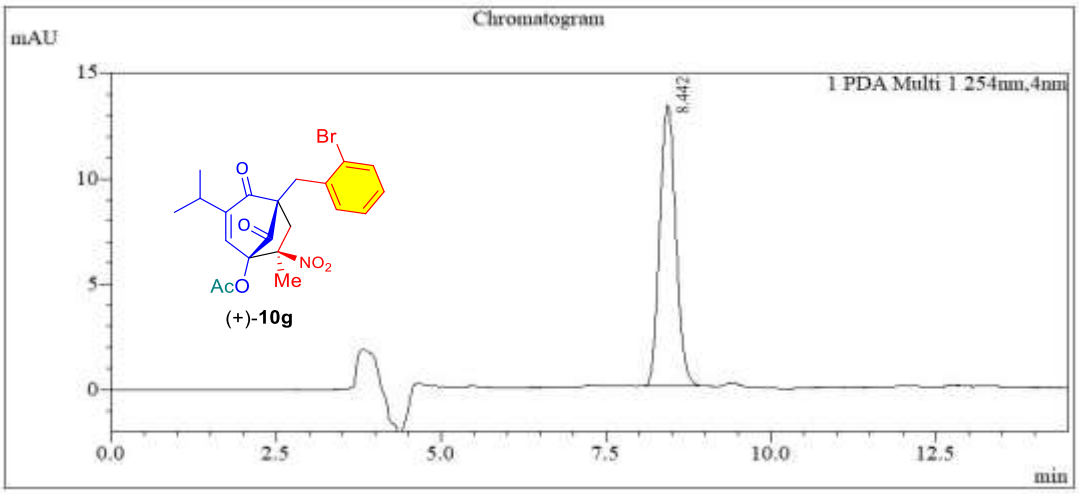
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT4.639	4.639	492579	33214	1.965	1.972
2	RT5.589	5.589	2397	17	0.010	0.001
3	RT7.006	7.006	23737855	1609417	94.691	95.550
4	RT11.348	11.348	835833	41719	3.334	2.477

Figure 34: HPLC spectra of (+)-**10g**.

Chiral-(+)-**10g** (Crystal):



Daicel Chiralpak IG, Hexane/ *i*-PrOH = 90:10, Flow Rate 0.8 mL/min 254 nm.

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:8.442	8.442	226759	13349	100.000	100.000
Total			226759	13349	100.000	100.000

Figure 35: HPLC spectra of diffracted crystal (+)-**10g**.

4.2.8 Mechanistic Insights: The plausible transition state and the mechanism can be inferred on the basis of these experimental results. As shown in **TS-1**, in situ generated *si* face of the enolate of **5** approaches the *si* face of **6,** due to the increased and stronger hydrogen bonding with **3g** and also decreased steric hindrance between **3g** and **5** favours **TS-1**, which also accounts for the formation of major enantiomer (+)-**10a** to (+)-**10aa**. Whereas, in the case of **TS-2** limited hydrogen interactions between the catalyst **3g** and substrate **6** makes this *Re-Si* face approach unfavourable which explains the inability for the generation of minor enantiomer (Figure 36).

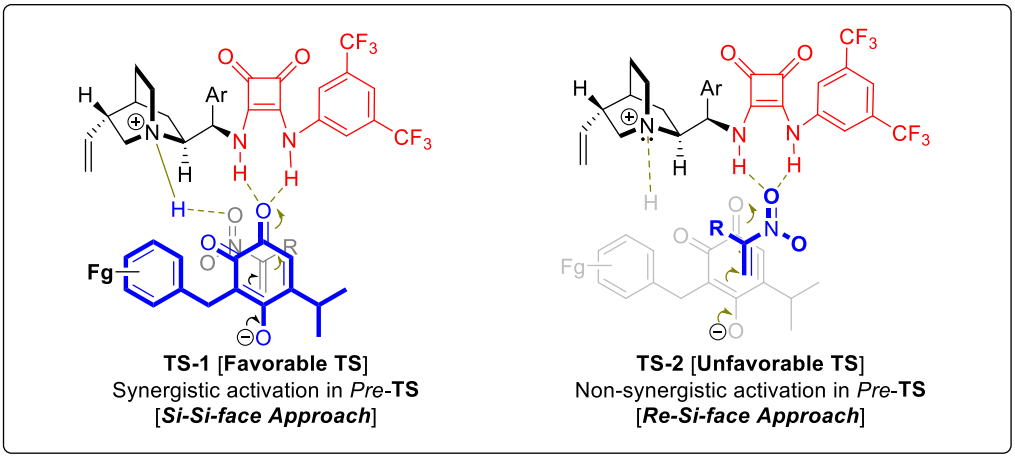


Figure 36: Proposed tentative transition state.

4.3 Conclusion

we have demonstrated the ppm-level asymmetric organocatalysis for the synthesis of a library of bicyclo[3.2.1]octanes in both achiral and chiral forms and studied the sustainability of the reaction by extending the substrate scope. The synthesized hydroxy-*p*-quinones **5** on treatment with **6** gave products (+)-**10a**-**10aa** within 1-5 h with excellent enantioselectivity and diastereoselectivity under quinine squaramide **3g** catalysis. Scale-up reactions are performed utilizing 1000-500 ppm of catalyst and further studies are in line to explore the biological activity and pharmaceutical activity of these synthesized bicyclo[3.2.1]octanes.

4.4 Experimental Section

General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 500, 400, 125 and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) 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. 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 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. 4-isopropyl phenol and 4-tertiary butyl phenol are utilized for the synthesis of **1a** and **1b** respectively nitroolefins **6a** to **6d** were prepared according to the literature procedures.[3]

Procedure A: Aniline induced Cascade Three-Component Reductive Alkylation (TCRA) Reactions with 2-Hydroxy-5-isopropyl-1,4-quinone:

For Table-2 and Table-3: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the aldehyde **2a**, 0.3 mmol of 2-Hydroxy-5-isopropyl-1,4-quinone **1a** and 0.6 mmol of Hantzsch ester **4** was added 1.0 mL of DCM, and aniline **3c** (1.0 equiv.) was added, and the reaction mixture was stirred at room temperature for 40 min-3 h. The crude reaction mixture was directly loaded onto a silica gel column without aqueous workup, and pure cascade products **5a**–**5bl** were obtained in 52-74% yield (silica gel, mixture of hexane/ethyl acetate).

Procedure B: **Preparation of Racemic Tandem Michael/Henry Annulation Products 10/11: For Table-4 and Table-5**: In an oven-dried round bottom flask equipped with a magnetic stirring bar, to 2-hydroxy-3-alkyl-5-isopropyl-1,4-quinones derivative **5** (0.15 mmol) and achiral thiourea catalyst **3k** (10 mol%) in 0.05 mL of toluene added 0.45 mmol (0.45 mL, 1.0 M in toluene) of nitro-olefins **6c**. The reaction mixture was stirred at rt for 5-30 min. After completion of the reaction, 8.0 equiv. of acetyl chloride followed by 0.3 equiv. conc. H_2SO_4 was added. The reaction mixture was allowed to stirred at rt for 30 min. The crude reaction mixture was directly loaded onto silica gel for column chromatography without aqueous workup pure racemic products **10c-10aa** were obtained in 60-96% yield (silica gel, mixture of hexane/ethyl acetate).

Procedure C: **Preparation of Chiral Tandem Michael/Henry Annulation Products 10/11: For Table-8 and Table-9**: In an oven-dried round bottom flask equipped with a magnetic stirring bar, to 2-hydroxy-3-alkyl-5-isopropyl-1,4-quinones derivative **5** (0.15 mmol) and chiral quinine squaramide **3g** (1 mol% or 500 ppm) in 0.05 mL of toluene at rt added 0.45 mmol (0.45 mL, 1.0 M in toluene) of nitro-olefins **6c**. The reaction mixture was stirred at rt for 1-4 h. After completion of the reaction, 8.0 equiv. of acetyl chloride followed by 0.3 equiv. of conc.H_2SO_4 was added. The reaction mixture was allowed to stirred at rt for 30 min. The crude reaction mixture was directly loaded onto silica gel for column chromatography without aqueous workup pure chiral annulation products **10/11** were obtained in 60-96% yield (silica gel, mixture of hexane/ethyl acetate).

Procedure D: **General Procedure for the Reduction of (1R,4R,5S,7R)-5-benzyl-3-(tert-butyl)-4-hydroxy-7-methyl-7-nitro-8-oxobicyclo[3.2.1]oct-2-en-1-yl acetate (+)-10p**:

In a 10 mL round-bottom flask equipped with a magnetic stirring bar, compound (+)-**10p** (0.3 mmol) was dissolved in dry MeOH (0.1 M) and then cooled to 0 ºC, followed by addition of $NaBH_4$ (2.0 equiv.) under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 4 h. The crude reaction mixture was work up with water, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried

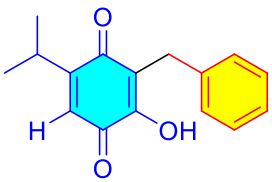
(Na_2SO_4), filtered, and concentrated. Pure product (+)-**12p/13p** was obtained in 80% yield without column chromatography.

Procedure E: **Preparation of Racemic 5-hydroxy-3-isopropyl-6-methyl-6-nitro-1-(2-nitropropyl)bicyclo[3.2.1]oct-3-ene-2,8-dione** (±)-**8bb**/**9bb**: In a 10 mL round-bottom flask equipped with a magnetic stirring bar to 0.03 mmol of the thiourea catalyst **3d** and 0.3 mmol of 2-Hydroxy-5-isopropyl-1,4-quinone **1a** was added 0.1 mL of toluene, and then 0.9 mmol of nitroethylene **6c** (0.9 mL, 1.0 M in toluene.) was added and the reaction mixture was stirred at room temperature for 20 min. The crude reaction mixture was directly loaded onto a silica gel column without aqueous workup, and pure products were obtained in 39% yield (silica gel, mixture of hexane/ethyl acetate).

Procedure F: **Preparation of Chiral 5-hydroxy-3-isopropyl-6-methyl-6-nitro-1-(2-nitropropyl)bicyclo[3.2.1]oct-3-ene-2,8-dione** (+)-**8bb**/**9bb**: In a 10 mL round-bottom flask equipped with a magnetic stirring bar to 0.03 mmol of the quinine squaramide catalyst **3g** and 0.3 mmol of 2-Hydroxy-5-isopropyl-1,4-quinone **1a** was added 0.1 mL of toluene, and then the 0.9 mmol of nitroethylene **6c** (0.9 mL, 1.0 M in toluene). was added and the reaction mixture was stirred at room temperature for 1 h. The crude reaction mixture was directly loaded onto a silica gel column without aqueous workup, and pure products were obtained in 76% yield (silica gel, mixture of hexane/ethyl acetate).

Procedure G: **Preparation of 3-isopropyl-7-methyl-7-nitro-5-(2-nitropropyl)-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (+)-10bb/11bb**: In an oven dried 10 mL round bottom flask equipped with a magnetic stirring bar, to the compound **8bb/9bb** (0.117 mmol), in dry toluene (0.4 mL), acetyl chloride (0.936 mmol, 8.0 equiv., 67 µl) and conc.H_2SO_4 (0.0351 mmol, 30.0 mol%, 1.88 µl) were added. The reaction mixture was stirred at 25 ºC for 0.5 h. Pure products (+)-**10bb/11bb** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

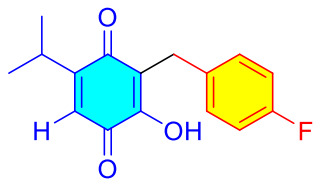
3-benzyl-2-hydroxy-5-isopropylcyclohexa-2,5-diene-1,4-dione (5aa): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a light brown solid. Yield: 70% (53.8 mg); Mp.: 80-82 ºC; IR (Neat): ν_{max} 3358, 2960, 2927, 2870, 1637, 1611, 1492, 1459, 1430, 1362, 1276, 1213, 1186, 1078, 972, 693, 630, 497, 450 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32 (2H, d, *J* = 7.0 Hz), 7.27 (2H, d, *J* = 6.5 Hz), 7.18 (1H, t, *J* = 7.5 Hz), 6.97 (1H, *br* s), 6.49 (1H, d, *J* = 1.0 Hz), 3.79 (2H, s), 1.11 (6H, d, *J* = 7.0 Hz); ^{13}C NMR



5aa

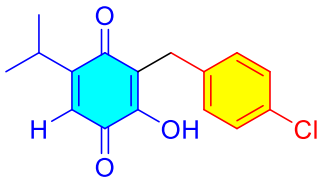
($CDCl_3$, 125 MHz, DEPT-135): δ 186.6 (C, *C*=O), 183.9 (C, *C*=O), 158.3 (C), 150.7 (C), 139.0 (C), 129.1 (2 x CH), 128.4 (2 x CH), 126.3 (CH), 125.6 (CH), 120.4 (C), 28.9 (CH_2), 27.3 (CH), 21.7 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}O_3Na$ 279.0997; Found 279.0995.

3-(4-fluorobenzyl)-2-hydroxy-5-isopropylcyclohexa-2,5-diene-1,4-dione (5ab): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.7:9.3 to 1.2:8.8) and isolated as a yellow solid. Yield: 72% (59 mg); Mp.: 110-112 ºC; IR (Neat): ν_{max} 3345, 2920, 2851, 1635, 1610, 1507, 1464, 1362, 1220, 1159, 935, 802, 746 and 687 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40 (2H, dd, *J* = 8.75, 5.5 Hz), 7.05 (2H, t, *J* = 8.5 Hz), 6.62 (1H, s), 3.88 (2H, s), 3.25-3.12 (1H, m), 1.23 (6H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 186.5 (C, *C*=*O*), 183.7 (C, *C*=*O*), 161.4 (C, d, *J* = 242.5 Hz), 158.2 (C), 150.6 (C), 134.6 (C, d, *J* = 3.75 Hz), 130.5 (2 x CH, d, *J* = 7.5 Hz), 125.6 (CH), 120.2 (C), 115.1 (2 x CH, d, *J* = 21.25 Hz), 28.0 (CH_2), 27.2 (CH_2), 21.6 (2 x CH_3);); ^{19}F NMR ($CDCl_3$, 470 MHz): δ = –116.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}FO_3H$ 275.1083; Found 275.1083.



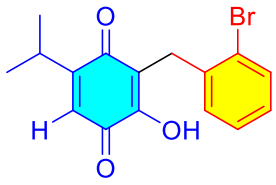
5ab

3-(4-chlorobenzyl)-2-hydroxy-5-isopropylcyclohexa-2,5-diene-1,4-dione (5ac): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.7:9.3 to 1.2:8.8) and isolated as a yellow solid; Yield: 60% (52 mg); Mp.: 105-107 ºC; IR (Neat): ν_{max}, 3340, 2987, 1634, 1612, 1363, 1216, 1090, 810, 685, 501 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30 (1H, d, *J* = 9.5 Hz), 6.93 (2H, tt, *J* = 9.0 Hz), 6.90 (1H, s), 6.56 (1H, s), 3.74 (2H, s), 1.27 (6H, s); ^{13}C NMR ($CDCl_3$, DEPT-135): δ 186.5 (*C*, *C*=*O*), 183.6 (*C*, *C*=*O*), 158.3 (C), 150.7 (C), 137.4 (C), 132.1 (C), 130.4 (2 x CH), 128.5 (2 x CH), 125.6 (CH), 119.9 (C), 28.2 (CH_2), 27.2 (CH), 21.6 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}ClO_3Na$ 313.0607; Found 313.0603.



5ac

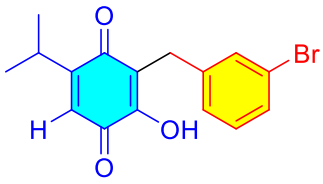
3-(2-bromobenzyl)-2-hydroxy-5-isopropylcyclohexa-2,5-diene-1,4-dione (5ad):



5ad

The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.7:9.3 to 1.2:8.8) and isolated as a pale yellow liquid; Yield: 88% (88.4 mg); IR (Neat): ν_{max} 3356, 2964, 1639, 1610, 1465, 1363, 1323, 1216, 1025 and 743 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.54 (1H, d, *J* = 8.0 Hz), 7.18 (1H, t, *J* = 7.5 Hz), 7.08 (1H, d, *J* = 7.5 Hz), 7.05 (1H, t, *J* = 7.5 Hz), 6.56 (1H, s), 3.93 (2H, s), 3.13 (1H, sept, *J* = 7.0 Hz), 1.13 (6H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 186.4 (C, *C*=*O*), 183.5 (C, *C*=*O*), 158.7 (C), 151.6 (C), 137.8 (C), 132.7 (CH), 129.7 (CH), 127.8 (CH), 127.2 (CH), 125.6 (CH), 124.5 (C), 118.7 (C), 29.3 (CH_2), 27.3 (CH), 21.6 (2 x CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}BrO_3H$ 335.0283; Found 335.0282.

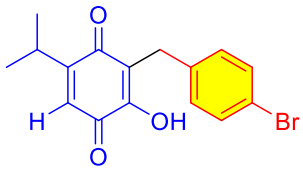
3-(3-bromobenzyl)-2-hydroxy-5-isopropylcyclohexa-2,5-diene-1,4-dione (5ae):



5ae

The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.7:9.3 to 1.2:8.8) and isolated as a light brown liquid; Yield: 68% (68.3 mg); IR (Neat): ν_{max}, 2970, 1718, 1441, 1368, 1280, 1220, 1099, 1042, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.46 (1H, s), 7.33-7.23 (2H, m), 7.12 (1H, t, *J* = 8.0 Hz), 7.01 (1H, s), 6.51 (1H, s), 3.75 (2H, s), 3.11 (1H, septet, *J* = 7.0 Hz) 1.12 (6H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 186.5 (C, *C*=*O*), 183.6 (C, *C*=*O*), 158.4 (C), 150.8 (C), 141.2 (C), 132.0 (CH), 130.0 (CH), 129.4 (CH), 127.8 (CH), 125.7 (CH), 122.4 (C), 119.6 (C), 28.5 (CH_2), 27.3 (CH), 21.7 (2 x CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}BrO_3H$ 335.0283; Found 335.0282.

3-(4-bromobenzyl)-2-hydroxy-5-isopropylcyclohexa-2,5-diene-1,4-dione (5af):

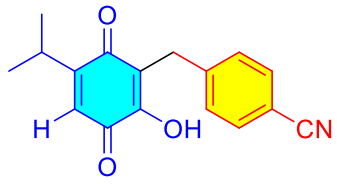


5af

The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.7:9.3 to 1.2:8.8) and isolated as light brown liquid; Yield: 67% (67.4 mg); IR (Neat): ν_{max} 3343, 2965, 1634, 1612, 1485, 1363, 1327, 1216, 1068, 1011, 979, 889, 808, 789, 715, 683, 642, 541, and 500, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37 (2H, d, *J* = 6.4 Hz), 7.20 (2H, d, *J* = 6.4 Hz), 6.50 (1H, s),

3.73 (2H, s), 3.10 (1H, septet, J = 5.6 Hz), 1.1 (6H, d, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 186.4 (C, *C*=*O*), 183.6 (C, *C*=*O*), 158.3 (C), 150.7 (C), 137.9 (C), 131.4 (2 x CH), 130.0 (2 x CH), 125.6 (CH), 120.1 (C), 119.7 (C), 28.3 (CH_2), 27.3 (CH), 21.6 (2 x CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}BrO_3H$ 335.0283; Found 335.0283.

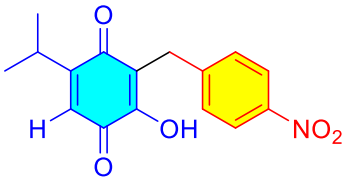
4-((2-hydroxy-5-isopropyl-3,6-dicyclohexa-1,4-dien-1-yl)methyl)benzonitrile (5ag): The



5ag

title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.7:9.3 to 1.2:8.8), and was isolated as a yellow solid. Yield: 72% (60.7 mg); MP.: 99-101 ºC; IR (Neat): ν_{max} 3259, 2228, 1636, 1605, 1380, 1357, 1268, 1210, 1186, 1020, 899, 818, 744, 689, 616 and 546 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (2H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.0 Hz), 6.53 (1H, s), 3.84 (2H, s), 3.10 (1H, sept, J = 7.0 Hz), 1.12 (6H, d, J = 7.0, Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 186.3 (C, *C*=*O*), 183.4 (C, *C*=*O*), 158.3 (C), 151.1 (C), 144.5 (C), 132.2 (2 x CH), 129.8 (2 x CH), 125.8 (CH), 118.9 (C), 118.8 (C), 110.2 (C), 29.0 (CH_2), 27.3 (CH), 21.6 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{15}NO_3Na$ 304.0950; Found 304.0955.

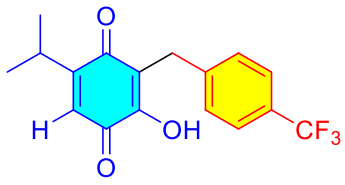
2-hydroxy-5-isopropyl-3-(4-nitrobenzyl)cyclohexa-2,5-diene-1,4-dione (5ah): The title



5ah

compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.0:8.0), and was isolated yellow solid. Yield: 70% (126 mg). Mp.: 120-122 ºC; IR (Neat): ν_{max} 3345, 2964, 1634, 1598, 1514, 1336, 1218, 1105, 890, 853, 743, 684 and 499 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (2H, d, J = 9.0 Hz), 7.49 (2H, d, J = 9.0 Hz), 7.21 (1H, *br* s), 6.55 (1H, d, J = 1.5 Hz), 3.11 (1H, d sept, J = 7.0, 1.0 Hz), 1.13 (6H, d, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 186.3 (C, *C*=*O*), 183.4 (C, *C*=*O*), 158.4 (C), 151.1 (C), 146.7 (C), 146.6 (C), 129.8 (2 x CH), 125.8 (CH), 123.6 (2 x CH), 118.7 (C), 28.8 (CH_2), 27.3 (CH), 21.6 (2 x CH_3), HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}NO_5Na$ 324.0848; Found 324.0851.

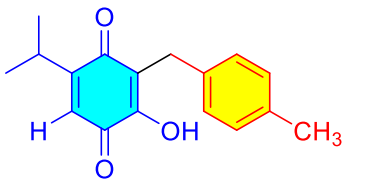
2-hydroxy-5-isopropyl-3-(4-(trifluoromethyl)benzyl)cyclohexa-2,5-diene-1,4-dione (**5ai**):



5ai

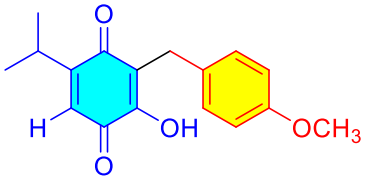
The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.8:9.2 to 1.3:8.7), and isolated as a yellow solid; MP.: 138-140 ºC; Yield: 74% (71 mg); IR (Neat): ν_{max} 3351, 2970, 1636, 1613, 1364, 1323, 1155, 1123, 1066, 821 and 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51 (2H, d, *J* = 8.0 Hz), 7.43 (2H, d, *J* = 8.0 Hz), 7.09 (1H, *br* s, O*H*), 6.51 (1H, s), 3.84 (2H, s), 3.10 (1H, d sept, *J* = 7.0 Hz, 1.5 Hz), 1.11 (6H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 186.4 (C, *C*=*O*), 183.5 (C, *C*=*O*), 158.4 (C), 150.9 (C), 143.0 (C), 129.3 (2 x CH), 128.9 (C, q, *J* = 32.5 Hz), 125.7 (CH), 125.3 (2 x CH, q, *J* = 3.75 Hz), 123.2 (C), 119.4 (C), 28.7 (CH_2,), 27.3 (CH), 21.6 (2 x CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}F_3O_3H$ 325.1051; Found 325.1054.

2-hydroxy-5-isopropyl-3-(4-methylbenzyl)cyclohexa-2,5-diene-1,4-dione (5aj): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.8:9.2 to 1.3:8.7) and isolated as a pale yellow liquid; Yield: 85% (69 mg); IR (Neat): ν_{max} 3350, 2968, 2918, 1634, 1612, 1387, 1362, 1315, 1216, 886, 806, 676 and 625 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (2H, d, *J* = 8.0 Hz), 7.06 (2H, d, *J* = 8.0 Hz), 7.02 (1H, *br* s), 6.47 (1H, s), 3.75 (2H, s), 3.11 (1H, d sept, *J* = 7.0 Hz, 1.0 Hz), 2.29 (3H, s), 1.10 (6H, d, *J* = 7.0 Hz), ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 186.6 (C, *C*=*O*), 183.8 (C, *C*=*O*), 158.2 (C), 150.6 (C), 135.9 (C), 135.7 (C), 129.1 (2 x CH), 128.9 (2 x CH), 125.5 (CH), 120.6 (C), 28.3 (CH_2), 27.2 (CH), 21.6 (2 x CH_3), 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}O_3H$ 271.1334; Found 271.1333.



5aj

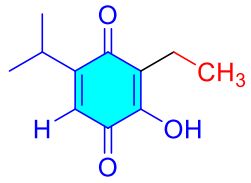
2-hydroxy-5-isopropyl-3-(4-methoxybenzyl) cyclohexa-2,5-diene-1,4-dione (5ak): The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.8:9.2 to 1.3:8.7) and isolated as a light brown liquid; Yield: 60% (51.5 mg); IR (Neat): ν_{max}, 3368, 2968, 1738, 1639, 1610, 1363, 1215, 805 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (2H, d, *J* = 8.0 Hz), 7.06 (2H, d, *J* = 7.5Hz), 6.98 (1H, br s), 6.47 (1H, s), 3.75 (2H, s), 3.10 (1H, septet, *J* = 7.0Hz), 2.29 (3H, s) 1.11(6H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-



5ak

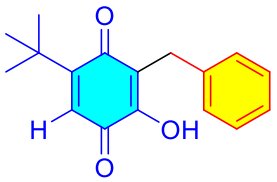
135): δ 186.6 (*C*, *C*=*O*), 183.8 (*C*, *C*=*O*), 158.2 (C), 150.5 (C), 135.9 (C), 135.8 (C), 129.1 (2 x CH), 128.9 (2 x CH), 125.5 (CH), 120.5 (C), 28.3 (CH_2), 27.2 (OCH_3), 21.6 (2 x CH_3), 21.0 (CH); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}O_4H$ 287.1283; Found 287.1280.

3-ethyl-2-hydroxy-5-isopropylcyclohexa-2,5-diene-1,4-dione (5al): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated yellow solid. Yield: 60% (35 mg). Mp.: 103-105 ºC; IR (Neat): ν_{max} 2965, 1785, 1757, 1679, 1551, 1459, 1369, 1205, 1108 and 847 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.95 (1H, *br* s), 3.12 (1H, sept, *J* = 7.0 Hz), 2.48 (2H, q, *J* = 7.5 Hz), 1.13 (6H, d, *J* = 7.0 Hz), 1.08 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 186.8 (C, *C*=*O*), 183.8 (C, *C*=*O*), 158.3 (C), 150.3 (C), 125.4 (CH), 123.0 (C), 27.1 (CH), 21.6 (2 x CH_3), 16.4 (CH_2), 12.7 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{14}O_3H$ 217.0841; Found 217.0838.



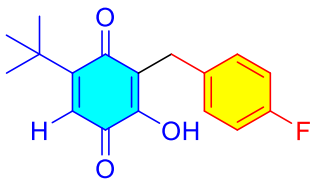
5al

3-benzyl-5-(tert-butyl)-2-hydroxycyclohexa-2,5-diene-1,4-dione (5ba): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as a pale yellow liquid; Yield: 95% (77 mg); IR (Neat): ν_{max} 3371, 2927, 1636, 1598, 1072, 1026, 923, 743, 628, 662 and 500 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.31 (2H, d, *J* = 7.5 Hz), 7.27 (1H, s), 7.24 (1H, s), 7.18 (1H, t, *J* = 7.5 Hz), 6.88 (1H, br s), 6.56 (1H, s), 3.78 (2H, s), 1.28 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135) δ 186.9 (C, *C*=*O*), 184.0 (C, *C*=*O*), 159.3 (C), 150.0 (C), 134.7 (C), 130.5 (CH), 130.5 (CH), 127.0 (CH), 121.4 (C), 115.3 (CH), 115.1 (CH), 36.0 (C), 29.6 (3 x CH_3), 29.1 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}O_3H$ 271.1334; Found 271.1334.



5ba

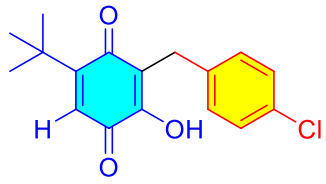
5-(tert-butyl)-3-(4-fluorobenzyl)-2-hydroxycyclohexa-2,5-diene-1,4-dione (5bb): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.7:9.3 to 1.2:8.8) and isolated as a light yellow solid; MP.: 105-107 ºC; Yield: 70% (60.5 mg); IR (Neat): ν_{max} 2957, 2922, 2852, 1644, 1508, 1462, 1380, 1260, 1221, 1096, 1023, 806, 595 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30 (1H, d, *J* = 9.5 Hz), 6.93 (2H, tt, *J* = 9.0 Hz), 6.90 (1H, s), 6.56 (1H, s), 3.74 (2H, s), 1.28 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 186.9 (C,



5bb

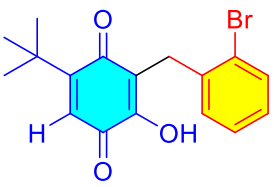
C=*O*), 184.0 (C, *C*=*O*), 161.5 (C, d, *J* = 242.5 Hz), 159.3 (C), 150.0 (C), 134.7 (C, d, *J* = 2.5 Hz), 130.5 (2 x CH, d, *J* = 7.5 Hz), 126.9 (CH), 121.4 (C), 115.1 (2 x CH, d, *J* = 21.25 Hz), 36.0 (C), 29.6 (3 x CH_3), 28.0 (CH_2); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{17}H_{17}O_3FNH_4$ 306.1505; Found 306.1500.

5-(tert-butyl)-3-(4-chlorobenzyl)-2-hydroxycyclohexa-2,5-diene-1,4-dione (5bc): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated yellow solid. Yield: 76% (139 mg). MP.: 102-104 ºC; IR (Neat): ν_{max} 3354, 2958, 1638, 1599, 1485, 1378, 1364, 1220, 1195, 1070, 1011, 981, 913, 808, 744, 675 and 501 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (2H, dd, *J* = 6.75, 2.5 Hz), 7.21 (2H, dd, *J* = 6.5, 2.5 Hz), 6.94 (1H, br s), 6.57 (1H, s), 3.73 (2H, s), 1.27 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 186.7(C, *C*=*O*), 183.9 (C, *C*=*O*), 159.3 (C), 150.1 (C), 137.5 (C), 132.0 (C), 130.4 (2 x CH), 128.5 (2 x CH), 126.9 (CH), 121.0 (C), 36.0 (C), 29.6 (3 x CH_3), 28.2 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}ClO_3H$ 305.0944; Found 305.0938.



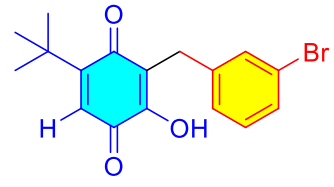
5bc

3-(2-bromobenzyl)-5-(tert-butyl)-2-hydroxycyclohexa-2,5-diene-1,4-dione (5bd): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and isolated as a pale-yellow liquid; Yield: 96% (100.5 mg). IR (Neat): ν_{max} 3369, 2960, 1640, 1597, 1418, 1377, 1363, 1335, 1223, 1193, 1025 and 741 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.53 (1H, dd, *J* = 8.25, 1.5 Hz), 7.18 (1H, dt, *J* =7.5, 1.5 Hz), 7.04 (2H, dt, *J* = 6.75, 1.5 Hz), 6.63 (1H, s), 3.91 (2H, s), 1.30 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135) δ 186.7 (C, *C*=*O*), 183.8 (C, *C*=*O*), 159.7 (C), 151.1 (C), 137.9 (C), 132.8 (CH), 129.5 (CH), 127.8 (CH), 127.2 (CH), 127.0 (CH), 124.6 (C), 119.9 (C), 36.1 (C), 29.6 (3 x CH_3), 29.4 (CH_2,); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{17}BrO_3Na$ 349.0439; Found 349.0440.



5bd

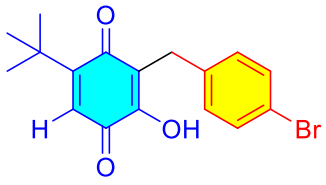
3-(3-bromobenzyl)-5-(tert-butyl)-2-hydroxycyclohexa-2,5-diene-1,4-dione (5be): The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (1.0:9.0 to 2.0:8.0) and isolated as a light brown liquid; Yield: 66% (69 mg); IR (Neat): ν_{max}, 3303, , 2977, 1706, 1656, 1591, 1553,1480, 1376, 1268, 1110, 1078, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.45



5be

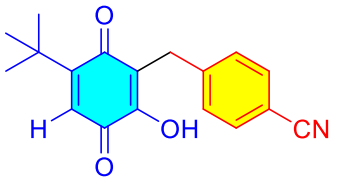
(1H, s), 7.31 (1H, d, J = 10.0 Hz), 7.24 (1H, d, J = 9.5 Hz), 7.12 (1H, t, J = 10.0 Hz), 6.90 (1H, br s), 6.58 (1H, s), 3.74 (2H, s), 1.28 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 186.7 (C, *C*=*O*), 183.9 (C, *C*=*O*), 159.4 (C), 150.2 (C), 141.3 (C), 132.0 (CH), 129.9 (CH), 129.4 (CH), 127.7 (CH), 127.0 (CH), 122.4 (C), 120.7 (C), 36.0 (C), 29.6 (3 x CH_3), 28.5 (CH_2); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{17}H_{17}BrO_3NH_4$ 366.0705; Found 366.0700.

3-(4-bromobenzyl)-5-(tert-butyl)-2-hydroxycyclohexa-2,5-diene-1,4-dione (5bf): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated yellow solid. Yield: 74% (77.5 mg). MP.: 106-108 ºC; IR (Neat): ν_{max} 3352, 2963, 1637, 1600, 1485, 1379, 1365, 1222, 1196, 1071, 1011, 982, 914, 898, 807, 745, 675 and 528 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz), 6.89 (1H, br *s*), 6.57 (1H, s), 3.72 (2H, s), 1.27 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 186.7 (C, *C*=*O*), 183.9 (C, *C*=*O*), 159.3 (C), 150.1 (C), 138.0 (C), 131.4 (2 x CH), 130.8 (2 x CH), 126.9 (CH), 120.9 (C), 120.0 (C), 36.0 (C), 29.6 (3 x CH_3), 28.3 (CH_2) HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}BrO_3H$ 349.0439; Found 349.0435.



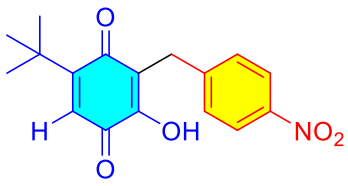
5bf

4-((5-(tert-butyl)-2-hydroxy-3,6-dioxocyclohexa-1,4-dien-1-yl)methyl)benzonitrile (5bg): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.7:9.3 to 1.2:8.8), and isolated as a yellow solid; MP.: 100-102 ºC; Yield: 72% (63.7 mg) IR (Neat): ν_{max} 3367, 2560, 2228, 1641, 1600, 1377, 1364, 1220, 1195, 916, 982, 916, 547 and 421 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (2H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.5 Hz), 6.98 (1H, br s, O*H*), 6.61 (1H, s), 3.84 (2H, s), 1.29 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 186.6 (C, *C*=*O*), 183.7 (C, *C*=*O*), 159.4 (C), 150.4 (C), 144.6 (C), 132.3 (2 x CH), 129.8 (2 x CH), 127.1 (CH), 120.0 (C), 119.0 (C), 110.2 (C), 36.0 (C), 29.6 (3 x CH_3), 26.4 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}NO_3H$ 296.1287; Found 296.1285.



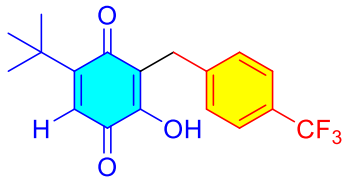
5bg

5-(tert-butyl)-2-hydroxy-3-(4-nitrobenzyl)cyclohexa-2,5-diene-1,4-dione (5bh): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.5:7.5), and was isolated yellow solid. Yield: 76% (72 mg). MP.: 142-144 ºC; IR (Neat): ν_{max} 3409, 2920, 1638, 1596, 1513, 1379, 1338, 1287, 1215, 1105, 979, 820, 700 and 495 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12 (2H, td, *J* = 8.5 Hz, 2.5 Hz), 7.47 (2H, td, *J* = 9.0 Hz, 2.5 Hz), 6.99 (1H, br *s*), 6.60 (1H, s), 3.86 (2H, s), 1.28 (9H, s). ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 186.5 (C, *C*=*O*), 183.6 (C, *C*=*O*), 159.4 (C), 150.5 (C), 146.7 (C), 146.5 (C), 129.8 (2 x CH), 127.1 (CH), 123.6 (2 x CH), 119.8 (C), 36.0 (C), 29.5 (3 x CH_3), 28.8 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NO_5Na$ 338.1004; Found 338.1009.



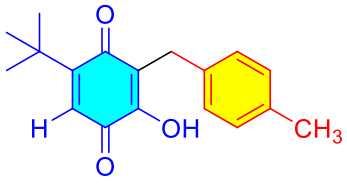
5bh

5-(tert-butyl)-2-hydroxy-3-(4-(trifluoromethyl)benzyl)cyclohexa-2,5-diene-1,4-dione (**5bi**): The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (0.8:9.2 to 1.3:8.7), and isolated as a yellow solid; Yield: 74% (75 mg); MP.: 117-119 ºC; IR (Neat): ν_{max} 3343, 2970, 1656, 1640, 1615, 1600, 1365, 1226, 1198, 1122, 1105, 1064, 1033, 681 and 650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51 (2H, dd, *J* = 8.0 Hz), 7.42 (2H, d, *J* = 8.0 Hz), 6.93 (1H, br s, O*H*), 6.58 (1H, s), 3.82 (2H, s), 1.28 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 186.7 (C, *C*=*O*), 183.8 (C, *C*=*O*), 159.4 (C), 150.3 (C), 143.1 (C), 129.3 (2 x CH), 128.6 (C, q, *J* = 32.5 Hz), 127.0 (CH), 125.3 (2 x CH, *J* = 3.75 Hz), 123.2 (C), 120.5 (C), 36.0 (C), 29.6 (3 x CH_3), 28.7 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}F_3O_3H$ 339.1208; Found 339.1205.



5bi

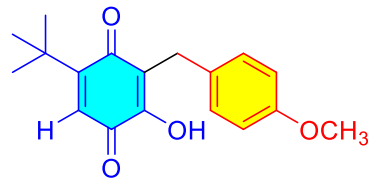
5-(tert-butyl)-2-hydroxy-3-(4-methylbenzyl)cyclohexa-2,5-diene-1,4-dione (5bj): The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.5:9.5 to 1.0:9.0) and isolated as a pale yellow liquid; Yield: 52% (44.3 mg); IR (Neat): ν_{max} 3383, 2959, 1639, 1598, 1376, 1362, 1336, 1217, 1193, 913 and 891 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21 (2H, d, *J* = 7.5 Hz), 7.07 (2H, d, *J* = 7.0 Hz), 6.86 (1H, br s), 3.74 (2H, s), 2.30 (3H, s), 1.28 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135) δ 187.0 (C, *C*=*O*), 184.1 (C, *C*=*O*), 159.2 (C), 150.0 (C), 136.0 (C), 135.8 (C), 129.1 (2 x CH), 128.9 (2 x CH), 126.9 (CH), 121.7



5bj

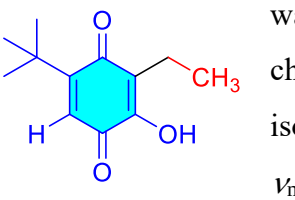
(C), 36.0 (C), 29.6 (3 x CH_3), 28.4 (CH_2), 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}O_3H$ 285.1491; Found 285.1494.

5-(tert-butyl)-2-hydroxy-3-(4-methoxybenzyl)cyclohexa-2,5-diene-1,4-dione (5bk): The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (1.0:9.0 to 2.0:8.0) and isolated as a light brown liquid; Yield: 60% (54 mg); IR (Neat): $\nu_{max,}$ 3339, 2957, 1642, 1599, 1510, 1458, 1378, 1299, 1246, 1220, 1195, 1033, 913, 821 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (2H, d, *J* = 9.0 Hz), 6.80 (2H, d, *J* = 9.0 Hz), 6.54 (1H, s), 3.76 (3H, s), 3.71 (2H, s), 1.27 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 186.9 (C, *C*=*O*), 184.1 (C, *C*=*O*), 159.2 (C), 158.0 (C), 149.9 (C), 131.1 (C), 130.0 (2 x CH), 126.8 (CH), 121.8 (C), 113.8 (2 x CH), 55.2 (CH_3), 35.9 (C), 29.6 (3 x CH_3), 27.9 (CH_2); HRMS (ESI-TOF) m/z: [M-H] Calcd for $C_{18}H_{20}O_4$-H 299.1284; Found 299.1284.



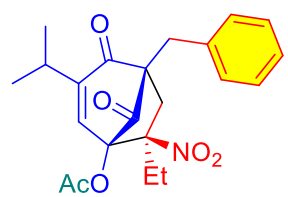
5bk

5-(tert-butyl)-3-ethyl-2-hydroxycyclohexa-2,5-diene-1,4-dione (5bl): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated yellow solid. Yield: 60% (75 mg). MP.: 108-110 ºC; IR (Neat): ν_{max} 3386, 2964, 1639, 1598, 1382, 1361, 1246, 1192, 1115, 891, 742 and 577 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.55 (1H, s), 2.46 (1H, q, *J* = 8.0 Hz), 1.29 (9H, s), 1.07 (3H, t, *J* = 7.5 Hz), ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 187.8 (C, *C*=*O*), 184.1 (C, *C*=*O*), 159.2 (C), 149.7 (C), 126.8 (CH), 124.3 (C), 35.9 (C), 29.6 (3 x CH_3), 16.5 (CH_2), 12.7 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{16}O_3H$ 209.1178; Found 209.1179.



5bl

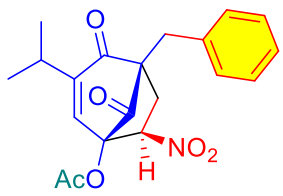
(1*R*,5*S*,7*R*)-5-benzyl-7-ethyl-3-isopropyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10a): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 93% (56 mg). Mp.: 128-130 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IG column (hexane/2-propanol = 90:10 flow rate 0.8 mL/min, λ = 254 nm), t_R = 4.674 min (major), t_R = 6.253 min (minor) [For major isomer]; t_R = 7.554 min (major), t_R = 13.145 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +175.0° [c = 0.100 g/100 mL, $CHCl_3$, 98.8% major *ee*, 86%



(+)-**10a**

minor *ee*, 1.4:1 *dr*]; IR (Neat): ν_{max} 2964, 1784, 1761, 1688, 1546, 1368, 1211, 1017, 962, 846, 737 and 704 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 1.4:1 *dr*, For major isomer): δ 7.35-7.25 (7H, m), 6.78 (1H, d, J = 1.0 Hz), 3.43 (1H, d, *J* = 14.5 Hz), 3.23 (1H, d, *J* = 15.0 Hz). 2.89 (1H, sept, *J* = 7.0, 1.0 Hz), 2.56 (1H, dd, *J* = 15.5, 1.0 Hz), 2.27 (3H, s), 1.62 (1H, d, *J* = 15.5 Hz), 1.08 (3H, d, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 0.40 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, 1.4:1 *dr*, For major isomer): δ 194.5 (C, *C*=*O*), 194.1 (C, *C*=*O*), 168.3 (C), 144.5(C), 141.1 (CH), 135.9 (C), 131.1 (2 x CH), 128.5 (2 x CH), 127.1 (CH), 93.5 (C), 87.5 (CH), 67.1 (C), 31.8 (CH_2), 31.1 (CH_2), 27.6 (CH_2), 27.0 (CH), 21.6 (CH_3), 20.9 (CH_3), 20.4 (CH_3), 7.1 (CH_3); ^1H NMR ($CDCl_3$, 500 MHz, 1.4:1 *dr*, For minor isomer): δ 7.37 (1H, d, *J* = 1.5 Hz), 7.24-7.21 (1H, m), 6.90 (1 H, d, *J* = 1.0 Hz), 3.55 (1H, d, *J* = 15.0 Hz), 3.32 (1H, d, *J* = 14.5 Hz), 2.97 (1H, septet, *J* = 7.0, 1.0 Hz), 2.68 (1H, d, *J* = 15.5 Hz), 2.16 (2H, s), 1.14 (2H, d, *J* = 6.5 Hz), 1.07 (2H, d, *J* = 7.0 Hz), 0.94 (2H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, 1.4:1 *dr*, For minor isomer): δ 195.2 (C, *C*=*O*), 194.1 (C, *C*=*O*), 168.1 (C), 145.7 (C), 141.0 (CH), 136.1 (C), 131.2 (2 x CH), 128.3 (2 x CH), 126.8 (CH), 94.0 (C), 89.2 (C), 66.1 (C), 36.1 (CH_2) 31.7 (CH_2), 31.1 (CH_2), 27.1 (CH_2), 25.5 (CH), 21.4 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 7.3 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{22}H_{29}N_2O_6NH_4$ 417.2026; Found 417.2030.

(1*R*,5*S*,7*R*)-5-benzyl-3-isopropyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-ylacetate

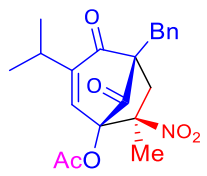


(+)-**10b**

(10b): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 72% (40 mg). Mp.: 124-126 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IG column (hexane/2-propanol = 90:10 flow rate 0.8 mL/min, λ = 254 nm), t_R = 8.106 min (major), t_R = 9.546 min (minor); $[\alpha]_D^{25}$ = +157.0° [c = 0.100 g/100 mL, $CHCl_3$, 70% major *ee*]; IR (Neat): ν_{max} 2967, 1784, 1755, 1681, 1560, 1369, 1213, 1164, 1041, 954, 854, 704, 595, and 508 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.27 (4H, m), 7.32 (1H, tt, *J* = 7.0, 1.5 Hz), 7.01 (1H, d, *J* = 1.0 Hz), 5.17 (1H, d, *J* = 8.0 Hz), 3.46 (1H, d, *J* = 14.5 Hz), 3.39 (1H, d, *J* = 14.5 Hz). 2.91 (1H, sept, *J* = 7.0, 1.0 Hz), 2.56 (1H, dd, *J* = 16.0, 1.0 Hz), 2.20 (3H, s), 2.01 (1H, q, *J* = 8.5 Hz), 1.11 (3H, d, *J* = 7.0 Hz), 1.06 (3H, d, *J* = 6.5 Hz) ; ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 194.8 (C, *C*=*O*), 193.9 (C, *C*=*O*), 168.9 (C), 147 3(C), 137.7 (CH), 135.6 (C), 131.1 (2 x CH), 128.4 (2 x CH), 127.0 (CH), 86.0 (C), 82.3 (CH), 65.1 (C), 31.5 (CH_2), 30.9 (CH_2),

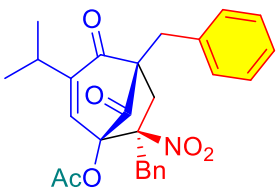
27.3 (CH_3), 21.4 (CH_3), 20.8 (CH), 20.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{20}H_{21}NO_6NH_4$ 389.1713; Found 389.1714.

(1*R*,5*S*,7*R*)-5-benzyl-3-isopropyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10c): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and was isolated white solid. (53 mg). Mp.: 138-140 °C. 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 = 4.789 min (major), t_R = 6.459 min (minor) [For minor isomer]; t_R = 7.958 min (major), t_R = 12.686 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +347.0° [c = 0.100 g/100 mL, $CHCl_3$, 93% major *ee*, 92% minor *ee*, and 14.3:1 *dr*]; IR (Neat): ν_{max} 2960, 1775, 1758, 1687, 1547, 1442, 1370, 1202, 1122, 1031, 927, 847, 761, 705 and 598 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (2H, d, *J* = 7.0 Hz), 7.28 (2H, d, *J* = 7.0 Hz), 7.22 (1H, t, *J* = 7.0, 6.0 Hz), 6.89 (1H, s), 3.52 (1H, d, *J* = 14.5 Hz), 3.34 (1H, d, *J* = 14.5 Hz). 2.98 (1H, pent, *J* = 7.0, 1.0 Hz), 2.66 (1H, d, *J* = 15.5 Hz), 2.17 (3H, s), 1.61 (3H, s), 1.59 (1H, d, *J* = 16.0 Hz), 1.14 (3H, d, *J* = 6.5 Hz), 1.07 (3H, d, *J* = 7.0 Hz), ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 195.1 (C, *C*=*O*), 193.5 (C, *C*=*O*), 168.1 (C), 145.8 (C), 140.1 (CH), 135.9 (C), 131.2 (2 x CH), 128.3 (2 x CH), 126.8 (CH), 89.7 (C), 88.9 (C), 66.4 (C), 38.3 (CH_2), 31.7 (CH_2), 27.1 (CH), 21.5 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 18.5 (CH_3), HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NO_6Na$ 408.1423; Found 408.1421.



(+)-**10c**

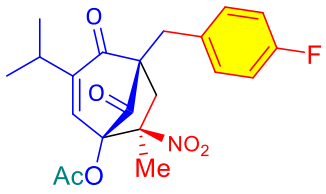
(1*R*,5*S*,7*R*)-5,7-dibenzyl-3-isopropyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10d): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0) and was isolated white solid. (53 mg). Mp.: 126-128 °C. The enantiomeric 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 = 4.654 min (major), t_R = 5.989 min (minor) [For major isomer]; t_R = 7.491 min (major), t_R = 13.381 min (minor) [For minor isomer]; $[\alpha]_D^{25}$ = +86.0° [c = 0.100 g/100 mL, MeOH, 86.7% major *ee*, 35.5 % minor *ee*, and 5.9:1 *dr*]; IR (Neat): ν_{max} 2962, 1776, 1762, 1543, 1494, 1452, 13701242, 1206, 1164, 1032, 978, 920, 789, 732, 702, 594, and 491 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.38 (3H, m), 7.34-7.32 (2H, m), 7.17 (1H, t, *J* = 7.5 Hz), 7.06 (2H, t, *J* = 7.5 Hz), 6.79 (1H, d, *J* = 1.0 Hz), 6.02 (2H, d, *J* =



(+)-**10d**

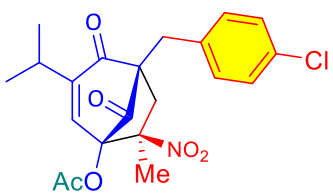
7.5 Hz). 3.77 (1H, d, *J* = 14.5 Hz), 3.49 (1H, d, *J* = 15.0 Hz), 3.26 (1H, d, *J* = 14.5 Hz), 2.88 (1H, septet, *J* = 6.5 Hz), 2.36 (4H, d, *J* = 4.0 Hz), 2.10 (1H, d, *J* = 14.5 Hz), 1.07 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.5 (C, *C*=*O*), 194.2 (C, *C*=*O*), 168.4 (C), 144.7 (C), 140.6 (CH), 136.5 (C), 131.5 (2 x CH), 131.5 (2 x CH), 121.6 (2 x CH), 129.1 (2 x CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 93.6 (C), 87.4 (C), 67.2 (C), 39.6 (CH_2), 30.9 (CH_2), 30.2 (CH_2), 27.0 (CH), 21.6 (CH_3), 20.1 (CH_3), 20.3 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{27}H_{27}NO_6NH_4$ 479.2182; Found 479.2183.

(1*R*,5*S*,7*R*)-5-(4-fluorobenzyl)-3-isopropyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10e): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1:9 to 1.5:8.5), and was isolated as a semi solid. Yield: 80% (48.4 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 0.8 mL/min, λ = 254 nm), t_R = 4.951 min (major), t_R = 7.643 min (minor) [For minor isomer]; t_R = 8.138 min (major), t_R = 14.347 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +181.0° [c = 0.100 g/100 mL, $CHCl_3$, 94% major *ee*, 96% minor *ee*, and 14:1 *dr*]; IR (Neat): ν_{max} 2923, 1785, 1686, 1552, 1508, 1369, 1205, 1007, 844, 761 and 484 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31-7.28 (2H, m), 6.96 (2H, t, *J* = 9.0 Hz), 6.90 (1H, d, *J* = 1.0 Hz), 3.45 (1H, d, *J* = 15 Hz), 3.34 (1H, d, *J* = 15.0 Hz), 2.97 (1H, sept, *J* = 6.5 Hz). 2.63 (1H, d, *J* = 15.5 Hz), 2.17 (3H, s), 1.62 (3H, s), 1.60 (1H, d, *J* = 15.5 Hz), 1.14 (3H, d, *J* = 6.5 Hz) 1.07 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 195.0 (C, *C*=*O*), 193.5 (C, *C*=*O*), 168.1 (C), 161.8 (C, d, *J* = 243.7 Hz), 145.8 (C), 140.2 (CH), 132.7 (2 x CH, d, *J* = 8.75 Hz), 131.5 (C), 115.1 (2 x CH, d, *J* = 20.0 Hz), 89.6 (C), 88.9 (C), 66.3 (C), 38.2 (CH_2), 31.0 (CH_2), 27.1 (CH), 21.5 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 18.5 (CH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ = –115.9; HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{21}H_{22}FNO_6NH_4$ 421.1775; Found 421.1778.



(+)-**10e**

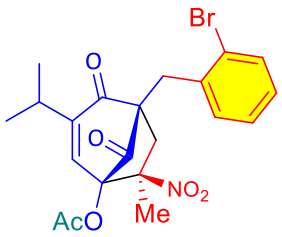
(1*R*,5*S*,7*R*)-5-(4-chlorobenzyl)-3-isopropyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10f); The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and isolated as a pale yellow liquid; Yield: 82% (51.6 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel



(+)-**10f**

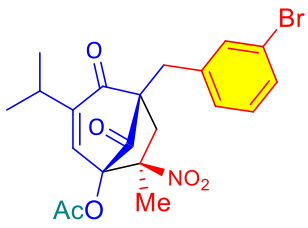
Chiralpak IG column (hexane/2-propanol = 90:10 flow rate 0.7 mL/min, λ = 254 nm), t_R = 4.951 min (major), t_R = 7.643 min (minor) [For minor isomer]; t_R = 7.834 min (major), t_R = 16.045 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +163.2 ° [c = 0.250 g/100 mL, $CHCl_3$, 95% major *ee*, >99% minor *ee*, and >20:1 *dr*]; IR (Neat): ν_{max} 2963 , 2927, 1787, 1767, 1686, 1554, 1369, 1205, 1012 and 847 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28 (2H, d, *J* = 8.5 Hz), 7.24 (2H, d, *J* = 8.5 Hz), 6.90 (1H, s), 3.46 (1H, d, *J* = 15.0 Hz), 3.32 (1H, d, J = 14.5 Hz), 2.96 (1H, sept, *J* = 7.0 Hz), 2.61 (1H, d, *J* = 15.5 Hz), 2.17 (3H, s), 3.15 (1H, dd, *J* = 13.0, 8.0 Hz), 1.14 (3H, d, *J* = 7.0 Hz), 1.07 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 194.9 (C, *C*=O), 193.4 (C, *C*=O), 168.1 (C), 145.8 (C), 140.2 (CH), 134.4 (C), 132.8 (C), 132.5 (2 x CH), 128.4 (2 x CH), 89.7 (C), 88.8 (C), 66.2 (C), 38.3 (CH_2), 31.2 (CH_2), 27.1 (CH), 21.4 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 18.5 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{21}H_{22}ONO_6NH_4$ 437.1479; Found 437.1479.

(1*R*,5*S*,7*R*)-5-(2-bromobenzyl)-3-isopropyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10g): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 90% (63 mg). Mp.: 136-138 °C. The enanantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IG column (hexane/2-propanol = 90:10 flow rate 0.8 mL/min, λ = 254 nm), t_R = 4.639 min (major), t_R = 5.589 min (minor) [For minor isomer]; t_R = 7.006 min (major), t_R = 11.348 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +65.0° [c = 0.100 g/100 mL, $CHCl_3$, 93% major *ee*, 99% minor *ee*, and >20:1 *dr*]; IR (Neat): ν_{max} 2961, 1785, 1689, 1551, 1440, 1370, 1204, 1120, 1007, 914, 846, 735, 629 and 446 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.62 (1H, dd, *J* = 8.0, 1.5 Hz), 7.49 (1H, dd, *J* = 8.0, 1.0 Hz), 7.27 (1H, dt, *J* = 7.5, 1.5 Hz), 7.09 (1H, dt, *J* = 7.5, 2.0 Hz), 6.91 (1H, d, *J* = 1.0 Hz), 3.85 (1H, d, *J* = 15.0 Hz). 3.54 (1H, d, *J* = 15.0, Hz), 2.99 (1H, sept, *J* = 7.0 Hz), 2.55 (1H, d, *J* = 15.5 Hz), 2.16 (3H, s), 1.82 (1H, d, *J* = 15.5 Hz), 1.62 (3H, s), 1.15 (3H, d, *J* = 7.0 Hz), 1.10 (3H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.0 (C, *C*=*O*), 193.5 (C, *C*=*O*), 168.1 (C), 145.5 (C), 140.4 (CH), 135.6 (C), 134.0 (CH), 132.4 (CH), 128.8 (CH), 127.6 (CH), 126.0 (C), 89.6 (C), 88.7 (C), 66.6 (C), 38.0 (CH_2), 30.5 (CH_2), 27.1 (CH), 21.4 (CH_3), 20.7 (CH_3), 20.66 (CH_3), 18.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}BrNO_6Na$ 486.0528; Found 486.0525.



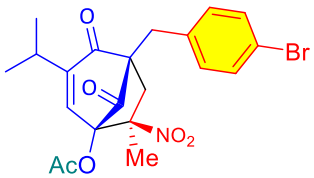
(+)-**10g**

(1*R*,5*S*,7*R*)-5-(3-bromobenzyl)-3-isopropyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10h): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 89% (62 mg). Mp.: 97-99 °C. 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 = 5.018 min (major), t_R = 6.995 min (minor) [For minor isomer]; t_R = 9.077 min (major), t_R = 18.681min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +241.0° [c = 0.100 g/100 mL, $CHCl_3$, 93% major *ee*, 91% minor *ee*, and 19.2:1 *dr*]; IR (Neat): ν_{max} 2964, 1787, 1762, 1687, 1554, 1369, 1204, 1097, 1006, 848, and 734 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.49 (1H, s), 7.36 (1H, d, *J* = 8.0 Hz), 7.29 (1H, d, *J* = 7.5 Hz), 7.15 (1H, t, *J* = 8.0 Hz), 6.90 (1H, s), 3.47 (1H, d, *J* = 14.5 Hz). 3.31 (1H, d, *J* = 14.5 Hz), 2.97 (1H, sept, *J* = 7.0 Hz), 2.61 (1H, d, *J* = 15.5 Hz), 2.18 (3H, s), 1.63 (3H, s), 1.62 (1H, d, *J* = 15.0 Hz), 1.14 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.8 (C, *C*=*O*), 193.2 (C, *C*=*O*), 168.1 (C), 145.8 (C), 140.2 (CH), 138.4 (C), 134.0 (CH), 130.1 (CH), 130.0 (CH), 129.8 (CH), 122.3 (C), 89.7 (C), 88.8 (C), 66.2 (C), 38.3 (CH_2), 31.5 (CH_2), 27.1 (CH), 21.5 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 18.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}BrNO_6Na$ 486.0528; Found 486.0527.



(+)-**10h**

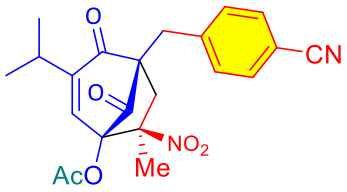
(1*R*,5*S*,7*R*)-5-(4-bromobenzyl)-3-isopropyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10i): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.0:9.0 to 2.0:8.0) and isolated as a light brown liquid; Yield: % (g); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IG column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 4.949 min (major), t_R = 9.906 min (minor). [for minor isomer], t_R = 8.070 min (major), t_R = 16.961 min (minor) (for major isomer]; $[\alpha]_D^{25}$ = +180.0° (c =, $CHCl_3$, 93.8% major *ee,* 66.7% minor ee and 9.7:1 *dr*); IR (Neat): ν_{max} 2963, 1786, 1466, 1687, 1553, 1487, 1369, 1204, 1010, 847, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (2H, d, *J* = 8.5 Hz), 7.22 (2H, d, *J* = 8.0 Hz), 6.89 (1H, s), 3.45 (1H, d, *J* = 14.5 Hz), 3.30 (1H, d, *J* = 14.5 Hz), 2.97 (1H, septet, *J* = 7.0 Hz), 2.61 (1H, d, *J* = 15.5 Hz), 2.17 (3H, s), 1.62 (3H, s), 1.60 (1H, d, *J* = 15.5 Hz), 1.14 (3H, d, *J* = 7.0 Hz), 1.06 (3H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135): δ 194.9 (C, *C*=*O*), 193.4 (C, *C*=*O*),



(+)-**10i**

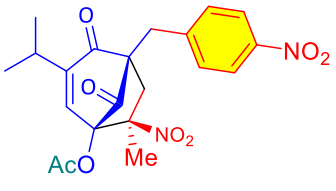
168.1 (C), 145.8 (C), 141.6 (CH), 140.25 (CH), 135.0 (C), 132.9 (2 x CH), 131.4 (2 x CH), 121.0 (C), 89.7 (C), 88.9 (C), 66.2 (C), 38.4 (CH_2), 31.3 (CH_2), 27.1 (CH), 21.5 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 18.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}O_6NBrNa$ 486.0528; Found 486.0529.

(1*R*,5*S*,7*R*)-5-(4-cyanobenzyl)-3-isopropyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10j): The title compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1:9 to 1.5:8.5) and isolated as a light brown semi solid; Yield: 90% (55.4 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IG column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 24.650 min (major), t_R = 49.225 min (minor). $[\alpha]_D^{25}$ = +191.03° (c = 0.290g/100ml, $CHCl_3$, 94.6% *ee* and >20:1 *dr*); IR (Neat): ν_{max} 2958, 2872, 2358, 2227, 1787, 1758, 1686, 1554, 1438, 1367, 1204, 1007, 846, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.57 (2H, d, *J* = 8.0 Hz), 7.47 (2H, d, *J* = 8.0 Hz), 6.92 (1H, s), 3.50 (1H, d, *J* = 14.5 Hz), 3.43 (1H, d, *J* = 14.5 Hz), 2.97 (1H, sept, *J* = 7.0 Hz), 2.56 (1H, d, *J* = 15.5 Hz), 2.17 (3H, s), 1.65 (1H, d, *J* = 15.5 Hz), 1.64 (3H, s) 1.15 (3H, d, *J* = 6.5 Hz), 1.08 (3H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.5 (C, *C*=O), 193.1 (C, *C*=O), 168.1 (C), 145.8 (C), 141.6 (C), 140. 4 (CH), 132.0 (4 x CH), 111.8 (C), 110.9 (C), 89.6 (C), 88.7 (C), 65.9 (C), 38.4 (CH_2), 32.2 (CH_2), 27.1 (CH), 21.4 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 18.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}N_2O_6H$ 411.1556; Found 411.1554.



(+)-**10j**

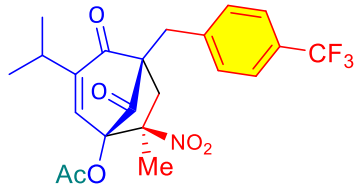
(1*R*,5*S*,7*R*)-3-isopropyl-7-methyl-7-nitro-5-(4-nitrobenzyl)-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10k): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.0:9.0 to 1.5:8.5) and isolated as a light brown liquid; Yield: 96% (61.9 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IG column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 21.413 min (major), t_R = 48.24 min (minor). $[\alpha]_D^{25}$ = +268° (c =, $CHCl_3$, 95.12% *ee* and 11.5:1 *dr*). IR (Neat): ν_{max} 2962, 2922, 2851, 1787, 1766, 1687, 1554, 1518, 1440, 1346, 1206, 1109, 1043, 1009, 849, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.14 (2H, d, *J* = 8.5 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 6.92 (1H, s), 3.54 (1H, d, *J* = 14.5 Hz), 3.48 (1H, d, *J* = 14.5 Hz), 2.97 (1H, septet, *J*



(+)-**10k**

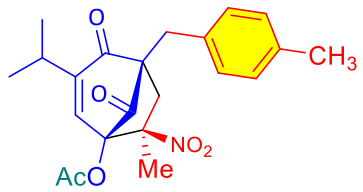
= 6.85 Hz), 2.57 (1H, d, *J* = 15.5 Hz), 2.18 (3H, s), 1.68 (1H, d, *J* = 15.4 Hz), 1.64 (3H, s), 1.15 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135): δ 194.5 (C = O), 193.1 (C, C = O), 168.1 (C = O), 146.9 (C), 145.8 (C), 143.7 (C), 140.5 (CH), 132.1 (2 x CH), 123.4 (2 x CH), 89.6 (C), 88.7 (C), 65.9 (C), 38.4 (CH_2), 31.9 (CH_2), 27.1 (CH), 21.5 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 18.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_2O_8Na$ 453.1274; Found 453.1273.

(1*R*,5*S*,7*R*)-3-isopropyl-7-methyl-7-nitro-4,8-dioxo-5-(4-(trifluoromethyl)benzyl)bicyclo[3.2.1]oct-2-en-1-yl acetate (10l): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated white solid. Mp.: 138-140 °C. Yield: 85% (57.8 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 = 4.499 min (major), [For minor isomer]; t_R = 6.368 min (major), t_R = 12.402 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +295.0° [c = 0.100 g/100 mL, $CHCl_3$, 95.5% major *ee*, >99% minor *ee*, and >20:1 *dr*]; IR (Neat): ν_{max} 2965, 1788, 1687, 1554, 1322, 1205, 1163, 1113, 1065, 1007, 846, 736, 594, and 410 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (2H, d, *J* = 8.0 Hz), 7.47 (2H, d, *J* = 8.5 Hz), 6.91 (1H, d, *J* = 1.0 Hz), 3.56 (1H, d, *J* = 14.5 Hz), 3.40 (1H, d, *J* = 14.5 Hz), 2.97 (1H, sept, *J* = 7.0 Hz). 2.60 (1H, d, *J* = 15.5 Hz), 2.17 (3H, s), 1.63 (1H, d, *J* = 15.5 Hz), 1.63 (3H, s), 1.15 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.8 (*C*, *C*=*O*), 193.3 (*C*, *C*=*O*), 168.1 (*C*), 145.8 (C), 140.3 (CH), 140.2 (C), 131.5 (2 x CH), 129.1 (*C*-CF_3, q, *J* = 32.5 Hz) 125.2 (2 x CH, q, *J* = 3.7 Hz), 124.2 (CF_3, q, *J* = 271.2 Hz), 89.6 (C), 88.8 (C), 66.0 (C), 38.4 (CH_2), 31.8 (CH_2), 27.1 (CH_3), 21.4 (CH_3), 20.7 (CH), 20.6 (CH_3), 18.5 (CH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ = –62.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{22}F_3NO_6Na$ 476.1297; Found 476.1297.



(+)-**10l**

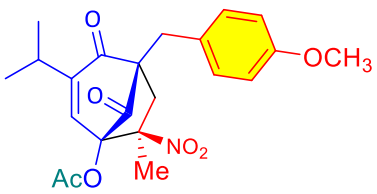
(1*R*,5*S*,7*R*)-3-isopropyl-7-methyl-5-(4-methylbenzyl)-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10m): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 78% (47 mg). Mp.: 105-107 °C. The enantiomeric excess (*ee*) was determined by chiral



(+)-**10m**

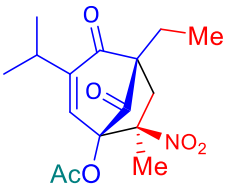
stationary phase HPLC using a Daicel Chiralpak ID column (hexane/2-propanol = 95:05 flow rate 0.8 mL/min, λ = 254 nm), t_R = 7.546 min (major), [For minor isomer]; t_R = 13.553 min (major), t_R = 26.552 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +297.0° [c = 0.100 g/100 mL, $CHCl_3$, 94% major *ee*, >99% minor *ee*, and 23:1 *dr*]; IR (Neat): ν_{max} 2963, 1786, 1686, 1552, 1439, 1368, 1203, 1006, 847, 734, 592 and 471 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.21 (2H, d, *J* = 8.0 Hz), 7.08 (2H, d, *J* = 8.0 Hz), 6.89 (1H, s), 3.48 (1H, d, *J* = 14.5 Hz), 3.29 (1H, d, *J* = 14.5 Hz), 2.97 (1H, sept, *J* = 6.5 Hz). 2.67 (1H, d, *J* = 15.5, Hz), 2.30 (3H, s), 2.16 (3H, s), 1.61 (3H, s), 1.57 (1H, d, *J* = 15.5 Hz), 1.14 (3H, d, *J* = 6.5 Hz). 1.07 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 195.2 (*C*, *C*=*O*), 193.6 (*C*, *C*=*O*), 168.1 (*C*), 145.8 (C), 140.0 (CH), 136.3 (C), 132.8 (C), 131.0 (2 x CH), 128.9 (2 x CH), 89.7 (C), 88.9 (C), 66.5 (C), 38.3 (CH_2), 31.3 (CH_2), 27.1 (CH_3), 21.5 (CH_3), 21.0 (CH), 20.7 (CH_3), 20.6 (CH_3), 18.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{25}NO_6Na$ 422.1580; Found 422.1580.

(1*R*,5*S*,7*R*)-3-isopropyl-5-(4-methoxybenzyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10n): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 88% (55 mg). Mp.: 114-116 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID column (hexane/2-propanol = 95:05 flow rate 0.7 mL/min, λ = 254 nm), t_R = 8.519 min (major), [For minor isomer]; t_R = 15.587 min (major), t_R = 32.717 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +178.0° [c = 0.100 g/100 mL, MeOH, 95.5% major *ee*, >99% minor *ee*, and >20:1 *dr*]; IR (Neat): ν_{max} 2964, 1786, 1685, 1553, 1514, 1369, 1203, 1006, 911, 847, 730 and 486 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.21 (2H, d, *J* = 8.0 Hz), 7.08 (2H, d, *J* = 8.0 Hz), 6.90 (1H, s), 3.50 (1H, d, J = 14.5 Hz), 3.30 (1H, d, *J* = 14.5 Hz), 2.97 (1H, sept, *J* = 7.0 Hz). 2.67 (1H, d, *J* = 15.5 Hz), 2.30 (3H, S), 2.16 (3H, s), 1.60 (3H, s), 1.57 (1H, d, *J* = 15.5 Hz), 1.14 (3H, d, *J* = 6.5 Hz), 1.06 (3H, d, *J* = 7.0 Hz), ^{13}C NMR ($CDCl_3$ 100 MHz, DEPT-135): δ 195.2 (C, *C*=*O*), 193.6 (C, *C*=*O*), 168.1 (C), 145.8 (C), 140.0 (CH), 136.3 (C), 132.8 (C), 131.0 (2 x CH), 128.9.(2 x CH), 89.7 (C), 89.0 (C), 66.5 (C), 38.3 (CH_2), 31.3 (CH_2), 27.0 (CH_3), 21.5 (CH_3), 21.0 (CH), 20.7 (CH_3), 20.6 (CH_3), 18.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{25}NO_7Na$ 438.1529; Found 438.1525.



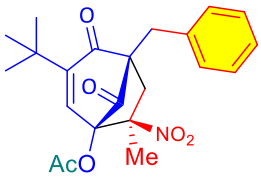
(+)-**10n**

(1*R*,5*S*,7*R*)-5-ethyl-3-isopropyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10o): The title compound was prepared following the procedure **C** purified by column chromatography using EtOAc/hexane (0.7:9.3 to 1.2:8.8) and was isolated as a white solid. Mp.: 145-147 °C. Yield: 82% (40 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 = 7.837 min (major), t_R = 9.353 min (minor); $[\alpha]_D^{25}$ = +261.0° [c = 0.100 g/100 mL, $CHCl_3$, 91.7% *ee* and >20:1 *dr*]; IR (Neat): ν_{max} 2960, 1786, 1755, 1673, 1554, 1448, 1370, 1207, 1055, 848, 594 and 404 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.89 (1H, s), 2.93 (1H, dsept, *J* = 7.0, 1.0 Hz), 2.74 (1H, d, *J* = 15.5 Hz), 2.18 (3H, s), 2.04 (2H, q, *J* = 7.5 Hz), 1.77 (1H, d, *J* = 15.5 Hz). 1.70 (3H, s), 1.12 (3H, d, *J* = 7.0 Hz), 1.09 (3H, t, *J* = 7.5 Hz), 1.07 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 195.5 (C, *C*=*O*), 193.9 (C, *C*=*O*), 168.2 (C), 145.9 (C), 139.9 (CH), 89.8 (C), 88.9 (C), 65.5 (C), 39.3.(CH_2), 26.9 (CH_3), 21.5 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 20.5 (CH_2), 18.8 (CH), 8.01 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{21}NO_6Na$ 346.1267; Found 346.1267.

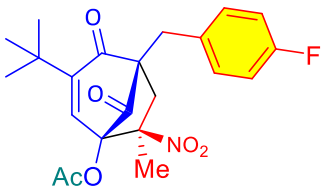


(+)-**10o**

(1*R*,5*S*,7*R*)-5-benzyl-3-(tert-butyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10p): The title compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.0:9.0 to 1.5:8.5) and isolated as a white semi solid. Yield: 93% (55.7 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 10.590 min (major), [for minor isomer], t_R = 16.727 min (major), 31.700 (minor) [for major isomer]; $[\alpha]_D^{25}$ = +194.0° (*c* = 0.100, $CHCl_3$, >98% *ee*); IR (Neat): ν_{max} 2957, 1785, 1762, 1688, 1553, 1364, 1202, 1007 and 704cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.26-7.22 (1H, m), 6.98 (1H, s), 3.51 (1H, d, *J* = 14.5 Hz), 3.36 (1H, d, *J* = 14.5 Hz), 2.66 (1H, *J* = 15.5 Hz), 2.19 (3H, s), 1.62 (3H, s), 1.27 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 194.7 (C, *C*=O), 193.1 (C, *C*=O), 168.1 (C), 147.0 (C), 140.9 (CH), 136.1 (C), 131.2 (2 x CH), 128.3 (2 x CH), 126.8 (CH), 89.6 (C), 88.9 (C), 67.2 (C), 38.2 (CH_2), 35.0 (C), 31.3 (C), 28.5 (3 x CH_3), 20.7 (CH_3), 18.6 (CH_3); HRMS (ESI-TOF) *m/z*: $(M + H^+)$ calcd for $C_{22}H_{25}NO_6NH_4$ 417.2026; Found 417.2024.

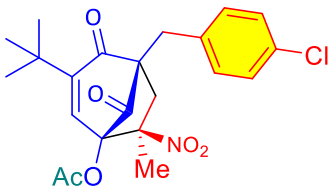


(1*R*,5*S*,7*R*)-3-(tert-butyl)-5-(4-fluorobenzyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10q): The title compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.0:9.0 to 1.5:8.5) and isolated as a white solid. Mp.: 145-147 °C. Yield: 96% (60 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 = 6.311 min (major), t_R = 14.004 min (minor). $[\alpha]_D^{25}$ = +108.47° (c = 0.118g/100ml, $CHCl_3$, 97% *ee* and 13.7:1 *dr*). IR (Neat): ν_{max} 3309, 1786, 1689, 1553, 1508, 1365, 1262, 1218, 1029, 848, 799, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.28 (2H, m), 6.98-6.94 (3H, m), 3.42 (1H, d, *J* = 14.5 Hz), 3.32 (1H, d, *J* = 15.0 Hz), 2.60 (1H, d, *J* = 15.0 Hz), 2.17 (3H, s), 1.62 (3H, s), 1.58 (1H, d, *J* = 15.0 Hz), 1.25 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 194.5 (C, *C*=*O*), 193.1 (C, *C*=*O*), 168.0 (C), 163.0 (C), 160.6 (C), 146.9 (C), 141.1 (CH), 132.6 (2 x CH), 131.6 (C), 115.1 (CH), 114.9 (CH), 89.5 (C), 88.8 (C), 67.1 (C), 38.1 (CH_2), 34.9 (C), 31.1 (CH_2), 28.4 (3 x CH_3), 20.6 (CH_3), 18.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{22}H_{24}FNO_6NH_4$ 435.1932; Found 435.1934.



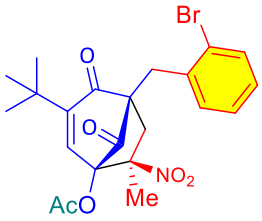
(+)-**10q**

(1*R*,5*S*,7*R*)-3-(tert-butyl)-5-(4-chlorobenzyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10r): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 86% (56 mg). Mp.: 165-167 °C. 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 = 4.202 min (major), [For minor isomer]; t_R = 6.174 min (major), t_R = 14.963 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +231.0° [c = 0.100 g/100 mL, $CHCl_3$, 94.6% major *ee*, >99.9% minor *ee*, and 4.5:1 *dr*]; IR (Neat): ν_{max} 2960, 1777, 1749, 1685, 1554, 1492, 1438, 1361, 1222, 1134, 1010, 847, 822, 590 and 484 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.22 (5H, m), 6.96 (1H, s), 3.44 (1H, d, *J* = 14.5 Hz), 3.30 (1H, d, *J* = 14.5 Hz), 2.58 (1H, d, *J* = 15.5 Hz), 2.17 (3H, s). 1.62 (3H, s), 1.59 (1H, d, *J* = 15.5 Hz), 1.24 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.5 (C, *C*=*O*), 193.0 (C, *C*=*O*), 168.1 (C), 146.9 (C), 141.0 (CH), 134.5 (C), 132.8 (C), 132.5 (2 x CH), 128.4 (2 x CH), 89.6 (C), 88.9 (C), 66.9 (C), 38.2 (CH_2), 34.9 (C), 31.3 (CH_2), 28.5 (3 x CH_3), 20.7 (CH_3), 18.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{22}H_{29}ClNO_6NH_4$ 451.1638; Found 451.1638.



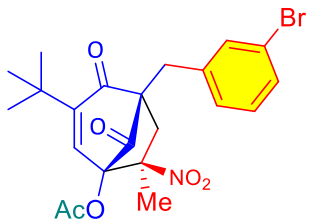
(+)-**10r**

(1*R*,5*S*,7*R*)-5-(2-bromobenzyl)-3-(tert-butyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10s): The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes and isolated as a pale yellow liquid; Yield: 85% (60.8 mg); $[\alpha]_D^{25}$ = +52.5° (*c* = 0.100, $CHCl_3$); IR (Neat): ν_{max} 2927, 1763, 1690, 1551, 1436, 1361, 1276, 1069, 1021, 761 and 602 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.62 (1H, d, *J* = 1.5 Hz), 7.47 (1H, d, *J* = 8.0 Hz), 7.28 (1H, d, *J* = 7.5 Hz), 6.97 (1H, s), 3.81 (1H, d, *J* = 14.5 Hz), 3.52 (1H, d, *J* = 15.0 Hz), 2.53 (1H, d, *J* = 15.5 Hz), 2.16 (3H, s), 1.79 (1H, d, *J* = 16.0 Hz), 1.61 (3H, s), 1.26 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135) δ 193.6 (C, *C*=O), 193.2 (C, *C*=O), 168.2 (C), 146.8 (C), 141.2 (CH), 135.7 (C), 134.1 (CH), 132.5 (CH), 128.8 (CH), 127.6 (CH), 126.1 (C), 89.6 (C), 88.7 (C), 67.3 (C), 38.0 (CH_2), 35.0 (C), 30.7 (CH_2), 28.5 (3 X CH_3), 20.7 (CH_3), 18..6 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{24}BrNO_6NH_4$ 495.1131; Found 495.1131.



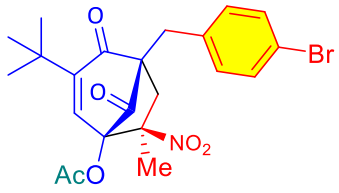
(+)-**10s**

(1*R*,5*S*,7*R*)-5-(3-bromobenzyl)-3-(tert-butyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10t): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 76% (55 mg). Mp.:166-168 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID column (hexane/2-propanol = 95:05 flow rate 0.5 mL/min, λ = 254 nm), t_R = 9.116 min (major), t_R = 14.420 min (minor) [For minor isomer]; t_R = 15.022 min (major), t_R = 36.013 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = 187.0° [c = 0.100 g/100 mL, $CHCl_3$, 95.5% major *ee*, 84% minor *ee*, and >20:1 *dr*]; IR (Neat): ν_{max} 2954, 1779, 1754, 1683, 1594, 1551, 1440, 1363, 1330, 1223, 1070, 877, 825 and 710 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.47 (1H, t, *J* = 2.0), 7.36 (1H, qd, *J* = 8.0 Hz), 7.28 (1H, d, *J* = 7.5 Hz), 7.15 (1H, t, *J* = 8.0 Hz), 6.96 (1H, s), 3.46 (1H, d, *J* = 15.0 Hz). 3.30 (1H, d, *J* = 14.5 Hz), 2.58 (1H, d, *J* = 15.5 Hz), 2.17 (3H, s), 1.63 3(3H, s), 1.25 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.4 (C, *C*=*O*), 192.0 (C, *C*=*O*), 168.1 (C), 146.9 (C), 141.0 (CH), 138.5 (C), 133.9 (CH), 130.0 (CH), 129.9 (CH), 129.8 (CH), 122.3 (C), 89.6 (C), 88.8 (C), 66.9 (C), 38.2 (CH_2), 35.0 (C), 31.6 (CH_2), 28.5 (3 x CH_3), 20.7 (CH_3), 18.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{22}H_{24}BrNO_6NH_4$ 495.1131; Found 495.1131.



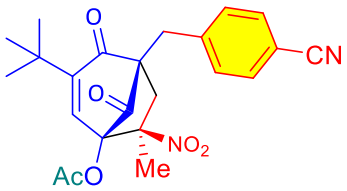
(+)-**10t**

(1*R*,5*S*,7*R*)-5-(4-bromobenzyl)-3-(tert-butyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10u): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 90% (65 mg). Mp.: 152-154 °C. 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 = 4.222 min (major), [For minor isomer]; t_R = 6.475 min (major), t_R = 17.202 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +197.0° [c = 0.100 g/100 mL, $CHCl_3$, 96% major *ee*, >99.9% minor *ee*, and 9.9:1 *dr*]; IR (Neat): ν_{max} 2960, 2360, 1777, 1686, 1593, 1554, 1360, 1278, 1218, 1136, 1069, 1008, 846, 815 and 422 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (2H, td, *J* = 8.5, 2.0 Hz), 7.20 (2H, td, *J* = 8.5, 2.5 Hz), 6.96 (1H, s), 3.43 (1H, d, *J* = 14.5 Hz), 3.28 (1H, d, *J* = 14.5 Hz), 2.58 (1H, d, *J* = 15.5 Hz). 2.17 (3H, s), 1.62 (3H, s), 1.59 (1H, d, *J* = 15.5 Hz); 1.24 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.5 (C, *C*=*O*), 193.0 (C, *C*=*O*), 168.1 (C), 146.9 (C), 141.0 (CH), 135.1 (C), 132.9 (2 x CH), 131.4 (2 x CH), 120.9 (C), 89.6 (C), 88.8 (C), 66.9 (C), 38.2 (CH_2), 35.0 (C), 31.4 (CH_2), 28.5 (3 x CH_3), 20.7 (CH_3), 18.6 (CH_3) HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{22}H_{24}BrNO_6NH_4$ 495.1131; Found 495.1129.



(+)-**10u**

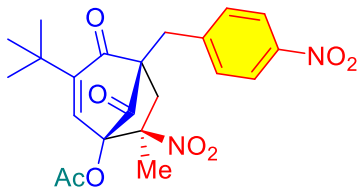
(1*R*,5*S*,7*R*)-3-(tert-butyl)-5-(4-cyanobenzyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10v): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1:9 to 1.5:8.5) and was isolated as a white solid; Mp.: 152-154°C; Yield: 74% (47 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 = 17.468 min (major), t_R = 41.718 min (minor); $[\alpha]_D^{25}$ = +231.0° [c = 0.100 g/100 mL, $CHCl_3$, 97.2% *ee* and >20:1 *dr*]; IR (Neat): ν_{max} 2962, 2224, 1786, 1770, 1685, 1547, 1508, 1360, 1284, 1203, 1184, 1011, 903, 849, 547, 474 and 419 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.57 (2H, d, *J* = 8.5 Hz), 7.45 (2H, d, *J* = 8.5 Hz), 6.98 (1H, s), 3.47 (1H, d, *J* = 14.5 Hz), 3.41 (1H, d, *J* = 14.5 Hz), 2.54 (1H, d, *J* = 15.0 Hz). 2.17 (3H, s), 1.65 (1H, d, *J* = 2.0 Hz), 1.63 (3H, s), 1.25 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.1 (C, *C*=*O*), 192.8 (C, *C*=*O*), 168.1 (C), 146.9 (C), 141.8 (C), 141.3 (CH), 132.0 (4 x CH), 118.8



(+)-**10v**

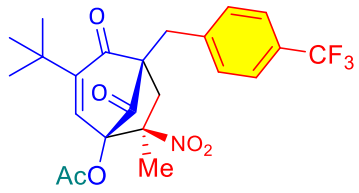
(C), 110.8 (C), 89.6 (C), 88.7 (C), 66.7 (C), 38.2 (CH_2), 35.0 (C), 32.3 (CH_2), 28.5 (3 x CH_3), 20.7 (CH_3), 18.5 (CH_3) HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{23}H_{24}N_2O_6NH_4$ 442.1974; Found 442.1974.

(1*R*,5*S*,7*R*)-3-(tert-butyl)-7-methyl-7-nitro-5-(4-nitrobenzyl)-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10w): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.5:7.5), and was isolated white solid. Yield: 84% (56 mg). Mp.: 186-188 °C. 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 = 7.188 min (major), [For minor isomer]; t_R = 15.742 min (major), t_R = 43.829 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +201.0° [c = 0.100 g/100 mL, $CHCl_3$, 98% major *ee*, >99.9% minor *ee*, and 5.2:1 *dr*]; IR (Neat): ν_{max} 2941, 1786, 1753, 1687, 1557, 1512, 1342, 1204, 1188, 1070, 850, 707, 565 and 482 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.13 (2H, d, *J* = 8.5 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 6.99 (1H, s), 3.50 (2H, d, *J* = 6.5 Hz), 2.56 (1H, d, *J* = 15.5 Hz), 2.18 (3H, S). 1.68 (1H, d, *J* = 15.5 Hz), 1.63 (3H, s), 1.25 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 194.0 (C, *C*=*O*), 192.7 (C, *C*=*O*), 168.1 (C), 146.9 (C), 143.9 (C), 141.3 (CH), 132.1 (2 x CH), 123.4 (2 x CH), 89.5 (C), 88.6 (C), 66.6 (C), 38.2 (CH_2), 35.0 (C), 32.0 (CH_2), 28.5 (3 x CH_3), 20.7 (CH_3), 18.5 (CH_3) HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{22}H_{24}N_2O_8NH_4$ 462.1876; Found 462.1870.



(+)-**10w**

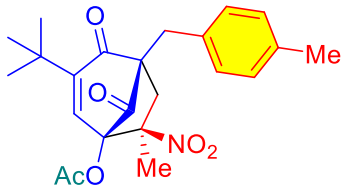
(1*R*,5*S*,7*R*)-3-(tert-butyl)-7-methyl-7-nitro-4,8-dioxo-5-(4-(trifluoromethyl)benzyl)bicyclo[3.2.1]oct-2-en-1-yl acetate (10x): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.5:7.5), and was isolated white solid. Mp.: 130-132 °C. Yield: 94% (66 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 5.267 min; $[\alpha]_D^{25}$ = +236.0° [c = 0.100 g/100 mL, $CHCl_3$, >99.9% *ee* and >20:1 *dr*]; IR (Neat): ν_{max} 2940, 1786, 1767, 1688, 1557, 1365, 1321, 1206, 1187, 1110, 1065, 1011, 849, 595, and 431 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.53 (2H, d, *J* = 8.0 Hz), 7.46 (2H, d, *J* = 8.0 Hz), 6.97 (1H, s), 3.54 (1H, d, *J* = 14.5 Hz), 3.39 (1H, d, *J* = 14.5 Hz), 2.57 (1H, d, *J* = 15.5 Hz). 2.17 (3H, s), 1.62 (3H, s), 1.62



(+)-**10x**

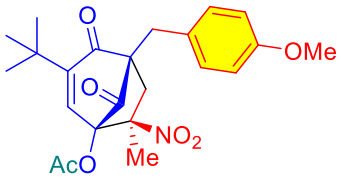
(1H, d, *J* = 15.5 Hz) 1.25 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 194.4 (C, *C*=*O*), 192.9 (C, *C*=*O*), 168.1 (C), 147.0 (C), 141.0 (2 x CH), 140.3 (C), 131.5 (2 x CH), 129.1 (C, CF_3, *J* = 33.0 Hz), 125.2 (2 x CH, *J* = 4.0 Hz), 89.6 (C), 88.8 (C), 66.8 (C) 38.3 (CH_2), 35.0 (C), 31.9 (CH_2), 28.5 (3 x CH_3), 20.7 (CH_3), 18.6 (CH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −62.5; HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{23}H_{24}F_3NO_6NH_4$ 485.1899; Found 485.1898.

(1*R*,5*S*,7*R*)-3-(tert-butyl)-7-methyl-5-(4-methylbenzyl)-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10y): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Yield: 80% (50 mg). Mp.: 156-158 °C. 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 = 4.994 min (major), [For minor isomer]; t_R = 7.277 min (major), t_R = 17.321 min (minor) [For major isomer]; $[\alpha]_D^{25}$ = +263.0° [c = 0.100 g/100 mL, $CHCl_3$, 96% major *ee*, >99.9% minor *ee*, and 24:1 *dr*]; IR (Neat): ν_{max} 2962, 1778, 1752, 1686, 1546, 1445, 1360, 1274, 1219, 1198, 1133, 1070, 848, 592 and 476 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20 (2H, d, *J* = 8.0 Hz), 7.07 (2H, d, *J* = 8.0 Hz), 6.95 (1H, s), 3.50 (1H, d, *J* = 14.5 Hz), 3.28 (1H, d, *J* = 14.5 Hz), 2.64 (1H, d, *J* = 15.5 Hz). 2.30 (3H, s), 2.16 (3H, s), 1.61 (3H, s) 1.57 (1H, d, *J* = 15.5 Hz), 1.24 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.8 (C, *C*=*O*), 193.2 (C, *C*=*O*), 168.1 (C), 147.0 (C), 140.8 (CH), 136.3 (C), 133.0 (C), 131.0 (2 x CH), 129.0 (2 x CH), 89.6 (C), 88.9 (C), 67.3 (C), 38.2 (CH_2), 34.9 (C), 31.4 (CH_2), 28.5 (3 x CH_3), 21.0 (CH_3), 20.7 (CH_3),18.6 (CH_3) HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{23}H_{27}NO_6NH_4$ 431.2183; Found 431.2183.



(+)-**10y**

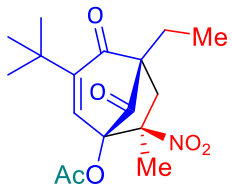
(1*R*,5*S*,7*R*)-3-(tert-butyl)-5-(4-methoxybenzyl)-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10z): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.0:9.0 to 2.0:8.0) and isolated as a light brown liquid; Yield: 60% (38.6 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel ID column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.025 min (major), t_R = 33.048 min (minor). $[\alpha]_D^{25}$ = +108.24° (c = 0.085g/100ml, $CHCl_3$, 89% *ee* and >99:1 *dr*), IR (Neat): ν_{max} 3329, 2968, 2161, 2026, 1737,



(+)-**10z**

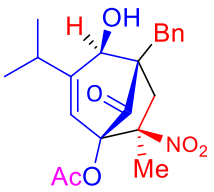
1466, 1377, 1306, 1159, 1127, 949, 815, 655 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.23 (2H, d, *J* = 8.5 Hz), 6.95 (1H, s), 6.80 (2H, d, *J* = 9.0 Hz), 3.77 (3H, s) 3.40 (1H, d, *J* = 15 Hz), 3.26 (1H, d, *J* = 15.0 Hz), 2.63 (1H, d, *J* = 15.5 Hz), 2.16 (3H, s), 1.61 (3H, s), 1.56 (1H, d, *J* = 15.5 Hz) 1.24 (9H, s); ^{13}C NMR ($CDCl_3$, 100MHz, DEPT-135): δ 194.8 (C, *C=O*), 193.3 (C, *C=O*), 168.1 (C), 158.4 (C), 147.0 (C), 140.9 (CH), 132.2 (2 x CH), 128.0 (C), 113.7 (2 x CH), 89.6 (C), 88.9 (C), 67.3 (C), 55.1 (CH_3), 38.2 (CH_2), 34.9 (C), 30.9 (CH_2), 28.5 (3 x CH_3), 20.7 (CH_3), 18.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{23}H_{27}NO_7NH_4$ 447.2131; Found 447.2132.

(1*R*,5*S*,7*R*)-3-(tert-butyl)-5-ethyl-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10aa): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated white solid. Mp.:148-150 °C. Yield: 84% (42 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 = 5.818 min (major), t_R = 7.717 min (minor); $[\alpha]_D^{25}$ = +163.0° [c = 0.100 g/100 mL, $CHCl_3$, 94% *ee* and >20:1 *dr*]; IR (Neat): ν_{max} 2941, 1786, 1760, 1677, 1552, 1459, 1390, 1364, 1280, 1191, 1060, 871, and 590 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.96 (1H, s), 2.72 (1H, d, *J* = 15.0 Hz), 2.17 (3H, s), 2.02 (2H, q, *J* = 7.5), 1.76 (1H, d, *J* = 15.5 Hz), 1.70 (3H, s). 1.23 (9H, s), 1.07 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 195.2 (C, *C=O*), 193.7 (C, *C=O*), 168.1 (C), 147.1 (C), 140.8 (CH), 89.7 (C), 88.8 (C), 66.2 (C), 39.1 (CH_2), 34.9 (C), 28.5 (3 x CH_3), 20.7 (CH_3), 20.5 (CH_3), 18.8 (CH_3), 8.01 (CH_3), HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{17}H_{23}NO_6NH_4$ 355.1869; Found 355.1867.

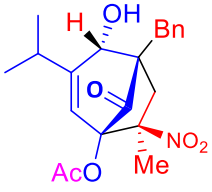


(+)-**10aa**

(1*R*,4*R*,5*S*,7*R*)-5-benzyl-4-hydroxy-3-isopropyl-7-methyl-7-nitro-8-oxobicyclo[3.2.1]oct-2-en-1-yl acetate (12c/13c): The title compound was prepared following the procedure **C**, crude compound was characterised in NMR spectroscopy. The compound is a white semi solid. Yield: 95% (111 mg); $[\alpha]_D^{25}$ = +46.50° [c = 0.100 g/100 mL, $CHCl_3$, 1.6:1 *dr*], IR (Neat): ν_{max} 3464, 2961, 2959, 1778, 1547, 1451, 1385, 1297, 1205, 1033, and 755 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 1.6:1 *dr*, major isomer): δ 7.34-7.20 (5H, m), 5.58 (1H, s), 4.18 (1H, br s), 3.57 (1H, d, *J* = 14.0 Hz), 3.15 (1H, d, *J* = 14.0 Hz), 2.81 (1H, d, *J* = 14.0 Hz), 2.61 (1H, d, *J* = 15.0 Hz), 2.53-2.50 (1H,



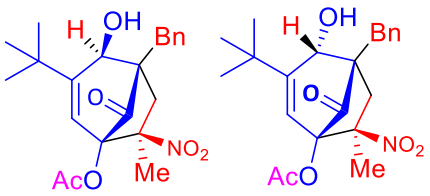
(±)-**12c**



(±)-**13c**

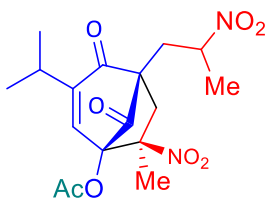
m), 2.09 (3H, s), 1.58 (3H, s), 1.07 (3H, d, *J* = 6.5 Hz), 0.98 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, 1.6:1 *dr*, major isomer): δ 204.1 (C, *C*=*O*), 168.1 (C, *C*=*O*), 146.4 (C), 135.9 (C), 130.4 (2 x CH), 128.5 (2 x CH), 126.8 (CH), 122.5 (CH), 91.2 (C), 86.6 (C), 81.4 (CH), 52.6 (C), 37.3 (CH_2), 34.4 (CH_2), 30.2 (CH_3), 22.0 (CH_3), 21.0 (CH_3), 17.5 (CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz, 1.6:1 *dr*, minor isomer): δ 7.34-7.20 (5H, m), 5.59 (1H, s), 4.60 (1H, br s), 3.22 (1H, d, *J* = 14.0 Hz), 2.53-2.50 (1H, m), 2.47 (1H, d, *J* = 15.5 Hz), 2.34 (1H, d, *J* = 15.5 Hz), 2.05 (3H, s), 1.66 (3H, s), 1.35 (1H, d, *J* = 15.0 Hz), 1.04 (3H, d, *J* = 6.5 Hz), 0.98 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135, 1.6:1 *dr*, minor isomer): δ 199.2 (C, *C*=*O*), 168.5 (C, *C*=*O*), 146.6 (C), 136.9 (C), 130.3 (2 x CH), 128.8 (2 x CH), 127.1 (CH), 124.9 (CH), 91.8 (C), 86.2 (C), 79.5 (CH), 55.3 (C), 40.7 (CH_2), 37.3 (CH_2), 28.9 (CH_3), 21.6 (CH_3), 21.1 (CH_3), 17.5 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{21}H_{25}NO_6NH_4$ 405.2026; Found 405.2028.

(1*R*,4*S*,5*S*,7*R*)-5-benzyl-3-(tert-butyl)-4-hydroxy-7-methyl-7-nitro-8-oxobicyclo[3.2.1]oct-2-en-1-yl acetate (12p/13p): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.0:8.0), and was isolated as a white solid. Mp.: 105-107 °C. Yield: 80% (48 mg); $[\alpha]_D^{25}$ = +85.0° [c = 0.100 g/100 mL, $CHCl_3$], IR (Neat): ν_{max} 3543, 2956, 1778, 1547, 1451, 1384, 1365, 1218, 1194, 1047, 1008, 755, 703 and 422 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.27 (5H, m), 5.76 (1H, s), 4.80 (1H, d, *J* = 4.5 Hz), 3.28 (1H, d, *J* = 14.0 Hz), 3.14 (1H, d, *J* = 14.0 Hz), 2.64 (1H, d, *J* = 15.0 Hz), 2.41 (1H, dd, *J* = 15.0, 1.5 Hz), 2.09 (3H, s) 1.70 (3H, d, *s*), 1.14 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 198.9 (C, *C*=*O*), 168.1 (C, *C*=*O*), 147.6 (C), 137.0 (C), 130.0 (2 x CH), 129.1 (2 x CH), 126.8 (CH), 124.0 (CH), 91.6 (C), 86.3 (C), 80.3 (CH), 55.2 (C), 37.9 (CH_2), 37.8 (CH_2), 35.1 (C), 30.0 (3 x CH_3), 21.1 (CH_3), 17.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{22}H_{27}NO_6NH_4$ 419.2182; Found 419.2183.



(±)-**12p** (±)-**13p**

(1*R*,5*S*,7*R*)-3-isopropyl-7-methyl-7-nitro-5-(2-nitropropyl)-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (10bb): The title compound was prepared following the procedure **G**, purified by column chromatography using EtOAc/hexane (0.9:9.1 to 1.4:8.6), and was isolated as a semi solid. Yield: 84% (32 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID column (hexane/2-propanol = 93:7 flow rate 0.7 mL/min, λ = 254 nm), t_R = 19.151 min (major), t_R = 24.316 min (minor), [For minor isomer]; t_R = 25.967 min (major), t_R = 28.551 min (minor), [For major isomer]; $[\alpha]_D^{27}$ = +23.70º [c = 0.100 g/100 mL, $CHCl_3$, 94% *ee* and 4.5:1 *dr*]; IR (Neat): ν_{max} 2964, 1788, 1764, 1686, 1550, 1446, 1388, 1356, 1200, 1009, 847, 735 and 591 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.90 (1H, s), 4.90 (1H, d sept, *J* = 7.0, 1.5 Hz), 3.0 (1H, q, *J* = 7.5 Hz), 2.93 (1H, pent, *J* = 7.5 Hz), 2.79 (1H, d, *J* = 16.0 Hz), 2.35 (1H, dd, *J* = 16.0, 2.5 Hz). 2.16 (3H, d, *J* = 1.0 Hz), 1.89 (1H, d, *J* = 16.0 Hz), 1.69-1.68 (6H, m), 1.11 (3H, d, *J* = 7.0 Hz), 1.05 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 194.0 (C, *C*=*O*), 193.5 (C, *C*=*O*), 168.0 (C), 145.6 (C), 140.4 (CH), 89.8 (C), 88.3 (C), 79.3 (CH), 64.4 (C), 39.3 (CH_2), 31.9 (CH_2), 27.0 (CH), 22.0 (CH_3), 21.3 (CH_3), 20.6 (CH_3), 20.5 (CH_3) 18.5 (CH_3), HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2O_8Na$ 405.1274; Found 405.1271.



(+)-**10bb**

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5. Total Synthesis of Natural *C*-Alkylated Hydroxyl-1,4-Benzoquinones

5.1 Introduction

Benzoquinones represents a versatile class of compounds containing multiple reactive sites such as C=C and C=O and the inherent feature of these compounds allows the molecules to be manipulated.[1] These molecules play a significant role in biological processes i.e., acts as a carrier in electron transport chain, oxidative phosphorylation and also exhibits anti-inflammatory, antimicrobial and anticancer activities thus providing a compelling motivation for its in-depth study.[1] Although there are several classes of benzoquinones each of them having their own peculiar prominence, our focus is limited to the importance of 2,5-dihydroxy benzoquinone which seems to be a simple structure having intriguing properties. It plays a pivotal role in metal organic frameworks and acts as a key chromophore in many compounds. Some of them include alkyl-1,4-benzoquinones like irisoquins,[2] embelin,[3] rapanone,[4] and polyanoquinones. Irisoquins isolated from *Iris missouriensis* acts as a potential antitumor agent and also exhibits cytotoxic properties. Rapanone and embelin has been showed to elicit a broad range of biological activities including antifertility, antihelmintic and antioxidant properties.[3,4]

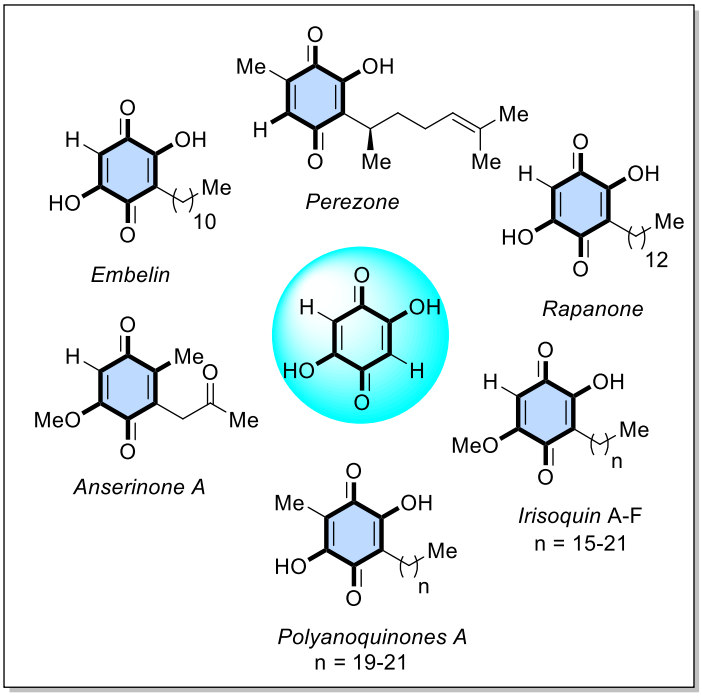


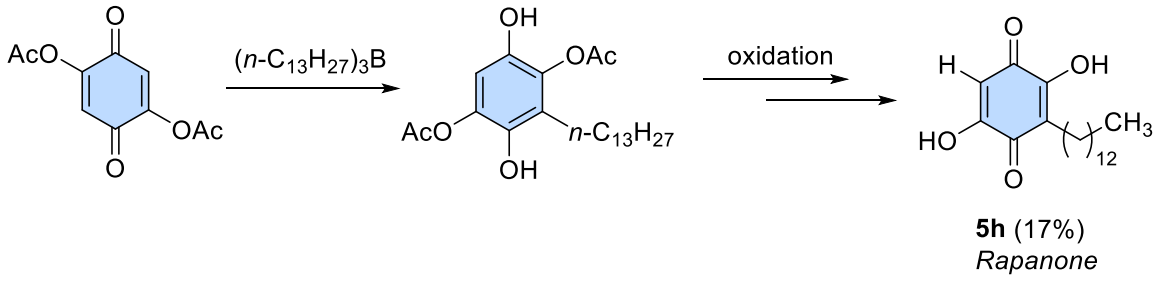
Figure 1: Representative examples of natural products containing hydroxyl-1,4-benzoquinones.

Some of other examples include polyanoquinones, ardisiaquinones and anserinone A demonstrating antifungal, antibacterial and antimicrobial activity. Due to their sheer abundance

and wide range of applications, these classes of compounds have grabbed considerable attention from synthetic chemists all over the world and various approaches have been made to synthesize and investigate them (Figure 1).

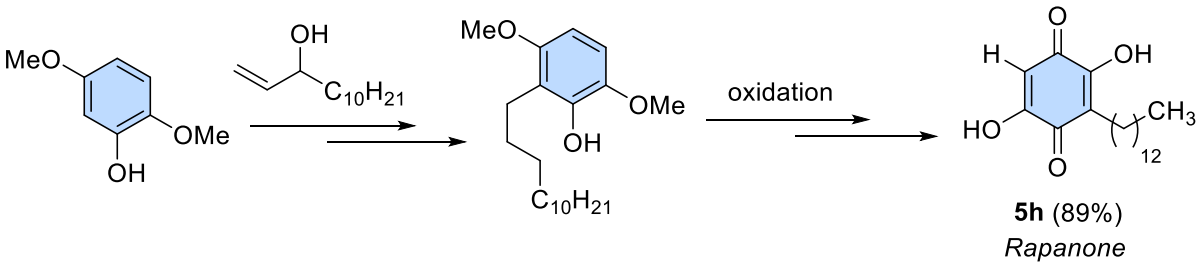
In current scenario, there are several methods describing the synthesis of alkyl 1,4-benzoquinones and some of them include classical approaches such as oxidation of the corresponding phenols. Although this method is least expensive and finds relevance in organic synthesis, prominent amount of by-product formation and extensive steps involved in the reaction encourages us to search for other alternative techniques (Scheme 1).

Maruyama et al (1978);



5h (17%)
Rapanone

Moody et al (2007);

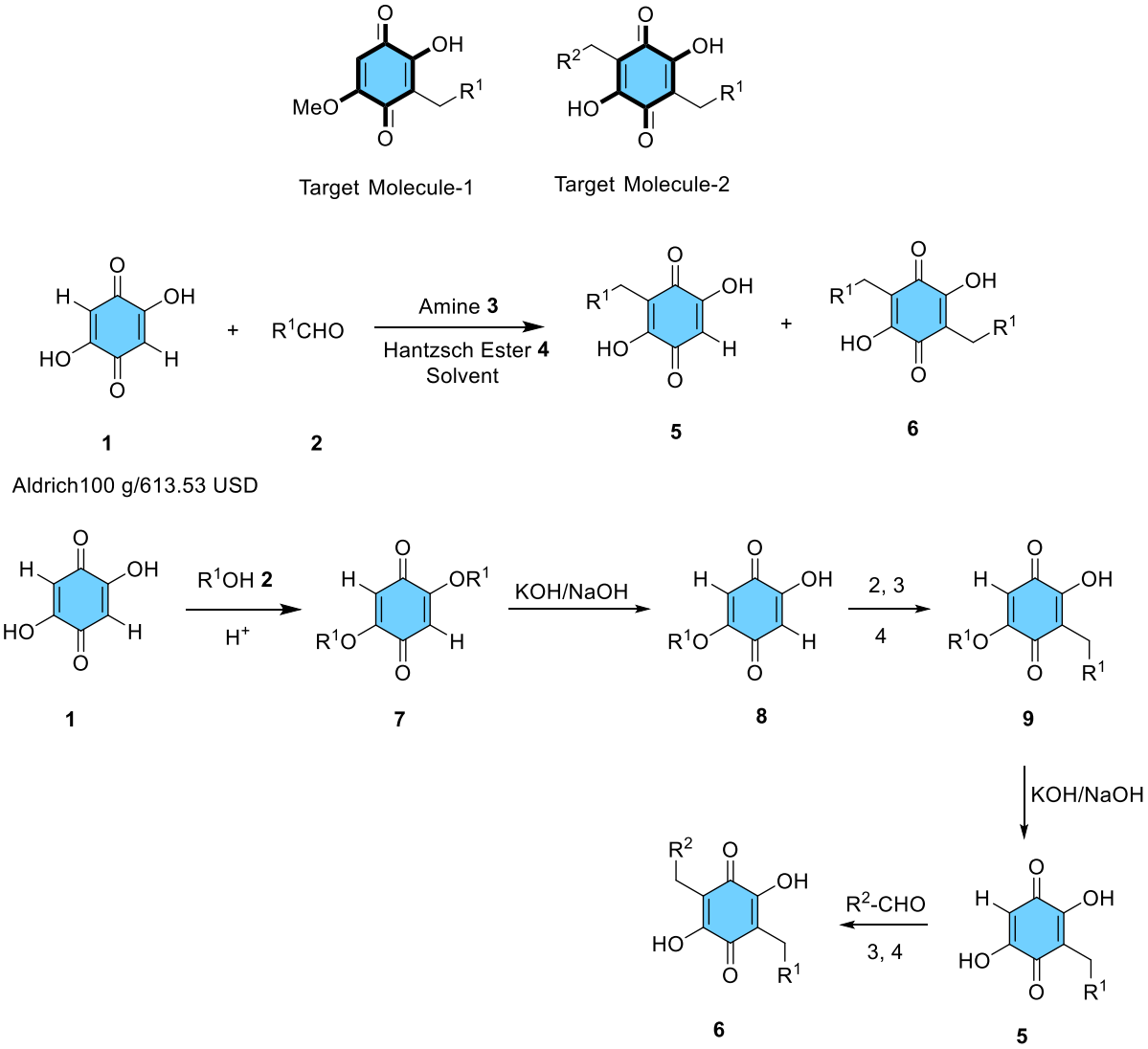


5h (89%)
Rapanone

Scheme 1: Previous strategies for the synthesis of alkyl 1,4-benzoquinones.

Our interest towards developing green reactions motivated us to come forward with a novel reaction design for the synthesis of alkyl 2,5-dihydroxy 1,4-benzoquinones. We chose to react commercially available 2,5-dihydroxy 1,4-benzoquinone **1** in the presence of suitable amine **3** with aldehyde **2** to generate an array of possible products i.e., **5** and **6**. This plausible product formation of **5** and **6** can be explained on the basis of susceptible nucleophilic attack on C_3 and C_6 which can give monoalkylated product **5** and dialkylated product **6**. The regioselective synthesis of **5** can be very much challenging owing to the symmetrical nature of **1**. This prompted us to think of an alternative reaction design which can lead to the selective synthesis of both **5** and **6**. Initially we chose **1** which upon reaction with any suitable alcohol can give **7** which upon selective deprotection with KOH or NaOH may give **8**. Utilizing the scope of

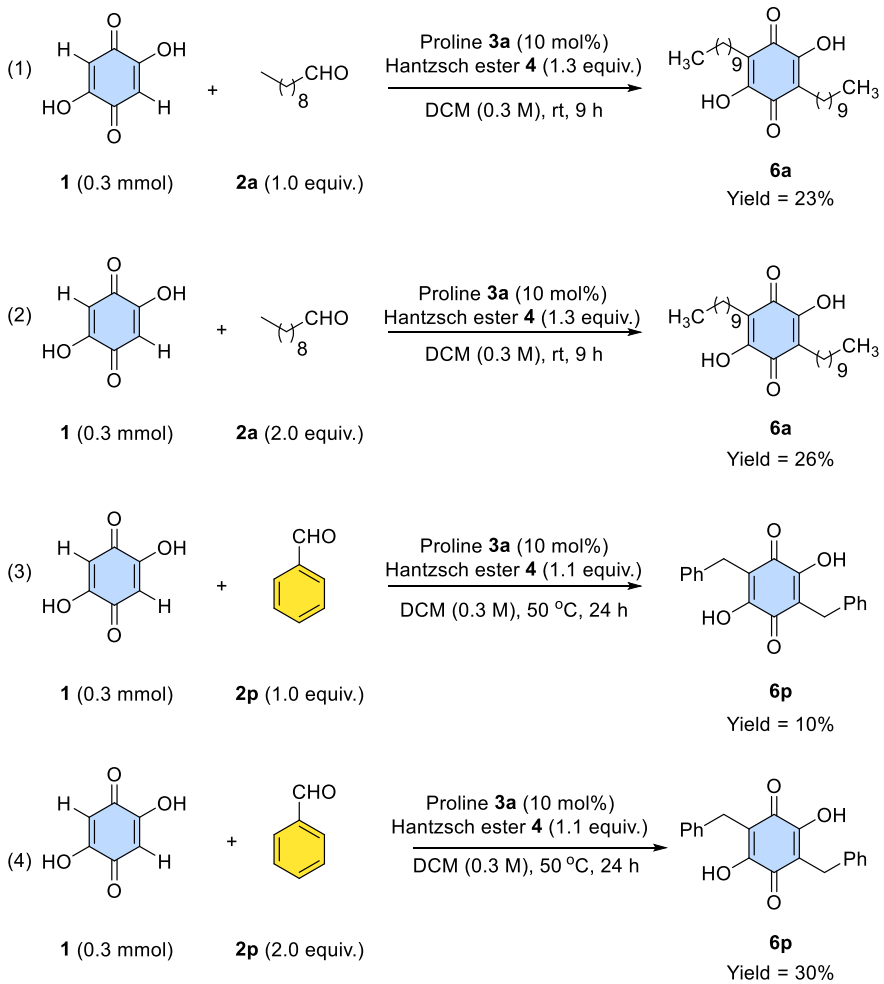
TCRA reaction, **8** can give alkylated product **9**. The alkylated product **9** upon further deprotection with KOH/NaOH can give rise to monoalkylated product **5** selectively. The product **5** upon further treatment with aldehyde **2** can give dialkylated product **6** selectively. This selective formation of **5** and **6** exclusively motivates us to move forward with the reaction design and investigate it in terms of regioselectivity and chemoselectivity (Scheme 2).



Scheme 2: Reaction design for the selective synthesis of **5** and **6**.

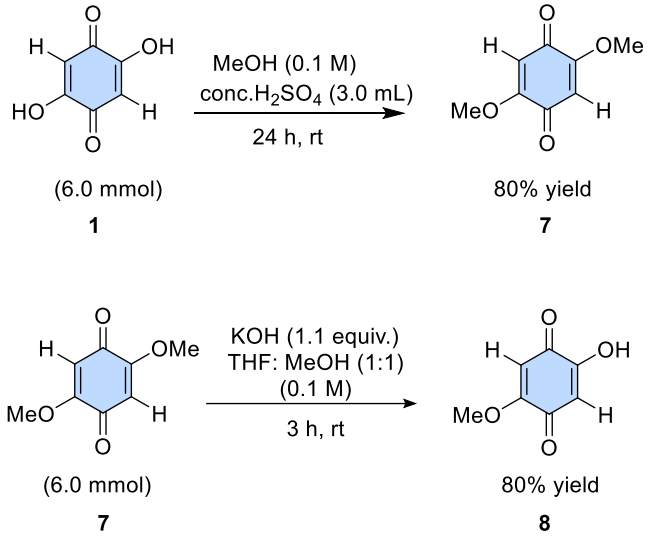
5.2 Initial studies for the proposed reaction design

In accordance with the reaction design, we went onto investigate the reactivity of **1** with both aliphatic and aromatic aldehyde **2**. Initially **1** was treated with 1.0 equiv of decanal **2a** in presence of 10 mol% of proline **3a** and 1.3 equiv. of hantzsch ester **4** in DCM solvent to give dialkylated product **6** exclusively in 9 h with 23% yield at room temperature (Scheme 3, Eq 1). We further altered the equiv. of **2a** to 2.0 equiv. maintaining consistent reaction conditions to observe an exclusive amount of formation of **6a** with 26% yield and no trace amount of **5a** to be detected (Scheme 3, Eq 2). Subsequently, **1** was further treated with aromatic aldehyde **2p** both 1.0 equiv. and 2.0 equiv. in the presence of proline **3a** as the catalyst at 50 °C to give **6p** in 10% yield and 30% yield in 24 h (Scheme 3, Eq 3 & 4). We can infer from the above findings that considerable amount of **6** is formed and **5** nowhere to be found even though the reaction was stirred for longer hours. We pursued an alternative approach to synthesize both **5** and **6** with better yields and better selectivity.



Scheme 3: Initial investigation for the proposed reaction design.

5.3 Synthesis of starting materials: We have synthesized the requisite precursor compounds with a slight modification in the mentioned literature protocol. Primarily, 6.0 mmol of **1** was treated with 0.1 M of methanol in the presence of 3 ml of conc. H_2SO_4 to give 2,5-dimethoxy 1,4-benzoquinone **7** with 80% yield in 24 h at room temperature (Scheme 4). Product **7** was further subjected to selective deprotection with KOH in equimolar amount of THF and methanol to give **8** with 80% yield in 3 h (Scheme 4).



Scheme 4: Synthesis of requisite precursor compounds.

^1H, ^{13}C and DEPT NMR spectra of **7** and **8** from scheme 4 have depicted in figure 2-5

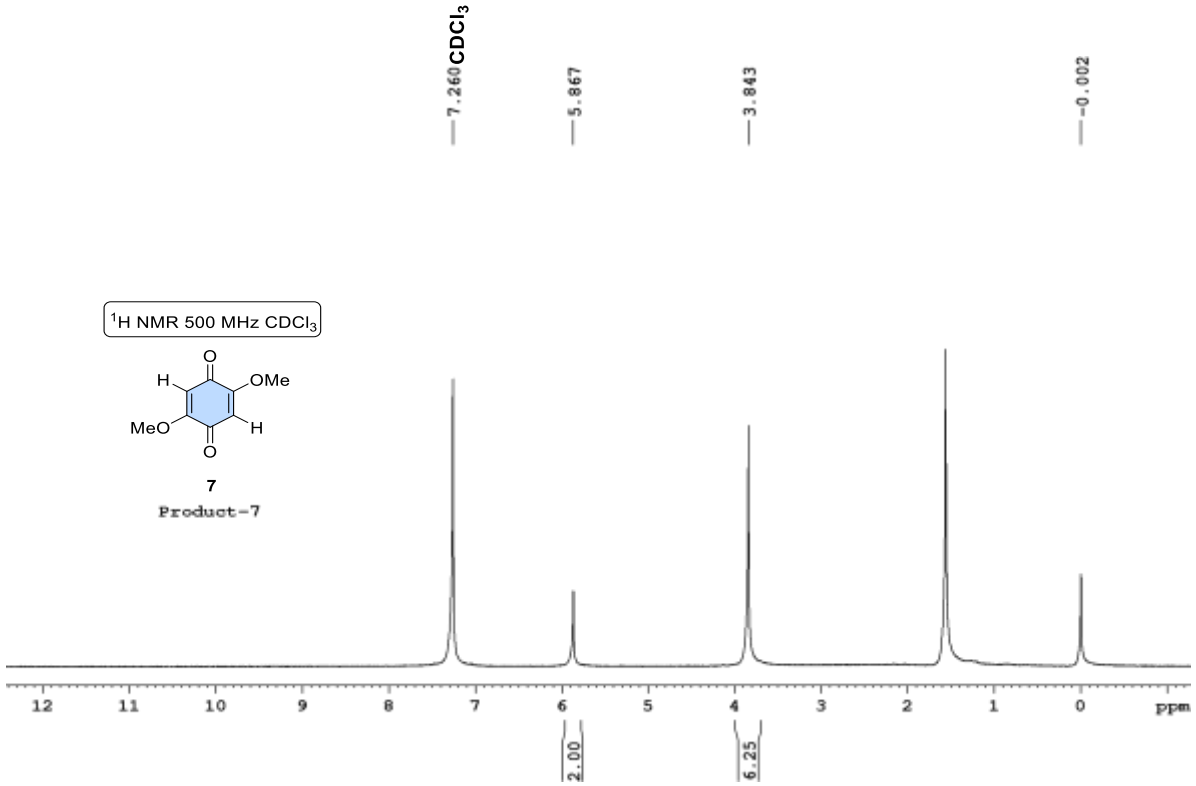


Figure 2: ^1H NMR spectrum of product **7**.

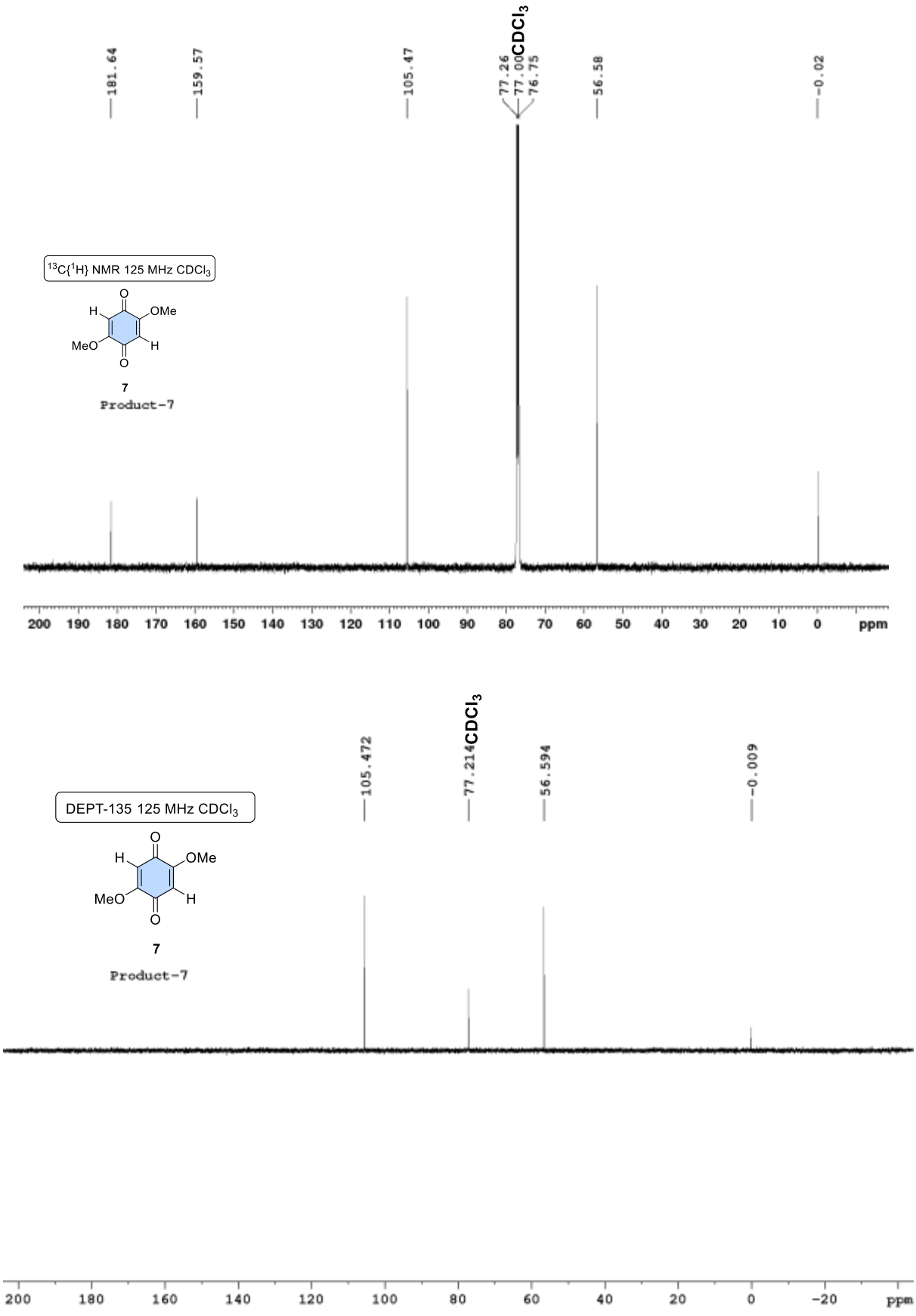


Figure 3: ^{13}C NMR and DEPT NMR spectrum of product **7**.

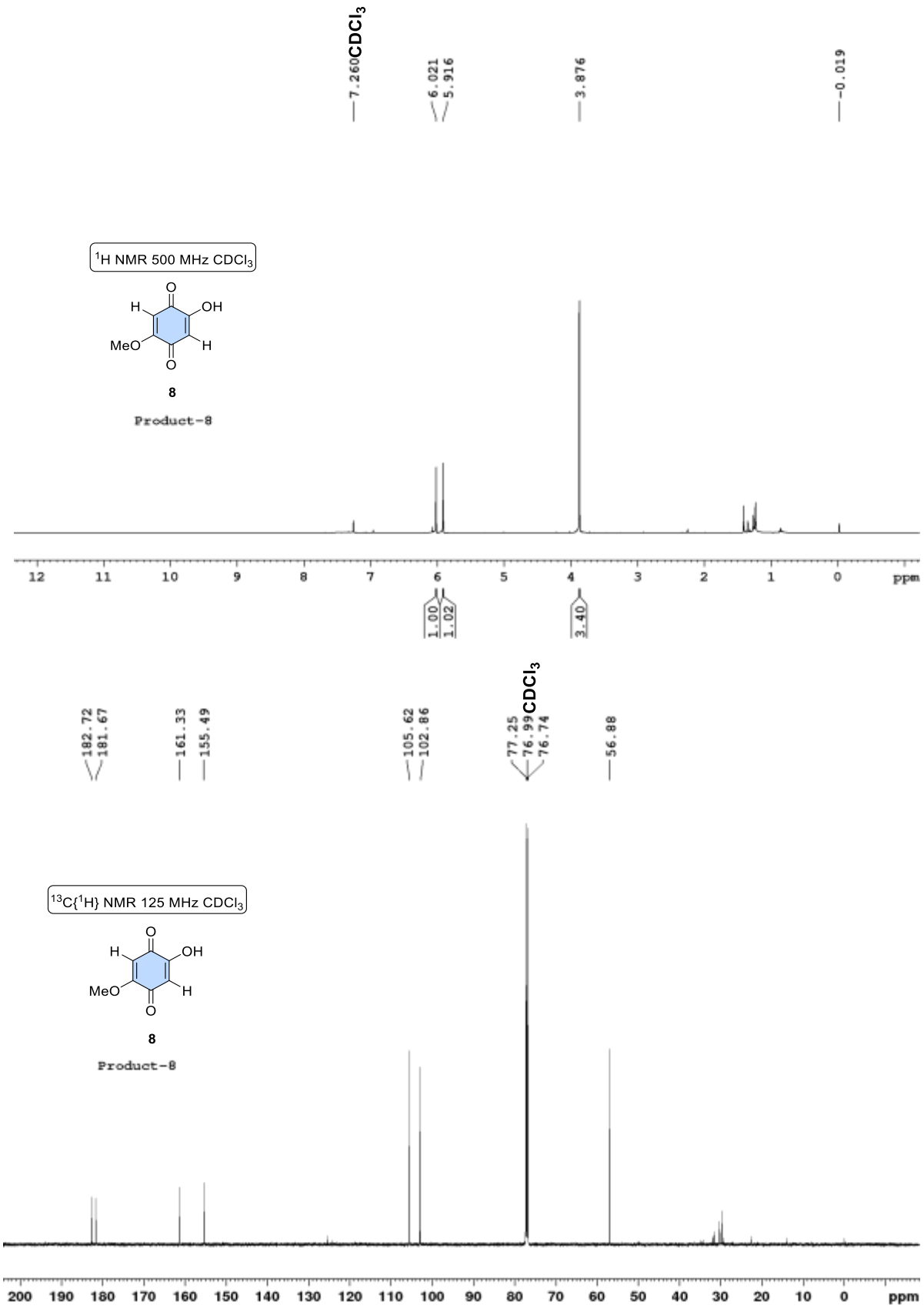


Figure 4: ^{1}H NMR and ^{13}C NMR spectrum of product **8**.

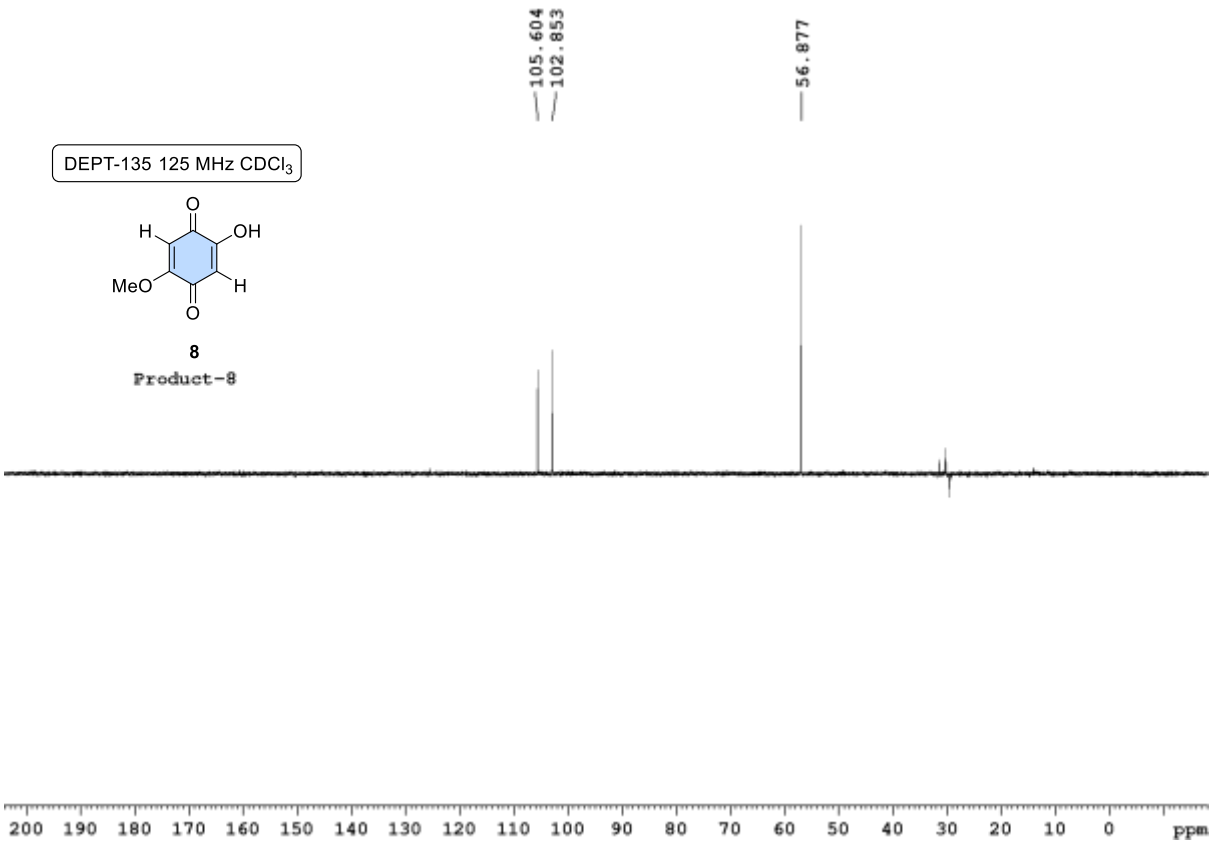
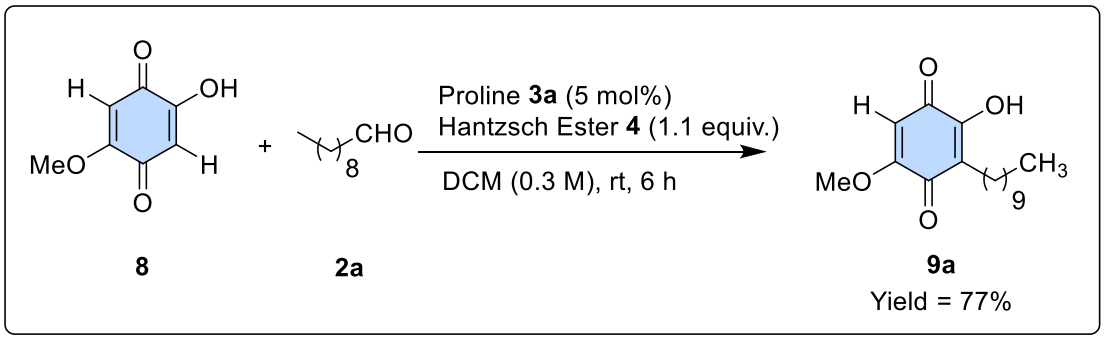


Figure 5: DEPT NMR spectrum of product **8**.

5.4 Results and Discussions:

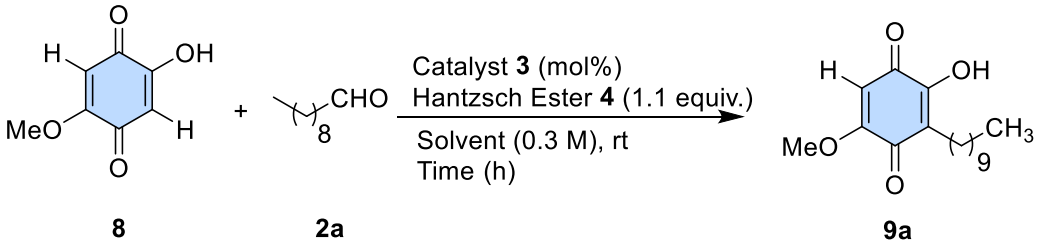
Having all the starting materials in hand, we proceeded with the initial reaction design. In accordance to that **8** was treated with **2a** in the presence of 5 mol% of proline **3a** and 1.1 equiv. of Hantzsch ester in DCM solvent to give 77% yield of monoalkylated product **9a** in 6 h and the structure of **9a** was further confirmed by IR/NMR/Mass experiments (Scheme 5).



Scheme 5: Synthetic strategy for the formation of **9a**.

With the established structure of **9a** in hand, we have tried to optimize the reaction conditions hoping for a better yield. Initially **8** was treated with 10 mol% of proline **3a** in DCM solvent for 5 h to give **9a** in 80% yield (Table 1, entry 2). We increased the catalyst loading from 10 mol% to 15 mol% hoping for a better yield and reaction time. The reaction went for 3.5 h with a diminished yield of 71%. (Table 1, entry 3). The same reaction went for 24 h with 10 mol% of glycine **3b** as the catalyst with a lower yield of 50%. (Table1, entry 4). Varying the catalyst from **3b** to pyrrolidine **3c** with consistent reaction conditions gave 62% yield of **9a** within 1 h and equimolar amount of acetic acid was also used with **3c** resulting in slight variation in the yield (Table 1, entries 5-6). Utilizing 10 mol% of benzylamine **3d** as catalyst, it gave promising results with 82% yield of **9a** within 1 h compared to the reaction with 5 mol% and 15 mol% of **3d** (Table 1, entries 7-9). Although the rate of the reaction was improved while utilizing aniline **3e** as the catalyst, drastic fall in the yield makes it unsuitable to move forward (Table 1, entry 10). We further varied the solvents from DCM to DCE, acetonitrile, THF and ethanol keeping 10 mol% of **3d** constant anticipating for a better yield (Table 1, entries 11-14). From the above findings we concluded that 10 mol% of benzylamine **3d** in 0.3 M DCM solvent with 1.1 equiv. of hantzsch ester **4** is regarded as the ideal condition for continuing forward with the reaction **9a** (Table 1, entry 8).

Table 1: Preliminary investigation of reaction conditions. [a-c]



8 **2a** **9a**

Entry	Catalyst **3** (mol%)	Solvent [0.3 M]	Time [h]	Yield[b] [%]
1	Proline **3a** (5)	DCM	6	77
2	Proline **3a** (10)	DCM	5	80
3	Proline **3a** (15)	DCM	3.5	71
4	Glycine **3b** (10)	DCM	24	50
5	Pyrrolidine **3c** (10)	DCM	1	62
6[c]	Pyrrolidine **3c** 10)	DCM	1.3	75
7	Benzylamine **3d** (5)	DCM	2	70
8	Benzylamine **3d** (10)	DCM	1	82
9	Benzylamine **3d** (15)	DCM	0.7	73
10	Aniline **3e** (10)	DCM	0.7	70
11	Benzylamine **3d** (10)	DCE	1	72
12	Benzylamine **3d** (10)	CH_3CN	4	68
13	Benzylamine **3d** (10)	THF	2	73
14	Benzylamine **3d** (10)	EtOH	5	60

[a] Reactions were carried out in DCM (0.3 M) with 1.0 equiv. of **2a** (0.3 mmol) and 1.1 equiv. of **4** relative to **8** (0.3 mmol) in presence of 10 mol% of **3d** at room temperature. [b] Yield refers to the column-purified product. [c] Reaction was performed utilizing pyrrolidine **3c** and acetic acid as catalyst in equimolar ratio (1:1).

^{1}H, ^{13}C and DEPT NMR spectra of **9a** from Table 1 have depicted in figure 6-7

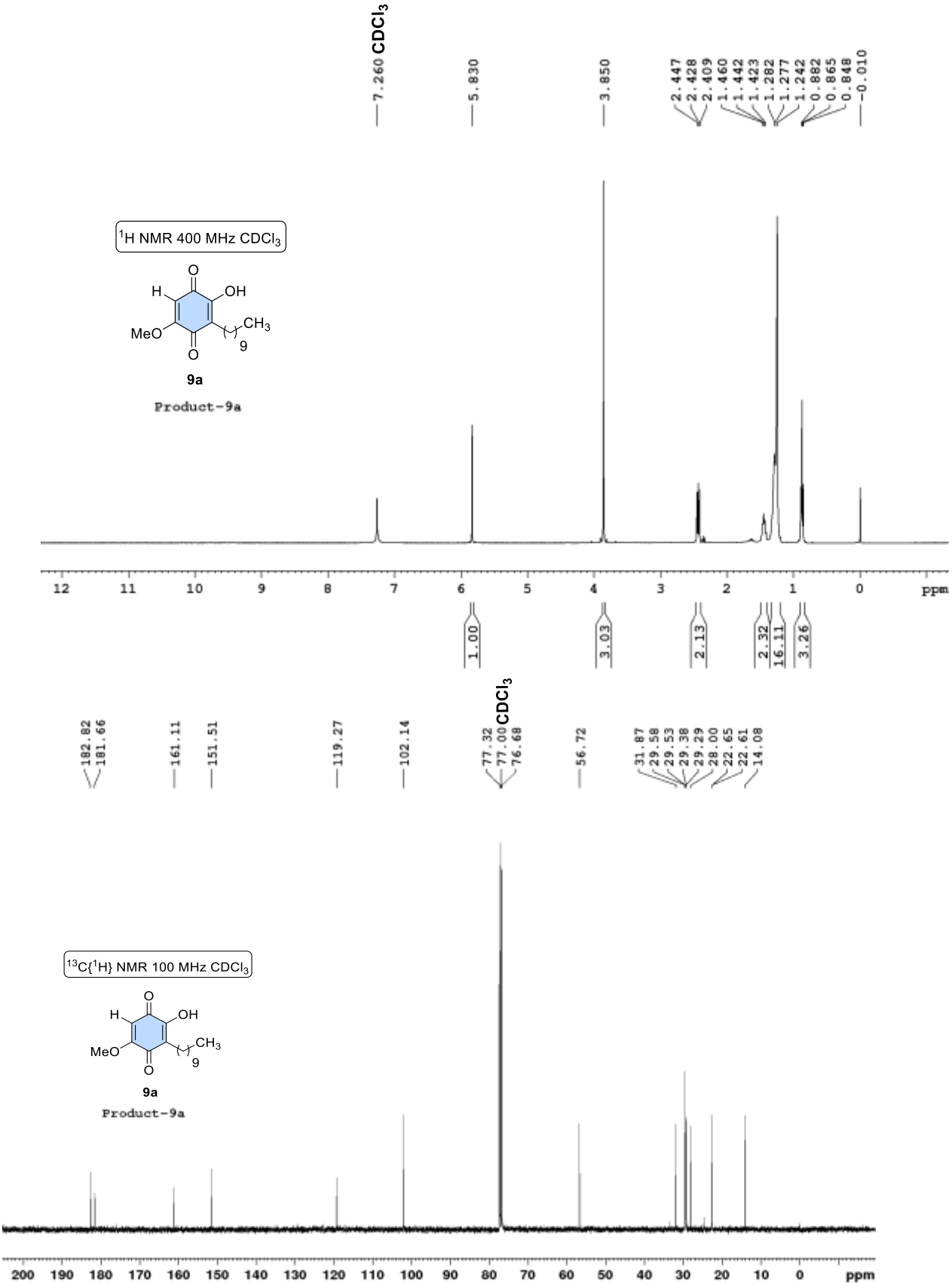


Figure 6: ^{1}H NMR and ^{13}C NMR spectrum of product **9a**.

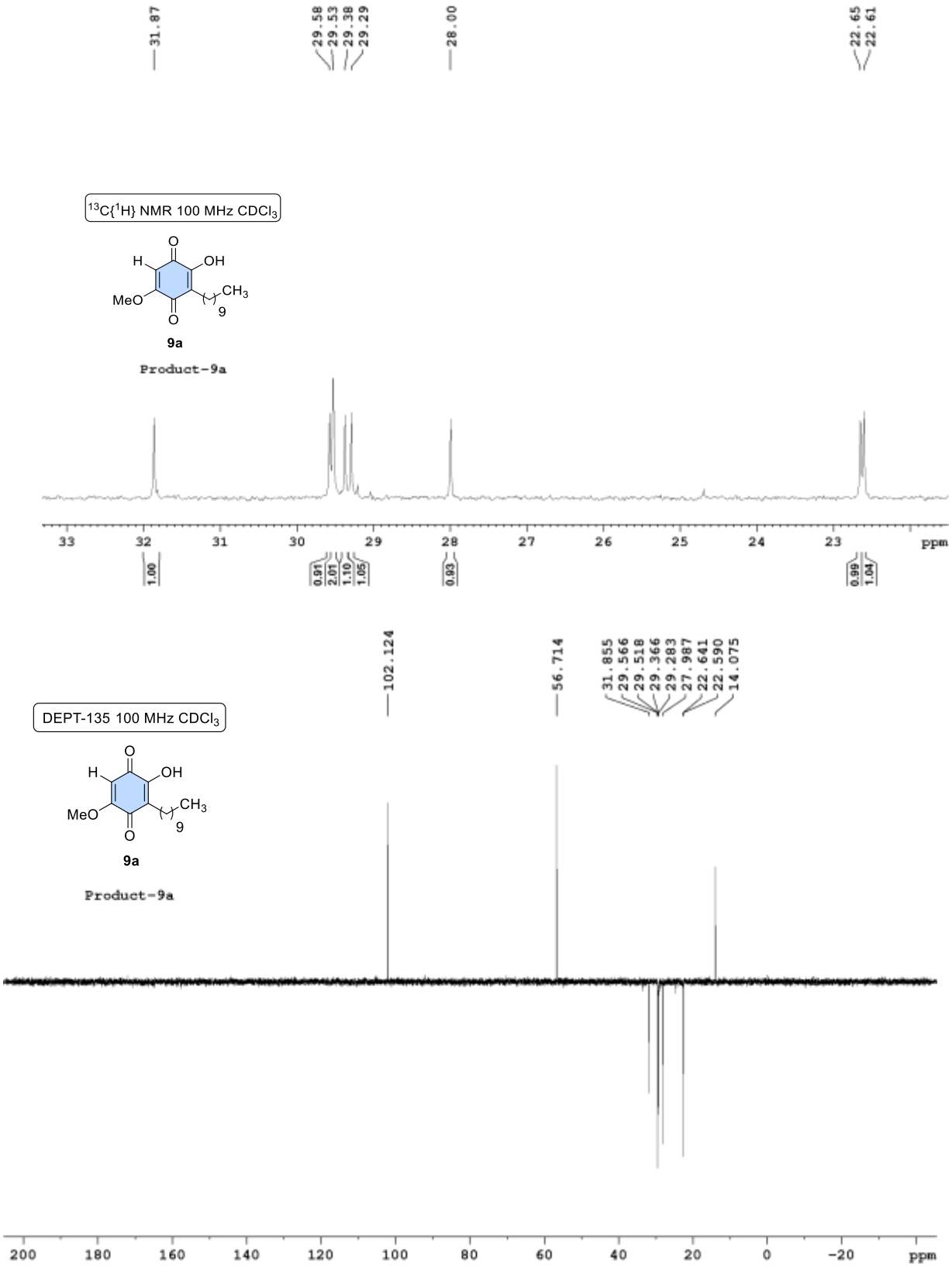
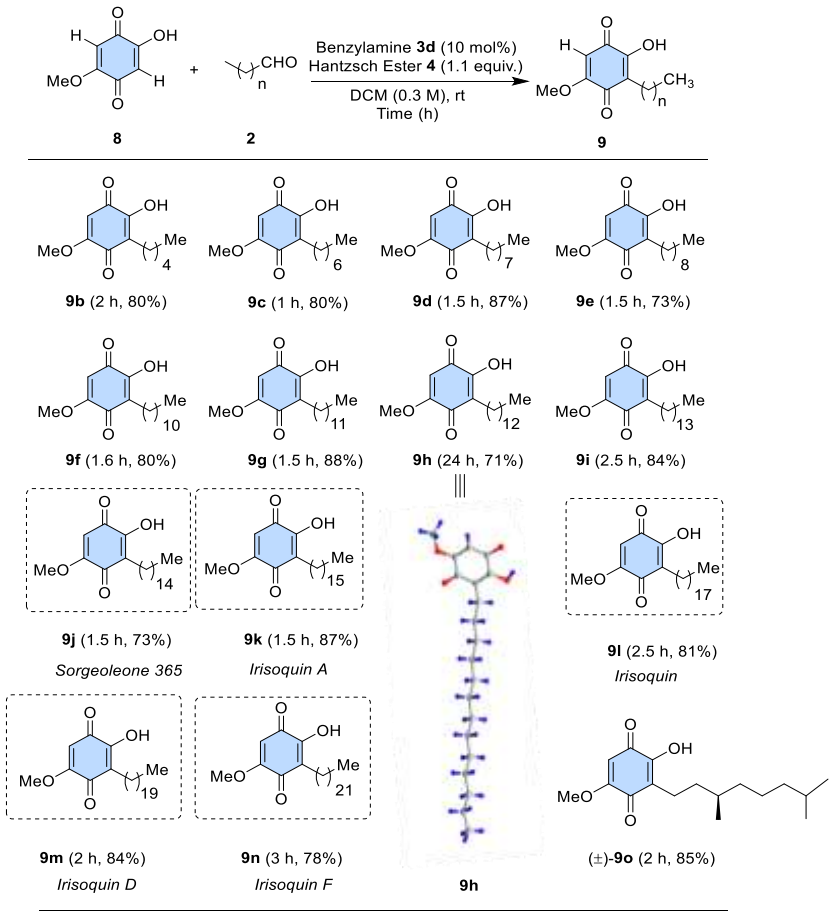


Figure 7: Expanded ^{13}C NMR and DEPT NMR spectrum of product **9a**.

5.4.1 Scope of quinones 8 with aliphatic aldehydes

We further checked the generality of the reaction by treating **8** with aliphatic aldehydes **2** following the optimized reaction conditions. Treatment of **8** with aliphatic aldehydes **2b-2d** gave **9b-9d** within 2 h with 80-87% yield. (Table 2). The same reaction of **8** with nonanal **2e** gave 73% yield of **9e** in 1.5 h (Table 2). Higher membered aldehydes **2f-2i** with **8** gave good yields of **9f-9i** within 1.5-2.5 h excluding **9h** which took 24 h for completion (Table 2). The structure of **9h** was further confirmed by single crystal X-ray diffraction studies. We got natural products sorgeoleone 365 **9j** and irisoquin A **9k** within 1.5 h in good yields by reacting them with linear aldehydes **2j** and **2k** (Table 2). Subjecting aldehydes **2l-2n** under similar reaction conditions gave family of irisoquins **9l-9n** within 3 h (Table 2). Lastly, branched aldehyde i.e., 3,7-dimethyloctanal (±)-**2o** on treatment with **8** gave (±)-**9o** in 85% yield within 2 h (Table 2).

Table 2: Reaction Scope of quinones **8** with aliphatic aldehydes **2.** [a-b]



[a]Reactions were carried out in DCM (0.3 M) with 1.0 equiv. of **2a** and 1.1 equiv. of **4** relative to **8** (0.3 mmol) in the presence of catalyst **3d** (10 mol%) at room temperature. [b] Yield refers to the column-purified product

^{1}H, ^{13}C and DEPT NMR spectra of few compounds from table 2 have been depicted in figure 8-17.

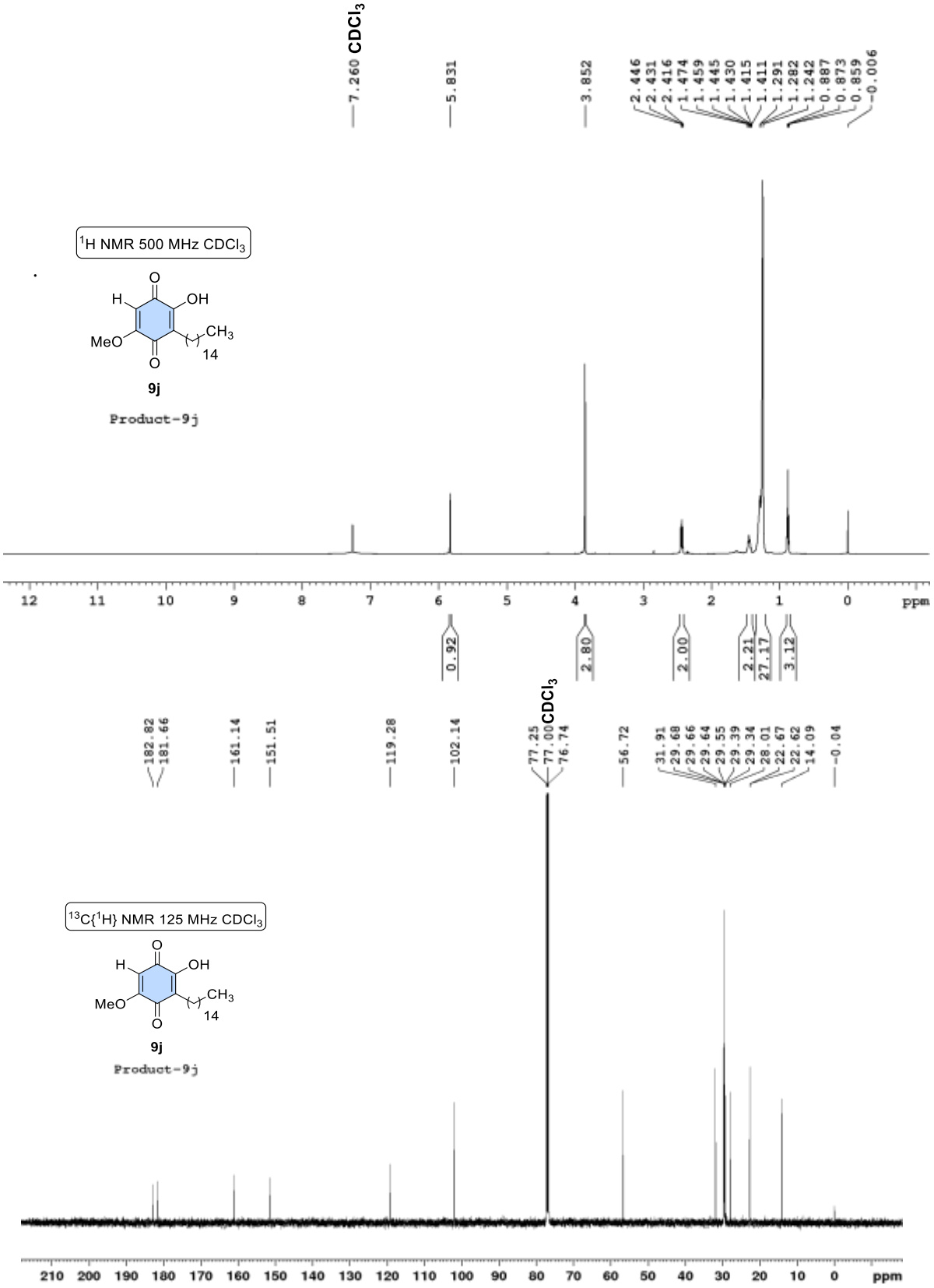


Figure 8: ^{1}H NMR and ^{13}C NMR spectrum of product **9j**.

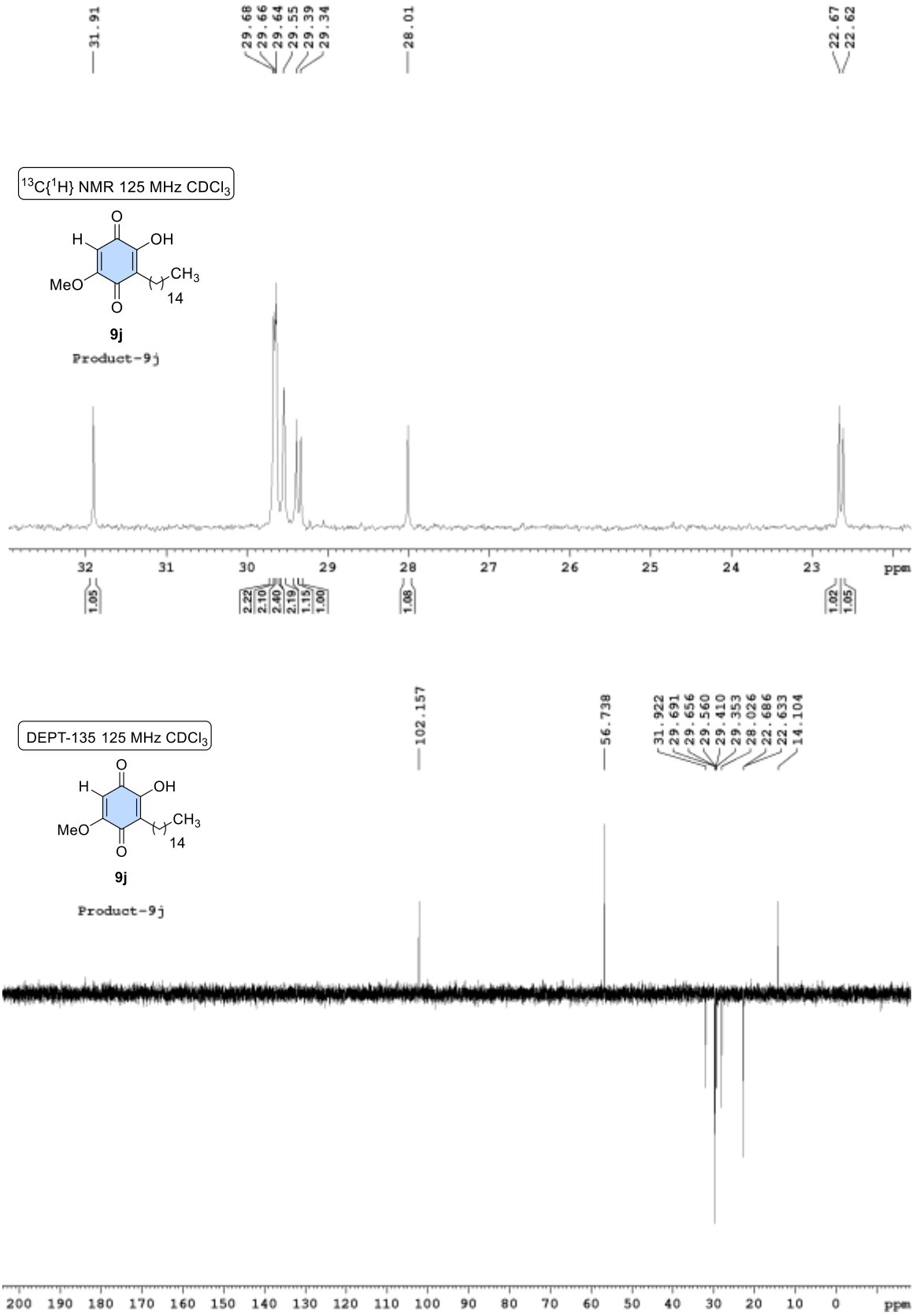


Figure 9: Expanded ^{13}C NMR and DEPT NMR spectrum of product **9j**.

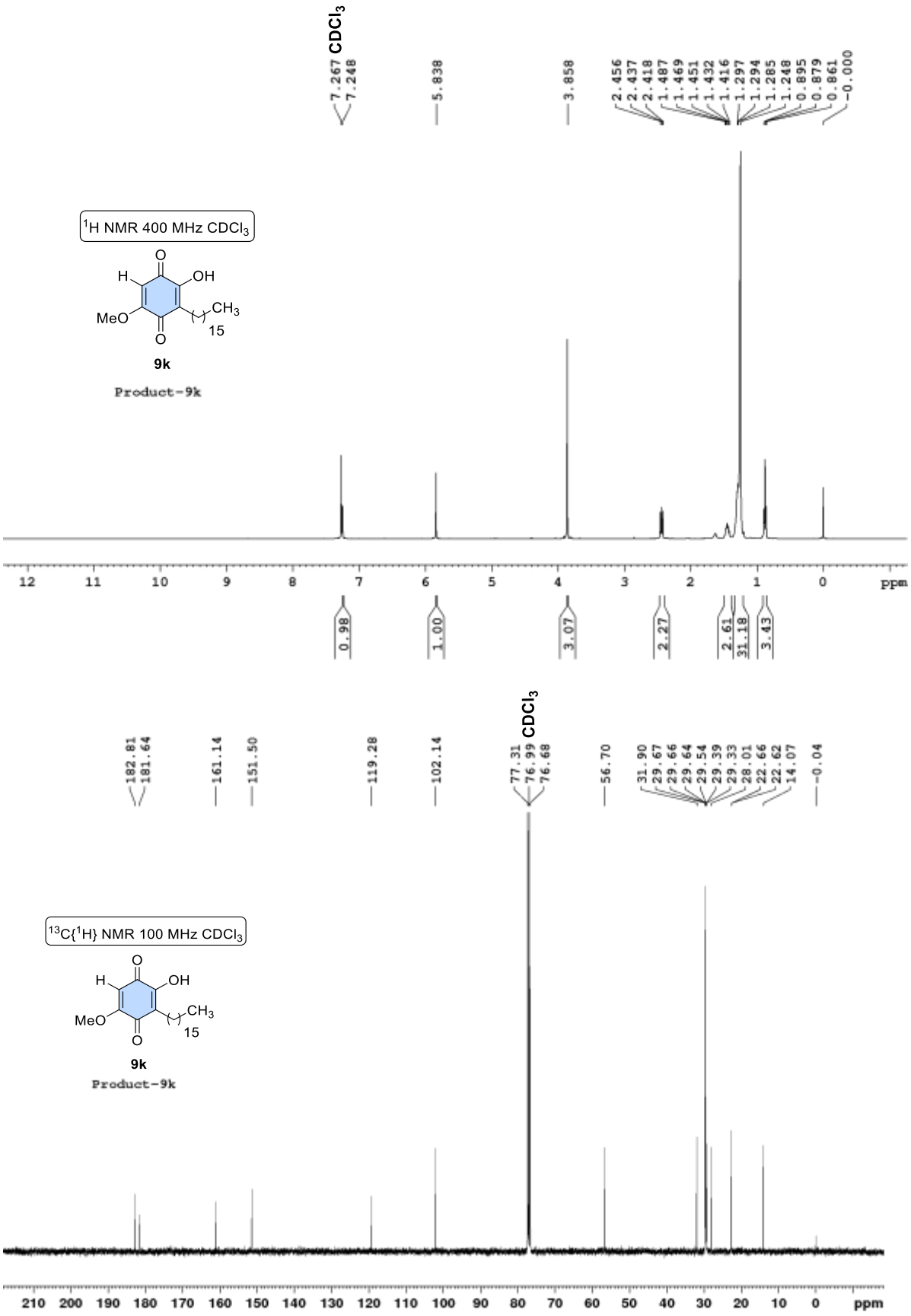


Figure 10: ^{1}H NMR and ^{13}C NMR spectrum of product **9k**.

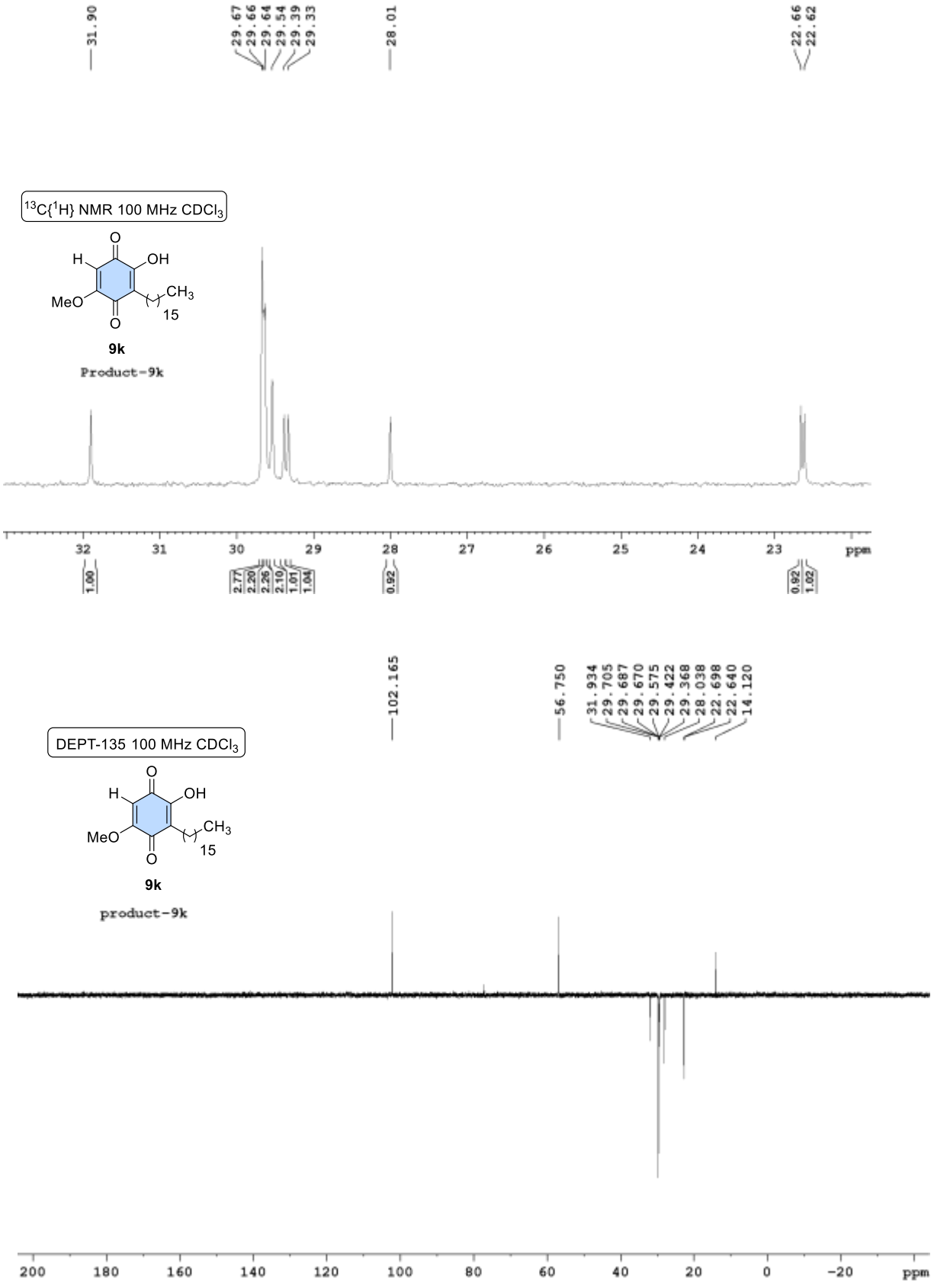
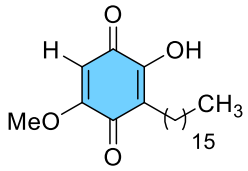


Figure 11: Expanded ^{13}C NMR and DEPT NMR spectrum of product **9k**.

Table 3. Correlation NMR data of compound **9k** (Irisoquin A):[2]

<table>
<tr><td colspan="2" rowspan="6"> 
Irisoquin A
3-ethyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9k)</td><td>Isolated compound ^{13}C NMR (75 MHz, $CDCl_3$)</td><td>Present synthetic compound ^{13}C NMR (100 MHz, $CDCl_3$)</td></tr>
<tr><td>182.8 (C, C=O)</td><td>182.8 (C, C=O)</td></tr>
<tr><td>181.7 (C, C=O)</td><td>181.6 (C, C=O)</td></tr>
<tr><td>161.1 (C)</td><td>161.1 (C)</td></tr>
<tr><td>151.5 (C)</td><td>151.5 (C)</td></tr>
<tr><td>119.3 (C)</td><td>119.3 (C)</td></tr>
<tr><td>Isolated compound ^{1}H NMR (300 MHz, $CDCl_3$)</td><td>Present synthetic compound ^{1}H NMR (400 MHz, $CDCl_3$)</td><td>102.2 (CH)</td><td>102.1 (CH)</td></tr>
<tr><td>7.29 (br s, OH)</td><td>7.25 (br s, OH)</td><td>56.8 (OCH$_3$)</td><td>56.7 (OCH$_3$)</td></tr>
<tr><td>5.86 (1H, s)</td><td>5.84 (1H, s)</td><td>31.9 (CH_2)</td><td>31.9 (CH_2)</td></tr>
<tr><td>3.86 (3H, s)</td><td>3.86 (3H, s)</td><td rowspan="6">29.7-29.3 (CH_2)</td><td>29.7 (3 x CH_2)</td></tr>
<tr><td>2.43 (2H, t, J = 6.5 Hz)</td><td>2.44 (2H, t, J = 7.6 Hz)</td><td>29.7 (2 x CH_2)</td></tr>
<tr><td>1.44 (2H, m)</td><td>1.49-1.40 (2H, m)</td><td>29.6 (2 x CH_2)</td></tr>
<tr><td>1.24 (br s)</td><td>1.25 (26H, br s)</td><td>29.5 (2 x CH_2)</td></tr>
<tr><td>0.87 (3H, t, J = 6.5 Hz)</td><td>0.88 (3H, t, J = 6.4 Hz)</td><td>29.4 (CH_2)</td></tr>
<tr><td>2.43 (2H, t, J = 6.5 Hz)</td><td>2.44 (2H, t, J = 7.6 Hz)</td><td>29.3 (CH_2)</td></tr>
<tr><td></td><td></td><td>28.0 (CH_2)</td><td>28.0 (CH_2)</td></tr>
<tr><td></td><td></td><td>28.0 (CH_2)</td><td>-</td></tr>
<tr><td></td><td></td><td>22.7 (CH_2)</td><td>22.7 (CH_2)</td></tr>
<tr><td></td><td></td><td>-</td><td>22.6 (CH_2)</td></tr>
<tr><td></td><td></td><td>14.1 (CH_3)</td><td>14.1 (CH_3)</td></tr>
</table>

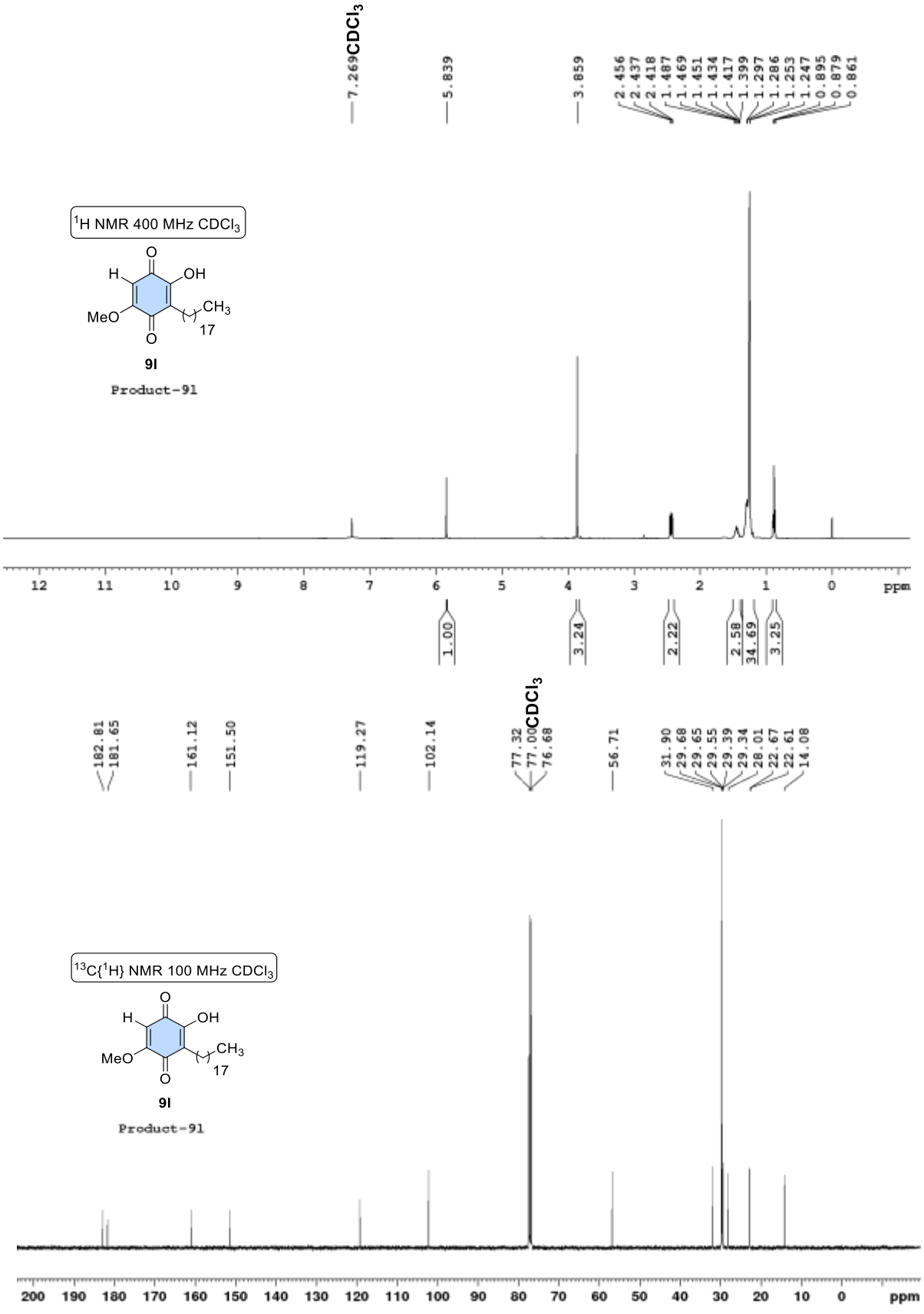


Figure 12: ^{1}H NMR and ^{13}C NMR spectrum of product **9l**

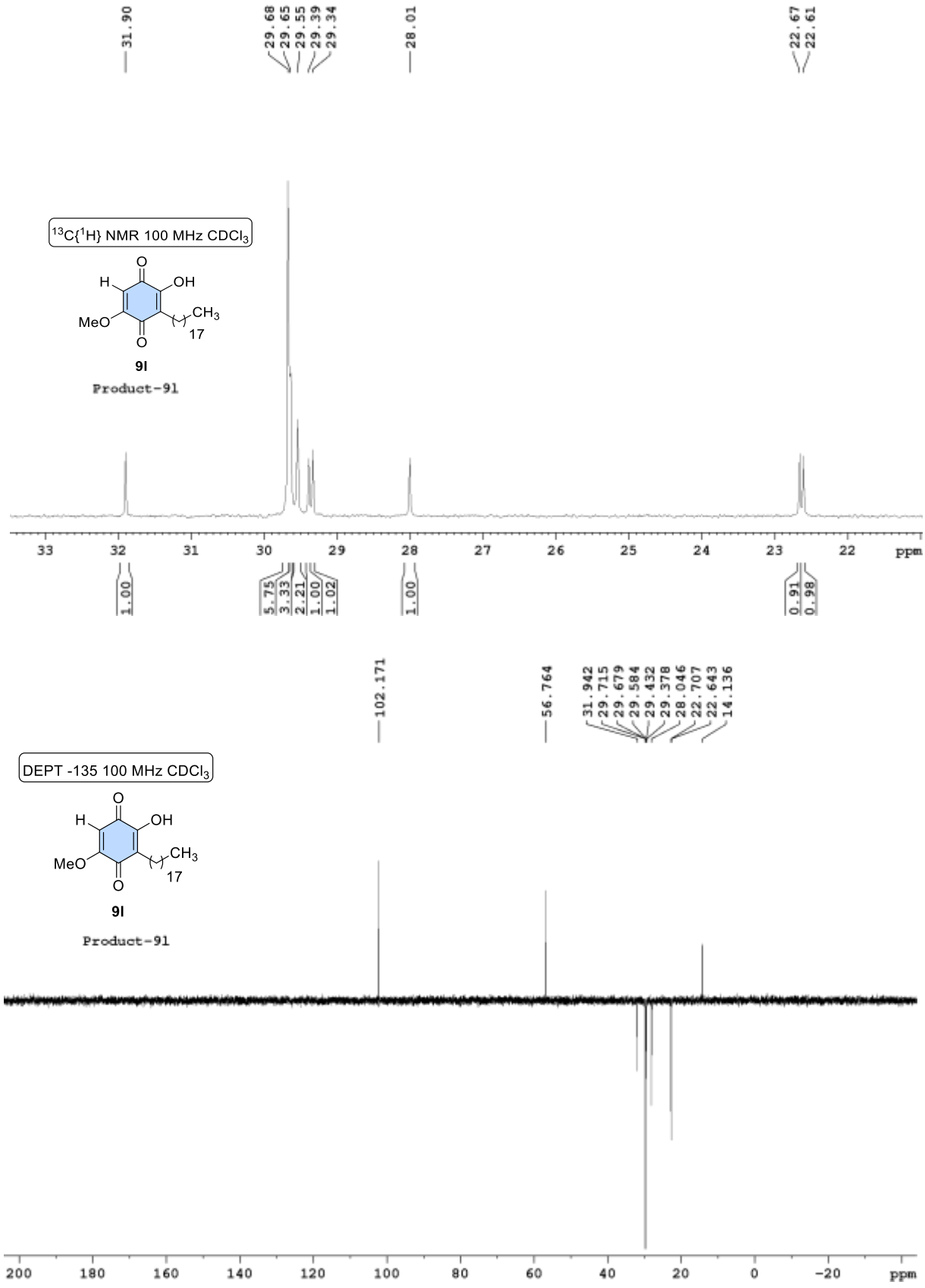
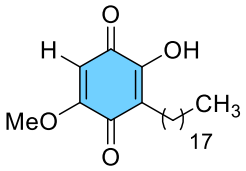


Figure 13: Expanded ^{13}C NMR and DEPT spectrum of product **9l**.

Table 4. Correlation NMR data of compound **9l** (Irisoquin):[2]

<table>
<tr><td colspan="2" rowspan="5"> 
Irisoquin
3-ethyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9l)</td><td>Isolated compound ^{13}C NMR (75 MHz, $CDCl_3$)</td><td>Present synthetic compound ^{13}C NMR (100 MHz, $CDCl_3$)</td></tr>
<tr><td>182.8 (C, C=O)</td><td>182.8 (C, C=O)</td></tr>
<tr><td>181.7 (C, C=O)</td><td>181.6 (C, C=O)</td></tr>
<tr><td>161.1 (C)</td><td>161.1 (C)</td></tr>
<tr><td>151.5 (C)</td><td>151.5 (C)</td></tr>
<tr><td colspan="2"></td><td>119.3 (C)</td><td>119.3 (C)</td></tr>
<tr><td>Isolated compound ^{1}H NMR (300 MHz, $CDCl_3$)</td><td>Present synthetic compound ^{1}H NMR (400 MHz, $CDCl_3$)</td><td>102.2 (CH)</td><td>102.1 (CH)</td></tr>
<tr><td>7.29 (br s, OH)</td><td>-</td><td></td><td></td></tr>
<tr><td>5.86 (1H, s)</td><td>5.84 (1H, s)</td><td>56.8 (OCH$_3$)</td><td>56.7 (OCH$_3$)</td></tr>
<tr><td>3.86 (3H, s)</td><td>3.86 (3H, s)</td><td>31.9 (CH_2)</td><td>31.9 (CH_2)</td></tr>
<tr><td rowspan="5">2.43 (2H, t, J = 6.5 Hz)</td><td rowspan="5">2.44 (2H, t, J = 7.6 Hz)</td><td rowspan="5">29.7-29.3 (CH_2)</td><td>29.7 (6 x CH_2)</td></tr>
<tr><td>29.6 (3 x CH_2)</td></tr>
<tr><td>29.5 (2 x CH_2)</td></tr>
<tr><td>29.4 (CH_2)</td></tr>
<tr><td>29.3 (CH_2)</td></tr>
<tr><td>1.44 (2H, m)</td><td>1.49-1.40 (2H, m)</td><td>28.0 (CH_2)</td><td>28.0 (CH_2)</td></tr>
<tr><td>1.24 (br s)</td><td>1.30-1.26 (32H, s)</td><td>28.0 (CH_2)</td><td>-</td></tr>
<tr><td>0.87 (3H, t, J = 6.5 Hz)</td><td>0.88 (3H, t, J = 6.4 Hz)</td><td>22.7 (CH_2)</td><td>22.7 (CH_2)</td></tr>
<tr><td></td><td></td><td>-</td><td>22.6 (CH_2)</td></tr>
<tr><td></td><td></td><td>14.1 (CH_3)</td><td>14.1 (CH_3)</td></tr>
</table>

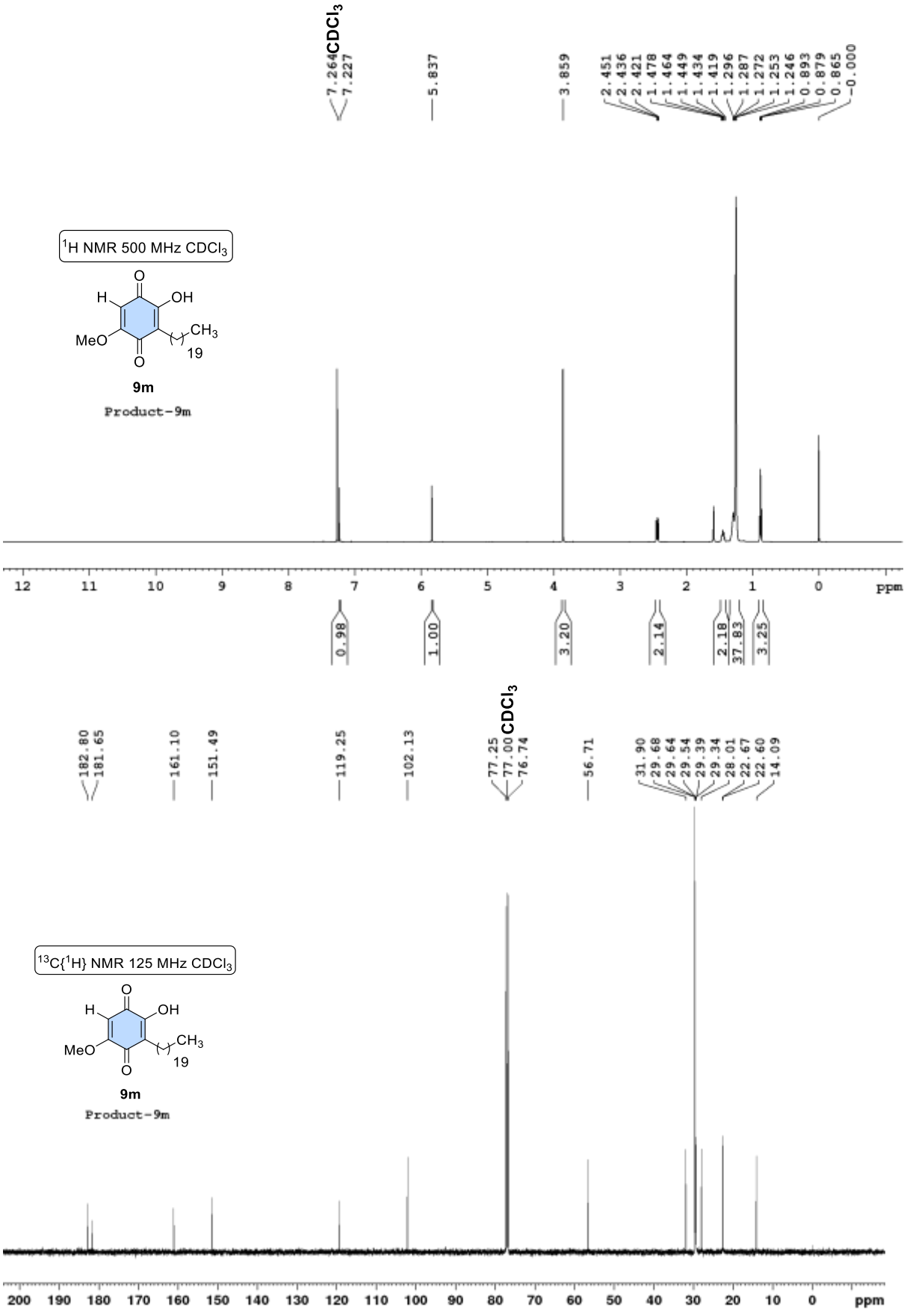


Figure 14: ^{1}H NMR and ^{13}C NMR spectrum of product **9m**.

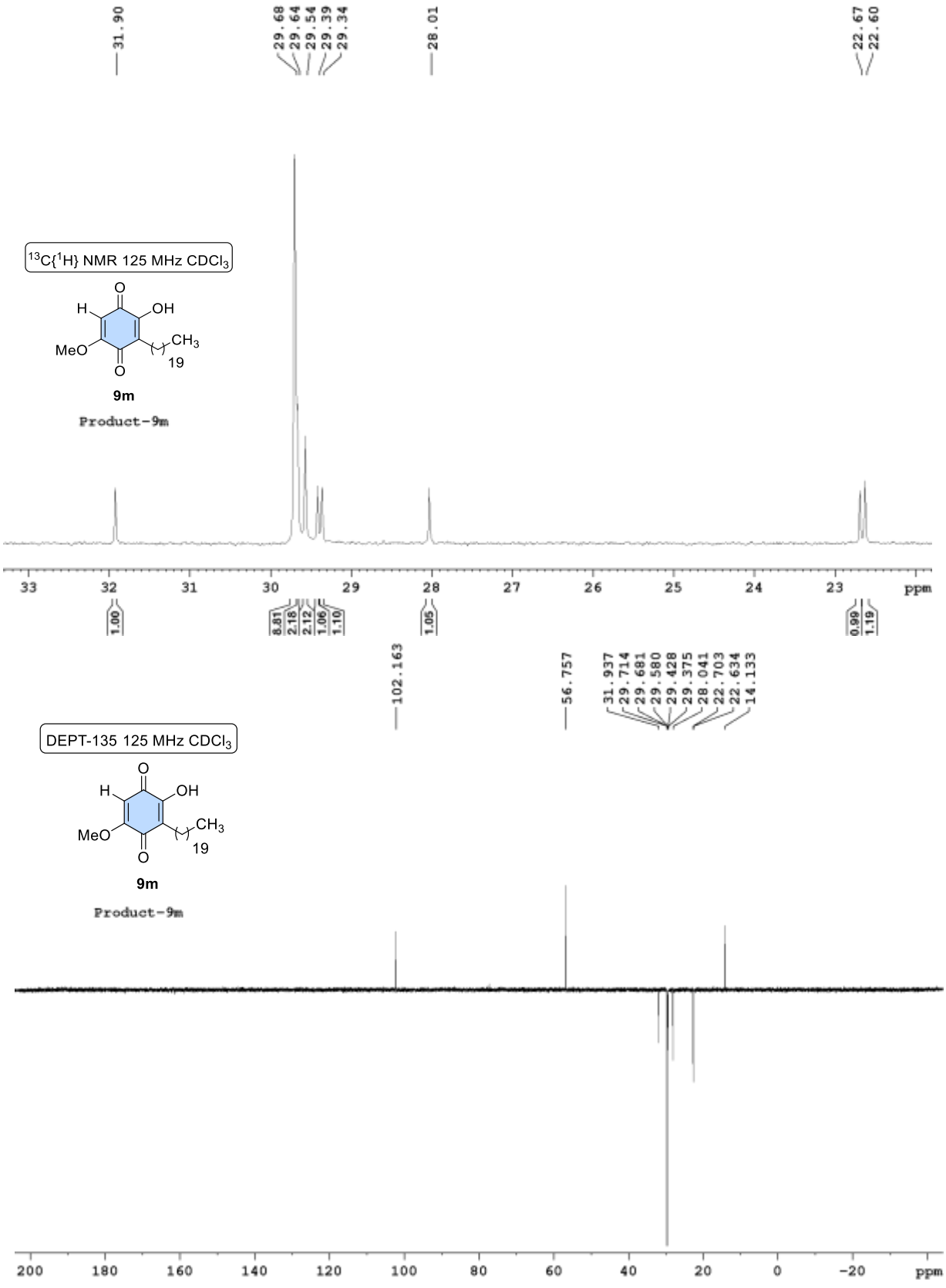
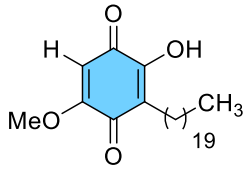


Figure 15: Expanded ^{13}C NMR and DEPT NMR spectrum of product **9m**.

Table 5. Correlation NMR data of compound **9m** (Irisoquin D):[2]

<table>
<tr><td colspan="2" rowspan="5"> 
Irisoquin D
3-ethyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9m)</td><td>Isolated compound ^{13}C NMR (75 MHz, $CDCl_3$)</td><td>Present synthetic compound ^{13}C NMR (125 MHz, $CDCl_3$)</td></tr>
<tr><td>182.8 (C, C=O)</td><td>182.8 (C, C=O)</td></tr>
<tr><td>181.7 (C, C=O)</td><td>181.6 (C, C=O)</td></tr>
<tr><td>161.1 (C)</td><td>161.1 (C)</td></tr>
<tr><td>151.5 (C)</td><td>151.5 (C)</td></tr>
<tr><td colspan="2"></td><td>119.3 (C)</td><td>119.2 (C)</td></tr>
<tr><td>Isolated compound ^{1}H NMR (300 MHz, $CDCl_3$)</td><td>Present synthetic compound ^{1}H NMR (500 MHz, $CDCl_3$)</td><td>102.2 (CH)</td><td>102.1 (CH)</td></tr>
<tr><td>7.29 (br s, OH)</td><td>7.23 (br s, OH)</td><td>56.8 (OCH$_3$)</td><td>56.7 (OCH$_3$)</td></tr>
<tr><td>5.86 (1H, s)</td><td>5.84 (1H, s)</td><td>31.9 (CH_2)</td><td>31.9 (CH_2)</td></tr>
<tr><td>3.86 (3H, s)</td><td>3.86 (3H, s)</td><td rowspan="5">29.7-29.3 (CH_2)</td><td>29.7 (9 x CH_2)</td></tr>
<tr><td>2.43 (2H, t, J = 6.5 Hz)</td><td>2.44 (2H, t, J = 7.5 Hz)</td><td>29.6 (2 x CH_2)</td></tr>
<tr><td>1.44 (2H, m)</td><td>1.48-1.42 (2H, m)</td><td>29.5 (2 x CH_2)</td></tr>
<tr><td>1.24 (br s)</td><td>1.30-1.26 (34H, s)</td><td>29.4 (CH_2)</td></tr>
<tr><td>0.87 (3H, t, J = 6.5 Hz)</td><td>0.88 (3H, t, J = 7.0 Hz)</td><td>29.3 (CH_2)</td></tr>
<tr><td></td><td></td><td>28.0 (CH_2)</td><td>28.0 (CH_2)</td></tr>
<tr><td></td><td></td><td>28.0 (CH_2)</td><td>-</td></tr>
<tr><td></td><td></td><td>22.7 (CH_2)</td><td>22.7 (CH_2)</td></tr>
<tr><td></td><td></td><td>-</td><td>22.6 (CH_2)</td></tr>
<tr><td></td><td></td><td>14.1 (CH_3)</td><td>14.1 (CH_3)</td></tr>
</table>

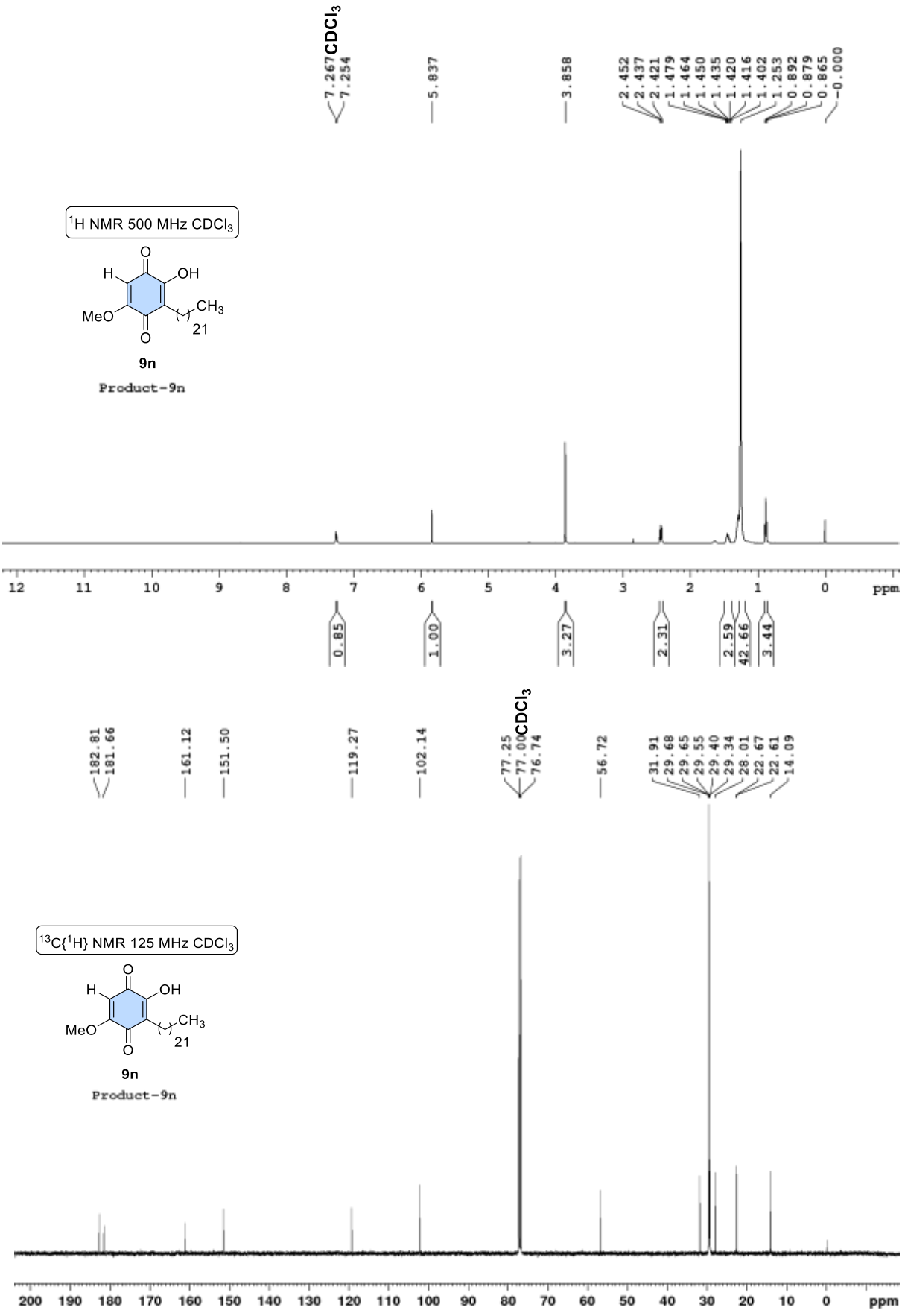


Figure 16: ^{1}H NMR and ^{13}C NMR spectrum of product **9n**.

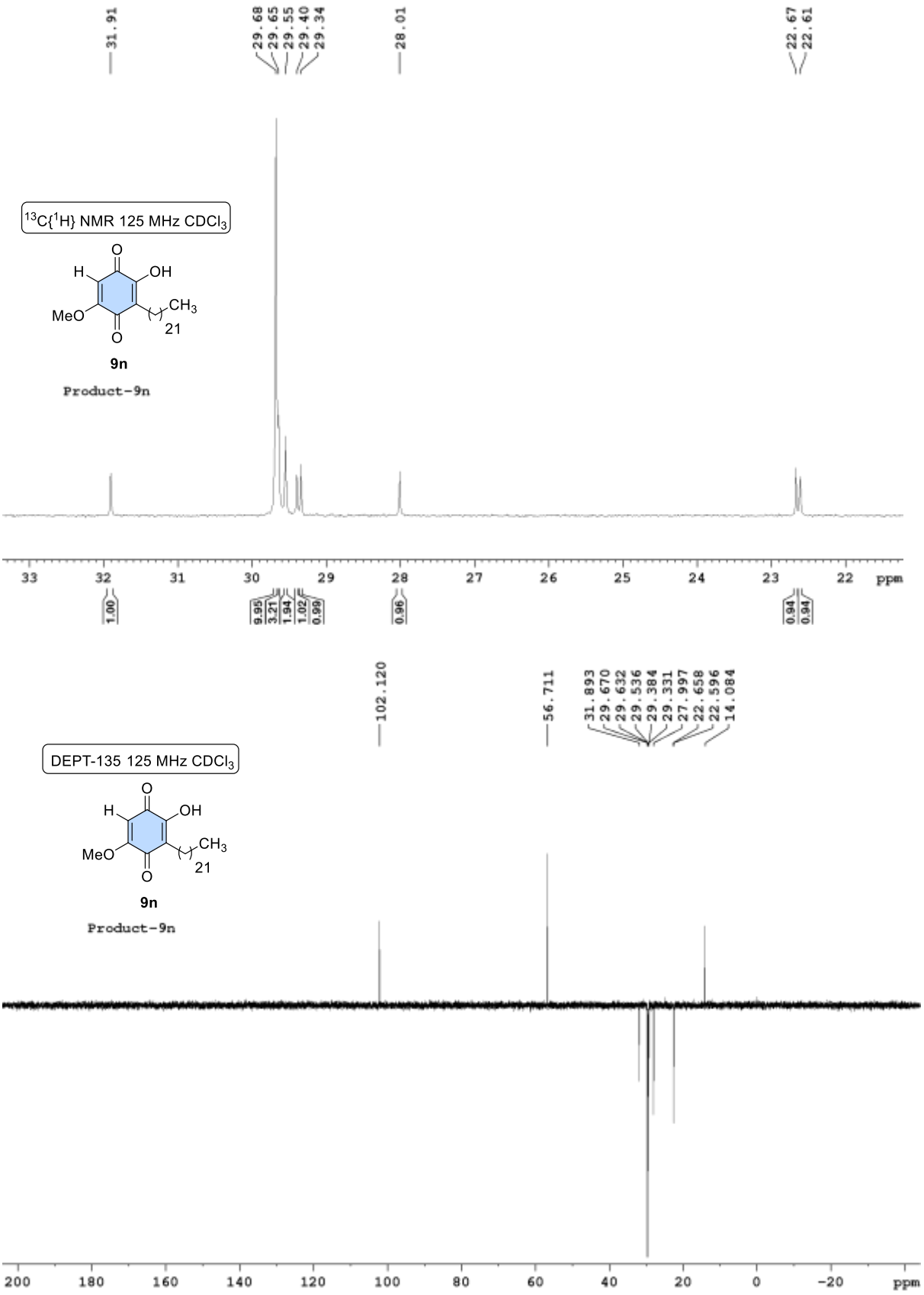
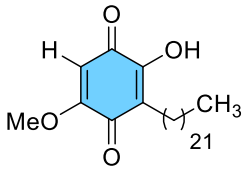


Figure 17: Expanded ^{13}C NMR and DEPT NMR spectrum of product **9n**.

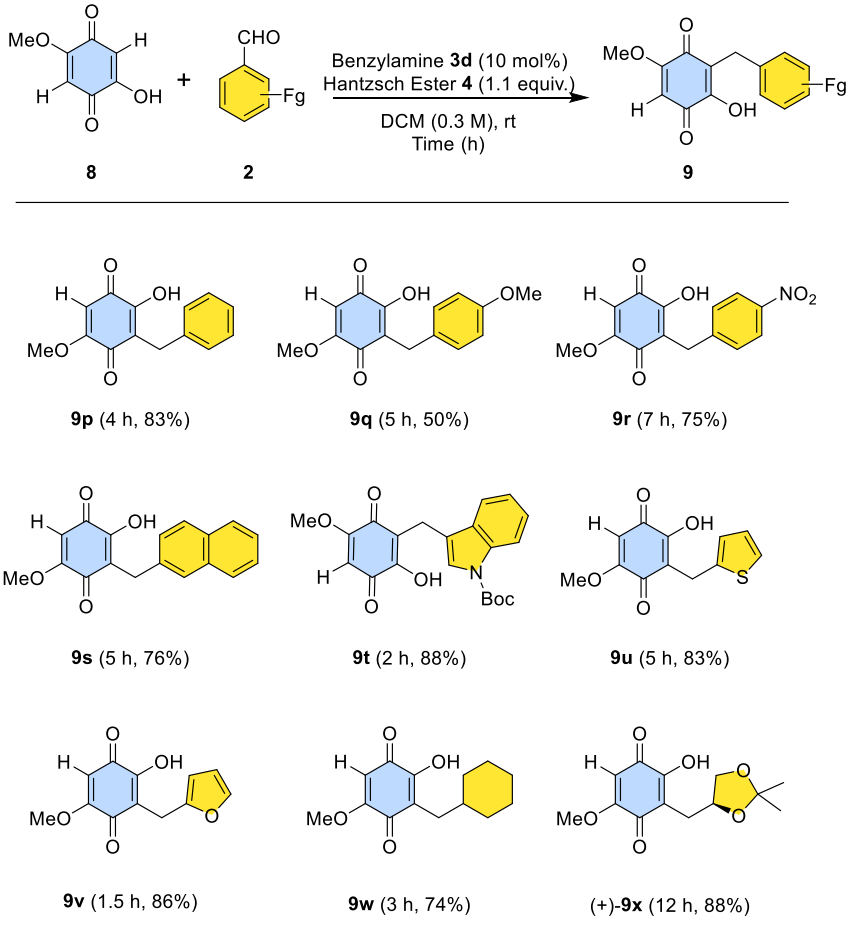
Table 6. Correlation NMR data of compound **9n** (Irisoquin F):[2]

		Isolated compound ^{13}C NMR (75 MHz, $CDCl_3$)	Present synthetic compound ^{13}C NMR (125 MHz, $CDCl_3$)
 Irisoquin F 3-ethyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (**9n**)		182.8 (C, *C*=*O*)	182.8 (C, *C*=*O*)
		181.7 (C, *C*=*O*)	181.7 (C, *C*=*O*)
		161.1 (C)	161.1 (C)
		151.5 (C)	151.5 (C)
		119.3 (C)	119.3 (C)
Isolated compound ^{1}H NMR (300 MHz, $CDCl_3$)	Present synthetic compound ^{1}H NMR (500 MHz, $CDCl_3$)	102.2 (CH)	102.1 (CH)
7.29 (br s, *OH*)	7.22 (br s, *OH*)	56.8 (OCH_3)	56.7 (OCH_3)
5.86 (1H, s)	5.84 (1H, s)	31.9 (CH_2)	31.9 (CH_2)
3.86 (3H, s)	3.86 (3H, s)	29.7-29.3 (CH_2)	29.7 (10 x CH_2)
2.43 (2H, t, J = 6.5 Hz)	2.44 (2H, t, J = 7.5 Hz)		29.6 (3 x CH_2)
1.44 (2H, m)	1.48-1.42 (2H, m)		29.5 (2 x CH_2)
1.24 (br s)	1.30-1.26 (38H, s)		29.4 (CH_2)
0.87 (3H, t, J = 6.5 Hz)	0.88 (3H, t, J = 7.0 Hz)		29.3 (CH_2)
		28.0 (CH_2)	28.0 (CH_2)
		28.0 (CH_2)	-
		22.7 (CH_2)	22.7 (CH_2)
		-	22.6 (CH_2)
		14.1 (CH_3)	14.1 (CH_3)

5.4.2 Scope of quinones 8 with aromatic aldehydes

The scope of the reaction was further tested with various aromatic aldehydes **2** and it would be very much interesting to investigate various electronic factors governing the reaction conditions. Initially, **8** was treated with benzaldehyde **2p** to give monoalkylated product **9p** in 4 h with 83% yield (Table 7). It took longer hours compared to linear and branched aliphatic aldehydes. The same reaction with electron donating 4-OMe benzaldehyde **2q** and electron withdrawing 4-NO_2 benzaldehyde **2r** gave **9q** and **9r** in 50% and 75% respectively within 5-7 h (Table 7). Treatment of **8** with napthaldehyde **2s** gave **9s** with 76% yield in 5 h (Table 7). We went onto check the scope of the reaction with different heterocyclic aldehydes **2t-2v** to give products **9t-9v** with good yields within 2-5 h (Table 7). Products **9w** and (+)-**9x** are synthesized in good yields by reacting with **2w** and chiral aldehyde **2x** (Table 7).

Table 7: Reaction Scope of quinones **8** with aromatic aldehydes **2**.[a-b]



[a]Reactions were carried out in DCM (0.3 M) with 1.0 equiv. of **2** and 1.1 equiv. of **4** relative to **8** (0.3 mmol) in the presence of **3d** (10 mol%) at room temperature. [b]Yield refers to the column-purified products.

^{1}H and ^{13}C NMR spectra of few compounds from Table 3 have depicted in figure 18-20.

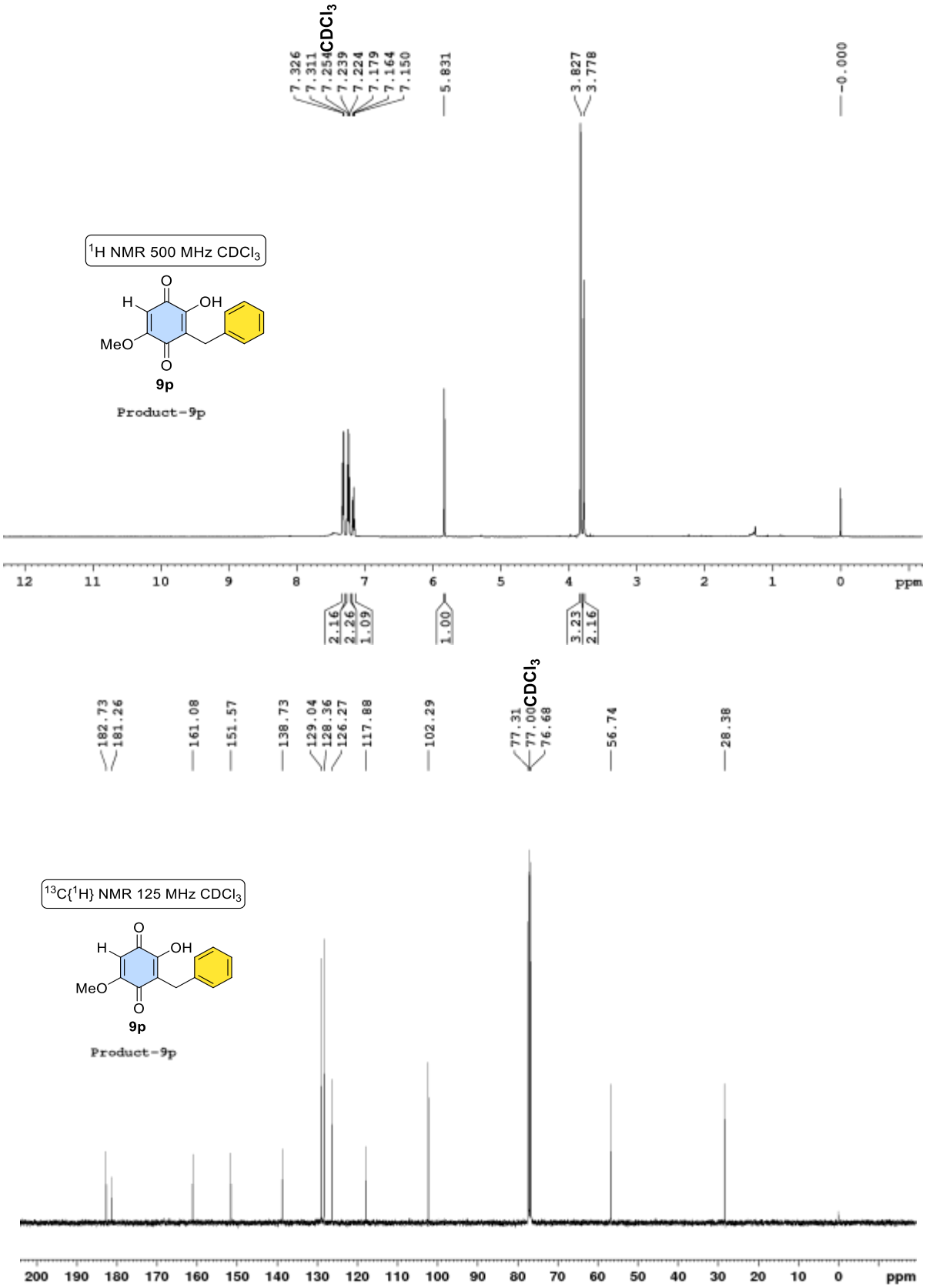


Figure 18: ^{1}H NMR and ^{13}C NMR spectrum of product **9p**.

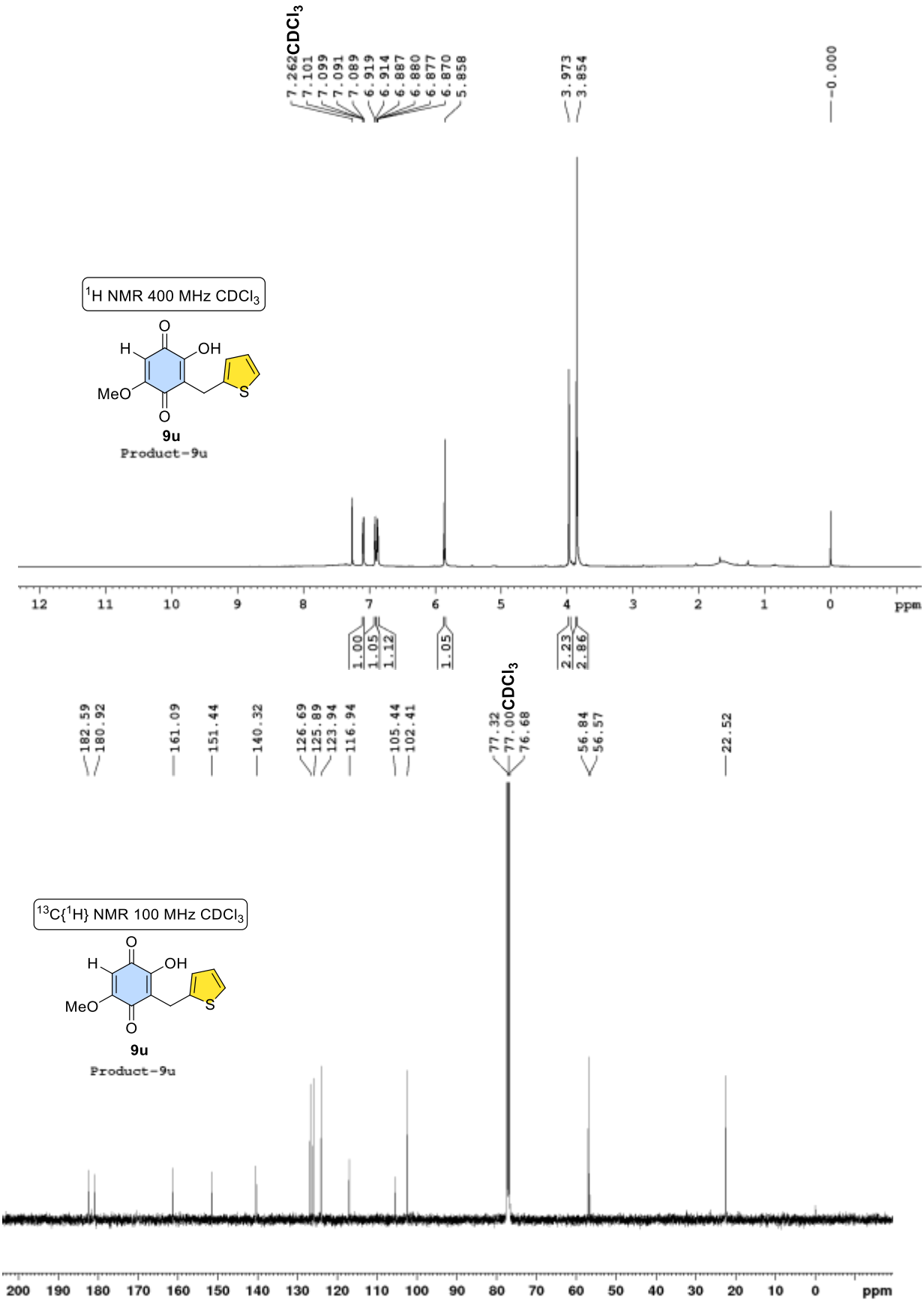


Figure 19: ^{1}H NMR and ^{13}C NMR spectrum of product **9u**.

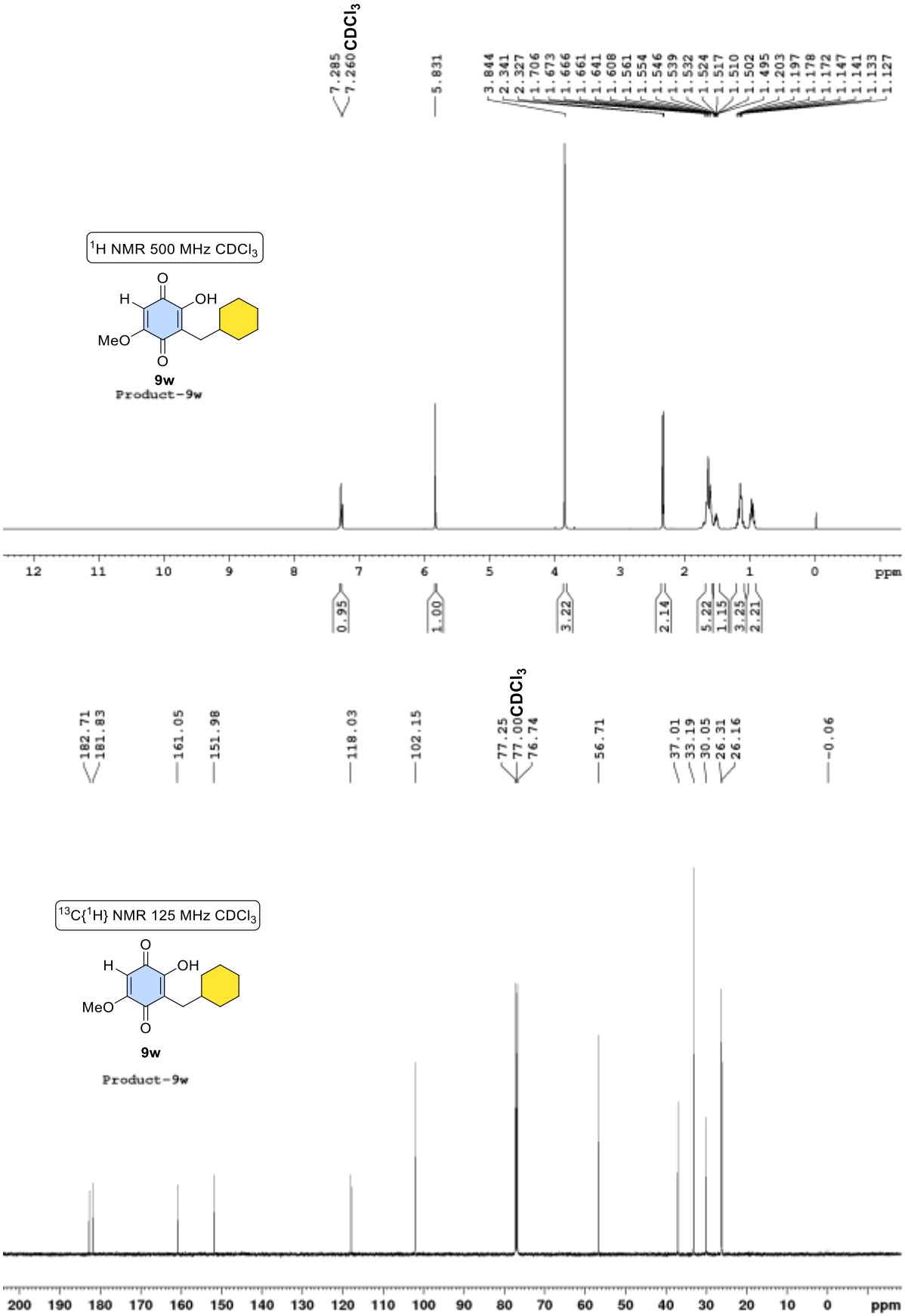
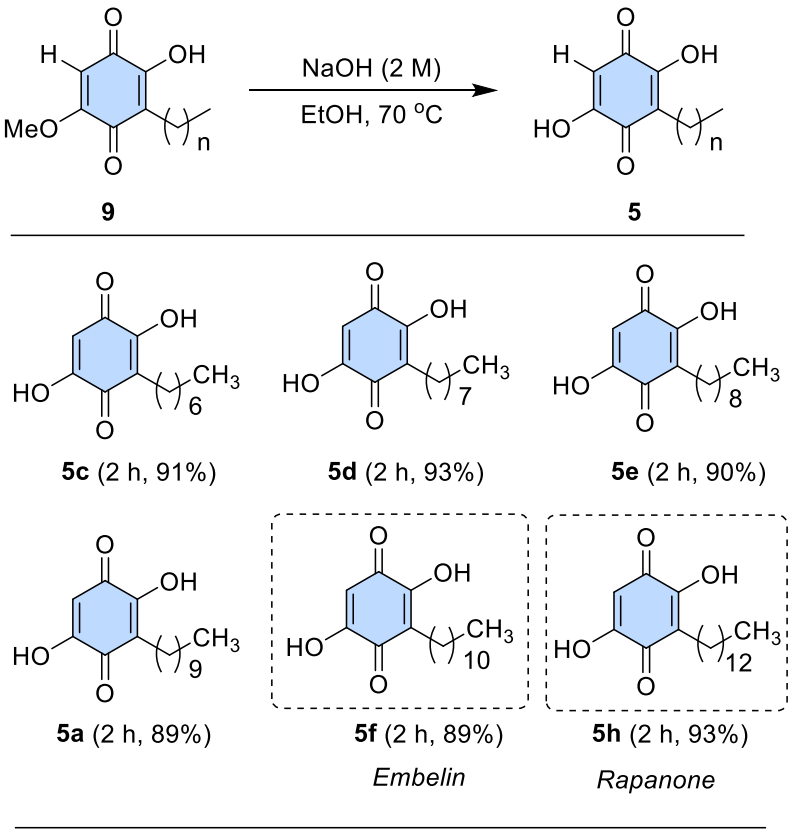


Figure 20: ^{1}H NMR and ^{13}C NMR spectrum of product **9w**.

5.4.3 Alkali mediated hydrolysis

Followed by a comprehensive exploration of scope of **8** with various aldehydes **2**, we shifted our attention towards synthesizing alkyl 2,5-dihydroxy benzoquinones **5** which forms the core moiety of various natural products. Adhering to a similar approach as evident from the reaction design, we have tried to displace the methoxy group of **9** with OH group. Rapid hydrolysis of **9** in the presence of 2 M NaOH solution in ethanol solvent at 70 °C gave **5** with excellent yields without the need for column chromatography. **9a**, **9c**, **9d**, **9e** were subjected to hydrolysis at 70 °C to give **5a**, **5c**, **5d**, **5e** with excellent yields i.e., >90% in 2 h (Table 8). Selective deprotection of **9f** gave natural product embelin **5f** within 2 h with 89% yield (Table 8). Naturally occurring *O*-methylrapanone **9h** was also converted into rapanone **5h** following the same reaction conditions with 93% yield in 2 h (Table 8).

Table 8: Alkali mediated hydrolysis of **9**.[a-b]



[a] Reactions were carried out in ethanol (0.3 M) with aqueous NaOH (2 M; 4.4 mL) relative to **9** (0.2 mmol) at reflux temperature of 70 °C for 2 h. [b] Yield refers to the crude product.

^{1}H, ^{13}C and DEPT NMR spectra of few compounds from Table 4 have depicted in figure 21-24.

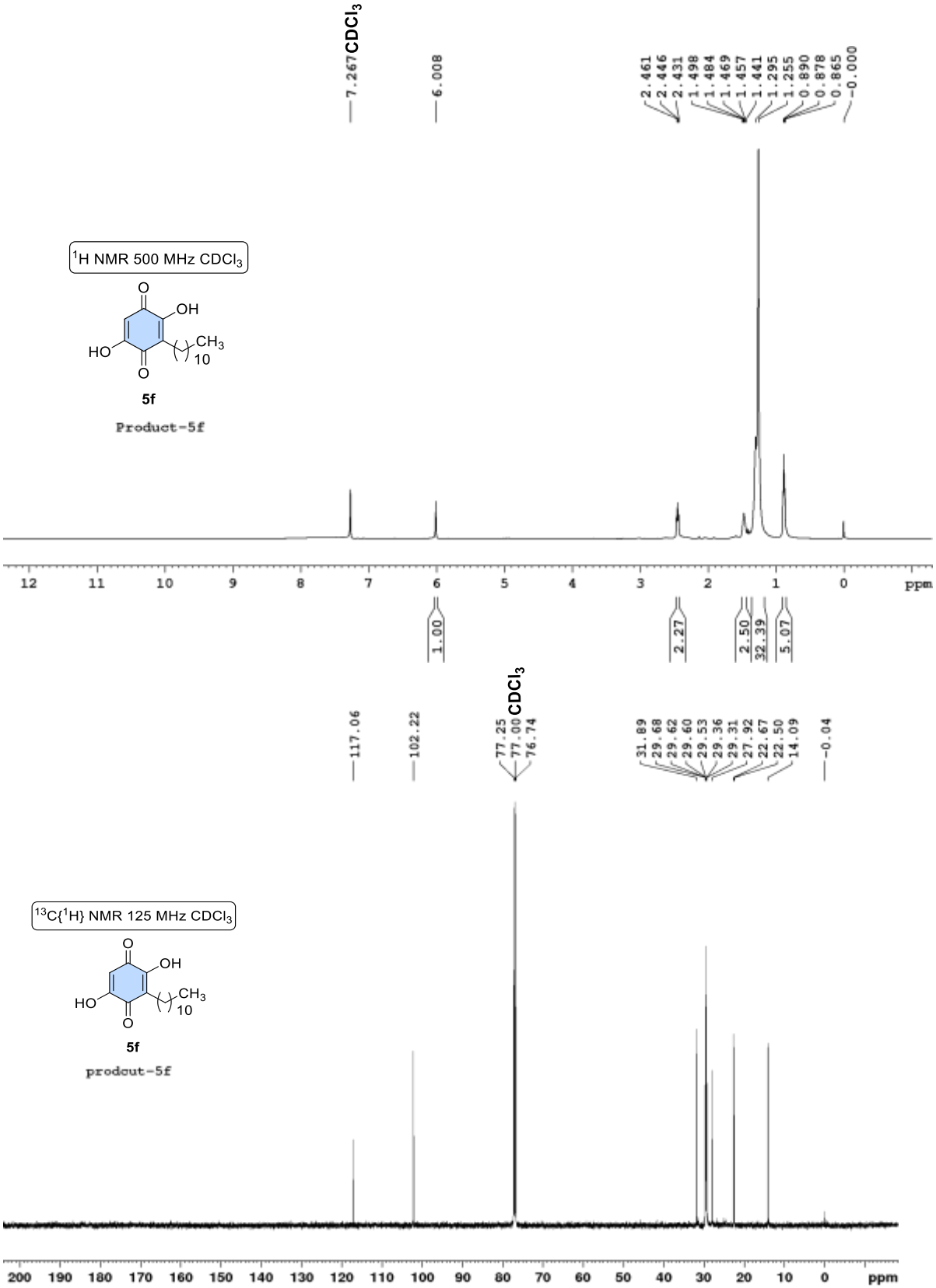


Figure 21: ^{1}H NMR and ^{13}C NMR spectrum of product **5f**.

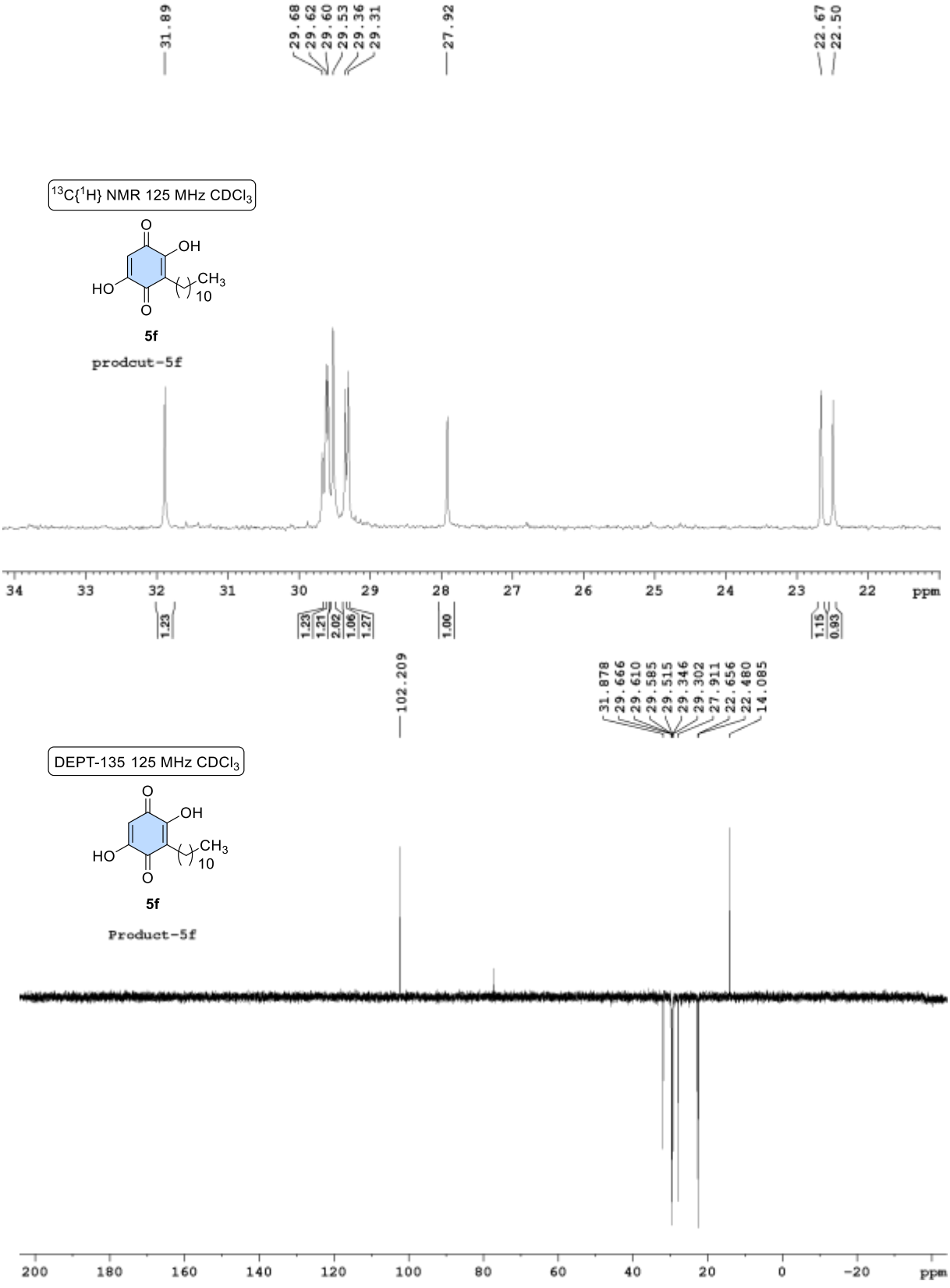
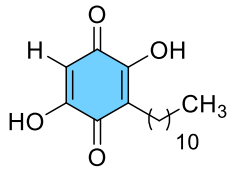


Figure 22: Expanded ^{13}C NMR and DEPT NMR spectrum of product **5f**.

Table 9. Correlation NMR data of compound **5f** (Embelin):[3]

<table>
<tr><td colspan="2"> 
Embelin
2,5-dihydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione (5f)</td><td>Isolated compound ^{13}C NMR (100 MHz, $CDCl_3$)</td><td>Present synthetic compound ^{13}C NMR (125 MHz, $CDCl_3$)</td></tr>
<tr><td colspan="2" rowspan="2"></td><td>117.4 (C)</td><td>117.1 (C)</td></tr>
<tr><td>103.9 (CH)</td><td>102.2 (CH)</td></tr>
<tr><td>Isolated compound ^{1}H NMR ($CDCl_3$)</td><td>Present synthetic compound ^{1}H NMR (500 MHz, $CDCl_3$)</td><td rowspan="11">31.3-22.04 (10 x CH_2)</td><td>31.9 (CH_2)</td></tr>
<tr><td>7.69 (2H, s)</td><td>-</td><td>29.6 (CH_2)</td></tr>
<tr><td>6.00 (1H, s)</td><td>6.01 (1H, s)</td><td>29.6 (2 x CH_2)</td></tr>
<tr><td>2.46-2.43 (2H, m)</td><td>2.45 (2H, t, J = 7.5 Hz)</td><td>29.5 (CH_2)</td></tr>
<tr><td>1.49-1.45 (2H, m)</td><td>1.50-1.44 (2H, m)</td><td>29.4 (CH_2)</td></tr>
<tr><td>1.29-1.26 (16H, m)</td><td>1.29-1.25 (16H, m)</td><td>29.3 (CH_2)</td></tr>
<tr><td rowspan="2">0.90 (3H, J = 8.0 Hz)</td><td rowspan="2">0.88 (3H, t, J = 6.5 Hz)</td><td>27.9 (CH_2)</td></tr>
<tr><td>22.7 (CH_2)</td></tr>
<tr><td></td><td></td><td>22.5 (CH_2)</td></tr>
<tr><td colspan="2"></td><td>14.02 (CH_3)</td><td>14.1 (CH_3)</td></tr>
</table>

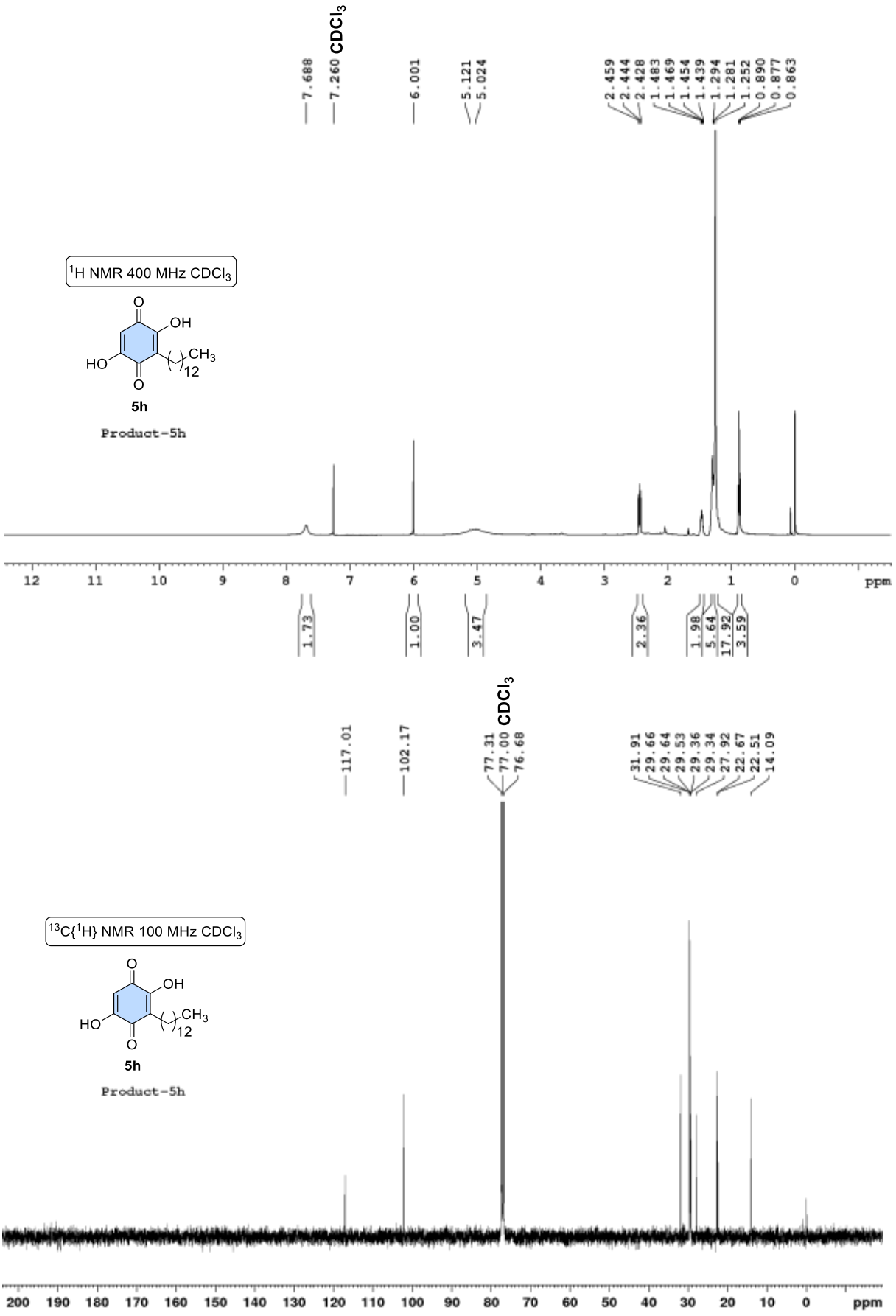


Figure 23: ^{1}H NMR and ^{13}C NMR spectrum of product **5h**.

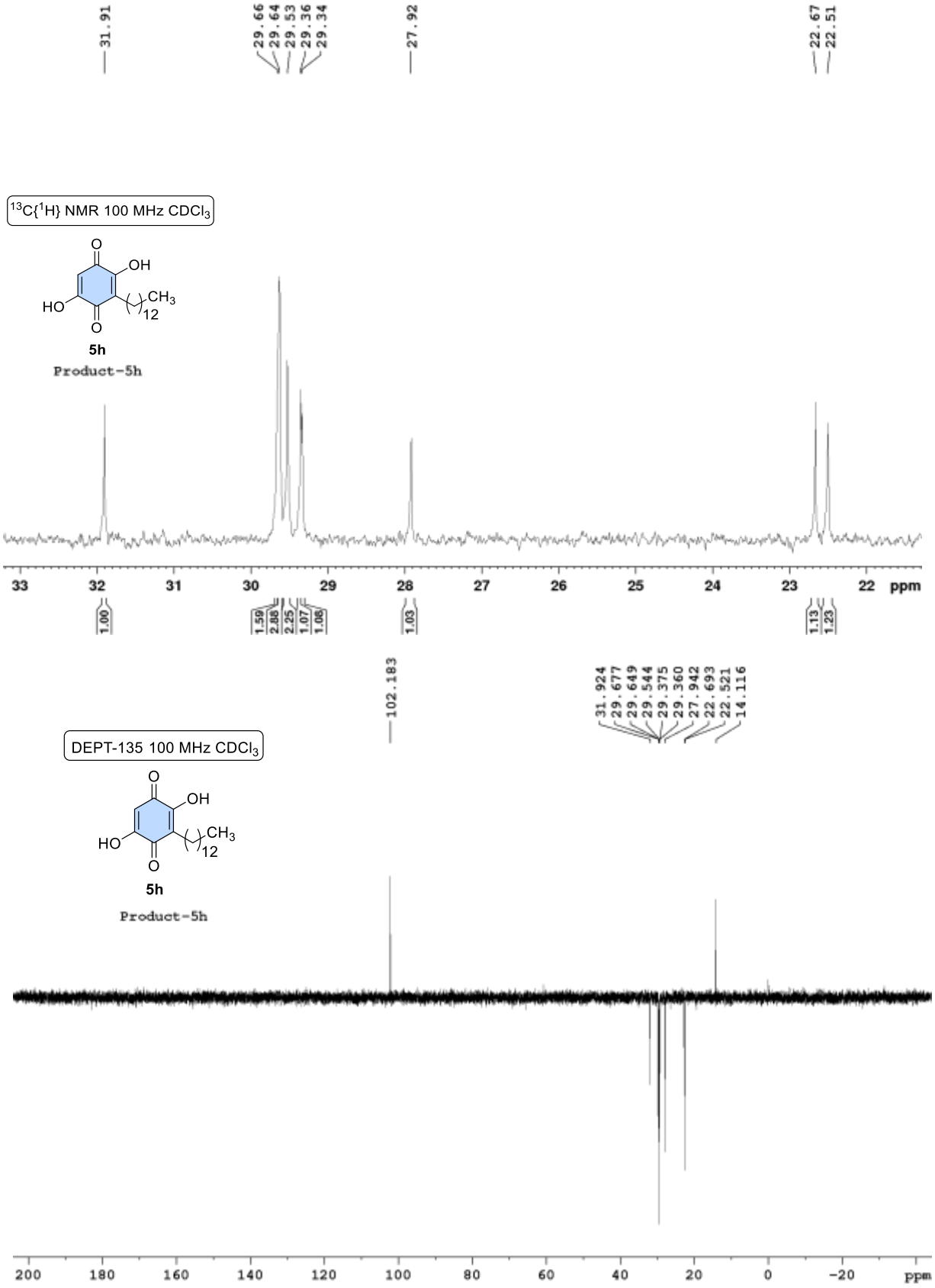
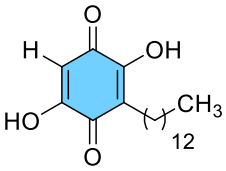


Figure 24: Expanded ^{13}C NMR and DEPT NMR spectrum of product **5h**.

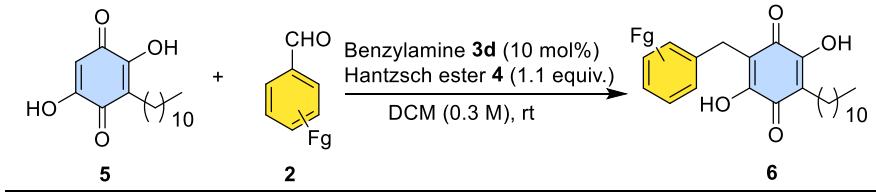
Table 10. Correlation NMR data of compound **5h** (Rapanone):[4]

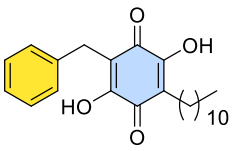
<table>
<tr><td colspan="2"> 
Rapanone
3-ethyl-2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (5h)</td><td>Isolated compound ^{13}C NMR (125 MHz, $CDCl_3$)</td><td>Present synthetic compound ^{13}C NMR (100 MHz, $CDCl_3$)</td></tr>
<tr><td colspan="2" rowspan="2"></td><td>117.1 (C)</td><td>117.0 (C)</td></tr>
<tr><td>102.2 (CH)</td><td>102.2 (CH)</td></tr>
<tr><td>Isolated compound 1H NMR (500 MHz, CDCl3)</td><td>Present synthetic compound ^{1}H NMR (400 MHz, $CDCl_3$)</td><td rowspan="11">31.9-14.0 (12 x CH_2, CH_3)</td><td>31.9 (CH_2)</td></tr>
<tr><td>7.6 (2H, br s, OH)</td><td>7.7 (2H, br s, OH)</td><td>29.7 (CH_2)</td></tr>
<tr><td>5.9 (1H, s)</td><td>6.0 (1H, s)</td><td>29.6 (3 x CH_2)</td></tr>
<tr><td>2.45 (2H, t)</td><td>2.44 (2H, t, J = 6.0 Hz)</td><td>29.5 (2 x CH_2)</td></tr>
<tr><td>1.48 (2H, t)</td><td>1.47 (2H, t, J = 7.5 Hz)</td><td>29.4 (CH_2)</td></tr>
<tr><td>1.26 (24H, br s)</td><td>1.27 (24H, br s)</td><td>29.3 (CH_2)</td></tr>
<tr><td>0.87 (3H, t)</td><td>0.88 (3H, t, J = 5.2 Hz)</td><td>27.9 (CH_2)</td></tr>
<tr><td rowspan="3"></td><td rowspan="3"></td><td>22.7 (CH_2)</td></tr>
<tr><td>22.5 (CH_2)</td></tr>
<tr><td>14.1 (CH_3)</td></tr>
</table>

5.4.4 Synthetic transformations

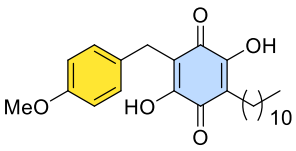
The synthetic utility of the reaction design was further demonstrated by reacting **5** with various aldehydes **2** to give dialkylated products **6** exclusively with higher yields. Initially **5f** was treated with benzaldehyde **2p** in the presence of 10 mol% of **3d** in DCM solvent to give **6fp** in 78% yield within 7 h (Table 11). The generality of the reaction was gain tested with electron donating 4-OMe and electron withdrawing 4-NO_2 benzaldehydes **2q** and **2r** with **5f** to give **6fq** and **6fr** with excellent yields in 5 h and 8 h respectively (Table 11). The same substrate **5f** was further treated with 4-Fluoro and 2-hydroxy benzaldehydes **2y** and **2z** to give **6fy** and **6fz** in higher yields within 6-7 h (Table 11). We altered the substrate from **5f** to **5a** with similar reaction conditions to give **6ap** in 1 h with 70% yield (Table 11). Aliphatic aldehyde **2d** was also treated with **5a** to give **6ad** in 7 h with 83% yield (Table 11).

Table 11: Results of synthetic transformations on **5**.[a-b]

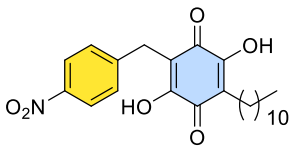




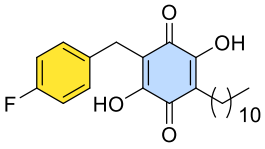
6fp (7 h, 78%)



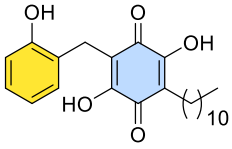
6fq (8 h, 91%)



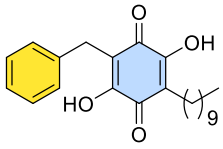
6fr (5 h, 81%)



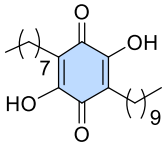
6fy (6 h, 86%)



6fz (7 h, 83%)



6ap (1 h, 70%)



6ad (7 h, 83%)

[a]Reactions were carried out in DCM (0.3 M) with 1 equiv. of **2** and 1.1 equiv. of **4** relative to the **5** (0.3 mmol) in the presence of **3d** (10 mol%) at room temperature.
[b]Yield refers to the column-purified products.

^{1}H, ^{13}C and DEPT NMR spectra of few compounds from Table 5 have depicted f

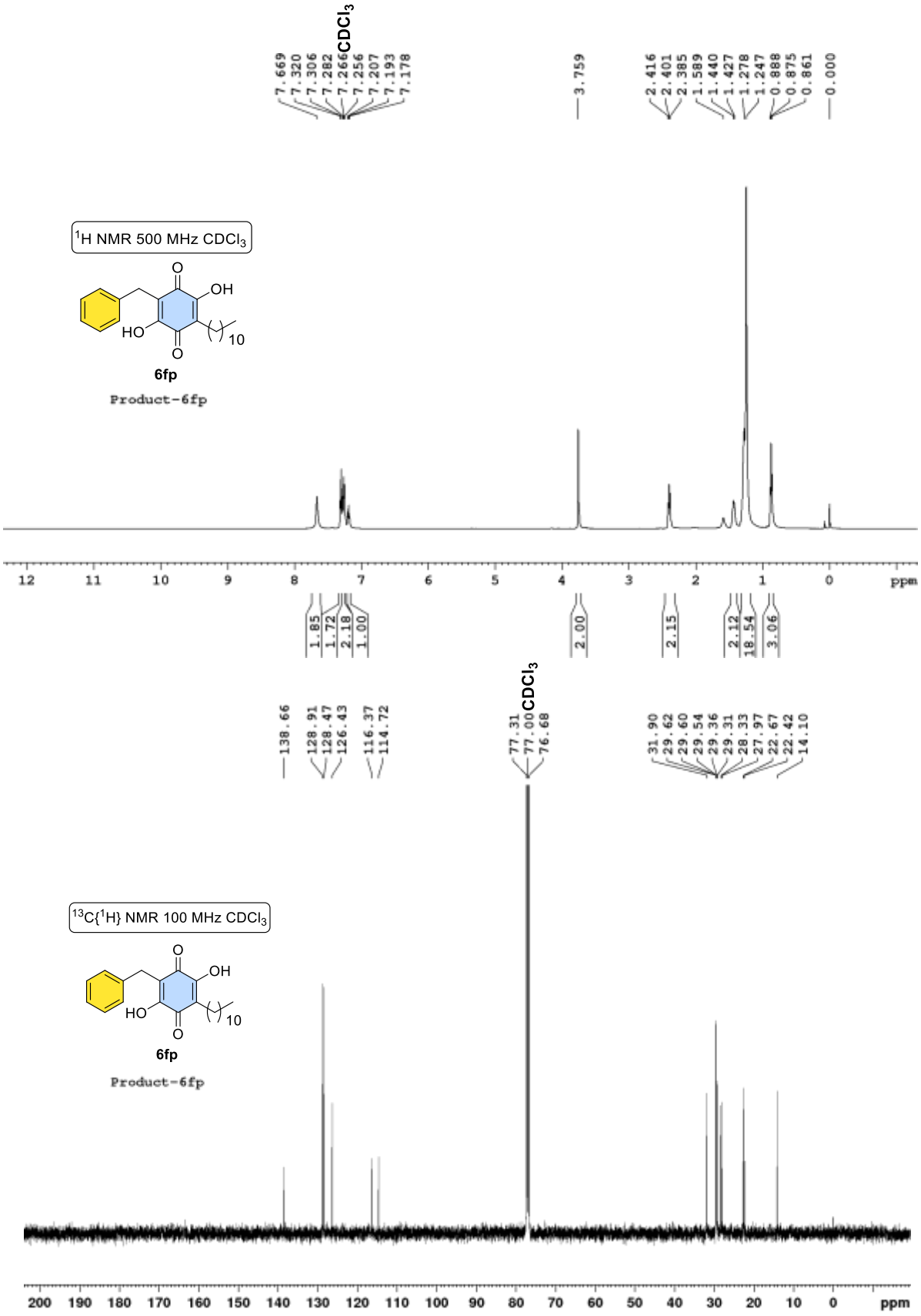


Figure 25: ^{1}H NMR and ^{13}C NMR spectrum of product **6fp**.

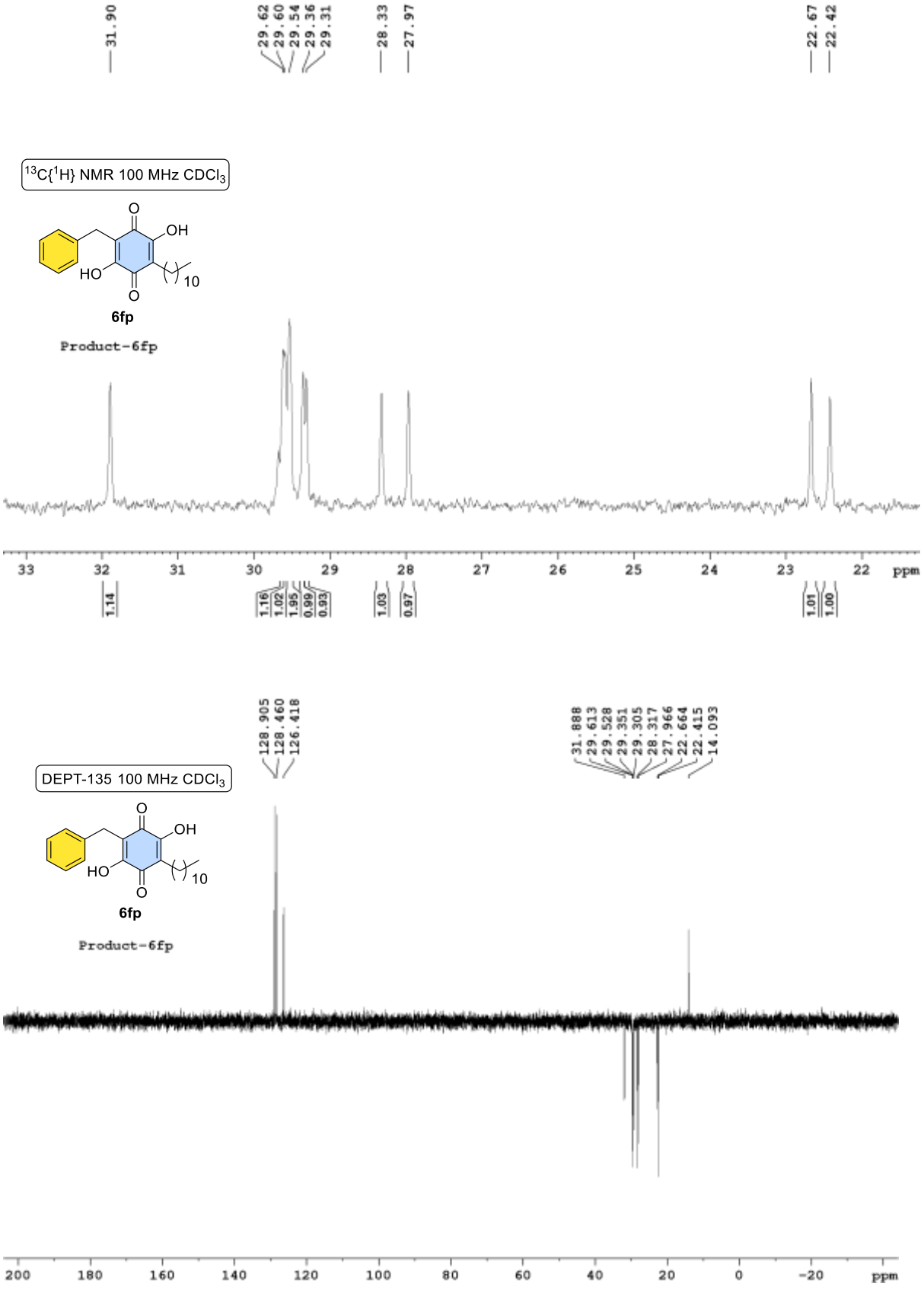


Figure 26: Expanded ^{13}C NMR and DEPT NMR spectrum of pr

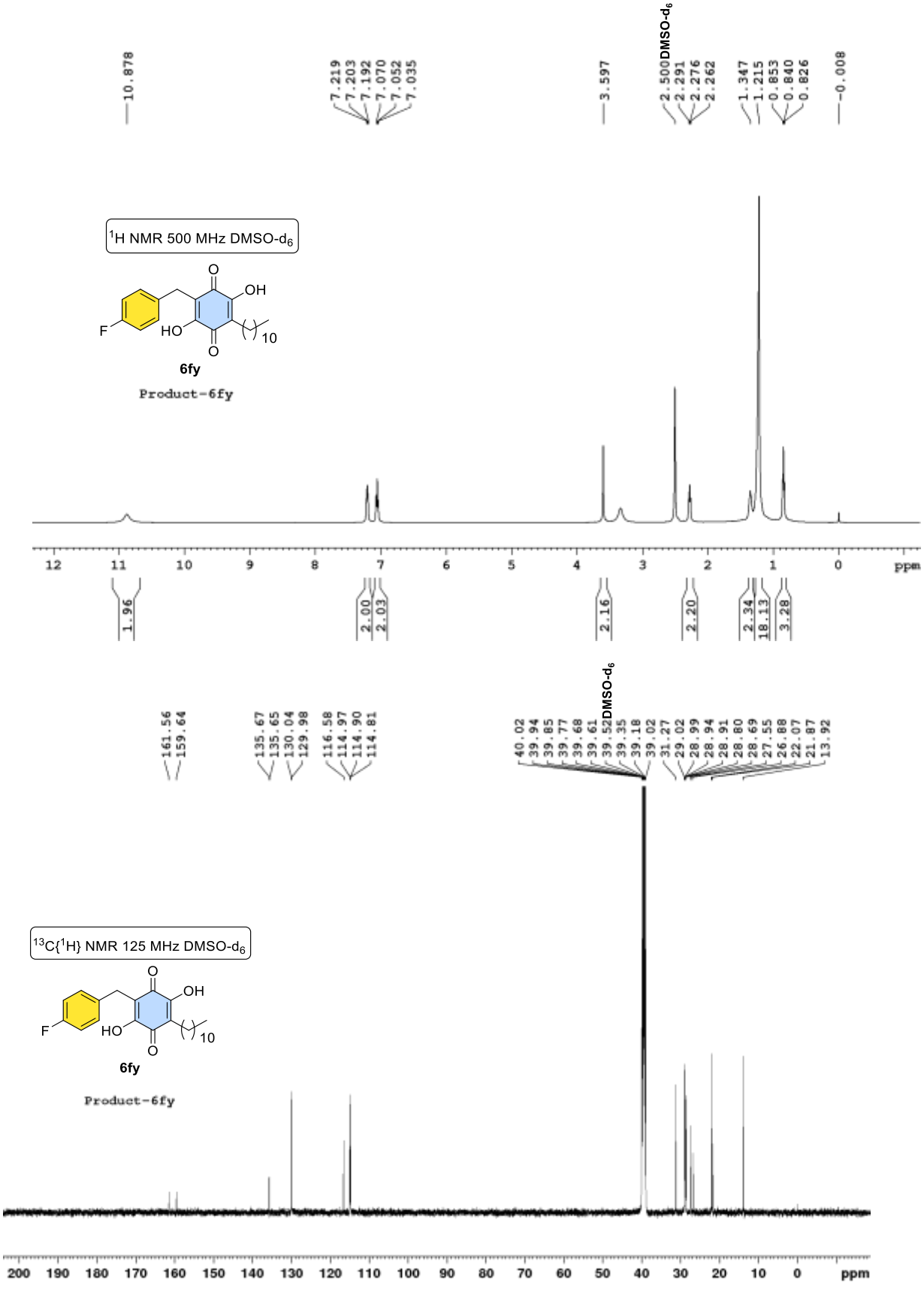


Figure 27: ^{1}H NMR and ^{13}C NMR spectrum of product **6fy**.

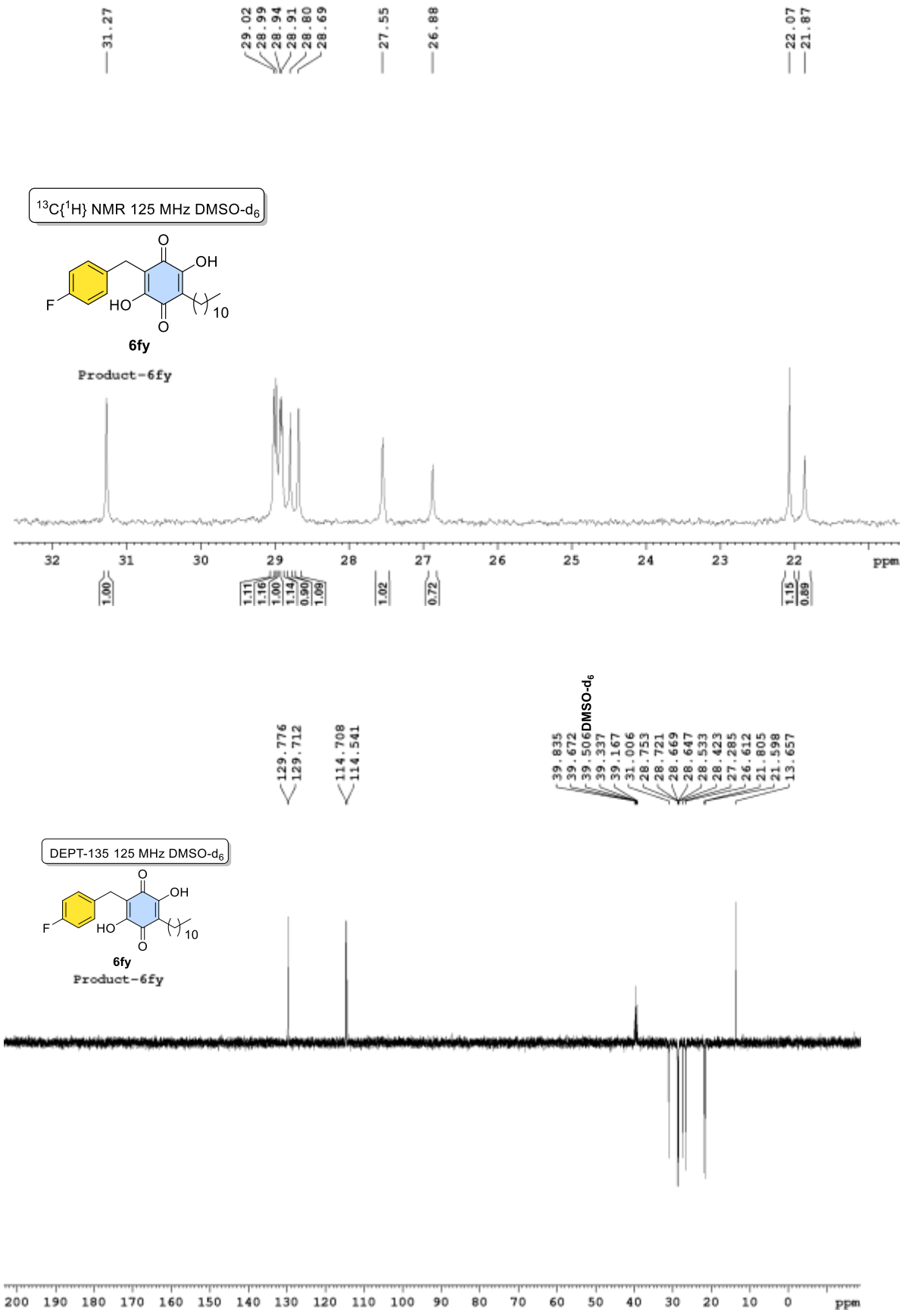


Figure 28: Expanded ^{13}C NMR and DEPT NMR spectrum of product **6fy**.

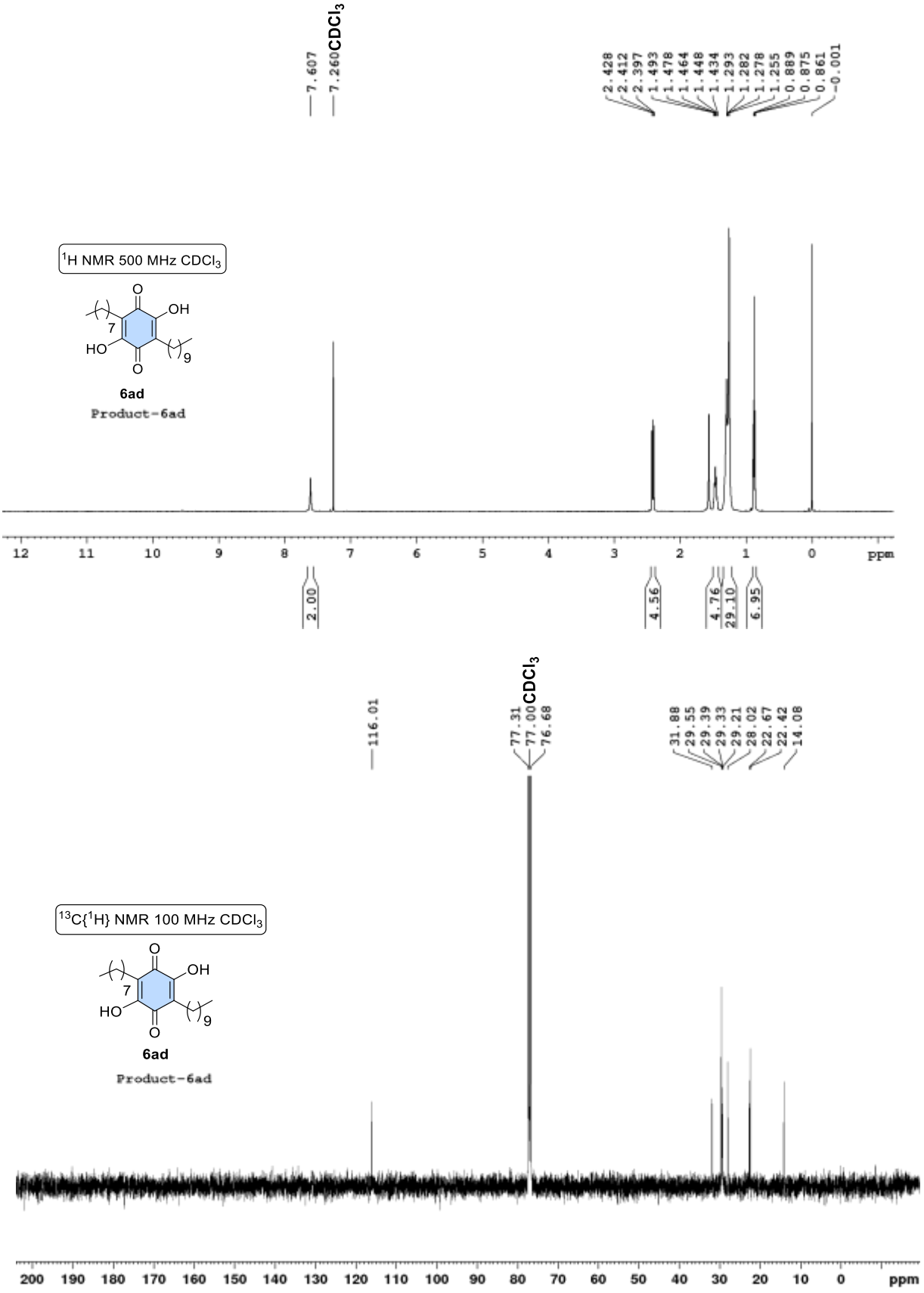


Figure 29: ^{1}H NMR and ^{13}C NMR spectrum of product **6ad**.

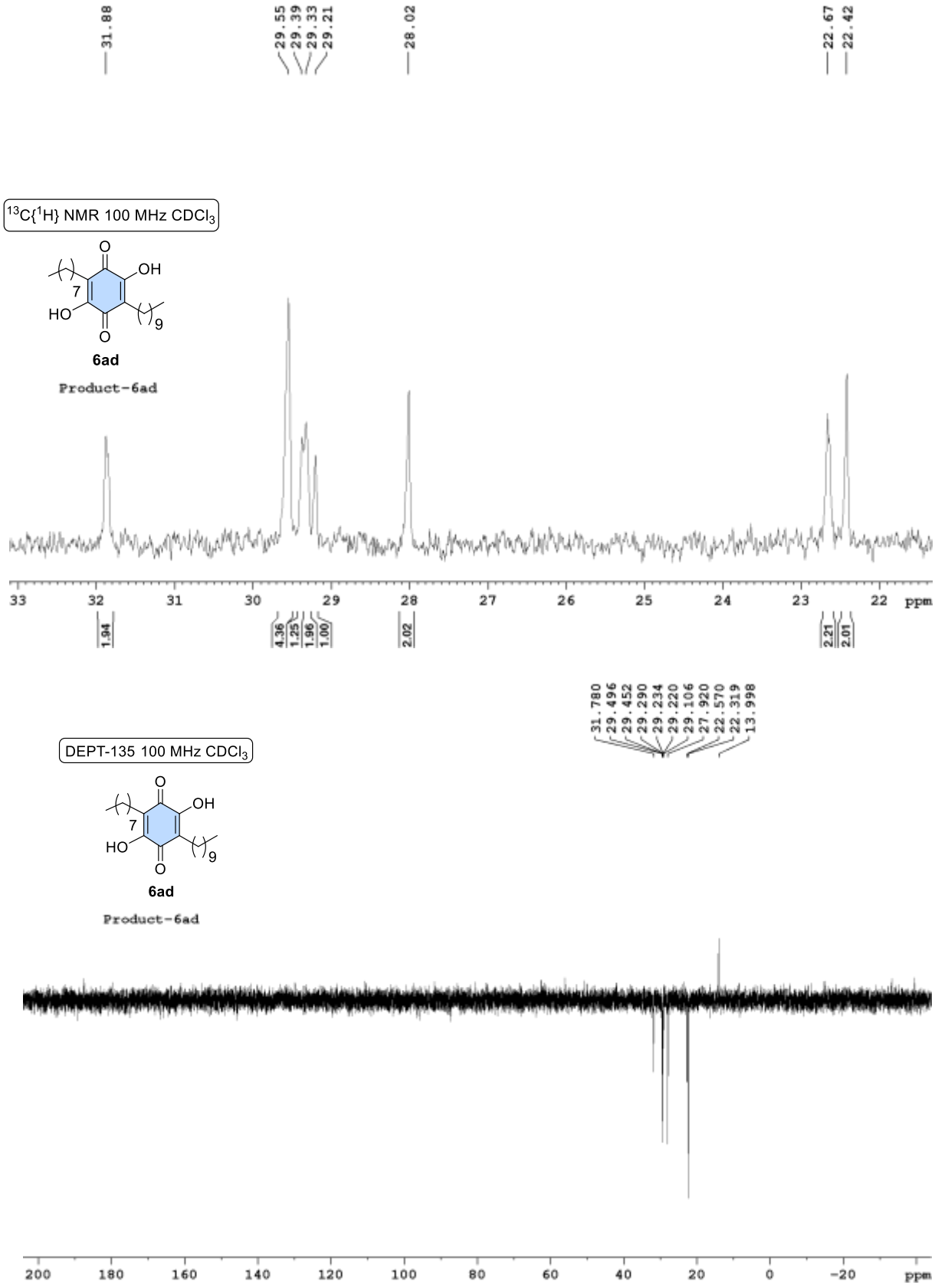
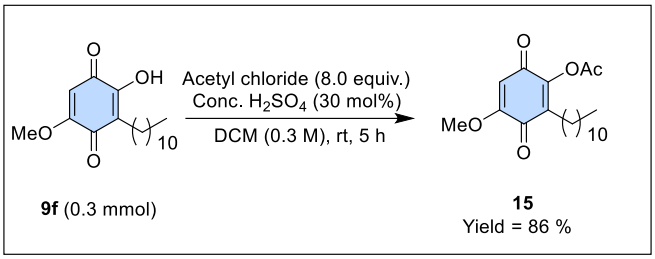


Figure 30: Expanded ^{13}C NMR and DEPT NMR spectrum of product **6ad**.

Subsequently, we went onto check the reactivity of hydroxy group in compounds **9**. O-methyl embelin **9f** having enhanced biological activity compared to its parent compound embelin 5f was treated with 8.0 equiv. of acetyl chloride with 30 mol% of conc.H_2SO_4 as catalyst in DCM solvent. The reaction went for 5 h at room temperature to give an acetyl derivative of embelin **15** (Scheme 6).



Scheme 6: Exploring the reactivity of *O*-methylembelin **9f**.

5.4.5 Retrosynthetic analysis for (+)-cyclospongiaquinone

After a detailed exploration of the reactivity of 2,5-dihydroxy 1,4-benzoquinones and synthesizing various natural products, we shifted our attention on synthesizing merosesquiterpenoids utilizing our methodology. In general, merosesquiterpenoids are described as a drimane system attached to a quinone moiety having signifiacant biological activities. One such example is (+)-cyclospongiaquinone derived from sponges known for its antibacterial activity. Herein, we chalked out a retrosynthetic analysis for synthesizing (+)-cyclospongiaquinone starting from commercially available (+)-sclareolide (Figure 31).

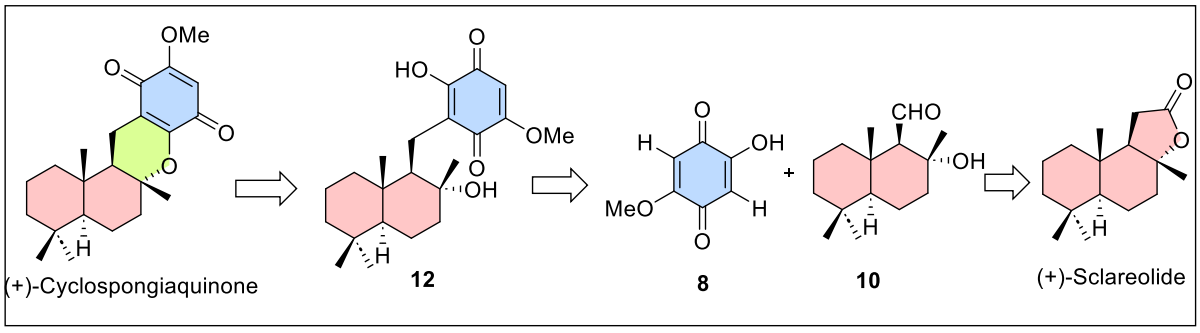
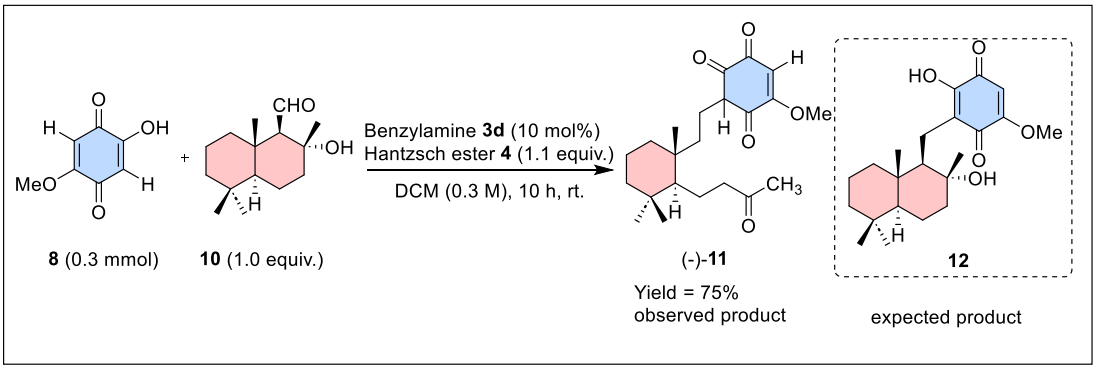


Figure 31: Retrosynthetic analysis for the formation of (+)-cyclospongiaquinone.

In accordance with the retrosynthetic analysis, we have successfully synthesized drimane aldehyde **10** from (+)-sclareolide within 3 steps following the literature protocol. We wanted to synthesize **12** utilizing similar reaction conditions as mentioned in the reaction design. We treated **8** with driminal aldehyde **10** in the presence of 10 mol% of benzylamine **3d** as a catalyst and 1.1 equiv. of hantzsch ester **4** in DCM solvent for the formation of **12**. We stirred the

reaction for 10 h at room temperature and found that instead of our expected product **12**, we got the C-C fragmentation product (-)-**11** in 75% yield. The structure of (-)-**11** was further confirmed by IR/NMR/Mass studies (Scheme 7).



Scheme 7: Attempt towards the synthesis of **12**.

^{1}H and ^{13}C NMR spectra of **12** from scheme 7 have depicted in figure 32-33

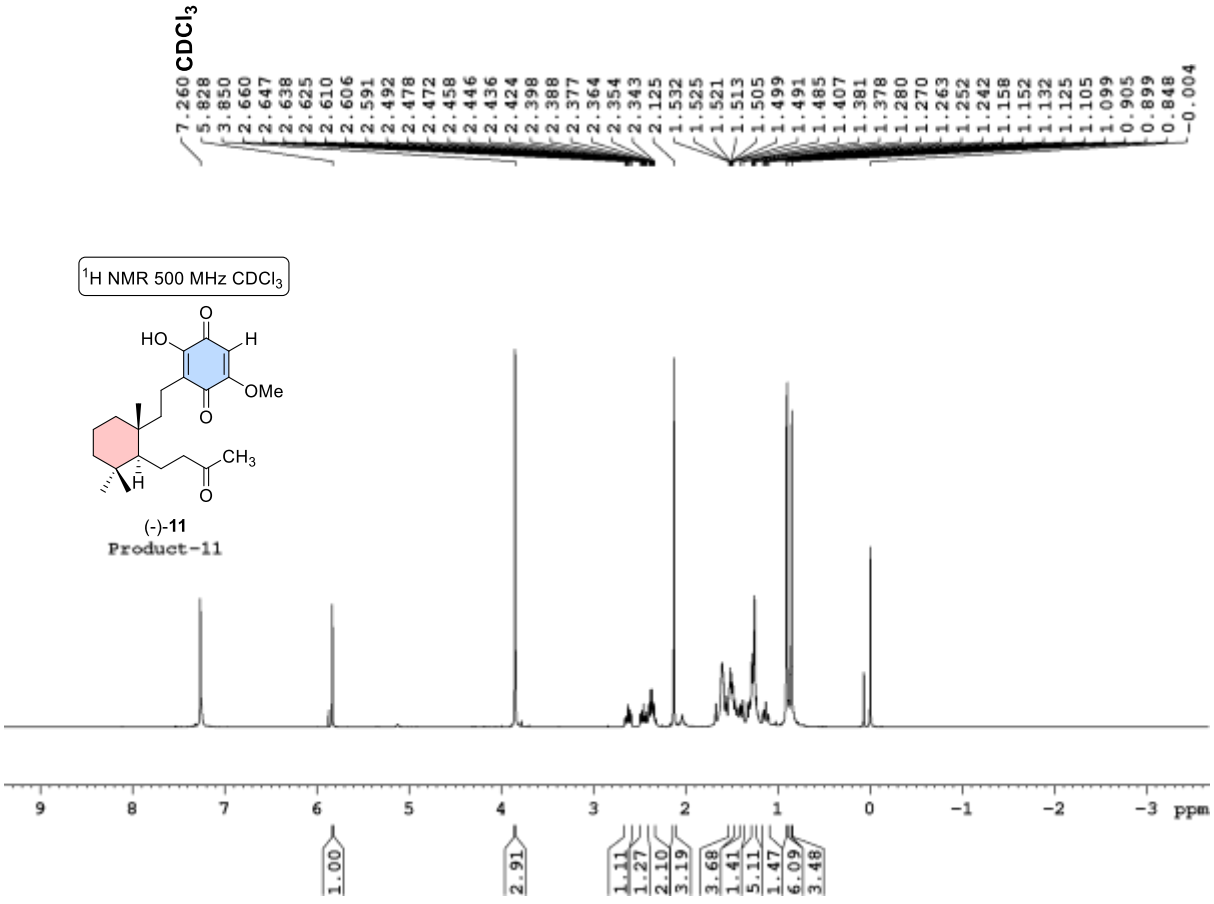


Figure 32: ^{1}H NMR spectrum of product **11**.

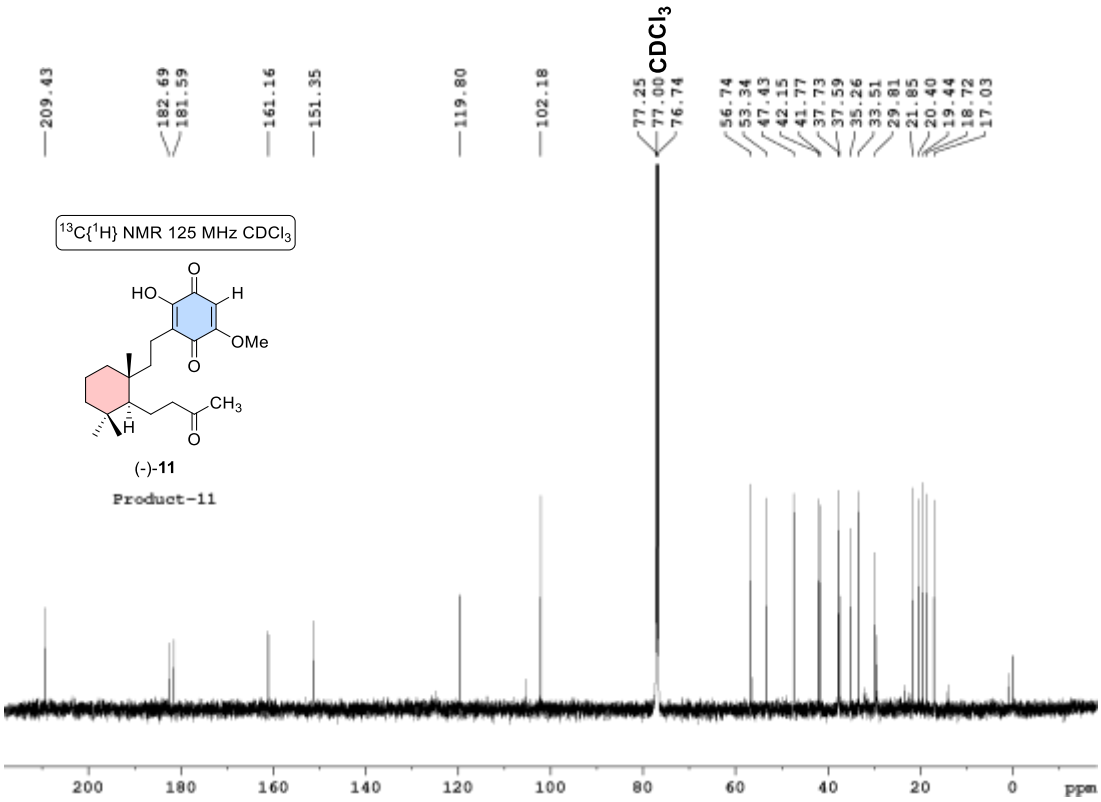
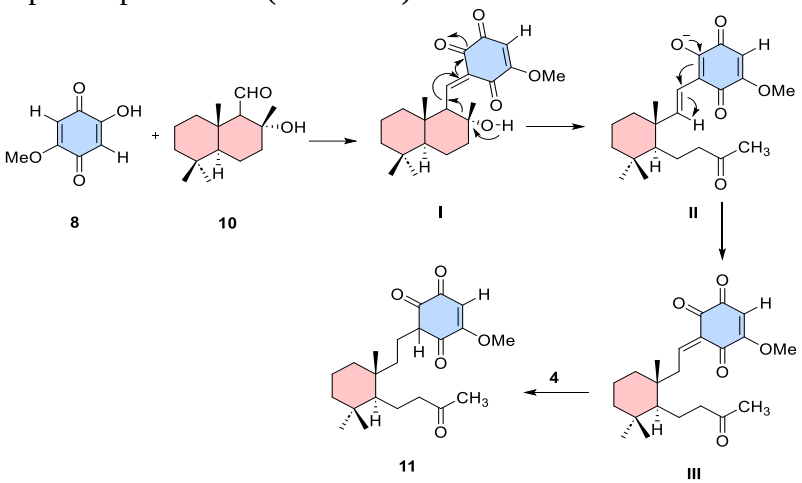
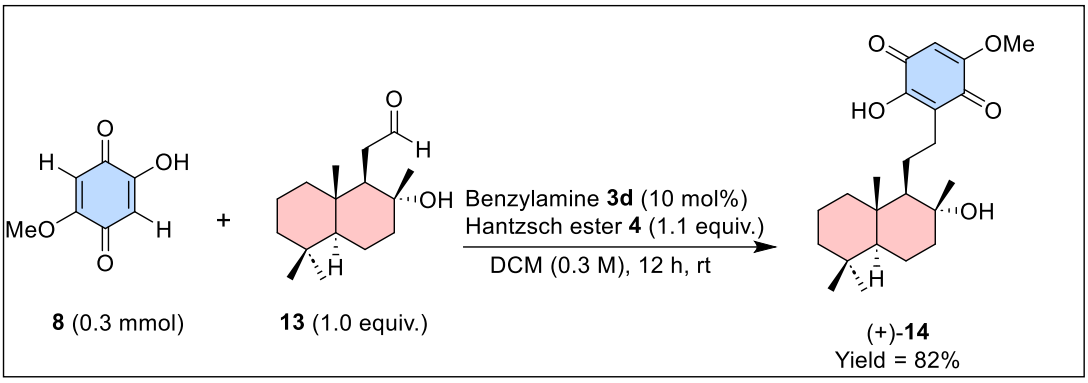


Figure 33: ^{13}C NMR spectrum of product **11**.

A plausible mechanistic approach has been proposed for the formation of product 11. Treatment of 8 with 10 results in the formation of Knoevenagel product **I**. This formation of product **1** acts a trigger for the C-C bond cleavage attached to the OH group which further results in the formation of ionic species **II**. The enolate ion formed returns back to its original state resulting in the formation of **III**. The double bond formed in **III** gets reduced by **4** to give the unexpected product **11** (Scheme 8).



Scheme 8: Plausible mechanistic outline for the formation of unexpected product **11**.



Scheme 9: Attempt towards the synthesis of analogues of (+)-cyclospongiaquinone.

Undeterred by the above outcome, we have tried to synthesize the analogues for (+)-cyclospongiaquione using similar reaction conditions. We have treated **8** with aldehyde **13** also prepared from (+)-sclareolide in the presence of 10 mol% of benzylamine and DCM solvent for 12 h at room temperature to give our expected product (+)-**14**. Product (+)-**14** was subjected to various catalysts for the preparation of desired cyclized analogue of cyclospongiaquinone, however no successful outcomes were obtained (Scheme 9).

^{1}H and ^{13}C NMR spectra of **14** from scheme 9 have depicted in figure 34-35

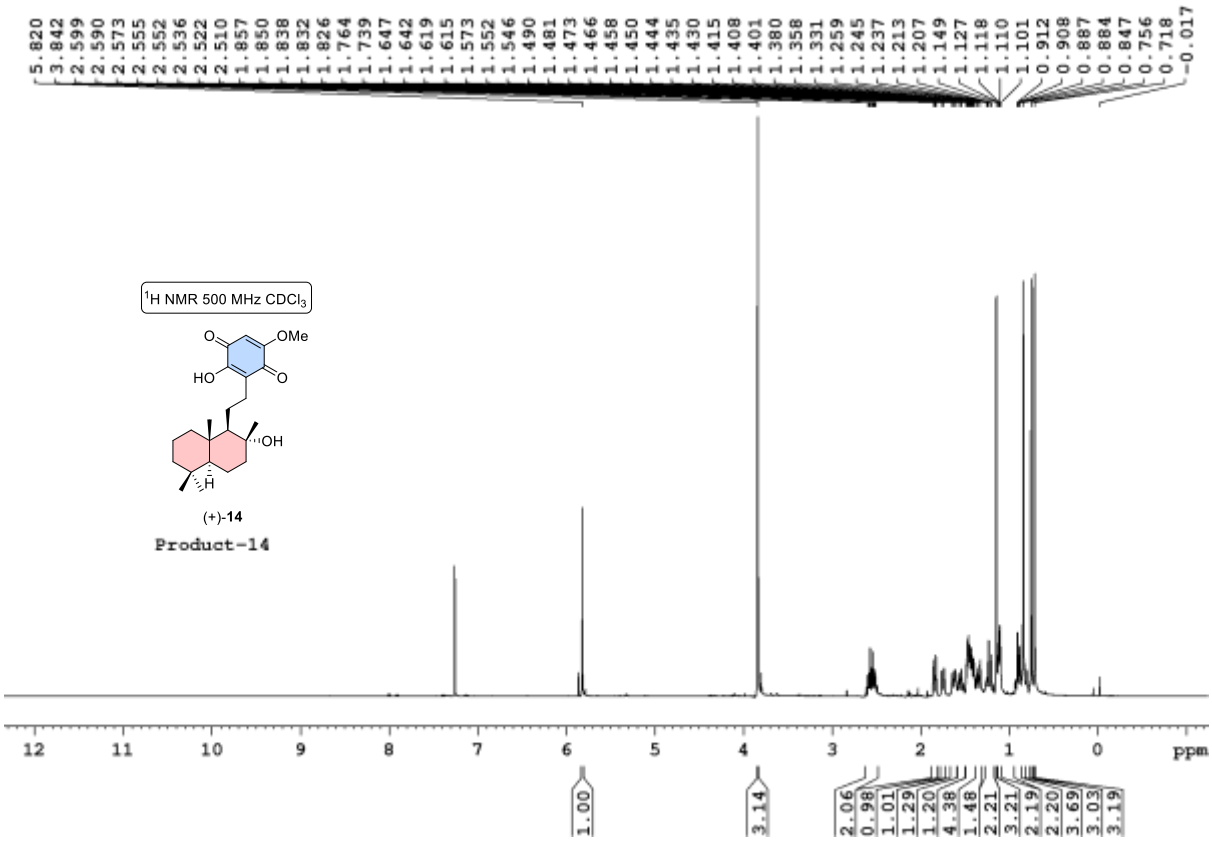


Figure 34: ^{1}H NMR spectrum of product **14**.

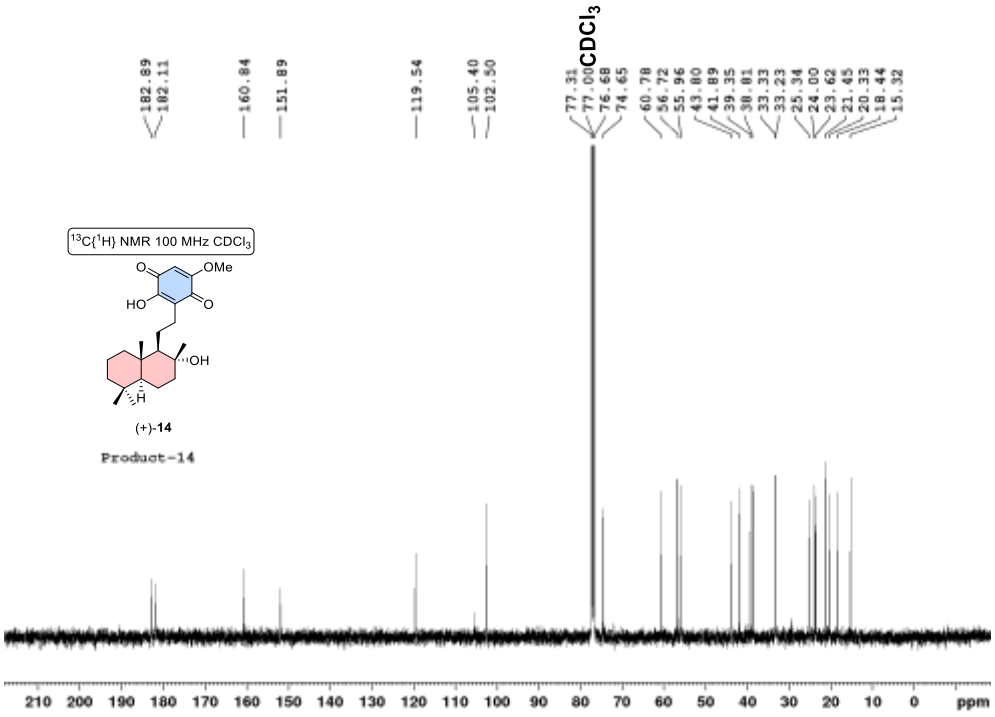
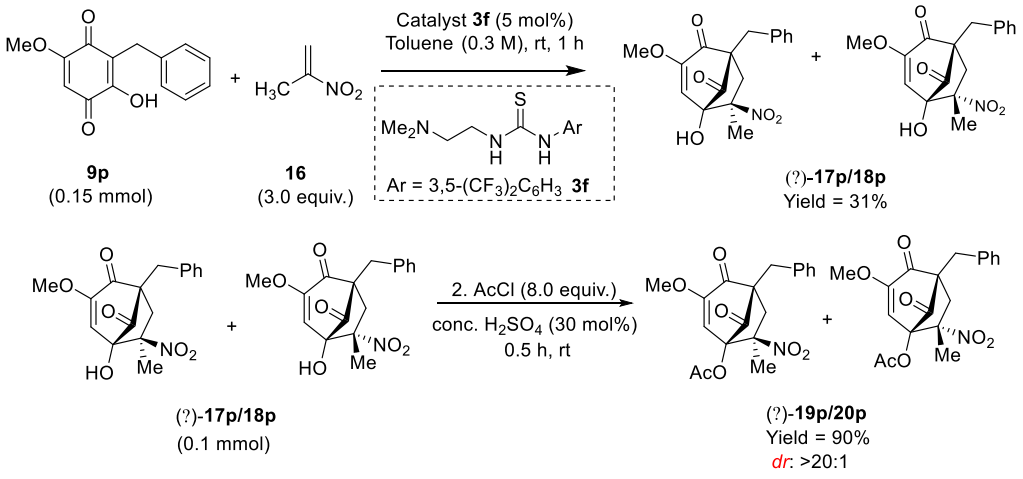


Figure 35: ^{13}C NMR spectrum of product **14**.

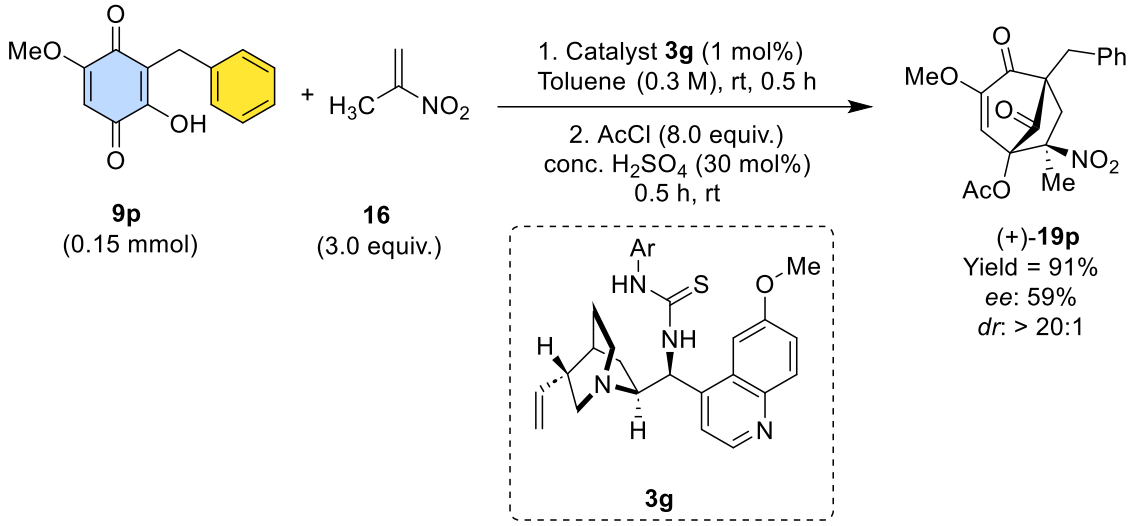
5.4.6 Further synthetic transformations on 9p.

To avoid the immediate discouragement from the latter results, we further tried to extend the applicability of synthesized quinones **9**. We treated **9p** with 3.0 equiv. of α-methyl nitroethylene **16** in toluene in the presence of 5 mol% of achiral thiourea **3f** catalyst at room temperature to give racemic mixture of (±)-**17p/18p** in 31% yield with *dr* of 3:1. Racemic mixture of (±)-**17p/18p** couldn't be separated in HPLC due to epimerization of *a*-tert hydroxyl group evident from our previous experience. 0.1 mmol of (±)-**17p/18p** was treated with 8.0 equiv. of acetyl chloride in the presence of 30 mol% of conc.H_2SO_4 to give acetylated (±)-**19p/20p** with 90% yield and a *dr* of 20:1 which was well separated in HPLC (Scheme 10).



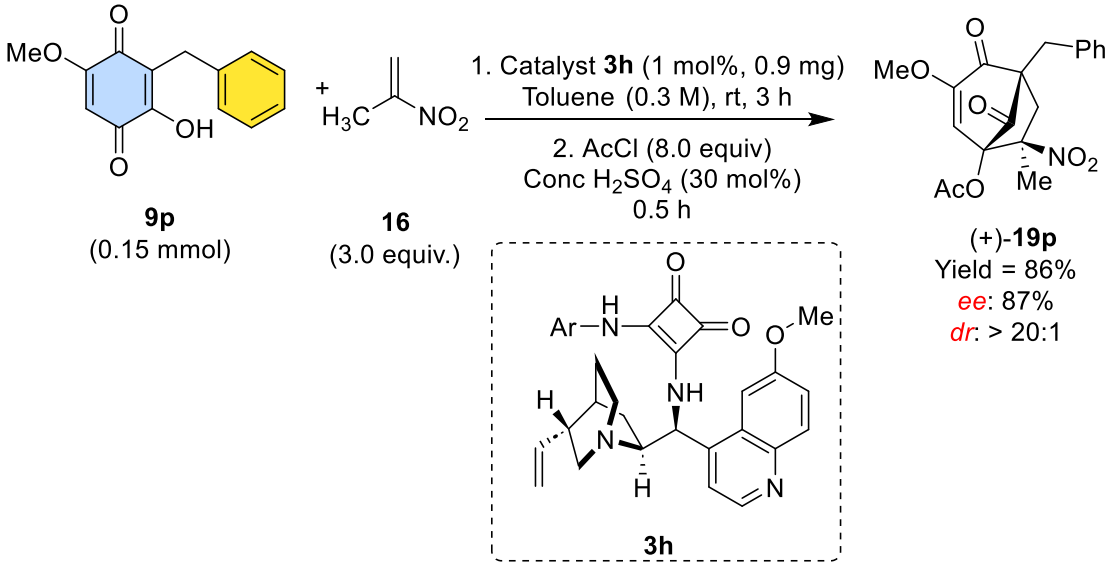
Scheme 10: Further synthetic transformations on **9p**.

We also wanted to develop a chiral version of the reaction design, simultaneously in one pot and in view of that we employed 1 mol% of chiral catalyst **3g** for 30 min to give (+)-**19p** with 91% yield and an excellent *dr* of 20:1 but a diminished *ee* of 59% (Scheme 11).



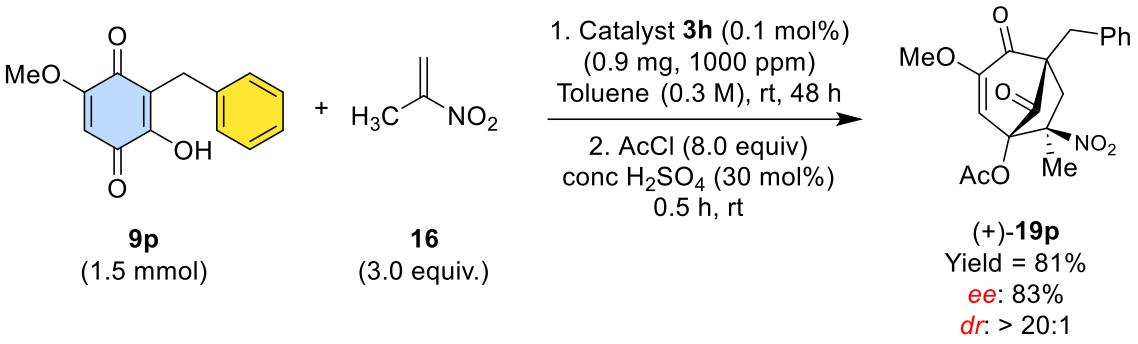
Scheme 11: A one-pot reaction on **9p** employing chiral catalyst **3g**.

In order to get a better *ee*, we changed the catalyst from **3g** to **3h** and checked for its reactivity. To our delight, we got a drastic jump in the *ee* of (+)-**19p** from 59% to 87% with excellent yield and excellent diastereoselectivity (Scheme 12).



Scheme 12: A one-pot reaction on **9p** employing chiral catalyst **3h**.

5.4.7 Investigation of low catalyst loading on [3+2]-annulation reactions: Although we have successfully synthesized (+)-**19p** with high enantioselectivity and diastereoselctivity utilizing only 1 mol% of **3h** catalyst, we further decreased the catalyst loading from 1 mol% to 0.1 mol% or 1000 ppm to check its reactivity. We have successfully synthesized (+)-**19p** in 81% yield with excellent *dr* of >20:1 but a slight decrement in the *ee* to 83% (Scheme 13).



9p
(1.5 mmol)

16
(3.0 equiv.)

(+)-**19p**
Yield = 81%
ee: 83%
dr: > 20:1

Scheme 13: Investigation of low catalyst loading on [3+2]-annulation reactions employing chiral catalyst **3h**.

^{1}H, ^{13}C NMR and HPLC spectra of (+)-**19p** from scheme 13 have depicted in figure 36-38.

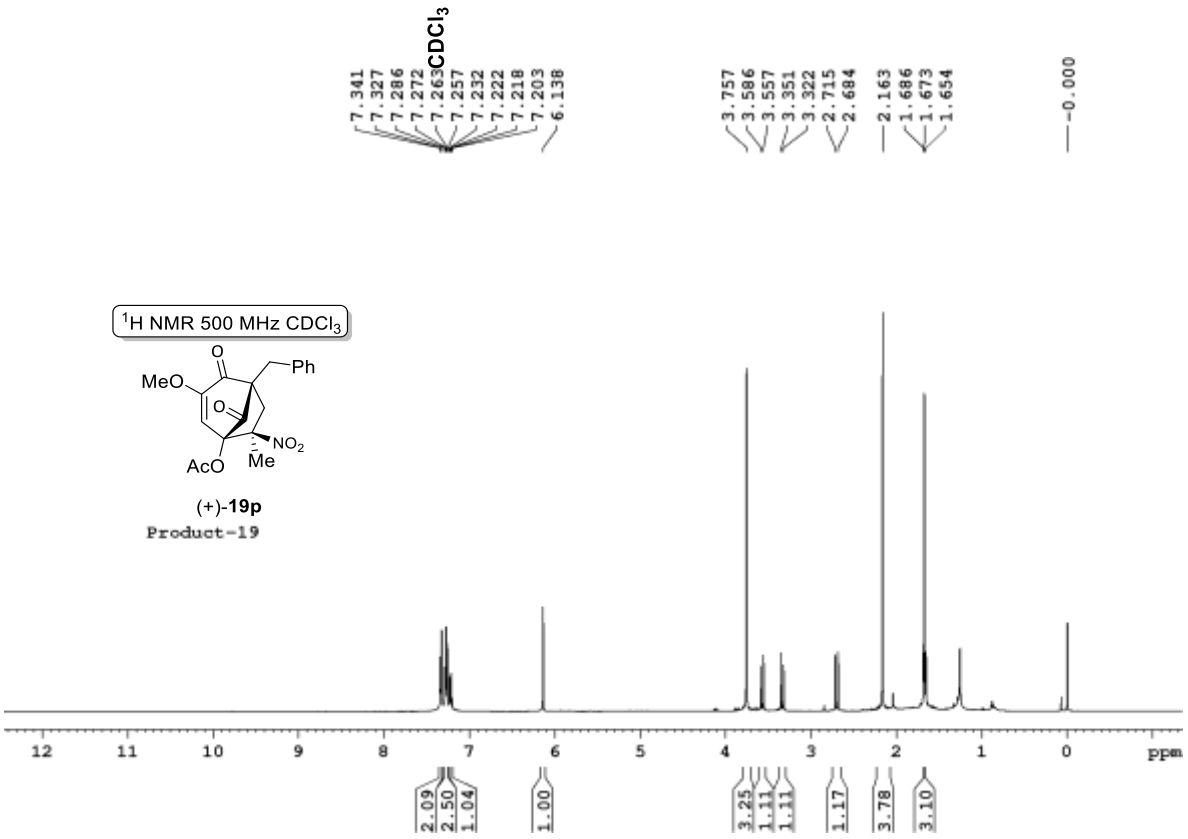


Figure 36: ^{1}H NMR spectrum of product **19p**.

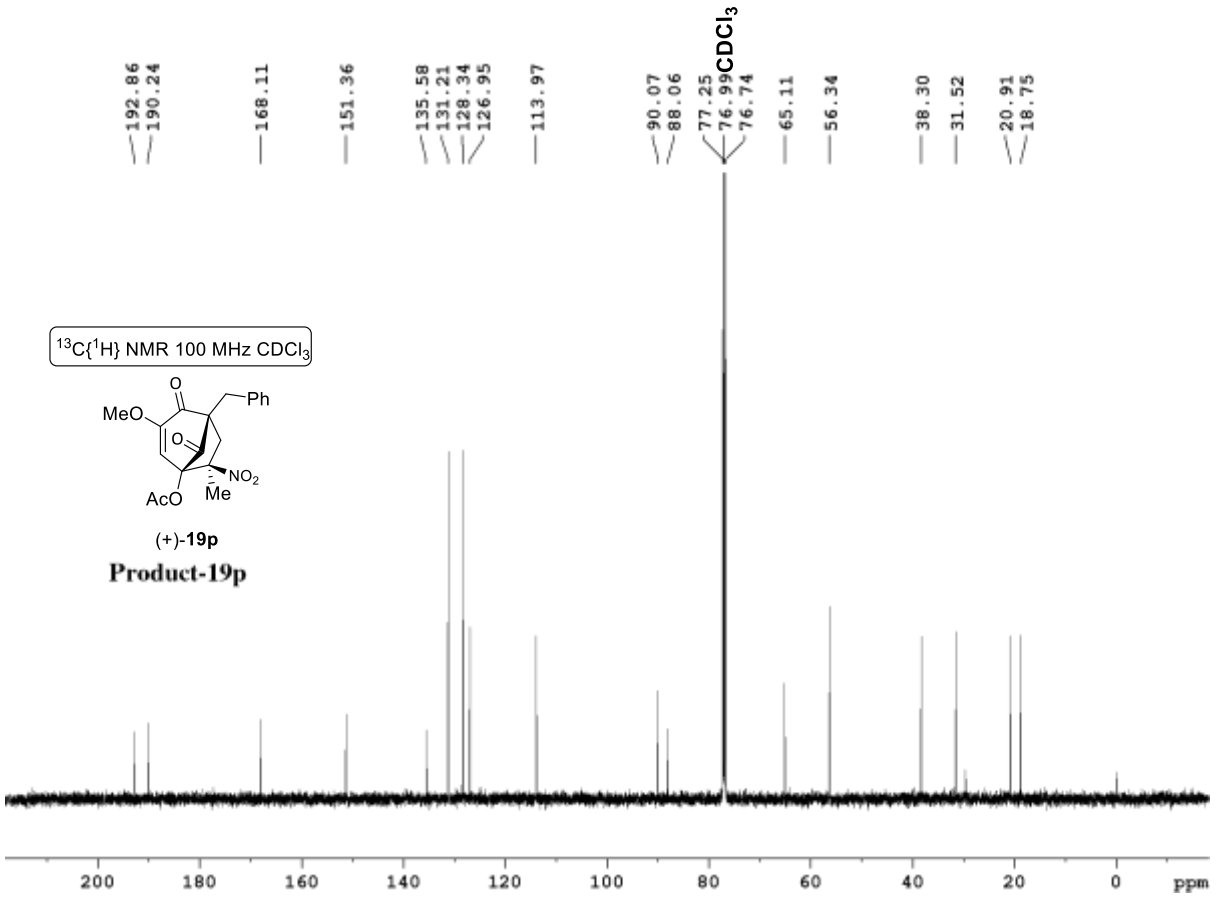
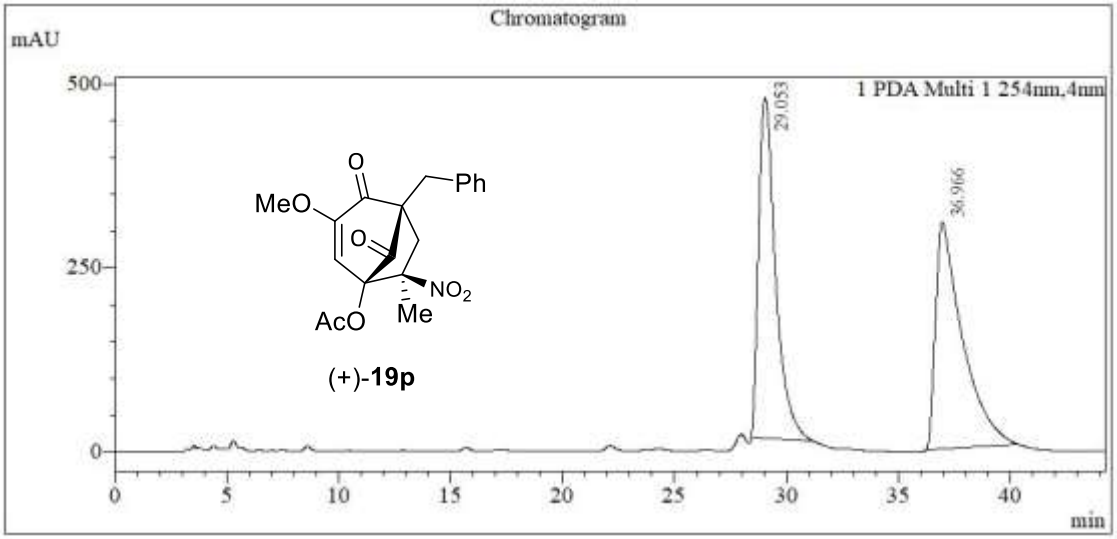


Figure 37: ^{13}C NMR spectrum of product **19p**.

Racemic (±)-**19p**



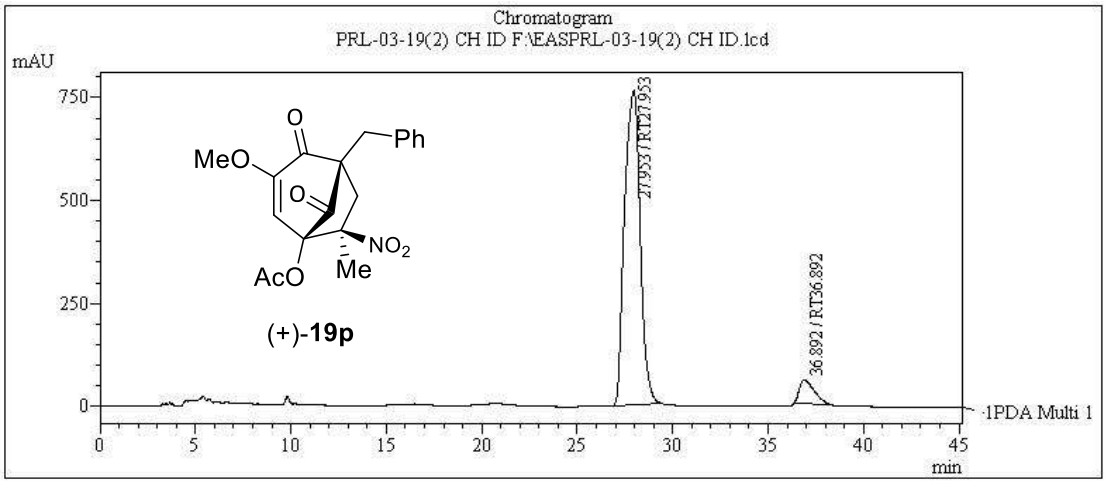
Chiralpak ID, Hexane/ *i*-PrOH = 90:10, Flow Rate 1.0 mL/min 254nm

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:29.053	29.053	24312581	461762	48.674	60.008
2	RT:36.966	36.966	25637756	307739	51.326	39.992
Total			49950337	769501	100.000	100.000

Chiral (+)-**19p (1.0 mol%)**



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

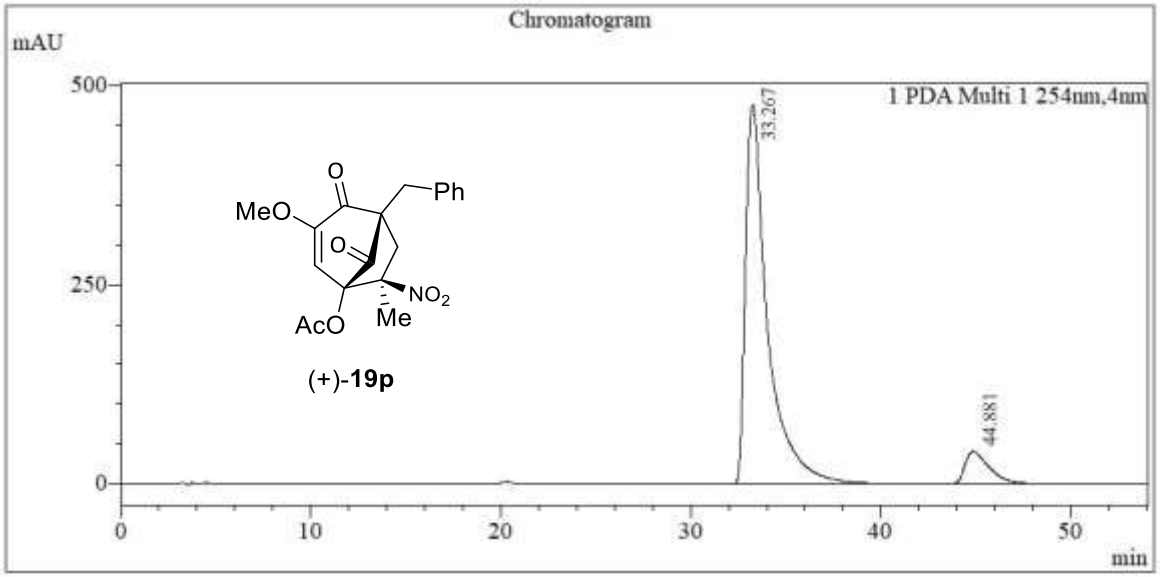
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT27.953	27.953	43587476	764156	93.396	92.982
2	RT36.892	36.892	3082122	57673	6.604	7.018
Total			46669598	821829	100.000	100.000

Figure 38: HPLC spectra of the product **(+) 19p**.

Chiral (+)-**19p (0.1 mol%)**



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

Peak Table

PDA Ch1 254nm

Peak#	Name	Ret. Time	Area	Height	Area%	Height%
1	RT:33.267	33.267	38200843	475291	91.620	92.199
2	RT:44.881	44.881	3493819	40216	8.380	7.801
Total			41694662	515507	100.000	100.000

Figure 39: HPLC spectra of the product (+) **19p**.

5.5 Conclusion

we have successfully synthesized various natural products in single step such as embelin **5f** irisoquin family **9k-9n**, rapanone **5h** having antifertility, antibacterial, analgesic and antitumour properties. A wide library of compounds **9a-9x** has been synthesized by treating **8** with various aliphatic and aromatic aldehydes **2**. Several synthetic illustrations have been demonstrated on the core moiety of **8** with various aldehydes. The applicability of reaction methodology is not only restricted to the synthesis of natural products but also to develop low catalyst loading reactions. We have successfully demonstrated ppm level loading reactions in this design and biological studies are underway for the synthesized products.

5.6 Experimental section:

General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 500, 400, 125 and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) 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. 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 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. 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione used in the synthesis of compound **8** and aldehydes **2a** to **2o** and nitroolefin **16** were prepared according to the literature procedures.

Procedure A: **Benzylamine Catalysed Cascade Three-Component Reductive Alkylation (TCRA) Reactions with 2-Hydroxy-5-isopropyl-1,4-quinone**:

For Table 2 and Table 3: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the aldehyde **2a**, 0.3 mmol of 2-Hydroxy-5-isopropyl-1,4-quinone **1a** and 0.33 mmol of Hantzsch ester **4** was added in 1.0 mL of DCM, and then catalyst benzylamine **3** (10 mol%) was added and the reaction mixture was stirred at room temperature for 40 min-3 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products **5a-5bl** were obtained in 52-74% yield (silica gel, mixture of hexane/ethyl acetate).

Procedure B: **Synthesis of 3-ethyl-2,5-dihydroxycyclohexa-2,5-diene-1,4-dione**:

For Table 8: **5c-5h** were synthesized according to the reported literature procedures.

Procedure C: **Synthesis of 2-benzyl-5-alkyl-3,6-dihydroxycyclohexa-2,5 diene-1,4-dione**:

For Table 5: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the aldehyde **2a**, 3-ethyl-2,5-dihydroxycyclohexa-2,5-diene-1,4-dione **5**, and 0.33 mmol of Hantzsch ester **4** was added 1.0 mL of DCM, and then the catalyst benzylamine **3** (10 mol%) was added, and the reaction mixture was stirred at room temperature for 1-8 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup,

and pure products **6fp-6ad** were obtained in 70-91% yield (silica gel, mixture of hexane/ethyl acetate).

Procedure D: 2-hydroxy-5-methoxy-3-(2-((1*R*,2*S*)-1,3,3-trimethyl-2-(3-oxobutyl)cyclohexyl)ethyl)cyclohexa-2,5-diene-1,4-dione (11): In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the aldehyde **10/13**, 0.3 mmol of 2-Hydroxy-5-isopropyl-1,4-quinone **1a** and 0.6 mmol of Hantzsch ester **4** was added in 1.0 mL of DCM, and benzylamine **3d** (0.03 mmol) was added and the corresponding reaction mixture was stirred at room temperature for 10-12 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products **11** and **14** were obtained in 75 and 82% yield respectively. (silica gel, mixture of hexane/ethyl acetate).

Procedure E: Preparation of racemic 5-benzyl-3-methoxy-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (17p/18p): In a 10 mL round-bottom flask equipped with a magnetic stirring bar, to 0.015 mmol of the thiourea catalyst **3f** and 0.3 mmol of 3-benzyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione **9p** was added 0.1 mL of toluene, 0.9 mmol of nitroethylene **16** (0.9 mL, 1.0 M in toluene.) was added and the reaction mixture was stirred at room temperature for 1 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products (±)-**17p**/**18p** were obtained in 31% yield (silica gel, mixture of hexane/ethyl acetate).

Procedure F: Preparation of racemic 1-benzyl-5-hydroxy-3-methoxy-6-methyl-6-nitrobicyclo[3.2.1]oct-3-ene-2,8-dione (±)-**19p**/**20p**: In an oven dried 10 mL round bottom flask equipped with a magnetic stirring bar, to the compound (±)-**17p/18p** (0.1 mmol) in dry toluene (0.4 mL), acetyl chloride (0.78 mmol, 8.0 equiv., 55.65 µl) and H_2SO_4 (0.0234 mmol, 30.0 mol%, 1.25 µl) were added. The reaction mixture was stirred at 25 ºC for 0.5 h. Pure products (±)-**19p**/**20p** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure G: Preparation of chiral 5-benzyl-3-methoxy-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (+)-**19p (one pot)**: In an oven-dried round bottom flask equipped with a magnetic stirring bar, to 0.3 mmol of 3-benzyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione **9p** (1.5 mmol) and chiral catalyst quinine squaramide **3h** (1.0 mol%) in 0.05 mL of toluene at rt was added 0.45 mmol (0.45 mL, 1.0 M in toluene) of nitroolefin **16**. The reaction mixture was stirred at rt for 48 h. After completion of the reaction, acetyl chloride (1.20 mmol, 8.0 equiv., 85.62 µl) and H_2SO_4 (0.045 mmol, 30.0 mol%,

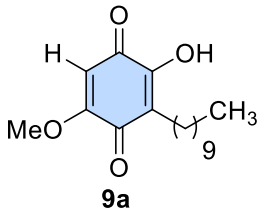
2.40 µl) were added. The reaction mixture was stirred at 25 ºC for 0.5 h. Pure products (+)-**19p** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure H: Preparation of 2-ethyl-4-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl acetate (15f): In an oven dried 10 mL round bottom flask equipped with a magnetic stirring bar, to the compound **9f** (0.3 mmol) in dry DCM (1.0 mL), acetyl chloride (8.0 equiv.) and H_2SO_4 (30.0 mol%,) were added. The reaction mixture was stirred at 25 ºC for 5 h. Pure products **15f** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure I: Preparation of 2,5-didecyl-3,6-dihydroxycyclohexa-2,5-diene-1,4-dione (6a): In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the aldehyde **2a**, 0.3 mmol of 2-Hydroxy-5-isopropyl-1,4-quinone **1a** and 0.39 mmol of Hantzsch ester **4** was added in 1.0 mL of DCM, and then catalyst proline **3a** (10 mol%) was added and the reaction mixture was stirred at room temperature for 9 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade product **6a** was obtained in 26% yield (silica gel, mixture of hexane/ethyl acetate).

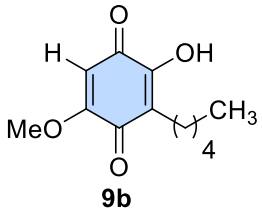
Procedure J: Preparation of 2,5-dibenzyl-3,6-dihydroxycyclohexa-2,5-diene-1,4-dione (6p): In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the aldehyde **2a**, 0.3 mmol of 2-Hydroxy-5-isopropyl-1,4-quinone **1a** and 0.33 mmol of Hantzsch ester **4** was added in 1.0 mL of DCM, and then catalyst proline **3a** (10 mol%) was added and the reaction mixture was stirred at 50 ºC for 24 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade product **6p** was obtained in 30% yield (silica gel, mixture of hexane/ethyl acetate).

3-Decyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9a): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated as yellow solid. Yield: 82% (72.4 mg). Mp.: 105-107 ºC; IR (Neat): ν_{max} 3349, 2953, 2915, 2848, 1632, 1594, 1467, 1442, 1307, 1196, 1111, 1030, 837 and 682 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.83 (1H, s), 3.85 (3H, s, *OCH*$_3$), 2.43 (2H, t, *J* = 7.6 Hz), 1.44 (2H, pentet, *J* = 7.6 Hz), 1.28-1.24 (14H, m), 0.86 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.7 (C, *C*=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH*$_3$), 31.9 (CH_2), 29.6 (CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{26}O_4H$ 295.1909; Found 295.1907.



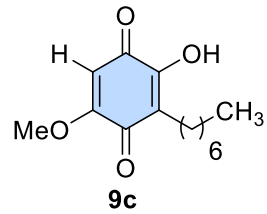
9a

2-hydroxy-5-methoxy-3-pentylcyclohexa-2,5-diene-1,4-dione (9b): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 80% (53 mg). Mp.: 90-92 ºC; IR (Neat): ν_{max} 3345, 2925, 1630, 1590, 1441, 1463, 1296, 1197, 1108, 1039, 837 and 683 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28 (1H, br s, *OH)*, 5.83 (1H, s), 3.84 (3H, s, *OCH_3*), 2.42 (2H, t, *J* = 7.5 Hz), 1.45 (2H, quintet, *J* = 7.0 Hz), 1.29 (4H, d, *J* = 3.0 Hz), 0.86 (3H, t, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.7 (C, *C*=O), 161.1 (C), 151.6 (C), 119.3 (C), 102.2 (CH), 56.7 (*OCH_3*), 31.7 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 13.9 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{16}O_4Na$ 247.0946; Found 247.0948.



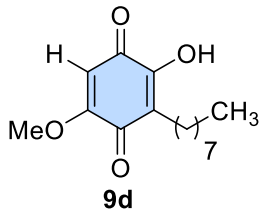
9b

3-heptyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9c): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow semi solid. Yield: 80% (60 mg). IR (Neat): ν_{max} 3337, 2922, 2845, 1630, 1594, 1462, 1442, 1442, 1355, 1234, 1203, 1111, 837 and 688 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.26 (1H br s, *OH*), 5.84 (1H, s), 3.86 (3H, s, *OCH_3*), 2.44 (2H, t, *J* = 7.5 Hz), 1.46 (2H, pentet, *J* = 7.5 Hz), 1.31-1.26 (8H, m), 0.88 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.6 (C, *C*=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH_3*), 31.7 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 28.0 (CH_2), 22.6 (2 x CH_2), 14.0 (CH_3), HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{20}O_4Na$ 275.1259; Found 275.1259.



9c

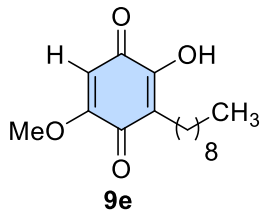
2-hydroxy-5-methoxy-3-octylcyclohexa-2,5-diene-1,4-dione (9d): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 87% (69 mg). Mp.: 128-130 ºC IR (Neat): ν_{max} 3338, 2915, 2847, 1630, 1595, 1463, 1442, 1352, 1383, 1304, 1202, 1113 1024, 983, 838, and 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (1H, br s, *OH*), 5.83 (1H, s), 3.85 (3H, s, *OCH_3*), 2.43 (2H, t, *J* = 7.5 Hz), 1.44 (2H, quintet, *J* = 7.5 Hz), 1.29-1.25 (10H, m), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.7 (C, *C*=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH_3*), 31.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 22.6 (CH_2),



9d

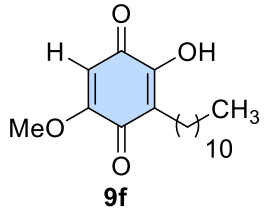
22.6 (CH_2), 14.0 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{22}O_4H$ 267.1596; Found 267.1596.

2-hydroxy-5-methoxy-3-nonylcyclohexa-2,5-diene-1,4-dione (9e): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 73% (61.4 mg). Mp.: 110-112 ºC; IR (Neat): ν_{max} 3337, 2917, 2849, 1659, 1630, 1593, 1463, 1442, 1382, 1200, 1113, 838 and 688 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.83 (1H, s), 3.85 (3H, s, *OCH₃*), 2.42 (2H, t, *J* = 7.5 Hz), 1.44 (2H, quintet, *J* = 7.0 Hz), 1.28-1.24 (12H, m), 0.87 (3H, t, *J* = 3.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.6 (C, *C*=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH₃*), 31.8 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.6 (CH_2), 22.60 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{24}O_4H$ 281.1753; Found 281.1753.



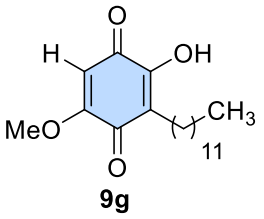
9e

2-hydroxy-5-methoxy-3-undecylcyclohexa-2,5-diene-1,4-dione (9f): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 80% (74 mg). Mp.: 104-106 ºC; IR (Neat): ν_{max} 3348, 2916, 2849, 1632, 1595, 1465, 1444, 1196, 1111, 1036, 839 and 682 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.23 (1H, br s, *OH*), 5.83 (1H, s), 3.85 (3H, s, *OCH₃*), 2.4 (2H, t, *J* = 8.0 Hz), 1.43 (2H, pent, *J* = 7.2 Hz), 1.24 (17H, s). 0.87 (3H, t, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.6 (C, *C*=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH₃*), 31.9 (CH_2), 29.63 (CH_2), 29.6 (CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.6 (CH_2) 22.61 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{28}O_4H$ 309.2066; Found 309.2066.



9f

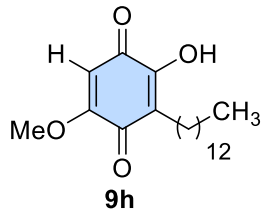
3-dodecyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9g): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 88% (85 mg). Mp.: 102-104 ºC; IR (Neat): ν_{max} 3351, 2914, 2848, 1632, 1596, 1468, 1442, 1304, 1198, 1111, 837 and 680 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.84 (1H, s), 3.86 (3H, s, *OCH₃*), 2.44 (2H, t, *J* = 7.5 Hz), 1.45 (2H, pentet, *J* = 7.0 Hz), 1.29-1.25 (18H, m), 0.88 (3H, t, *J* = 6.5); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.7 (C,



9g

C=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH₃*), 31.9 (CH_2), 29.6 (CH_2), 29.6 (2 x CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{30}O_4H$ 323.2222; Found 323.2220.

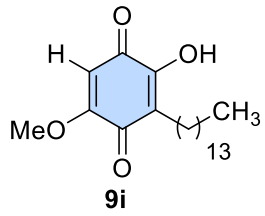
2-hydroxy-5-methoxy-3-tridecylcyclohexa-2,5-diene-1,4-dione (9h): The title compound



9h

was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 71% (100 mg). Mp.: 98-100 ºC; IR (Neat): ν_{max} 3349, 2916, 2849, 1717, 1632, 1594, 1443, 1377, 1287, 1199, 1109, 1041, 885 and 683 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.82 (1H, s), 3.84 (3H, s, O*CH₃*), 2.45 (2H, t, *J* = 7.5 Hz), 1.40 (2H, pentet, *J* = 7.5 Hz), 1.40-1.35 (21H, m), 0.82 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.7 (C, *C*=O), 161.5 (C), 151.8 (C), 119.8 (C), 102.6 (CH), 56.8 (O*C*H_3), 31.5 (CH_2), 29.7 (CH_2), 29.4 (2 x CH_2), 29.6 (3 x CH_2), 29.1 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 28.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{32}O_4H$ 337.2379; Found 337.2377.

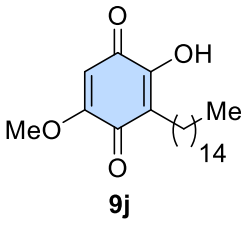
2-hydroxy-5-methoxy-3-tetradecylcyclohexa-2,5-diene-1,4-dione (9i): The title compound



9i

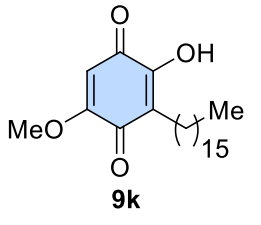
was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 84% (88 mg). Mp.: 98-100 ºC; IR (Neat): ν_{max} 3351, 2913, 2848, 1633, 1596, 1470, 1378, 1199, 1110, 1037, 837 and 681 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.84 (1H, s), 3.86 (3H, s, O*CH₃*), 2.43 (2H, t, *J* = 7.5 Hz), 1.44 (2H, pentet, *J* = 7.5 Hz), 1.30-1.25 (24H, m), 0.88 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.7 (C, *C*=O), 161.1 (C), 151.5 (C), 119.2 (C), 102.1 (CH), 56.7 (O*C*H_3), 31.9 (CH_2), 29.7 (CH_2), 29.6 (2 x CH_2), 29.6 (3 x CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{34}O_4H$ 351.2534; Found 351.2531.

2-Hydroxy-5-methoxy-3-pentadecylcyclohexa-2,5-diene-1,4-dione (9j): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 73% (80 mg). Mp.: 96-98 ºC. IR (Neat): ν_{max} 3349, 2915, 2848, 1634, 1596, 1466, 1303, 1230, 1198 1111, 1032, 839 and 684 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.83 (1H, s), 3.85 (3H, s, O*CH*$_3$), 2.43 (2H, t, *J* = 7.5 Hz), 1.44 (2H, pentet, *J* = 7.5 Hz), 1.29-1.24 (25H, m), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.7 (C, *C*=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (O*C*H$_3$), 31.9 (CH_2), 29.7 (3 x CH_2), 29.7 (2 x CH_2), 29.6 (2 x CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{36}O_4H$ 365.2692; Found 365.2692.



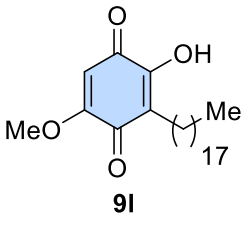
9j

3-Hexadecyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9k): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 87% (99 mg). Mp.: 142-144 ºC. IR (Neat): ν_{max} 3351, 2913, 2848, 1633, 1595, 1469, 1443, 1378, 1357, 1306, 1197, 1111, 1031, 837 and 681 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25 (1H, br s, *OH*), 5.84 (1H, s), 3.86 (3H, s, *OCH*$_3$), 2.44 (2H, t, *J* = 7.6 Hz), 1.45 (2H, pentet, *J* = 7.5 Hz), 1.25 (26H, s), 0.88 (3H, t, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.6 (C, *C*=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH*$_3$), 31.9 (CH_2), 29.7 (3 x CH_2), 29.7 (2 x CH_2), 29.6 (2 x CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{38}O_4H$ 379.2848; Found 379.2848.



9k

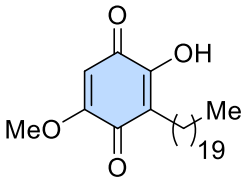
2-Hydroxy-5-methoxy-3-octadecylcyclohexa-2,5-diene-1,4-dione (9l): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 81% (95.4 mg). Mp.: 130-132 ºC. IR (Neat): ν_{max} 3351, 2913, 2848, 1633, 1596, 1471, 1442, 1378, 1310, 1197, 1111, 1035, 842 and 682 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.84 (1H, s), 3.86 (3H, s, *OCH*$_3$), 2.44 (2H, t, *J* = 7.6 Hz), 1.44 (2H, quintet, *J* = 7.2 Hz), 1.30-1.25 (30H, m), 0.88 (3H, t, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.8 (C,



9l

C=O), 181.6 (C, *C*=O), 162.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH*$_3$), 31.9 (CH_2), 29.7 (6 x CH_2), 29.6 (3 x CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{42}O_4H$ 407.3161; Found 407.3161.

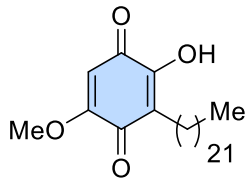
2-Hydroxy-3-icosyl-5-methoxycyclohexa-2,5-diene-1,4-dione (9m): The title compound



9m

was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 84% (109 mg). Mp.: 138-140 ºC. IR (Neat): ν_{max} 3350, 2912, 2848, 1633, 1595, 1470, 1378, 1308, 1198, 1111, 1033, 837 and 682 cm^{-1}; ^1H NMR ($CDCl_3$, 125 MHz, 500 MHz): δ 7.22 (1H, br s, *OH*), 5.84, (1H, s), 3.86 (3H, s, *OCH*$_3$), 2.44 (2H, t, *J* = 7.5 Hz), 1.48-1.42 (2H, pentet, *J* = 7.5 Hz), 1.30-1.24 (35H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.6 (C, *C*=O), 161.1 (C), 151.5 (C), 119.2 (C), 102.1 (CH), 56.7 (*OCH*$_3$), 31.9 (CH_2), 29.7 (9 x CH_2), 29.6 (2 x CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{46}O_4H$ 435.3474; Found 435.3472.

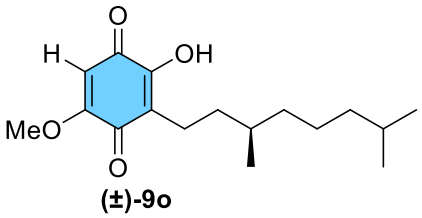
3-Docosyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9n): The title compound



9n

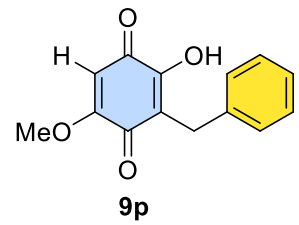
was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 78% (108.3 mg). Mp.: 120-122 ºC; IR (Neat): ν_{max} 3352, 2913, 2848, 1635, 1596, 1471, 1439, 1378, 1308, 1199, 1111, 1033, 837, 715 and 683 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (1H, br s, *OH*), 5.84, (1H, s), 3.86 (3H, s, OC*H*$_3$), 2.44 (2H, t, *J* = 7.5 Hz), 1.44 (2H, septet, *J* = 7.0 Hz), 1.25 (42 H, s), 0.88 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.7 (C, *C*=O), 161.1 (C), 151.5 (C), 119.3 (C), 102.1 (CH), 56.7 (*OCH*$_3$), 31.9 (CH_2), 29.7 (10 x CH_2), 29.6 (3 x CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{50}O_4H$ 463.3787; Found 463.3788.

3-(3,7-dimethyloctyl)-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (±)-9o: The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Yield: 85% (75 mg). Mp.: 90-92 ºC; IR (Neat): ν_{max} 3342, 2952, 1633, 1593, 1444, 1360, 1283, 1196, 1115, 837, 760 and 688 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (1H, br s, *OH*), 5.84, (1H, s), 3.86 (3H, s, *OCH₃*), 2.46-2.41 (2H, m), 1.52-1.40 (3H, m), 1.33-1.20 (4H, m), 1.15-1.08 (3H, m), 0.92 (3H, d, *J* = 6.5 Hz), 0.86 (6H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.6 (C, *C*=O), 161.1 (C), 151.4 (C), 119.6 (C), 102.2 (CH), 56.7 (*OCH₃*), 39.3 (CH_2), 36.9 (CH_2), 35.0 (CH_2), 32.9 (CH), 29.9 (CH), 24.6 (CH_2), 22.7 (CH_3), 22.6 (CH_3), 20.3 (CH_2), 19.4 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{26}O_4H$ 295.1909; Found 295.1909.



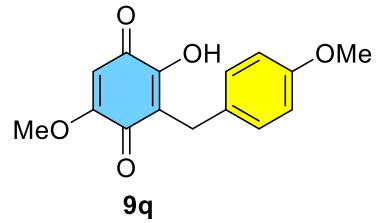
(±)-9o

3-Benzyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9p): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.2:8.8 to 2.0:8.0), and was isolated yellow solid. Mp.: 155-157 ºC. Yield: 83% (60.7 mg). IR (Neat): ν_{max} 3341, 2922, 1640, 1596, 1356, 1221, 1034, 978, 865, 742, 695 and 626 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (2H, d, *J* = 7.5 Hz), 7.24, (2H, t, *J* = 7.5 Hz), 7.16 (1H, t, *J* = 7.5 Hz), 5.83 (1H, s), 3.83 (3H, s, *OCH₃*), 3.78 (2H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.7 (C, *C*=O), 181.3 (C, *C*=O), 161.1 (C), 151.6 (C), 138.7 (C), 129.0 (2 x CH), 128.4 (2 x CH), 126.3 (CH), 117.9 (C), 102.3 (CH), 56.7 (*OCH₃*), 28.4 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{12}O_4H$ 245.0814; Found 245.0814.



9p

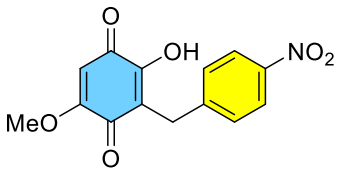
2-hydroxy-5-methoxy-3-(4-methoxybenzyl)cyclohexa-2,5-diene-1,4-dione (9q): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 2.0:8.0), and was isolated yellow semi solid. Yield: 50% (41 mg). IR (Neat): ν_{max} 3315, 2812, 1612, 1577, 1556, 1382, 1260, 1066, 1031, 952, 924, 814 and 612 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (1H, br s, *OH*), 7.24, (2H, d, *J* = 8.5 Hz), 6.78 (2H, d, *J* = 8.5 Hz), 5.82 (1H, s), 3.83 (3H, s, *OCH₃*), 3.75 (3H, s, *OCH₃*), 3.71 (2H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.4 (C, *C*=O), 161.0 (C), 158.0 (C), 151.3 (C), 130.8 (C), 130.0 (2



9q

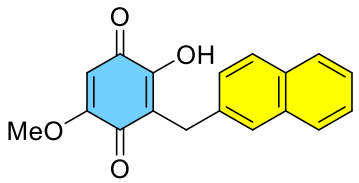
x CH), 118.2 (C), 113.7 (2 x CH), 102.2 (CH), 56.7 (*OCH₃*), 55.2 (*OCH₃*), 27.4 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{14}O_5Na$ 297.0739; Found 297.0741.

2-hydroxy-5-methoxy-3-(4-nitrobenzyl)cyclohexa-2,5-diene-1,4-dione (9r): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (2.0:8.0 to 1.0:1.0), and was isolated yellow solid. Mp.: 148-150 ºC Yield: 75% (65.0 mg). IR (Neat): ν_{max} 3321, 1647, 1597, 1512, 1376, 1346, 1304, 1210, 1166, 1041, 982, 934, 849 and 708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.12 (2H, d, *J* = 8.5 Hz), 7.49 (2H, d, *J* = 8.5 Hz), 5.91 (1H, s), 3.88 (5H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.2 (C, *C*=O), 181.0 (C, *C*=O), 161.1 (C), 152.0 (C), 146.6 (C), 146.3. (C), 129.9 (2 x CH), 123.7 (2 x CH), 116.2 (C), 102.5 (CH), 56.9 (*OCH₃*), 28.4 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{11}NO_6Na$ 312.0484; Found 312.0489.



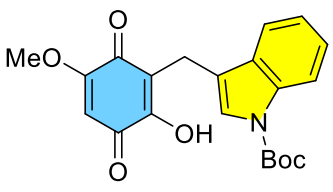
9r

2-hydroxy-5-methoxy-3-(naphthalen-2-ylmethyl)cyclohexa-2,5-diene-1,4-dione (9s): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.8:8.2 to 2.8:7.2), and was isolated yellow solid. Yield: 76% (67 mg). Mp.: 190-192 ºC; IR (Neat): ν_{max} 3328, 3066, 1656, 1595, 1356, 1310, 1211, 1032, 992, 867, 806 and 638 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.76 (2H, s), 7.73, (1H, d, *J* = 8.5 Hz), 7.47-7.40 (4H, m), 5.84 (1H, s), 3.94 (2H, s), 3.8 (3H, s, *OCH₃*); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.7 (C, *C*=O), 181.3 (C, *C*=O), 161.1 (C), 151.6 (C), 136.2 (C), 133.5 (C), 132.1 (C), 128.0 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 125.9 (CH), 125.4 (CH), 117.8 (C), 102 (CH), 56.8 (*OCH₃*), 28.5 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{14}O_4Na$ 317.0790; Found 317.0792.



9s

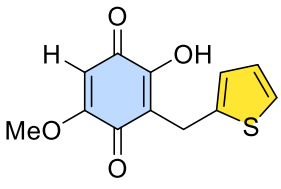
tert-butyl 3-((2-hydroxy-5-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)methyl)-1H-indole-1-carboxylate (9t): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.8:8.2 to 2.8:7.2), and was isolated yellow solid. Yield: 88% (101 mg). Mp.: 142-144 ºC; IR (Neat): ν_{max} 3331, 2926, 1726, 1646, 1605, 1452, 1360, 1308, 1254, 1214, 1155, 1081, 1036 and 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.72 (1H, d, *J* = 7.5 Hz), 7.72 (1H, d, *J* = 7.5 Hz), 7.48 (1H, s), 7.29-7.28 (1H, m), 7.21 (1H, dt, *J* = 7.7, 1.0 Hz), 5.83 (1H, s),



9t

3.85-3.84 (2H, m), 3.84 (3H, s), 1.65 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.5 (C, *C*=O), 181.0 (C, *C*=O), 161.3 (C), 151.5 (C), 149.7 (C), 135.5. (C), 130.3 (C), 124.4 (CH), 124.1 (CH), 122.4 (CH), 119.3 (CH), 117.1 (C), 116.8 (C), 115.1 (CH), 102.3 (CH), 83.3 (C), 56.6 (*OCH*$_3$), 28.2 (3 x CH_3), 18.0 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}NO_6Na$ 406.1267; Found 406.1270.

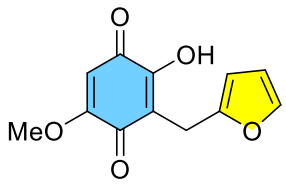
2-Hydroxy-5-methoxy-3-(thiophen-2-ylmethyl)cyclohexa-2,5-diene-1,4-dione (9u): The



9u

title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.2:8.8 to 2.0:8.0), and was isolated yellow solid. Yield: 83% (62.3 mg). Mp.: 118-120 ºC; IR (Neat): ν_{max} 3318, 2921, 1645, 1603, 1384, 1358, 1308, 1213, 1119, 1040, 844 and 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09 (1H, dd, *J* = 5.0, 1.0 Hz), 6.92 (1H, d, *J* = 2.5 Hz), 6.89 (1H, dd, *J* = 5.0, 3.5 Hz), 5.86 (1H, s), 3.97 (2H, s), 3.85 (3H, s, *OCH*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.6 (C, *C*=O), 180.9 (C, *C*=O), 161.1 (C), 151.4 (C), 140.3 (C), 126.7 (CH), 125.9 (CH), 123.9 (CH), 116.9 (C), 102.4 (CH), 56.8 (*OCH*$_3$), 22.5 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{10}O_4SNa$ 273.0197; Found 273.0196.

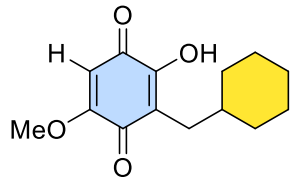
3-(furan-2-ylmethyl)-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9v): The title



9v

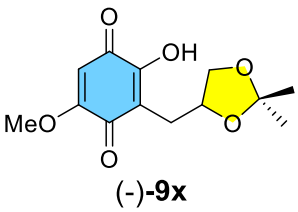
compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.2:8.8 to 2.0:8.0), and was isolated yellow solid. Yield: 86% (60.4 mg). Mp.: 110-112 ºC. IR (Neat): ν_{max} 3331, 1642, 1595, 1382, 1355, 1304, 1203, 1117, 1038, 841and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (1H, br s, *OH*), 6.25 (1H, dd, *J* = 3.0 Hz, 2.0 Hz), 6.07 (1H, dd, *J* = 3.0, 0.5 Hz), 5.87 (1H, s), 3.86 (3H, s, *OCH*$_3$), 3.82 (2H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.5 (C, *C*=O), 180.8 (C, *C*=O), 161.1 (C), 152.1 (C), 151.4 (C), 141.2 (CH), 114.6 (C), 110.3 (CH), 106.3 (CH), 102.4 (CH), 56.8 (*OCH*$_3$), 21.3 (CH_2); HRMS (ESI-TOF) m/z: $[M + K]^+$ Calcd for $C_{12}H_{10}O_5K$ 273.0165; Found 273.0169.

3-(cyclohexylmethyl)-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione (9w): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.0), and was isolated yellow solid. Mp.: 160-162 ºC. Yield: 74% (55.5 mg). IR (Neat): ν_{max} 3368, 2926, 1628, 1590, 1448, 1379, 1298, 1245, 1202, 1120, 1029, 969, 835, and 675 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30 (1H, br s, *OH*), 5.85 (1H, s), 3.86 (3H, s), 2.35 (2H, d, *J* = 7.0 Hz), 1.72-1.5 (5H, m), 1.22-1.09 (3H, m), 1.01-0.94 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 182.8 (C, *C*=O), 181.9 (C, *C*=O), 161.1 (C), 152.0 (C), 118.1 (C), 102.2 (CH), 56.8 (*OCH*$_3$), 37.1 (CH), 33.2 (2 x CH_2), 30.1 (CH_2), 26.4 (CH_2), 26.2 (2 x CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{18}O_4H$ 251.1283; Found 251.1285



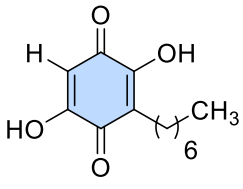
9w

3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione ((-)-9x): The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.2:8.8 to 2.0:8.0), and was isolated yellow semi solid. Yield: 88% (70.8 mg). IR (Neat): ν_{max} 3296, 2926, 1648, 1605, 1380, 1305, 1213, 1152, 1064, and 842 cm^{-1}; $[\alpha]_D^{25}$ = -2.50° [c = 0.100 g/100 mL, $CHCl_3$; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.65 (1H, br s, *OH*), 5.86 (1H, s), 4.32 (1H, sextet, *J* = 6.0 Hz), 4.02 (1H, dd, *J* = 8.5, 6.0 Hz), 3.85 (3H, s, *OCH*$_3$), 3.68 (1H, dd, *J* = 8.0, 6.0 Hz), 2.84 (1H, dd, *J* = 13.5, 7.5 Hz), 2.65 (1H, dd, *J* = 13.5, 6.0 Hz), 1.43 (3H, s), 1.31 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.3 (C, *C*=O), 181.4 (C, *C*=O), 161.0 (C), 153.1 (C), 114.6 (C), 109.3 (C), 102.6 (CH), 74.2 (CH), 56.8 (*OCH*$_3$), 69.2 (CH_2), 27.5 (CH_2), 26.8 (CH_3), 25.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{16}O_6Na$ 291.0845; Found 291.0847.



(-)-9x

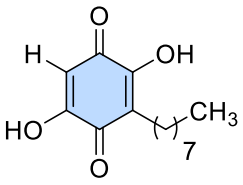
3-heptyl-2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (5c): The title compound was prepared following the procedure **B**, purified by column chromatography using EtOAc/hexane (3.0:7.0 to 4.0:6.0), and was isolated yellow solid. Yield: 91%. Mp.: 112-114 ºC; IR (Neat): ν_{max} 3304, 2954, 2922, 2854, 1611, 1393, 1346, 1322, 1188, 1113, 944, 884, 767 and 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.71 (2H, br s, *OH*), 6.00 (1H, s), 2.44 (2H, t, *J* = 7.5 Hz), 1.47 (2H, quintet, *J* = 7.5 Hz), 1.31-1.27 (8H, m), 0.87 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 117.0 (C), 102.2 (CH), 31.7



5c

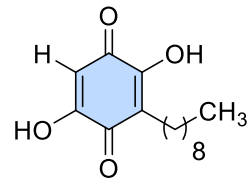
(CH_2), 29.5 (CH_2), 29.0 (CH_2), 27.9 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 14.0 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{18}O_4H$ 239.1283; Found 239.1283.

2,5-dihydroxy-3-octylcyclohexa-2,5-diene-1,4-dione (5d): The title compound was prepared following the procedure **B**, purified by column chromatography using EtOAc/hexane (3.0:7.0 to 4.0:6.0), and was isolated red solid. Yield: 93%. Mp.: 150-152 ºC; IR (Neat): ν_{max} 3301, 2920, 2851, 1611, 1460, 1330, 1272, 1184, 956, 904, 767 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.72 (2H, br s, *OH*), 6.01 (1H, s), 2.45 (2H, t, *J* = 7.5 Hz), 1.47 (2H, quintet, *J* = 7.0 Hz), 1.30-1.26 (10H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 117.0 (C), 102.2 (CH), 31.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.9 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{20}O_4Na$ 275.1529; Found 275.1259



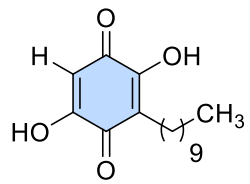
5d

2,5-dihydroxy-3-nonylcyclohexa-2,5-diene-1,4-dione (5e): The title compound was prepared following the procedure **B**, purified by column chromatography using EtOAc/hexane (3.0:7.0 to 4.0:6.0), and was isolated yellow solid. Yield: 90% (72 mg). Mp.: 145-147 ºC; IR (Neat): ν_{max} 3303, 2918, 2848, 1610, 1460, 1323, 1262, 1181, 965, 859, 767 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.23 (2H, br s, *OH*), 6.0 (1H, s), 2.44 (2H, t, *J* = 7.5 Hz), 1.47 (2H, quintet, *J* = 7.5 Hz), 1.29-1.25 (12H, m), 0.87 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 117.0 (C), 102.2 (CH), 31.8 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{22}O_4H$ 267.1596; Found 267.1591.



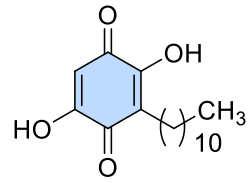
5e

3-decyl-2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (5a): The title compound was prepared following the procedure **B**, purified by column chromatography using EtOAc/hexane (3.0:7.0 to 4.0:6.0), and was isolated semi solid. Yield: 89% (74.8 mg). IR (Neat): ν_{max} 3302, 2919, 2850, 1699, 1612, 1331, 1318, 1181, 1117, 767 and 709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.71 (2H, br s, *OH*), 6.00 (1H, s), 2.44 (2H, t, *J* = 7.5 Hz), 1.47 (1H, quintet, 7.5 Hz), 1.29-1.25 (11H, m), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 117.0 (C), 102.2 (CH), 31.9 (CH_2), 29.6 (CH_2), 29.5 (2 x CH_2), 29.3 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{24}O_4Na$ 303.1572; Found 303.1573.



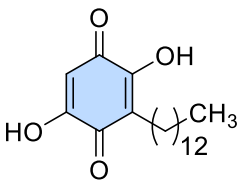
5a

2,5-Dihydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione (5f): The title compound was prepared following the procedure **B**, purified by column chromatography using EtOAc/hexane (2.0:8.0 to 3.0:7.0), and was isolated yellow solid. Mp.: 150-152 ºC. Yield: 89% (52.4 mg). IR (Neat): ν_{max} 3304, 2918, 2848, 1713, 1641, 1612, 1461, 1324, 1190, 1116, 943, 901, 859, 767, 707 and 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.01 (1H, s), 2.45 (2H, t, *J* = 7.5 Hz), 1.45 (2H, quintet, *J* = 7.0 Hz), 1.29- 1.25 (16H, m), 0.88 (3H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 117.1 (C), 102.2 (CH), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{26}O_4H$ 295.1909; Found 295.1900



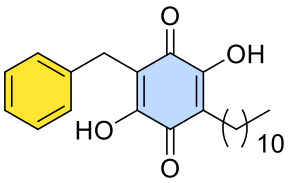
5f

2,5-Dihydroxy-3-tridecylcyclohexa-2,5-diene-1,4-dione (5h): The title compound was prepared following the procedure **B**, purified by column chromatography using EtOAc/hexane (2.0:8.0 to 3.0:7.0), and was isolated yellow solid. Yield: 93% (60 mg). Mp.: 105-107 ºC; IR (Neat): ν_{max} 3316, 2917, 2847, 1736, 1607, 1370, 1305, 1233, 1042, 769, 722 and 553 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.69 (2H, br s, *OH*), 6.0 (1H, s), 2.44 (2H, t, *J* =7.5 Hz), 1.47 (2H, pentet, *J* = 7.5 Hz), 1.25 (15H, br s), 0.88 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 117.0 (C), 102.2 (CH), 31.9 (CH_2), 29.7 (CH_2), 29.6 (3 x CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{30}O_4Na$ 345.2042; Found 345.2042.



5h

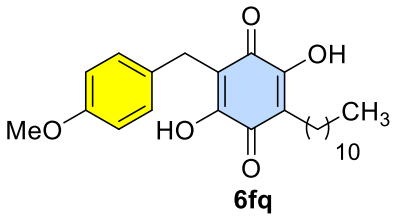
2-Benzyl-3,6-dihydroxy-5-undecylcyclohexa-2,5-diene-1,4-dione (6fp): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.5:7.5), and was isolated yellow solid. Mp.: 120-122 ºC. Yield: 78% (90 mg). IR (Neat): ν_{max} 3306, 2917, 2849, 1612, 1493, 1463, 1362, 1301, 1165, 1118, 1077, 1030, 893, 1000, 765, 696, 662 and 613 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.67 (2H, br s, 2 x *OH*), 7.30 (2H, d, *J* = 7.0 Hz), 7.27 (2H, t, *J* = 7.0), 7.19 (1H, t, *J* = 7.0 Hz), 3.76 (2H, s), 2.40 (2H, t, *J* = 7.5 Hz), 1.43 (2H, d, *J* = 6.5 Hz), 1.28-1.25 (16H, m), 0.87 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 138.7 (C), 128.9 (2 x CH), 128.5 (2 x CH), 126.4 (CH), 116.4 (C), 114.7 (C), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (2 x CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.4



6fp

(CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{32}O_4H$ 385.2379; Found 385.2378.

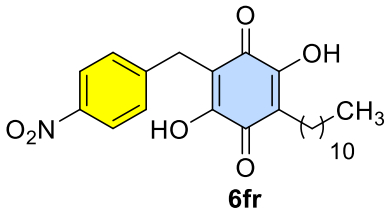
2,5-dihydroxy-3-(4-methoxybenzyl)-6-undecylcyclohexa-2,5-diene-1,4-dione (6fq): The



6fq

title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.5:7.5), and was isolated yellow solid. Yield: 91% (113 mg). Mp.: 110-112 ºC; IR (Neat): ν_{max} 3322, 2917, 2846, 1608, 1511, 1460,1302, 1239, 1177, 1120, 1029, 1005, 804, 764, 699, 676 and 593 cm^{-1}; ^1H NMR (DMSO d_6, 500 MHz): δ 11.05 (1H, br s, *OH*), 7.32 (2H, d, *J* = 8.5 Hz), 7.02 (2H, d, *J* = 8.5 Hz), 3.91 (3H, s), 3.77 (2H, s), 3.55 (1H, br s, *OH*), 2.73 (4H, s), 1.60 (2H, s), 1.44 (17H, s), 1.07 (3H, t, *J* = 6.5 Hz); ^{13}C NMR (DMSO d_6, 100 MHz, DEPT-135): δ 157.5 (C), 131.4 (C), 129.3 (2 x CH), 116.4 (C), 115.5 (C), 113.7 (2 x CH), 54.9 (*OCH_3*), 31.3 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 28.9 (2 x CH_2), 28.8 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 26.8 (CH_2), 22.1 (CH_2), 21.8 (CH_2), 13.9 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{34}O_5H$ 415.2484; Found 415.2484.

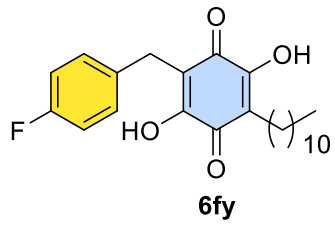
2,5-dihydroxy-3-(4-nitrobenzyl)-6-undecylcyclohexa-2,5-diene-1,4-dione (6fr): The title



6fr

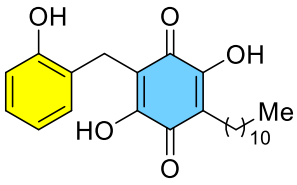
compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (1.5:8.5 to 2.5:7.5), and was isolated yellow solid. Yield: 81% (104 mg). Mp.: 98-100 ºC; IR (Neat): ν_{max} 3310, 2918, 2846, 1607, 1527, 1460, 1342, 1299, 1187, 1119, 1029, 1005, 795, 765, 718, 686 and 578 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.12 (2H, d, *J* = 8.5 Hz), 7.72 (1H, s, *OH*), 7.46 (2H, d, *J* = 8.5 Hz), 3.85 (2H, s), 2.41 (2H, t, *J* = 7.5 Hz), 1.45 (2H, quintet, *J* = 6.0 Hz), 1.33-1.24 (17H, m), 0.87 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135): δ 146.7 (C), 146.2 (C), 129.7 (2 x CH), 173.7 (2 x CH), 116.9 (C), 113.1 (C), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}NO_6H$ 430.2230; Found 430.2229.

2-(4-fluorobenzyl)-3,6-dihydroxy-5-undecylcyclohexa-2,5-diene-1,4-dione (6fy): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (3.0:7.0 to 4.0:6.0), and was isolated yellow solid. Mp.: 175-177 ºC. Yield: 86% (103.8 mg). IR (Neat): ν_{max} 3307, 2917, 2847, 1608, 1509, 1461, 1363, 1319, 1299, 1230,1161, 1118, 1027, 1000, 760, 708, 662 and 595 cm^{-1}; ^{1}H NMR (DMSO d_6, 500 MHz): δ 10.90 (2H, br s, 2 x *OH*), 7.20 (2H, t, *J* = 8.0 Hz), 7.05 (2H, t, *J* = 8.5 Hz), 3.6 (2H, s), 2.28 (2H, t, *J* = 7.5 Hz), 1.35 (2H, s), 1.21 (16H, s), 0.84 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (DMSO d_6, 125 MHz, DEPT-135): δ 161.6 (C), 159.6 (C), 135.7 (C), 135.6 (C), 130.0 (2 x CH), 130.0 (2 x CH), 116.6 (C), 115.0 (C), 115.0 (CH), 114.8 (CH), 31.3 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.7 (CH_2) 27.5 (CH_2), 26.9 (CH_2), 22.1 (CH_2), 21.9 (CH_2), 13.9 (CH_3); ^{19}F NMR (DMSO d_6, 375 MHz): δ -117.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}FO_4H$ 403.2285; Found 403.2284.



6fy

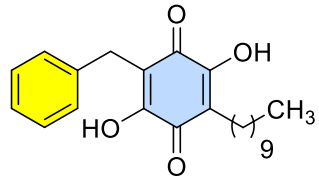
2,5-dihydroxy-3-(2-hydroxybenzyl)-6-undecylcyclohexa-2,5-diene-1,4-dione (6fz):



6fz

The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (3.0:7.0 to 4.0:6.0), and was isolated yellow solid. Mp.: 110-112 ºC. Yield: 83% (99.7 mg). IR (Neat): ν_{max} 3324, 2917, 2849, 1647, 1623, 1491, 1458, 1346, 1289, 1239, 1177, 1120, 1079, 960, 899, 750, and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24-7.17 (4H, m), 3.73 (2H, s), 2.47 (2H, t, *J* = 7.5 Hz), 2.04 (1H, q, *J* = 7.0 Hz), 1.49 (2H, q, *J* = 7.5 Hz), 1.25 (18H, br s), 0.88 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (CDCl3, 125 MHz, DEPT-135): δ 182.5 (C, *C=O*), 180.5 (C, *C=O*), 151.1 (C), 151.0 (C), 149.4 (C), 129.5 (CH), 128.5 (CH), 125.7 (CH), 118.9 (C), 118.4 (C), 117.9 (CH), 112.2 (C), 31.9 (CH_2), 29.7 (4 x CH_2), 29.6 (2 x CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.3 CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{32}O_5H$ 401.2328; Found 401.2326.

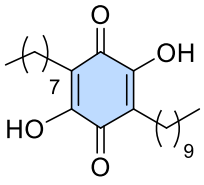
2-benzyl-5-decyl-3,6-dihydroxycyclohexa-2,5-diene-1,4-dione (6ap): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (3.0:7.0 to 4.0:6.0), and was isolated yellow solid. Yield: 70% (77.8 mg). Mp.: 132-134 ºC; IR (Neat): ν_{max} 3324, 2919, 2848, 1741, 1644, 1612, 1494, 1461, 1362, 1306, 1210, 1192, 1119, 1027, 999, 764, 711, 699 and 664



6ap

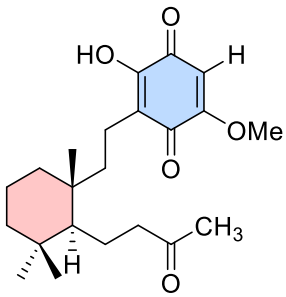
cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.70 (2H, br s, 2 x *OH*), 7.31 (2H, d, *J* = 7.0 Hz), 7.28-7.25 (3H, m), 7.21-7.17 (1H, m), 2.40 (2H, t, *J* = 7.5 Hz), 1.4 (2H, quintet, *J* = 7.0 Hz), 1.29-1.25 (16H, m), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 138.7 (C), 128.9 (2 x CH), 128.5 (2 x CH), 126.4 (CH), 116.4 (C), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 22.7 (CH_2), 22.4 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}O_4H$ 371.2222; Found 371.2225.

2-decyl-3,6-dihydroxy-5-octylcyclohexa-2,5-diene-1,4-dione (6ad): The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (2.0:8.0 to 3.0:7.0) and was isolated as a slight red solid. Mp.: 140-142 ºC. Yield: 83% (97.7 mg). IR (Neat): ν_{max} 3314, 2956, 2918, 2849, 1608, 1467, 1284, 1126, 763, 716 and 603 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.61 (2H, br s, 2 x *OH*), 2.41 (4H, t, *J* = 8.0 Hz), 1.4 (4H, quint, *J* = 7.5 Hz), 1.29-1.25 (24H, m), 0.87 (6H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 116.0 (C), 31.9 (2 x CH_2), 29.5 (4 x CH_2), 29.4 (CH_2), 29.3 (2 x CH_2), 29.2 (CH_2), 28.0 (2 x CH_2), 22.7 (2 x CH_2), 22.4 (2 x CH_2), 14.0 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{40}O_4H$ 393.3005; Found 393.3005.



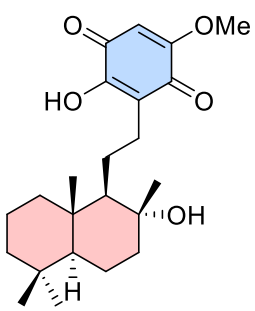
6ad

2-Hydroxy-5-methoxy-3-(2-((1*R*,2*S*)-1,3,3-trimethyl-2-(3-oxobutyl)cyclohexyl)ethyl)cyclohexa-2,5-diene-1,4-dione (11): The title compound was prepared following the procedure **D**, purified by column chromatography using EtOAc/hexane (4.0:6.0 to 5.0:5.0), and was isolated as a yellow semi solid. Yield: 75% (84.7 mg). IR (Neat): ν_{max} 3334, 2924, 1709, 1647, 1605, 1458, 1380, 1358, 1222, 1039, 841 and 647 cm^{-1}; $[\alpha]_D^{25}$ = +23.0° [c = 0.100 g/100 mL, $CHCl_3$; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.83 (1H, s), 3.85 (3H, s, *OCH₃*), 2.70-2.59 (1H, m), 2.49-2.42 (1H, m), 2.40-2.34 (2H, m), 2.12 (3H, s), 1.53-1.48 (4H, m), 1.41-1.38 (1H, m), 1.28-1.24 (5H, m), 1.13 (1 H, tt, *J* = 13.5, 3.5 Hz), 0.90 (6H, d, *J* = 3.0 MHz), 0.85 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 209.4 (C, *C*=*O*), 182.7 (C, *C*=*O*), 181.6 (C, *C*=*O*), 161.2 (C), 151.3 (C), 119.8 (C), 102.2 (CH), 56.7 (*OCH₃*), 53.3 (CH), 47.4 (CH_2), 42.1 (CH_2), 41.8 (CH_2), 37.7 (C), 37.6 (CH_2), 35.3 (C), 33.5 (CH_3), 29.8 (CH_3), 21.8 (CH_3), 20.4 (CH_2), 19.4 (CH_3), 18.7 (CH_2), 17.0 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{32}O_5Na$ 399.2147; Found 399.2148.



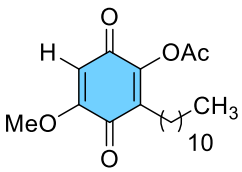
(-)-**11**

2-Hydroxy-3-(2-((1*R*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)ethyl)-5-methoxycyclohexa-2,5-diene-1,4-dione (14): The title compound was prepared following the procedure **D**, purified by column chromatography using EtOAc/hexane (3.0:7.0 to 4.0:6.0), and was isolated yellow semi solid. Yield: 82% (96 mg). IR (Neat): ν_{max} 3332, 2924, 2852, 1645, 1604, 1457, 1383, 1361, 1313, 1213, 1123, 1039, 937, 842, 736 and 559 cm^{-1}. $[\alpha]_D^{25}$ = +23.0° [c = 0.100 g/100 mL, $CHCl_3$, ^1H NMR ($CDCl_3$, 500 MHz): δ 5.80 (1H, s), 3.80 (3H, s, *OCH₃*), 2.62-2.50 (2H, m), 3.69 (1H, td, *J* = 12.5, 3.0 Hz), 1.75 (1H, d, *J* = 12.5 Hz), 1.65-1.59 (1H, m), 1.55 (1H, tt, *J* = 14.0, 3.5 Hz), 1.49-1.40 (4H, m), 1.34 (1H, d, *J* = 13.5 Hz), 1.26-1.21 (2H, m), 1.15 (3H, s), 1.11 (2H, q, *J* = 4.5 Hz), 0.90 (2H, dd, *J* = 12.5, 2.0 Hz), 0.85 (3H, s), 0.76 (3H, s), 0.72 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135): δ 182.9 (C, *C*=*O*), 182.1 (C, *C*=*O*), 160.8 (C), 151.9 (C), 119.5 (C), 102.5 (CH), 74.6 (C), 60.8 (CH), 56.7 (*OCH₃*), 55.9 (CH), 43.8 (CH_2), 41.9 (CH_2), 39.3 (CH_2), 38.8 (C), 33.3 (CH_3), 33.2 (C), 25.3 (CH_2), 24.0 (CH_3), 23.6 (CH_2), 21.4 (CH_3), 20.3 (CH_2), 18.4 (CH_2), 15.3 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{34}O_5Na$ 413.2304; Found 413.2306.



(+)-**14**

2-ethyl-4-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl acetate (15f): The title compound was prepared following the procedure **H**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated yellow solid. Mp.: 85-87 ºC. Yield: 86% (57.8 mg). IR (Neat): ν_{max} 2916, 2848, 1770, 1667, 1647, 1605, 1463, 1331, 1370, 1241, 1176, 1140, 1079, 1050, 1006, 962, 844, 718, 581 and 438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.89 (1H, s), 3.83 (3H, s, *OCH₃*), 2.41 (2H, t, *J* = 7.5 Hz), 2.35 (3H, s, *OCH₃*), 1.42 (2H, quintet, *J* = 7.5 Hz), 1.28 (4H, s), 1.25 (12H, s), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 181.6 (C, *C*=O), 179.8 (C, *C*=O), 167.9 (C), 159.0 (C), 149.3 (C), 105.5 (CH), 56.5 (*OCH₃*), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.2 (CH_2), 23.6 (CH_2), 22.6 (CH_2), 20.3 (CH_3) 14.1 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{30}O_5H$ 351.2171; Found 351.2171.



15f

(1*R*,5*S*,7*R*)-5-benzyl-3-methoxy-7-methyl-7-nitro-4,8-dioxobicyclo[3.2.1]oct-2-en-1-yl acetate (19p): The title compound was prepared following the procedure **G**, purified by column chromatography using EtOAc/hexane (1.0:9.0 to 1.5:8.5), and was isolated as white solid. MP.: 102-104 ºC. Yield: 81% (453 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 = 27.953 min (major), t_R = 36.892 min (minor); $[\alpha]_D^{25}$ = +257.0° [c = 0.100 g/100 mL, $CHCl_3$, 87% *ee*, and >20:1 *dr*]; IR (Neat): ν_{max} 1977, 1758, 1692, 1545, 1203, 1013, 841, 713, 595, 515 and 476 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (2H, d, *J* = 7.0 Hz), 7.29-7.26 (2H, m), 7.23-7.20 (1H, m), 6.14 (1H, s), 3.76 (3H, s, *OCH*$_3$), 3.57 (1H, d, *J* = 5.0 Hz), 3.34 (1H, d, *J* = 14.5 Hz), 2.70 (1H, d, *J* = 15.5 Hz), 2.16 (3H, s), 1.67 (1H, d, *J* = 15.0 Hz), 1.67 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 192.9 (C, *C*=*O*), 190.2 (C, *C*=*O*), 168.1 (C), 151.4 (C), 135.6 (C), 131.2 (2 x CH), 128.3 (2 x CH), 126.9 (CH), 114.0 (CH), 90.1 (C), 88.1 (C), 65.1 (C), 56.3 (CH_3), 38.3 (CH_2), 31.5 (CH_2), 20.9 (CH_3), 18.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{19}H_{19}NO_7NH_4$ 391.1505; Found 391.1505.

(+)-**19p**

2,5-didecyl-3,6-dihydroxycyclohexa-2,5-diene-1,4-dione (6a):

The title compound was prepared following the procedure **J**, purified by column chromatography using EtOAc/hexane (2.0:8.0 to 3.0:7.0), and was isolated yellow semi solid. Yield: 26% (33.0 mg); IR (Neat): ν_{max} 3314, 2956, 2918, 2849, 1608, 1467, 1284, 1126, 763, 716 and 603 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.62 (2H, br s, *OH*), 2.41 (4H, t, *J* = 7.5 Hz), 1.46 (4H, pentet , *J* = 7.5 Hz), 1.25 (21 H), 0.87 (6H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135): δ 116.0 (2 x C), 31.9 (2 x CH_2), 29.6 (2 x CH_2), 29.5 (4 x CH_2), 29.4 (2 x CH_2), 29.3 (2 x CH_2), 28.1 (2 x CH_2), 22.7 (2 x CH_2), 22.4 (2 x CH_2), 14.1 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{44}O_4Na$ 443.3137; Found 443.3137.

6a

2,5-dibenzyl-3,6-dihydroxycyclohexa-2,5-diene-1,4-dione (6p): The title compound was prepared following the procedure **J**, purified by column chromatography using EtOAc/hexane (2.0:8.0 to 3.0:7.0), and was isolated yellow semi solid. Yield: 30% (28.8 mg); IR (Neat): ν_{max} 3298, 2922, 2852, 1729, 1616, 1451, 1373, 1294, 1252, 1182, 1077, 1017, 860, 761, 699, 620, and 447 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.71 (2H, br s, *OH*), 7.29-7.28 (4H, m), 7.25-7.23 (4H, m), 7.19-7.16 (2H, tt, *J* = 7.0, 1.5 Hz), 3.74 (4H, s); ^{13}C NMR

6p

($CDCl_3$, 125 MHz, DEPT-135): δ 138.5 (2 x C), 128.9 (4 x CH), 128.5 (4 x CH), 126.5 (2 x CH), 115.1 (2 x C), 28.4 (2 x CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}O_4H$ 321.1127; Found 321.1126.

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The author Mr. Etikala Ashok was born on 14th June 1990 in Mallampally, Siddipet, Telangana. After his initial schooling at ZPHS, Mallampally, he finished his Intermediate (10+2) at Sathavahana Junior College, Husnabad in 2007. Later he obtained B.Sc (B.Z.C) Vivekananda Degree College, Husnabad in 2010 affiliated to Kakatiya University Warangal. After that he obtained Master of Science in Organic Chemistry Palamuru University, Mahabubnagar in 2013. Afterwards, he worked for one year as a junior lecturer in Sri Gayatri junior college, Ameerpet, Hyderabad. Next, he joined in Sreepathi Pharmaceuticals limited and worked for two years in QC department. Jeedimetla, Hyderabad. After all distaste, he prepared for CSIR exam and cleared. Then, he joined the Ph.D. programme under the supervision of Prof. D. B. Ramachary, School of Chemistry, University of Hyderabad and he continued there as a research scholar from 10th April 2017 onwards. His major research focus is on **"Discovery of Parts-per-Million Level, Organocatalytic Asymmetric Annulations: Synthesis of Chiral Drug Like Molecules"** with the objective of asymmetric organocatalysis.

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

1. Parts-per-Million-Level, Catalytic [3+2]-Annulations for the Asymmetric Synthesis of Methanobenzo[7]annulenes. G. Thirupathi, E. Ashok, A. S. Kumar D. B. Ramachary*, *Chem. Eur. J.* **2021**, *27,* 18033–18038.
2. Chiral Bicyclo[3.2.1]octanes Construction *via* Low-catalyst Loading Asymmetric Tandem Michael/Henry Reactions. E. Ashok, P. R. Lakshmi, R. Sravanthi, D. B. Ramachary* (*Manuscript under preparation*)
3. Total Synthesis of Natural C-Alkylated Hydroxyl-1,4-Benzoquinones. E. Ashok, P. R. Lakshmi, D. B. Ramachary* *(Manuscript under preparation)*

❖ Other publication as a co-author during the PhD tenure:

1. Organocatalytic Reductive Propargylation: Scope and Applications. M. A. Pasha, A. V. Krishna, E. Ashok, D. B. Ramachary*, *J. Org. Chem*. **2019**, *84*, 15399-15416.

❖ Presentations and conferences attended:

1. Oral Presentation in **ChemFest 2022**. (National Level) (Sponsered by Royal Society of Chemistry). Title of the talk: *Parts-per-Million-Level, Catalytic [3+2]-Annulations for the Asymmetric Synthesis of Methanobenzo[7]annulenes*.
2. Poster Presentation in **CHEMFEST 2022** with the title "Parts-per-Million-Level, Catalytic [3+2]-Annulations for the Asymmetric Synthesis of Methanobenzo[7]annulenes organized by the School of Chemistry, University of Hyderabad.
3. Oral Presentation in International Conference on Chemistry and Allied Sciences (**ICCAS-2022**) (International Level) (Sponsered by DST-SERB, CSIR and TSCHE). Title of the talk: *Parts-per-Million-Level, Catalytic [3+2]-Annulations for the Asymmetric Synthesis of Methanobenzo[7]annulenes*.
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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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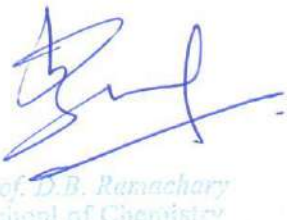

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