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# *Development of Direct Organocatalytic Reactions on Syncarpic Acid: Scope and Applications*

**A**

**Thesis**

**Submitted for the Degree of**

# Doctor of Philosophy

**By**


## Pritam Roy


हैदराबाद विश्वविद्यालय
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**August 2022**

# Dedicated to……..

*My father Sadhan Roy and mother Padmabati Roy*

**A quote from Albert Einstein which I found very significance during my Ph.D.**

# *“Imagination is more important than knowledge”*

# DECLARATION

I hereby declare that the matter embodied in the thesis entitled **"Development of Direct Organocatalytic Reactions on Syncarpic Acid: Scope and Applications"** is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Prof. Dhevalapally B. Ramachary.**

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# CERTIFICATE

Certified that the work contained in the thesis entitled **"Development of Direct Organocatalytic Reactions on Syncarpic Acid: Scope and Applications"** has been carried out by **Mr. Pritam Roy** 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.

**A. Parts of the thesis have been published in following publications:**

1. One-Pot Knoevenagel and [4+2] Cycloaddition as a Platform for Calliviminones. Pritam Roy, S. Rehana Anjum, D. B. Ramachary, *Org. Lett.* **2020**, *22*, 2897.
2. Organocatalytic Reductive Alkylation of Syncarpic Acid: Formal Total Synthesis of Monomeric Phloroglucinol Natural Products. Pritam Roy, A. Vamshi Krishna, D. B. Ramachary, *Manuscript submitted for publication.*
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# CONTENTS

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***Pritam Roy***

# *PREFACE*

*Syncarpic acid is a very important molecule in the world of natural products and medicinal chemistry. More than 70 natural products such as Callistilone A, rhodomyrtosones, myrtucommulones, watsonianone A and B, calliviminones, tomentosones A and B, are available containing syncarpic acid as a core structure. Syncarpic acid has somewhat similar structure with 1,3-cyclohexadione, but shows many different reactivities. Hence, there is a huge demand to develop new synthetic methodologies based on syncarpic acid. The demand not only limited up to development of methodologies but also in an environmentally friendly way like organocatalysis. The present thesis entitled* ***"Development of Direct Organocatalytic Reactions on Syncarpic Acid: Scope and Applications"*** *is an honest attempt to develop synthetic strategies based on syncarpic acid using organocatalysis. A large library of spiro, monocyclic, bicyclic and tricyclic heterocycles have been synthesized using these protocols which opens up large prospects for their further biological or material studies. The total/formal synthesis of more than 15 natural products and biologically important molecules such as Calliviminones A-H, triumphalone, isotriumphalone, (±)-Alline, (±)-CPC-I etc. were contented in the thesis. 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 bioactive compounds featuring an unusual core of spiro[5.5]undecenes and calliviminones with excellent yield and very good regio-/diasteroselectivities through a one-pot Knoevenagel and [4 + 2]-cycloaddition from the readily available aldehydes, cyclic-1,3-diones, dienes, and a catalytic amount of (S)-proline. This sequential one-pot method is a flawless technique to synthesize the entire family of calliviminone natural products.*

*The second chapter describes an attempt to look at the tolerance of syncarpic acid towards a three-component reductive alkylation (TCRA) reaction for the preparation of C-alkylated syncarpic acid. This methodology is engaged with catalytic amount of benzylamine as a source of organocatalyst and an excess amount of Hantzsch ester in acetonitrile solvent. Both aromatic and aliphatic aldehydes have behaved well in this method. According to our knowledge, this is the first report of a methodology for direct C-alkylation of syncarpic acid. Further, C-alkylation of syncarpic acids were converted into the more functionally rich molecules containing syncarpic acid and few natural products like triumphalone, isotriumphalone and monomeric phloroglucinol derivatives.*

*The third chapter is an attempt to look at 1,1,3,3-tetramethylguanidine (TMG) catalyzed oxidation of 3-vinyl indole has done for the direct access to 3-substituted-3-hydroxy oxindole derivatives utilizing soluble oxygen in THF as an oxidant. This is an efficient catalytic method which can be used for the oxidation of 2-alkyl substituted syncarpic acid to furnish 2-alkyl-2-hydroxy syncarpic acid with stoichiometric yield. This methodology has an advantage with reference to rate, yield, selectivity, operational simplicity, substrate scope, catalyst simplicity, and vast applicability.*

*In the fourth chapter, a green methodology has developed towards self-catalyzed Diels-Alder reaction of 3-vinyl indoles for the preparation of 1-amino-hydrocarbazole with excellent yield and diastereoselectivity. Output of our investigation showed that the molecular orbital interactions preferably occurred in endo approach. In this methodology, we have utilized 3-vinyl-2-oxindole as a source of both diene and dienophile based on the choice of the opponent molecule.*

# *LIST OF ABBREVIATIONS*

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

| | |
|---|---|
| Hz | hertz |
| Hex | hexyl |
| HIV | human immunodeficiency virus |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| $^{i}$Pr | isopropyl |
| IR | infrared |
| $LiAlH_4$ | lithium aluminum hydride |
| lit. | literature |
| m | multiplet |
| *m*-CPBA | *m*-chloro perbenzoic acid |
| M | molarity |
| Mp. | melting point |
| Me | methyl |
| mg | milligram (s) |
| mGluR1 | metabotropic glutamate receptor 1 |
| mL | milliliter |
| mmol | millimole |
| MW | microwave |
| NMR | nuclear magnetic resonance |
| NMP | *N*-methylpyrrolidine |
| OrgRC | organocatalytic reductive coupling |
| PCC | pyridinium chlorochromate |
| PET | positron emission tomography |
| Ph | phenyl |
| ppm | parts per million |
| *p*-TSA | *p*-toluenesulfonic acid |
| py | pyridine |
| pr | propyl |
| q | quartet |
| *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 |
| TMG | 1,1,3,3-tetramethylguanidine |
| TMS | trimethylsilyl |
| Ts | toluenesulphonyl |
| UV | ultraviolet |

# Development of Direct Organocatalytic Reactions on Syncarpic Acid: Scope and Applications

## 1.0 Abstract

Chapter 1 contains a synthetic methodology for the preparation of bioactive compounds featuring an unusual core of spiro[5.5]undecenes and calliviminones with excellent yield and very good regio-/diasteroselectivities through a one-pot Knoevenagel and [4 + 2]-cycloaddition from the readily available aldehydes, cyclic-1,3-diones, dienes, and a catalytic amount of (*S*)-proline. This sequential one-pot method is a flawless technique to synthesize the entire family of calliviminone natural products.

Chapter 2 is an attempt to look at the tolerance of syncarpic acid towards a three-component reductive alkylation (TCRA) reaction for the preparation of *C*-alkylated syncarpic acid. This methodology is engaged with catalytic amount of benzylamine as a source of organocatalyst and an excess amount of Hantzsch ester in acetonitrile solvent. Both aromatic and aliphatic aldehydes have behaved well in this method. According to our knowledge, this is the first report of a methodology for direct *C*-alkylation of syncarpic acid. Further, *C*-alkylation of syncarpic acids were converted into the more functionally rich molecules containing syncarpic acid and few natural products.

Chapter 3 deals with 1,1,3,3-tetramethylguanidine (TMG) catalyzed oxidation of 3-vinyl indole for the direct access to 3-substituted-3-hydroxy oxindole derivatives utilizing soluble oxygen in THF as an oxidant. This is an efficient catalytic method which can be used for the oxidation of 2-alkyl substituted syncarpic acid to furnish 2-alkyl-2-hydroxy syncarpic acid with stoichiometric yield. This methodology has an advantage with reference to rate, yield, selectivity, operational simplicity, substrate scope, catalyst simplicity, and vast applicability.

Chapter 4 presents a green methodology towards self-catalyzed Diels-Alder reaction of 3-vinyl indoles for the preparation of 1-amino-hydrocarbazole with excellent yield and diastereoselectivity. Output of our investigation showed that the molecular orbital interactions

preferably occurred in *endo* approach. In this methodology, we have utilized 3-vinyl-2-oxindole as a source of both diene and dienophile based on the choice of the opponent molecule.

# 2.0 Introduction

Since the last two decades "syncarpic acid" grabs the attention of synthetic organic chemist around the globe because of its availability as a core structure in more than 70 natural products.[1] Callistilone A, rhodomyrtosones, myrtucommulones, watsonianone A and B, calliviminones, tomentosones A and B are few examples of such kind of natural products (Figure 1).

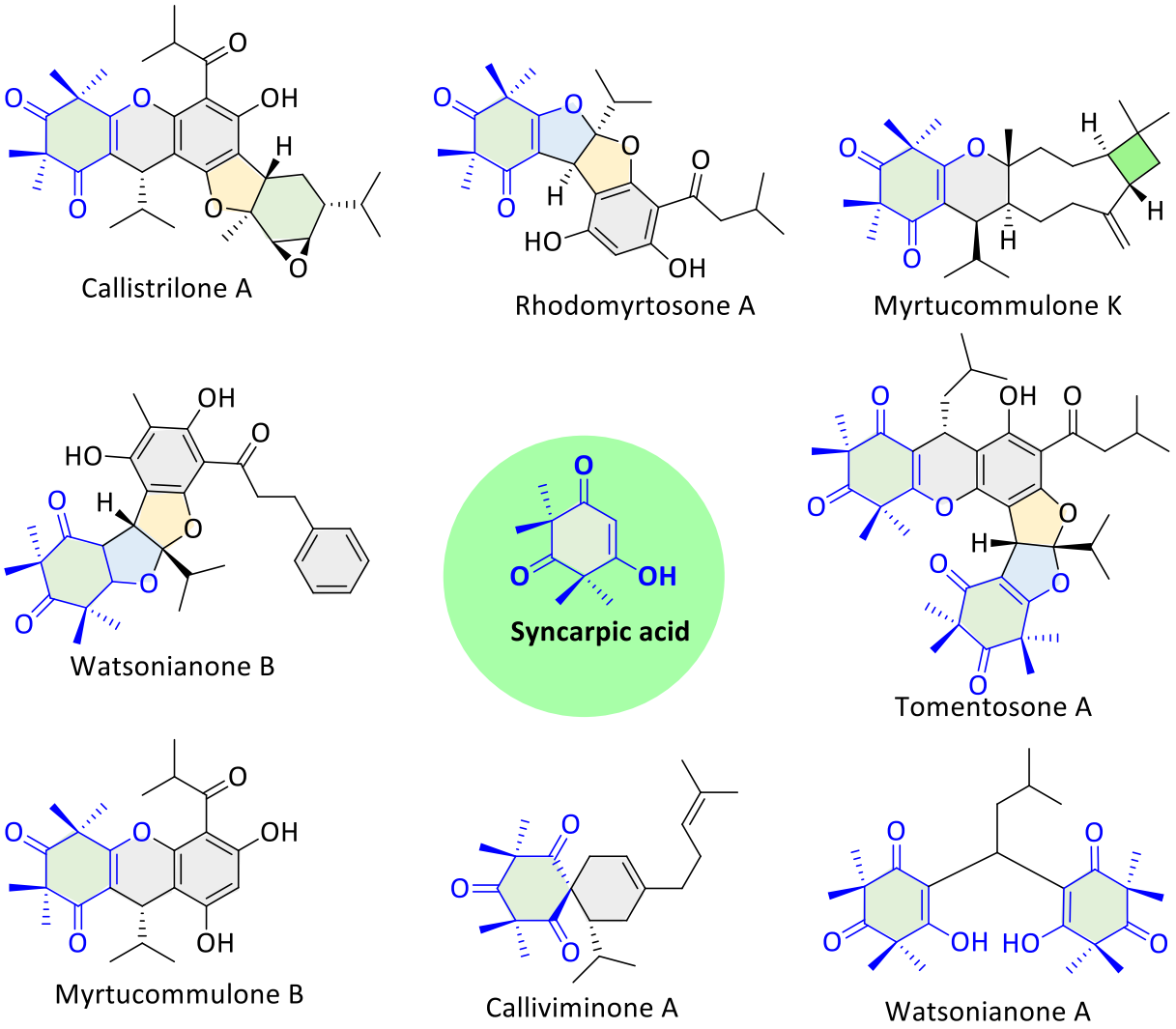



**Figure 1**: Natural products containing syncarpic acid as a core structure.

Even though syncarpic acid has not been derived from isoprene unit, it resembles monoterpenoid properties with 10 carbon atoms, which has been derived from phloroglucinol in plant kingdom. Syncarpic acid itself is a natural product, isolated from *Syncarpia laurifolia Tenn.*, family Myrtaceace, commonly found in the coastal regions of New South Wales.[2] Since, syncarpic acid ($pK_a$ = 4.1) claims to be more acidic than acetic acid ($pK_a$ = 4.7), it mostly resides in its enol form (Figure 2).[2]

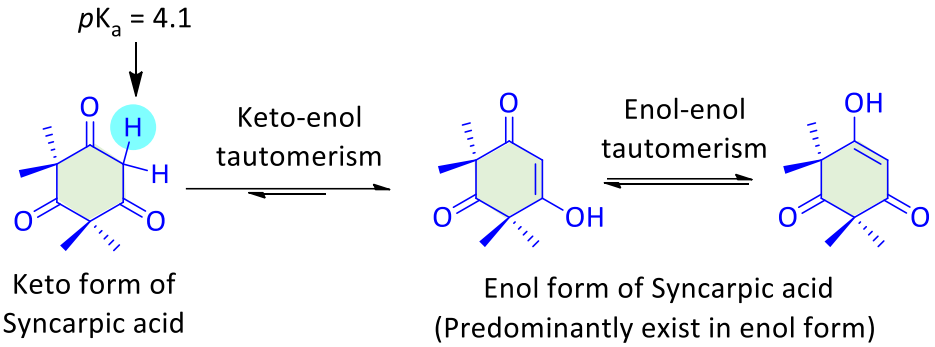
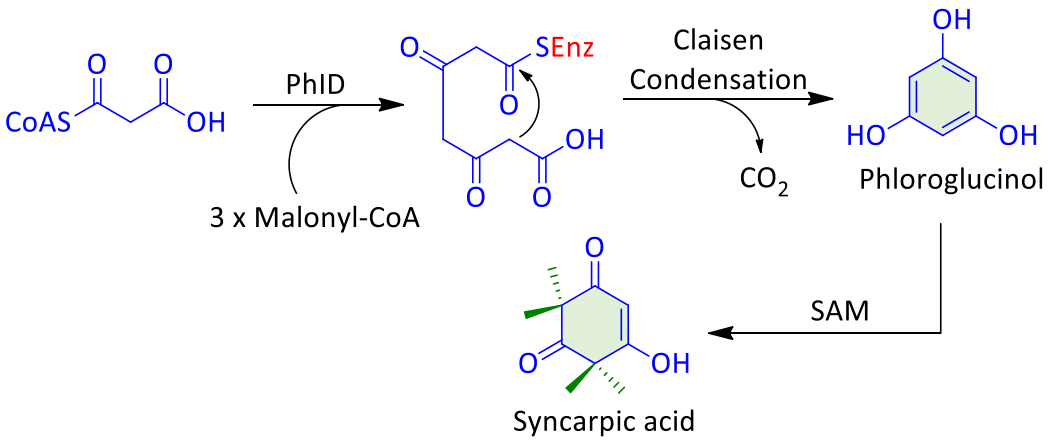



**Figure 2**: Keto-enol and enol-enol tautomerism of syncarpic acid.

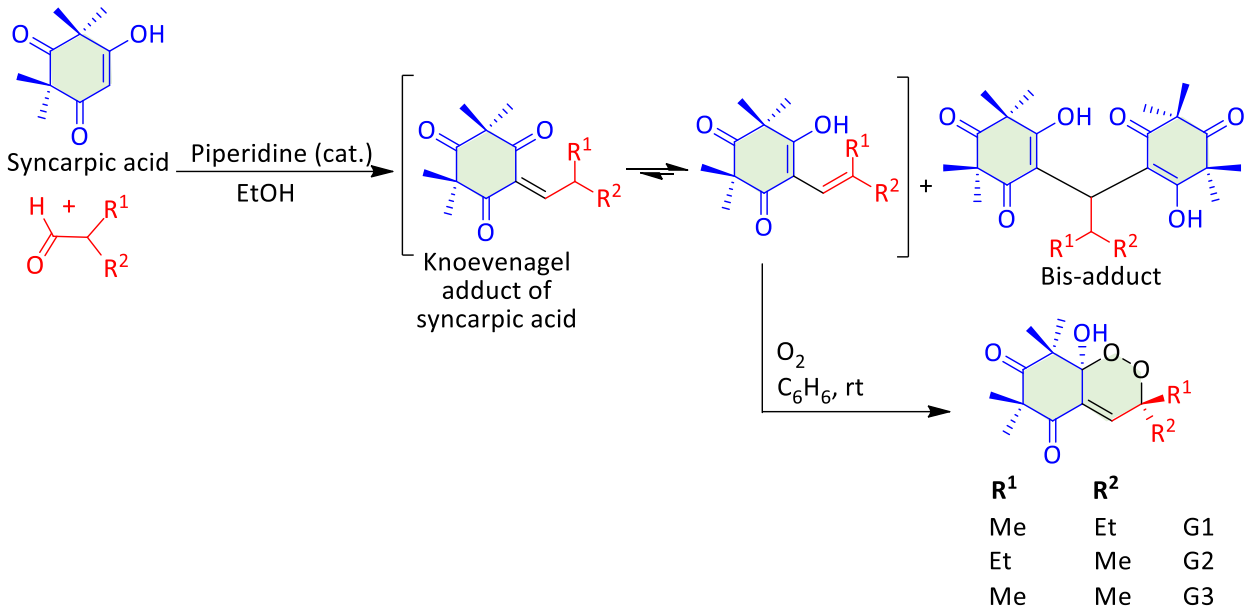
In 2005, Achkar *et al.* proposed that phloroglucinol synthase, PhID, condenses three malonyl-CoAs to form phloroglucinol, which may upon methylation with S-Adenosylmethionine (SAM), produces syncarpic acid (Scheme 1).[3]




**Scheme 1**: Biosynthesis of syncarpic acid.

G-factors (G1, G2 and G3), which are the first natural products derived from syncarpic acid, were isolated from *Eucalyptus grandis* (Scheme 2).[4] G-factors act as phytohormones and growth regulators, which are considered to be involved in plant defense.[4] These peroxides (G-factors),

despite their toxicity for the plant, are synthesized *in situ*. They are probably present in an inactive form and readily released if necessary. The biochemical pathways allowing an intermediate to be oxidized or to the peroxides to be metabolized are still unknown. In the year 2001, Gavrilan et al. proposed the total synthesis of G-factors, which involved a Knoevenagel reaction between syncarpic acid and corresponding aldehydes in the presence of catalytic amount of piperidine, followed by spontaneous oxygen uptake furnished three different G-factors (Scheme 2).[4]



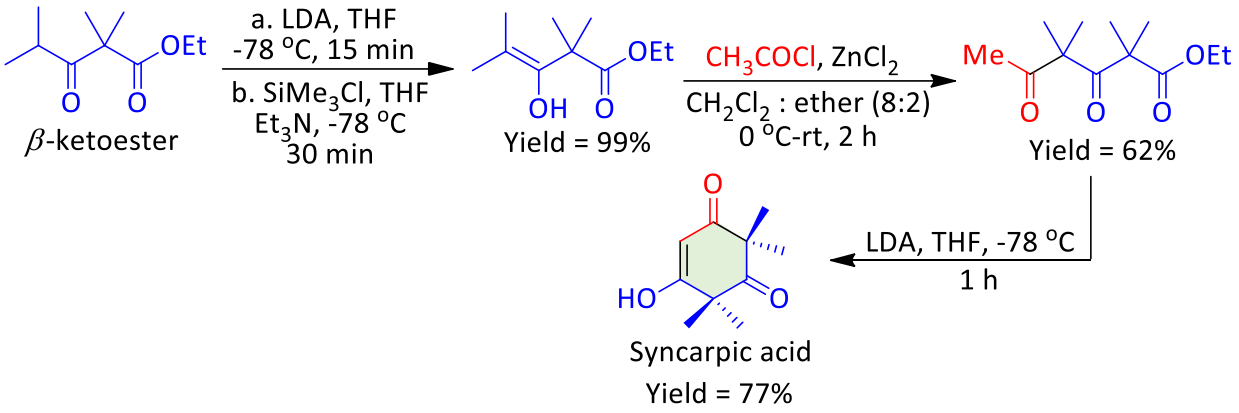

**Scheme 2**: Synthesis of G-factors from syncarpic acid.

In this reaction, alkylidene syncarpic acid acted as an intermediate which underwent a spontaneous 1,3-proton migration at room temperature to become an effective diene molecule (Scheme 2), which was reacted further with molecular oxygen in a step-wise manner to generate G-factors. This tendency of spontaneous rearrangement makes alkylidene syncarpic acid unstable at room temperature.

## 2.1 Previous Approach for the Synthesis of Syncarpic Acid:

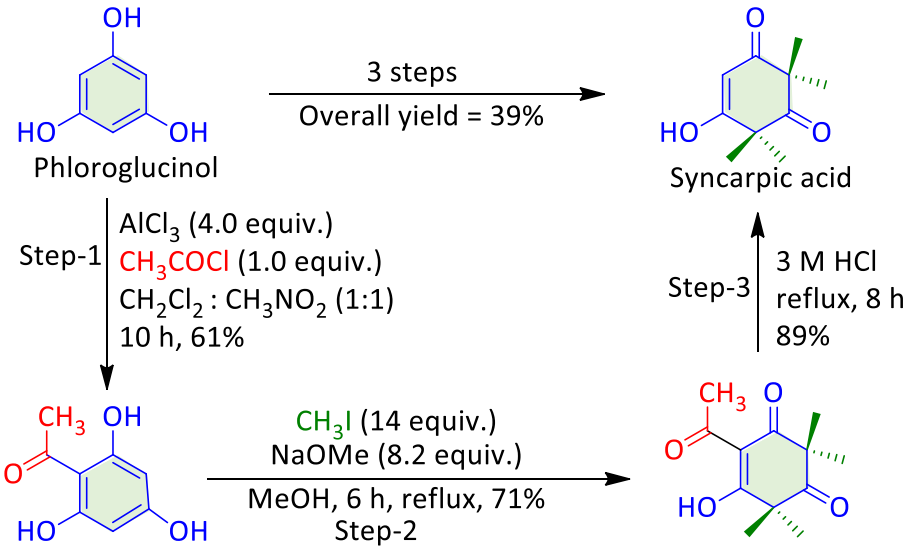
In the year 1989, Benbakkar and co-workers postulated a synthetic method for the preparation of syncarpic acid.[5] In this approach, first of all, a *β*-ketoester was prepared by condensation of isobutyrate enolate and isobutyrylchloride and it was converted to its corresponding enol which

again reacted with $CH_3COCl$ followed by an intramolecular cyclization to furnish syncarpic acid (Scheme 3).[5] Use of hazardous chemicals like LDA, $SiMe_3Cl$, transition metal salt like $ZnCl_2$, extreme reaction condition like -78 °C and an overall yield of less than 50%, making this methodology merely attractive to chemists. As phloroglucinol can be a better precursor for the synthesis of syncarpic acid, later approaches have used it as the starting material.




**Scheme 3**: Synthesis of syncarpic acid using *β*-ketoester as starting material.

Wu and co-workers, in the year 2015, carried out the synthesis of syncarpic acid using phloroglucinol as the starting material (Scheme 4).[6] A Friedel-Crafts acylation of phloroglucinol followed by tetra-methylation and de-acylation fabricated syncarpic acid with an overall yield of 39%.

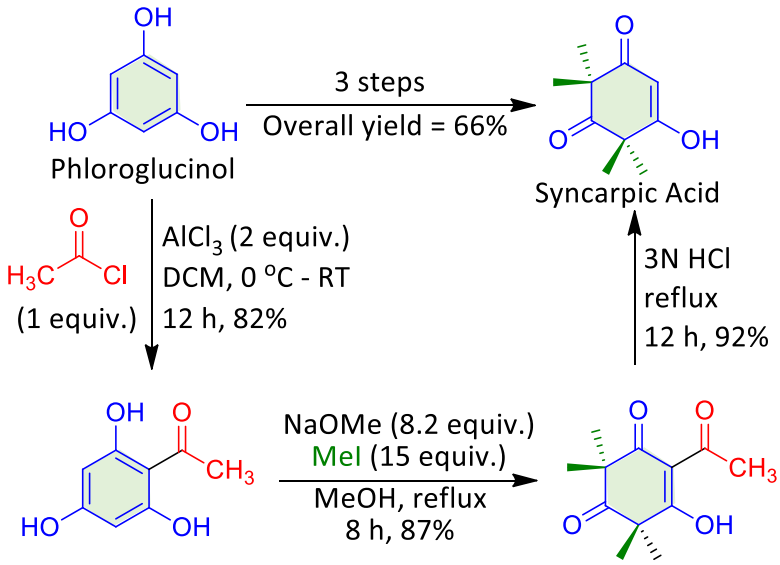



**Scheme 4**: Synthesis of syncarpic acid from phloroglucinol.

Liu and co-workers, in 2017, have used similar approach to furnish syncarpic acid with slight modifications in each step to achieve a better yield.[7] Initial step was carried out involving DCE / $PhNO_2$ (1:1) as a solvent system and 1.2 equiv. of acetyl chloride with respect to phloroglucinol and refluxed for 3 h to get a better yield (79%) of acyl phloroglucinol.[7] In the second step, only 7 equiv. of MeI was used and reaction was carried out in room temperature for 24 h to produce 4-acyl syncarpic acid with 86% of yield.[7] In the last step, 4-acyl syncarpic acid was refluxed in 6 N HCl for 24 h, but a decrease in yield (78%) was observed. Even though overall yield of syncarpic acid was increased to 53%.[7]

### 2.1.1 Our Modified Approach for the Synthesis of Syncarpic Acid:

To accomplish a better overall yield of syncarpic acid, we have introduced minor modifications in each step compared to the previous method (Scheme 5) and we have achieved successfully 66% overall yield of syncarpic acid within 3 steps starting from phloroglucinol.

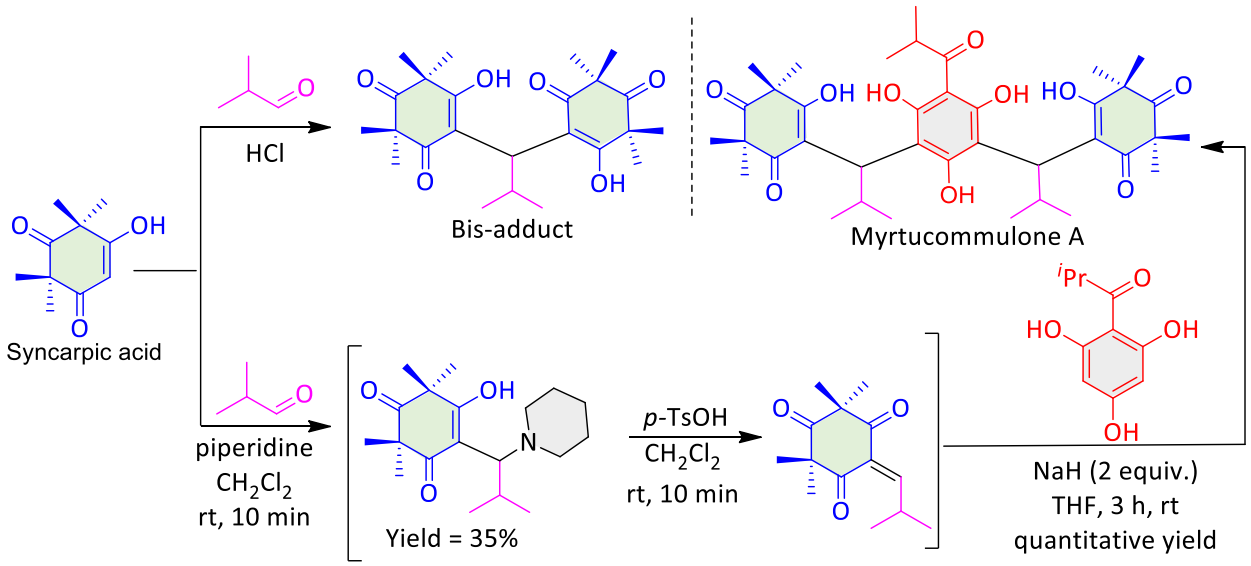



**Scheme 5**: Synthesis of syncarpic acid using our modified protocol.

## 2.2 Synthesis of Few Important Natural Products with Syncarpic Acid Core:

In the year 2010, Jauch and co-workers have done the total synthesis of Myrtucommulone A.[8] Myrtucommulones shows very significant anti-inflammatory and apoptosis-inducing activities. Synthesis of Myrtucommulone A began with the preparation of alkylidene syncarpic acid.

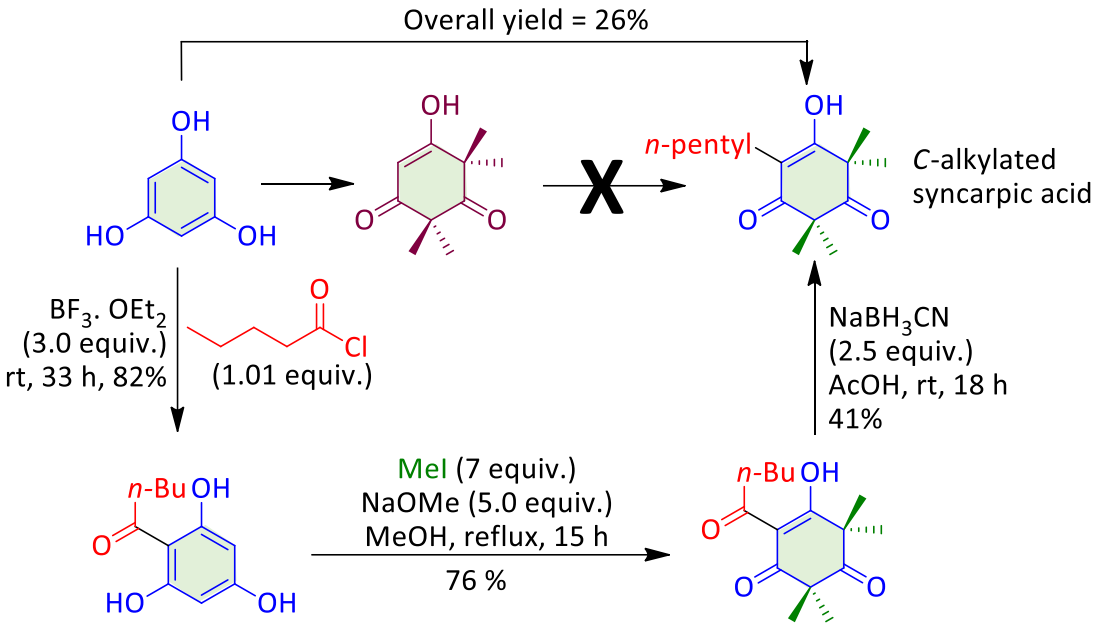
Reaction of syncarpic acid with isobutyraldehyde under acidic condition resulted in unwanted bis-product instead of Knoevenagel adduct. To avoid this side reaction, they treated syncarpic acid with isobutyraldehyde in presence of piperidine to obtain the Mannich base which was again treated with *p*-TsOH in a sequential one-pot manner to achieve alkylidene syncarpic acid. Alkylidene syncarpic acid was further treated with 2-isobutyric phloroglucinol in presence of 2 equiv. of sodium hydride, within 3 h furnished quantitative yield of myrtucommulone A (Scheme 6).[8]



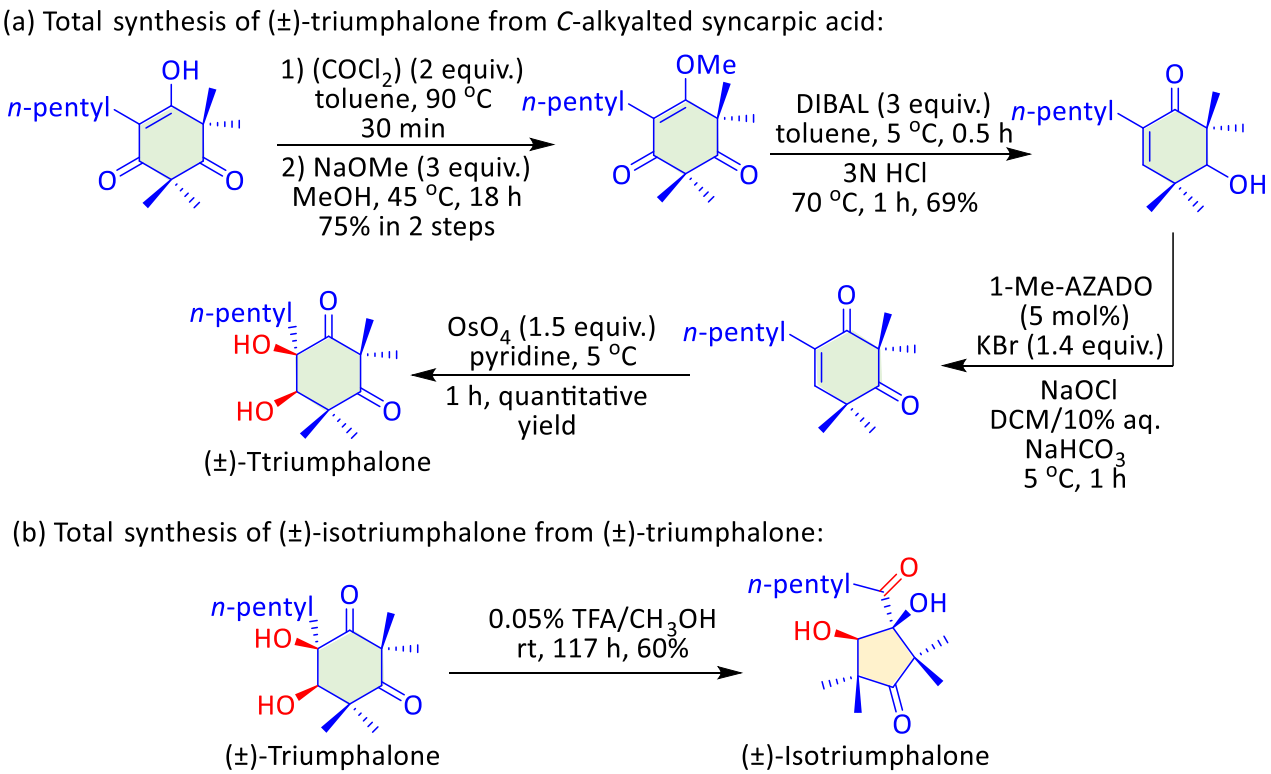

**Scheme 6**: Total synthesis of myrtucommulone A.

Shinada and co-workers (2015) reported first total synthesis of (±)-triumphalone in 8 steps from phloroglucinol.[9] For the synthesis of triumphalone, *C*-alkylated syncarpic acid played the role of an important intermediate. Shinada and co-workers have examined various alkylation reaction conditions, but in most of the cases *O*-alkylated product was observed predominantly.[9] A Friedel-Crafts acylation of phloroglucinol followed by tetramethylation and reduction fabricated *C*-alkylated syncarpic acid with an overall yield of 26% (Scheme 7).[9]

(±)-Triumphalone was produced from *C*-alkylated syncarpic acid in 5 tedious steps (Scheme 8).[9] (±)-Triumphalone was converted to (±)-isotriumphalone in one step by the acid promoted $\alpha$-ketol rearrangement with good yield of 60% in 117 h (Scheme 8).[9]

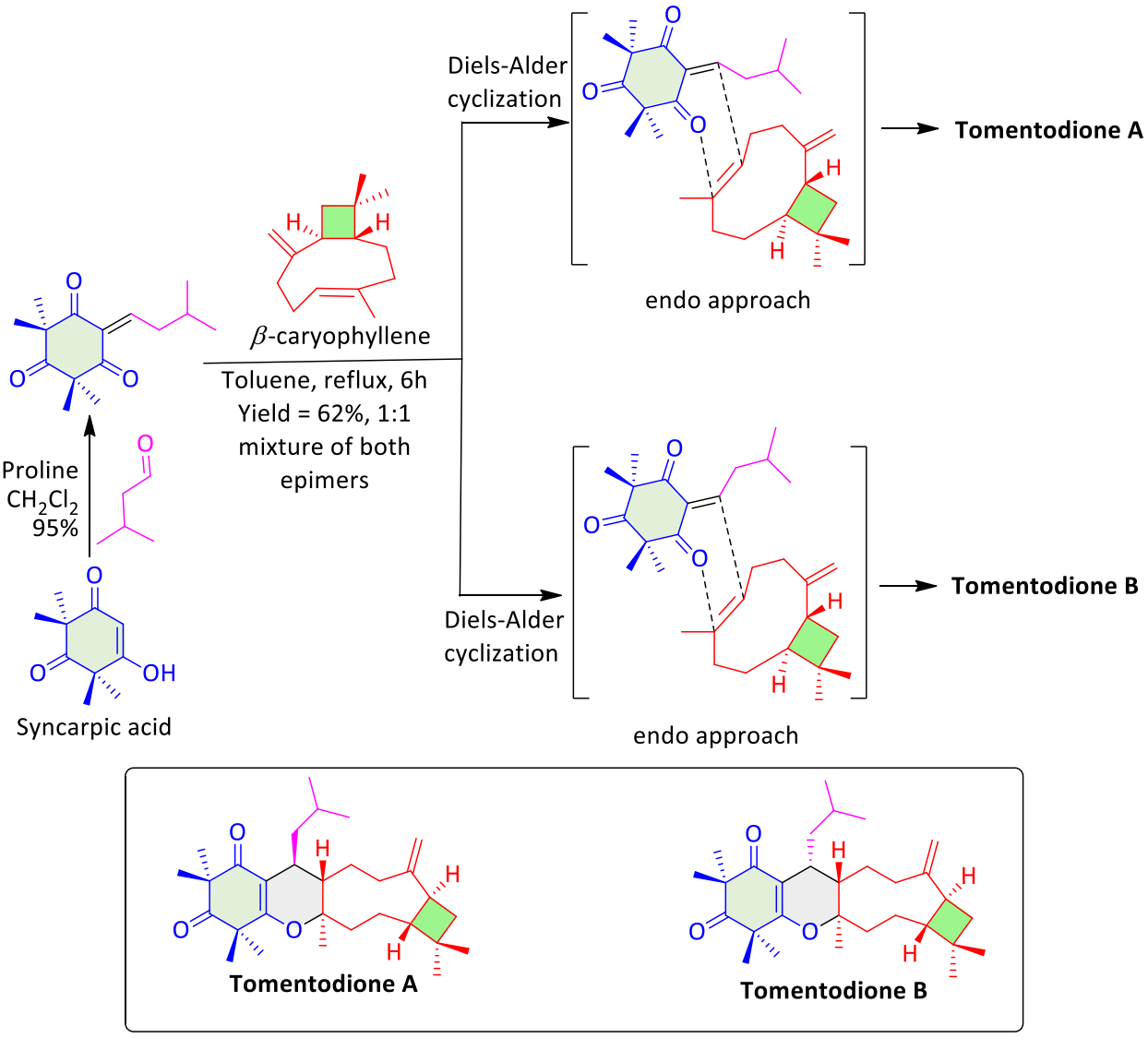



**Scheme 7**: Synthesis of *C*-alkylated syncarpic acid from phloroglucinol.




**Scheme 8**: Total synthesis of (±)-triumphalone and (±)-isotriumphalone from *C*-alkylated syncarpic acid.

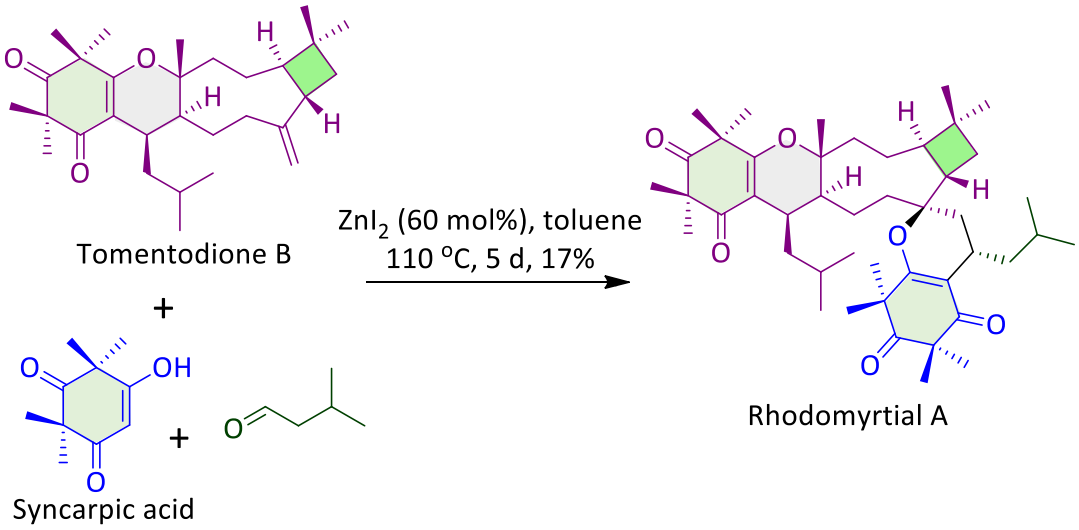
The above research group has also reported the total synthesis of monomeric phloroglucinol derivative, 2-hydroxy-2-isobutyl-4,4,6,6-tetramethyl-3,5-dioxocylohexyl acetate, which was isolated from *Myrtus communis*.[10] 2-Hydroxy-2-isobutyl-4,4,6,6-tetramethyl-3,5-dioxocylohexyl acetate has been widely used as a traditional medicine. *C*-alkylated syncarpic acid acted as an important intermediate for the synthesis of monomeric phloroglucinol derivative. They have done a similar approach to achieve *C*-alkylated syncarpic acid with very poor yield. A total synthesis of 2-hydroxy-2-isobutyl-4,4,6,6-tetramethyl-3,5-dioxocylohexyl acetate was done in 10 steps from phloroglucinol with an overall yield of 10%.[10]




**Scheme 9**: Biomimetic total synthesis of tomentodiones A and B.

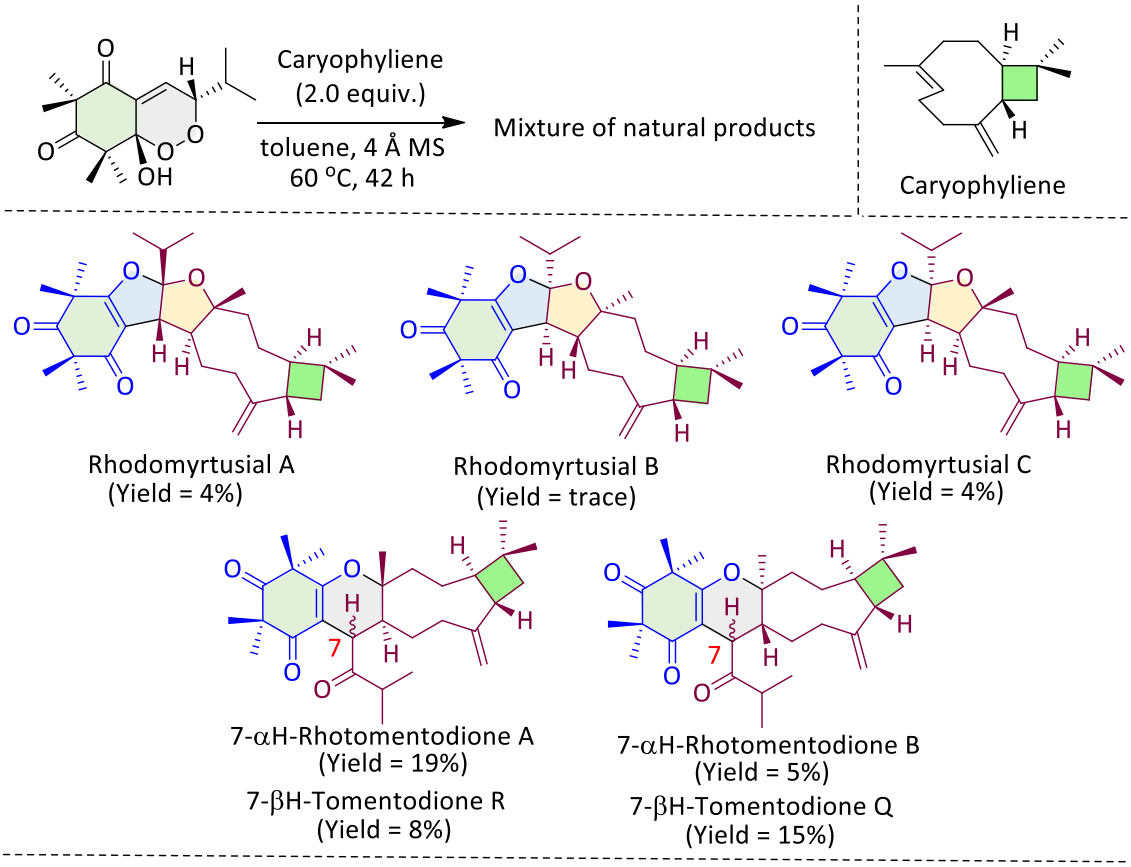
In the year 2016, Qiu and his group isolated tomentodiones A and B, a pair of epimers of caryophyllene-conjugated phloroglucinols with an unprecedented skeleton from the leaves of *Rhodomyrtus tomentosa*, which are being used as a remedy for dysentery, colic diarrhea, gynecopathy, abscesses and hemorrhage in traditional Chinese medicine.[11] They have also proposed biogenetic pathways for both tomentodiones A and B which involve an intermolecular, inverse electron demand Diels-Alder cycloaddition reaction as the key step. They have accomplished a biomimetic total synthesis of tomentodiones A and B (Scheme 9).[11]

A well number of meroterpenoids with diverse structure and a broad spectrum of biological activities were isolated from plants of the family Myrtaceae. A phloroglucinol moiety coupled with a terpenoid unit will generate the structure of most of this meroterpenoids. Rhodomyrtials A and B are two meroterpenoids with a triketone-sesquiterpene-triketone skeleton isolated from *Rhodomyrtus tomentosa* by Kong and his group in 2016.[12] Rhodomyrtials A and B were synthesized bio-mimetically from tomentodiones B and A respectively (Scheme 10).[12]

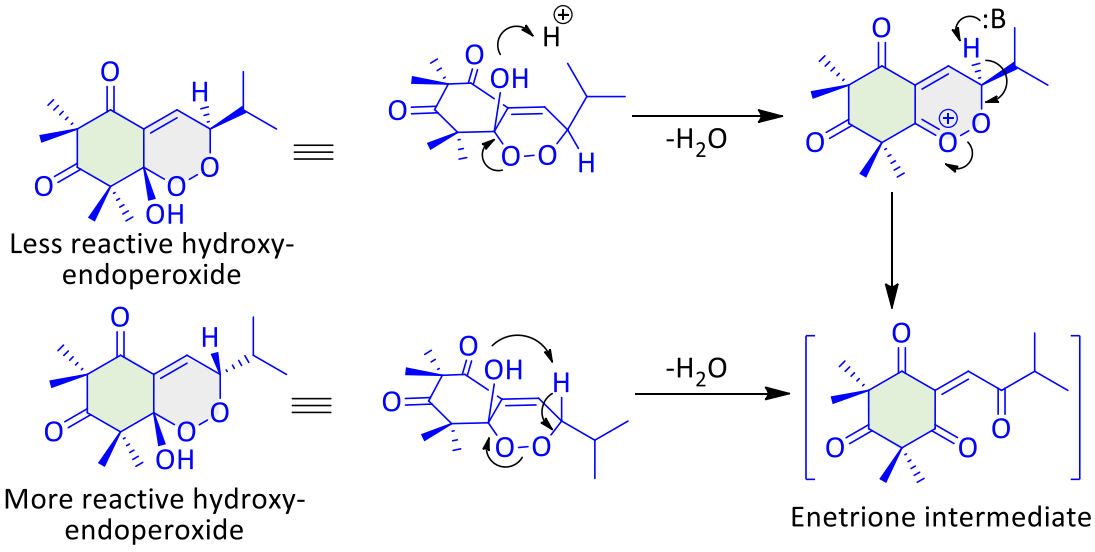



**Scheme 10**: Biomimetic synthesis of rhodomyrtials A.

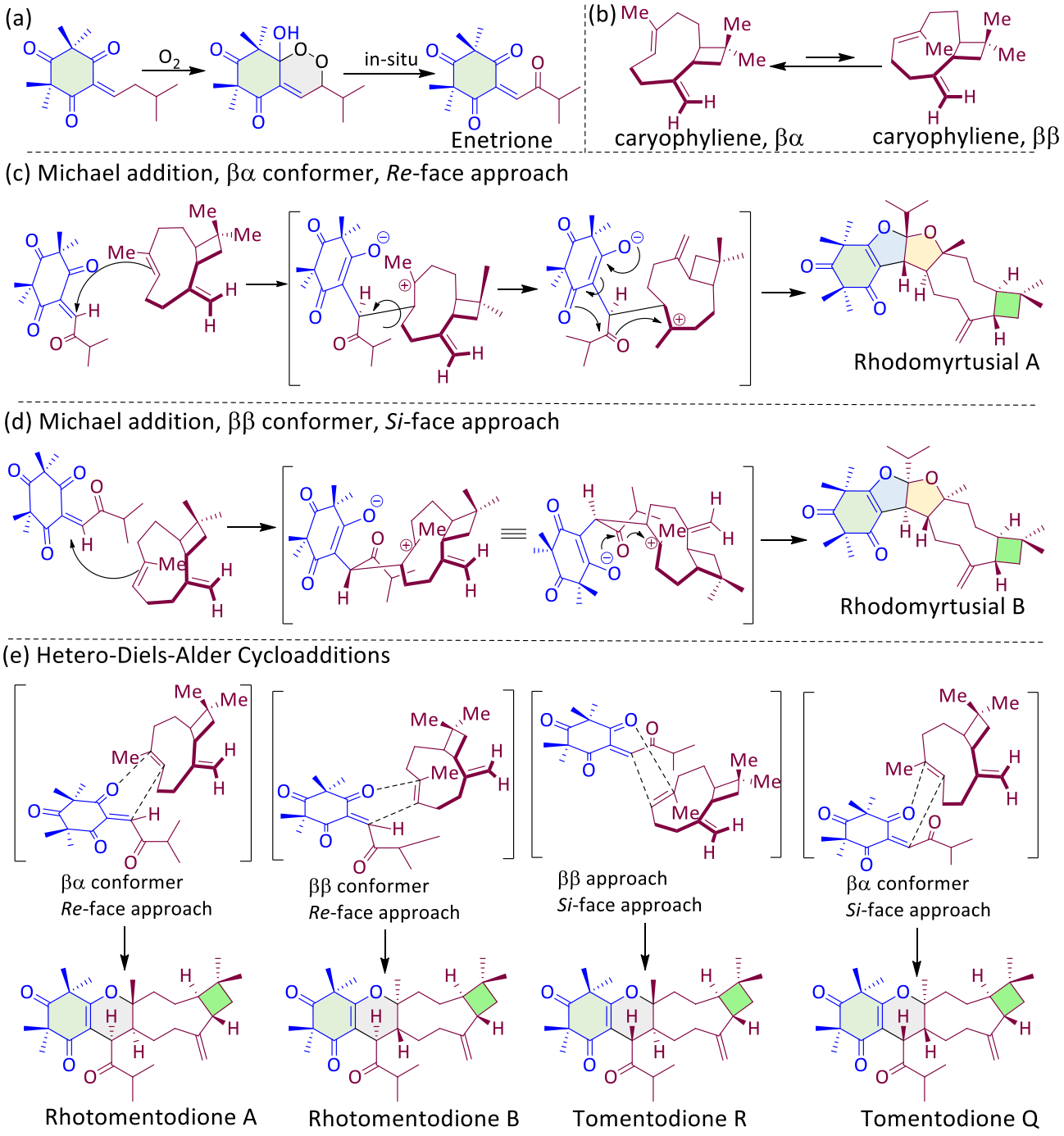
In the year 2019, Qin et al. reported a total synthesis of rhodomyrtusial A-C, rhotomentodione A and B, tomentodione R and Q, using enetrione as a common precursor (Scheme 11).[13] Alkylidene syncarpic acid underwent a spontaneous autoxidation to afford hydroxy-endoperoxide which then converted to enetrione in an *in-situ* manner. When hydroxy-endoperoxide was treated with caryophyliene at 60 °C in toluene, a mixture of 7 natural products were obtained (Scheme 11).




**Scheme 11**: Natural products synthesized from enetrione precursor.




**Scheme 12**: *In situ* generation of enetrione from hydroxy-endoperoxide.




**Scheme 13**: Biosynthesis of natural products. (a) Synthesis of enetrione. (b) Conformations of *trans*-caryophyllene. (c) Step-wise Michael addition leading to Rhodomyrtusial A. (d) Step-wise Michael addition leading to Rhodomyrtusial B. (e) Hetero-Diels-Alder (HAD) cycloadditions leading to 4 different natural products.

The diastereomer of hydroxy-endoperoxide, which has *syn*-stereochemical relationship of the $\alpha$-peroxy hydroxyl group and $\alpha$-peroxy methine hydrogen has displayed more reactivity than the other diastereomer of it. Even though both the diastereomers of hydroxy-endoperoxide have transformed to enetrione during the reaction (Scheme 12).

In the reaction condition, both $\beta\alpha$- and $\beta\beta$-conformations of caryophyliene underwent either Michael addition reaction with *in-situ* generated enetrione to furnish rhodomyrtusial A and B or hetero-Diels-Alder (HDA) reactions with *in-situ* generated enetrione to furnish rhotomentodione A and B, tomentodione R and Q (Scheme 13).[13]

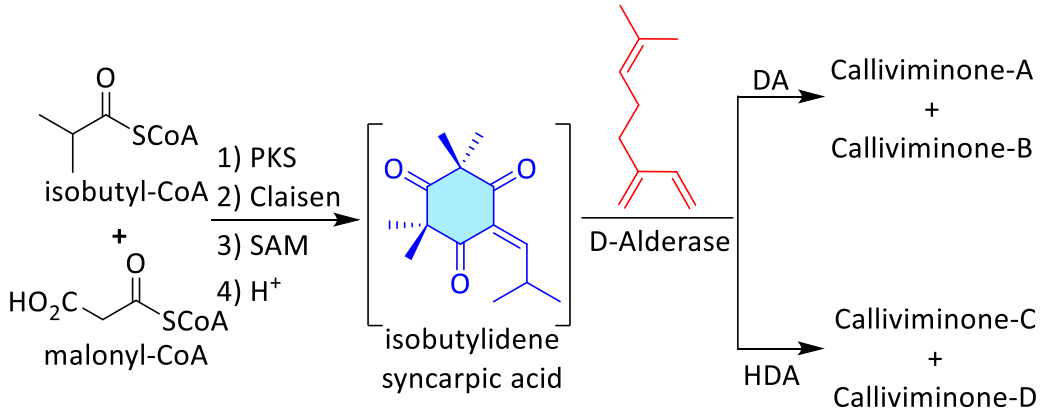
Due to the enormous significance of syncarpic acid in the world of natural products and medicinal chemistry, there is a huge demand to develop synthetic methodologies based on syncarpic acid. Syncarpic acid exhibits different chemical properties compared to 1,3-cyclohexadione in numerous aspects due to an additional carbonyl group with four methyl groups in the cyclohexane ring system and hence the same methodology which is applicable to 1,3-cyclohexadione may not always be applicable on syncarpic acid. Developments of synthetic methodologies using syncarpic acid are rarely explored till now. On the other hand, in the last few decades, organocatalysis, which utilizes minute organic molecules to catalyze asymmetric organic transformations, has emerged impeccable enough as a powerful tool for enantioselective synthesis, almost mimicking enzyme catalysis. Therefore, due to the renaissance of this venerable organocatalysis, whose advantages being limitless, like easy availability, low cost, high selectivity and environmentally friendly, we have taken up a challenge to develop various organocatalytic reaction methodologies on syncarpic acid and results are presented in this thesis.

# 3. One-pot Knoevenagel and [4+2]-Cycloaddition as a Platform to Calliviminones

## *3.1 Introduction*

Even in these modern times, organic chemistry with its myriad evolved reactions, the eminent Diels-Alder (DA) reaction has not lost its original vigor and potency.[14a-g] Its dichotomous nature of being elegantly simple and introducing intricate complexity into the products is extremely fascinating.[2] Its integral and frequent association with the synthesis of several sophisticated organic scaffolds of natural products and pharmaceutically important molecules and its encounter in the natural biosynthetic pathways to polyketides, terpenoids and alkaloids renders it a stimulating evergreen topic.[15]

Alkylidene- or arylidene-cyclic-1,3-diones, play crucial role in [4+2]-cycloadditions.[16] High-yielding synthesis of alkylidene- or arylidene-cyclic-1,3-diones and their instantaneous utilization as dienophiles in DA reaction are extremely demanding tasks. The reason is ascribed to the fact that they subsequently undergo side-reaction to form bis-adducts.[17] So, it became necessary to trap them in the designed reaction with specific substrates, before they can undergo bis-adduct formation with another molecule of the cyclic-1,3-dione. And this was earlier done by sulfa-Michael reaction or reduction with Hantzsch ester.[18a,b] Sterically more crowded alkylidene-cyclic-1,3-dione (isobutylidene syncarpic acid) was observed to be forming through enzyme catalysis and undergoing both homo- and hetero-DA reaction with myrcene to produce calliviminones A-D (Scheme 14).[19a-d]




**Scheme 14:** Biological approach towards the synthesis of calliviminones.

This evoked us to look for the viable deployment of alkylidene-cyclic-1,3-diones in [4+2]-cycloadditions. To serve the dual-purpose of thwarting the bis-adduct formation and utilizing the alkylidene-cyclic-1,3-diones in [4+2]-cycloaddition is a highly challenging task. The

enterprise mostly rested on the selection of a suitable reaction partner, whose energy should be in comparable spectrum to that of the arylidene-cyclic-1,3-diones. It would be fascinating to know if the reaction would take place first of all, in case it proceeds, it could be through either DA or HDA. In either case, the reaction products would be stimulating as they are known biologically active compounds, calliviminones A-H (Figure 3).[19a-d]

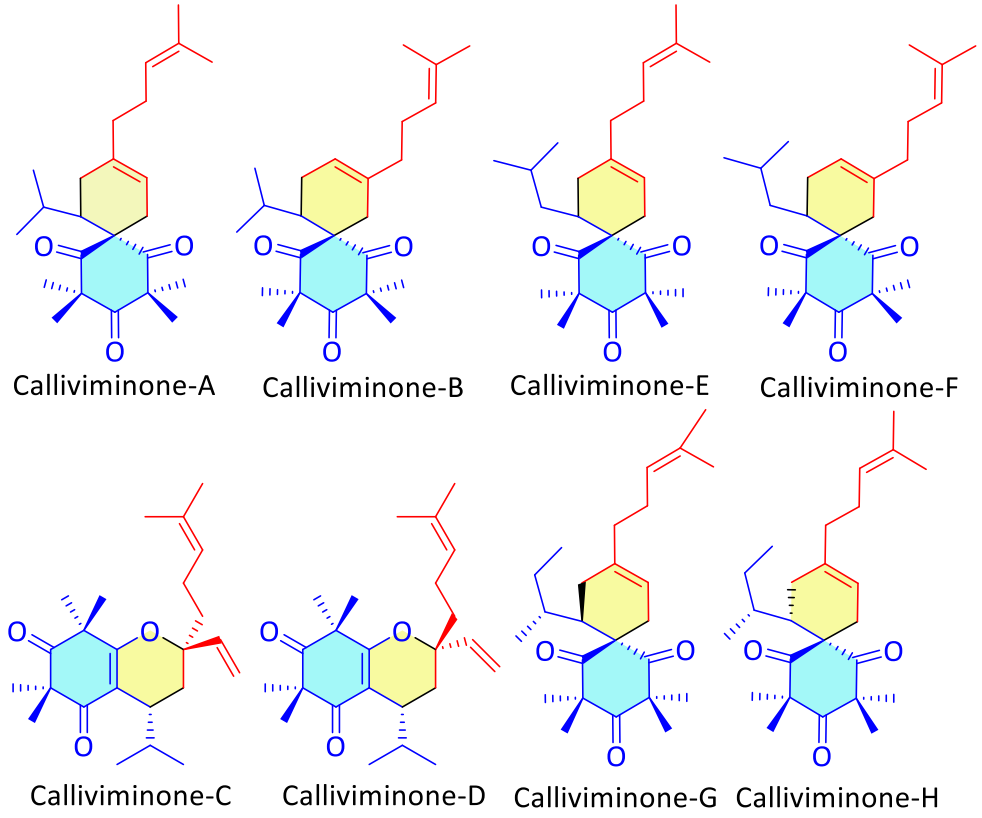
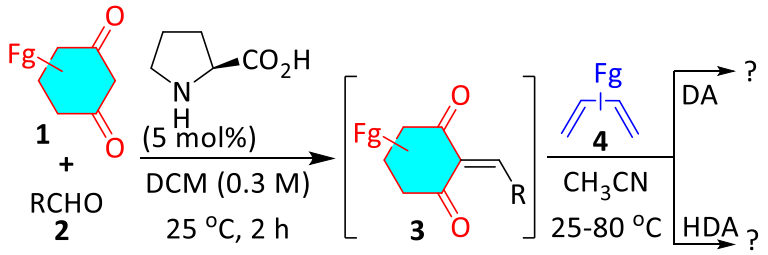



**Figure 3:** Natural products based on the syncarpic acid.

For nearly one and a half decades, we are working persistently and extensively on the construction of various alkylidene-cyclic-1,3-diones from different cyclic-1,3-diones and their utilization in diverse reactions such as transfer hydrogenation, Michael additions, [3+2]- and [4+2]-cycloadditions.[20]




**Scheme 15:** Reaction design for the one-pot synthesis of calliviminones.

Corollary to this, the present protocol was designed in a such a way that cyclic-1,3-diones undergo Knoevenagel condensation (KC) with aldehydes in presence of (*S*)-proline and

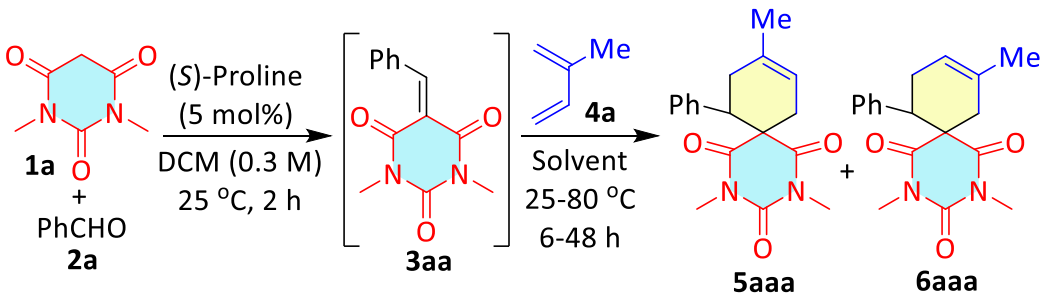
subsequently participate in DA reaction with simple dienes in one-pot manner (Scheme 15). Initially, we oriented toward the KC of an aldehyde and *N*,*N*-dimethylbarbituric acid, as the derivatives of pyrimidinetriones (barbiturates) have wide applications in pharmaceutical and medicinal chemistry.

## 3.2 Results and Discussion

### 3.2.1 Reaction Preliminary Optimization

To test our hypothesis, we initiated the KC of *N*,*N*-dimethylbarbituric acid **1a** with benzaldehyde **2a** in the presence of (*S*)-proline (5 mol%) in DCM. After the completion of the KC in 2 h at 25 °C, on addition of isoprene **4a** in same DCM solvent, at 25 °C, the DA reaction took 36 h to complete and delightfully the expected DA products **5aaa** and **6aaa** were formed in 84% yield as an inseparable 7.7:1 regioisomers (Table 1, entry 1). On raising the DA reaction temperature to 80 °C, though the reaction completed within 8 h, the yield of the products **5aaa** and **6aaa** (6.0:1 *rr*) plummeted hugely to 46% (Table 1, entry 2). After the KC reaction, DCM was evaporated under reduced pressure and consecutively the DA reaction was conducted in different solvents such as DCE, $CH_3CN$, $C_6F_6$, $CHCl_3$, $CH_3C_6H_5$ and $CF_3C_6H_5$ and at two different temperatures (25 °C and 80 °C). The reaction outcome in DCE at 25 °C was almost identical to that in DCM, except that it completed faster (within 24 h, Table 1, entry 3), whereas at 80 °C, the yield improved even more (86%) with 5.6:1 *rr* (Table 1, entry 4). To our delight, in acetonitrile at 25 °C both the reaction yield and the regioselectivity enhanced greatly (Table 1, entry 5). Providentially, at 80 °C too, the reaction yield maintained delightfully at 90%, with beneficial curtailment of reaction time to just 6 h, but with dwindled 5.3:1 *rr* (Table 1, entry 6). In $C_6F_6$, at 25 °C, the yield was only 49% with a higher *rr* of 10.0:1 (Table 1, entry 7) and at 80 °C, the yield ameliorated to 71% with diminution in *rr* to a 7.7:1 (Table 1, entry 8). More often than not, the reactivity and the regioselectivity seem to be displaying conflict. At 25 °C, the reactivity was low but the regioselectivity was high and at 80 °C this was reversed with high reactivity and low regioselectivity with exception in DCM. The DA reactions performed in $CHCl_3$, toluene and $CF_3C_6H_5$ at 80 °C were no better (Table 1, entries 9-11).

**Table 1:** Reaction Optimization [a]




| Entry | Solvent (0.3 M) | *t* (h) | T (°C) | Yield (%)[b] [**5aaa** + **6aaa**] | *rr*[c] [**5aaa** : **6aaa**] |
|---|---|---|---|---|---|
| 1 | DCM | 36 | 25 | 84 | 7.7:1 |
| 2 | DCM | 8 | 80 | 46 | 6.0:1 |
| 3 | DCE | 24 | 25 | 83 | 7.2:1 |
| 4 | DCE | 8 | 80 | 86 | 5.6:1 |
| 5 | $CH_3CN$ | 36 | 25 | 92 | 9.1:1 |
| 6 | $CH_3CN$ | 6 | 80 | 90 | 5.3:1 |
| 7 | $C_6F_6$ | 48 | 25 | 49 | 10.0:1 |
| 8 | $C_6F_6$ | 7 | 80 | 71 | 7.7:1 |
| 9 | $CHCl_3$ | 8 | 80 | 81 | 6.3:1 |
| 10 | $CH_3C_6H_5$ | 9 | 80 | 77 | 5.6:1 |
| 11 | $CF_3C_6H_5$ | 6 | 80 | 84 | 5.6:1 |
| 12[d] | $CH_3CN$ | 12 | 80 | 86 | 7.0:1 |

[a]Reactions were carried out in DCM (0.3 M) with 1 equiv. of **1a** and 1 equiv. of **2a** (0.3 mmol) in the presence of 5 mol% of proline for 2h at 25 °C followed by removal of DCM and addition of 1 equiv. of **4a** in solvent (0.3 M). [b]Yields refers to the column purified products. [c]Ratio of regioisomers determined by NMR spectroscopy. [d] Both reactions was performed in $CH_3CN$ one-pot manner.

These studies illustrated acetonitrile to be an excellent solvent for DA reaction (Table 1, entries 5 and 6). On conducting both the KC and the DA reactions in one-pot manner in acetonitrile at 80 °C, opportunely the KC/DA products **5aaa** and **6aaa** were produced in 86% yield with 7.0:1 *rr* in 12 h (Table 1, entry 12). Either of the reaction conditions (entries 5 and 6) or even the above one-pot process could be elected, as per the prerequisite reaction time, yield and *rr*. $^1H$ and $^{13}C$ NMR spectra of the mixture of compounds **5aaa** and **6aaa** has depicted below (Figure 4).

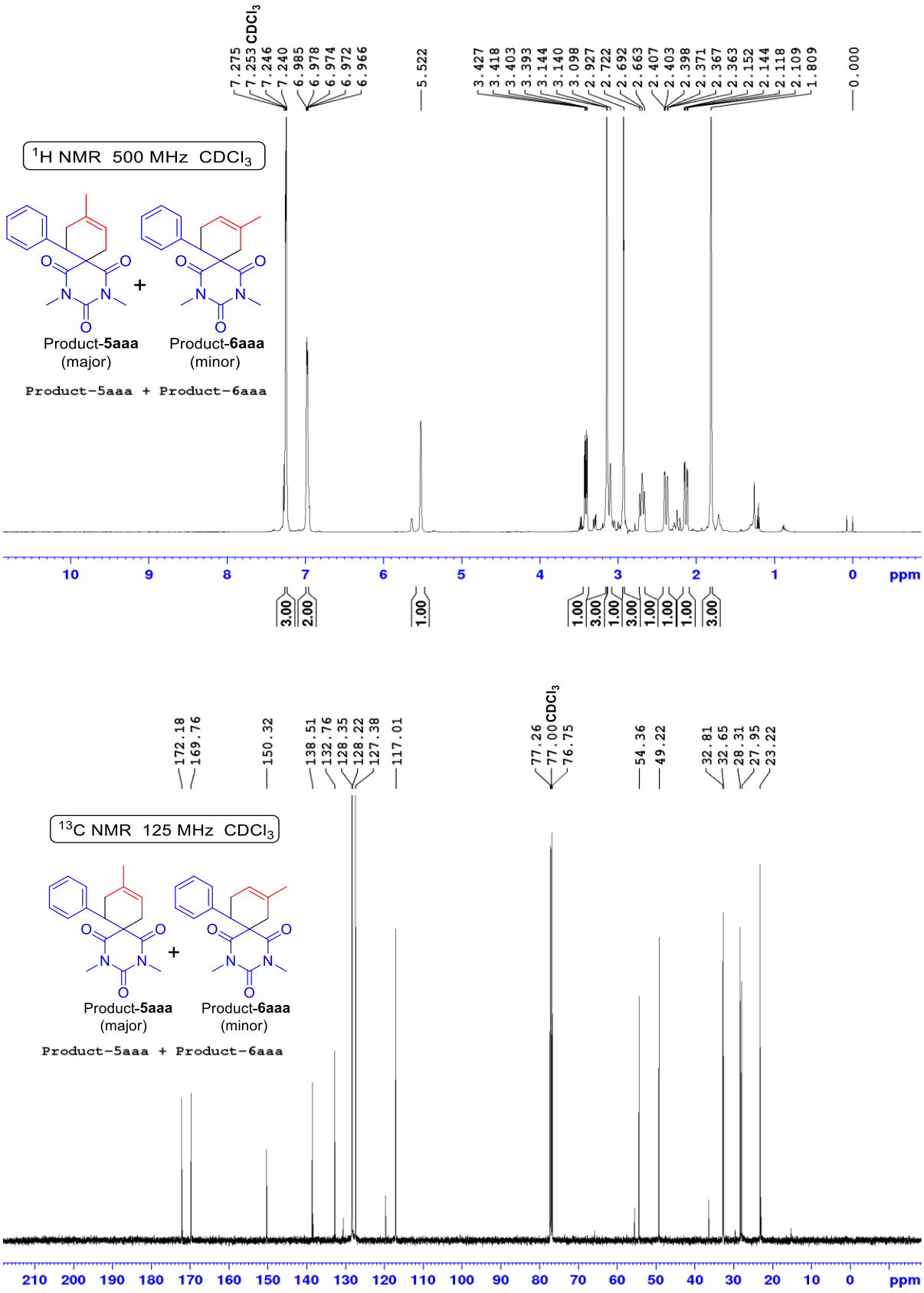



**Figure 4:** $^1$H NMR and $^{13}$C NMR spectrum of products **5aaa** and **6aaa.**

The structure of compound **5aaa** was further confirmed by X-Ray crystallography (Figure 5).[21]

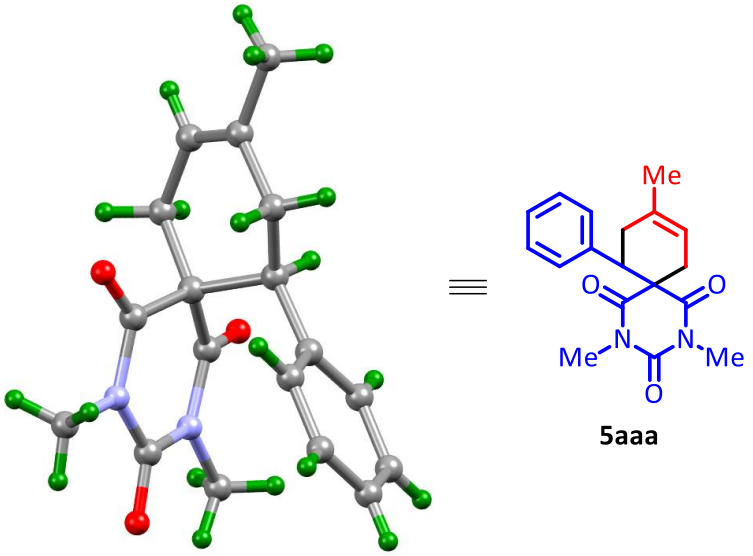


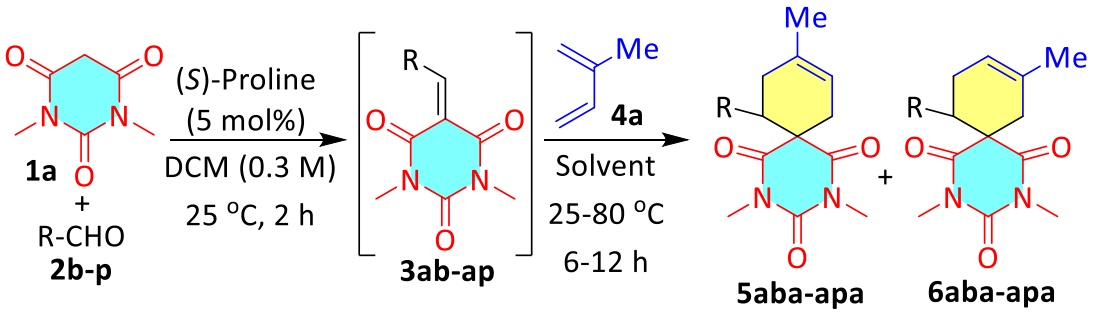

**Figure 5:** X-Ray crystal structure of 2,4,9-trimethyl-11-phenyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (**5aaa**).

### *3.2.2 Substrate Scope of the Organocatalyzed [4+2]-Cycloaddition Reaction:*

#### *3.2.2.1 Substrate Scope with Different Aldehydes:*

On arriving at the acceptable reaction conditions for the proposed reaction sequence, we were obligated to study the participation of diverse aldehydes **2b**-**p** in the sequence of KC with **1a** and DA reaction with isoprene **4a** (Table 2). Respective one-pot KC/DA products were engendered in moderate to good yields in all the cases. Aromatic aldehydes, **2b**-**m** substituted with either halogens (F, Cl, and Br), or electron-donating (Me, OMe, $NMe_2$) or electron-withdrawing ($CF_3$, $NO_2$ and CN) groups mostly at the *para*-position or at *ortho*- or *meta*-position were well compatible under the reaction conditions and afforded the products in moderate to good yields (41-88%) with *rr* 4.0:1 to 8.3:1 (Table 2, entries 1–12). Even the aliphatic aldehyde **2n** reacted satisfactorily to furnish the products **5ana** and **6ana** in 71% yield with 9.0:1 *rr* (Table 2, entry 13). In the case of the hetero aromatic aldehyde, furfural **2o**, the products were obtained in 83% yield with relatively a high *rr* of 20.0:1 (Table 2, entry 14).

**Table 2:** Reaction Scope with Aldehydes [a]




| Entry | R | Time (h) | Yield[b] (%) [5+6] | *rr*[c] [5:6] |
|---|---|---|---|---|
| 1 | 4-$FC_6H_4$ (**2b**) | 6 | **5aba** + **6aba** (85) | 6.3:1 |
| 2 | 4-$ClC_6H_4$ (**2c**) | 5 | **5aca** + **6aca** (81) | 5.3:1 |
| 3 | 4-$BrC_6H_4$ (**2d**) | 6 | **5ada** + **6ada**(67) | 8.3:1 |
| 4 | 4-$MeC_6H_4$ (**2e**) | 5 | **5aea** + **6aea** (86) | 6.7:1 |
| 5 | 4-$MeOC_6H_4$ (**2f**) | 5 | **5afa** + **6afa** (81) | 7.1:1 |
| 6 | 4-$NMe_2C_6H_4$ (**2g**) | 8 | **5aga** + **6aga** (72) | 8.0:1 |
| 7 | 4-$CF_3C_6H_4$ (**2h**) | 5 | **5aha** + **6aha** (78) | 4.0:1 |
| 8 | 4-$NO_2C_6H_4$ (**2i**) | 5.5 | **5aia** + **6aia** (78) | 5.0:1 |
| 9 | 4-$CNC_6H_4$ (**2j**) | 9 | **5aja** + **6aja** (88) | 5.3:1 |
| 10 | 3-$CNC_6H_4$ (**2k**) | 12 | **5aka** + **6aka** (66) | 6.0:1 |
| 11 | 2-$CNC_6H_4$ (**2l**) | 10 | **5ala** + **6ala** (41) | 4.5:1 |
| 12 | 2-$ClC_6H_4$ (**2m**) | 6 | **5ama** + **6ama** (70) | 5.3:1 |
| 13 | $CH_2CH(CH_3)_2$ (**2n**) | 12 | **5ana** + **6ana** (71) | 9.0:1 |
| 14 | 2-furyl (**2o**) | 12 | **5aoa** + **6aoa** (83) | 20.0:1 |
| 15[d] | chiral aldehyde (**2p**) | 12 | **5apa** + **7apa** (65) | 11.0:1 |

[a]Reactions were carried out in DCM (0.3 M) with 1 equiv. of **1a** and 1 equiv. of **2** (0.3 mmol) in the presence of 5 mol% of proline followed by removal of DCM and addition of 1 equiv. of **4a** in $CH_3CN$ (0.3 M). [b] Yields refers to the column purified products. [c] Ratio of regioisomers determined by NMR spectroscopy. [d] 2 equiv. of isoprene **4a** was used along with (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **2o** and 11:1 ratio of *dr*'s are formed.

Astonishingly, for the chiral aliphatic aldehyde (*R*)-glyceraldehyde acetonide **2p**, the KC/DA products (+)-**5apa** and (+)-**7apa** obtained in 65% yield were exclusively diastereomers in the ratio of 11.0:1 (Table 2, entry 15).

$^1H$ and $^{13}C$ NMR spectra of few compounds from Table 2 have depicted below (Figure 6-10).

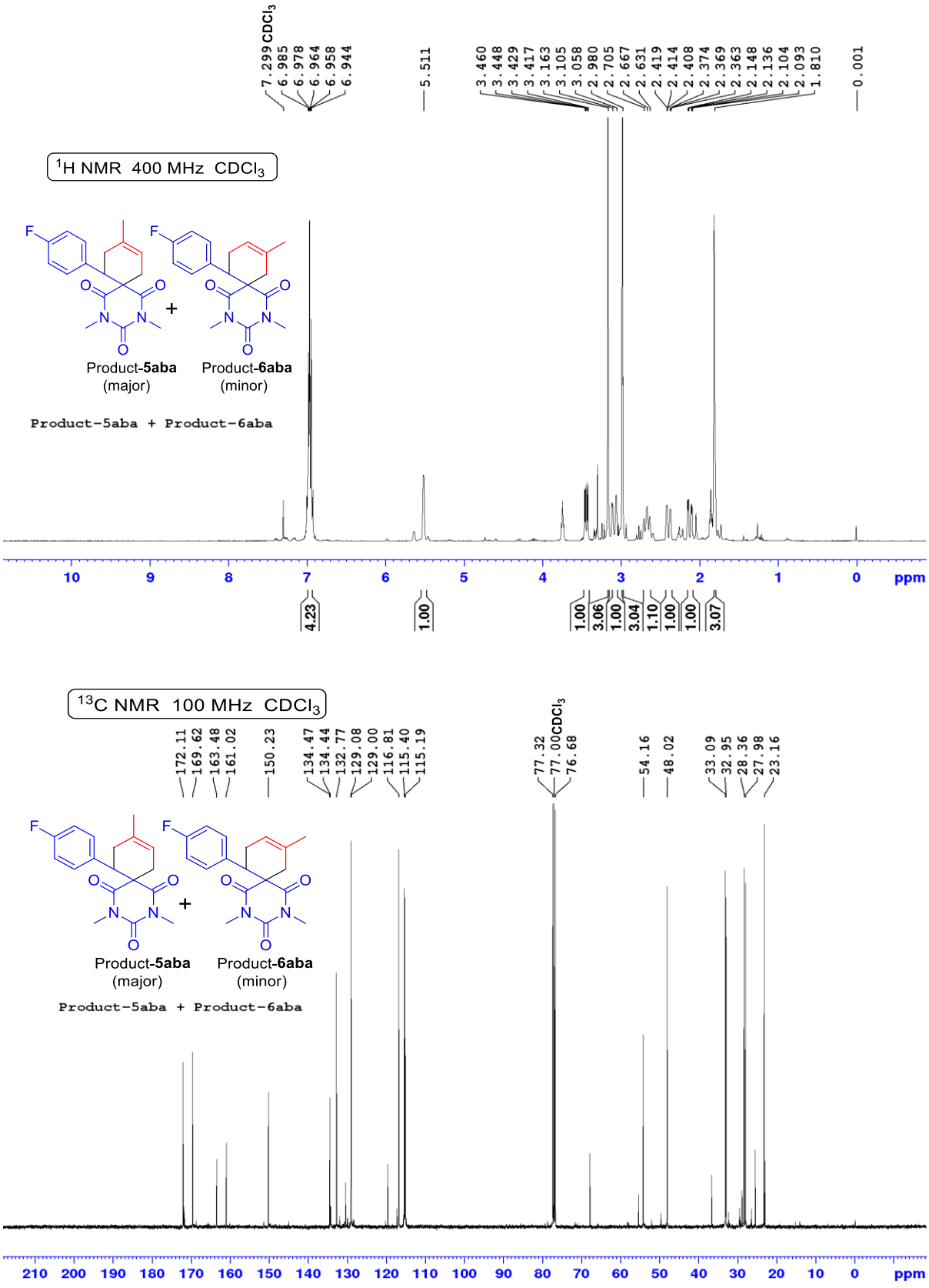



**Figure 6:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5aba** and **6aba.**

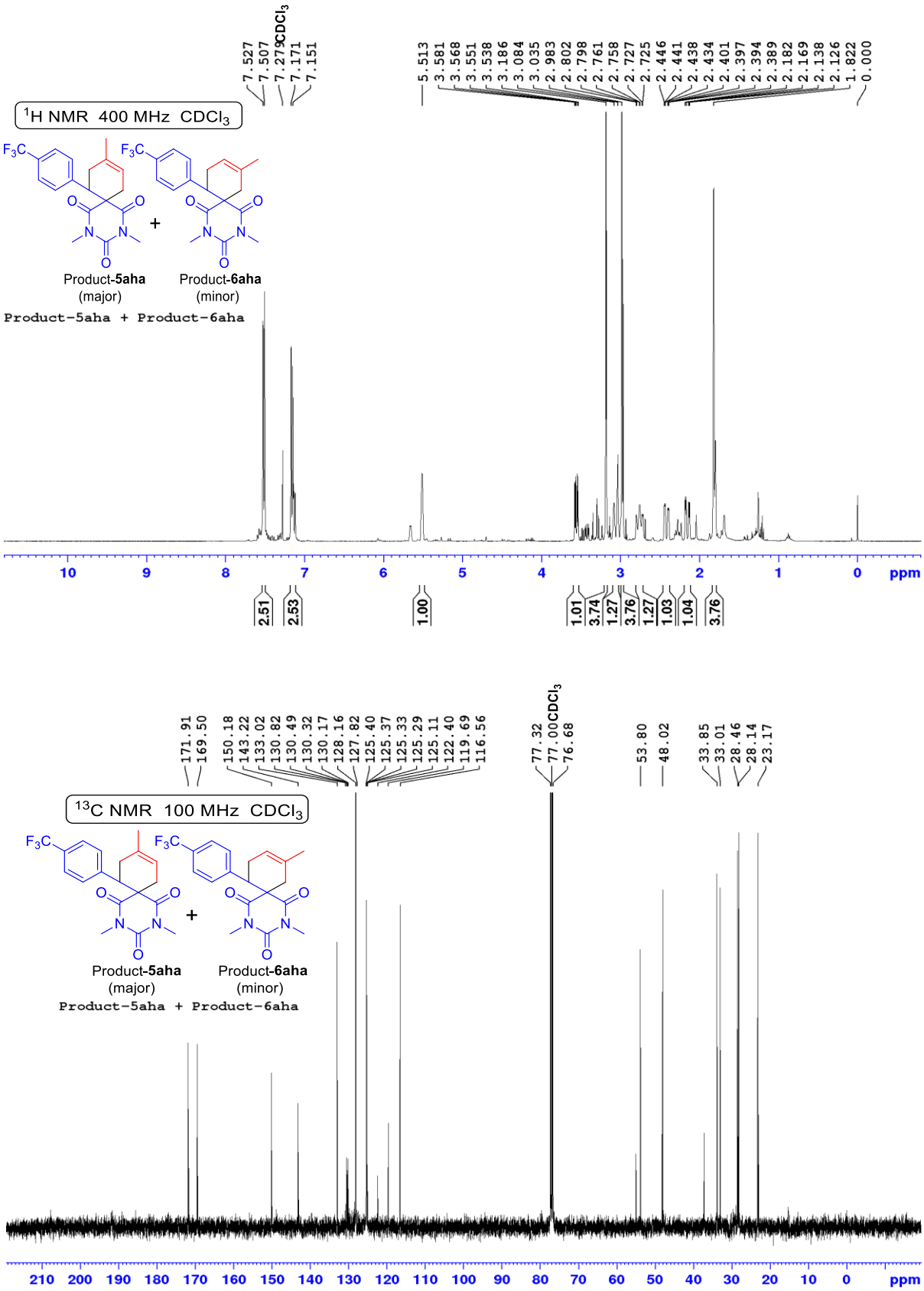



**Figure 7:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5aha** and **6aha.**

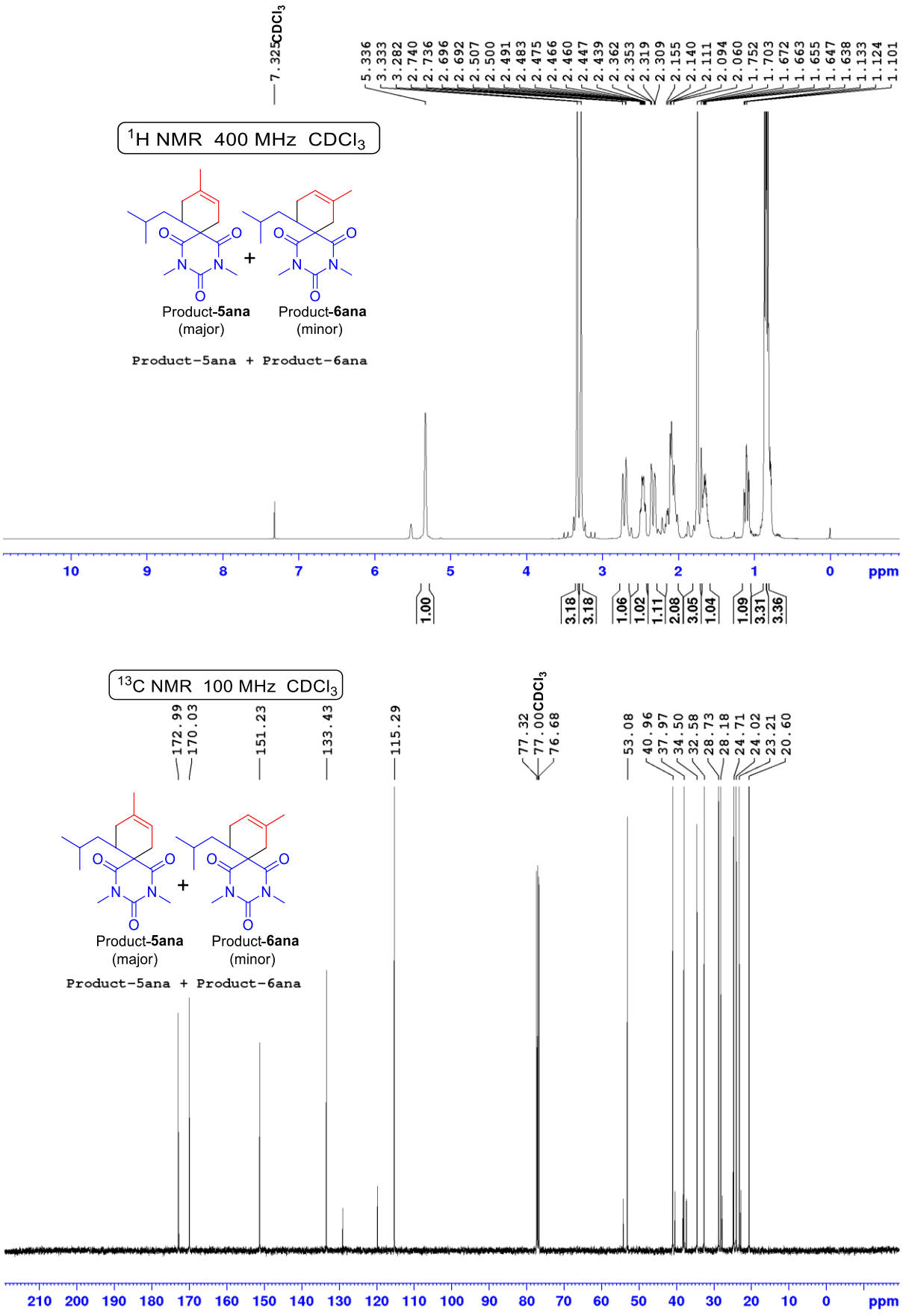



**Figure 8:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5ana** and **6ana.**

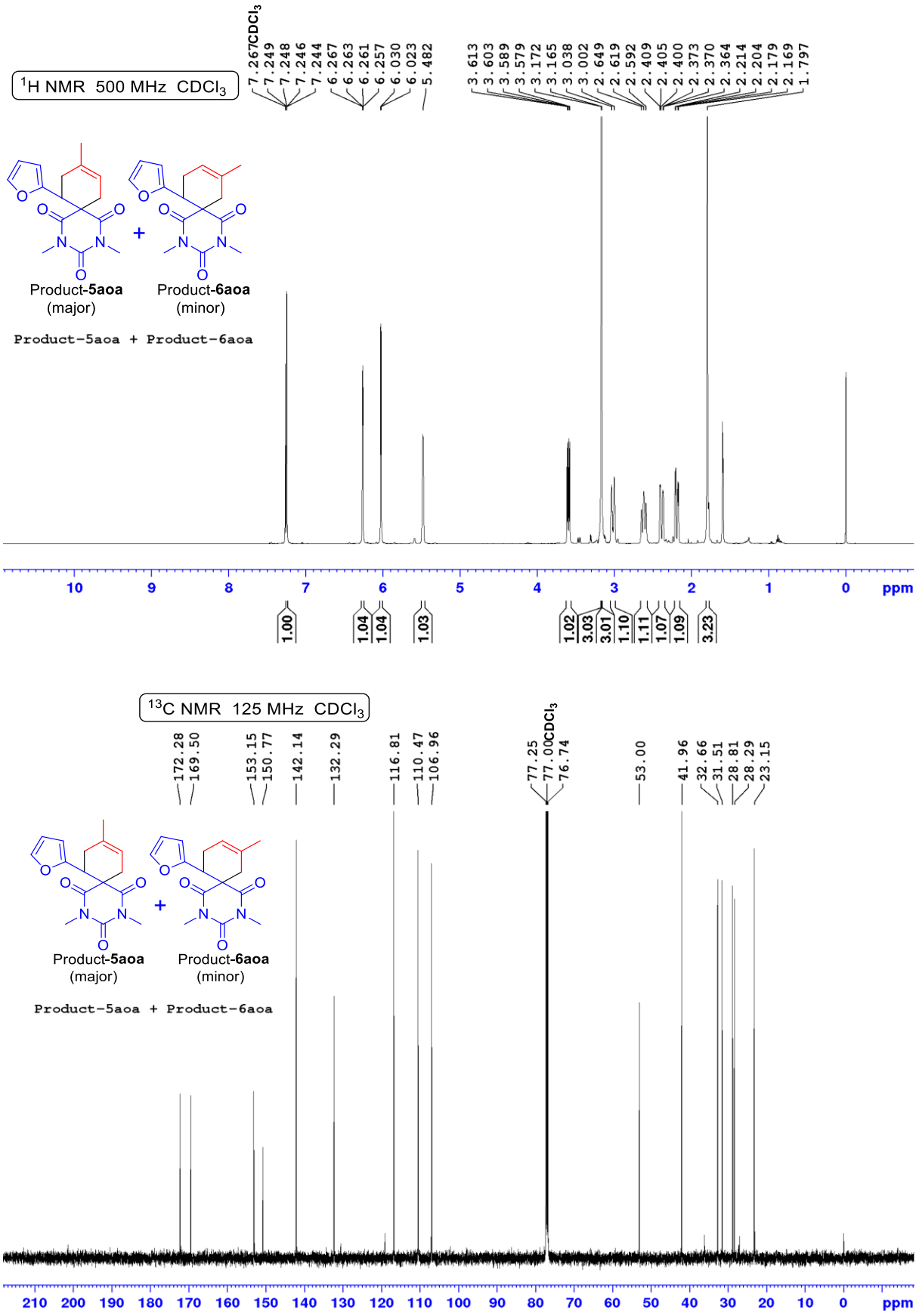



**Figure 9:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5aoa** and **6aoa.**

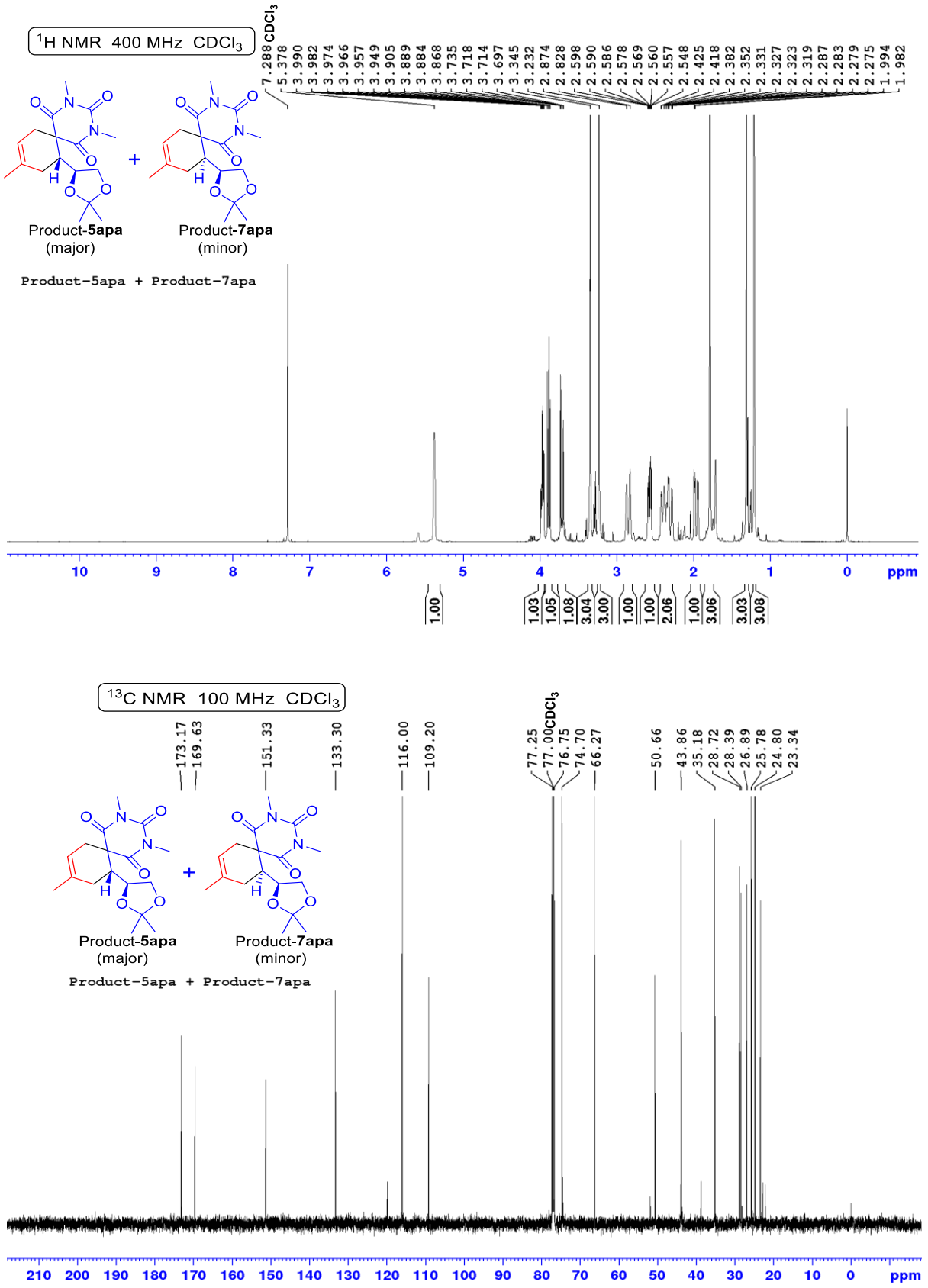



**Figure 10:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5apa** and **7apa.**

The structure and relative stereochemistry of compound (+)-**5apa** was further confirmed by X-Ray crystallography (Figure 11).[21]

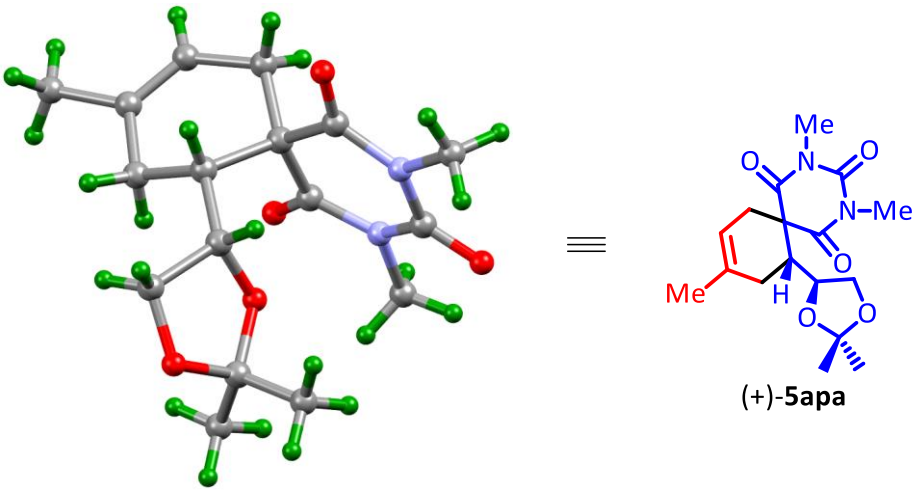


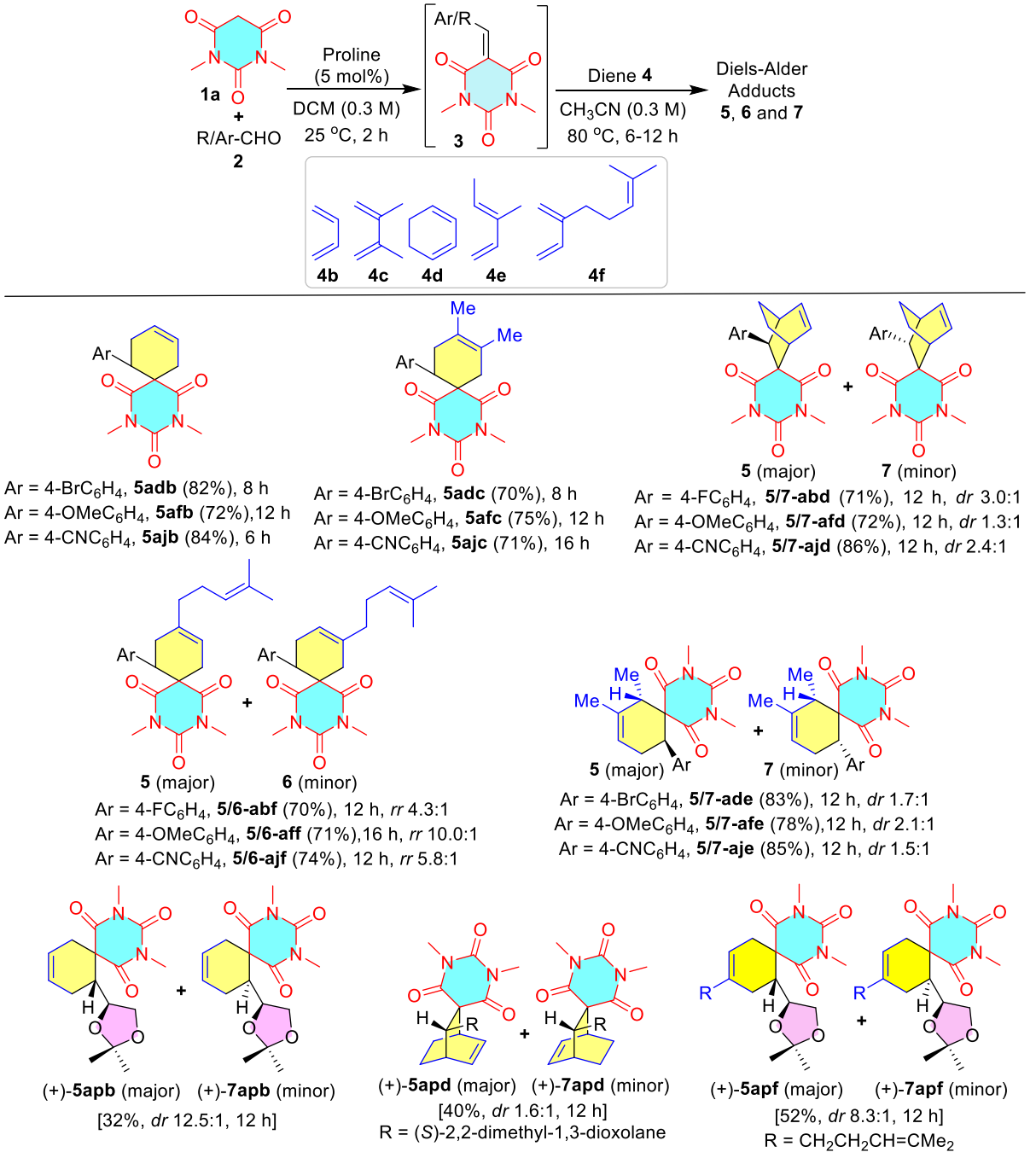

**Figure 11:** X-Ray crystal structure of (*R*)-11-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (**5apa**).

### *3.2.2.2 Substrate Scope with Different Aldehydes and Dienes:*

After establishing the protocol thus, we steered to probe the reaction sequence in depth for the performance of a few symmetric and asymmetric dienes **4b-f**. In all the cases the reaction was studied for three different aldehydes. All the dienes **4b-f** conducted well and produced the corresponding KC/DA products in good yields with moderate regioselectivity and diastereoselectivity (wherever applicable). With the symmetrical dienes, unsubstituted 1,3-butadiene **4b** and 2,3-dimethyl-1,3-butadiene **4c**, the *in-situ* generated benzylidene barbiturates **3ad**, **3af**, and **3aj** as dienophiles reacted efficiently and produced the respective products **5** as the solitary products in 70-84% yields (Table 3, entries 1-6). And 1,3-cyclohexadiene **4d** being a good DA reactive partner due to its inherent *cisoid* confirmation, on reaction with the *in-situ* made benzylidene barbiturates **3ab**, **3af**, and **3aj** generated the corresponding diastereomeric mixture of bridged KC/DA products **5** and **7** in 71-86% yields with 1.3:1 to 3.0:1 *dr* (Table 3, entries 7-9). In case of the unsymmetrical diene, *trans*-3-methyl-1,3-pentadiene **4e**, the terminal electron donating methyl on the double bond regioselectively facilitated the DA reaction with **3ad**, **3af**, and **3aj** powerfully to furnish the relevant regioselective products **5** and **7** in good 78-85% yields with a moderate diastereoselectivity of 1.5:1 to 2.1:1 *dr*, irrespective of the steric hindrance at the bonding site, indicating that electronic factors are more domineering than steric factors (Table 3, entries 10-12). Appreciatively, the monoterpene, myrcene **4f**, upon

reaction with the *in-situ* prepared dienophiles **3ab**, **3af**, and **3aj** gave the respective desired regioisomeric products **5** and **6** in 70-74% yields with 4.3:1 to 10.0:1 *rr* (Table 3, entries 13-15). With the chiral alkylidene barbiturate **3ap**, the dienes **4b**, **4d** and **4f** reacted fairly to produce the corresponding diastereomeric mixtures of products (+)-**5** and (+)-**7** in moderate 32-52% yields with 1.6:1 to 12.5:1 *dr* (Table 3, entries 16-18).

**Table 3:** Reaction Scope with Aldehydes and Dienes




Some of the compounds $^{1}H$ and $^{13}C$ NMR spectra have shown in Figure 12-15.

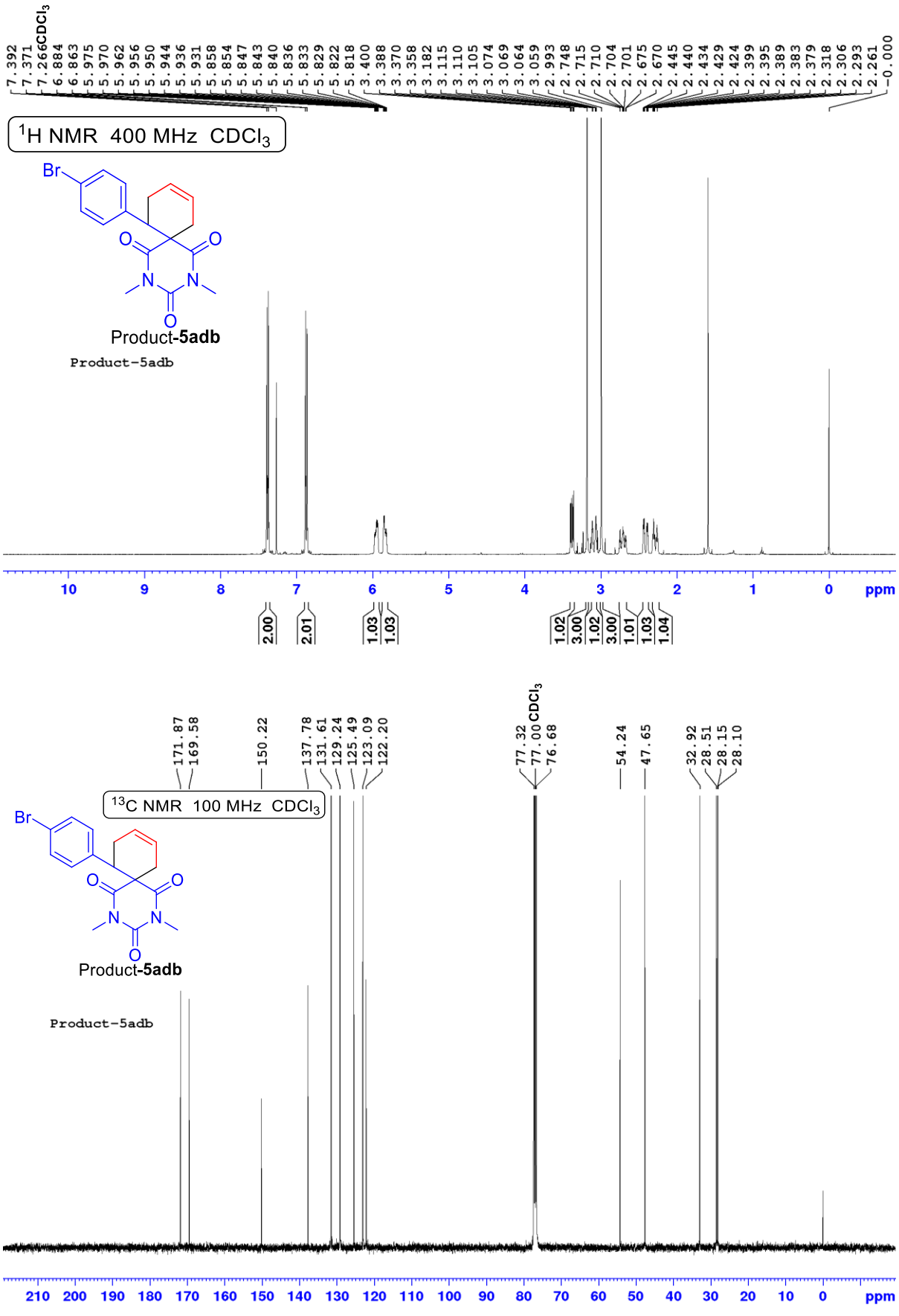



**Figure 12:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5adb** and **6adb.**

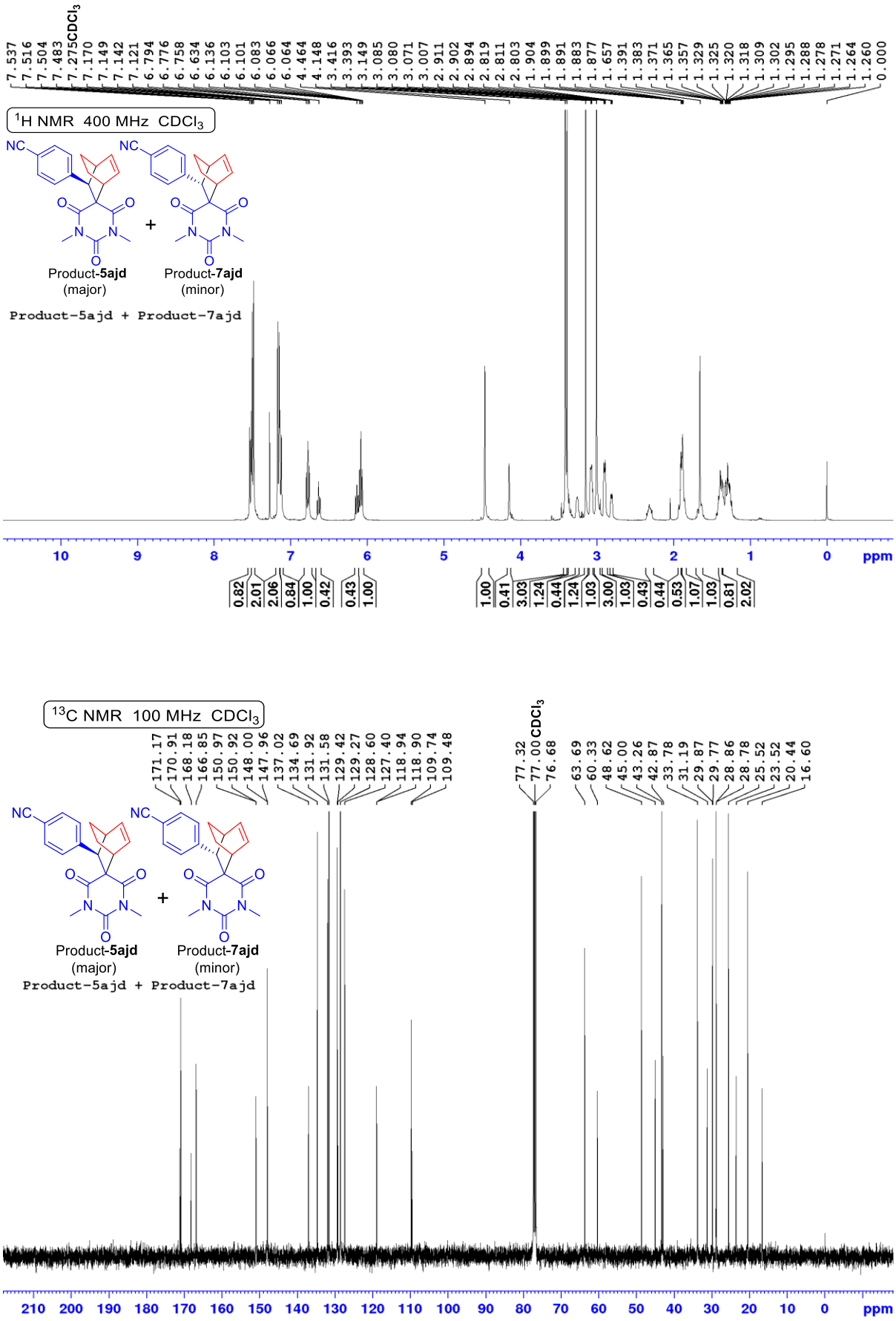



**Figure 13:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5ajd** and **7ajd.**

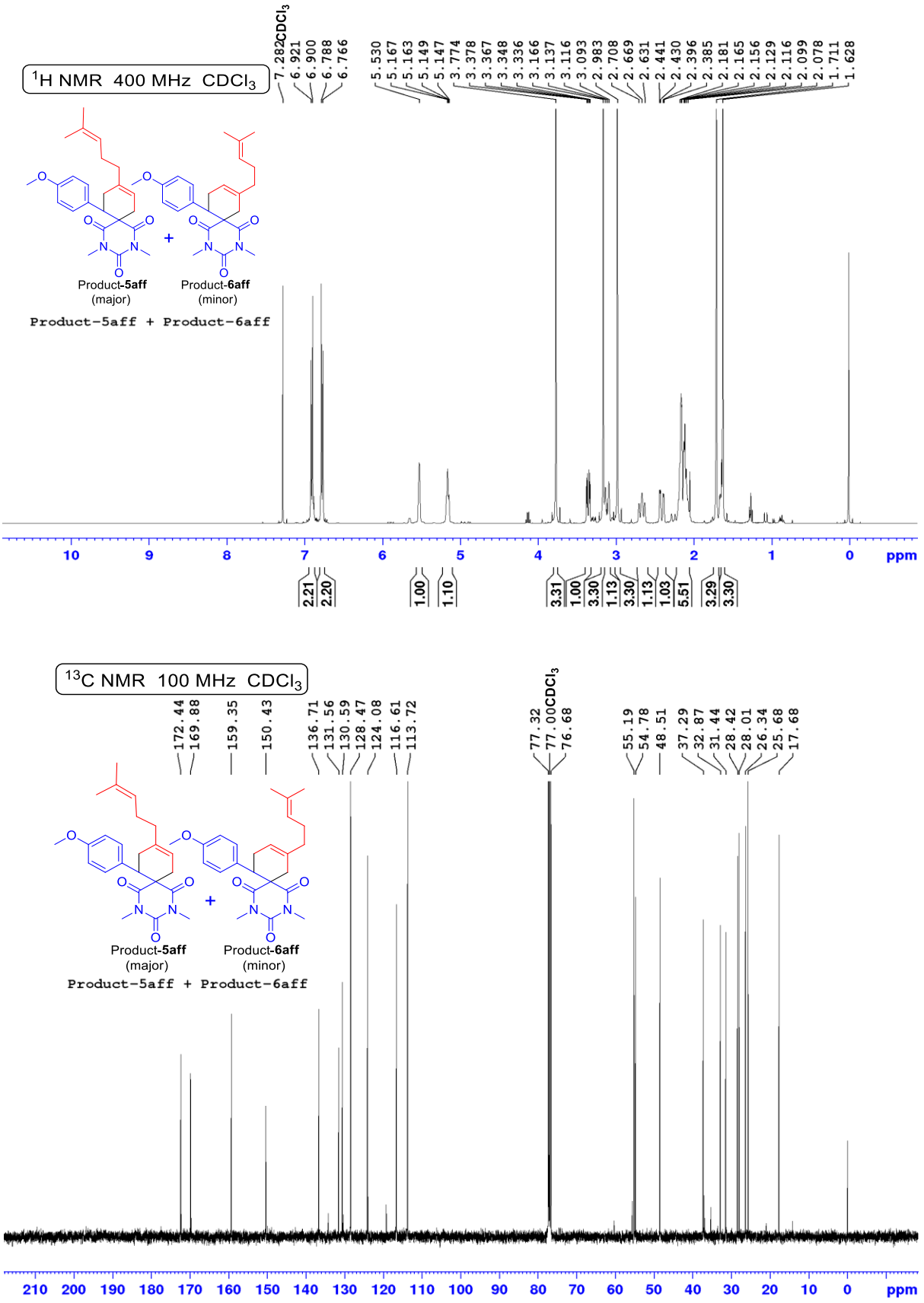



**Figure 14:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5aff** and **6aff.**

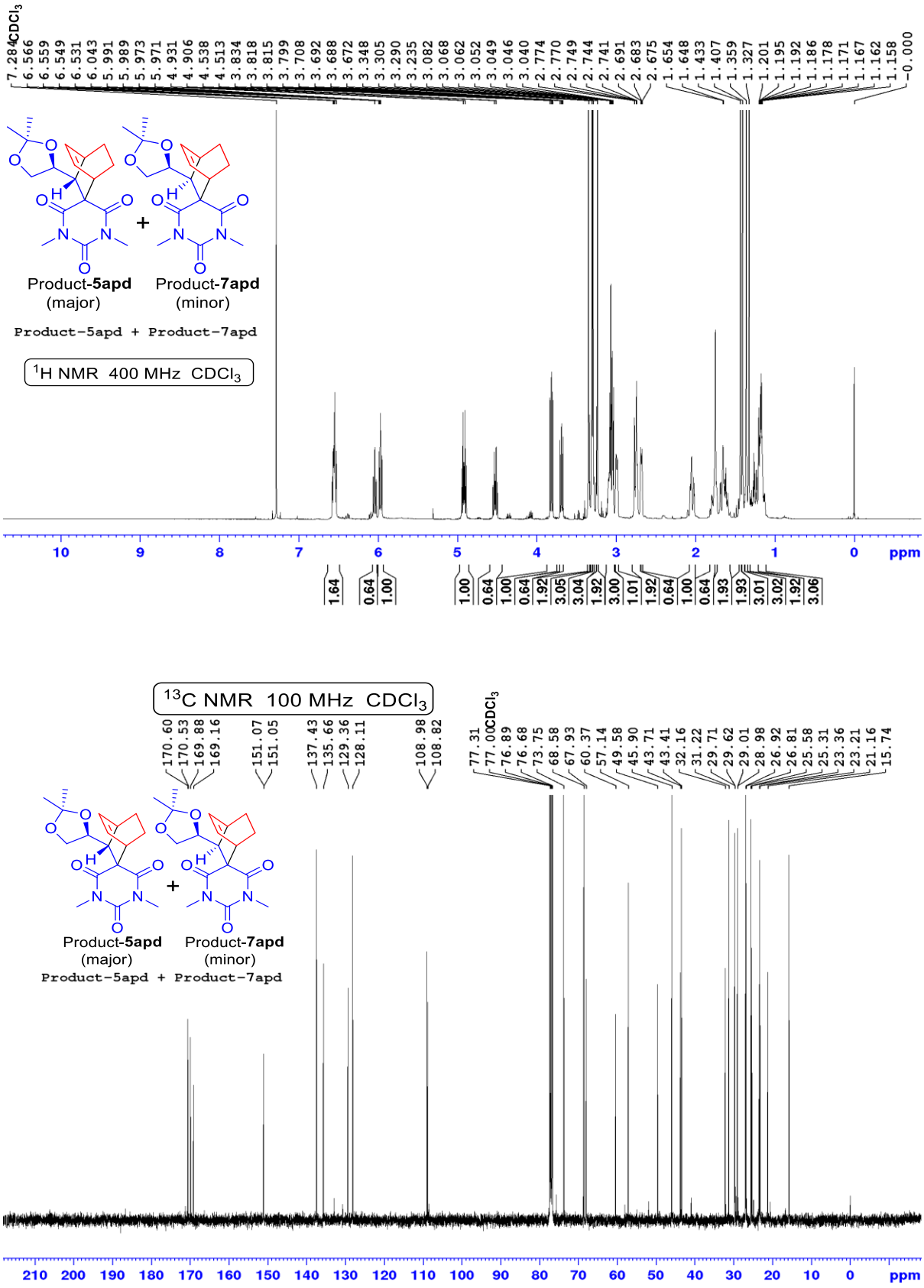
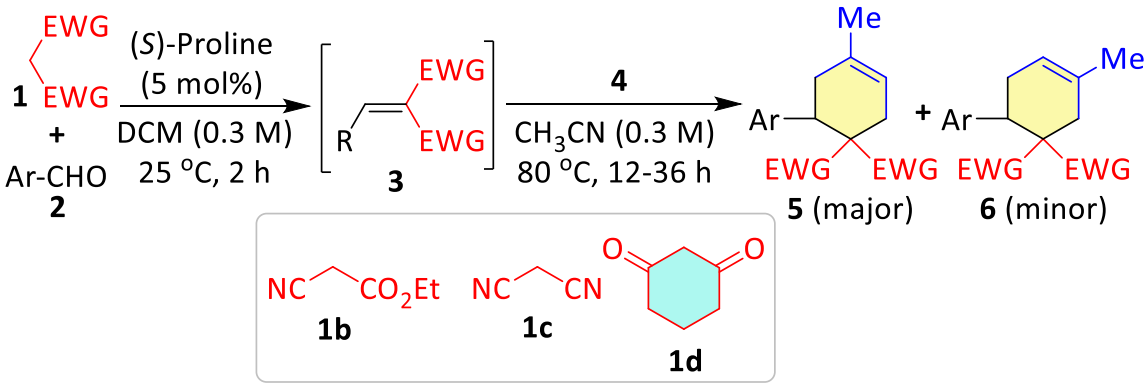


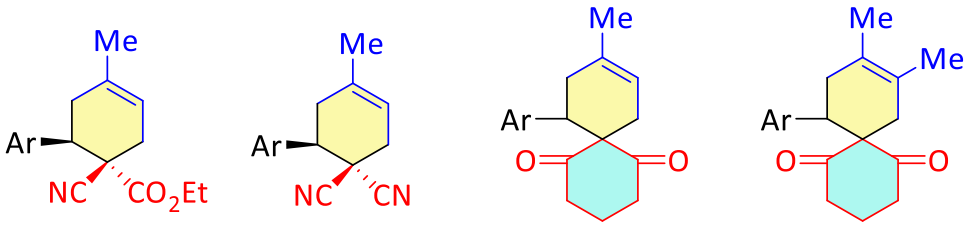

**Figure 15:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of products **5apd** and **7apd.**

### 3.2.2.3 Substrate Scope with Different C-H Acids:

To illustrate the versatility of the one-pot reaction, it was further extended to various other dienophiles generated by utilizing diverse active methylene compounds such as **1b-d** in the KC with 4-cyanobenzaldehyde **2j** (Table 4).

**Table 4**: Reaction Scope with CH-Acids [a]




[a]Experiments were conducted in an optimized manner, and dienes **4** were used in 3.0 equiv. [b]Reaction was performed in one pot method in $CH_3CN$.

Delightfully, all the arylidenes **3bj**, **3cj**, and **3dj** generated *in situ* under the optimized conditions, underwent the DA reaction with the diene **4a** to generate the respective regioisomeric mixtures of products **5** and **6** in moderate to good yields with good regioselectivity. When the dienophile **3dj** was reacted with the symmetrical diene, 2,3-dimethyl-1,3-butadiene **4c** the DA product **5djc** formed in 56% yield.

Synthesized compounds in Table 4 have characterized using NMR, IR and HRMS. $^{1}H$ and $^{13}C$ NMR spectra of **5dja** and **6dja** are given below (Figure 16).

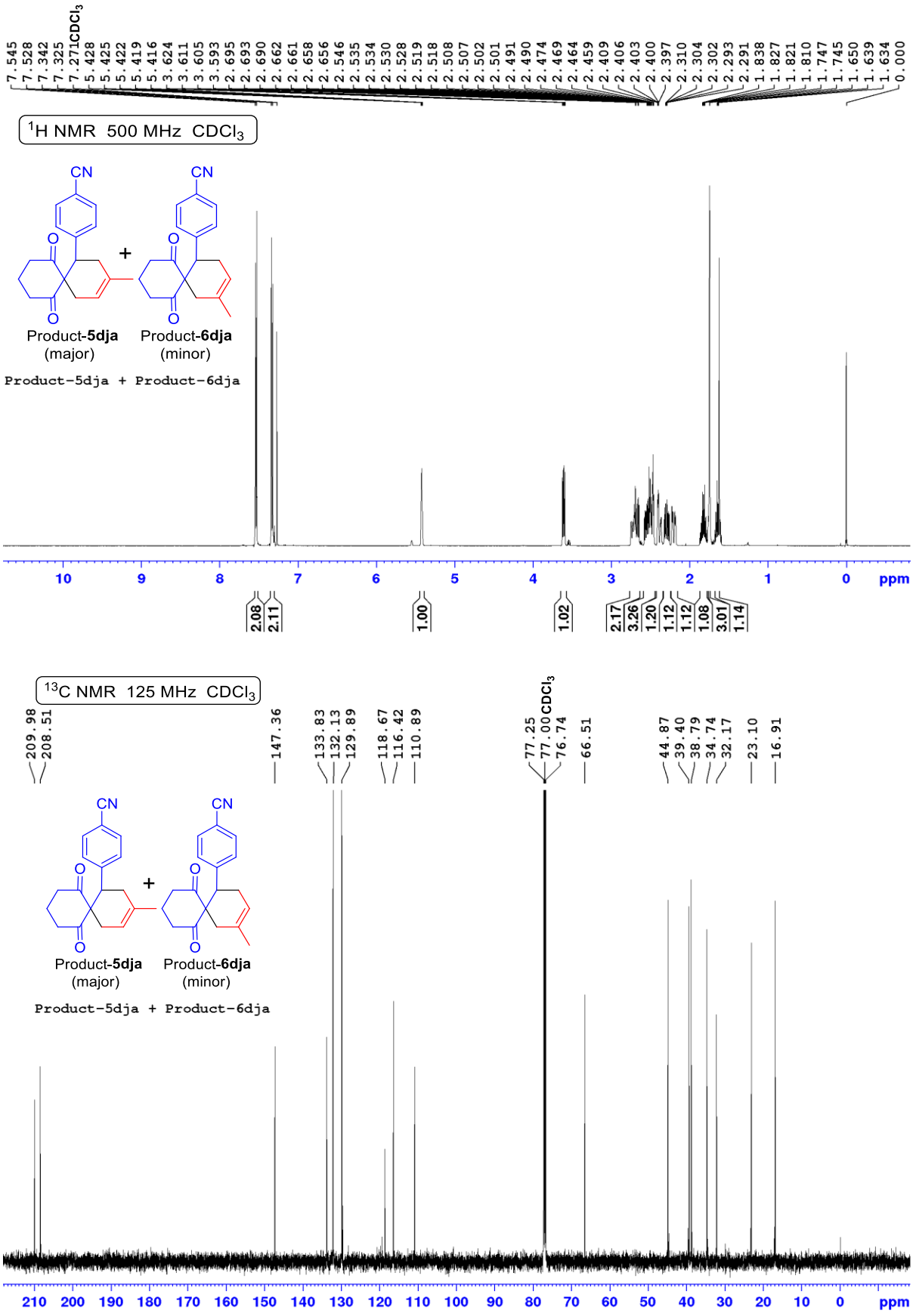
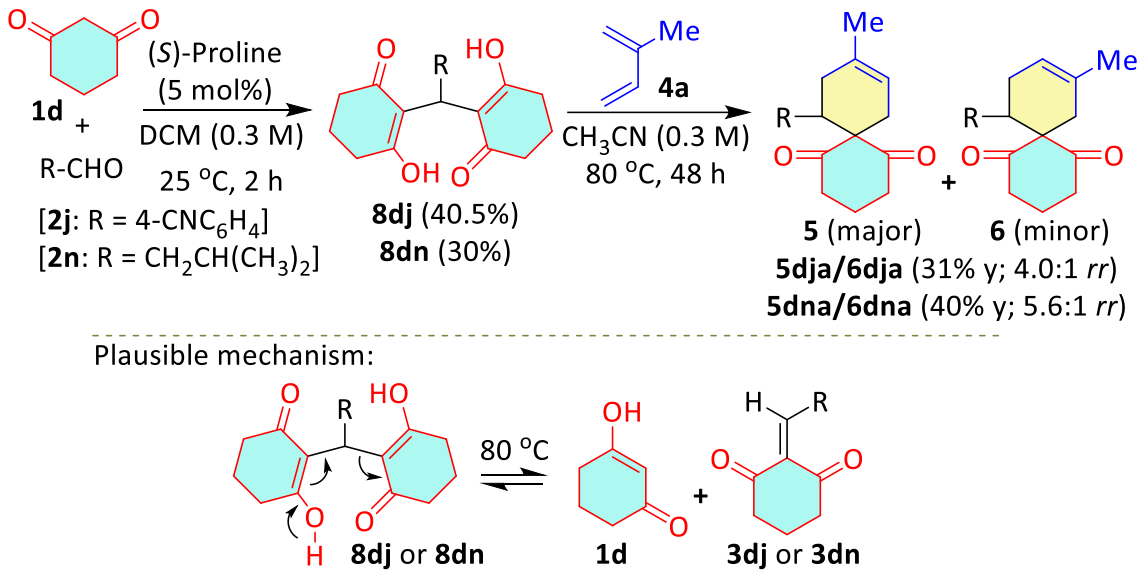



**Figure 16:** $^1$H NMR and $^{13}$C NMR spectrum of products **5dja** and **6dja.**

### 3.2.3 *Controlled Experiments to Prove the Formation of Olefins from Bis-product:*

The results from **1d** prompted us to investigate this reaction further to get some insights into the mechanics of the reaction sequence, as it is well known that the cyclic-1,3-diketones have predilection to form the Knoevenagel-Michael adduct (*bis*-adduct).[17,18] When the Knoevenagel condensation was conducted between **1d** and **2j**, the *bis*-adduct **8dj** was generated exclusively in 40.5% yield (Scheme 16). Amazingly, this isolated *bis*-adduct **8dj** on subjection to DA reaction with the diene **4a** under the optimized reaction condition produced the regioisomeric mixture of DA products **5dja** and **6dja** in 31% yield with 4.0:1 *rr*, revealing the unprecedented existence of equilibrium between the *bis*-adduct **8dj** and its constituents **1d** and **3dj** under the reaction condition, through *retro*-Michael addition and thereby liberating the Knoevenagel product **3dj** for reaction with the diene **4a** (Scheme 16). Similar type reaction mechanism was confirmed by another example with aliphatic aldehyde **2n** with **1d** to furnish the DA products **5dna/6dna** in 40% yield with 5.6:1 *rr* (Scheme 16).



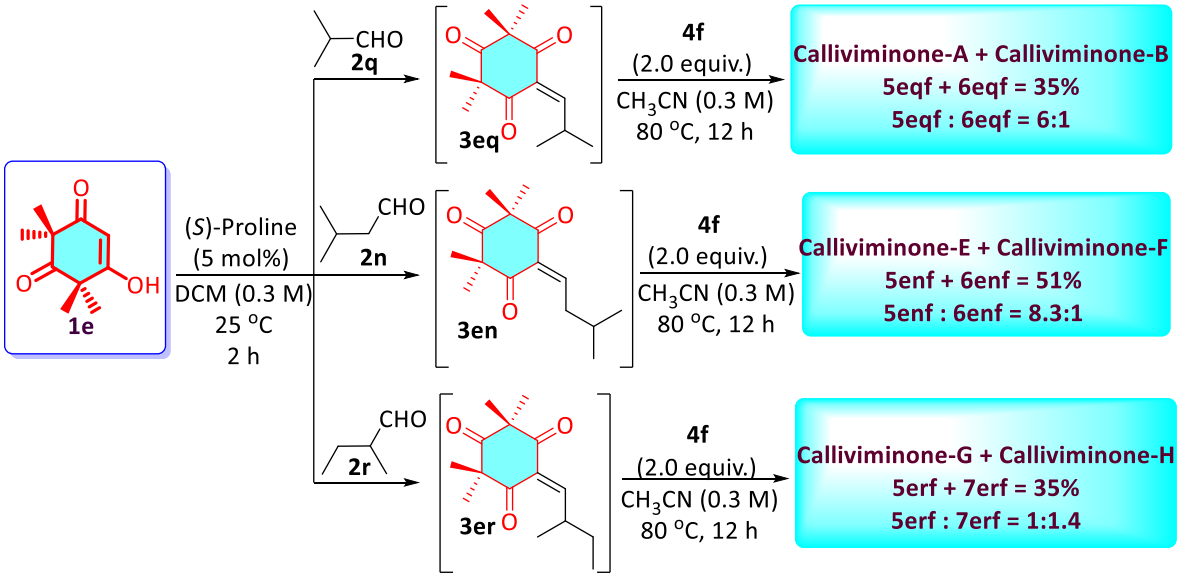

**Scheme 16**: Controlled Experiments to Prove the Formation of Olefins **3dj/3dn** from *bis*-Adducts **8dj/8dn**.

### 3.2.4 *One-pot Total Synthesis of Calliviminones A-H:*

From the illustration of Scheme 14 and Figure 3, we were elated that this strategy could be conjectured conveniently for accomplishing the total synthesis of calliviminone A, B, E, F, G and H under ambient reaction conditions. Calliviminones were isolated from the fruits of *Callistemon viminalis*, which is herb used to treat gastroenteritis, diarrhoea and skin infections.[19a-d] The syncarpic acid **1e** and myrcene **4f** under enzyme-catalysis, undergo [4+2]-

cycloaddition, which follows either DA or HDA reaction resulting in the formation of calliviminone A, B, E, F, G and H or calliviminone C, and D respectively (Figure 3).[19a-d]

The total synthesis started with the preparation of syncarpic acid **1e** through a sequence of Friedel-Crafts acylation, selective *C*-methylation and *retro*-Friedel-Crafts acylation of phloroglucinol with acyl chloride and methyl iodide as starting materials. With compound **1e** in hand, the synthesis commenced with the KC with isobutyraldehyde **2q**, isovaleraldehyde **2n** and 2-methylbutanal **2r**, followed by the DA reaction with myrcene **4f** to afford mixtures of calliviminones A and B (35%, 6:1), calliviminones E and F (51%, 8.3:1), and calliviminones G and H, (35%, 1:1.4), respectively (Scheme 17). The natural products yields were only moderate and did not improve either on lengthening the reaction time as such (at 80 °C) or by performing the reaction at 25 °C for long hours.




**Scheme 17**: One-pot total synthesis of calliviminones.

Structures of synthesized calliviminones A-H were established by correlation with naturally isolated NMR data (Figure 17 and 18).[19]

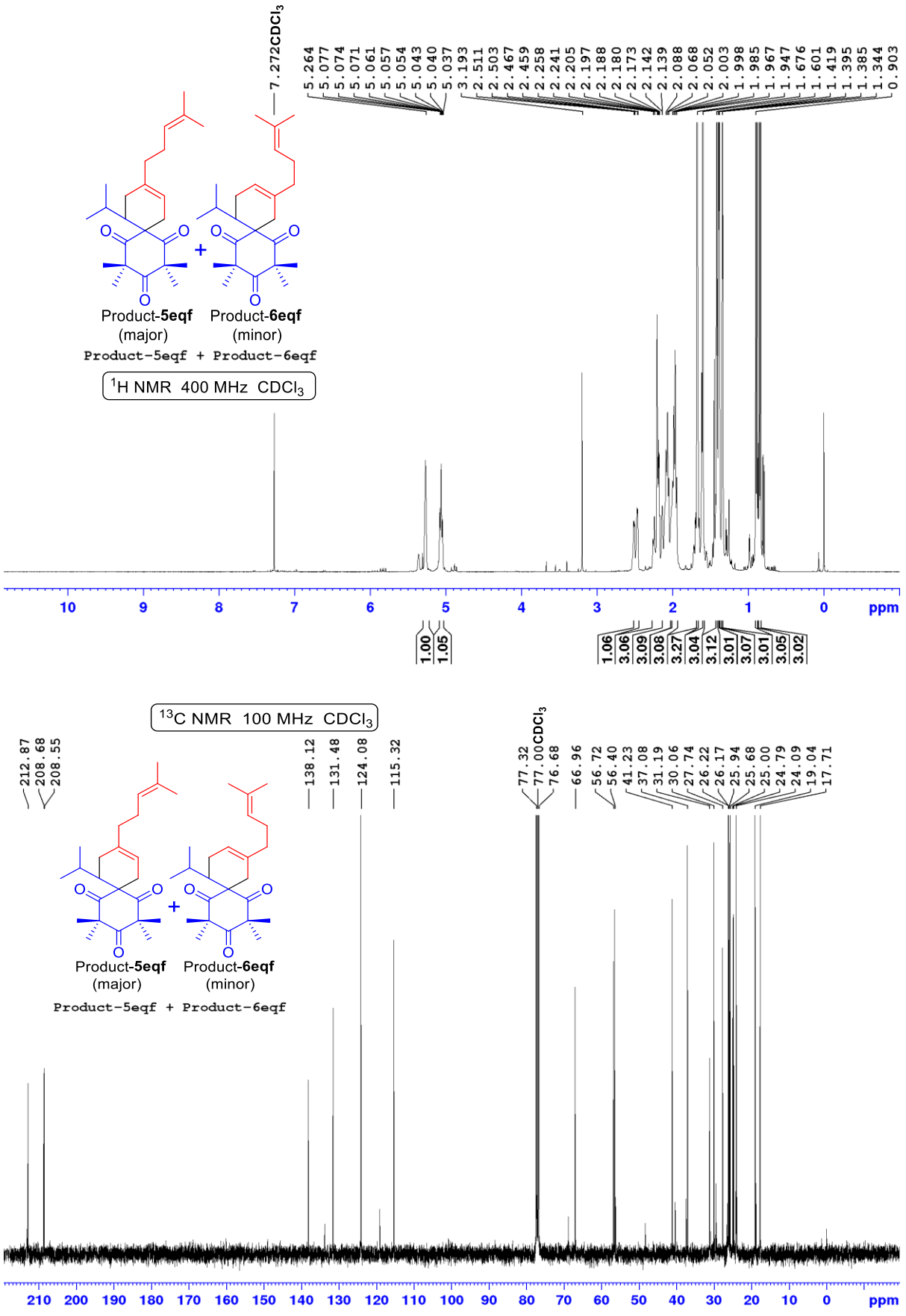
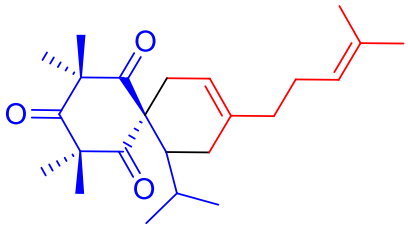
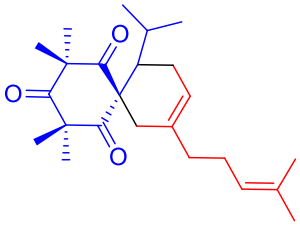
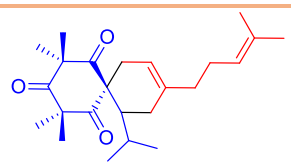
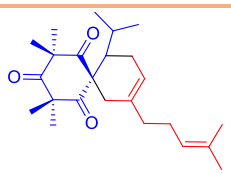



**Figure 17:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5eqf** and **6eqf.**

## Correlation of Natural and Synthetic NMR Data of (±)-Calliviminone A and (±)-Calliviminone B

| (±)-Calliviminone A | (±)-Calliviminone B | Synthetic DA Products |
|---|---|---|
|  |  | Calliviminone-A [**5eqf,** major] + Calliviminone-B [**6eqf,** minor] |
| **$^1$H NMR (500 MHz)** | **$^1$H NMR (500 MHz)** | **$^1$H NMR (400 MHz)** (*rr* = 6.0:1, major isomer) |
| 5.26 (1H, br s) | 5.35 (1H, br s) | 5.26 (1H, br s) |
| 5.05 (1H, t, *J* = 7.0 Hz) | 5.07 (1H, tt, *J* = 7.0,1.5 Hz) | 5.06 (1H, tt, *J* = 6.8, 1.2 Hz) |
| 2.48 (1H, dd, *J* = 17.5,3.0 Hz) | 2.49 (1H, dd, *J* = 17.5,1.5 Hz) | 2.48 (1H, dd, *J* = 17.6, 3.2 Hz) |
| 2.23 (1H, m)<br>2.18 (1H, m)<br>2.14 (1H, m)<br>2.07 (2H, m) 9H<br>2.00 (1H, m)<br>1.97 (2H, m)<br>1.68 (1H, m) | 2.21 (1H, d, *J* = 17.5 Hz)<br>2.10 (2H, m)<br>2.07 (1H, m)<br>2.06 (1H, m) 9H<br>1.98 (2H, m)<br>1.98 (1H, m)<br>1.58 (1H, m) | 2.26 – 2.17 (3H, m)<br>2.14 - 2.05 (3H, m) 9H<br>2.00 - 1.95 (3H, m) |
| 1.67 (3H, s) | 1.66 (3H, s) | 1.67 (3H, s) |
| 1.59 (3H, s) | 1.59 (3H, s) | 1.60 (3H, s) |
| 1.41 (3H, s) | 1.44 (3H, s) | 1.41 (3H, s) |
| 1.39 (3H, s) | 1.40 (3H, s) | 1.39 (3H, s) |
| 1.38 (3H, s) | 1.38 (3H, s) | 1.38 (3H, s) |
| 1.34 (3H, s) | 1.33 (3H, s) | 1.34 (3H, s) |
| 0.88 (3H, d, *J* = 7.0 Hz) | 0.88 (3H, d, *J* = 7.0 Hz) | 0.89 (3H, d, *J* = 6.8 Hz) |
| 0.83 (3H, d, *J* = 7.0 Hz) | 0.79 (3H, d, *J* = 7.0 Hz) | 0.84 (3H, d, *J* = 6.8 Hz) |

## Correlation of Natural and Synthetic NMR Data of (±)-Calliviminone A and (±)-Calliviminone B

| (±)-Calliviminone A | (±)-Calliviminone B | Synthetic DA Products |
|---|---|---|
|  |  | Calliviminone-A [**5eqf,** major] + Calliviminone-B [**6eqf,** minor] |
| **$^{13}$C NMR (125 MHz)** | **$^{13}$C NMR (125 MHz)** | **$^{13}$C NMR (100 MHz)** (*rr* = 6.0:1, major isomer) |
| 213.0 (C, *C*=O) | 213.2 (C, *C*=O) | 212.9 (C, *C*=O) |
| 208.8 (C, *C*=O) | 208.9 (C, *C*=O) | 208.7 (C, *C*=O) |
| 208.7 (C, *C*=O) | 208.9 (C, *C*=O) | 208.5 (C, *C*=O) |
| 138.4 (C) | 133.7 (C) | 138.1 (C) |
| 131.6 (C) | 131.7 (C) | 131.5 (C) |
| 124.3 (CH) | 124.3 (CH) | 124.1 (CH) |
| 115.4 (CH) | 119.3 (CH) | 115.3 (CH) |
| 67.1 (C) | 68.8 (C) | 67.0 (C) |
| 56.9 (C) | 56.3 (C) | 56.7 (C) |
| 56.6 (C) | 56.4 (C) | 56.4 (C) |
| 41.4 (CH) | 40.5 (CH) | 41.2 (CH) |
| 37.2 ($CH_2$) | 37.6 ($CH_2$) | 37.1 ($CH_2$) |
| 31.5 ($CH_2$) | 24.1 ($CH_2$) | 31.2 ($CH_2$) |
| 30.2 (CH) | 29.7 (CH) | 30.1 (CH) |
| 28.0 ($CH_2$) | 31.3 ($CH_2$) | 27.7 ($CH_2$) |
| 26.4 ($CH_3$) | 26.3 ($CH_3$) | 26.22 ($CH_3$) |
| 26.4 ($CH_2$) | 26.2 ($CH_2$) | 26.17 ($CH_2$) |
| 26.1 ($CH_3$) | 26.6 ($CH_3$) | 25.9 ($CH_3$) |
| 25.8 ($CH_3$) | 25.8 ($CH_3$) | 25.7 ($CH_3$) |
| 25.2 ($CH_3$) | 26.1 ($CH_3$) | 25.0 ($CH_3$) |
| 24.9 ($CH_3$) | 24.4 ($CH_3$) | 24.8 ($CH_3$) |
| 24.2 ($CH_3$) | 24.3 ($CH_3$) | 24.1 ($CH_3$) |
| 19.2 ($CH_3$) | 19.0 ($CH_3$) | 19.0 ($CH_3$) |
| 17.8 ($CH_3$) | 17.8 ($CH_3$) | 17.7 ($CH_3$) |

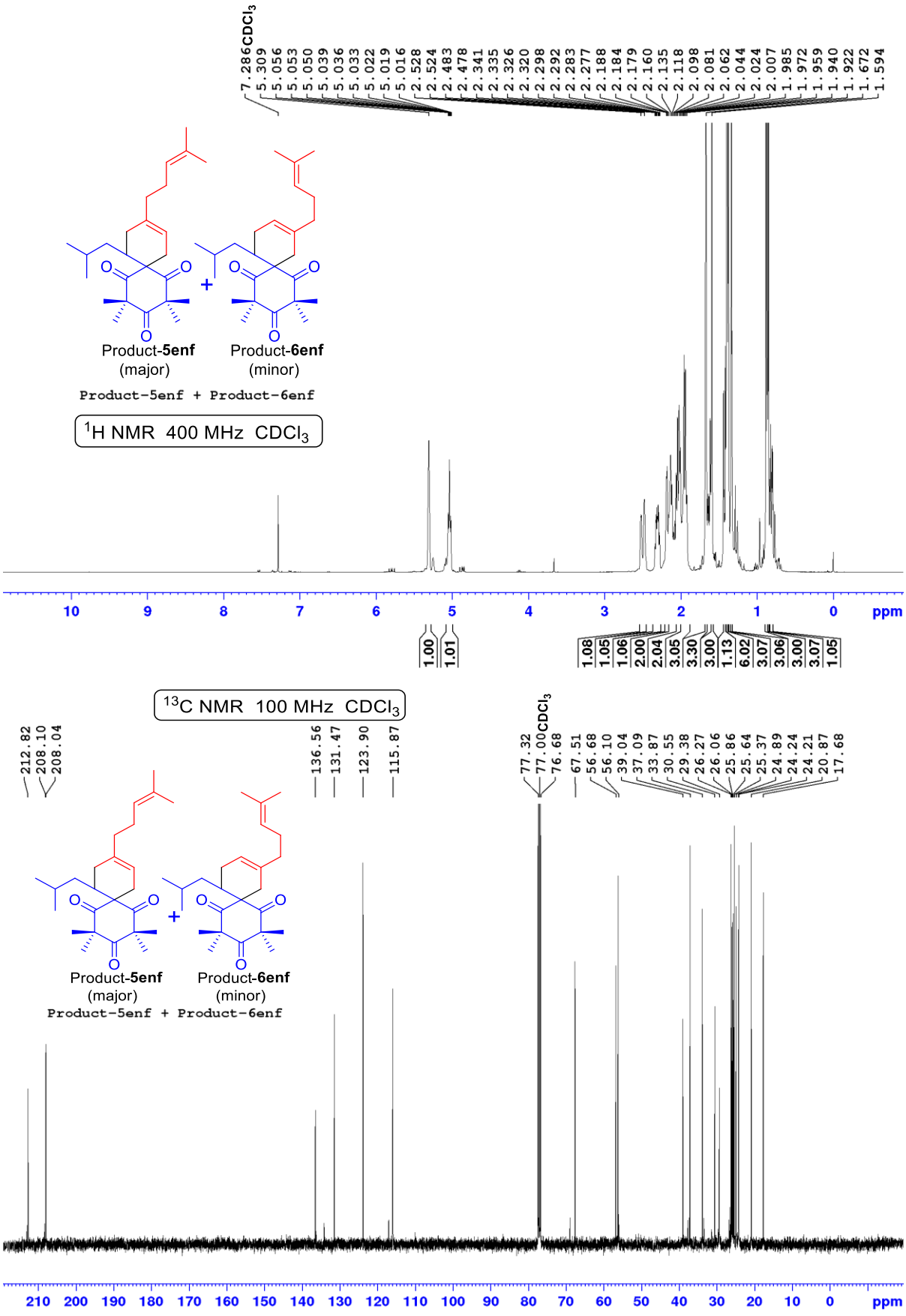
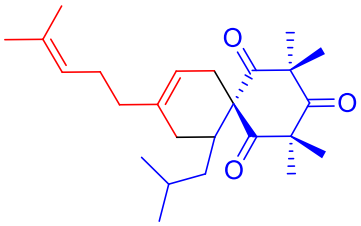
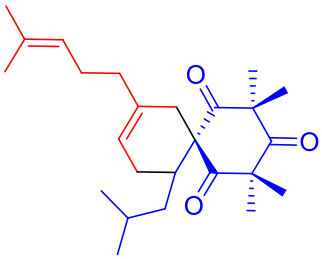
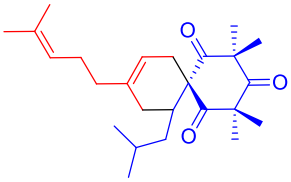
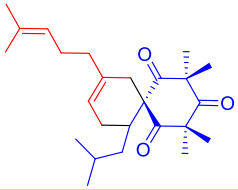



**Figure 18:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5enf** and **6enf.**

## Correlation of Natural and Synthetic NMR Data of (±)-Calliviminone E and (±)-Calliviminone F

| (±)-Calliviminone E | (±)-Calliviminone F | Synthetic DA Products |
|---|---|---|
|  |  | Calliviminone-E [**5enf,** major] + Calliviminone-F [**6enf,** minor] |
| **$^1$H NMR (500 MHz)** | **$^1$H NMR (500 MHz)** | **$^1$H NMR (400 MHz)** (*rr* = 8.3:1, major isomer) |
| 5.30 (1H, br s) | 5.24 (1H, br s) | 5.30 (1H, br s) |
| 5.03 (1H, t, *J* = 7.0 Hz) | 5.08 (1H, t, *J* = 7.0 Hz) | 5.04 (1H, tt, *J* = 6.8, 1.2 Hz) |
| 2.49 (1H, dd, *J* = 17.5,1.5 Hz) | 2.47 (1H, d, *J* = 18.0 Hz) | 2.50 (1H, dd, *J* = 18.0, 2.0 Hz) |
| 2.30 (1H, m) | 2.20 (1H, m) | 2.31 (1H, dq, *J* = 6.0, 2.4 Hz) |
| 2.16 (1H, m)<br>2.14 (1H, m)<br>2.04 (2H, m)<br>2.02 (1H, m) 8H<br>1.94 (2H, m)<br>1.64 (1H, m) | 2.12 (2H, m)<br>2.07 (1H, m)<br>2.02 (2H, m) 8H<br>1.95 (2H, m)<br>1.58 (1H, m) | 2.19 - 2.16 (1H, m)<br>2.14 - 2.08 (2H, m)<br>2.06 - 2.01 (2H, m)<br>8H<br>1.99 - 1.92 (3H, m) |
| 1.67 (3H, s) | 1.67 (3H, s) | 1.67 (3H, s) |
| 1.59 (3H, s) | 1.61 (3H, s) | 1.59 (3H, s) |
| 1.42 (1H, m) | 1.32 (1H, m) | 1.43 (1H, d, *J* = 9.6 Hz) |
| 1.39 (3H, s) | 1.43 (3H, s) | 1.39 (3H, s) |
| 1.39 (3H, s) | 1.41 (3H, s) | 1.39 (3H, s) |
| 1.37 (3H, s) | 1.37 (3H, s) | 1.37 (3H, s) |
| 1.33 (3H, s) | 1.32 (3H, s) | 1.33 (3H, s) |
| 0.86 (3H, d, *J* = 7.0 Hz) | 0.85 (3H, d, *J* = 7.0 Hz) | 0.87 (3H, d, *J* = 6.4 Hz) |
| 0.85 (3H, d, *J* = 7.0 Hz) | 0.81 (3H, d, *J* = 7.0 Hz) | 0.85 (3H, d, *J* = 6.4 Hz) |
| 0.79 (1H, m) | 0.71 (1H, m) | 0.83 - 0.79 (1H, m) |

## Correlation of Natural and Synthetic NMR Data of (±)-Calliviminone E and (±)-Calliviminone F

| (±)-Calliviminone E | (±)-Calliviminone F | Synthetic DA Products |
|---|---|---|
|  |  | Calliviminone-E [**5enf,** major] + Calliviminone-F [**6enf,** minor] (*rr* = 8.3:1, major isomer) |
| **$^{13}$C NMR (125 MHz)** | **$^{13}$C NMR (125 MHz)** | **$^{13}$C NMR (100 MHz)** |
| 213.0 (C, *C*=O)<br>208.3 (C, *C*=O)<br>208.2 (C, *C*=O) | 213.2 (C, *C*=O)<br>208.5 (C, *C*=O)<br>208.2 (C, *C*=O) | 212.8 (C, *C*=O)<br>208.1 (C, *C*=O)<br>208.0 (C, *C*=O) |
| 136.8 (C) | 134.4 (C) | 136.5 (C) |
| 131.7 (C) | 131.7 (C) | 131.5 (C) |
| 124.1 (CH) | 124.1 (CH) | 123.9 (CH) |
| 116.0 (CH) | 117.2 (CH) | 115.9 (CH) |
| 67.7 (C) | 69.0 (C) | 67.5 (C) |
| 56.9 (C) | 56.3 (C) | 56.7 (C) |
| 56.3 (C) | 56.1 (C) | 56.1 (C) |
| 39.3 ($CH_2$) | 38.0 ($CH_2$) | 39.0 ($CH_2$) |
| 37.3 ($CH_2$) | 37.4 ($CH_2$) | 37.1 ($CH_2$) |
| 34.1 (CH) | 33.7 (CH) | 33.9 (CH) |
| 30.8 ($CH_2$) | 29.8 ($CH_2$) | 30.5 ($CH_2$) |
| 29.6 ($CH_2$) | 27.0 ($CH_2$) | 29.4 ($CH_2$) |
| 26.4 ($CH_2$) | 26.3 ($CH_2$) | 26.3 ($CH_2$) |
| 26.2 ($CH_3$) | 26.7 ($CH_3$) | 26.1 ($CH_3$) |
| 26.0 ($CH_3$) | 26.1 ($CH_3$) | 25.9 ($CH_3$) |
| 25.8 ($CH_3$) | 25.8 ($CH_3$) | 25.4 ($CH_3$) |
| 25.6 (CH) | 25.6 (CH) | 25.6 (CH) |
| 25.1 ($CH_3$) | 24.4 ($CH_3$) | 24.9 ($CH_3$) |
| 24.4 ($CH_3$) | 24.3 ($CH_3$) | 24.24 ($CH_3$) |
| 24.3 ($CH_3$) | 25.8 ($CH_3$) | 24.21 ($CH_3$) |
| 21.0 ($CH_3$) | 21.1 ($CH_3$) | 20.9 ($CH_3$) |
| 17.8 ($CH_3$) | 17.8 ($CH_3$) | 17.7 ($CH_3$) |

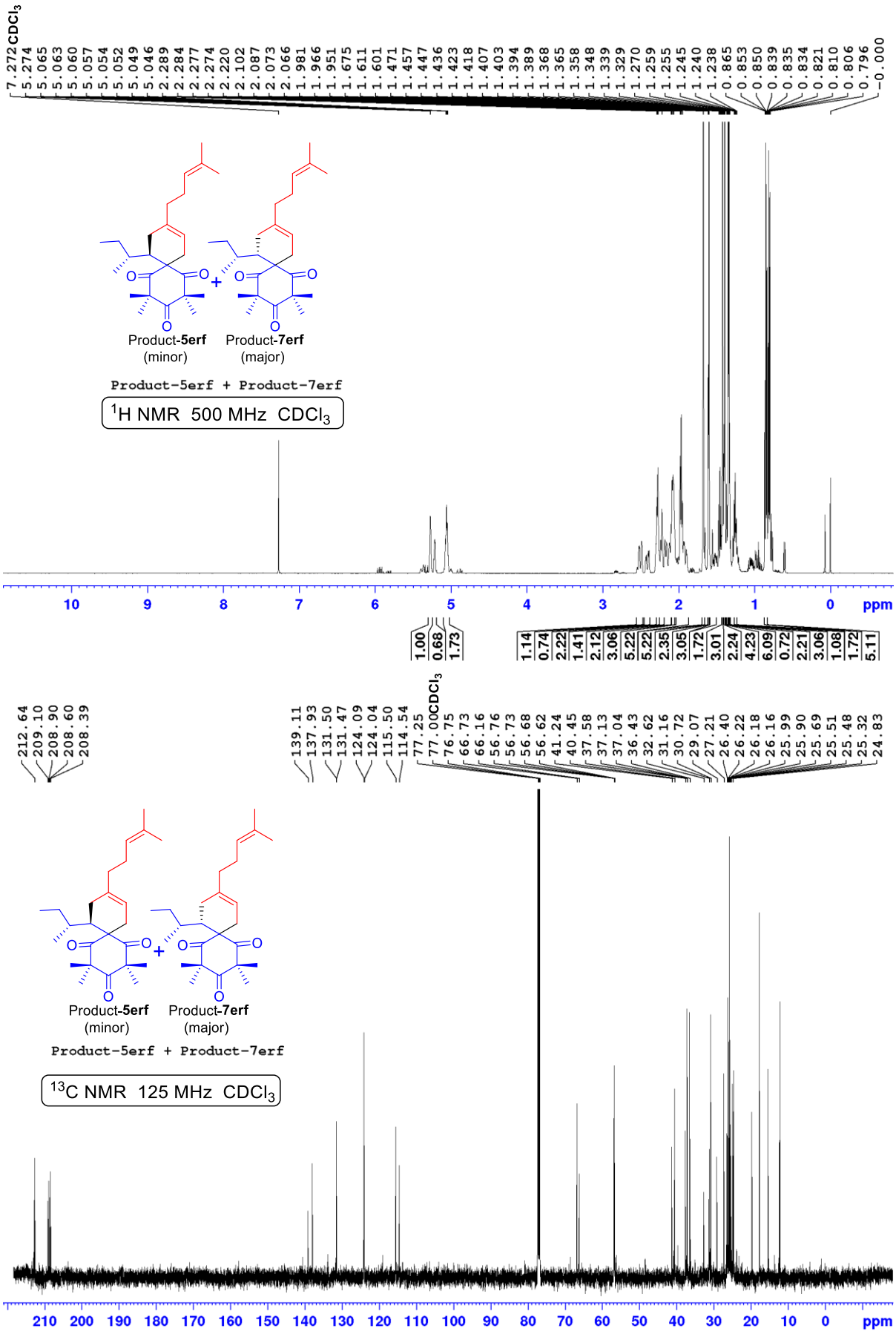
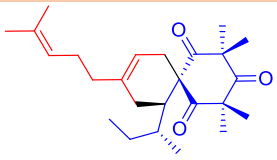
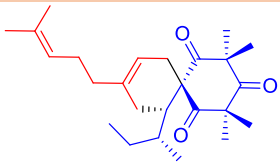
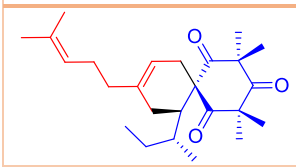
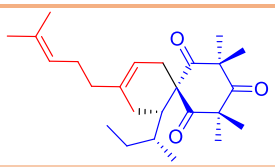



**Figure 19:** $^{1}$H NMR and $^{13}$C NMR spectrum of products **5erf** and **6erf.**

# Correlation of Natural and Synthetic NMR Data of (±)-Calliviminone G and (±)-Calliviminone H

| (±)-Calliviminone G | (±)-Calliviminone H | Synthetic DA Products | |
|---|---|---|---|
|  |  | Calliviminone-H [**7erf**] | Calliviminone-G [**5erf**] |
| **$^1$H NMR (500 MHz)** | **$^1$H NMR (500 MHz)** | **$^1$H NMR (500 MHz)** (*dr* = 1.4:1, major isomer) | **$^1$H NMR (500 MHz)** (*dr* = 1.4:1, minor isomer) |
| 5.21 (1H, br s) | 5.27 (1H, br s) | 5.27 (1H, br s) | 5.21 (1H, br s) |
| 5.04 (1H, t, *J* = 7.0 Hz) | 5.05 (1H, t, *J* = 7.0 Hz) | 5.08 - 5.04 (1H, m) | 5.08 - 5.04 (1H, m) |
| 2.41 (1H, dd, *J* = 17.5, 4.5 Hz) | 2.50 (1H, dd, *J* = 17.5, 2.0 Hz) | 2.50 (1H, dd, *J* = 18.0, 4.5 Hz) | 2.41 (1H, dd, *J* = 17.5, 5.0 Hz) |
| 2.28 (1H, m)<br>2.28 (1H, m)<br>2.15 (1H, m)<br>2.09 (1H, m) 8H<br>2.07 (2H, m)<br>1.97 (2H, m) | 2.24 (1H, m)<br>2.29 (1H, m)<br>2.21 (1H, m)<br>2.07 (2H, m) 8H<br>1.97 (2H, m)<br>1.93 (1H, m) | 2.30 – 2.26 (2H, m)<br>2.12 – 2.07 (3H, m)<br>8H<br>1.98 – 1.89 (3H, m) | 2.24 – 2.22 (2H, m)<br>2.18 - 2.16 (3H, m)<br>8H<br>1.98 - 1.89 (3H, m) |
| 1.67 (3H, s) | 1.67 (3H, s) | 1.67 (3H, s) | 1.67 (3H, s) |
| 1.59 (3H, s) | 1.59 (3H, s) | 1.60 (3H, s) | 1.61 (3H, s) |
| 1.52 (1H, m) | 1.25 (1H, m) | 1.49 – 1.44 (1H, m) | 1.49 – 1.44 (1H, m) |
| 1.43 (1H, m) | 1.36 (1H, m) | 1.33 – 1.32 (1H, m) | 1.37 – 1.36 (1H, m) |
| 1.41 (3H, s) | 1.42 (3H, s) | 1.423 (3H, s) | 1.418 (3H, s) |
| 1.39 (3H, s) | 1.38 (3H, s) | 1.389 (3H, s) | 1.394 (3H, s) |
| 1.39 (3H, s) | 1.38 (3H, s) | 1.389 (3H, s) | 1.394 (3H, s) |
| 1.34 (3H, s) | 1.33 (3H, s) | 1.339 (3H, s) | 1.348 (3H, s) |
| 1.03 (1H, m) | 1.25 (1H, m) | 1.27 – 1.23 (1H, m) | 1.27 – 1.23 (1H, m) |
| 0.84 (3H, d, *J* = 7.0 Hz) | 0.79 (3H, d, *J* = 7.0 Hz) | 0.79 (3H, d, *J* = 7.0 Hz) | 0.82 (3H, d, *J* = 7.0 Hz) |
| 0.81 (3H, t, *J* = 7.0 Hz) | 0.84 (3H, t, *J* = 7.5 Hz) | 0.85 (3H, t, *J* = 7.5 Hz) | 0.84 (3H, t, *J* = 7.5 Hz) |

## Correlation of Natural and Synthetic NMR Data of (±)-Calliviminone G and (±)-Calliviminone H

| (±)-Calliviminone G | (±)-Calliviminone H | Synthetic DA Products | |
|---|---|---|---|
|  |  | Calliviminone-H [**7erf**] | Calliviminone-G [**5erf**] |
| **$^{13}$C NMR (125 MHz)** | **$^{13}$C NMR (125 MHz)** | **$^{13}$C NMR (125 MHz)** (*dr* = 1.4:1, major isomer) | **$^{13}$C NMR (125 MHz)** (*dr* = 1.4:1, minor isomer) |
| 212.9 (C, *C*=O)<br>209.2 (C, *C*=O)<br>208.7 (C, *C*=O) | 212.7 (C, *C*=O)<br>209.0 (C, *C*=O)<br>208.5 (C, *C*=O) | 212.6 (C, *C*=O)<br>208.9 (C, *C*=O)<br>208.4 (C, *C*=O) | 212.7 (C, *C*=O)<br>209.1 (C, *C*=O)<br>208.6 (C, *C*=O) |
| 139.4 (C) | 138.3 (C) | 137.9 (C) | 139.1 (C) |
| 131.6 (C) | 131.6 (C) | 131.5 (C) | 131.5 (C) |
| 124.2 (CH) | 124.3 (CH) | 124.1 (CH) | 124.0 (CH) |
| 114.6 (CH) | 115.6 (CH) | 115.5 (CH) | 114.5 (CH) |
| 66.3 (C) | 66.8 (C) | 66.7 (C) | 66.2 (C) |
| 57.0 (C) | 56.9 (C) | 56.73 (C) | 56.76 (C) |
| 56.8 (C) | 56.9 (C) | 56.7 (C) | 56.6 (C) |
| 41.4 (CH) | 40.7 (CH) | 40.5 (CH) | 41.2 (CH) |
| 37.2 ($CH_2$) | 37.3 ($CH_2$) | 37.1 ($CH_2$) | 37.0 ($CH_2$) |
| 37.8 (CH) | 36.6 (CH) | 36.4 (CH) | 37.6 (CH) |
| 32.9 ($CH_2$) | 31.6 ($CH_2$) | 31.2 ($CH_2$) | 32.6 ($CH_2$) |
| 29.3 ($CH_2$) | 27.5 ($CH_2$) | 30.7 ($CH_2$) | 29.1 ($CH_2$) |
| 26.3 ($CH_2$) | 26.4 ($CH_2$) | 27.2 ($CH_2$) | 25.5 ($CH_2$) |
| 26.5 ($CH_3$) | 26.3 ($CH_3$) | 26.2 ($CH_3$) | 26.4 ($CH_3$) |
| 25.5 ($CH_2$) | 30.9 ($CH_2$) | 26.2 ($CH_2$) | 26.2 ($CH_2$) |
| 25.8 ($CH_3$) | 25.8 ($CH_3$) | 25.7 ($CH_3$) | 25.9 ($CH_3$) |
| 25.7 ($CH_3$) | 24.8 ($CH_3$) | 25.5 ($CH_3$) | 25.3 ($CH_3$) |
| 25.8 ($CH_3$) | 25.9 ($CH_3$) | 24.8 ($CH_3$) | 24.6 ($CH_3$) |
| 24.7 ($CH_3$) | 26.0 ($CH_3$) | 19.7 ($CH_3$) | 24.6 ($CH_3$) |
| 19.8 ($CH_3$) | 15.5 ($CH_3$) | 17.7 ($CH_3$) | 17.7 ($CH_3$) |
| 17.8 ($CH_3$) | 17.8 ($CH_3$) | 15.3 ($CH_3$) | 15.3 ($CH_3$) |
| 12.3 ($CH_3$) | 12.2 ($CH_3$) | 12.1 ($CH_3$) | 12.2 ($CH_3$) |

The structure and relative stereochemistry of the domino products **5-7** were established by IR, NMR, and mass analysis and also finally confirmed by correlation with the X-ray crystal structure of **5abd**, **5ajd**, **7ajd** and **7aje** (Figures 20-23).[21]

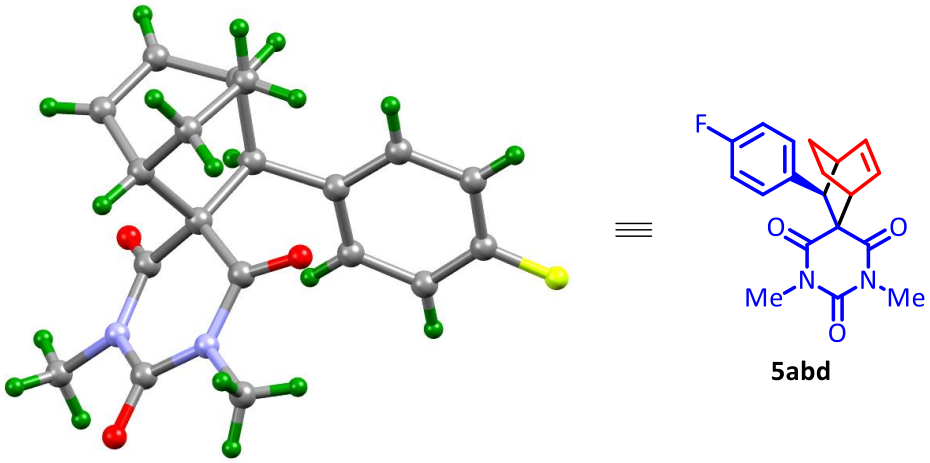



**Figure 20:** X-Ray crystal structure of 3-(4-fluorophenyl)-1',3'-dimethyl-1'H-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidine]-2',4',6'(3'*H*)-trione (**5abd**).

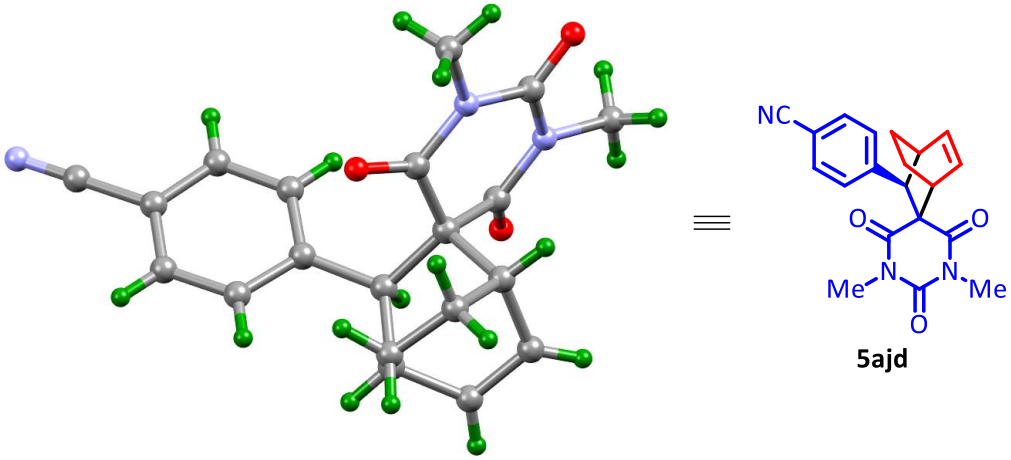



**Figure 21:** X-Ray crystal structure of 4-((1*R*,3*R*,4*S*)-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6'-tetrahydro-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidin]-3-yl)benzonitrile (**5ajd**).

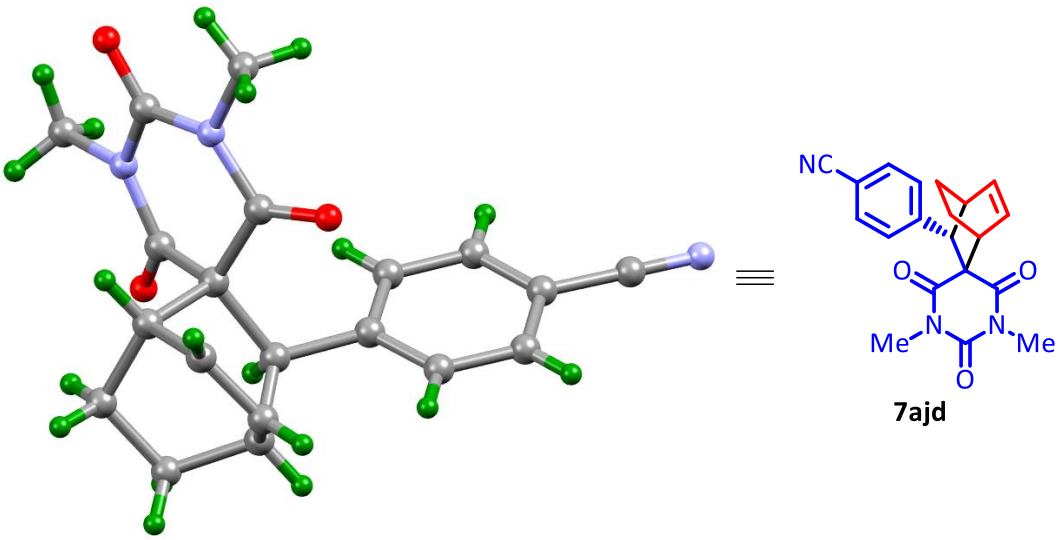



**Figure 22**: X-Ray crystal structure of 4-((1*R*,3*R*,4*S*)-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6'-tetrahydro-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidin]-3-yl)benzonitrile (**7ajd**).

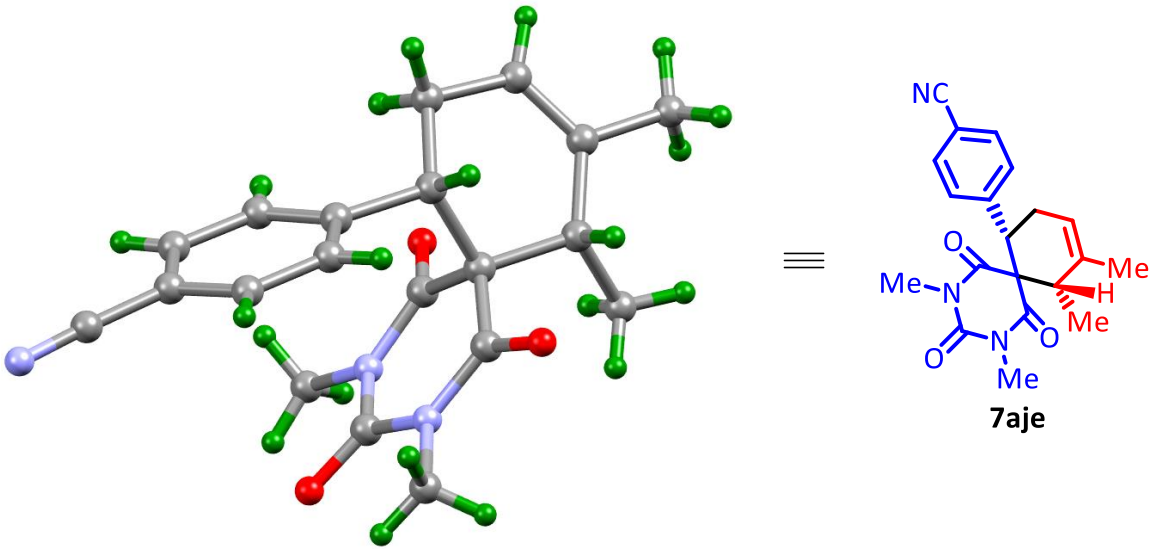
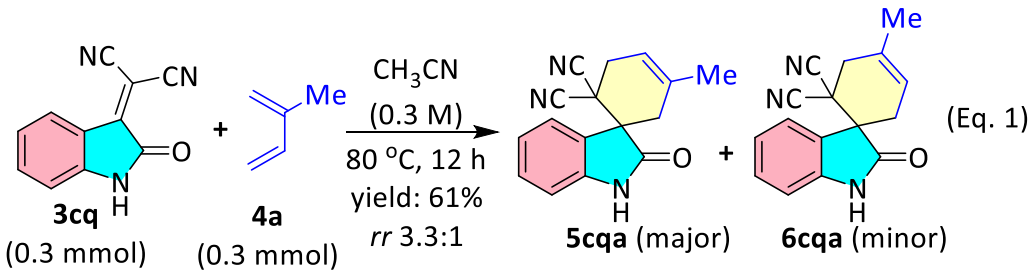


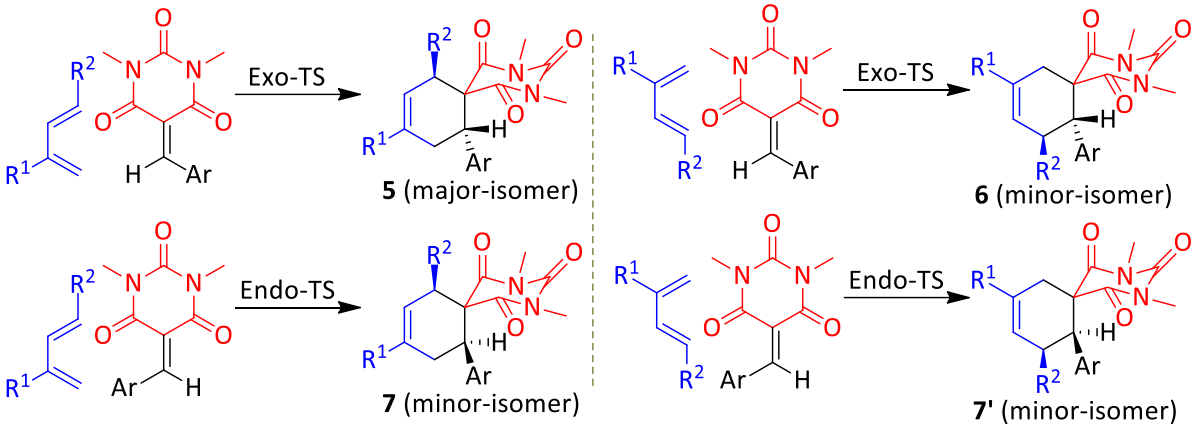

**Figure 23**: X-Ray crystal structure of 4-((7*S*,11*S*)-2,4,10,11-tetramethyl-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7-yl)benzonitrile (**7aje**).

### 3.2.5 *Mechanistic Rationale:*

Further we are able to apply this methodology to synthesize functionalized spirooxindoles **5cqa/6cqa** and explained the observed selectivities through mechanistic discussion as shown in Eq-1 and Scheme 18.




**Discussion for Eq-1:** Spirooxindoles have emerged as promising synthetic targets for drug discovery, as they are privileged heterocycles present in pharmaceutical and naturally occurring compounds with diverse biological properties such as anticancer, antimicrobial, antivirus etc.[1] In connection with this, we broadened the horizon of the present reaction sequence for the synthesis of functionalized spirooxindoles, by conducting the reaction between the Knoevenagel product, 2-(2-oxoindolin-3-ylidene)malononitrile **3cqa** and the diene **4a**, which produced the spirooxindoles **5cqa** and **6cqa** in 61% yield with 3.3:1 *rr*, under mild reaction conditions (Eq. 1).

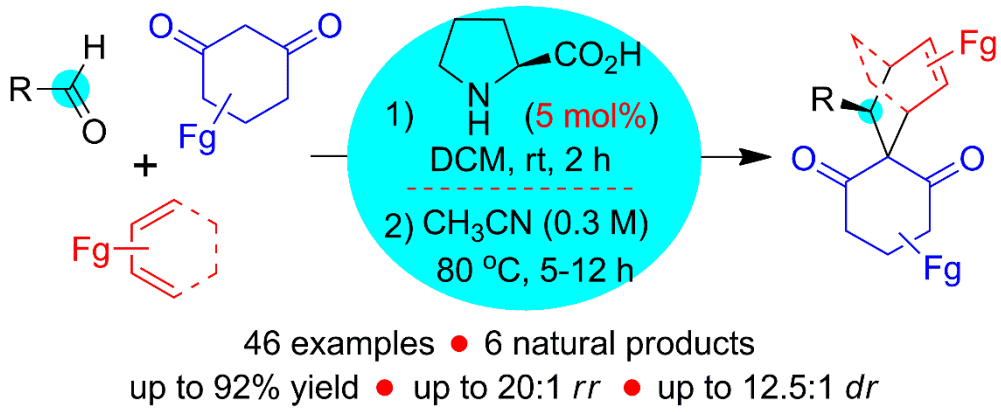



**Scheme 18:** Reaction Mechanism.

**Discussion for Scheme-18:** For symmetric dienes such as 1,3-butadiene **4b** and 2,3-dimethyl-1,3-butadiene **4c** there is no possibility of regioisomers, and the *exo*- and *endo*-transition states lead to two enantiomers that comprise the racemic product **5**. However, for the reaction of **4b** with (+)-**3ap**, a diastereomeric mixture was obtained, arising from the already existing chiral carbon (Table 3, entry 16). In case of isoprene **4a** ($R^1 = CH_3$, $R^2 = H$) and myrcene **4f** ($R^1 = CH_2CH_2CH(CH_3)_2$, $R^2 = H$), there are two possible approaches (origin of regioisomers), and in principle each of the approaches can give rise to *exo*- and *endo*-transition states, depending on

the orientation of the diene with respect to the dienophile. As discussed earlier, each pair of *exo*- and *endo*-transition states leads to a set of two enantiomers that comprise the racemic product, thus generating in total two regioisomers **5** and **6**. The unsymmetrical diene, *trans*-3-methyl-1,3-pentadiene **4e**, having a terminal methyl group, exhibits highest proclivity for one particular orientation, which through *exo*- and *endo*-transition states, produces the two diastereomers **5** and **7**. 1,3-Cyclohexadiene **4d**, has no possibility of generating regioisomers, nevertheless, it discerns the approach of the dienophile from its two faces, as it is forming a bicyclic adduct with two additional stereocenters. Besides, each approach goes through *exo*- and *endo*-transition states creating a prospect of four different diastereomers and only two of them, **5** and **7** were observed (Scheme 18).

## 3.3 *Conclusions:*




In summary, we have developed a common methodology for the one-pot two-step total synthesis of library of important natural products, calliviminones A-H and an unusual core of spiro[5.5]undecenes from readily available simple substrates through a sequential one-pot combination of domino Knoevenagel condensation and Diels-Alder reactions respectively. This sequential one-pot protocol is an ideal method to synthesize the entire family of calliviminone natural products.

# 4. Organocatalytic Reductive Alkylation of Syncarpic Acid: Formal Total Synthesis of Monomeric Phloroglucinol Natural Products

## *4.1 Introduction*

Syncarpic acid (2,2,4,4-tetramethylcyclohexane-1,3,5-trione), unlike terpenoids, derived from phloroglucinol in plant kingdom exactly resembles a monoterpenoid properties which usually derives from isoprene unit.[2,13,22] Syncarpic acid itself isolated from *Syncarpia laurifolia* Tenn., family Myrtaceae, commonly found in the coastal regions of New South Wales.[2] More than 70 natural products such as Calliviminones, Myrtucommulones, antibiotic Rhodomyrtosones isolated from the nature has the backbone of syncarpic acid.[23a-c] Same time scientific community showed huge interest in investigating the reactivity and applications of syncarpic acid in the field of medicinal chemistry.[24a-c] Since syncarpic acid (p$K_a$ = 4.1) claims to be more acidic than acetic acid (p$K_a$ = 4.7), we are very much interested in investigating its reactivity as a mild nucleophile in organocatalysis through iminium and enamine mediated reactions.[2]

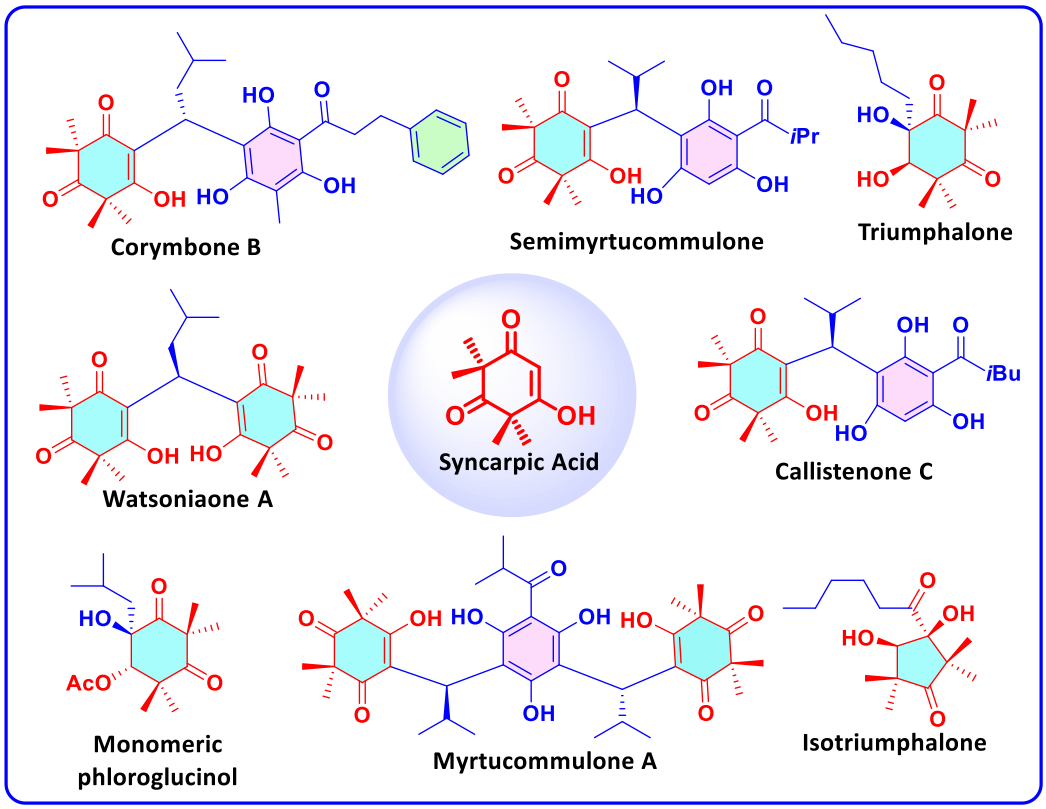
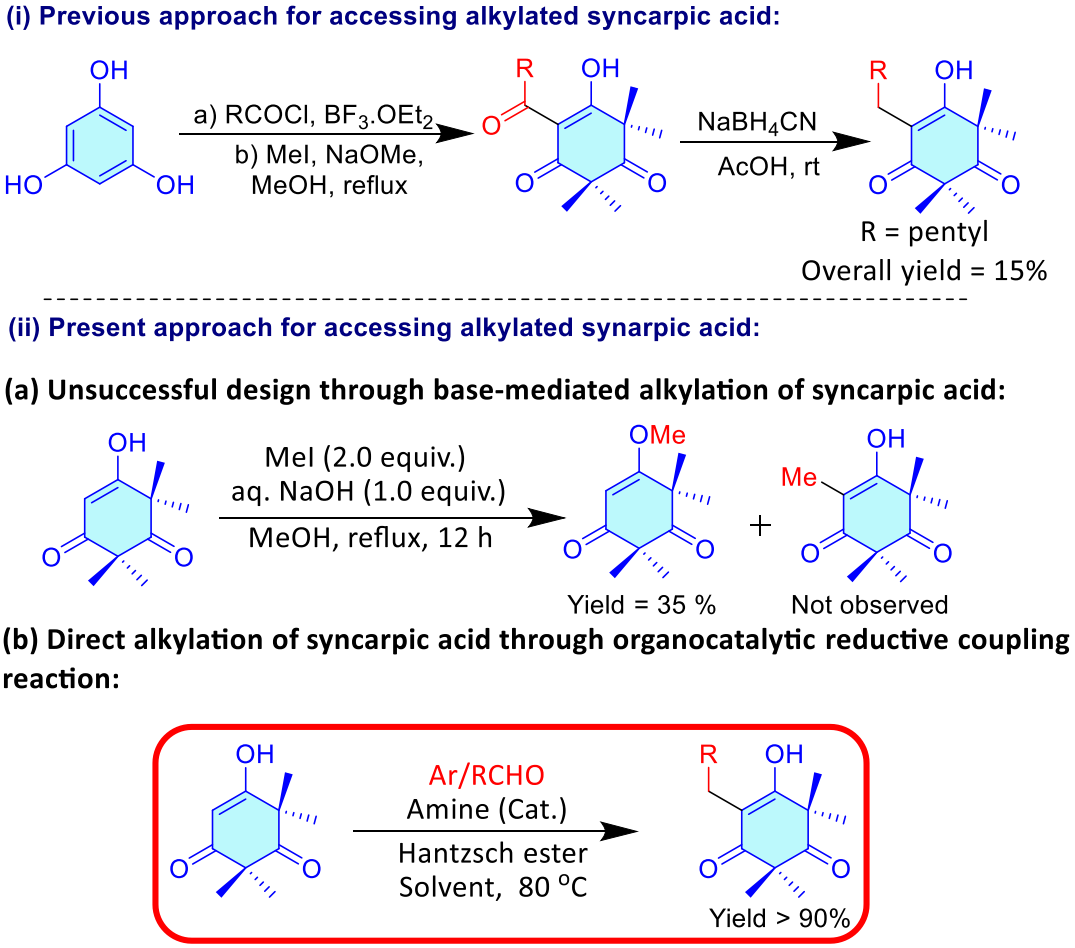



**Figure 24**: Natural products available with syncarpic acid core.

To our surprise, most of the natural products listed in Figure 24 such as Corymbone B, Semimyrtucommulone, Triumphalone, Isotriumphalone, Watsonianone A, monomeric phoroglucinol etc. are the *C*-alkylated products of syncarpic acid.[9,10,25a,b]

This shows the significance of the selective *C*-alkylation of syncarpic acid which is very challenging. Attempts to furnish 4-alkylated syncarpic acid failed resulting in *O*-alkylated product under various classical alkylation conditions.[9] Basic conditions using methyl iodide also furnished *O*-alkylated product exclusively (Scheme 19). In other route, Friedel-Crafts acylation of phloroglucinol followed by tetra-methylation and reduction furnished *C*-alkylated syncarpic acids but the number of steps involved, usage of hazardous chemicals such as $BF_3.OEt_2$, moderate to low reaction yields made this protocol least attractive (Scheme 19).[9,10] From past one and half decades, we have developed green methodology for the alkylation on various CH-acids.[20,26a,b] This gave us enough motivation to take up the challenge of selective *C*-alkylation on syncarpic acid in one-pot manner using potential three component reductive alkylation (TCRA) protocol.



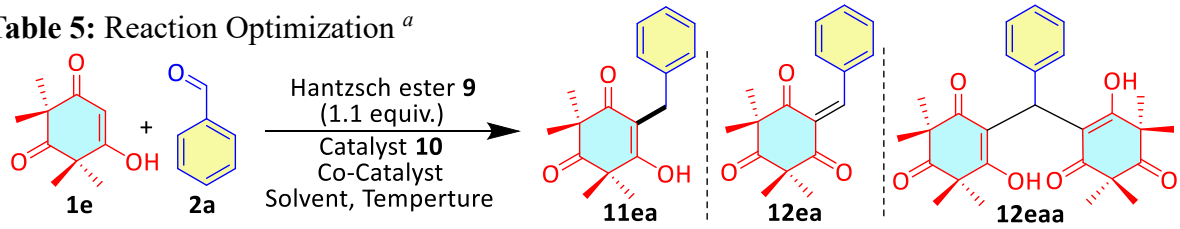

**Scheme 19:** Reaction design for the selective *C*-alkylation of syncarpic acid.

## *4.2 Results and Discussion*

### *4.2.1 Reaction Preliminary Optimization*

We have chosen syncarpic acid and benzaldehyde for investigating alkylation. When Syncarpic acid **1e** (0.3 mmol, 1.0 equiv.) reacted with benzaldehyde **2a** (0.45 mmol, 1.5 equiv.) in the presence of 10 mol % (*S*)-proline **10a**, Hantzsch ester **9** (0.33mmol, 1.1 equiv.) in DCM (0.3 M) at 25 °C, excitingly reaction furnished the desired *C*-alkylated product **11ea** with 40% yield in 8 h (Table 5, entry 1).

**Table 5:** Reaction Optimization [a]




| Entry | Solvent (0.3 M) | Catalyst **10** (10 mol%) | Co-catalyst (10 mol%) | T (°C) | *t* (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | DCM | (*S*)-Proline (**10a**) | – | 25 | 8 | 40 |
| 2 | DCM | (*S*)-Proline (**10a**) | – | 50 | 5 | 47 |
| 3 | DCM | (*S*)-Proline (**10a**) | – | 25 | 2.5 | 41 – *c* |
| 4 | DCM | (*S*)-Proline (**10a**) | – | 25 | 5.5 | 31 – *d* |
| 5 | DCM | Benzylamine (**10b**) | – | 50 | 5.5 | 54 |
| 6 | DCM | Piperidine (**10c**) | AcOH | 50 | 4.5 | 41 |
| 7 | DCM | Pyrrolidine (**10d**) | AcOH | 50 | 5 | 50 |
| 8 | DCM | Morpholine (**10e**) | AcOH | 50 | 6 | 51 |
| 9 | DCM | Aniline (**10f**) | – | 50 | 8 | 45 |
| 10[e] | DCM | Benzylamine (**10b**) | – | 50 | 5 | 52 |
| 11[f] | DCM | Benzylamine (**10b**) | – | 50 | 6 | 48 |
| 12[g] | DCM | Benzylamine (**10b**) | – | 50 | 5.5 | 49 |
| 13[h] | DCM | Benzylamine (**10b**) | – | 50 | 4.5 | 52 |
| 14 | DCE | Benzylamine (**10b**) | – | 80 | 6 | 55 |
| 15 | $CHCl_3$ | Benzylamine (**10b**) | – | 50 | 5 | 55 |
| 16 | THF | Benzylamine (**10b**) | – | 60 | 9 | 89 |
| 17 | $CH_3CN$ | Benzylamine (**10b**) | – | 80 | 6 | 91 |
| 18 | EtOH | Benzylamine (**10b**) | – | 80 | 7 | 66 |

[a]Reactions were carried out in solvent (0.3 M) with 1.5 equiv. of **2a** and 1.1 equiv. of **9** relative to **1e** (0.3 mmol) in the presence of 10 mol % of catalyst **10**. [b]Yield refers to the column purified products. [c]Reaction was performed without **9**, Knoevenagel product **12ea** was obtained with 41% of yield. [d]Reaction was performed without **9**, Bis-adduct **12eaa** was obtained with 31% of yield. [e]Catalyst **10b** used 15 mol%. [f]Catalyst **10b** used 5 mol%. [g]**2a** used 1.2 equiv. [h]**2a** used 2.0 equiv.

Doubling the temperature from 25 °C to 50 °C improved the yield by 7% and reduced the reaction time to 5 h showing the effect of temperature on the reaction (Table 5, entry 2). In the absence of Hantzsch ester **9**, the reaction afforded Knoevenagel product **12ea** with 41% yield in just 2.5 h at room temperature (Table 5, entry 3). Under similar reaction conditions, when we extended the reaction time to 5.5 h, we observed the formation of bis-adduct **12eaa** in 31% yield (Table 5, entry 4). This clearly shows the significance of Hantzsch ester **9** in our protocol since the reduction by **9** to afford **11ea** is much faster than the subsequent Michael reaction to afford **12eaa.**

When the reactions were performed using the catalysts benzylamine **10b**, 1:1 piperidine **10c**/AcOH, pyrrolidine **10d**/AcOH, morpholine **10e**/AcOH and aniline **10f** at 50 °C in DCM, the product **11ea** formed with 54, 41, 50, 51 and 45% yield in 5.5, 4.5, 5, 6 and 8 h respectively, showing **10b** as the best catalyst (Table 5, entries 5-9). Varying the catalyst loading to 15 and 5 mol%, benzaldehyde equivalents to 1.2 and 2.0 equivalents, didn't show any positive impact on the reaction yield (Table 5, entries 10-13). After understanding the effect of catalysts and temperature, we extended our investigation using other chlorinated solvents such as DCE and chloroform at 80 and 50 °C which yielded **11ea** with 55% yield in 6 and 5 h respectively (Table 5, entries 14-15). When THF is used as solvent at 60 °C, surprisingly, reaction yielded **11ea** with 89% yield in 9 h (Table 5, entry 16). Acetonitrile at 80 °C further improved the reaction with stunning yield of 91% in 6 h (Table 5, entry 17). Alcoholic solvent such as ethanol at 80 °C disappointed by yielding **11ea** with 66% yield in 7 h (Table 5, entry 18). With this thorough investigation, we finalized 0.3 mmol of **1e** reacting with 1.5 equiv. of **2a** in the presence of 1.1 equiv. of **9**, 10 mol% of **10b** in acetonitrile at 80 °C as the optimized reaction condition.

The synthesized compounds **11ea**, **12ea** and **12eaa** in Table 5 have characterized using NMR, IR and HRMS. $^{1}H$ and $^{13}C$ NMR spectra of **11ea** and **12ea** are given below (Figure 25-27). In $CDCl_3$ solvent compound 11ea existed both in its enol (**11ea**) and keto (**11ea'**) form (Figure 25). But in $CD_3OD$ solvent exclusively enol form **11ea** was found in NMR spectroscopy (Figure 26).

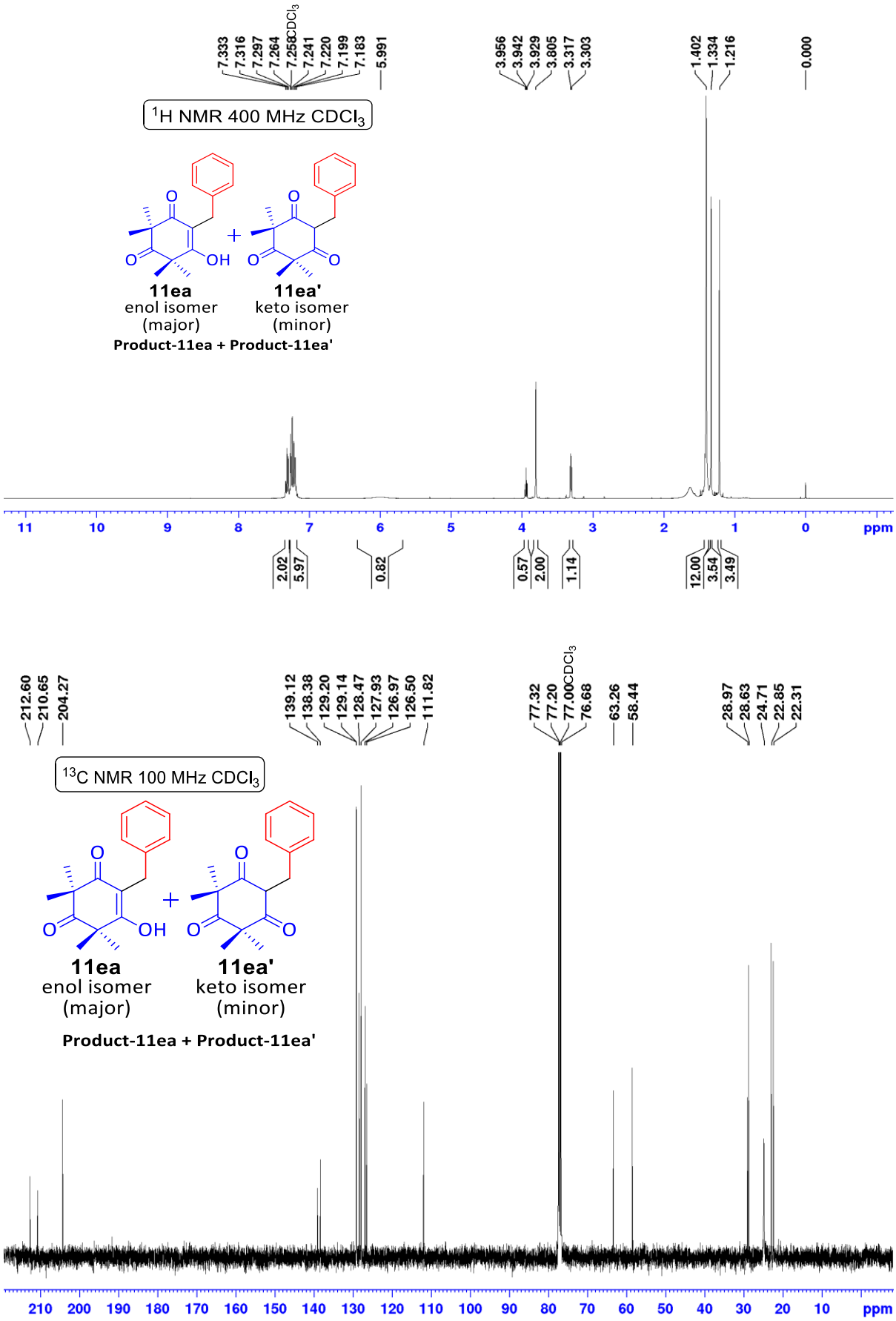



**Figure 25:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **11ea** and **11ea'.**

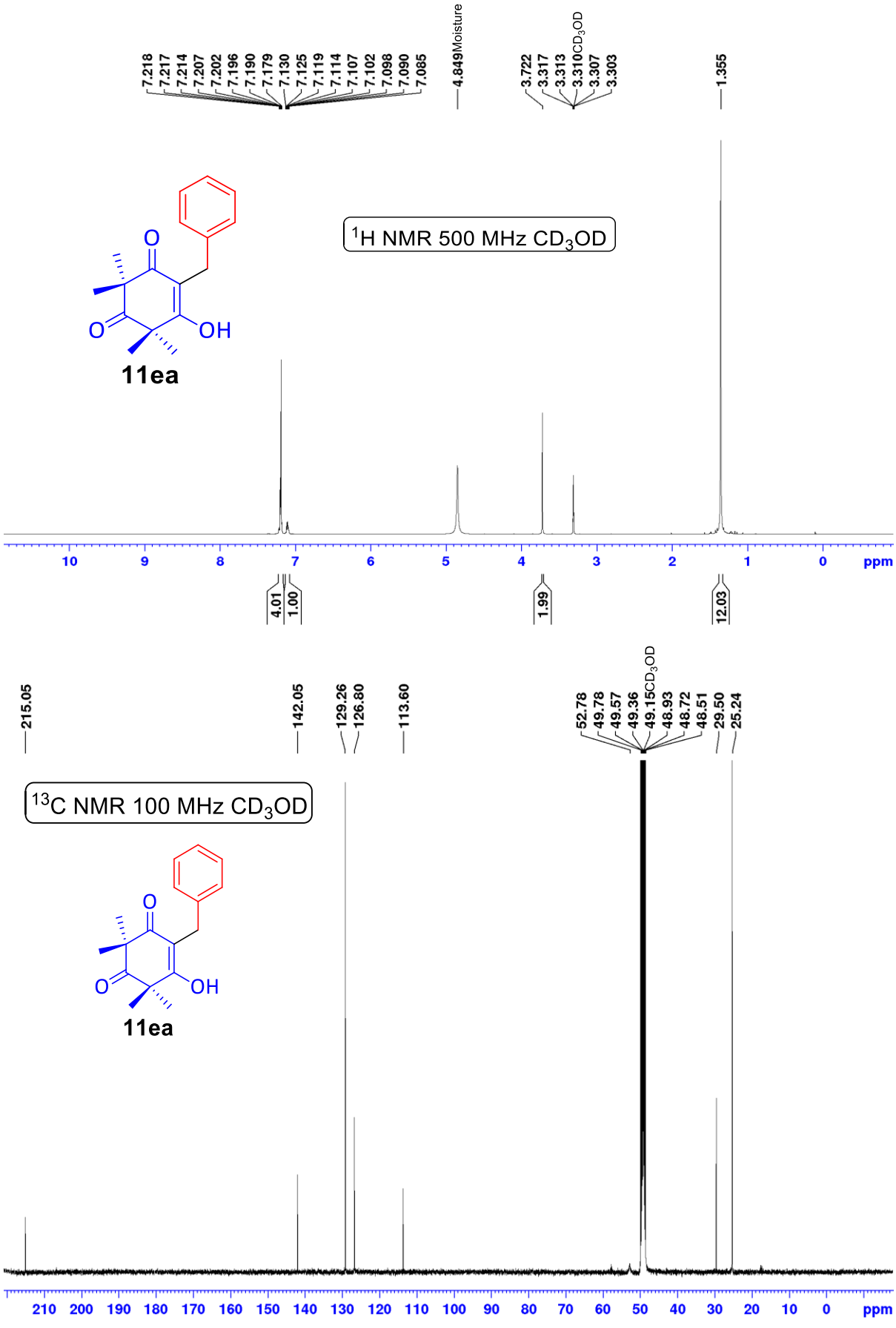



**Figure 26:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **11ea**.

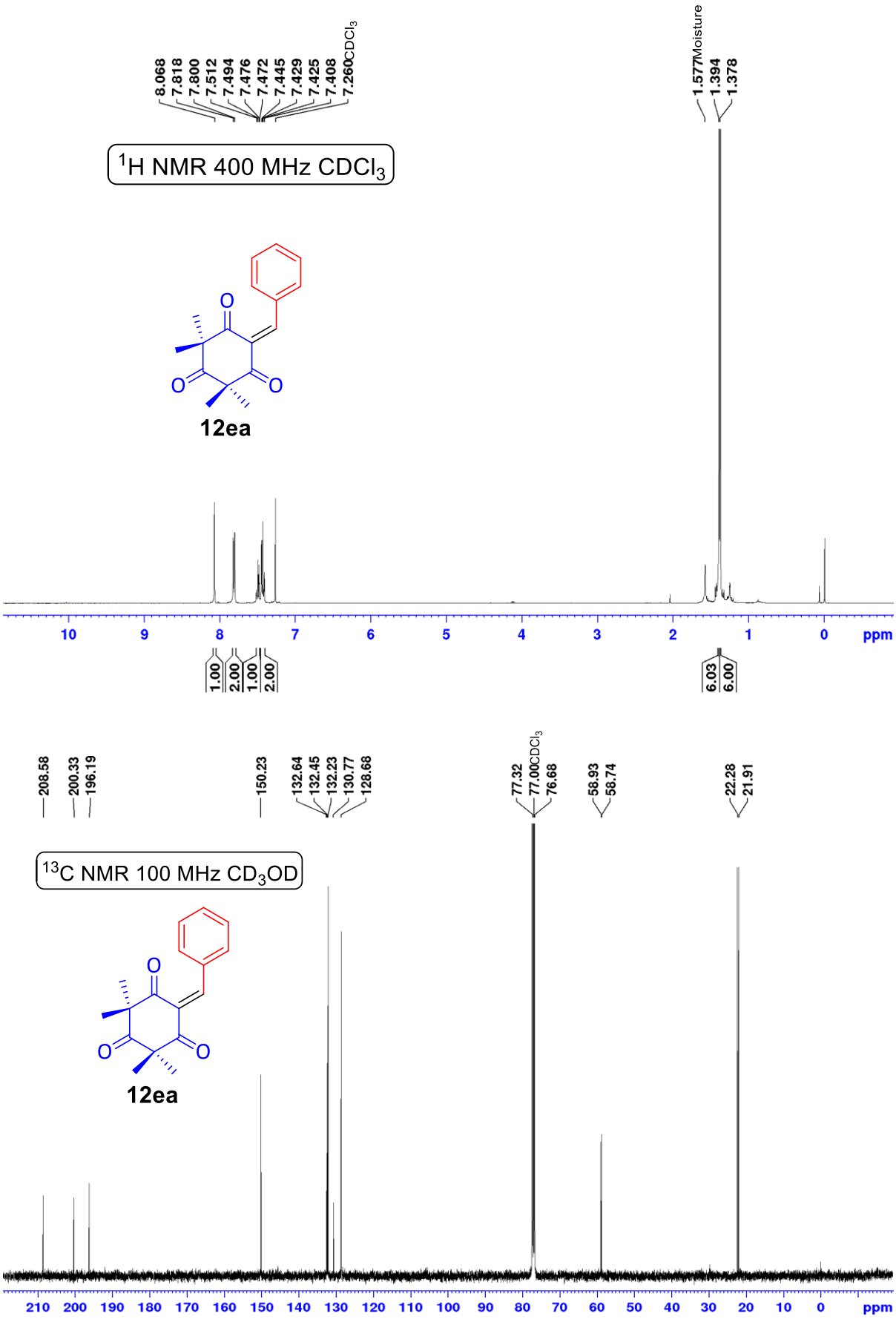
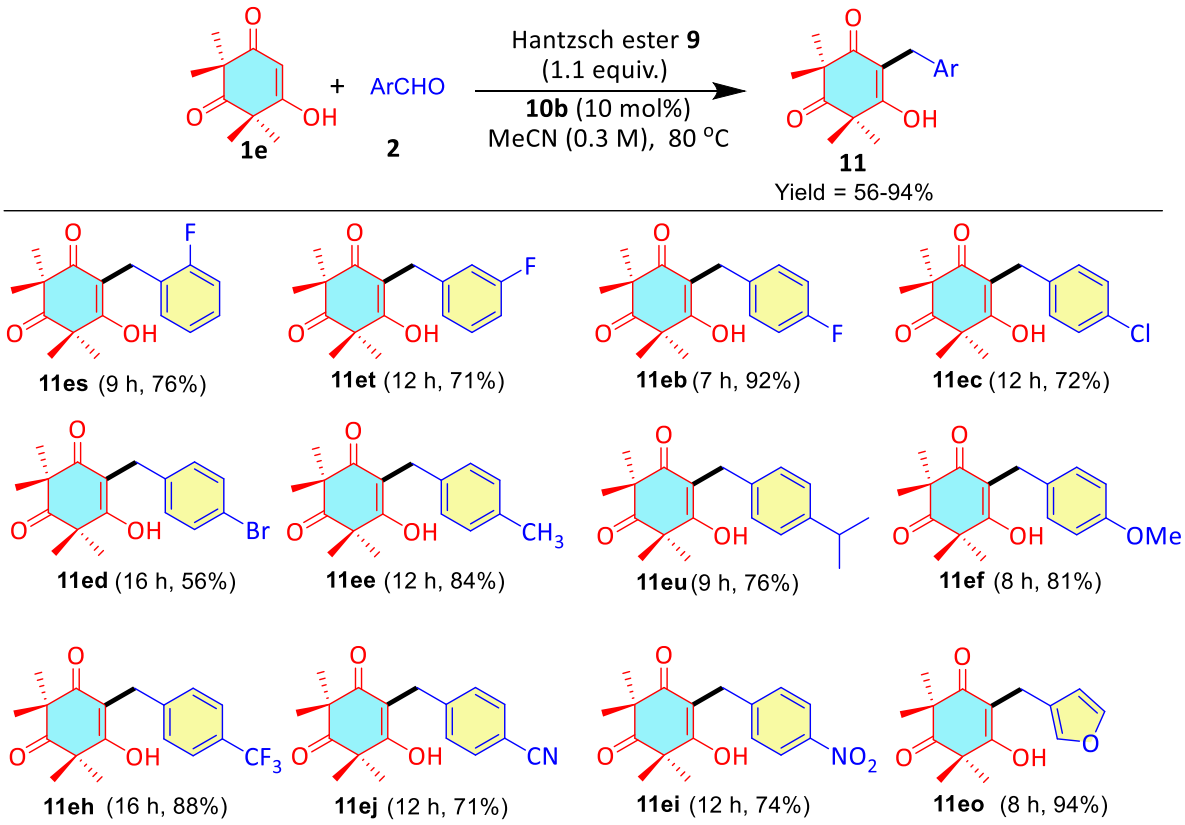



**Figure 27:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **12ea**.

### *4.2.2 Substrate Scope of the Three-Component Reductive Alkylation Reaction:*

With this optimized condition in hand, we investigated scope of the reaction with various aromatic aldehydes. The reaction is well tolerated with all benzaldehydes **2** with electron donating, withdrawing and halogen substituents. The reaction of *ortho*-, *meta*- and *para*-fluoro benzaldehydes **2s**, **2t** and **2b** (0.45 mmol, 1.5 equiv.) with **1e** (0.3 mmol, 1.0 equiv.) in the presence of **9** (0.33 mmol, 1.1 equiv.), 10 mol% of **10b** in MeCN (0.3 M) at 80 °C yielded **11es, 11et** and **11eb** with 76, 71 and 92% yield in 9, 12 and 7 h respectively showing the clear effect of electronic factors on the reaction (Table 6).

**Table 6:** Reaction substrate scope with different aromatic aldehydes [a,b]



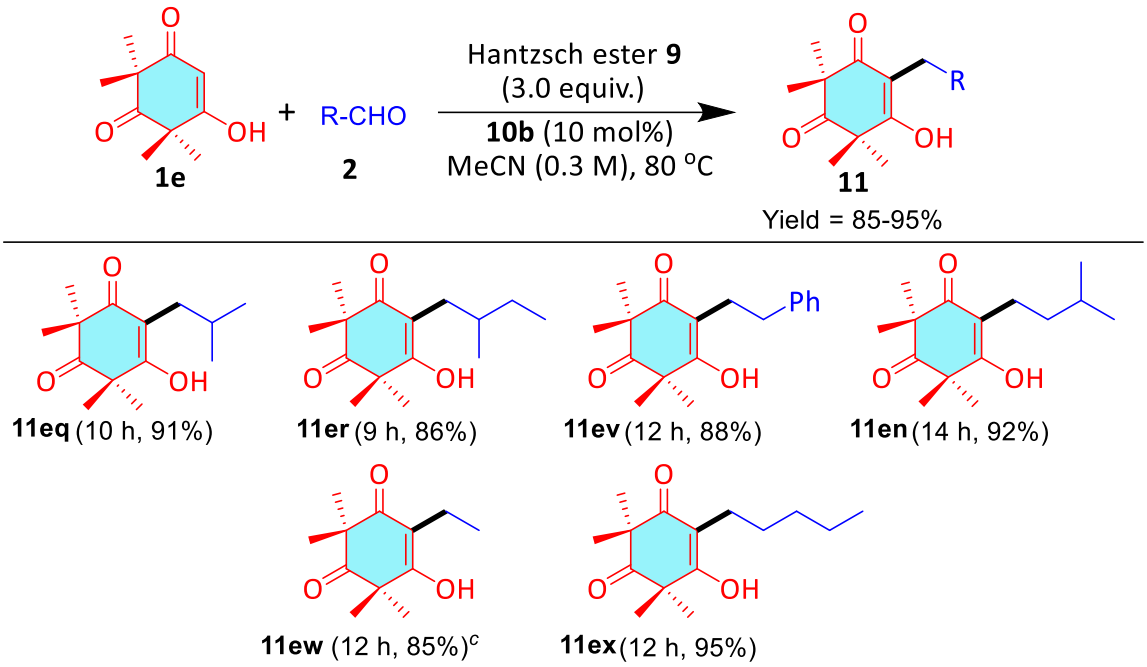

[a]Reactions were carried out in MeCN (0.3 M) with 1.5 equiv. of **2** and 1.1 equiv. of **9** relative to **1e** (0.3 mmol) in the presence of 10 mol % of **10b** at 80 °C. [b]Yield refers to the column purified products.

In case of halogen substituents, *para*-fluoro, chloro, bromo benzaldehydes **2b**, **2c** and **2d** reacted with **1e** under optimized conditions yielding **11eb**, **11ec** and **11ed** with 92, 72, 56% yield in 7, 12, 16 h respectively (Table 6) showing the inverse effect on yield and reaction time with respect to the size of the halogen. Electron rich aldehydes such as *para*-methyl, isopropyl, methoxy benzaldehydes **2e**, **2u** and **2f** reacted with **1e** under optimized conditions with great ease affording **11ee**, **11eu** and **11ef** with very good yield of 84, 76, 81% in 12, 9, 8 h respectively

(Table 6). Electron deficient aldehydes such as *para*- $CF_3$, cyano, nitro benzaldehydes **2h**, **2j** and **2i** yielded **11eh**, **11ej** and **11ei** with 88, 71, 74% yield in 16, 12, 12 h respectively (Table 6). Hetero aromatic aldehyde such as furfural reacted with **1e** under optimized conditions and yielded **11eo** with excellent 94% yield in 8 h (Table 6).

We further extended our investigation towards various linear chain and branched chain aliphatic aldehydes **2**. As expected, the reaction of all the aliphatic aldehydes **2** proceeded very smoothly with **1e** under optimized conditions affording TCRA products **11** with excellent 85-95% yield in 9-14 h (Table 7).

**Table 7:** Reaction substrate scope with different aliphatic aldehydes [a, b]




[a]Reactions were carried out in MeCN (0.3 M) with 1.5 equiv. of **2** and 3.0 equiv. of **9** relative to **1e** (0.3 mmol) in the presence of 10 mol % of **10b** at 80 °C. [b]Yield refers to the column purified products. [c]5.0 equiv. of **2w** was used.

Only in the case of acetaldehyde **2w**, since the boiling point is very low, we have taken 5.0 equiv. of **2w**, in order to improve the reaction yield (Table 7).

The synthesized compounds in Table 6 and Table 7 have characterized using NMR, IR and HRMS. Some of their $^{1}H$ and $^{13}C$ NMR spectra are given below (Figure 28-35).

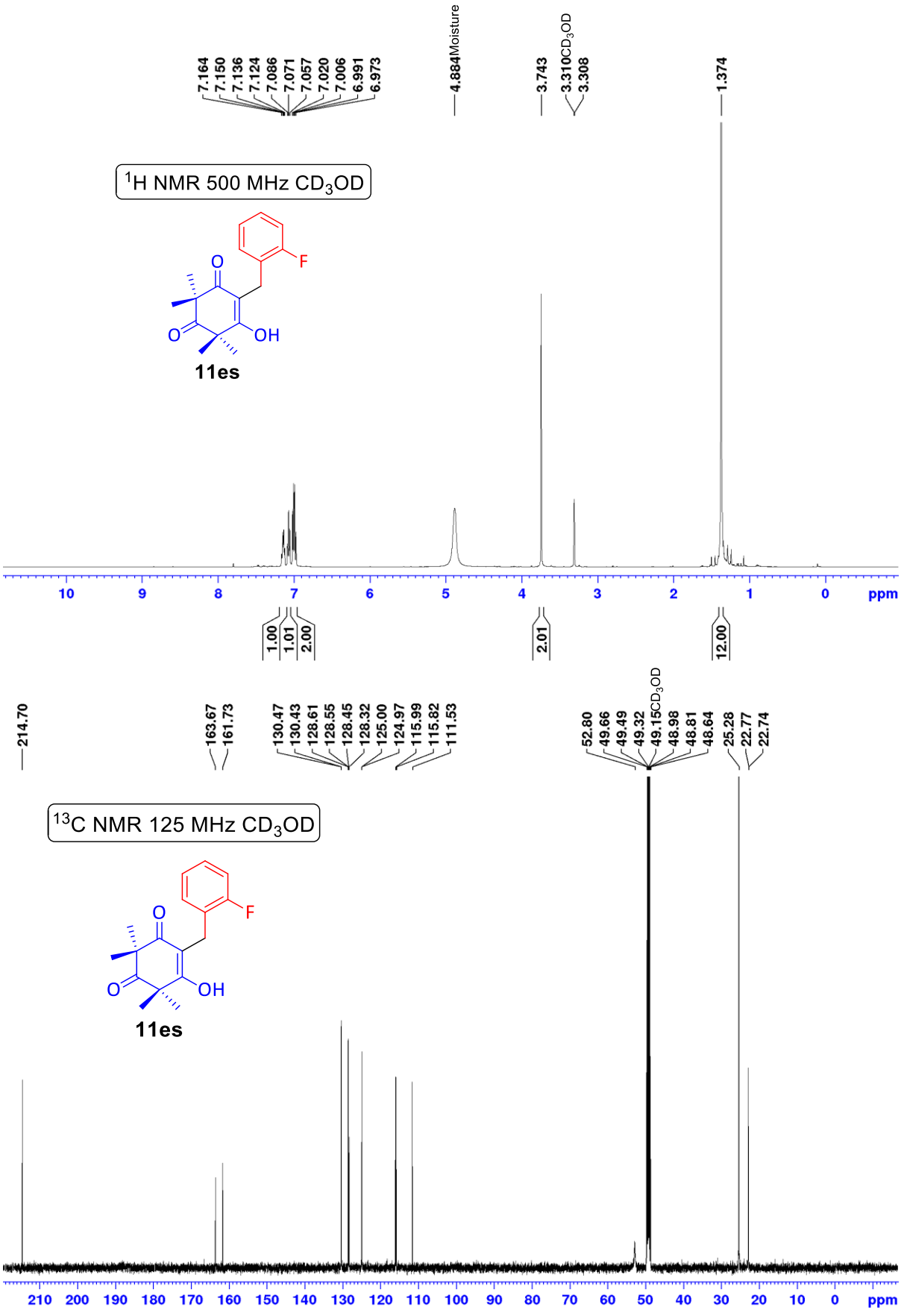



**Figure 28:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **11es**.

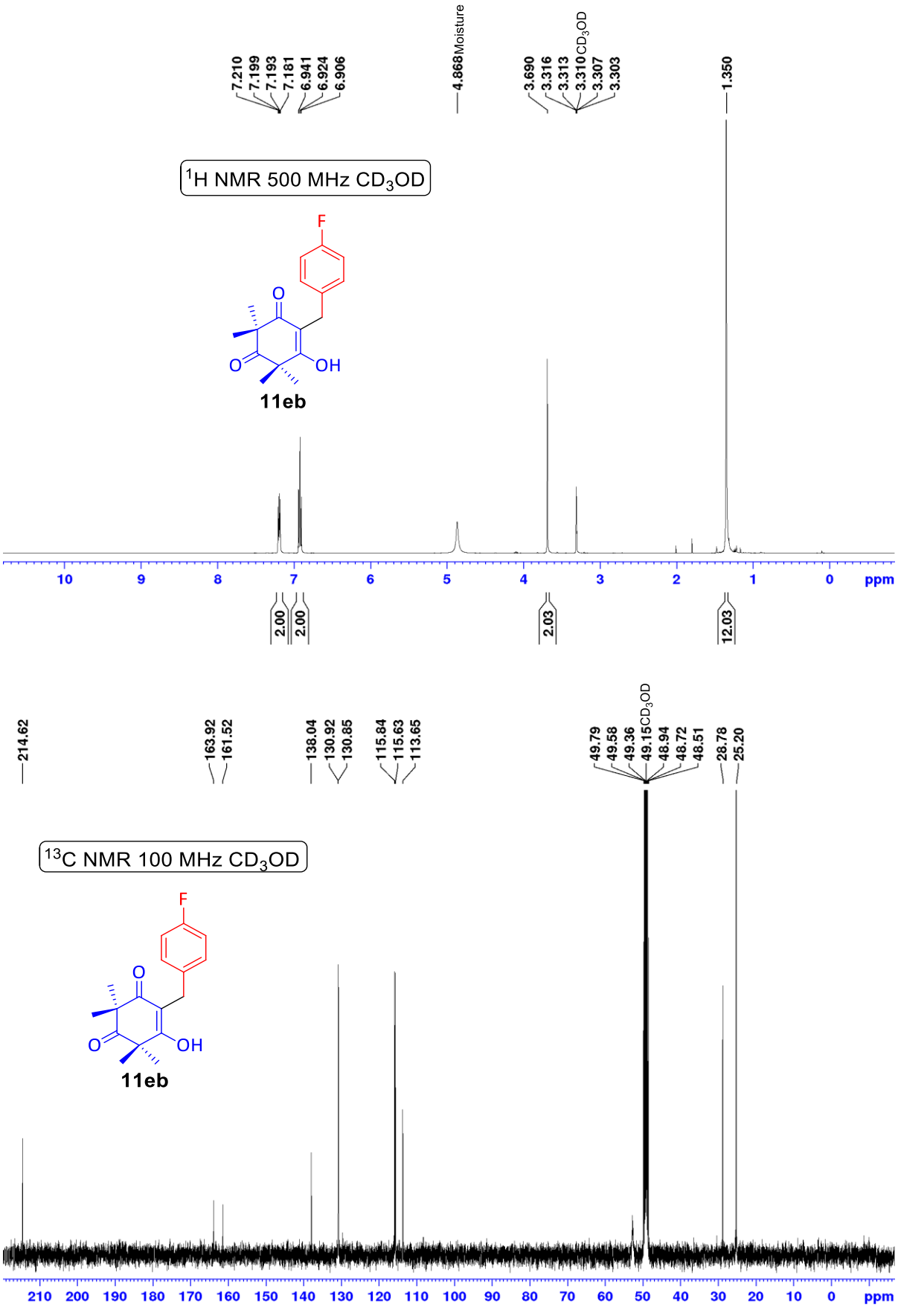



**Figure 29:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **11eb**.

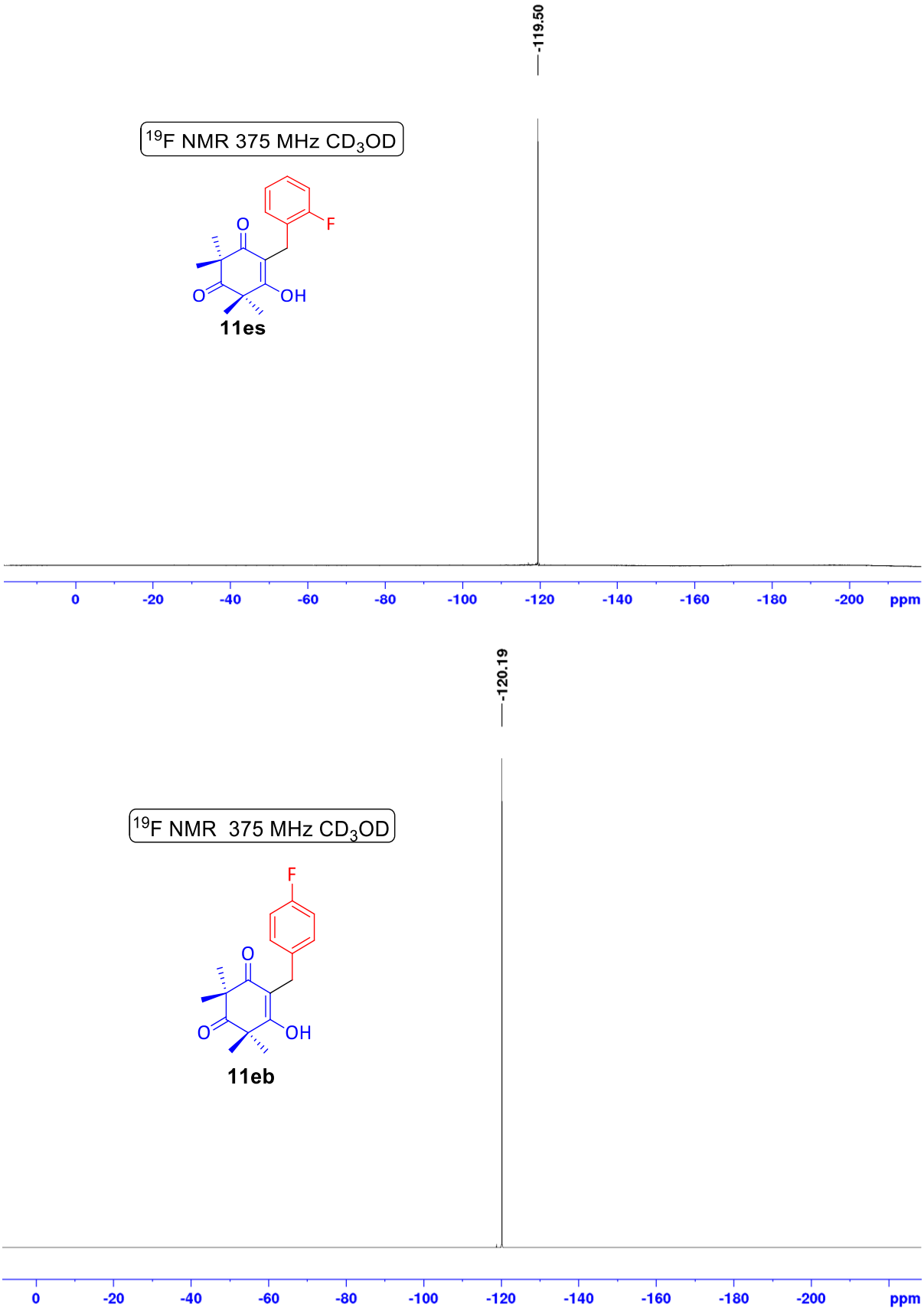



**Figure 30:** $^{19}$F NMR spectrum of product **11es** and **11eb**.

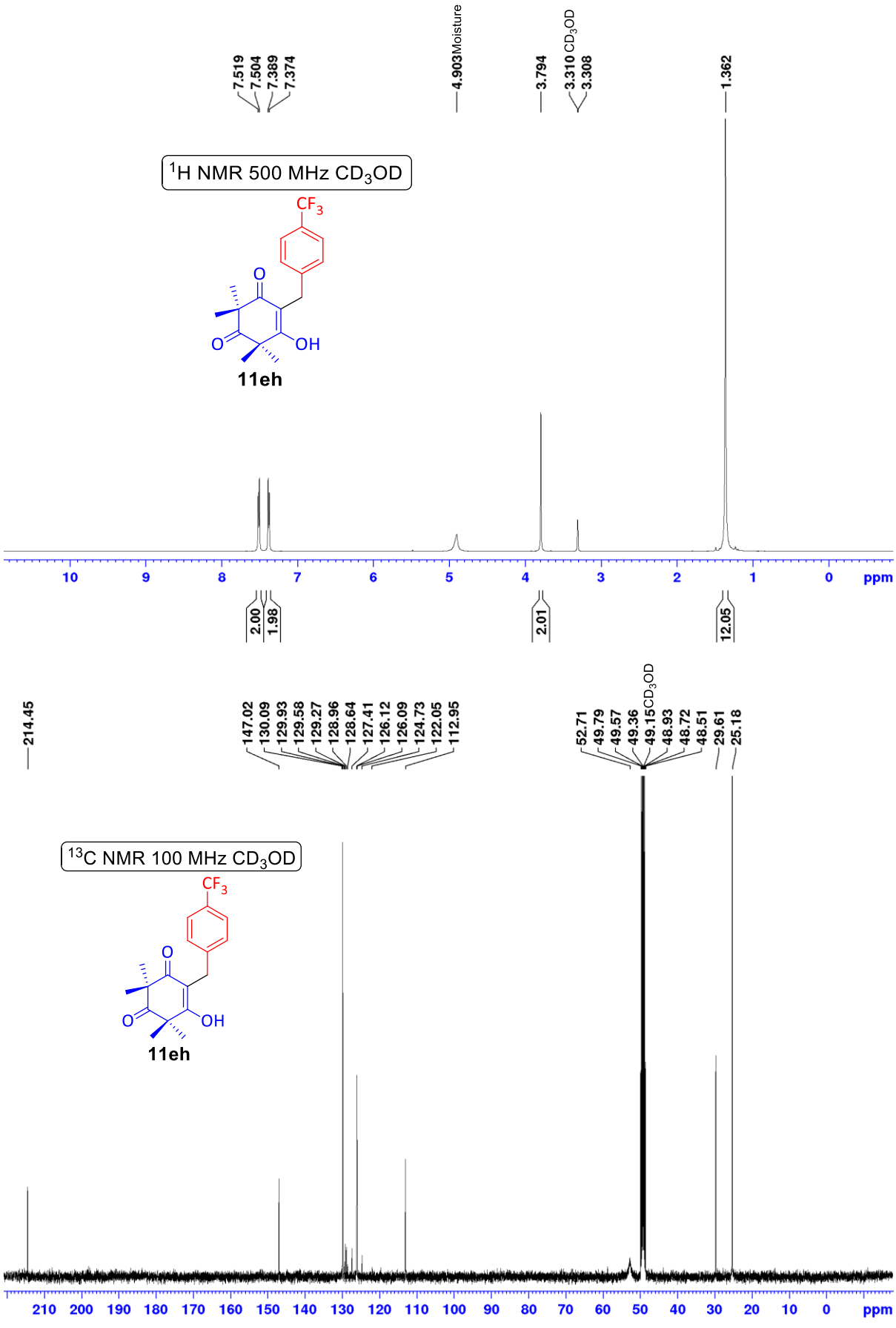



**Figure 31:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **11eh**.

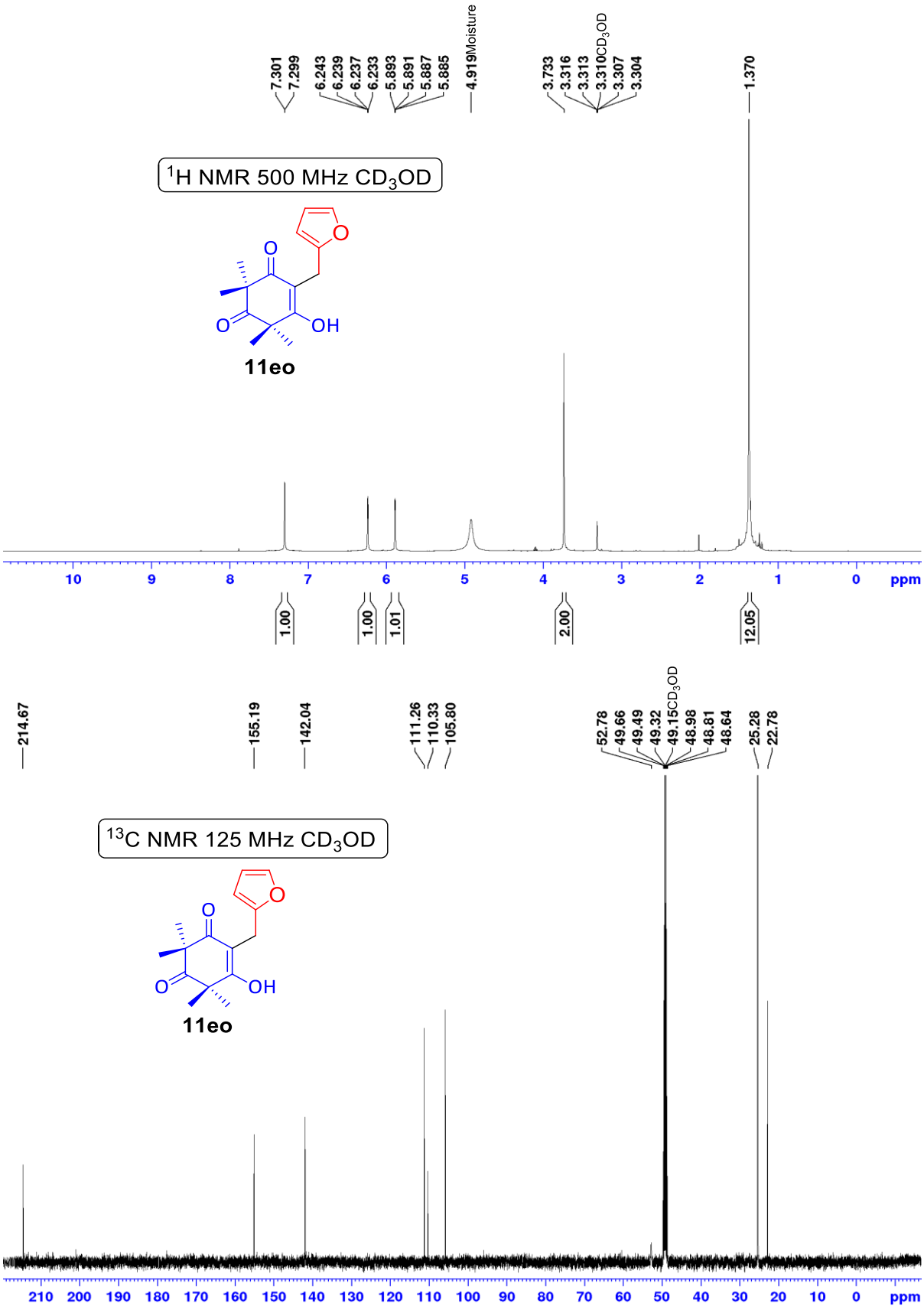



**Figure 32:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **11eo**.

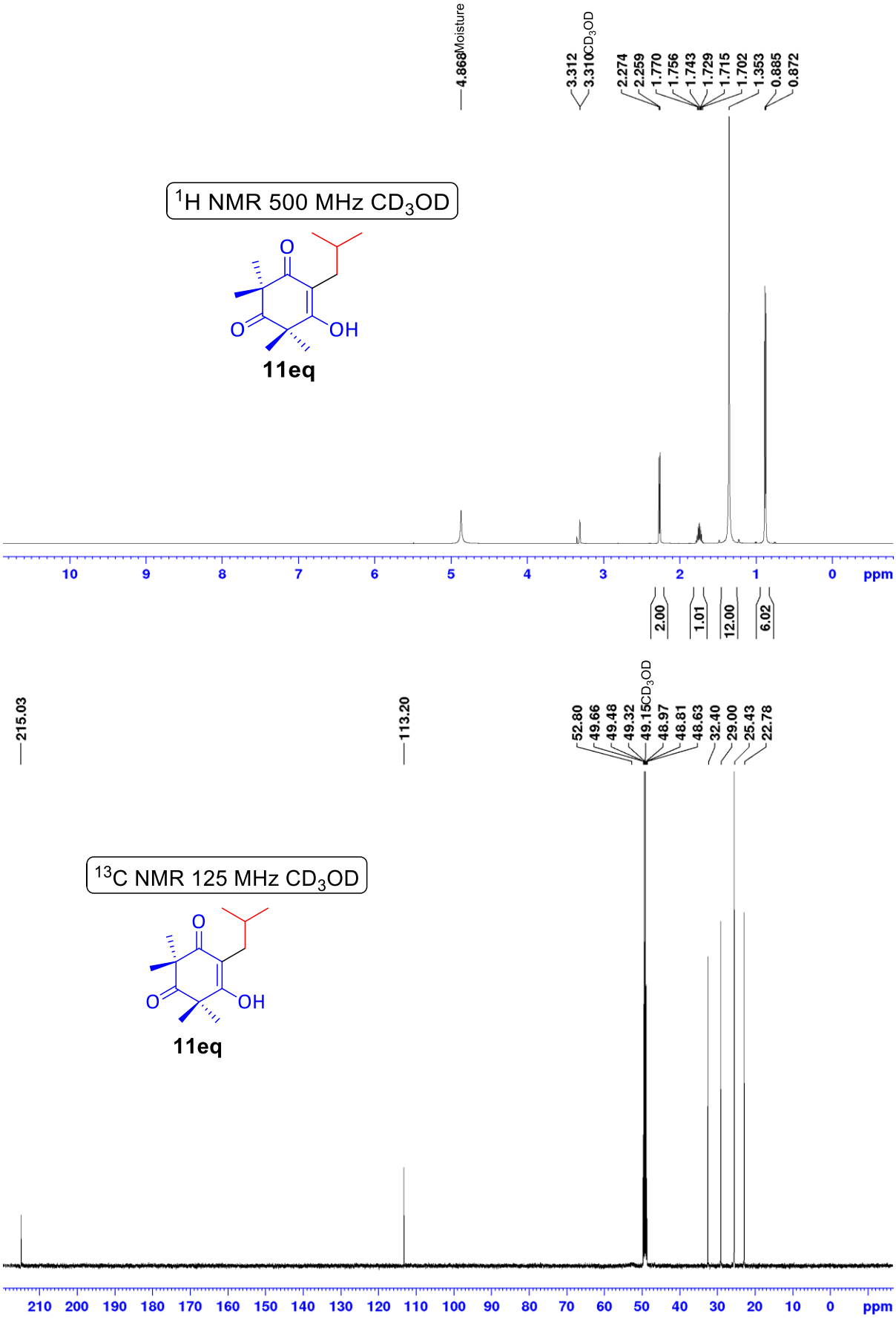



**Figure 33:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **11eq**.

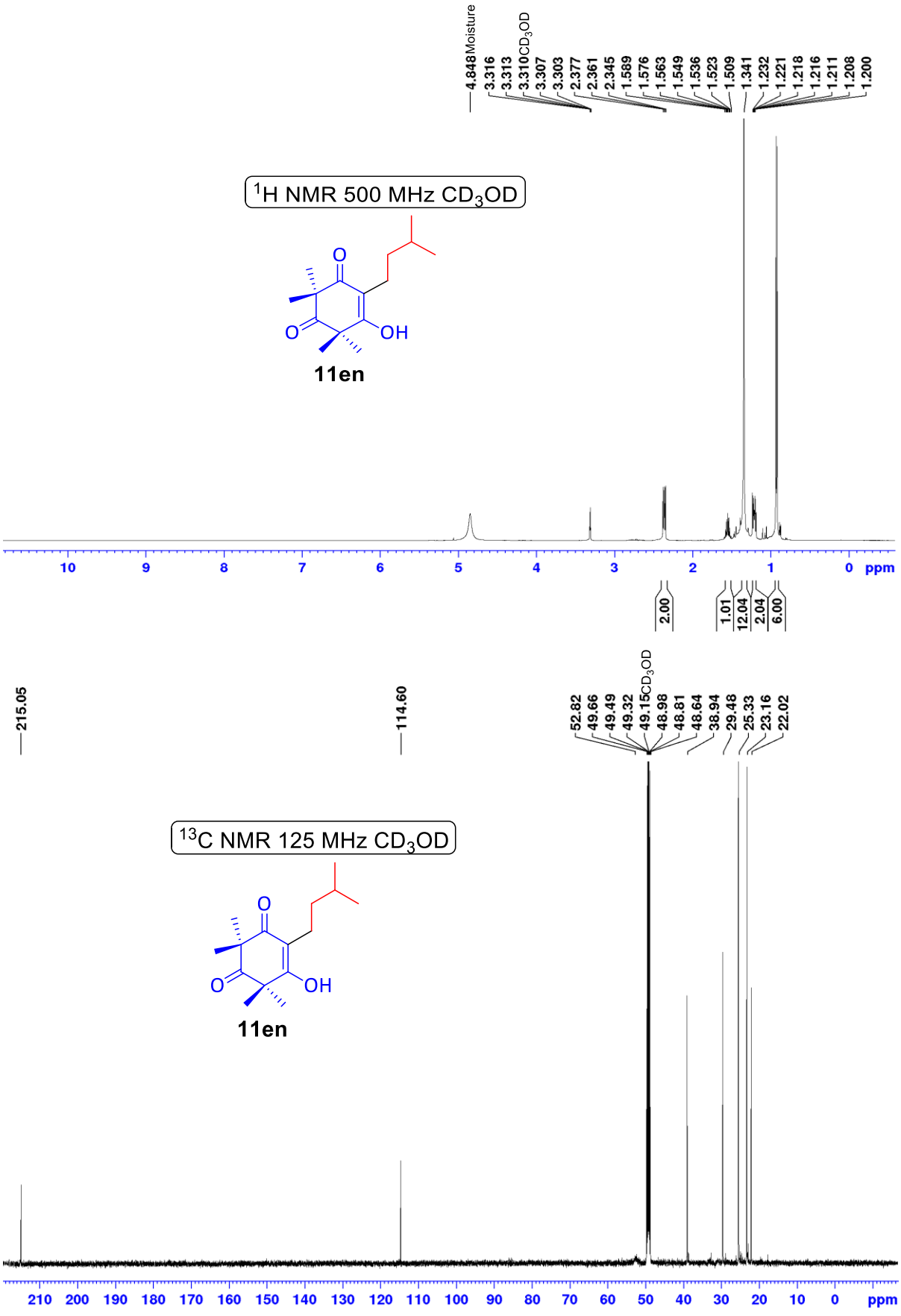



**Figure 34:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **11en**.

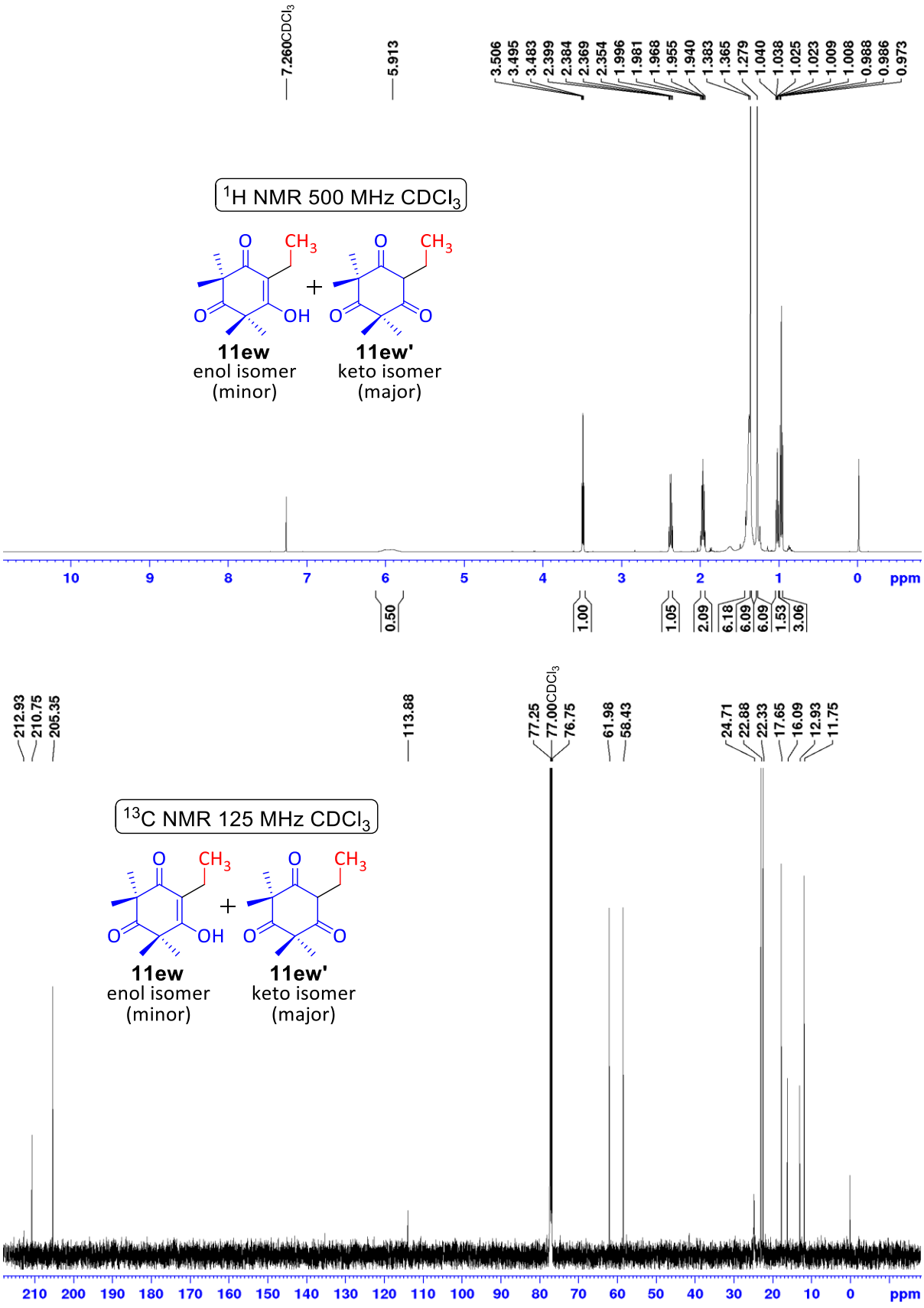
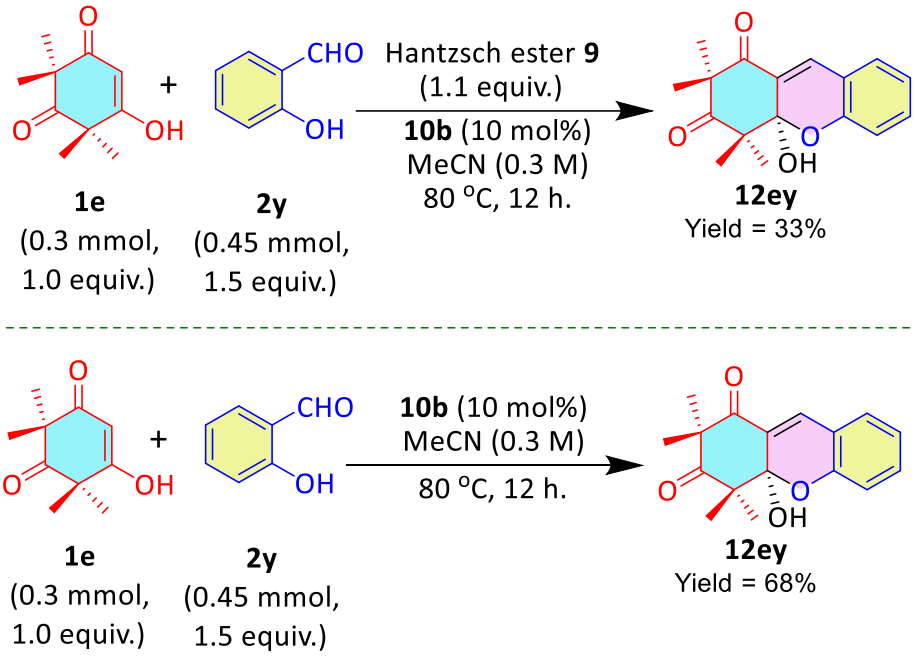



**Figure 35:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **11ew**.

When Syncarpic acid reacted with salicylaldehyde **2y**, for our surprise, reaction did not afford alkylated product, instead soon after the Knoevenagel condensation, annulation occurred via attack of hydroxyl group of salicylaldehyde **2y** onto the carbonyl of Syncarpic acid **1e** in 1,2 addition fashion affording **12ey** with 33% yield in 12 h (Scheme 20).




**Scheme 20:** Reaction substrate scope with salicylaldehyde.

In this reaction Hantzsch ester **9** unable to reduce the olefin, we further investigated the role of Hantzsch ester **9** in this reaction. For the same, a reaction has designed in absence of Hantzsch ester, resulted **12ey** with a hike in yield of 68% (Scheme 20).

$^{1}$H and $^{13}$C NMR spectra of compound **12ey** has depicted below (Figure 36).

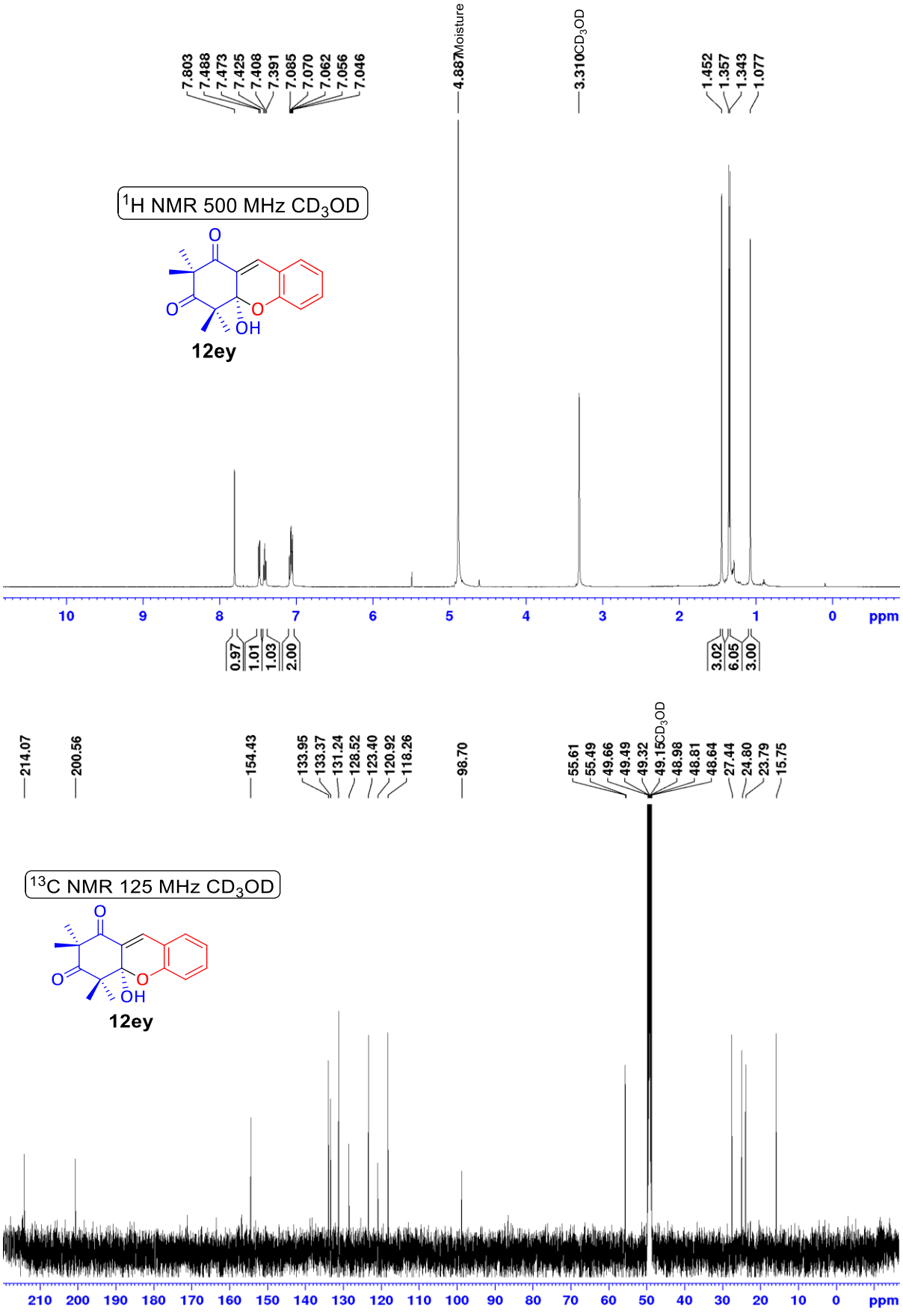
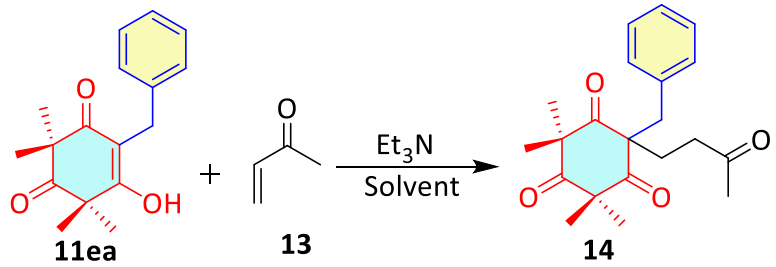



**Figure 36:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **12ey**.

### *4.2.3 Synthetic Applications of TCRA Products:*

Since 4-alkylated syncarpic acids are medicinally important, we were interested in investigating the potential of **11ea** as a Michael donor. For this, we have chosen well known Michael acceptor methyl vinyl ketone **7** as the counter substrate in order to investigate the Michael reaction. To our delight, the reaction of 4-benzylsyncarpic acid **11ea** (0.3 mmol, 1.0 equiv.) with methyl vinyl ketone **7** (0.36 mmol, 1.2 equiv.) in the presence of TEA (0.06 mmol, 0.2 equiv.) in DMSO at 80 °C afforded Michael adduct **14** with 30% yield in 10 h (Table 8, entry 1).

**Table 8:** Investigation of **11ea** as a Michael Donor [a]




| Entry | Solvent (0.3 M) | $Et_3N$ (equiv.) | **13** (equiv.) | T (°C) | *t* (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | DMSO | 0.2 | 1.2 | 80 | 10 | 30 |
| 2 | Neat | 0.1 | 1.2 | 25 | 6 | 32 |
| 3 | Neat | 1.0 | 1.2 | 25 | 12 | 42 |
| **4** | **Neat** | **1.0** | **3.0** | **25** | **15** | **92** |
| 5 | Neat | 0.5 | 3.0 | 25 | 12 | 56 |

[a]Reactions were carried out either in neat codition or in DMSO (0.3 M) relative to **11ea** (0.3 mmol). [b]Yield refers to the column purified products.

Since Michael reactions show better results in neat conditions,[27] we have performed the same reaction without any solvent at 25 °C which afforded Michael adduct **14** with a slightly improved yield of 32% in 6 h (Table 8, entry 2). Increasing the loading of TEA to 1.0 equiv. enhanced the reaction yield to 42% in 12 h (Table 8, entry 3). Surprisingly, when we increased the equivalents of 7 from 1.2 to 3.0 equiv., reaction afforded **14** at 25 °C with an excellent yield of 92 % in 15 h (Table 8, entry 4). Reducing the equivalents of TEA showed negative impact on the reaction furnishing **14** with poor yield of 56% in 12 h (Table 8, entry 5).

$^{1}H$ and $^{13}C$ NMR spectra of compound **14** has depicted below (Figure 37).

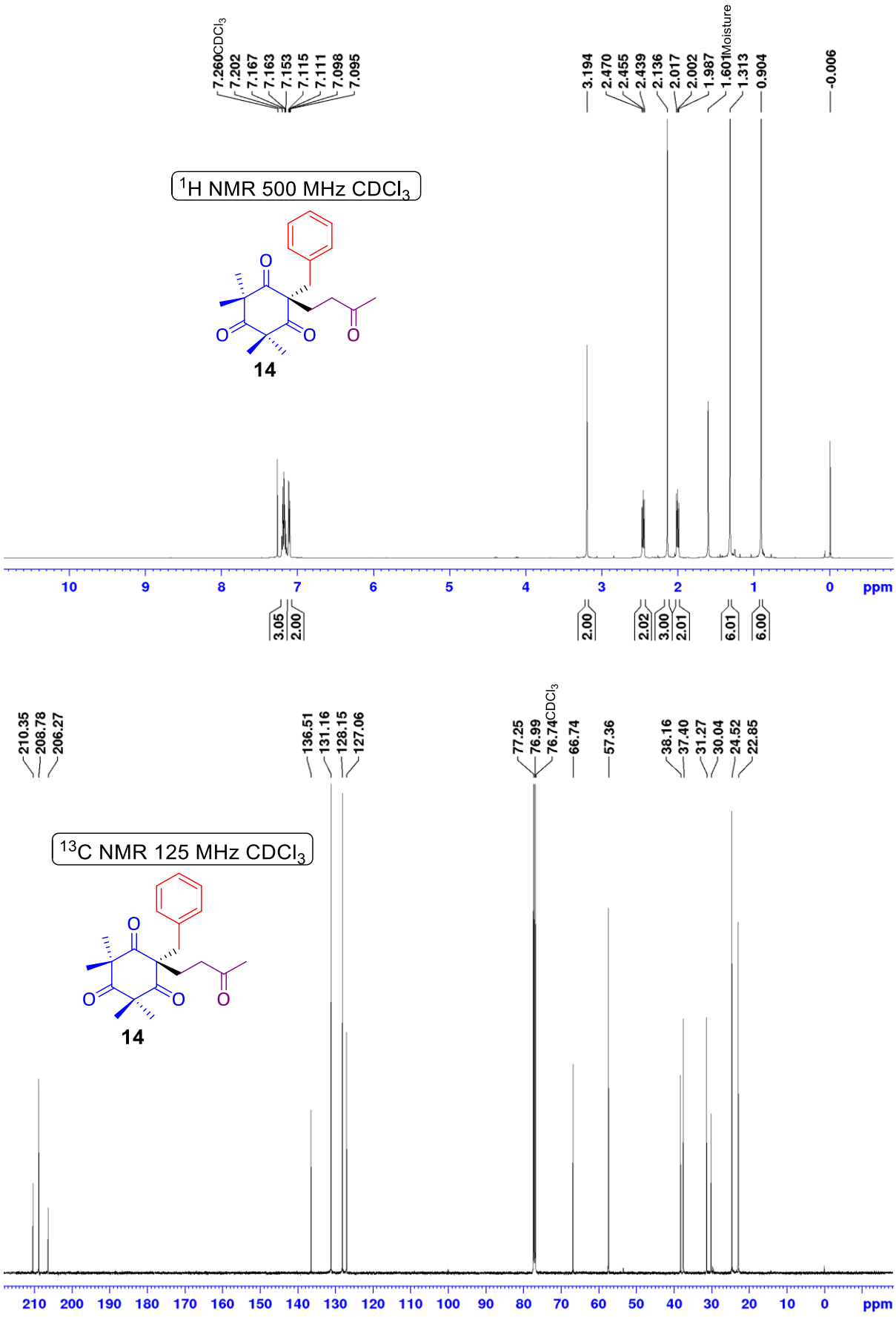
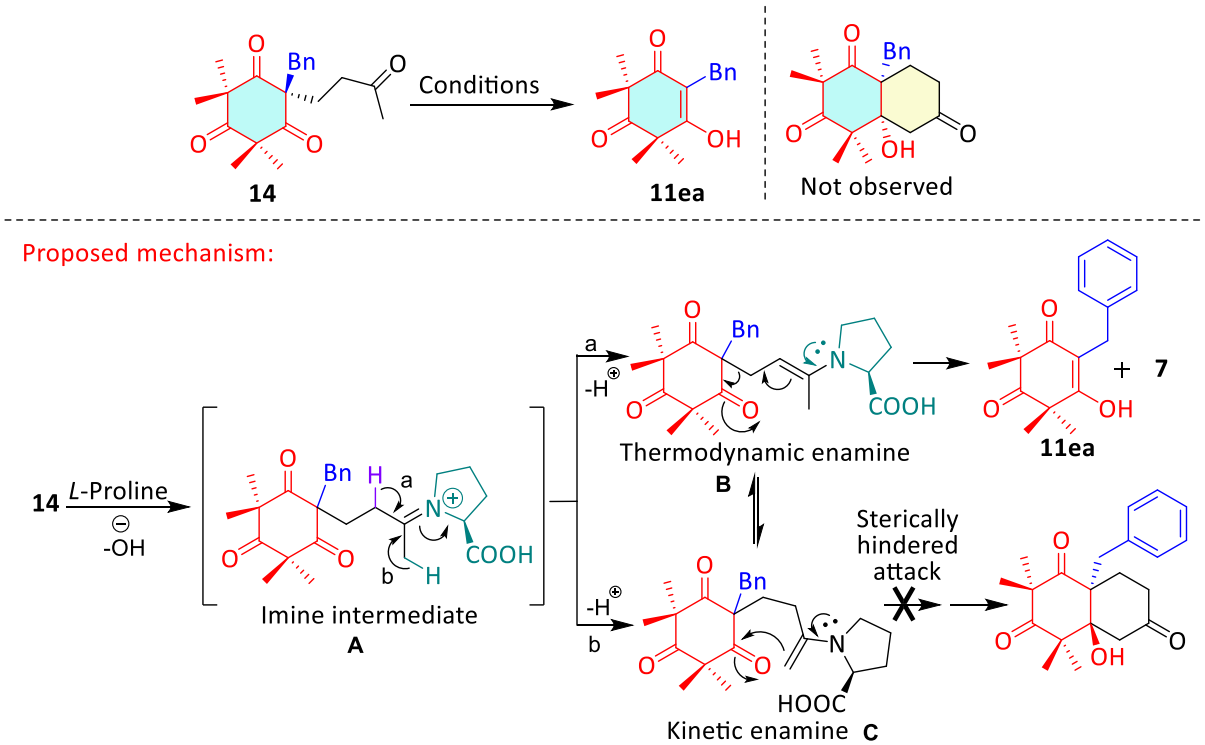



**Figure 37:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **14**.

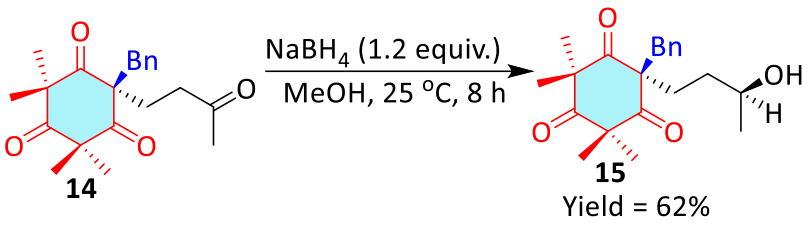
We further tried the annulation of the Michael adduct **14** through various conditions (Scheme 21) to furnish the cyclic decalanes. To our surprise, the reaction followed retro-Michael pathway affording 4-benzylsyncarpic acid **11ea** with excellent recovery yields. The possibility for the retro-Michael pathway can be well explained using the mechanism of the reaction under (*S*)-proline catalysis. The Michael adduct **14** reacts with (*S*)-proline forming an imine intermediate **A**, which upon the abstract of proton has a possibility of forming both thermodynamic enamine **B** and kinetic enamine **C** which exists in an equilibrium. Since kinetic enamine **C**, cannot proceed via the attack of terminal alkene on to the carbonyl group of Syncarpic core due to the steric hindrance, it will be equilibrating itself more into thermodynamic enamine **B**, which follows a retro-Michael pathway forming **11ea** in almost quantitative yields as shown in Scheme 20. Same result was observed in case of various reaction conditions (Scheme 21). Since the Michael adduct **14** releases 4-alkylated syncarpic acid **11** under amino acid-catalysis conditions, we can use **14** as a pro-drug[28] in the cellular systems.




**Conditions:** (a) *L*-Proline (30 mol%), DMSO, 36 h, 96%; (b) KO$^t$Bu (20 mol%), THF, 1 h at 0 $^o$C, 12 h at 25 $^o$C, 98%; (c) Methyltriphenylphosphonium Bromide (1 eq.), KO$^t$Bu (1 eq.), benzene, 12 h, 95%; (d) *p*-Methoxyaniline (1.1 eq.), *p*-TSA (5 mol%), benzene, reflux, 12 h, 94%.

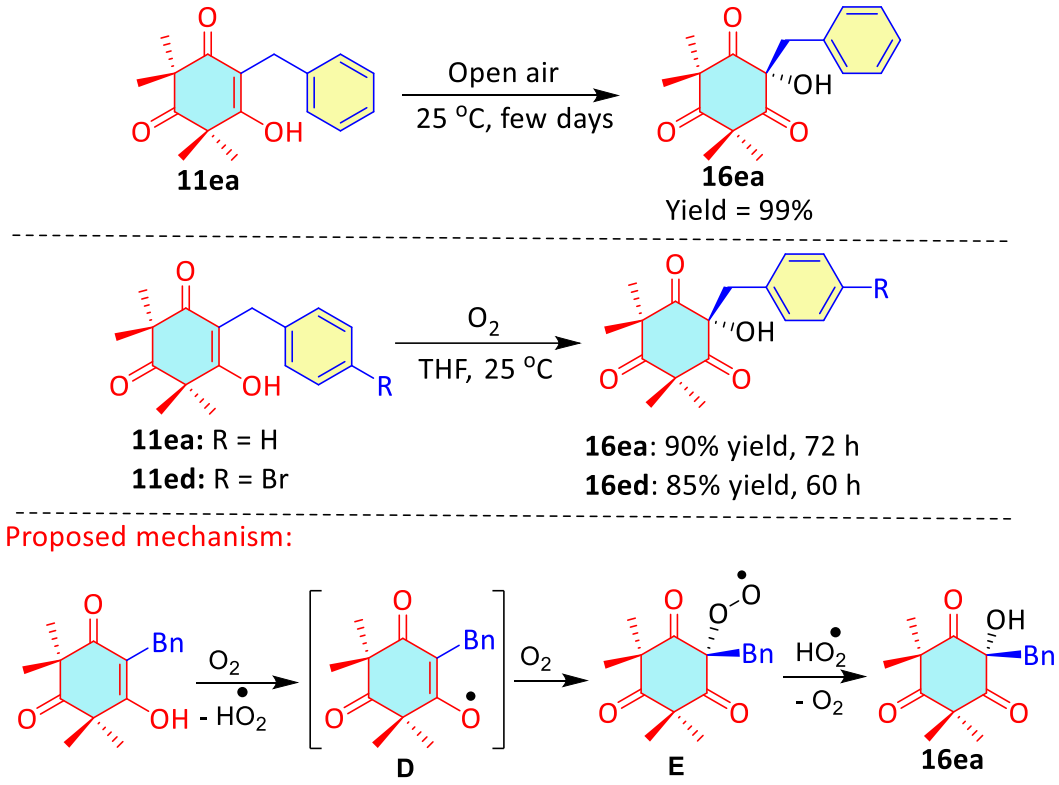
**Scheme 21:** Unsuccessful attempts for annulation: Observation of retro-Michael reaction.

We have also performed a chemoselective remote reduction of the Michael adduct **14** (0.3 mmol, 1.0 equiv.) with sodium borohydride (0.36 mmol, 1.2 equiv.) in methanol at 25 °C for 12 h which afforded the chemoselective reduced compound **15** in 62% yield (Scheme 22).




**Scheme 22:** Chemoselective reduction of compound **14**.

Stunningly, 4-benzylsyncarpic acid **11ea** when kept in open air at 25 °C for few days, it undergone complete air oxidation furnishing the oxidized product **16ea** in quantitative yield.




**Scheme 23:** Air-oxidation of TCRA products.

Then we tried improving the conditions for oxidation by providing external oxygen to the reaction through $O_2$ balloon. 4-benzylsyncarpic acid **11ea** (0.3 mmol) in THF under oxygen atmosphere at 25 °C produced the oxidized product **16ea** with 90% yield in 72 h whereas 4-bromobenzylsyncarpic acid **11ed** produced **16ed** with 85% yield in 60 h (Scheme 23). The oxidation of **11ea** proceed through radical mechanism with the triplet oxygen. Firstly, triplet

oxygen abstracts the proton from the hydroxyl group of **11ea** leaving the oxygen radical forming **D**. The radical shifts to *C*-4 position in order to attain stability and reacts with another triplet $O_2$ forming **E** which upon reaction with $HO_2$ radical present in the reaction mixture forms the oxidised product **10a** releasing $O_2$ molecule (Scheme 23). These results inspired us to investigate the anti-oxidative nature[29] of the products **11** to behave as drug candidates.

The structure and relative stereochemistry of **16ea** was further confirmed by X-Ray crystallography (Figure 38).

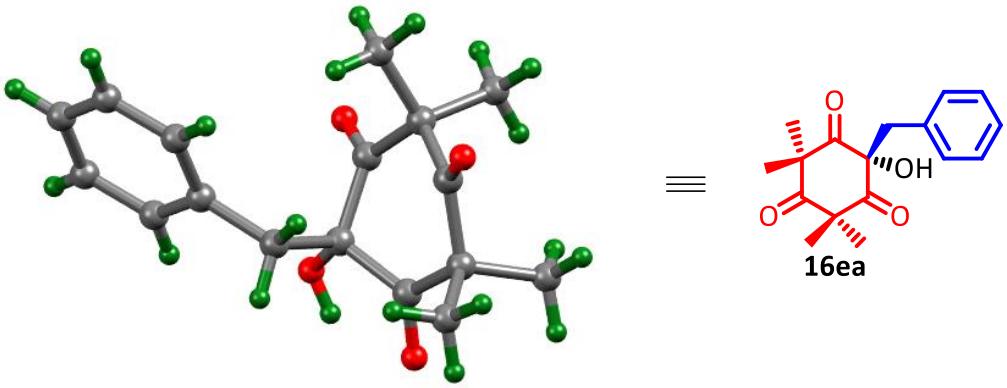



**Figure 38:** Crystal structure of 2-benzyl-2-hydroxy-4,4,6,6-tetramethyl cyclohexane-1,3,5-trione **(16ea)**.

The synthesized compound **16ea** has characterized using NMR, IR and HRMS. $^{1}H$ and $^{13}C$ NMR spectra of compound **16ea** has depicted below (Figure 39).

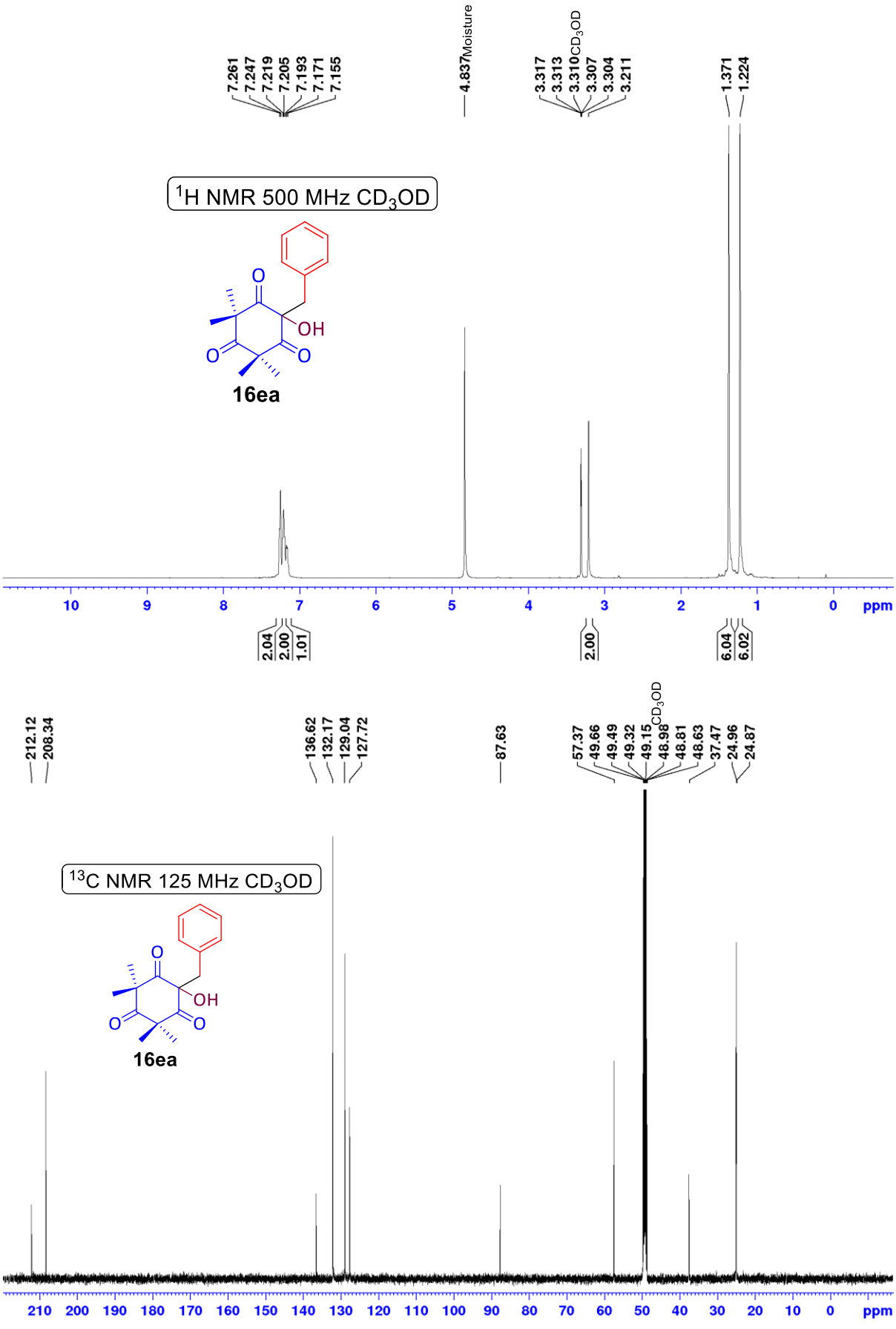



**Figure 39:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **16ea**.

We have confirmed the structures of compounds **11ee**, **12ey**, **14** using X-Ray crystallography (Figure 40-42).

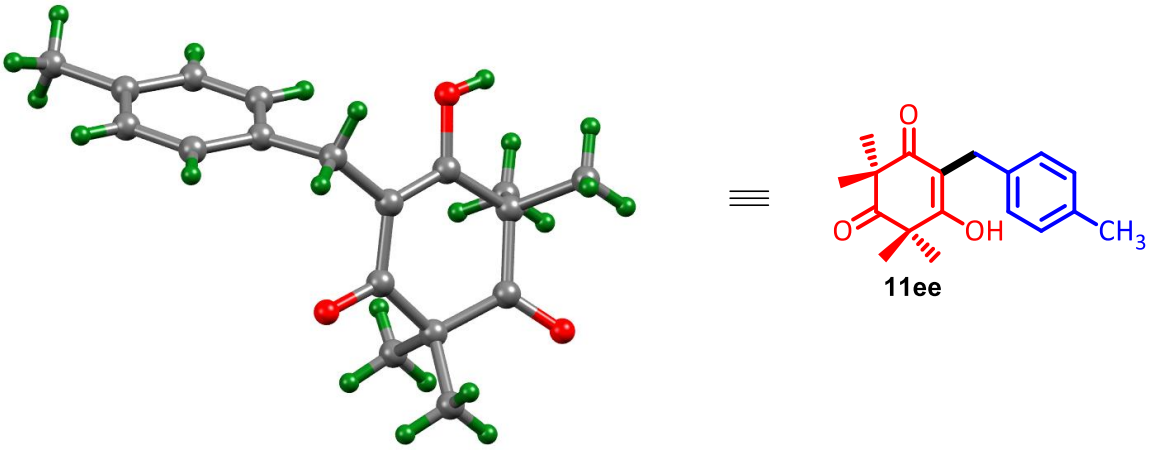



**Figure 40:** Crystal structure of 5-hydroxy-2,2,6,6-tetramethyl-4-(4-methylbenzyl) cyclohex-4-ene-1,3-dione **(11ee)**.

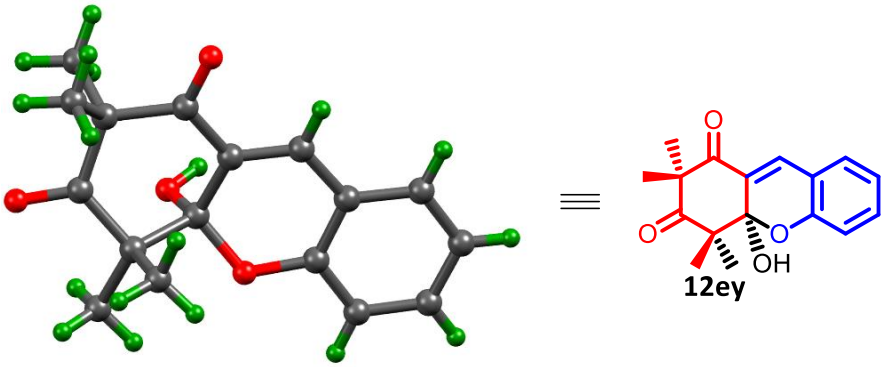



**Figure 41:** Crystal structure of 4a-hydroxy-2,2,4,4-tetramethyl-4,4a-dihydro-1*H*-xanthene-1,3-(2*H*)-dione **(12ey)**.

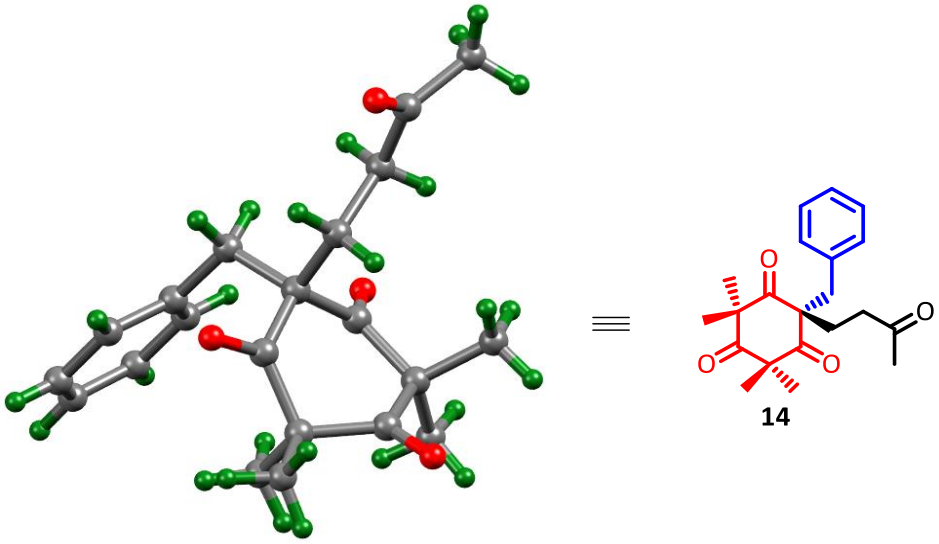
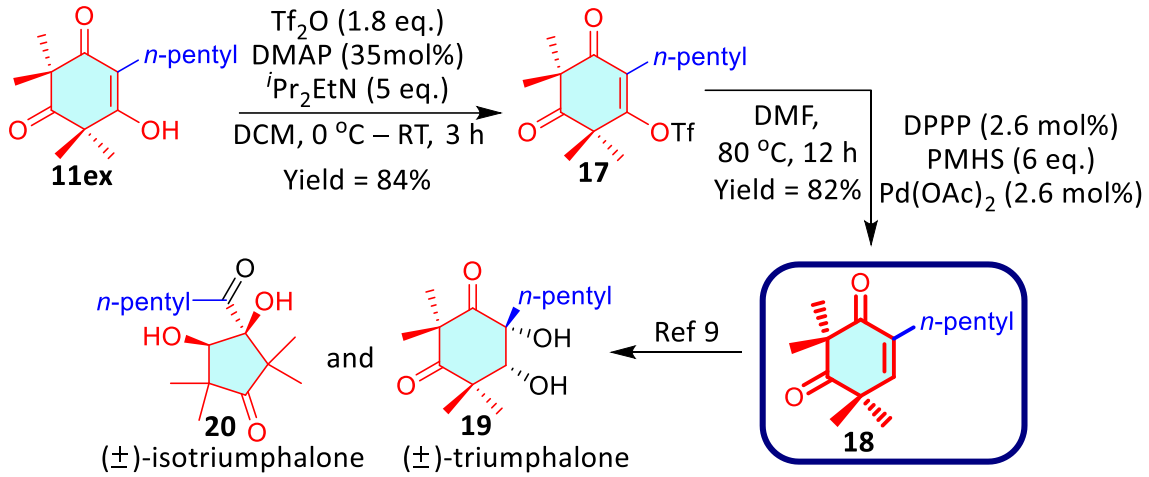



**Figure 42:** Crystal structure of 2-benzyl-4,4,6,6-tetramethyl-2-(3-oxobutyl) cyclohexane-1,3,5-trione **(14)**.

### *4.2.4 Formal Total Synthesis of Monomeric Phloroglucinol Natural Products:*

(±)-Triumphalone and (±)-Isotriumphalone are one of the important natural products having the core structure of Syncarpic acid **1e**. 4-pentyldehydroxysyncarpic acid **17** is a potential intermediate for the synthesis of the natural products **19** and **20**. T. Shinada *et al.* reported the total synthesis of (±)-triumphalone **19** and (±)-Isotriumphalone **20** in five steps starting from 4-pentylsyncarpic acid **11ex** where they have achieved 4-pentyldehydroxysyncarpic acid **18** in four tedious steps (ref. 9). Following our protocol, we have synthesized the 4-pentyldehydroxysyncarpic acid **18** in two simple steps. Firstly, 4-pentylsyncarpic acid **11ex** reacted with $Tf_2O$ (1.8 equiv.) in the presence of DMAP (35 mol%), diisopropylethylamine (5.0 equiv.) in DCM for 3 h affording 4-pentylsyncarpic acid triflate **17** with an excellent yield of 84%. Later triflate **17** in the presence of DPPP (2.6 mol%), $Pd(OAc)_2$ (2.6 mol%), PHMS (6.0 equiv.) in DMF at 80 °C afforded the detriflated 4-pentylsyncarpic acid **18** with good yield of 82% in 12 h (Scheme 24).




**Scheme 24:** Formal total synthesis of (±)-triumphalone and (±)-isotriumphalone.

$^{1}H$ and $^{13}C$ NMR spectra of compound **18** has depicted below (Figure 43).

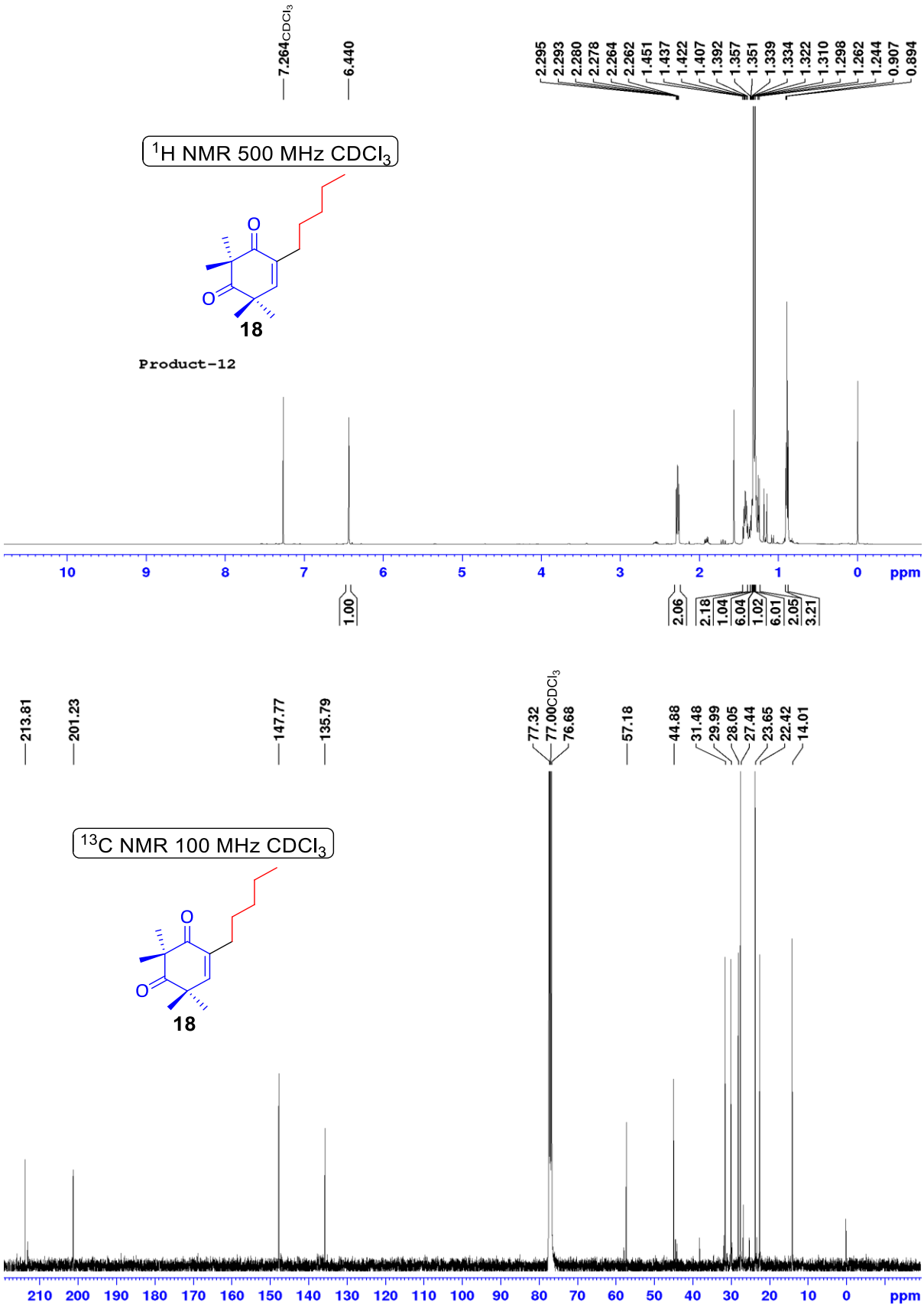
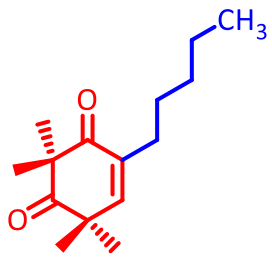
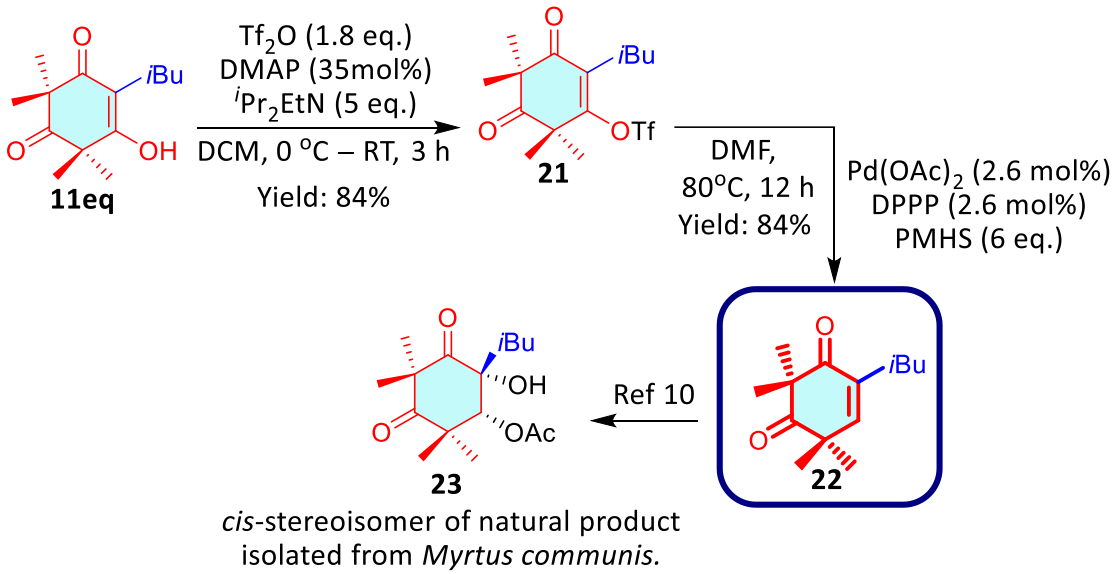



**Figure 43:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **18**.

## Correlation between Reported (Ref. 9) and Our Experimental NMR Data of Compound (18):

<table>
<tr><td colspan="2" rowspan="5">  <br>2,2,6,6-tetramethyl-4-pentylcyclohex-4-ene-1,3-dione (18)</td><td>Reported $^{13}$C NMR (75 MHz)</td><td>Experimental $^{13}$C NMR (100 MHz)</td></tr>
<tr><td>213.7 (C, C=O)</td><td>213.8 (C, C=O)</td></tr>
<tr><td>201.2 (C, C=O)</td><td>201.2 (C, C=O)</td></tr>
<tr><td>147.7 (CH)</td><td>147.8 (CH)</td></tr>
<tr><td>135.8 (C)</td><td>135.8 (C)</td></tr>
<tr><td colspan="2"></td><td>57.1 (C)</td><td>57.2 (C)</td></tr>
<tr><td>Reported $^{1}$H NMR (300 MHz)</td><td>Experimental $^{1}$H NMR (500 MHz)</td><td>44.8 (C)</td><td>44.9 (C)</td></tr>
<tr><td>6.42 (1H, t, J = 1.2 Hz)</td><td>6.44 (1H. br s)</td><td>31.4 ($CH_2$)</td><td>31.5 ($CH_2$)</td></tr>
<tr><td>2.26 (2H, m)</td><td>2.28 (2H, dt, J = 1.0 Hz)</td><td>30.0 ($CH_2$)</td><td>30.0 ($CH_2$)</td></tr>
<tr><td rowspan="2">1.43-1.25 (6H, m)</td><td>1.42 (2H, pent, J = 7.0 Hz)</td><td>28.0 ($CH_2$)</td><td>28.1 ($CH_2$)</td></tr>
<tr><td>1.36-1.24 (4H, m)</td><td>27.4 (2 x $CH_3$)</td><td>27.4 (2 x $CH_3$)</td></tr>
<tr><td>1.30 (6H, s)</td><td>1.32 (6H, s)</td><td>23.6 (2 x $CH_3$)</td><td>23.7 (2 x $CH_3$)</td></tr>
<tr><td>1.26 (6H, s)</td><td>1.30 (6H, s)</td><td>22.4 ($CH_2$)</td><td>22.4 ($CH_2$)</td></tr>
<tr><td>0.87 (3H, t, J = 6.9 Hz)</td><td>0.89 (3H, t, J = 6.5 Hz)</td><td>14.0 ($CH_3$)</td><td>14.0 ($CH_3$)</td></tr>
</table>

In the same way we have also synthesized 4-isobutyldehydroxysyncarpic acid **22** which is a potential intermediate in the synthesis of monomeric phloroglucinol derivative isolated from *Myrtus communis* using the same two-step strategy starting from 4-isobutylsyncarpic acid **11eq**. T. Shinada *et al.* reported the total synthesis of monomeric phloroglucinol derivative isolated from *Myrtus communis* in six steps starting from 4-isobutylsyncarpic acid **11eq** where they have achieved 4-isobutyldehydroxysyncarpic acid **22** in four tedious steps (ref. 10). Similar to the previous case protection of 4-isobutylsyncarpic acid **11eq** with $Tf_2O$ afforded 4-isobutylsyncarpic acid triflate **21** in 84% yield. Later palladium catalyzed detriflation of **21** afforded the 4-isobutyldehydroxysyncarpic acid **22** in 74% yield (Scheme 25).




**Scheme 25:** Formal total synthesis of monomeric pholoroglucinol derivative.

$^{1}H$ and $^{13}C$ NMR spectra of compound **22** has depicted below (Figure 44).

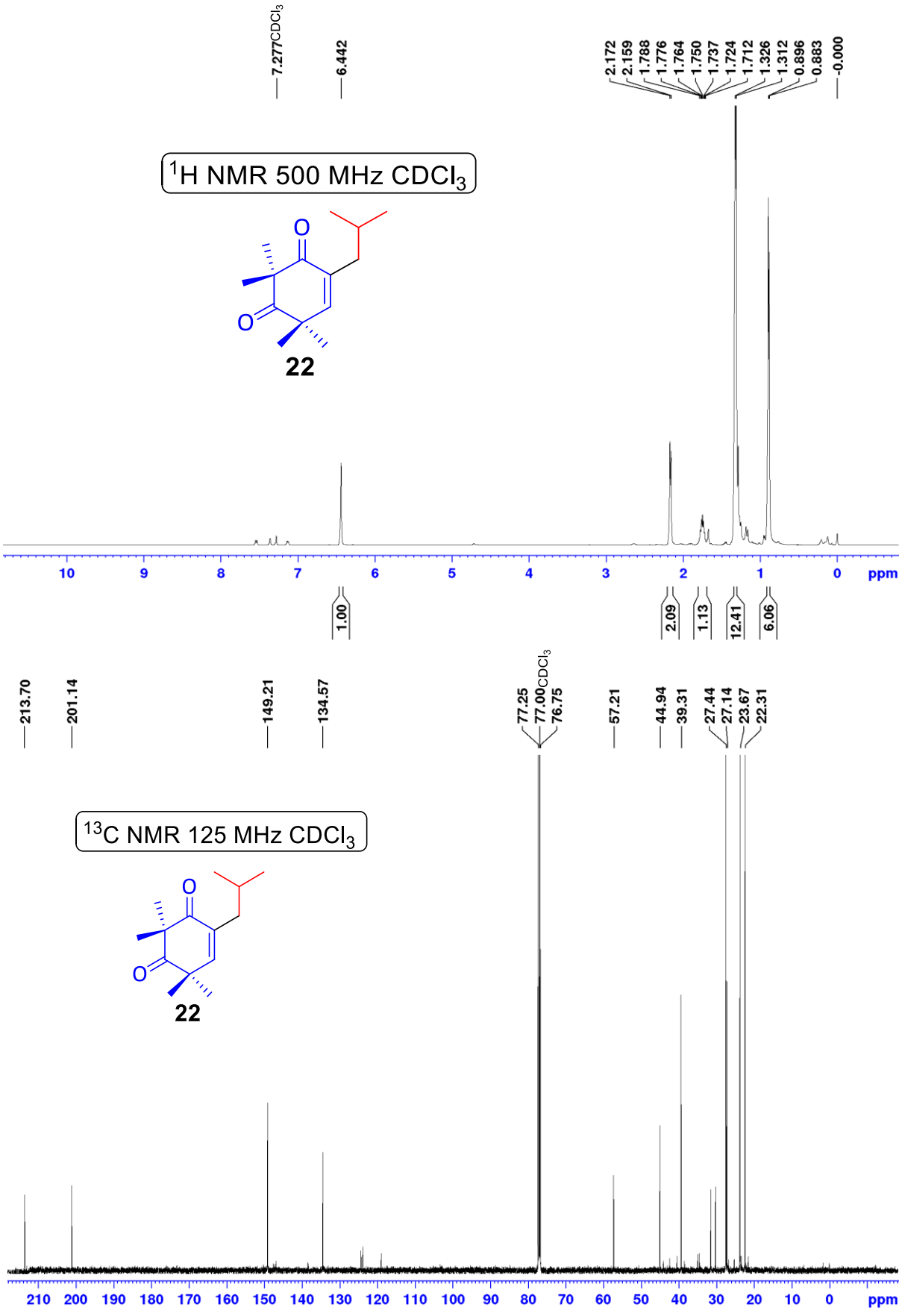
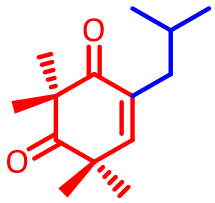
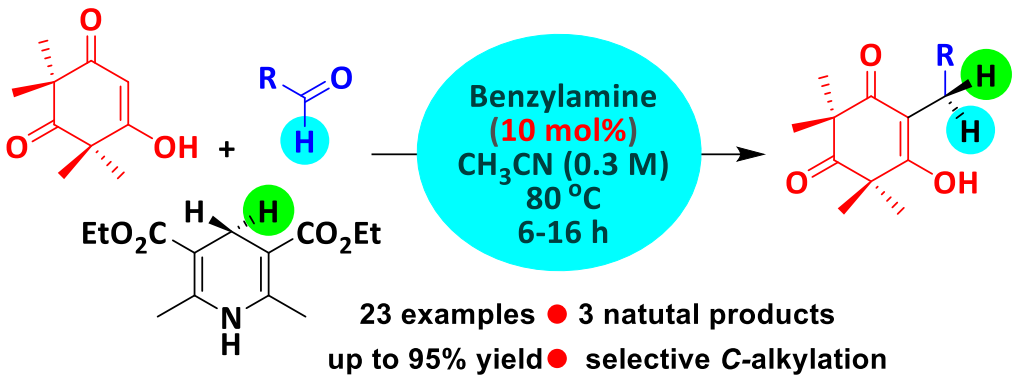



**Figure 44:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **22**.

## Correlation between Reported (Ref. 10) and Our Experimental NMR Data of Compound (22):

<table>
<tr><td colspan="2" rowspan="5">  <br>4-isobutyl-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (22)</td><td>Reported $^{13}$C NMR (75 MHz)</td><td>Experimental $^{13}$C NMR (125 MHz)</td></tr>
<tr><td>213.8 (C, C=O)</td><td>213.7 (C, C=O)</td></tr>
<tr><td>201.2 (C, C=O)</td><td>201.1 (C, C=O)</td></tr>
<tr><td>149.2 (CH)</td><td>149.2 (CH)</td></tr>
<tr><td>134.6 (C)</td><td>134.6 (C)</td></tr>
<tr><td>Reported $^{1}$H NMR (300 MHz)</td><td>Experimental $^{1}$H NMR (500 MHz)</td><td>57.2 (C)</td><td>57.2 (C)</td></tr>
<tr><td>6.43 (1H. br s)</td><td>6.44 (1H. br s)</td><td>45.0 (C)</td><td>44.9 (C)</td></tr>
<tr><td>2.17 (2H, dd, J = 6.8, 0.9 Hz)</td><td>2.17 (2H, d, J = 1.0 Hz)</td><td>39.3 ($CH_2$)</td><td>39.3 ($CH_2$)</td></tr>
<tr><td>1.74 (1H, m)</td><td>1.75 (1H, sept, J = 6.0 Hz)</td><td>27.5 (2 x $CH_3$)</td><td>27.4 (2 x $CH_3$)</td></tr>
<tr><td>1.32 (6H, s)</td><td>1.33 (6H, s)</td><td>27.2 (CH)</td><td>27.1 (CH)</td></tr>
<tr><td>1.30 (6H, s)</td><td>1.31 (6H, s)</td><td>23.7 (2 x $CH_3$)</td><td>23.7 (2 x $CH_3$)</td></tr>
<tr><td>0.88 (6H, d, J = 6.6 Hz)</td><td>0.89 (6H, d, J = 6.5 Hz)</td><td>22.3 (2 x $CH_3$)</td><td>22.3 (2 x $CH_3$)</td></tr>
</table>

## *4.3 Conclusions:*




In conclusion, for the first time, we have successfully developed an efficient methodology for the alkylation of syncarpic acid with well tolerance towards wide substrate scope. We thoroughly investigated the reactivity of 4-alkylsyncarpic acids as Michael donor and oxidation with air. Our initial studies revealing that 4-alkylsyncarpic acids can become very good drug candidates as anti-oxidants.

# 5. Organocatalytic C-H Oxidation: High-Yielding Synthesis of 3-Hydroxy-3-alkyloxindoles

## *5.1 Introduction*

Over the decades various attempts are being made to carry chemical process in sustainable manner, which includes use of environmentally and ecologically benign solvents and reagents, which gives maximum of desired product and minimum hazardous by-products.[30] Particularly, the utilization of molecular oxygen for transformation of chemical compounds is a fascinating and interesting research subject.[31a-c] The oxidation reactions are exceptionally essential where synthetic compounds are oxygenated which are significant in pharmaceutical industries.[32a-c] Numerous approaches have been developed using molecular oxygen for oxidation of different functional groups and other oxidative transformations as it is abundantly available and economically feasible oxidizing agent. Especially tertiary alcohols are extremely important motifs as they are part of natural products and biologically active compounds,[33] which can be synthesized in presence of various oxidant sources.

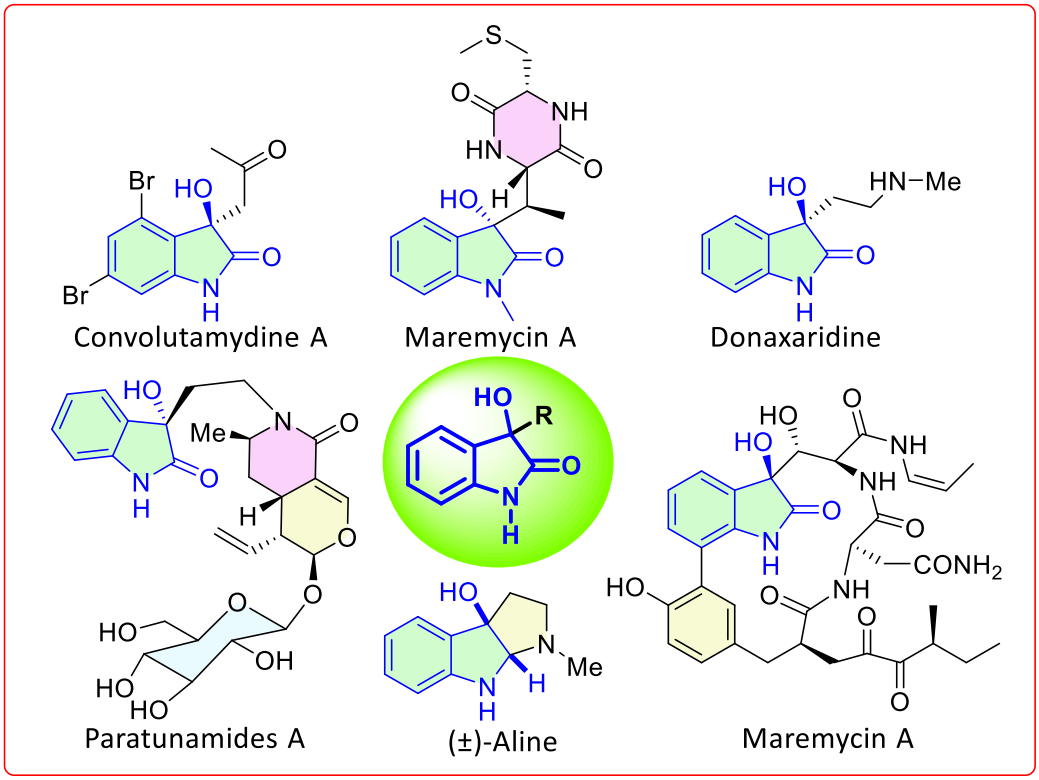
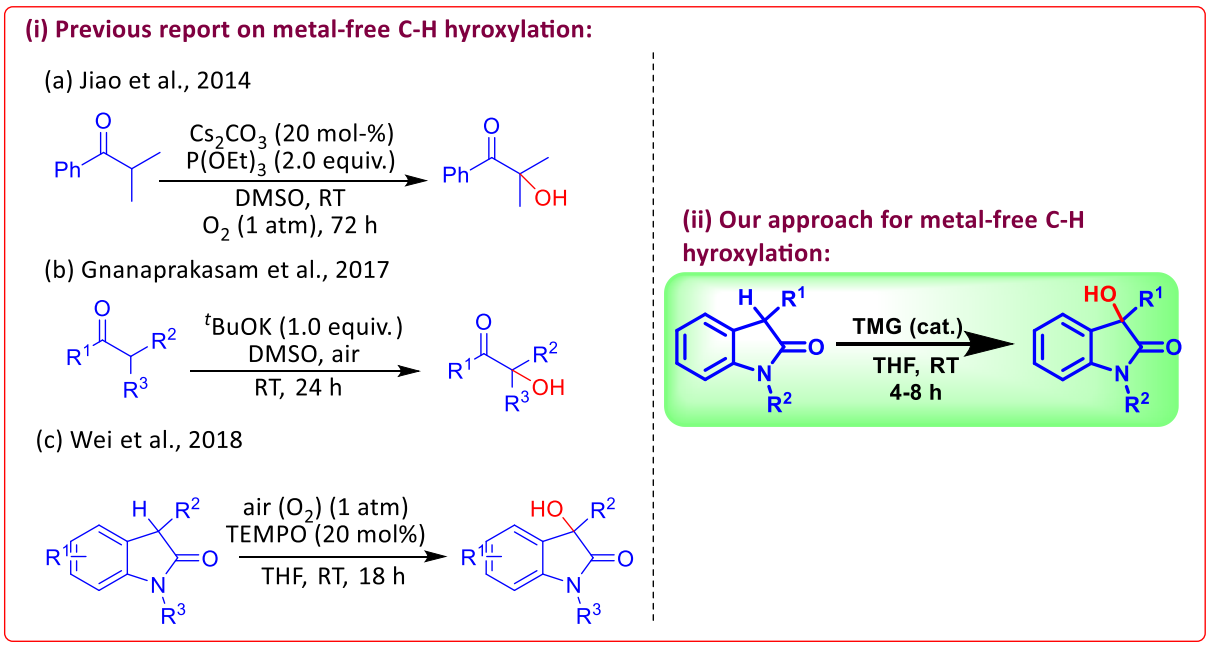



**Figure 45:** Bioactive molecules related to 3-substituted 3-hydroxy oxindoles.

There is an expanding interest for all the naturally favorable methodologies maintaining a strategy for not using costly metal catalyst and unsafe oxidants. On the other hand, the significance of 3-substituted-3-hydroxy-2-oxindoles is constantly increasing as it forms basic scaffolds of many natural products and biologically active molecules such as convolutamydines, donaxaridine, maremycins, paratunamide, celogentin K, TMC-95AD, flustraminol A and B, pyrrolidinoindoline-type alkaloid, CPC-1 (Figure 45).[34a-g] 3-Hydroxyoxindoles, are the metabolites of indole 3-acetic acid, isolated from different plants and few marine animals, which exhibits radical scavenging activity comparable to known powerful antioxidants like uric acid and indoles in humans.[35] Radicals sometimes show phagocytic activity but mostly they damage macromolecules. During their oxidation radicals are generated, which are responsible for the decay in the plants and animals. Scientific evidence suggests that 3-hydroxyoxindoles act as antioxidants which reacts with free radicals to form stable complexes and reduces the risk of chronic diseases.[36]

Accordingly, many synthetic methods have been developed for the construction of 3-substituted 3-hydroxy oxindoles derivatives.[37a,b] In the year 2014, Jiao group reported $Cs_2CO_3$ catalyzed direct hydroxylation of carbonyl compounds in presence of excess of $O_2$ and more than two equivalence of triethyl phosphate as base in DMSO at room temperature (Scheme 26).[38a]




**Scheme 26**: Synthesis of 3-substituted-3-hydroxy-2-oxindoles.

Gnanaprakasam group in 2017 used one equivalence of $^{t}$BuOK and atmospheric air as an oxidant at room temperature to synthesize tertiary hydroxyl compounds of various ketones and amides (Scheme 26).[38b] Similarly, In 2018, Wei group reported TEMPO catalyzed direct hydroxylation of carbonyl compounds in presence of atmospheric $O_2$ in THF solvent at room temperature (Scheme 26).[38c] In all this cases, reactions took a long time (more than 24 h), additionally the use of corrosive reagents like $Cs_2CO_3$, $^{t}$BuOK and TEMPO made all this protocols least attractive. On the other hand, dissolved oxygen in solvent is considered to be a better parameter for oxidation as in this way, pure environmental air oxygen is not an essential condition. Here in we report the synthesis of 3-substituted-3-hydroxy oxindoles using a simple organic base and dissolved oxygen in solvent which is atom economic and produces desired product with excellent yield.

## *5.2 Results and Discussion*

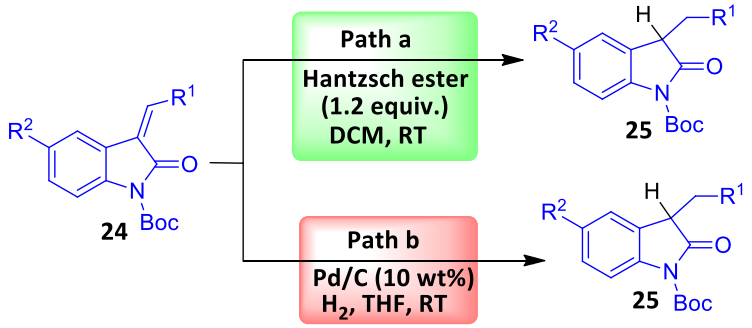
### *5.2.1 Comparison between Hantzsch Ester Reduction and Pd/C/H₂ Reduction for the Preparation of Starting Materials:*

For the same, 3-alkylated oxindoles **25** have taken as the starting material. In terms of achieving the 3-alkylated oxindole, 3-alkylidene oxindoles **24**, which has prepared either by a (*S*)-proline catalyzed Knoevenagel condensation between oxindole with different aldehyde or a Wittig reaction between isatin and different Wittig salts, was reduced through Pd/C hydrogenation method or using Hantzsch ester as a reducing agent. Delightfully, we observed a better yield in Hantszch ester reduction, which is a green method,[20,25a-b] compare to Pd/C hydrogenation because of its uncontrolled reactivity towards over-reduction of 3-alkylidene oxindoles.
Pd/C/$H_2$ reduction is a well-known method for reduction of an olefin bond to a C-C single bond.[39] On the other hand, reduction of olefin using Hantzsch ester is a much greener method as no metal has involved in this process. We performed the reduction of 3-alkylidene-2-oxindoles **24** using Hantzsch ester reduction method (path a) and Pd/C/$H_2$ reduction method (path b, procedure mentioned in ref. 38). To our surprise, we found that most of the cases Hantzsch ester reduction worked better than the Pd/C/$H_2$ hydrogenation process in terms of yield and time required for the reaction (Table 9).

In few cases Pd/C/$H_2$ hydrogenation process failed to furnish the desired product or a good yield of desired product due it's high reactivity towards dehalogenation of aromatic ring (Table 9, entry 2, 3, 12 and13). Therefore, the success of Hantzsch ester reduction over Pd/C/$H_2$

hydrogenation was mostly glorified in case of halogen contained starting materials (Table 9, entry 2, 3, 12 and13). Lesser yields (41% and 38% respectively) were observed in case of **24o** and **24p** when treated with Pd/C/$H_2$ condition, may be due to the over-reduction of nitro and nitrile group, but Hantzsch ester worked well in both cases with 80% and 92% of yield respectively (Table 9, entry 9, 10). In case of tert-butyl 3-(furan-2-ylmethylene)-2-oxoindoline-1-carboxylate **24w**, Hantzsch ester procedure did not work, while Pd/C/$H_2$ hydrogenation furnished an over-reduced product **25w** containing tetrahydrofuran ring (Table 9, entry 16). Few of the $^1$H and $^{13}$C NMR spectra of the synthesized compounds in Table 9 are given below (Figure 46-47).

**Table 9:** Two types of reduction Hantzsch ester and Pd/C [a]




| Entry | 24 | Path a | | Path b | |
|---|---|---|---|---|---|
| | | Time (h) | Yield [%][b] | Time (h) | Yield [%][b] |
| 1 | $R^1$= Ph, $R^2$= H (**24a**) | 8 | 94 | 16 | 88 |
| 2 | $R^1$= 4-Cl$C_6H_4$, $R^2$= H (**24h**) | 12 | 95 | 16 | 51 |
| 3 | $R^1$= 4-Br$C_6H_4$, $R^2$= H (**24i**) | 8 | 90 | 16 | 5 |
| 4 | $R^1$= 4-Me$C_6H_4$, $R^2$= H (**24j**) | 8 | 86 | 16 | 85 |
| 5 | $R^1$= 4-$^i$propyl$C_6H_4$, $R^2$= H (**24k**) | 8 | 91 | 16 | 88 |
| 6 | $R^1$= 4-MeO$C_6H_4$, $R^2$= H (**24l**) | 12 | 88 | 16 | 65 |
| 7 | $R^1$= 4-N$Me_2C_6H_4$, $R^2$= H (**24m**) | 8 | 81 | 12 | 92 |
| 8 | $R^1$= 4-$CF_3C_6H_4$, $R^2$= H (**24n**) | 12 | 89 | 12 | 85 |
| 9 | $R^1$= 4-$NO_2C_6H_4$, $R^2$= H (**24o**) | 12 | 80 | 16 | 41 |
| 10 | $R^1$= 4-C$NC_6H_4$, $R^2$= H (**24p**) | 7 | 92 | 16 | 38 |
| 11 | $R^1$= Ph,$R^2$= Me (**24r**) | 12 | 96 | 12 | 88 |
| 12 | $R^1$= Ph, $R^2$= Cl (**24s**) | 6 | 91 | 15 | 68 |
| 13 | $R^1$= Ph, $R^2$= F (**24t**) | 8 | 89 | 15 | 33 |
| 14 | $R^1$= Ph, $R^2$= OMe (**24u**) | 12 | 80 | 12 | 88 |
| 15 | $R^1$= $CO_2$Et, $R^2$= H (**24v**) | 12 | 56 | 16 | 89 |
| 16[c] | $R^1$= furyl,$R^2$= H (**24w**) | 24 | nr | 16 | 87 |

[a]Path a: Reactions were performed in DCM (0.3 M) with 1.2 equiv. of Hantzsch ester relative to **24** (3.0 mmol) at 25 °C. Path b: Reactions were performed in THF (0.3 M) with 10 wt% of Pd/C relative to **24** (3.0 mmol) in the presence of $H_2$ gas containing balloons at 25 °C. [b]Yield refers to the column purified products. [c]Over-reduced Product **25w** was obtained with *dr* = 1.2:1.

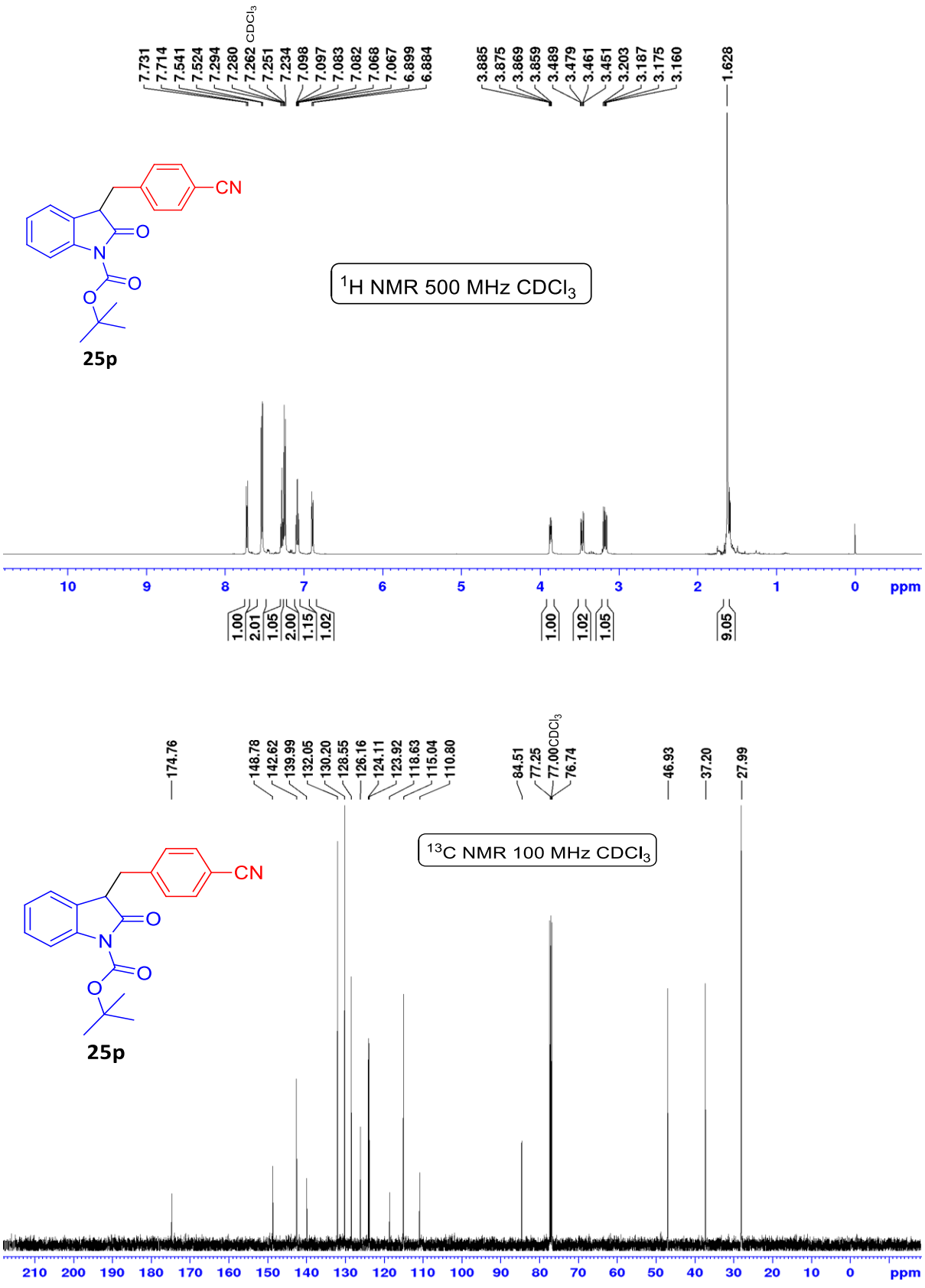



**Figure 46:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **25p**.

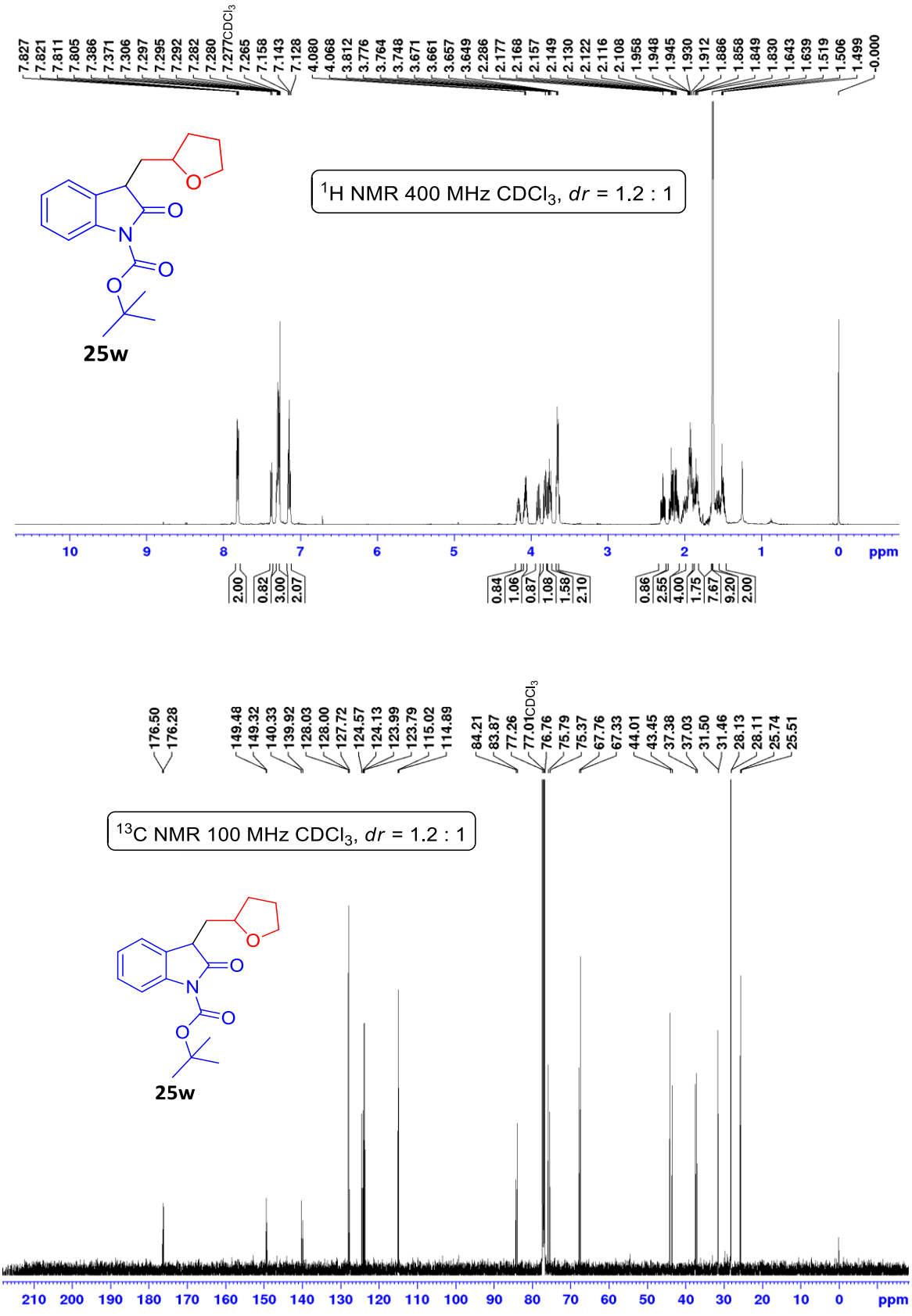
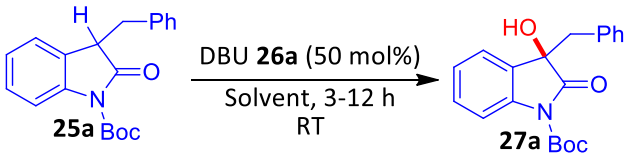



**Figure 47:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **25w**.

### *5.2.2 Reaction Preliminary Optimization:*

We commenced our reaction conditions by treating **25a** with DBU **26a** (50 mol%) in toluene at room temperature. Pleasurably, within 3 hours, we observed the formation of our desired product **27a** with 38% of yield (Table 10, entry 1). A further dilution by doubling the volume of toluene decrease the yield dramatically (Table 10, entry 2). Yield was decreased once more upon addition of 20 mol% of thiourea as co-catalyst, even in absence of base, thiourea alone unable to produce our desire product (Table 10, entry 3,4).

**Table 10:** Solvent Optimization [a]



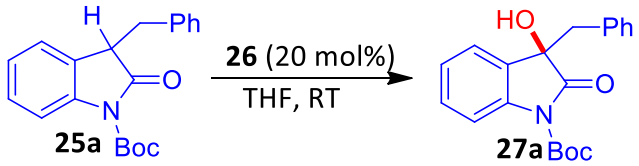

| Entry | Solvent | Time (h) | Yield [%][b] |
|---|---|---|---|
| 1 | Toluene | 3 | 38 |
| 2[c] | Toluene | 3 | 21 |
| 3[d] | Toluene | 4 | 19 |
| 4[d,e] | Toluene | 12 | nr |
| 5[f] | Toluene | 6 | 29 |
| 6 | DMSO | 5 | 32 |
| 7 | $CHCl_3$ | 5 | 33 |
| **8** | **THF** | **5** | **87** |
| 9 | $Et_2O$ | 8 | 53 |
| 10 | DMF | 5 | 52 |
| 11 | Dioxane | 5.5 | 54 |
| 12 | $CH_3CN$ | 5 | 35 |

[a]Reactions were performed in solvent (0.1 M) with 0.5 equiv. of **26a** relative to **27a** (0.2 mmol) at 25 °C. [b] Yield refers to the column purified product. [c]Reaction was performed in toluene (0.1 M) relative to **25a** (0.2 mmol). [d]Reaction was carried out in presence of thiourea (20 mol%) as a co-catalyst with respect to **25a**. [d]Reaction was carried out in absence of **26a**. [e]Reaction was carried out in presence of $O_2$.

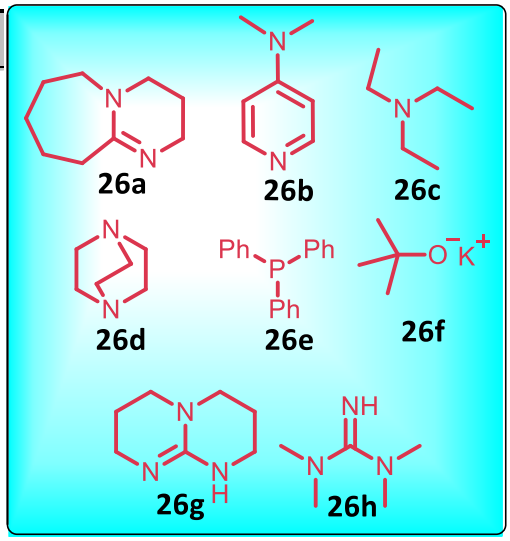
This reaction was also monitored in presence of external oxygen source providing through $O_2$ balloon, ironically yield was decreased in this case (Table 10, entry 5). Then we carried out our reaction in different solvents such as DMSO, $CHCl_3$, THF, diethyl ether, DMF, dioxane and $CH_3CN$ (Table 10, entry 6-12). In all the cases yield of reaction lies between 32-54%, except THF as a solvent with a promising yield of 87% (Table 10, entry 8), considered as the optimized solvent for this reaction.

Next, the suitability of various bases has been investigated (Table 11). When **25a** was treated with 30 mol% of **26a**, product **27a** was obtained in 91% yield within 7.5 h (Table 11, entry 1). The catalyst loading was further reduced to 20 mol% of **26a**, **27a** was obtained in 88% yield in 5 h (Table 11, entry 2). Further study has been done in presence of oxygen, supplied through $O_2$-balloon, but the reaction was disinclined to produce better yield (Table 11, entry 3). Reactions were performed in presence of different bases such as DMAP, TEA, DABCO, $PPh_3$, TBD, *t*BuOK and TMG (Table 11, entry 5-10).

**Table 11:** Optimization for the catalyst [a]




| Entry | Catalyst **26** | Time (h) | Yield [%][b] |
|---|---|---|---|
| 1[c] | **26a** | 7.5 | 91 |
| 2 | **26a** | 5 | 88 |
| 3[d] | **26a** | 12 | 69 |
| 4 | **26b** | 24 | 5 |
| 5 | **26c** | 24 | 10 |
| 6 | **26d** | 24 | 15 |
| 7 | **26e** | 24 | nr |
| 8 | **26f** | 7 | 60 |
| 9 | **26g** | 6 | 70 |
| 10 | **26h** | 5.5 | 95 |
| **11[e]** | **26h** | **6** | **96** |
| 12[f] | **26h** | 8 | 82 |




[a]Reactions were performed in THF (0.2 M) relative to **25a** (0.2 mmol) in the presence of 20 mol% of catalyst **26** at 25 °C. [b]Yield refers to the column purified products. [c]Reaction was performed with 30 mol% of **26a.** [d]Reaction was performed in presence of $O_2$. [e]Reaction was carried out 10 mol% of **26h**. [f]Reaction was carried out 5 mol% of **26h**.

Among these all, TMG **26h** was found to be most effective with 95% of yield within 5.5 h (Table 11, entry 10). To understand the efficiency of TMG as a catalyst for this reaction, we decreased the catalyst loading from 20 mol% to 10 mol% and 5 mol% (Table 11, entry 11, 12). We noticed that 10 mol% of TMG is almost equally efficient like 20 mol% of it and able to produce 96% yield of product **27a** within 6 h (Table 11, entry 11), hence considered as the optimized condition. $^1H$ and $^{13}C$ NMR spectra of compound **27a** are given below (Figure 48).

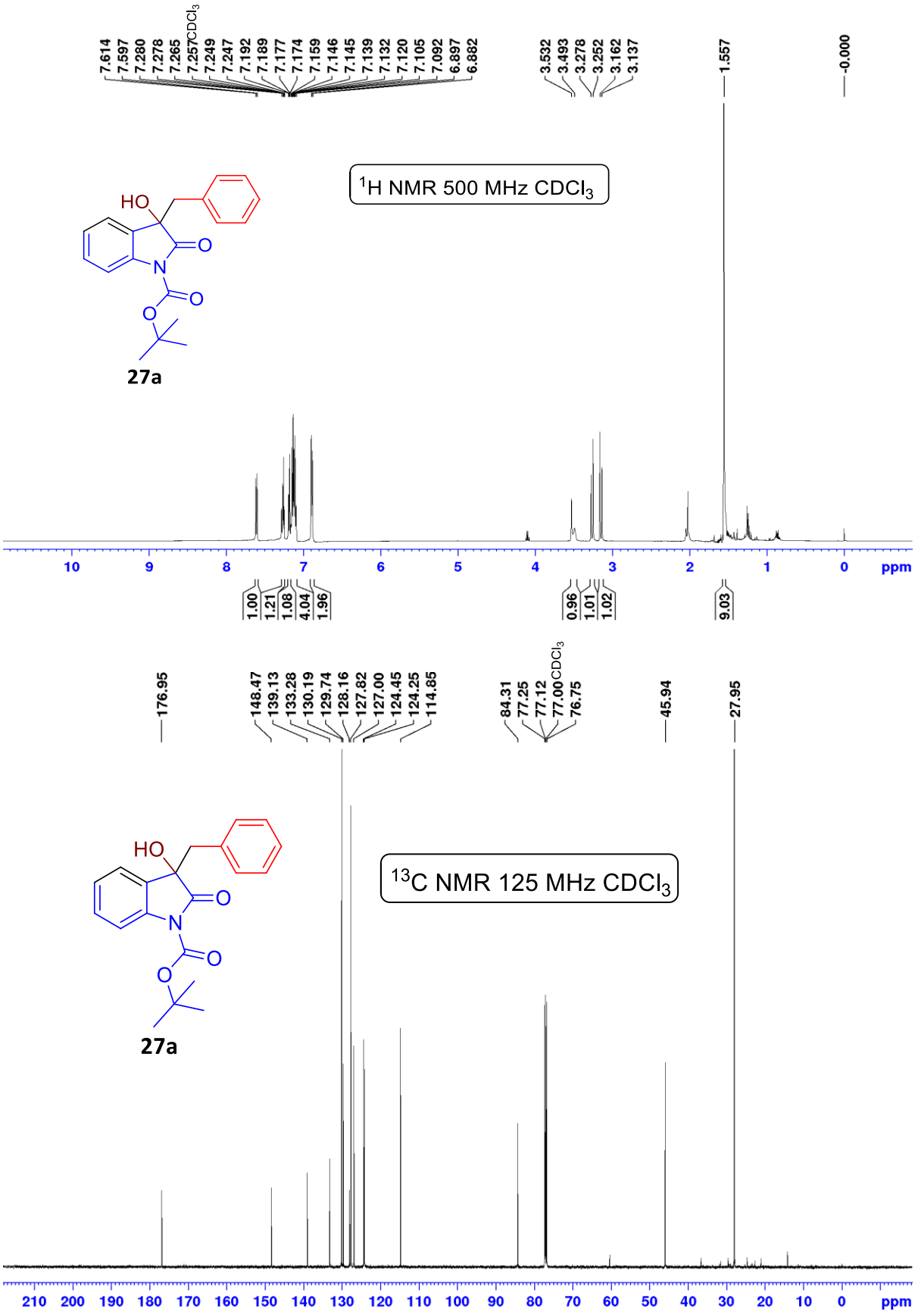
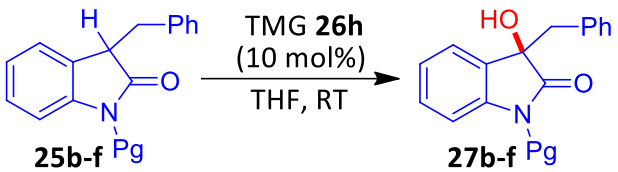



**Figure 48:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **27a**.

Soonafter, we tested the efficiency of our reaction with various *N*-protecting groups such as Boc, acetyl, tosyl, benzyl and methyl. Electron withdrawing protecting group like acetyl and tosyl furnished 91% and 90% yield within 3 h and 7 h respectively (Table 12, entry 1, 2). Electron donating protecting group such as benzyl and methyl showed poor result and after 12 h generated 59 and 56% yield respectively (Table 12, entry 3, 4).

**Table 12:** Optimization for N-Protecting groups [a]




| Entry | Pg | Time (h) | Yield [%][b] |
|---|---|---|---|
| 1 | Ac (**25b**) | 3 | 91 (**27b**) |
| 2 | Ts (**25c**) | 7 | 90 (**27c**) |
| 3 | Bn (**25d**) | 12 | 59 (**27d**) |
| 4 | Me (**25e**) | 12 | 56 (**27e**) |
| 5 | H (**25f**) | 24 | 59 (**27f**) |
| 6[c] | Me (**25e**) | 12 | 35 (**27e**) |
| 7[c] | H (**25f**) | 24 | 51 (**27f**) |

[a] Reactions were performed in THF (0.2 M) relative to **25b-f** (0.2 mmol) in the presence of 10 mol% of **26h** at 25 °C. [b] Yield refers to the column purified products. [c] Reaction was performed at 60 °C.

Electron withdrawing protecting groups worked better compare to electron donating protecting groups, which can be explained by the higher acidity of the α-proton of 3-alkylated oxindoles in the former case. In the absence of a protecting group, the reaction is much slower and within 24 h product **27** was obtained with only 59% of yield (Table 12, entry 5). A rise in temperature to 60 °C showed a decrease in yield in the case of methyl-protected and unprotected 3-alkylated oxindoles (Table 12, entry 6,7), which is expressing a directly proportional relation between the amount of dissolve oxygen in THF and the yield of the reaction. Outcome of the investigation on different protecting group showed that previously used Boc-protected substrate worked better than any other protecting group (Table 11, entry 11). Some of the compounds $^{1}H$ and $^{13}C$ NMR spectra have shown in Figure 49 and 50.

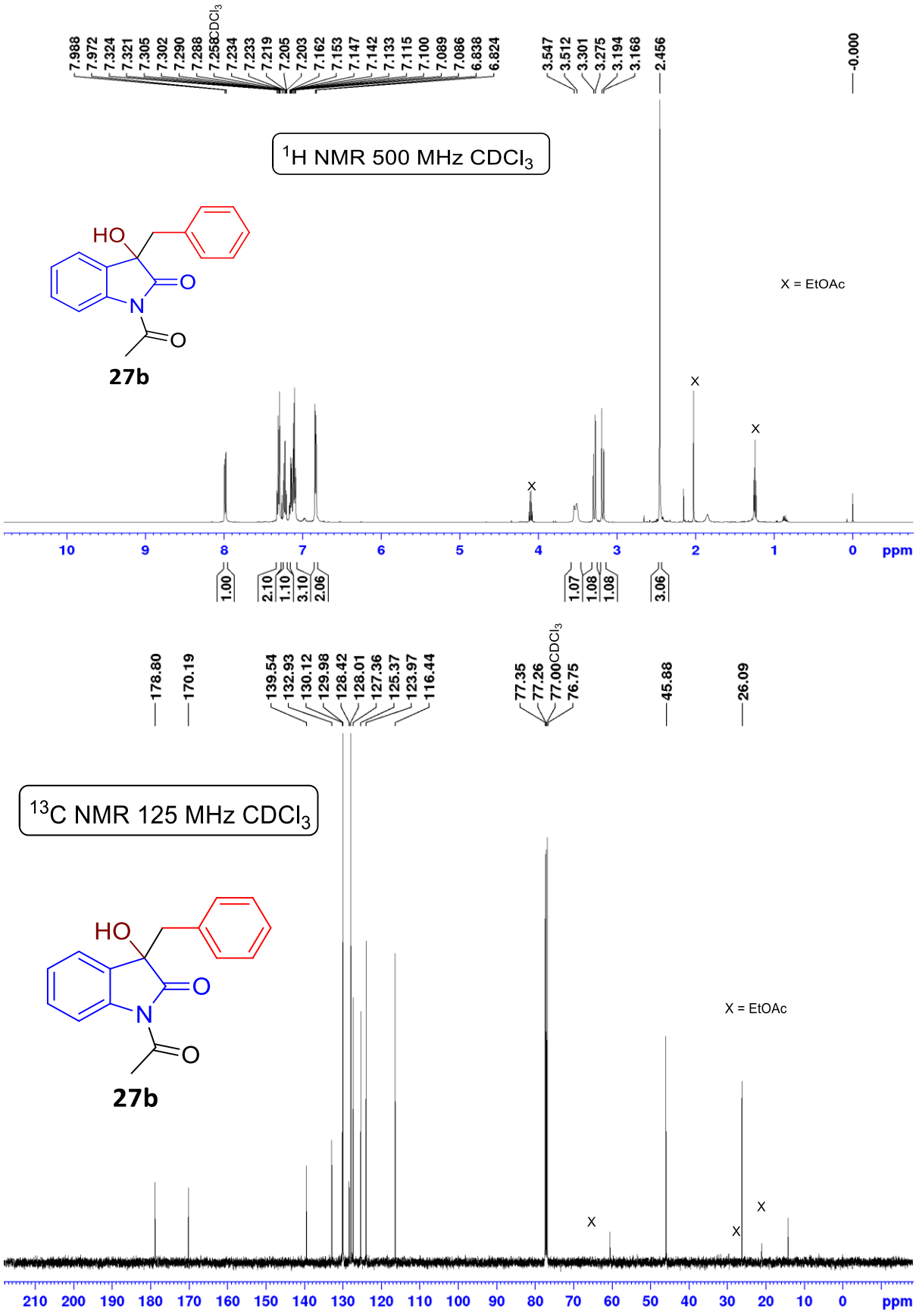



**Figure 49:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **27b**.

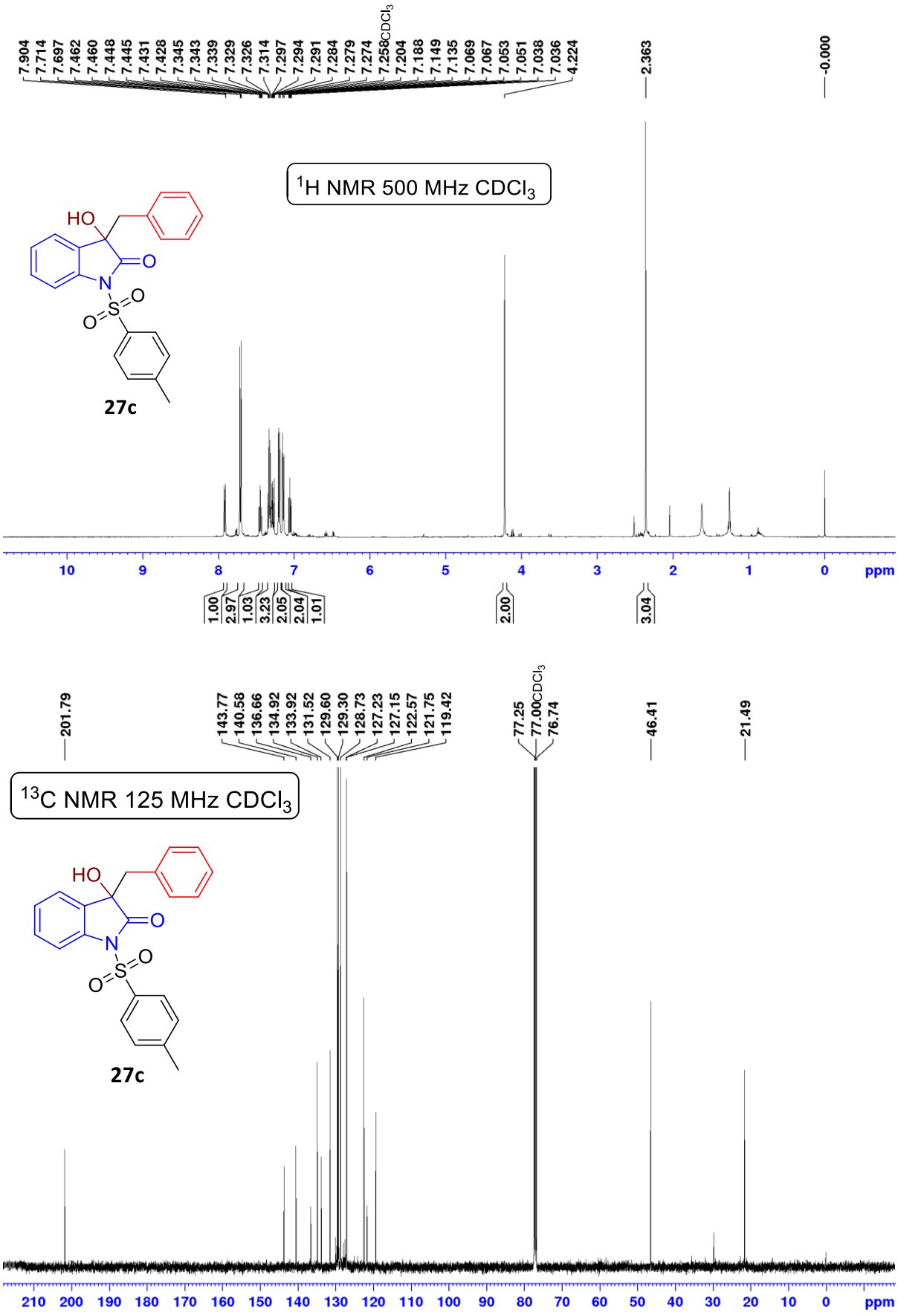
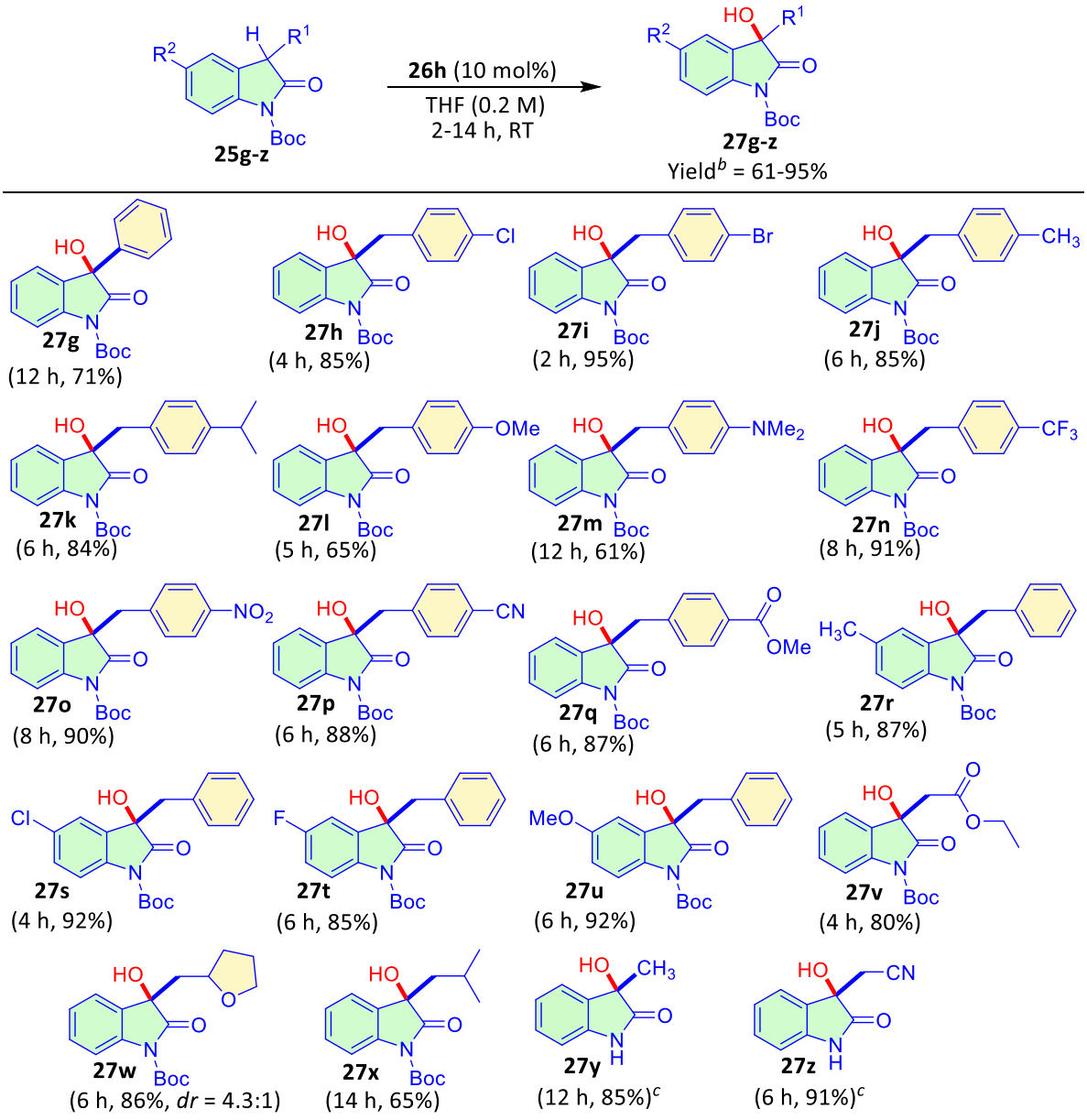



**Figure 50:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **27c**.

### *5.2.3 Substrate Scope of the C-H oxidation Reaction:*

Prompted by the result obtained in optimized condition, different substrates **25g-z**, obtained by varying the alkyl group $R^1$ and changing the substitution $R^2$ on aromatic ring of oxindole core of 3-alkylated oxindole, were utilized for the synthesis 3-substituted-3-hydroxyoxindoles **27g-z** (Table 13).

**Table 13**: Reaction substrate scope [a]




[a] Reactions were performed in THF (0.2 M) relative to **25g-z** (0.2 mmol) in the presence of 10 mol% of catalyst **26h** at 25 °C. [b] Yield refers to the column purified products. [c] Reaction was performed without protecting group at N (Pg=H).

Direct phenyl substitution at 3-position of oxindole worked well with 71% of yield within 12 h. Benzylic alkyl group, with *para* substituents like halogen (chloro and bromo) and alkyl groups (methyl and isopropyl), furnished desired products **27h-k** with excellent yield ranging from 84% to 95% (Table 13). Electron donating groups such as -OMe and $-NMe_2$ at *para* position of aromatic ring at $R^1$ resulted **27l** and **27m** with moderate yields of 65% and 61% respectively (Table 13). On the other hand, electron withdrawing groups such as $-CF_3$, $-NO_2$, -CN and $-CO_2Et$ at *para* position of aromatic ring at $R^1$ served better to produce **27n-q** with the yield ranging from 87 to 91% (Table 13). Introduction of different functional group at $R^2$ position such as methyl, chloro, fluoro, methoxy exhibited well tolerance and furnished **27r-u** with yields ranging from 85% to 92%. Various functional groups at $R^1$ such as ester, furan, iso-butyl groups underwent smooth oxidation to form desired products **27v-x** in good yields (Table 13). Methyl and nitrile group at $R^2$ position of unprotected 3-alkylated indole worked in an excellent manner to achieve **27y** and **27z** with 85% and 91% yield respectively (Table 13).

We have confirmed the structure and relative stereochemistry of compound **27t** using X-Ray crystallography (Figure 51).

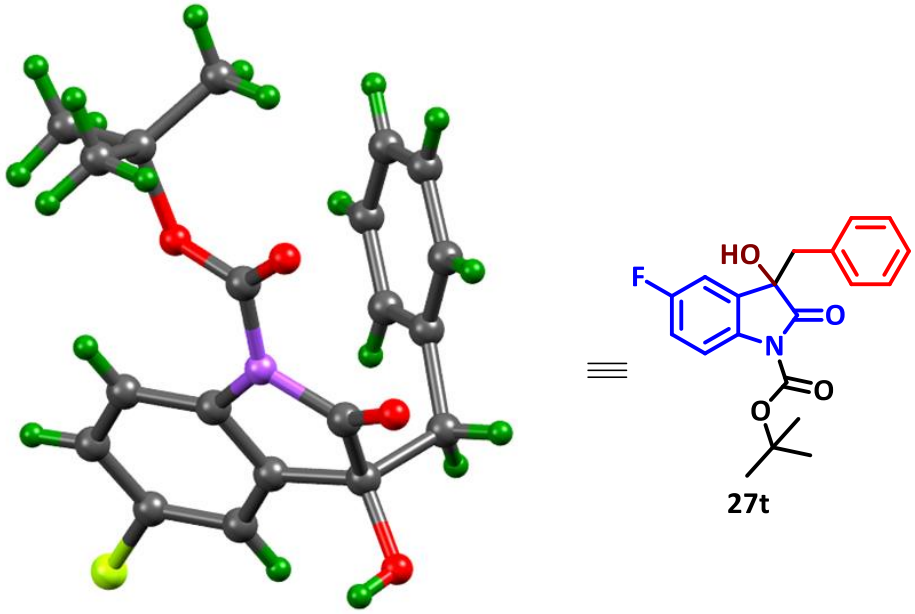



**Figure 51:** Crystal structure of *tert*-Butyl 3-benzyl-5-fluoro-3-hydroxy-2-oxoindoline-1-carboxylate **(27t)**.

The synthesized compounds in Table 13 have characterized using NMR, IR and HRMS. Some of their $^1H$ and $^{13}C$ NMR spectra are given below (Figure 52-56).

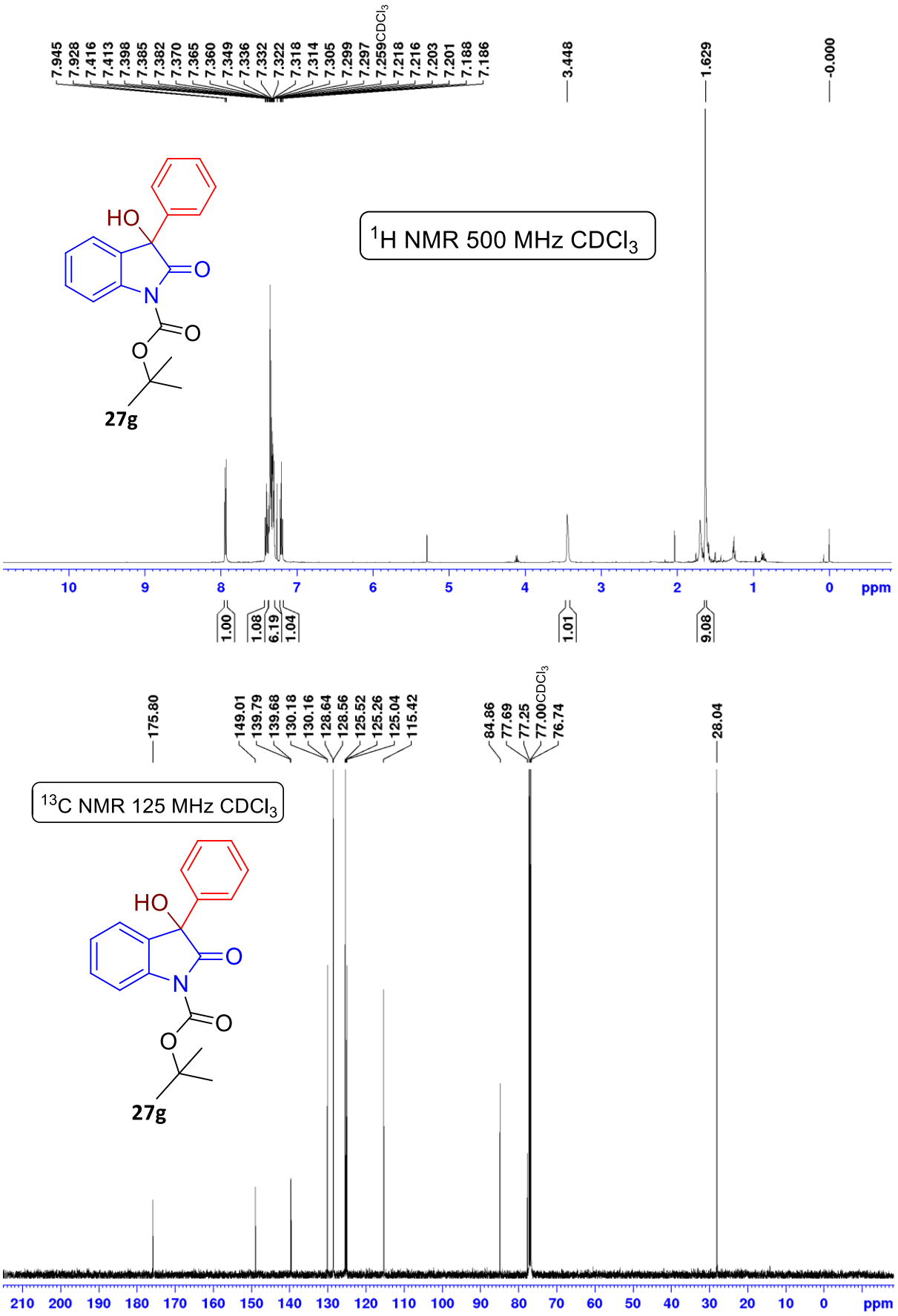



**Figure 52:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **27g**.

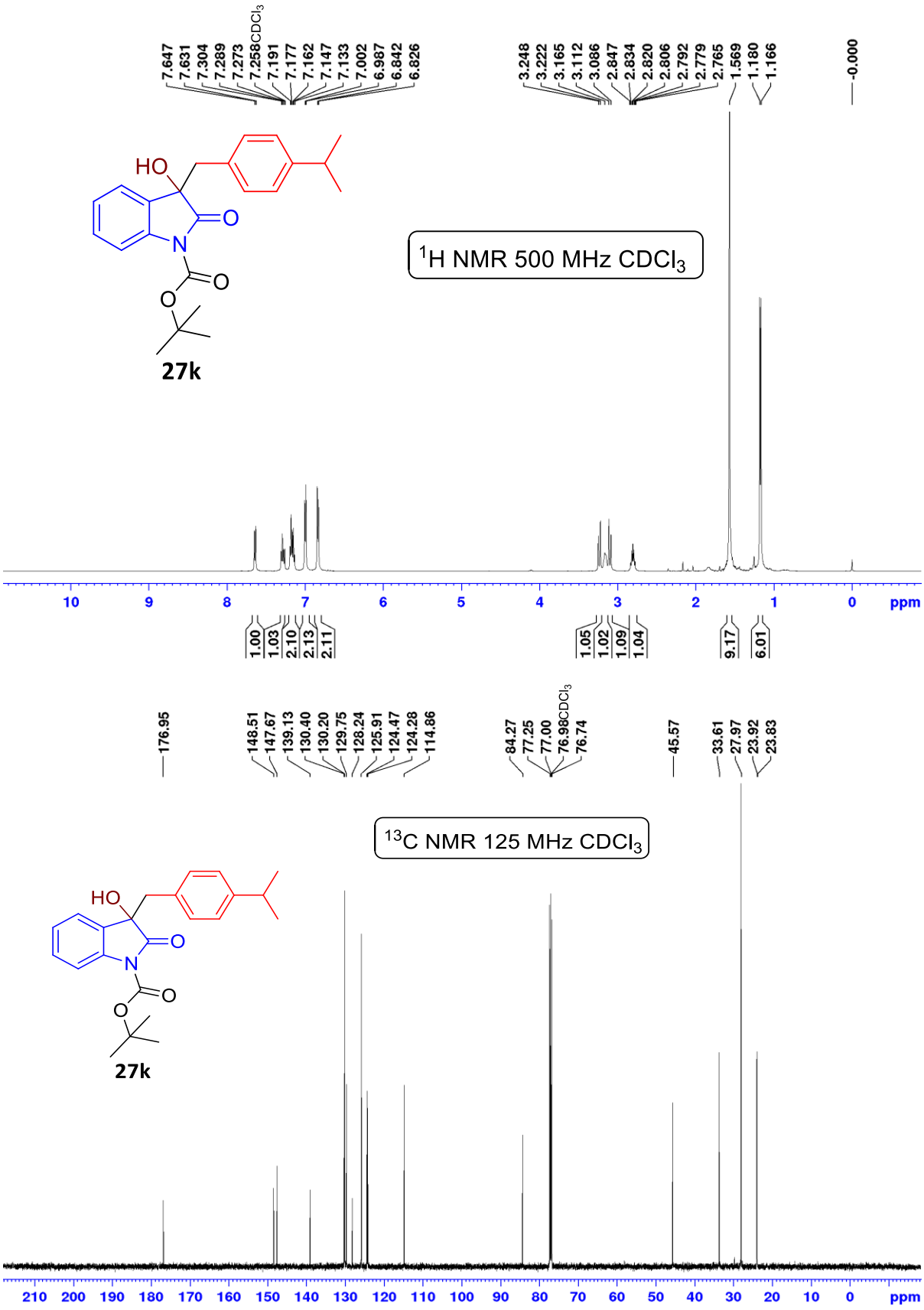



**Figure 53:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **27k**.

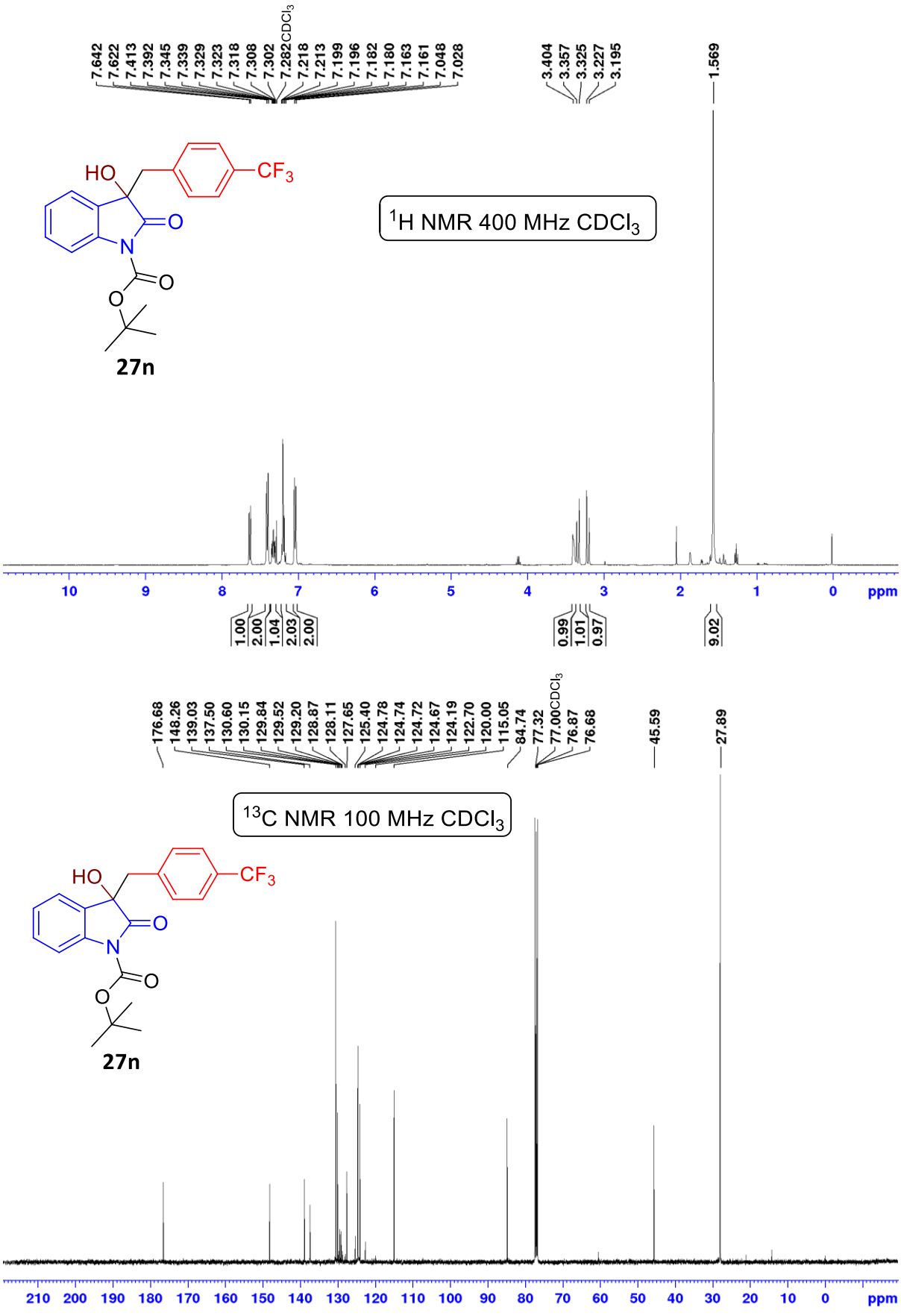



**Figure 54:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **27n**.

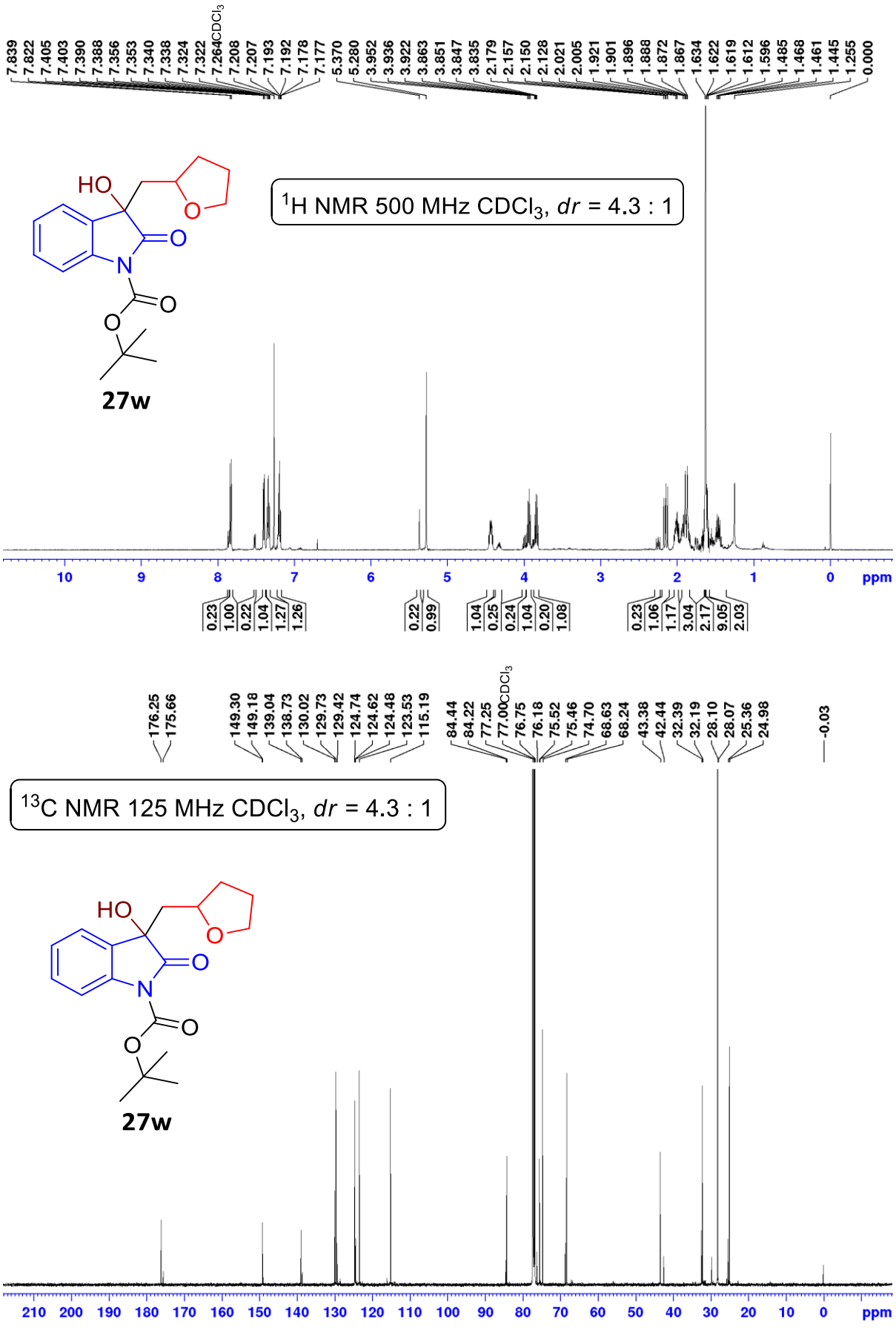



**Figure 55:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **27w**.

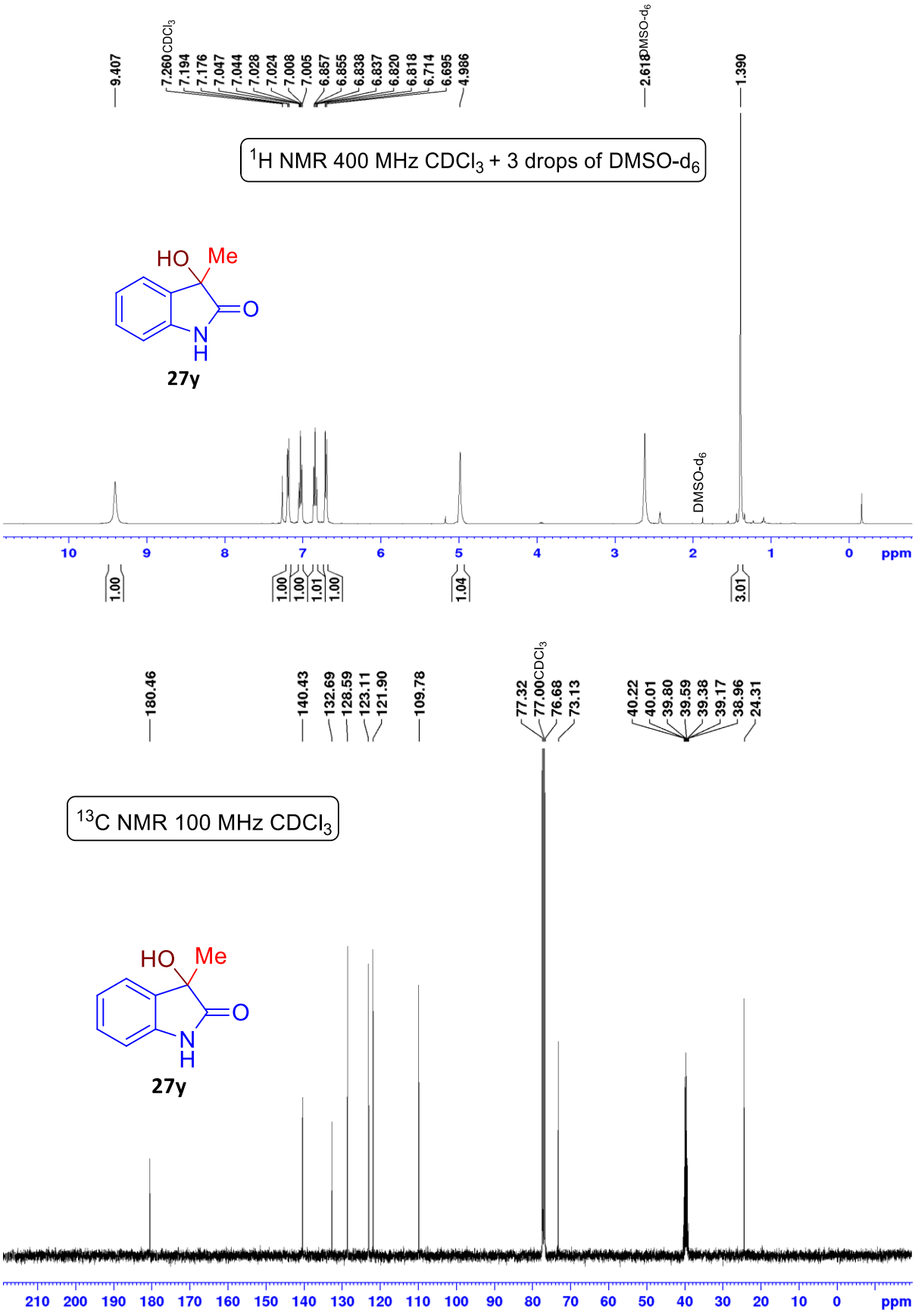
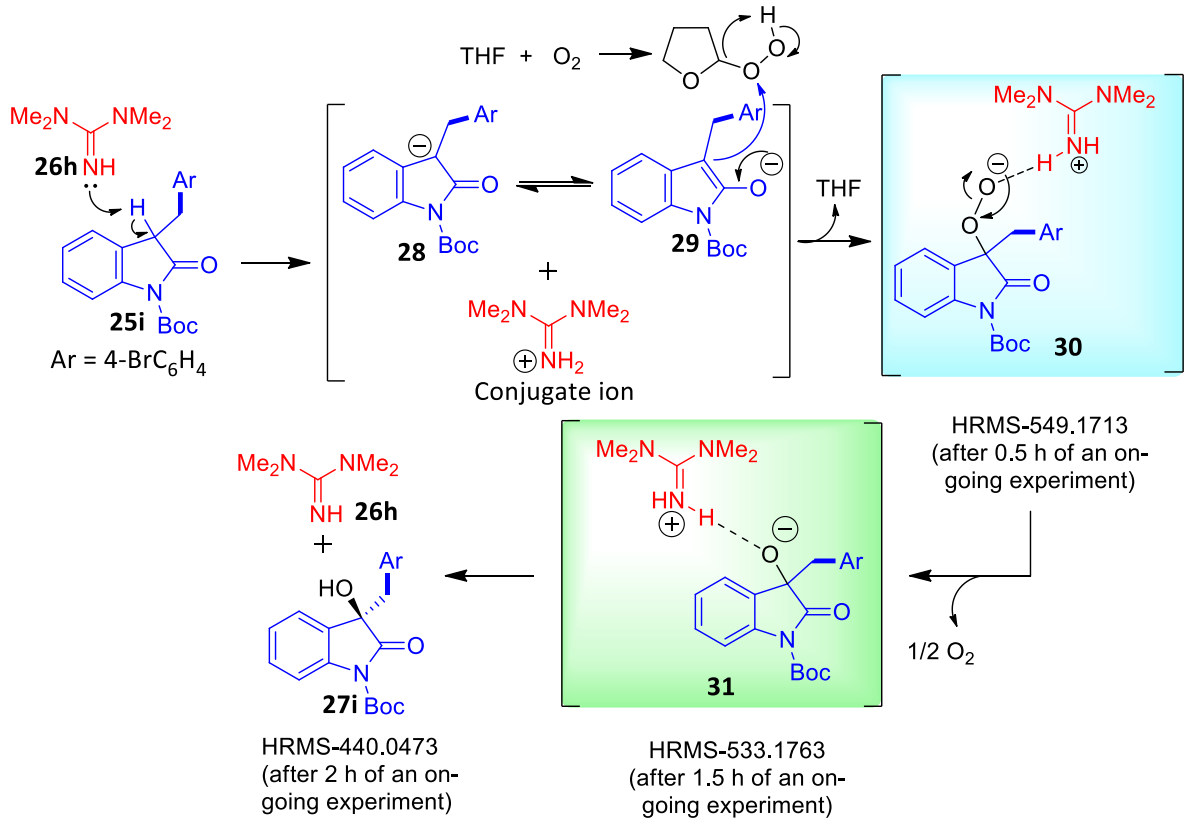



**Figure 56:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **27y**.

### 5.2.4 *Mechanistic Rationale:*

On the basis of the controlled experiments and literature studies, a possible mechanism of hydroxylation of 3-alkylated oxindoles to 3-substituted-3-hydroxyoxindoles is proposed (Scheme 27). TMG **26h** initially abstract the acidic proton from **25i** to produce a carbanion **28** which can also exist as enol tautomer **29**. Carbanion **5** reacts with dissolved $O_2$ which is in the form of hydroperoxyl form with THF,[40] resulting in the formation of an ion pair **30** consist a peroxide anion and conjugate acid of **26h**. Formation of ion pair **30** was confirmed with ESI-HRMS spectrum (m/z 549.1713), injecting after 0.5 hours of an on-going reaction of **25i** with **26h** (10 mol%) in THF at room temperature. Ion pair **30** again transform spontaneously to more stable ion pair **31** consist an oxyanion and conjugate acid of **26h**, *via* losing an oxygen molecule.



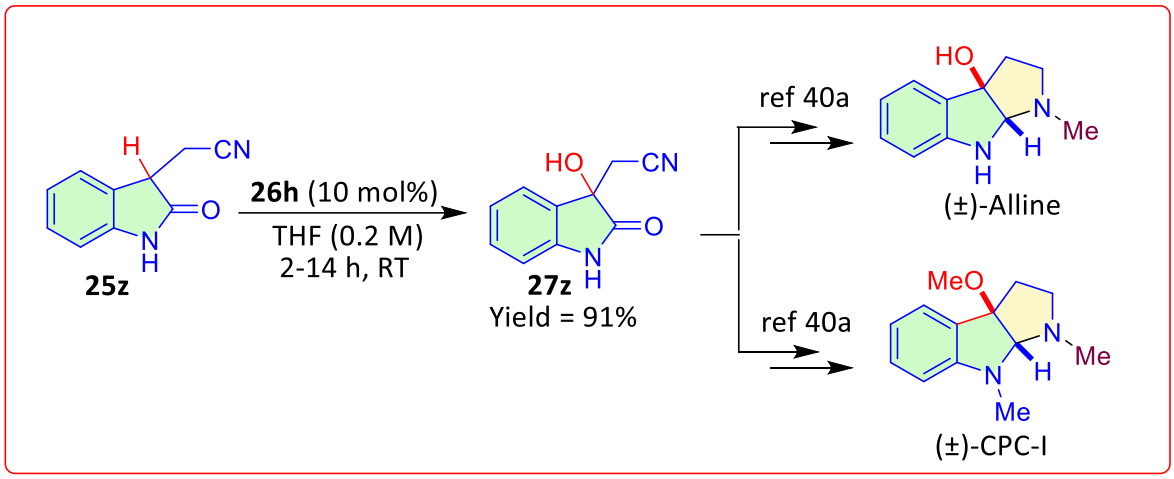

**Scheme 27**: Plausible mechanism based on the controlled HRMS experiment.

The reaction mixture was injected for HRMS after 1.5 h of an on-going experiment, showed the generation of ion pair **31** (m/z 533.1763). Finally, an injection of sample from the same on-going experiment after 2 h, ESI-HRMS revealed the production of final product **27i** (m/z 440.

0473) with a major peak. Therefore, protonation of ion pair **31** produced the final product **27i** and reproduced the catalyst **26h**, which undergoes a recyclization.

### 5.2.5 *Formal Total Synthesis of (±)-Alline and (±)-CPC-I:*

Komakine et. al. in 2005, isolated 3-cyanomethyl-3-hydroxyoxindoles (**27z**) from the seeds extract of *Rheum maximawiczii* which was used as folk medicine and treatment of auto immune diseases.[41] Previous report showed that the synthesis of **27z** involved a greater number of steps, use of hazardous chemicals, low yield and longer time.[42a,b]




**Scheme 28**: Formal total synthesis of (±)-alline and (±)-CPC-1.

Using our protocol, we have successfully synthesized 3-cyanomethyl-3-hydroxyoxindoles (**27z**) with 91% of yield within 6 h (Table 13). To demonstrate the wide synthetic application of this methodology, we embraced the formal synthesis of few natural products like (±)-alline and (±)-CPC-I (Scheme 28).[42a]

$^{1}$H and $^{13}$C NMR spectra of compound **27z** have depicted below (Figure 57).

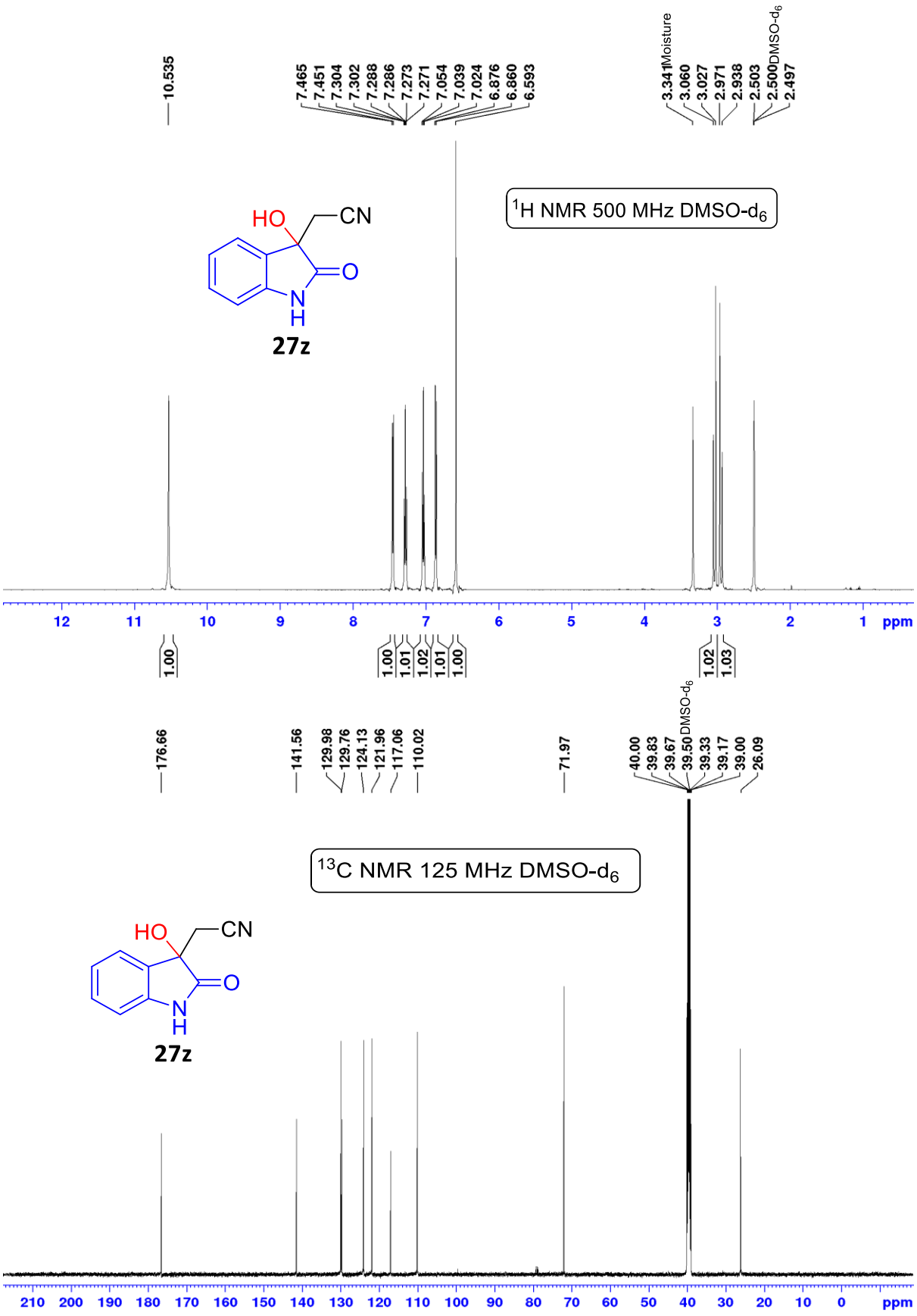
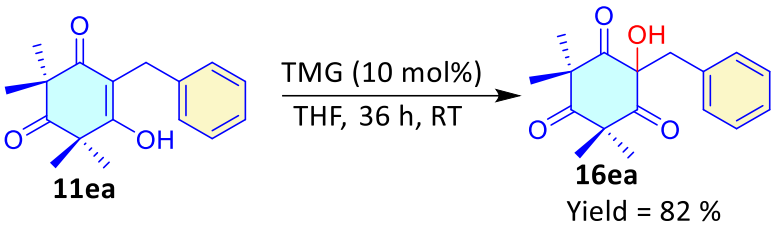



**Figure 57:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **27z**.

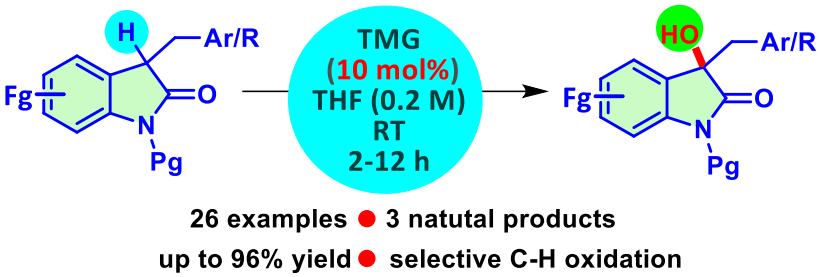
### *5.2.5 C-H Oxidation of 4-Benzylsyncarpic Acid:*

4-Benzylsyncarpic acid **11ea** was oxidized using this present protocol. Oxidized product **16ea** was obtained with 82% yield within 36 h at room temperature (Scheme 29).




**Scheme 29**: C-H oxidation of 4-benzylsyncarpic acid **11ea**.

## *5.3 Conclusions:*




In summary we have developed a novel synthetic strategy for the synthesis of 3-substituted-3-hydroxy oxindoles without any external oxidising agent. Reaction proceeds in presence of organic base TMG and the little amount of dissolved oxygen in THF acts as an oxidant at room temperature. Using our strategy, we have developed an atom economic and simple route for synthesis of a natural product **27z** and formal total synthesis of (±)-alline and (±)-CPC-I.

# 6. Self-Induced [4+2]-Cycloaddition Reaction to Access Bioactive Tetrahydro-carbazoles Scaffolds

## *6.1 Introduction*

The significance of Diels-Alder reaction in organic synthesis is undeniable till today, because the reaction has the potency of fasten two active synthons, as diene and dienophile to generate six membered cyclic structure with several stereo-centers in a single concerted step.[23a,43] Diels-Alder reaction is particularly alluring on account of its high atom economy and as it provides efficient access to various synthetically useful heterocycles like 1-aminohydrocarzoles which can be constructed by choosing 3-vinylindole as a diene partner and electron withdrawing group substituted olefin as a dienophile partner.[44] Recently, 1-aminohydrocarbazoles grab the attention of synthetic chemist because of its presence in many natural products and drug candidates.

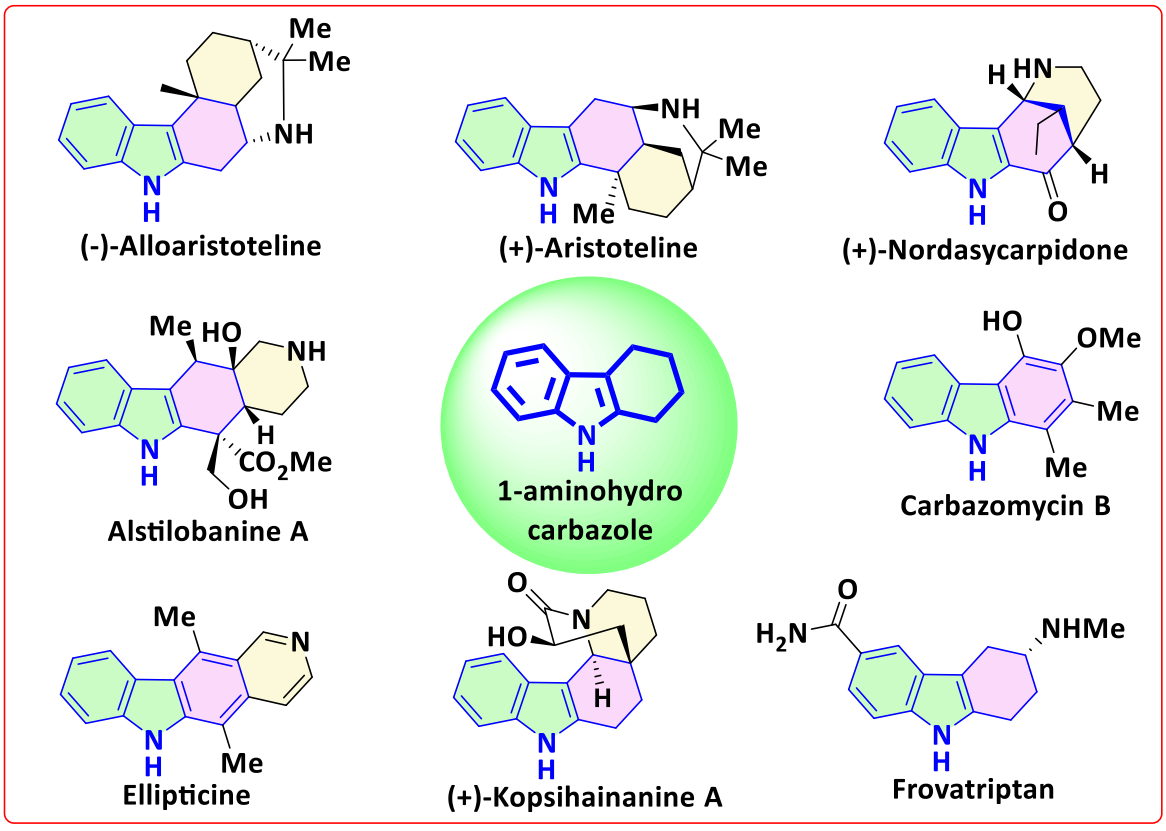
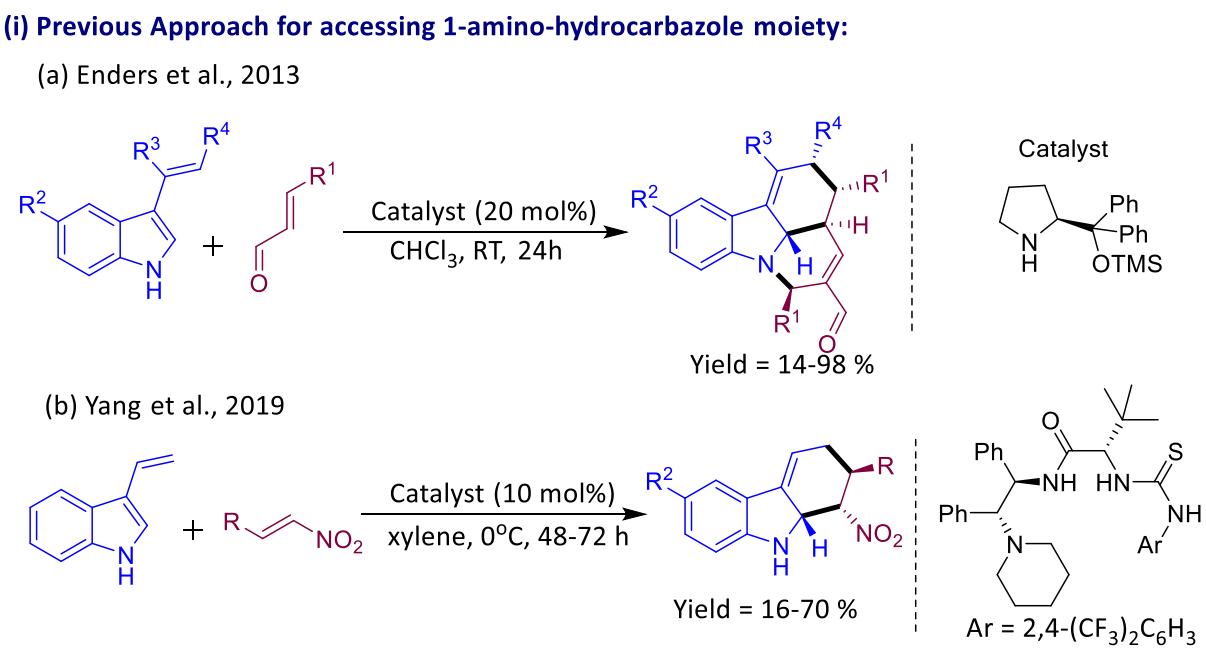
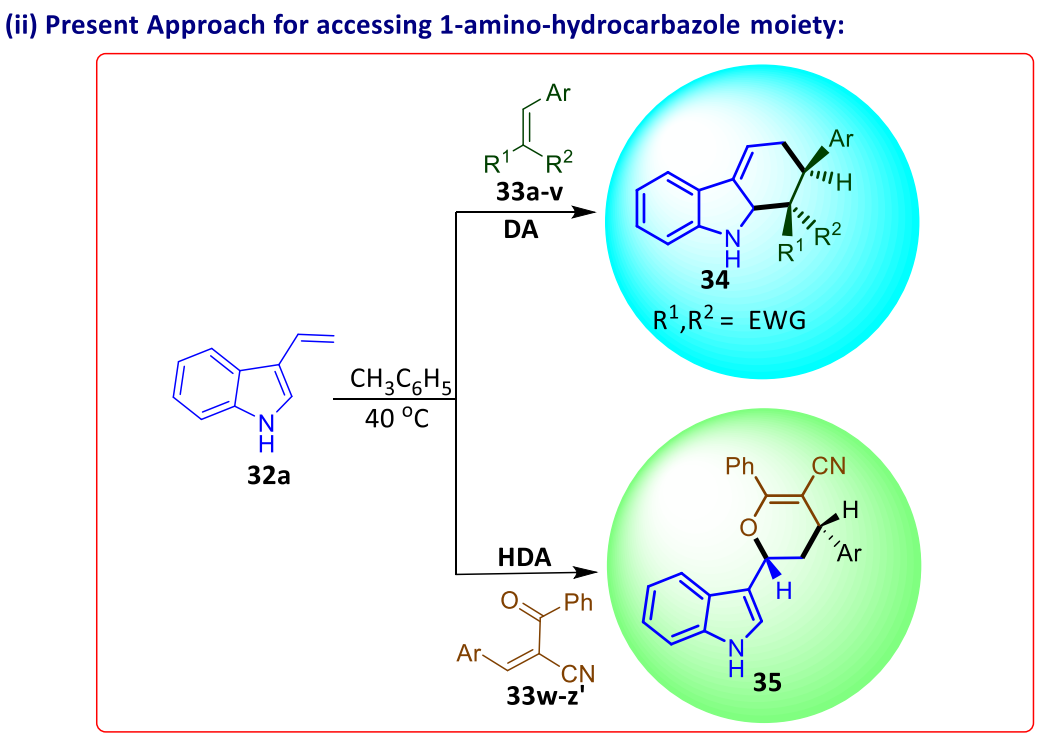



**Figure 58**: 1-Aminohydrocarbazole core containing natural products and bioactive molecules.

The 1-aminohydrocarbazoles is frequently observed as a subset of biologically active akuammiline alkaloids like (-)-alloaristoteline, (+)-aristoteline, (+)-nordasycarpidone,

carbazomycin B, frovatriptan, alstilobanine A, (+)-kopsihainanine A, ellipticine etc. (Figure 58).[45a-g]




**Scheme 30:** Reaction design with 3-vinyl indole as diene and dienophile.

Hence there is a huge demand to develop a synthetic methodology for the preparation of 1-aminohydrocarbazoles. In the year 2013, Enders and co-workers reported an organocatalytic

asymmetric three-component triple cascade of 3-vinylindoles with $\alpha,\beta$-unsaturated aldehydes following a sequential Diels-Alder reaction followed by *aza*-Michael reaction and intramolecular aldol reaction yielding partially unsaturated tetracyclic pyridocarbazole derivatives (Scheme 30).[46] In the year 2019, Guo and co-workers have developed a methodology involving a Diels-Alder reaction between 3-vinylindoles and nitroolefins promoted by multiple hydrogen bond catalyst based on thiourea to achieve 1-aminohydrocarbazoles (Scheme 30).[44] Though the good enantioselectivity of the products brought this protocol to its own greatness, but a low yield and requirement of long time, decreased the glory of this protocol. Even though, 3-vinylindoles are the source of a diene in most of the cases, but it has the potency to act as a dienophile using the exocyclic vinylic olefin in [4+2]-cycloaddition rection.[47] An inverse-electron-demand Diels-Alder reaction between a hetero-diene and 3-vinylindole constructs biologically active indole-containing heterocycles (Figure 59), hence it has proven to be an important reaction.[48a-c]

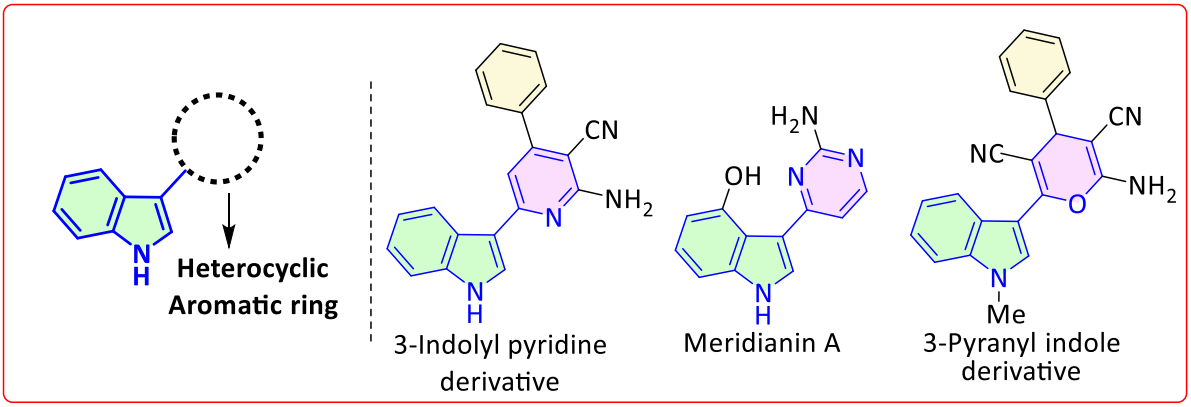



**Figure 59**: Biologically active indole-containing heterocycles.

Despite of a huge demand of such methodology, no protocol has developed till now where 3-vinylinodoles can act as either a diene or a dienophile depending on the choice of opponent molecule. Hence, developing of such protocols and overcoming the associated inherent challenges are urgently required. To fulfil this task and in developing a methodology to construct 1-aminohydrocarbazoles or indole-containing heterocycles, we designed a self-promoted diastereoselective Diels-Alder reaction of 3-vinylindoles with electron withdrawing group substituted olefins and in the same reaction conditions, $\alpha,\beta$-unsaturated ketones undergo a self-promoted hetero-Diels-Alder reaction with 3-vinylindoles. Within this design scheme, a

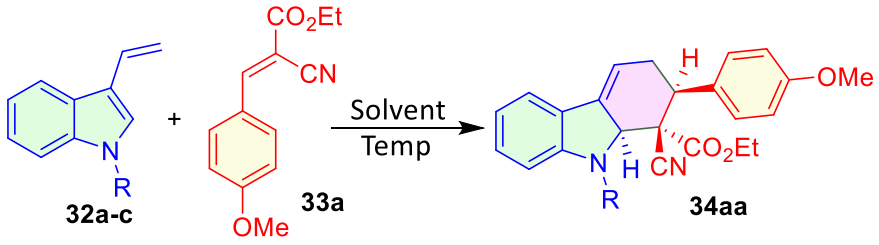
self-activated Diels-Alder reaction between 3-vinylinoles and activated olefins, affording 1-aminohydrocarbazole derivatives.

## 6.2 Results and Discussion

### 6.2.1 Reaction Preliminary Optimization

In begaining of our investigation, we envisioned one-pot synthesis of 1-aminohydrocarbazole, by treating vinyl indole **32a**, 4-methoxy benzaldehyde and ethyl-2-cyanoacetate, in presence of catalytic amount of *L*-proline in DCM. This one-pot strategy did not work well and unable to furnish our desired 1-aminohydrocarbazole derivative.

**Table 14**: Solvent optimization and *N*-protecting group screening [a]




| entry | R | solvent | *t* (°C) | *t* (h) | yield (%)[b] | *dr*[c] |
|---|---|---|---|---|---|---|
| 1 | -H | $CH_2Cl_2$ | 25 | 24 | 15 | >95:1 |
| 2 | -H | $CH_2Cl_2$ | 40 | 24 | 24 | >95:1 |
| 3 | -H | $CHCl_3$ | 25 | 24 | 19 | >95:1 |
| 4 | -H | $CHCl_3$ | 40 | 24 | 28 | >95:1 |
| 5 | -H | DCE | 25 | 24 | 15 | >95:1 |
| 6 | -H | DCE | 40 | 24 | 22 | >95:1 |
| 7 | -H | $C_6H_6$ | 25 | 24 | 47 | >95:1 |
| 8 | -H | $C_6H_6$ | 40 | 17 | 78 | >95:1 |
| 9 | -H | $CH_3C_6H_5$ | 25 | 24 | 40 | >95:1 |
| **10** | **-H** | **$CH_3C_6H_5$** | **40** | **16** | **85** | >95:1 |
| 11 | -H | $CF_3C_6H_5$ | 25 | 24 | 22 | >95:1 |
| 12 | -H | $CF_3C_6H_5$ | 40 | 17 | 27 | >95:1 |
| 13 | -H | EtOH | 25 | 24 | 36 | >95:1 |
| 14 | -H | EtOH | 40 | 16 | 41 | >95:1 |
| 15 | -H | DMSO | 25 | 24 | 23 | >95:1 |
| 16 | -H | DMSO | 40 | 16 | 26 | >95:1 |
| 17[d] | $-CH_3$ | $CH_3C_6H_5$ | 40 | 24 | 56 | >95:1 |
| 18[e] | -Boc | $CH_3C_6H_5$ | 40 | 24 | nr | – |

[a]Reactions were performed in solvent (0.2 M) with 1.2 equiv. of **33a** relative to **32a** (0.2 mmol). [b]Yield refers to the column purified products. [c]*dr* determined by NMR spectroscopy. [d]Formation of product **34ba** was observed. [e]nr = no reaction.

With the initial disappointment we explored other alternative where isolated proline catalyzed Knoevenagel product **33a** was treated with **32a** in DCM solvent at 25 $^{o}$C and within 24 h we found the formation our desired Diels-Alder product **34aa** with only 15% of yield as single diastereomer (Table 14, entry 1). A slight hike in temperature up to 40 $^{o}$C, increased the yield by 9% with no change in diastereoselectivity (Table 14, entry 2). To understand the solvent effect in our reaction, we have screened different solvents like chloroform, DCE, benzene, toluene, trifluoro toluene, ethanol, DMSO in both 25 $^{o}$C and 40 $^{o}$C (Table 14, entry 3-16). After an ample screening of solvents, the best yield (85%) of **34aa**, as a single diastereomer, was found in toluene at 40 $^{o}$C within 16 h (Table 14, entry 10). To understand the contribution of different protecting group on nitrogen of 3-vinylindole, we tested our hypothesis with *N*-methyl and *N*-Boc protected 3-vinyl indoles, in case of *N*-methyl-3-vinyl indole **32b**, desired product **34ba** was formed with 56% yield as a single diastereomer, whereas *N*-Boc-3-vinyl indole **32c**, did not lead to the formation of expected product **34ca** (Table 14, entry 17, 18). The ability to enhance the rate of a Diels Alder reaction via increasing the electron density in the diene partner by a conjugate nitrogen, has drastically reduced in presence of an electron withdrawing group on it and therefore in the particular case of **32c**, the reaction did not proceed further (Table 14, entry 18).

Even though we able to synthesized Diels-Alder adduct **34aa** with a good yield, but we observed that **34aa** was unstable in room temperature and decomposing during column chromatography. To overcome this issue, we have done acid catalyzed rearrangement of compound **34aa**, before loading it in column, to achieve a stable isomer **36aa**.

$^{1}$H and $^{13}$C NMR spectra of compound **34aa** have depicted below (Figure 60). COSY and NOESY NMR spectra of compound **34aa** also shown in Figure 61.

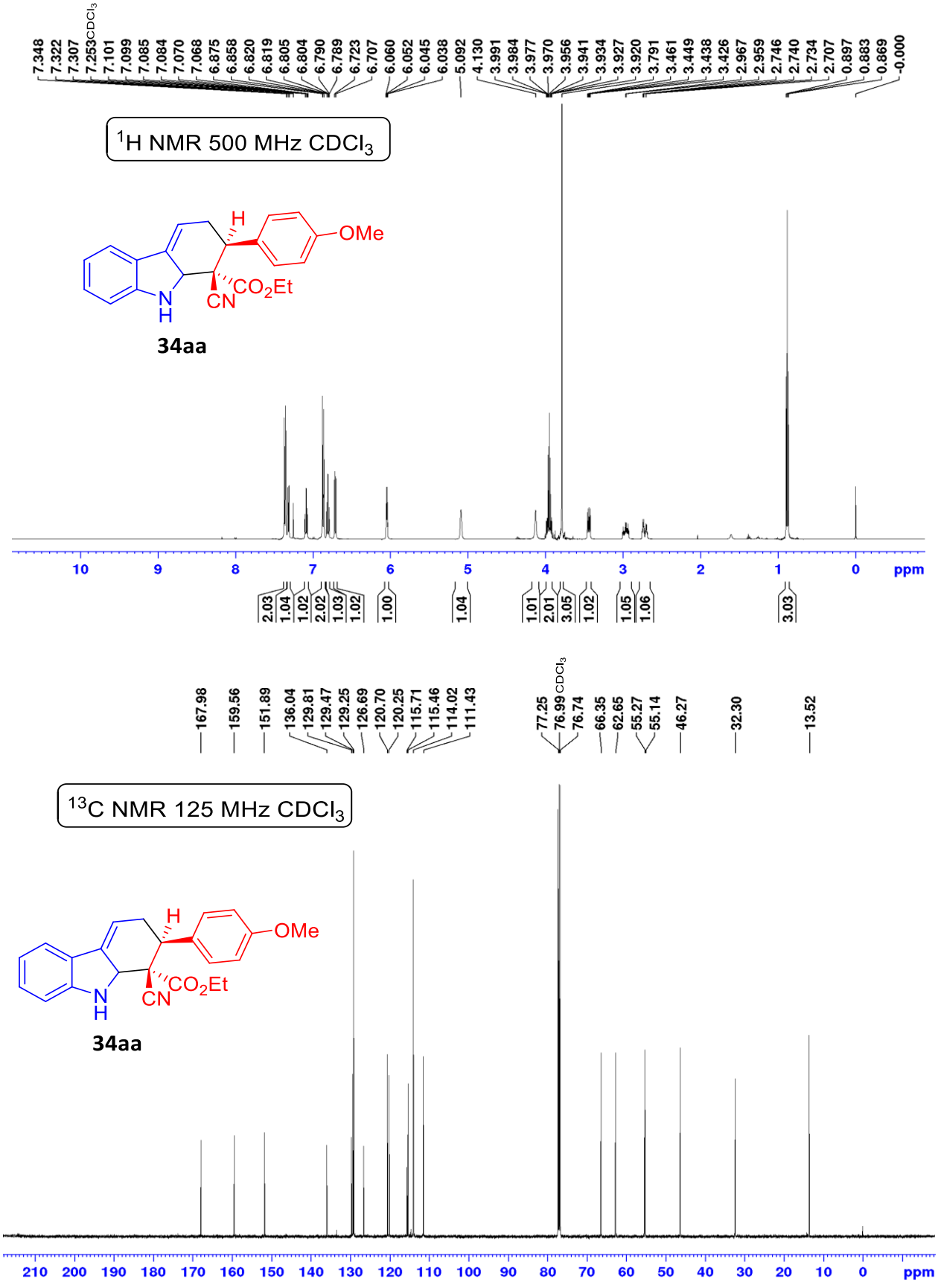



**Figure 60:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **34aa**.

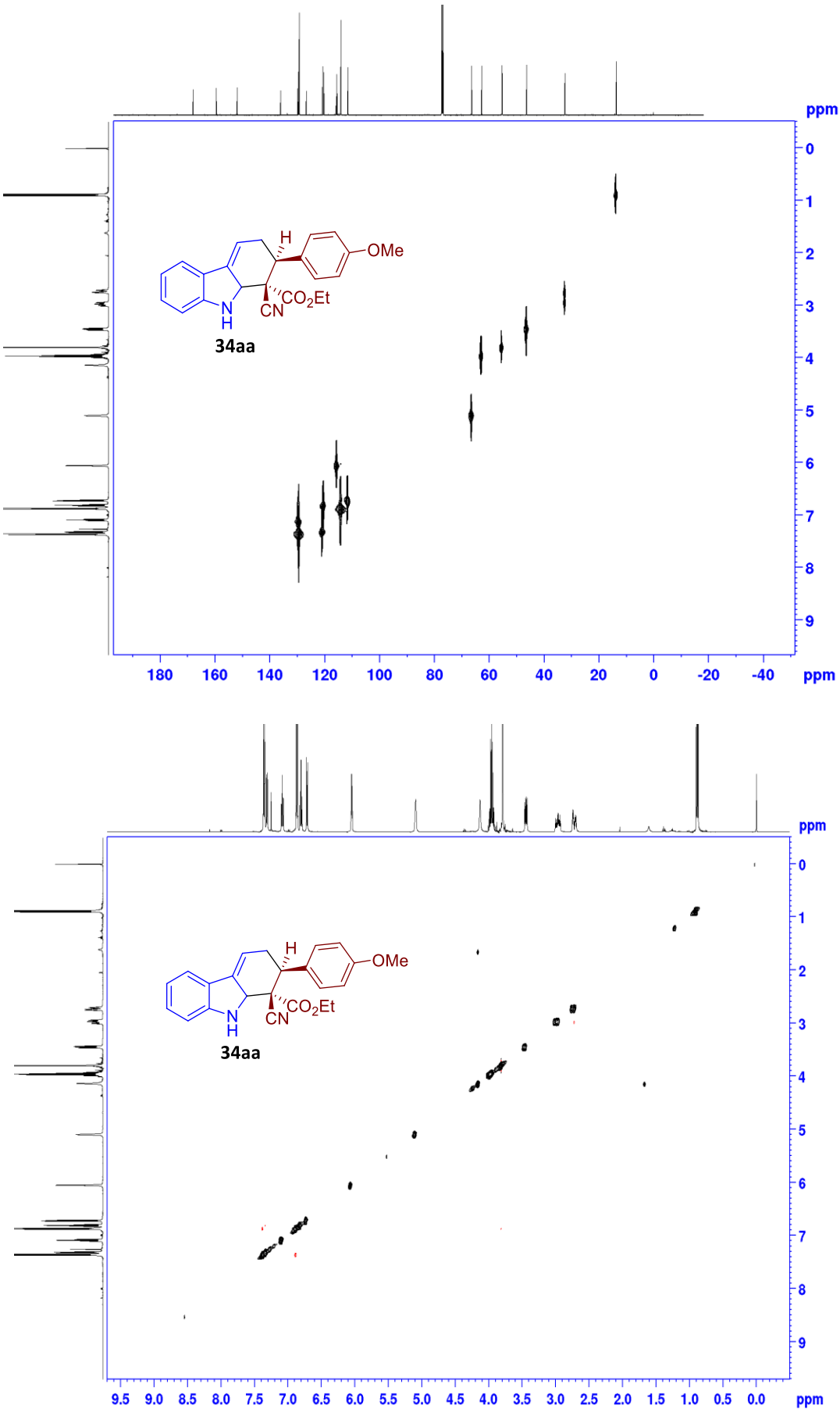
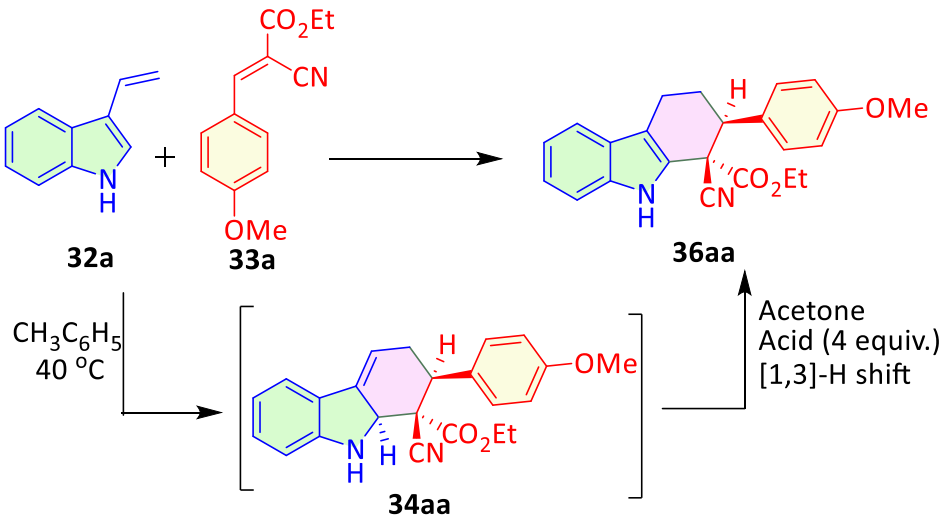



**Figure 61:** Hetero COSY and NOESY spectrum of product **34aa**.

A further acid catalyzed [1,3]-H shift rearrangement of **34aa** has done to stop the decomposition of it at room temperature by achieving more stable aromatic product **36aa** which was easy to isolate through column chromatography. For the same, 1 ml of acetone and 4 equiv. of acid were added to the rection mixture after completion of the previous step and stirred for some time to furnish product **36aa**. A mini optimization has done to find out suitable acid for this step (Table 15). We found that 4M HCl has served better than others (86% yield with single diastereomer) and reached to competition within half an hour (Table 15, entry 3).

**Table 15**: Optimization of suitable acid for rearrangement of the product [a]




| entry | acid | *t* (h) | yield (%)[b] | *dr*[c] |
|---|---|---|---|---|
| 1 | TFAA | 1 h | 84 | > 95:1 |
| 2 | $CH_3COCl$ | 2 h | 86 | > 95:1 |
| 3 | 4 M HCl | 0.5 h | 86 | > 95:1 |

[a]Reactions were performed in $CH_3C_6H_5$ (0.2 M) with 1.2 equiv. of **33a** relative to **32a** (0.2 mmol), after completion of the reaction, 1 ml of acetone and 4 equiv. of acid were added to it and stirred for sometime. [b]Yield refers to the column purified products. [c]*dr* >95:1 determined by NMR spectroscopy.

$^{1}H$ and $^{13}C$ NMR spectra of compound **36aa** have show in Figure 62.

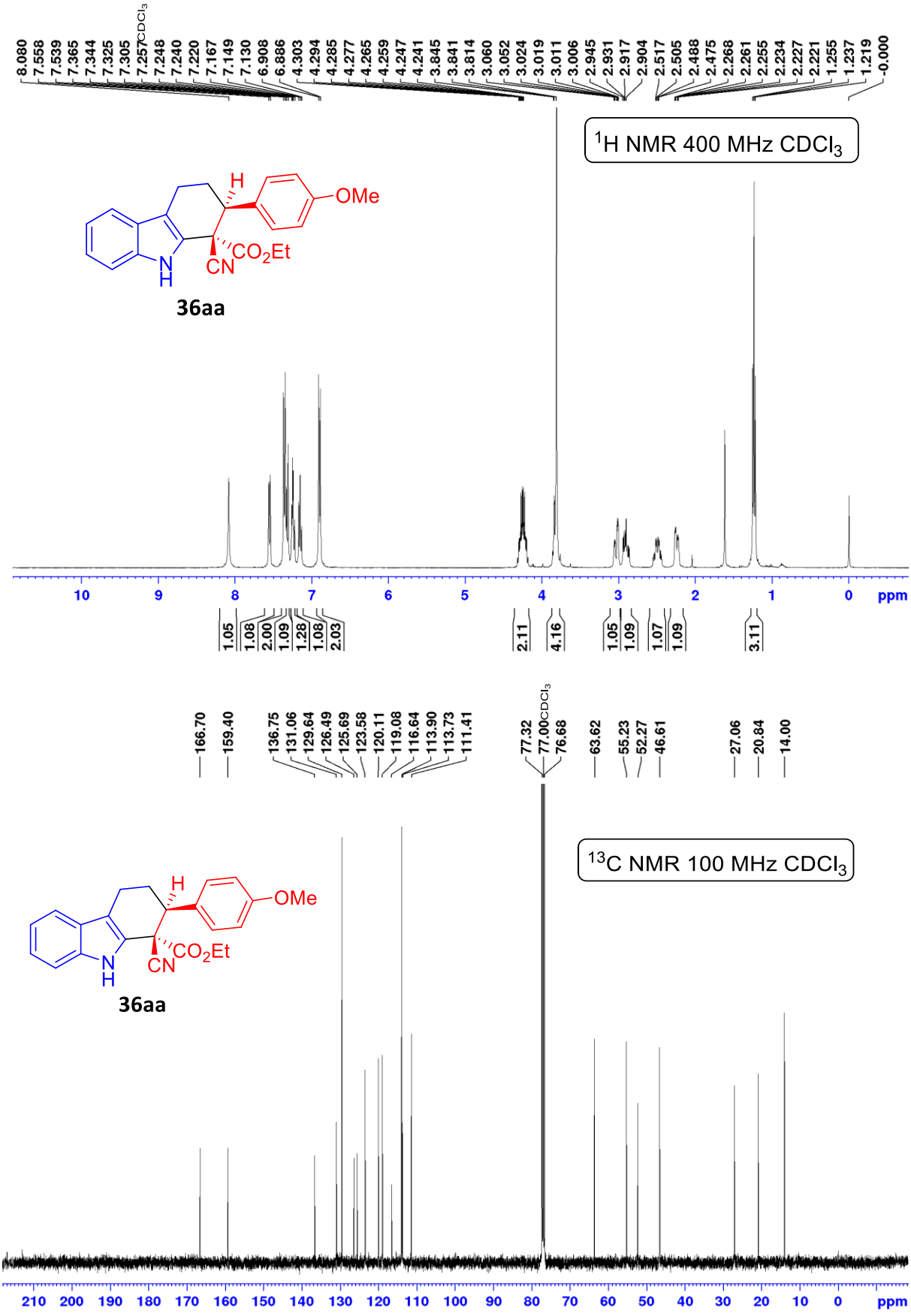



**Figure 62:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **36aa**.

After confirming the structure of the compound **36aa** using NMR, IR, HRMS, we have further confirmed the structure of compound **36aa** using X-Ray crystallography (Figure 63).

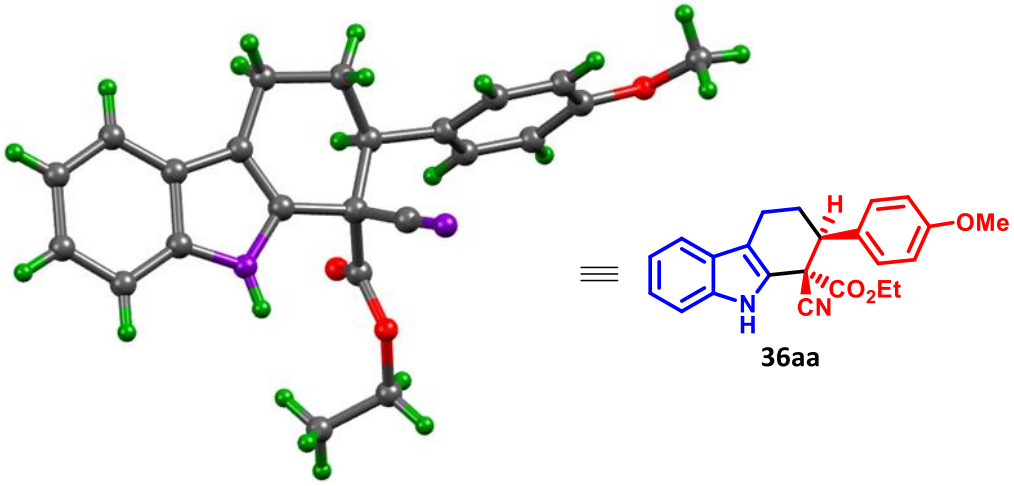



**Figure 63:** Crystal structure of ethyl-1-cyano-2-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate **(36aa).**

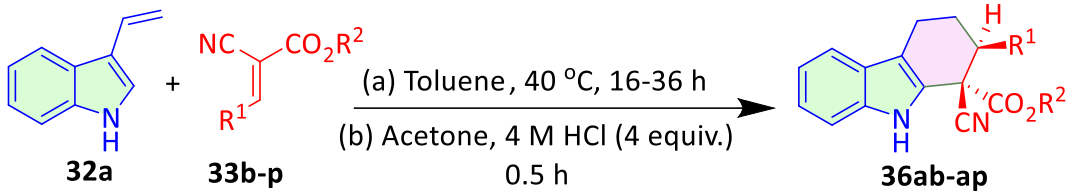
### *6.2.2 Substrate Scope of Alkylidene Cyano-ester:*

With optimized condition in hand, we exploited our protocol for the construction of different 1-aminohydocarbazole derivatives by using different alkylidene cyano-ester **33b-p** as the source of dienophile (Table 16).

We started our substate scope with various electronically diverse substituents on the phenyl ring of the dienophile, which provides the corresponding carbazole derivatives **36ab-ap** bearing two quaternary stereogenic centers, in moderate to good yield and excellent diastereoselectivity (Table 16, entry 1-11). The rate and the yield of the reaction gradually decreased from *p*-F, *p*-Cl to *p*-Br substituents (18 h, 20 h, 22 h and 88%, 81%, 77% respectively) on the $R^1$ position, which illustrates a clear effect of steric factor on this reaction (Table 16, entry 2-4). Electron donating groups like methyl and isopropyl at the *p*-position of the phenyl ring at $R^1$, reacted smoothly leading to the desired product with high yield of 87 and 82% respectively (Table 16, entry 5, 6). To get a clear understanding about the substituents position on phenyl ring at $R^1$, we performed the reaction with *p*-$CF_3$, *m*-$CF_3$ and *o*-$CF_3$ substituents and we found a gradual increase in reaction time (17 h, 20 h and 24 h respectively) and decrease in yield (82%, 71% and 62% respectively) (Table 16, entry 7-9). Usually, the presence of electron withdrawing groups on dienophile facilitate the Diels-Alder reaction, but EWG on the *p*-position of phenyl ring at $R^1$, impedes the reaction by nullifying the electron withdrawing capacity of CN and $CO_2Et$ groups which are present on the other terminal of the

olefin and hence, lesser yields were achieved in case of *p*-CN and *p*-$NO_2$ substituted phenyl ring (78% and 71% respectively) (Table 16, entry 10, 11).

**Table 16**: Substate scope for alkylidene cyano-ester [a]




**32a** **33b-p** **36ab-ap**

| entry | $R^1$ | *t* (h) | yield (%)[b] | *dr*[c] |
|---|---|---|---|---|
| 1 | $R^1$ = Ph, $R^2$ = $C_2H_5$ (**33b**) | 22 | 83 | >95:1 |
| 2 | $R^1$ = 4-$FC_6H_4$, $R^2$ = $C_2H_5$ (**33c**) | 18 | 88 | >95:1 |
| 3 | $R^1$ = 4-$ClC_6H_4$, $R^2$ = $C_2H_5$ (**33d**) | 20 | 81 | >95:1 |
| 4 | $R^1$ = 4-$BrC_6H_4$, $R^2$ = $C_2H_5$ (**33e**) | 18 | 77 | >95:1 |
| 5 | $R^1$ = 4-$MeC_6H_4$, $R^2$ = $C_2H_5$ (**33f**) | 18 | 87 | >95:1 |
| 6 | $R^1$ = 4-$CH(CH_3)_2C_6H_4$, $R^2$ = $C_2H_5$ (**33g**) | 22 | 82 | >95:1 |
| 7 | $R^1$ = 4-$CF_3C_6H_4$, $R^2$ = $C_2H_5$ (**33h**) | 17 | 84 | >95:1 |
| 8 | $R^1$ = 3-$CF_3C_6H_4$, $R^2$ = $C_2H_5$ (**33i**) | 20 | 71 | >95:1 |
| 9 | $R^1$ = 2-$CF_3C_6H_4$, $R^2$ = $C_2H_5$ (**33j**) | 24 | 68 | >95:1 |
| 10 | $R^1$ = 4-$CNC_6H_4$, $R^2$ = $C_2H_5$ (**33k**) | 20 | 78 | >95:1 |
| 11 | $R^1$ = 4-$NO_2C_6H_4$, $R^2$ = $C_2H_5$ (**33l**) | 20 | 71 | >95:1 |
| 12 | $R^1$ = 2-furyl, $R^2$ = $C_2H_5$ (**33m**) | 22 | 61 | >95:1 |
| 13 | $R^1$ = $CH_2CH(CH_3)_2$, $R^2$ = $C_2H_5$ (**33n**) | 48 | 62 | >95:1 |
| 14 | $R^1$ = 4-$BrC_6H_4$, $R^2$ = (3*R*,6*R*)-3-isopropyl -6-methylcyclohexane **(33o)** | 36 | 65 | 0.8:1 |
| 15[d] | $R^1$ = (5*S*)-2,2-dimethyl-1,3-dioxolane, $R^2$ = $C_2H_5$ **(33p)** | 32 | 42 | 7.1:1 |

[a]Reactions were performed in $CH_3C_6H_5$ (0.2 M) with 1.2 equiv. of **33** relative to **32a** (0.2 mmol), after completion of the reaction, 1 ml of acetone and 0.2 ml of 4M HCl were added to it and stirred for 0.5 h. [b]Yield refers to the column purified products. [c]*dr* determined by NMR spectroscopy. [d]Intermediate **34ap** was isolated.

Interestingly, furyl and aliphatic groups also well proceeded affording desired product with 61% and 62% yields respectively (Table 16, entry 12, 13). For understanding the selectivity of this rection, we used chiral auxiliary **33o** as the dienophile precursors, the cyclized product was proven to be feasible in a moderate yield of 65% with almost 1:1 diastereomeric ratio (Table 16, entry 14). In case of another chiral auxiliary **33p**, 42% of yield of **34ap** was achieved with almost 7:1 diastereomeric ratio, a further acid hydrolysis has not done as it leaded to the decomposition instead of the formation of **36ap** (Table 16, entry 15). Some of the compounds $^1H$ and $^{13}C$ NMR spectra have shown in Figure 64-67.

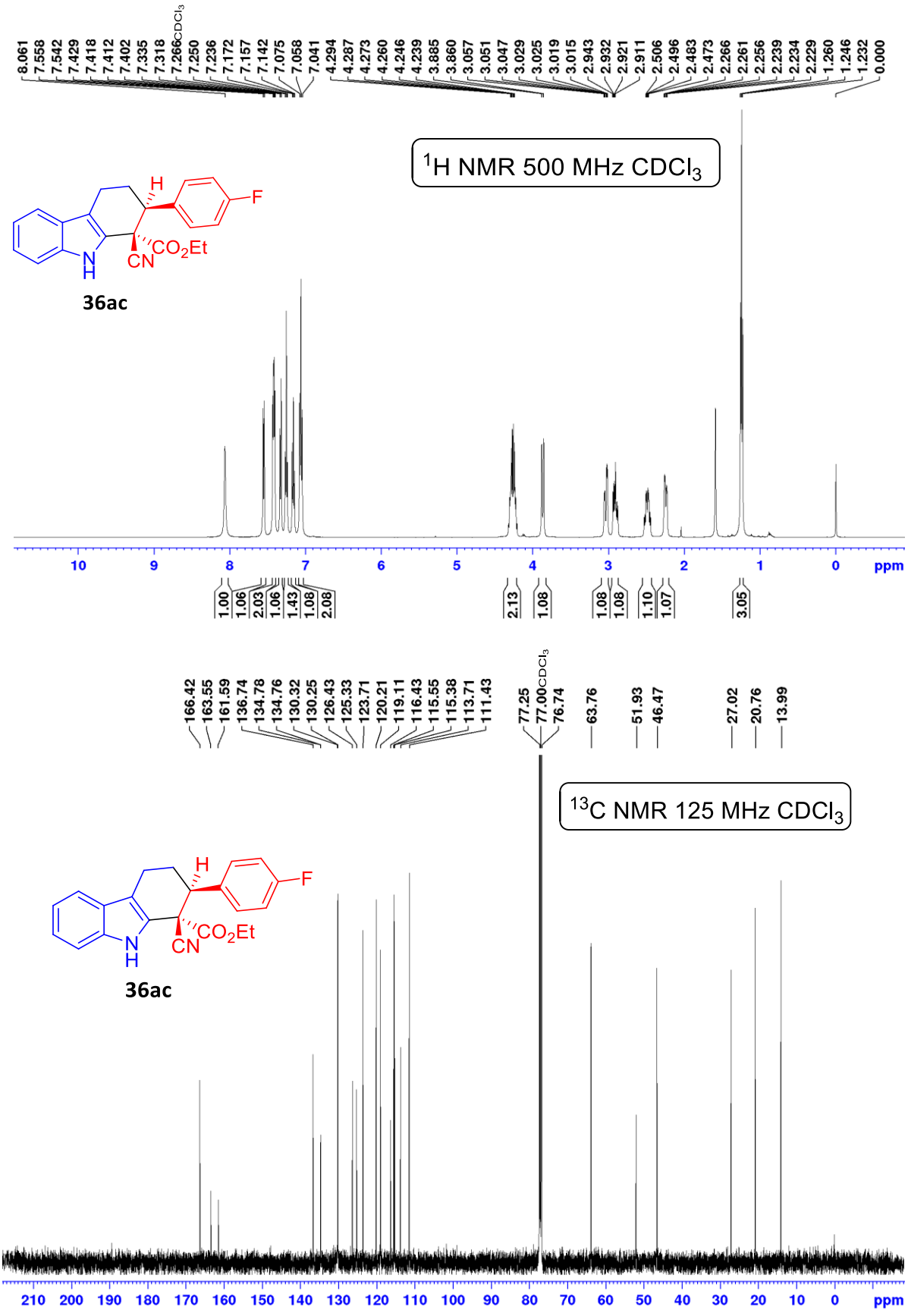



**Figure 64:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **36ac**.

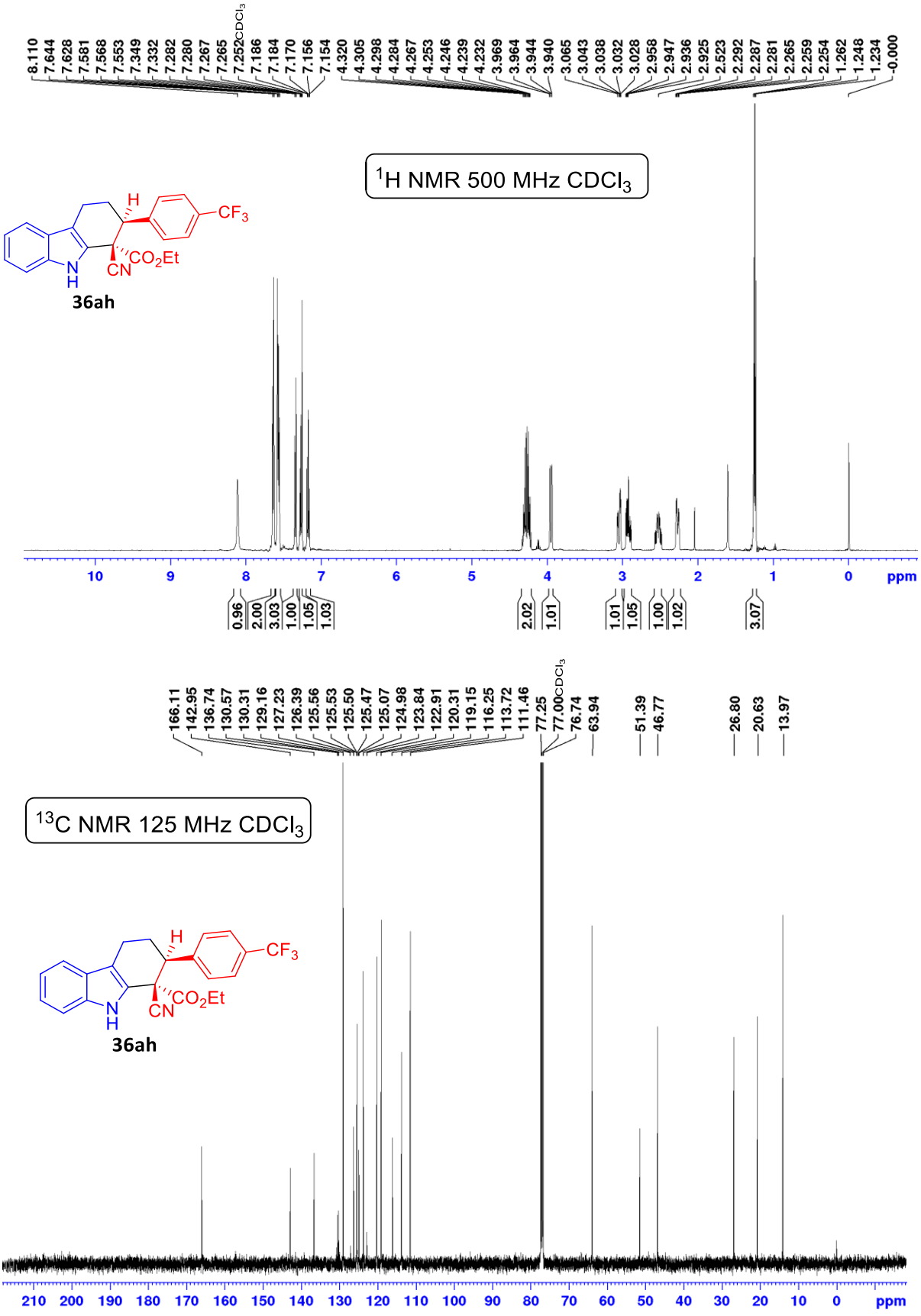



**Figure 65:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **36ah**.

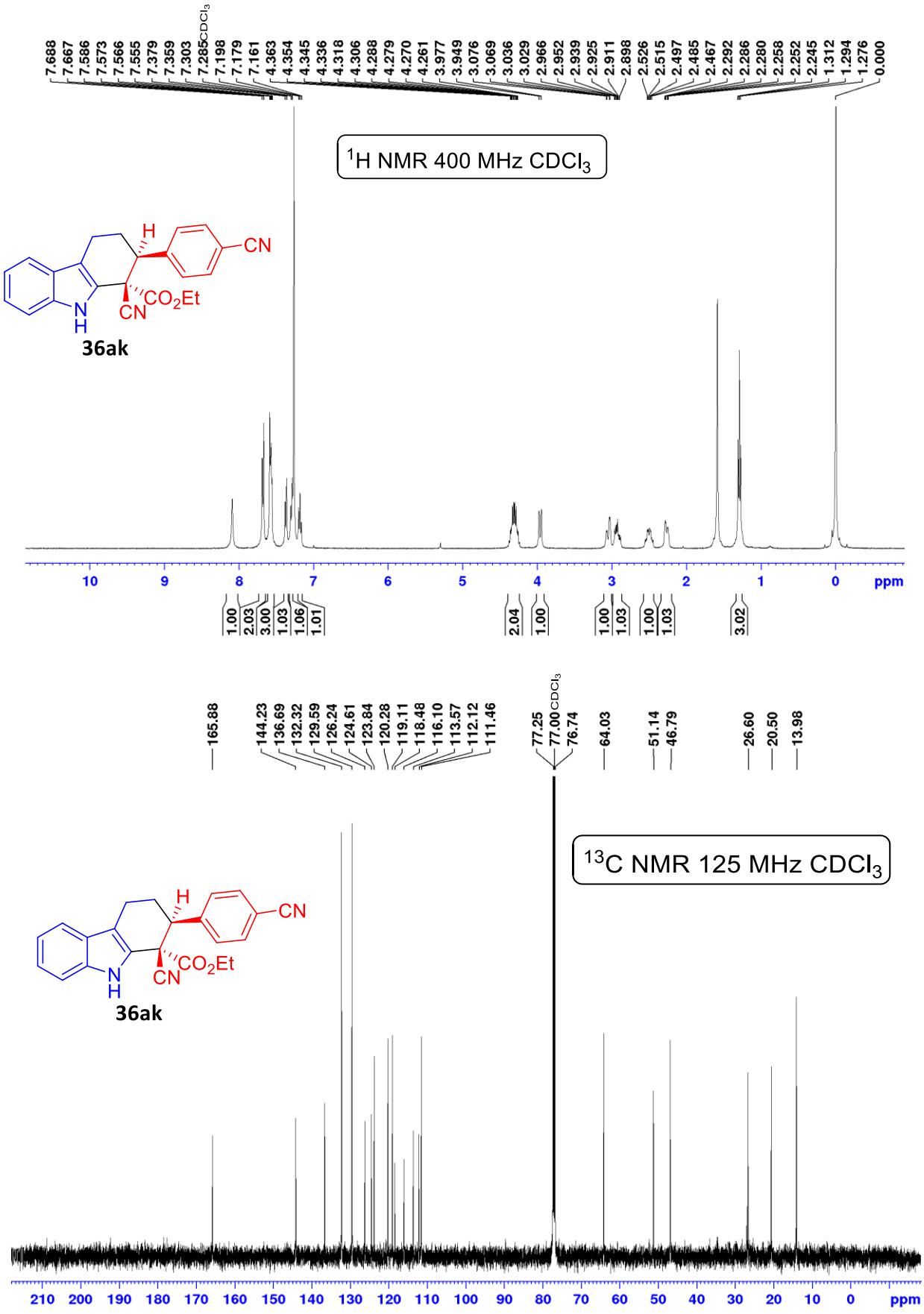



**Figure 66:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **36ak**.

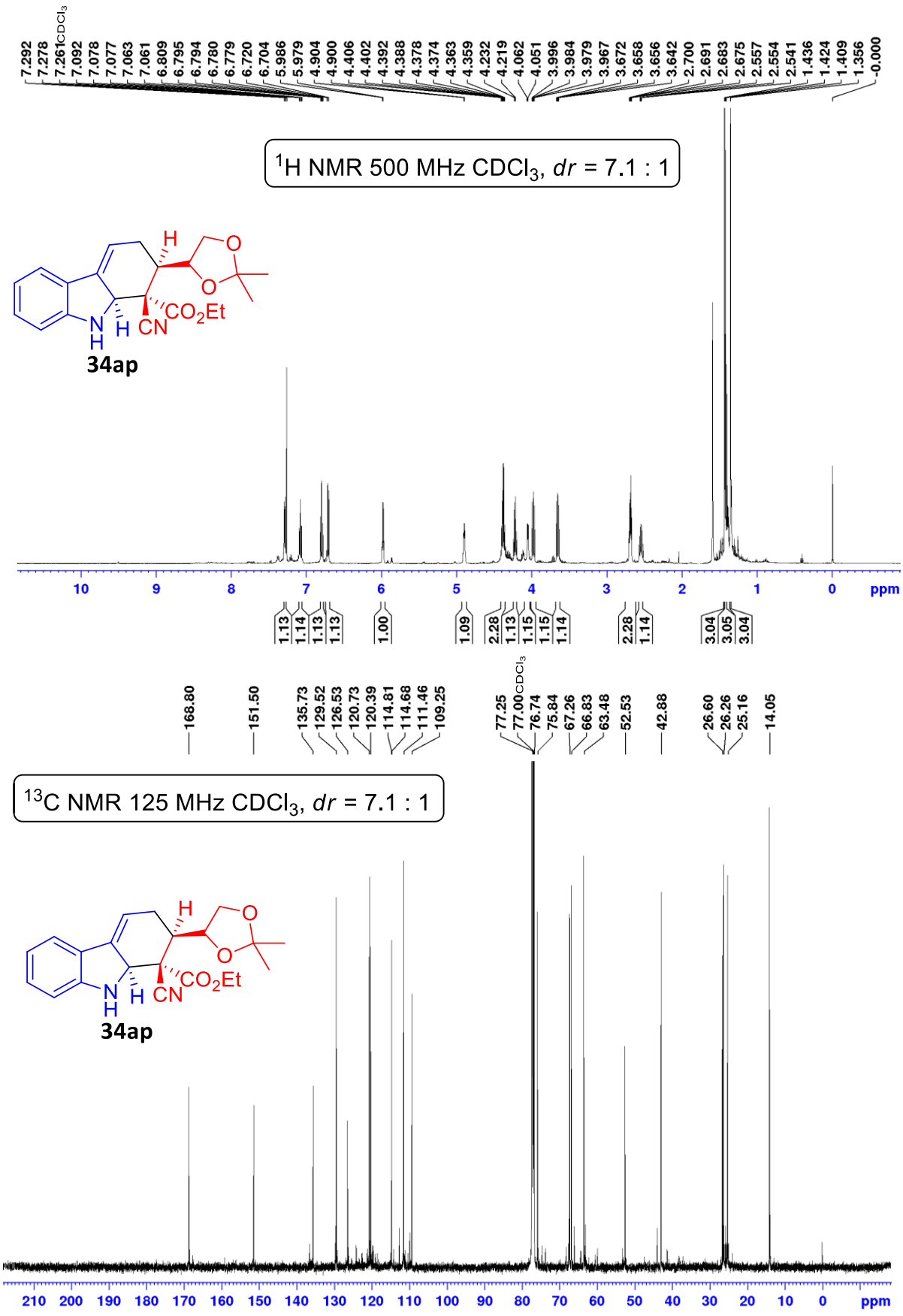
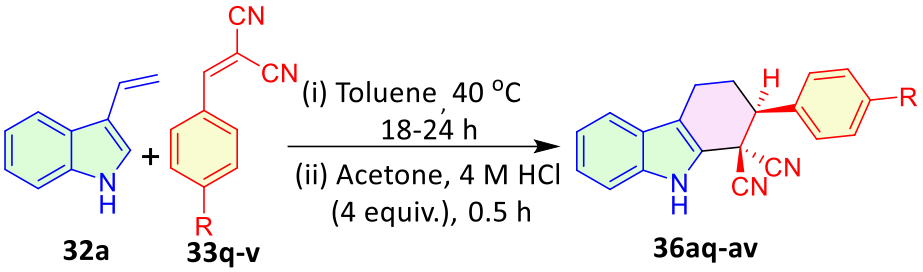



**Figure 67:** $^1$H NMR and $^{13}$C NMR spectrum of product **34ap**.

### *6.2.3 Substrate Scope with 2-Arylidenemalononitriles:*

Using our protocol, different 2-arylidenemalononitriles **33q-v** have been examined which ended up forming desired cyclized products **36aq-av** with high yield ranging from 72-86% and excellent diastereoselectivity of more than 95:1 (Table 17, entry 1-6).

**Table 17**: Substate scope with 2-Arylidenemalononitriles [a]




**32a** **33q-v** **36aq-av**

| entry | R | *t* (h) | yield (%)[b] | *dr*[c] |
|---|---|---|---|---|
| 1 | H (**33q**) | 20 | 84 | > 95:1 |
| 2 | F (**33r**) | 21 | 86 | > 95:1 |
| 3 | Br (**33s**) | 18 | 82 | > 95:1 |
| 4 | $CH_3$ (**33t**) | 19 | 84 | > 95:1 |
| 5 | OMe(**33u**) | 20 | 79 | > 95:1 |
| 6 | CN (**33v**) | 24 | 72 | > 95:1 |

[a]Reactions were performed in $CH_3C_6H_5$ (0.2 M) with 1.2 equiv. of **33** relative to **32a** (0.2 mmol), after completion of the reaction, 1 ml of acetone and 0.2 ml of 4 M HCl were added to it and stirred for 0.5 h. [b]Yield refers to the column purified products. [c]*dr* determinded by NMR spectroscopy.

Same trend of steric factors and electronic factors were observed here. *p*-F substituent in the phenyl ring at R position, produced better yield (86%) compare to *p*-Br substituent (82%) (Table 17, entry 2, 3) and electron donating *p*-Me and *p*-OMe groups in phenyl ring at R position, served better yield (84% and 79% respectively) in a shorter time compare to electron withdrawing *p*-CN group at the same position (72%) (Table 17, entry 4-6).

The synthesized compounds in Table 17 have characterized using NMR, IR and HRMS. $^1H$ and $^{13}C$ NMR spectra of few compounds have depicted in Figure 68-70.

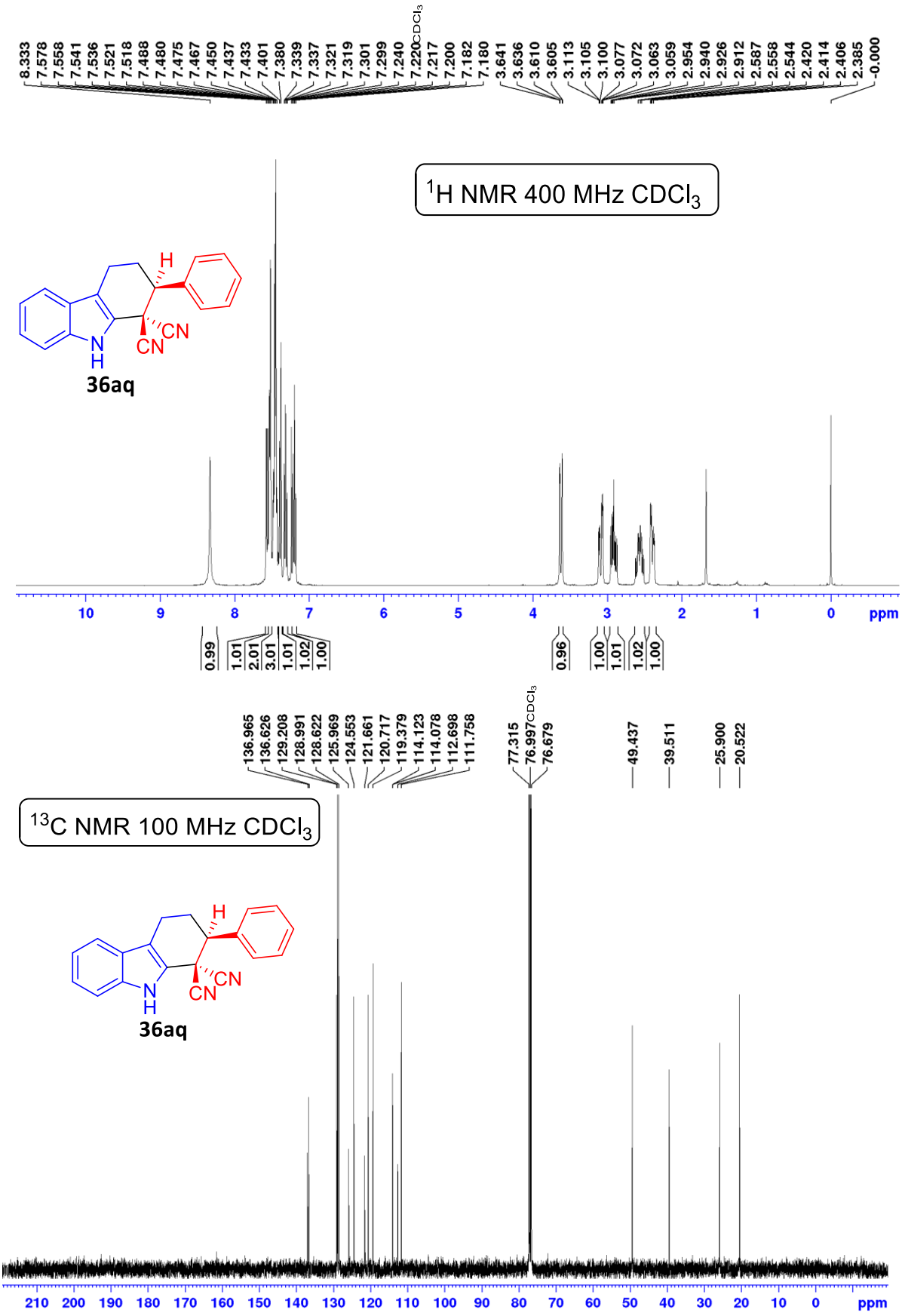



**Figure 68:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **36aq**.

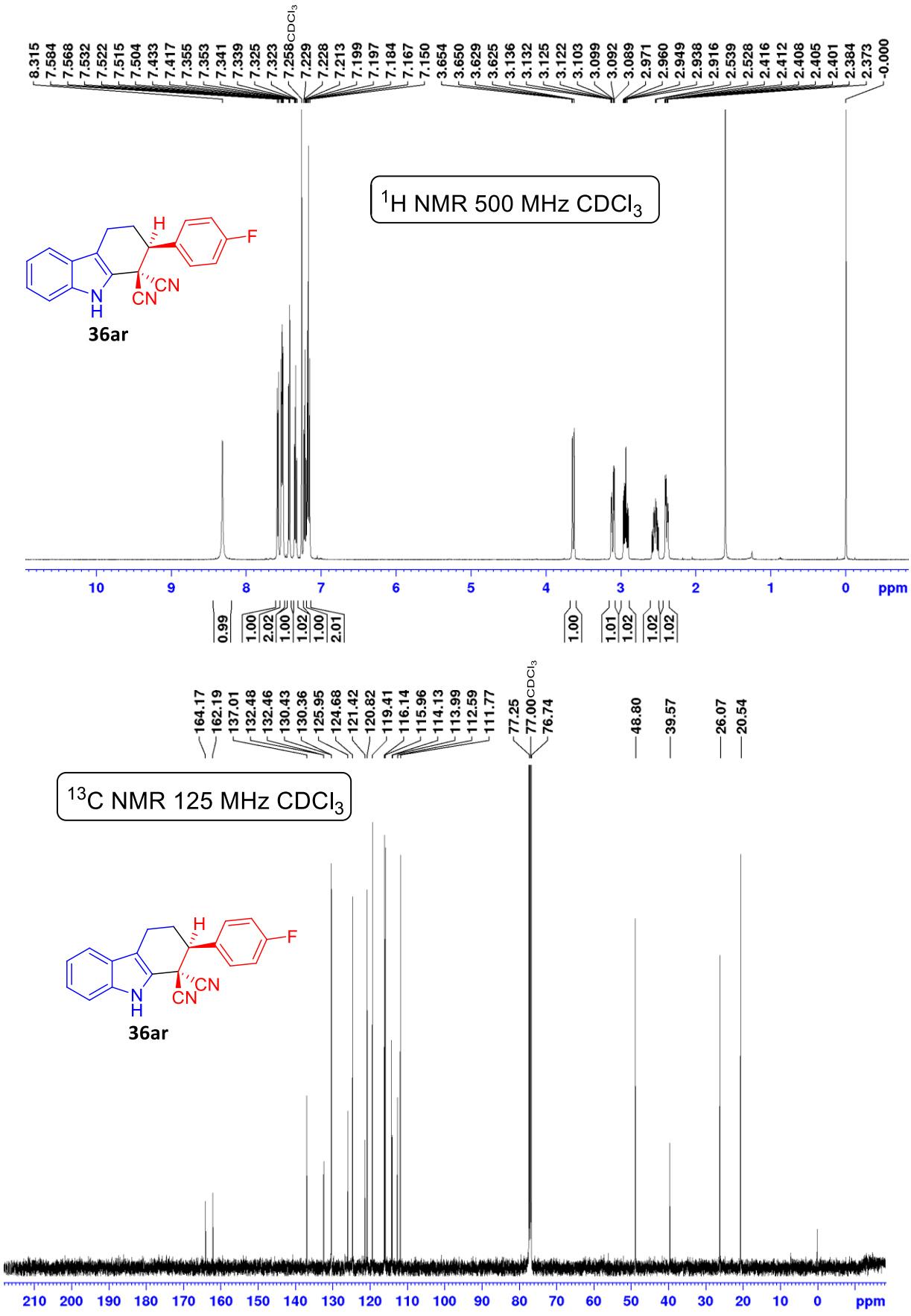



**Figure 69:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **36ar**.

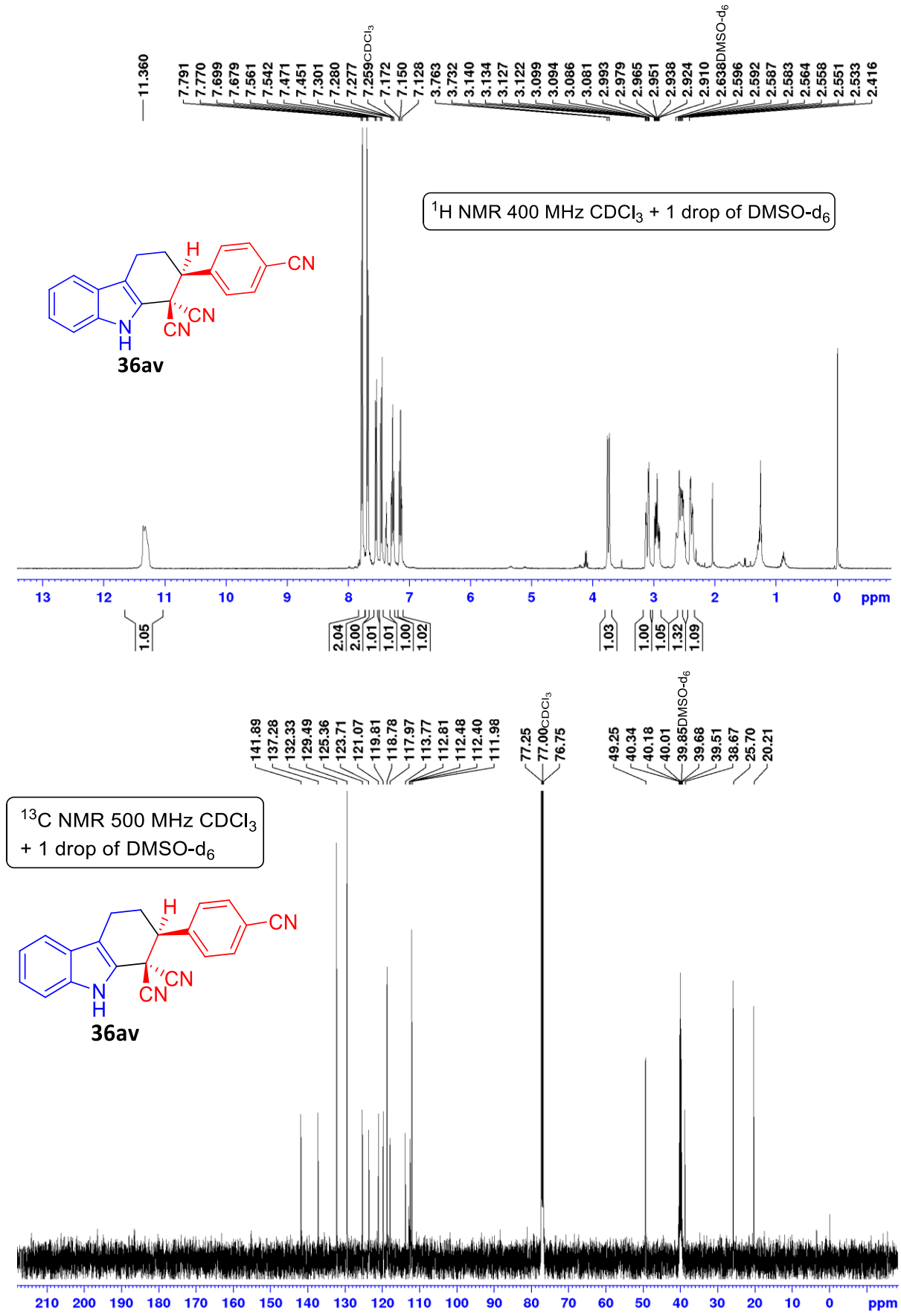
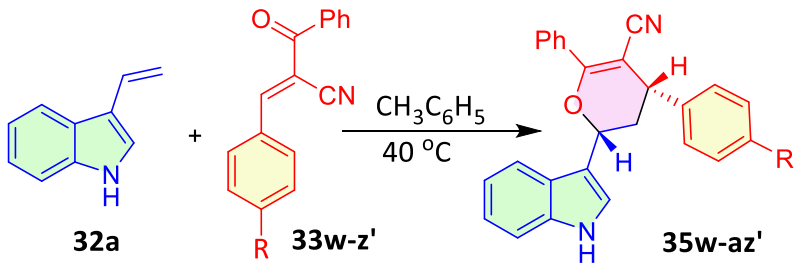



**Figure 70:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **36av**.

When we treated 2-benzoyl-3-arylacrylonitrile **33w-z'** with 3-vinylindole **32a**, in the same reaction condition, we found the formation of 3-pyranyl indoles **35aw-az'**, which was a hetero-Diels-Alder adduct of both the reactant.

**Table 18:** Substate scope for hetero Diels-Alder reaction [a]




| entry | R | *t* (h) | yield (%)[b] | *dr*[c] |
|---|---|---|---|---|
| 1 | H (**33w**) | 16 | 74 | 6.7:1 |
| 2 | Br (**33x**) | 18 | 79 | 1.1:1 |
| 3 | Me (**33y**) | 22 | 73 | 9.1:1 |
| 4 | OMe(**33z**) | 18 | 78 | 1.6:1 |
| 5 | CN (**33z'**) | 19 | 71 | 7.7:1 |

[a]Reactions were carried out in toluene (0.2 M) with 1.2 equiv. of **33** relative to **32a** (0.2 mmol). [b]Yield refers to the column purified products. [c]*dr* determined by NMR spectroscopy.

It is note-worthy that the hetero-Diels-Alder reaction proceeded with same reaction condition as the Diels-Alder reaction and 3-vinylindole **32a** shifted its role from a diene to a dienophile when treated with $\alpha,\beta$-unsaturated ketone. We tested various substituents like electronically neutral (H), halogen (Br), electron donating (Me and OMe) and withdrawing (CN) groups in R position, we observed good yield ranging from 71-79% with low to moderate diastereoselectivity of 1:1 to 9:1 (Table 18, entry 1-5).

The synthesized compound **36aw** have characterized using $^{1}H$ and $^{13}C$ NMR spectra shown in Figure 71. COSY and NOESY spectra of compound **36aw** was depicted in Figure 72. $^{1}H$ and $^{13}C$ NMR spectra of compound **36az'** has shown in Figure 73.

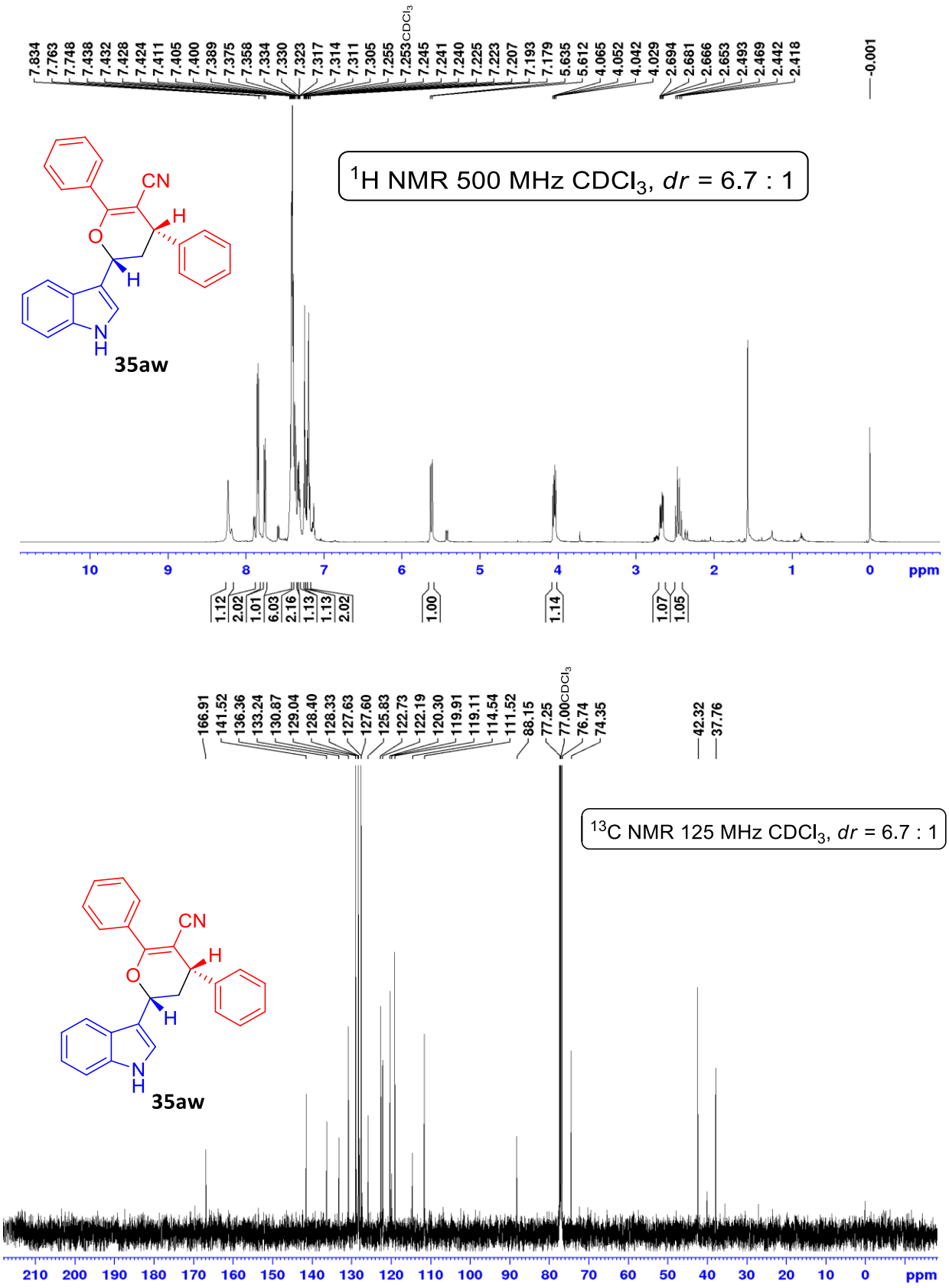



**Figure 71:** $^1$H NMR and $^{13}$C NMR spectrum of product **35aw**.

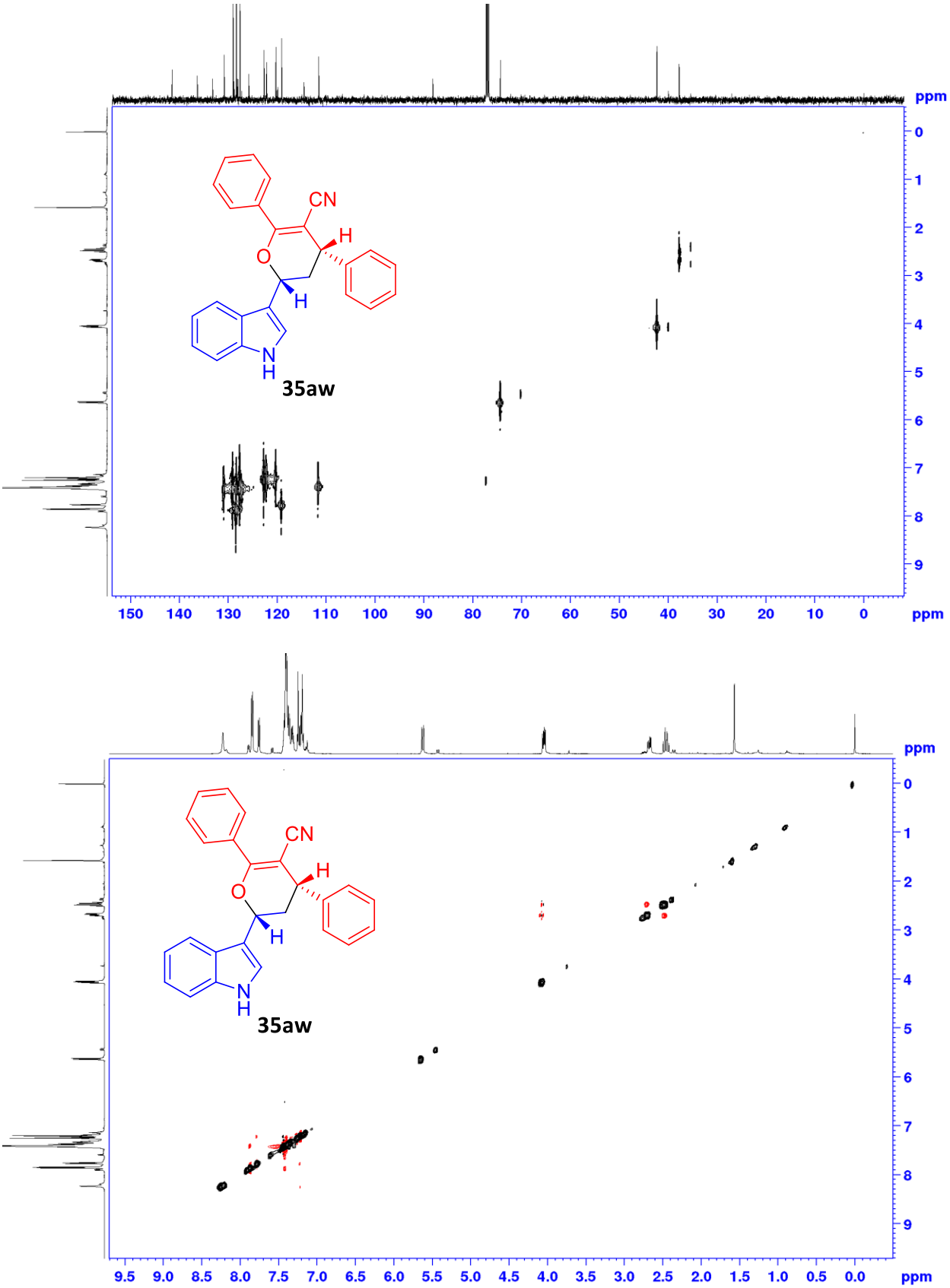



**Figure 72:** Hetero COSY and NOESY spectrum of product **35aw**.

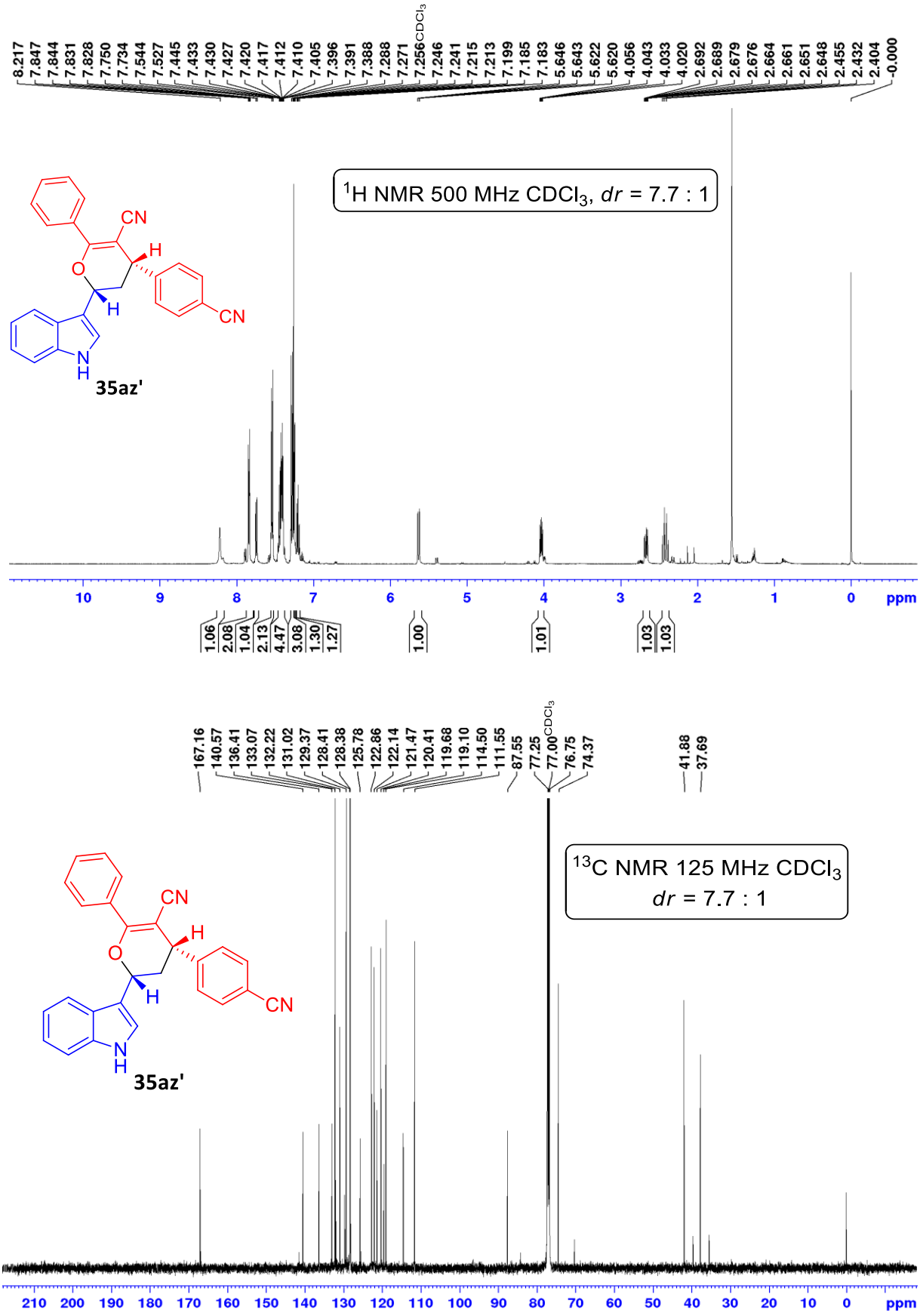



**Figure 73:** $^1$H NMR and $^{13}$C NMR spectrum of product **35az'**.

We have further confirmed the structure of **35az** (Figure 74) using X-ray crystallography.

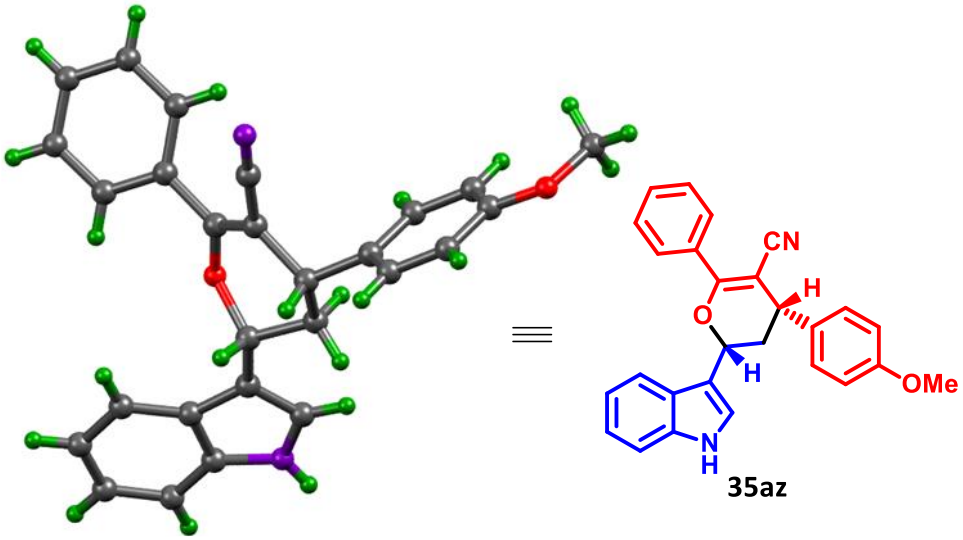


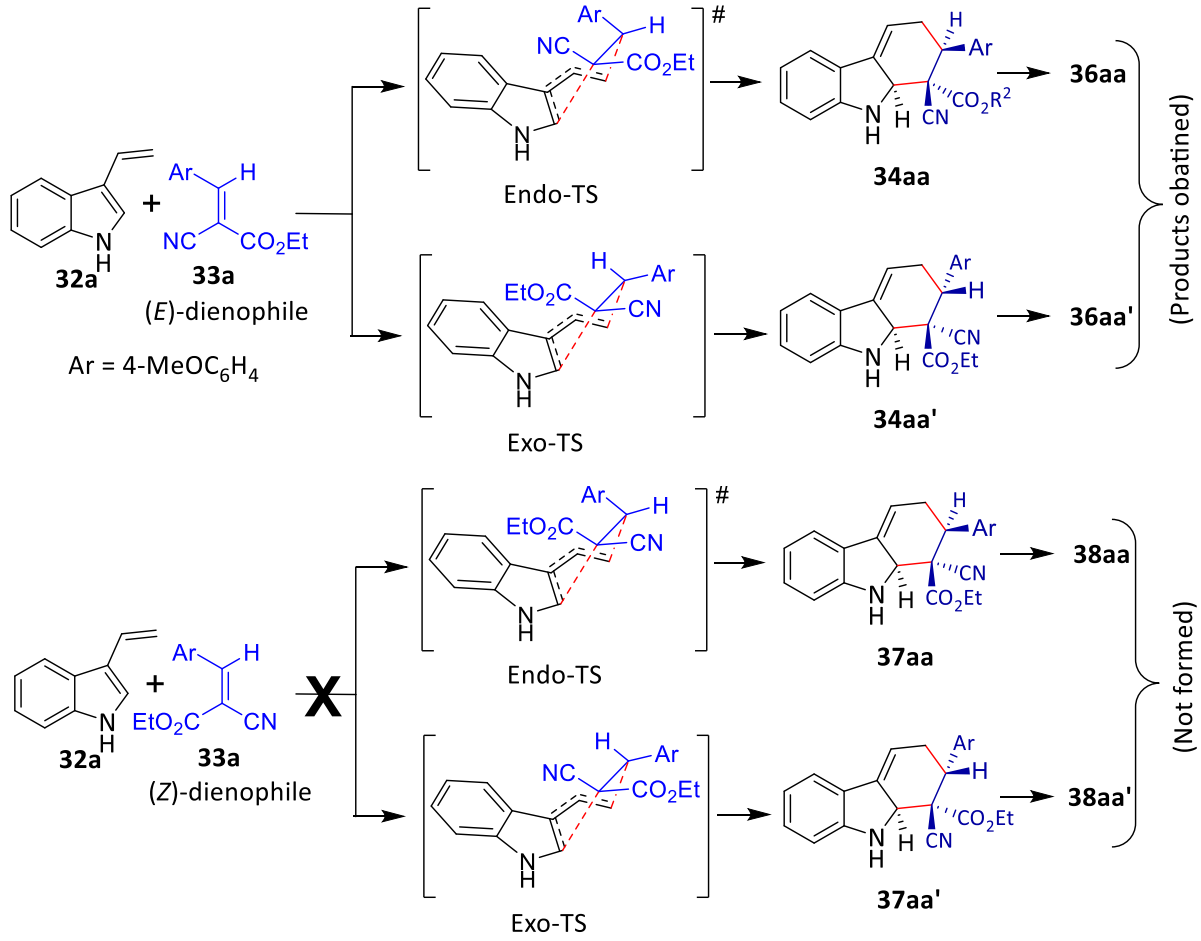

**Figure 74:** Crystal structure of 2-(1*H*-indol-3-yl)-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile **(35az)**.

### 6.2.4 *Mechanistic Rationale:*

Based on the absolute structure we proposed the most possible transition state and the reaction mechanism. Dienophiles can participate in the reaction in both (*E*) and (*Z*) confirmations. Again, each of this confirmation can consist of *exo*- and *endo*-transition states, depending on the orientation of dienophile with respect to diene, which lead to the formation of a mixture of two enantiomers. On the other hand, (*E*) and (*Z*) confirmations of dienophile lead to the formation of different diastereomers. Formation of a single diastereomer as the product, clearly indicates that the reaction went through either (*E*)-dienophile or (*Z*)-dienophile.

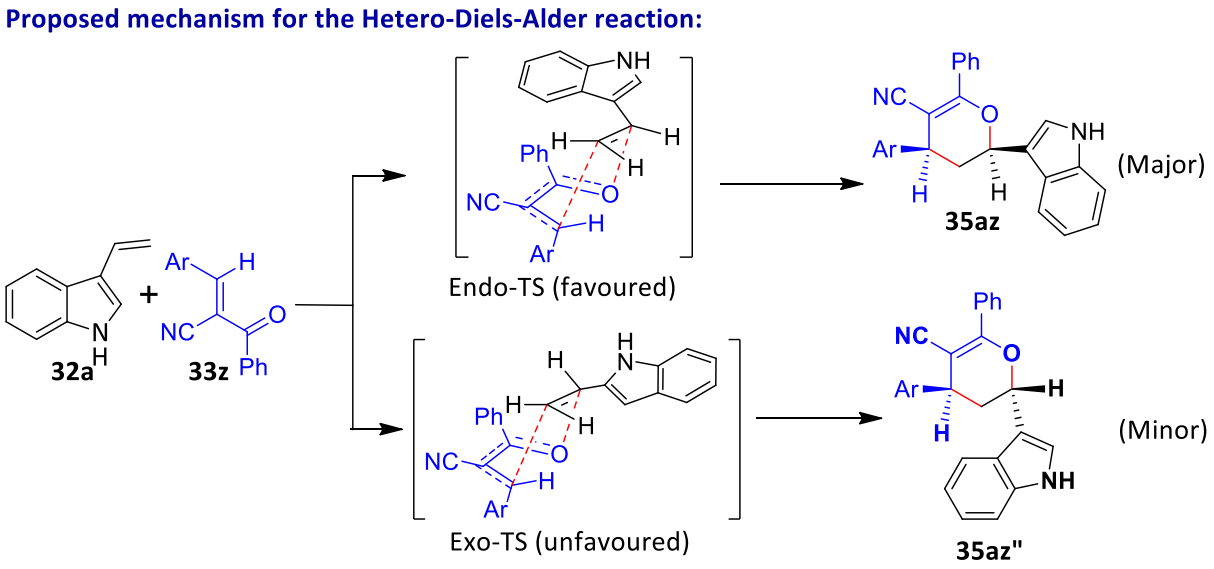
Crystal structure of **36aa** suggested that (*E*)-isomer of the dienophile is the responsible one, for the product formation. Hence, the solely formed (*E*)-isomer of the dienophile participated in the reaction to produce a mixture of two enantiomers through *exo*- and *endo*-transition states of a single diastereomer (Scheme 31).

**Proposed mechanism for the Diels-Alder reaction:**




**Scheme 31:** Plausible transition states (TS) based on the X-Ray crystallographic structure of **36aa**.

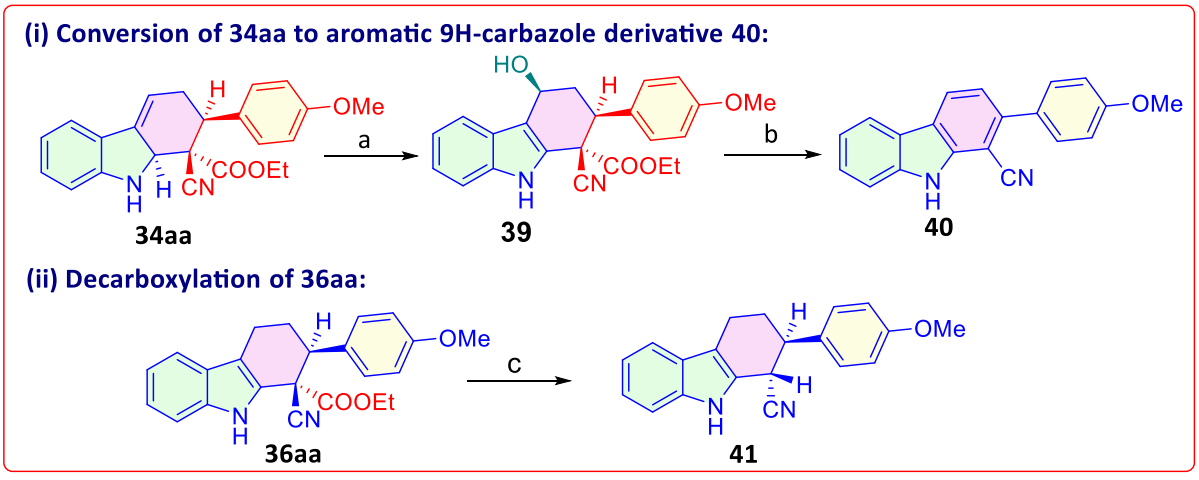
Similarly, in case of hetero-Diels-Alder reaction, *exo*- and *endo*-transition states can be formed, based on the orientation of diene (*α,β*-unsaturated ketone) and dienophile (3-vinylindole). Absolute configuration of the major diastereomer of **35az**, obtained from X-ray crystallography, recommended the *endo*-transition state to be slightly more favoured compare to *exo*-transition state (Scheme 32).




**Scheme 32:** Plausible transition states (TS) based on the X-Ray crystallographic structure of **35az**.

### 6.2.5 *Aromatization and Decarboxylation Reaction:*

Considering the vast importance of indole-based scaffolds, we have utilized user-friendly methods to access interesting tetrahydrocarbazoles using **34aa** and **36aa**. Upon oxidation with *m*cpba, **34aa** oxidized to form a secondary alcohol **39** which was obtained as a single diastereomer with 56% of yield (Scheme 33).




**Scheme 33:** Synthetic applications of tetrahydro-1*H*-carbazoles. Reaction conditions (a) **34aa** (0.2 mmol), *m*-CPBA (1.2 equiv.) in DCM, 0 °C-25 °C, 0.5 h, 56%, *dr* > 99:1. (b) **39** (0.1 mmol), KO$^t$Bu (1.5 equiv.) in THF, reflux, 6 h, 64%. (c) **36aa** (0.1 mmol), NaOH (3.0 equiv.) in MeOH, reflux, 2 h, 61%, *dr* > 99:1.

Compound **39** was further converted to an aromatic compound **40** with 64% of yield, using $^{t}$BuOK and reflux condition in THF solvent within 6 h. Compound **36aa** was utilized towards decarboxylation using NaOH in methanol, within 2 h in reflux condition, product **41** was obtained with 61% of yield as a single diastereomer (Scheme 32).

We have further confirmed the structure of **40** (Figure 75) and **41** (Figure 76) using X-Ray crystallography.

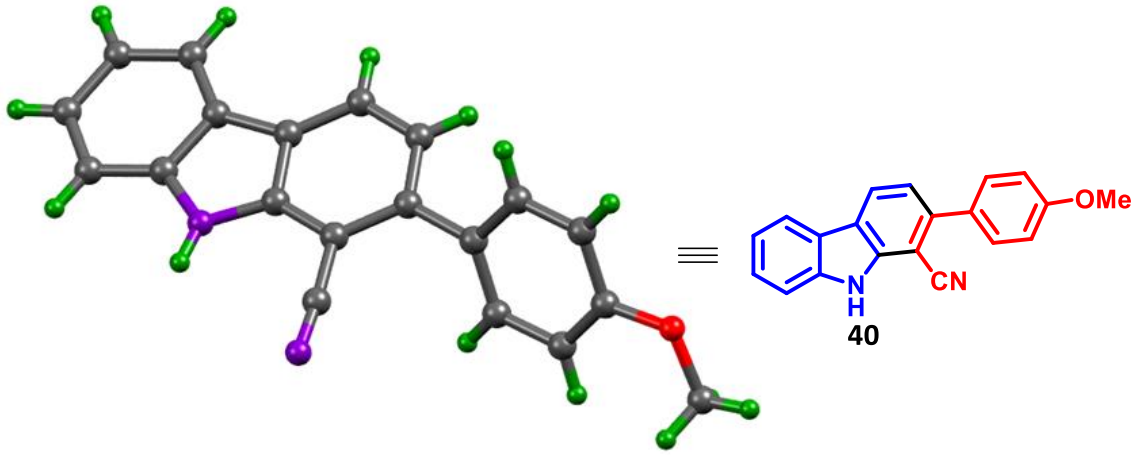



**Figure 75:** Crystal structure of 2-(4-Methoxyphenyl)-9*H*-carbazole-1-carbonitrile **(40)**.

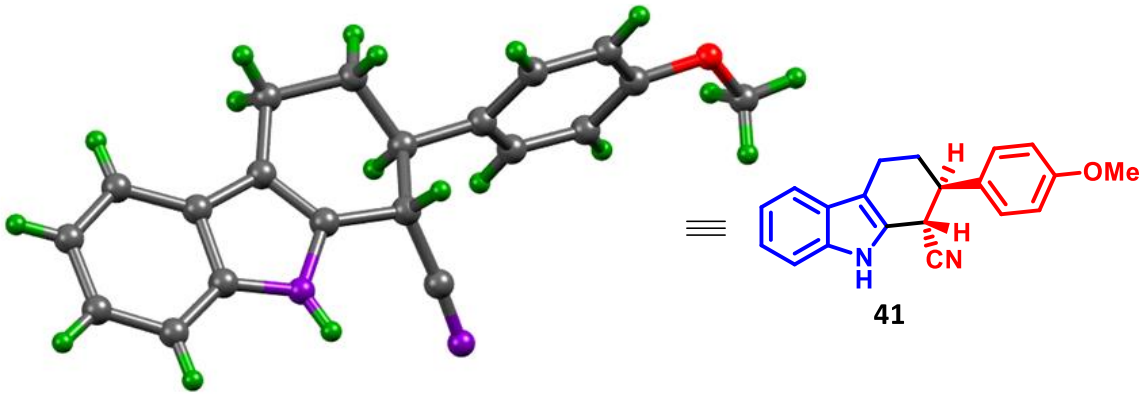



**Figure 76:** Crystal structure of 2-benzyl-2-hydroxy-4,4,6,6-tetramethylcyclohexane-1,3,5-trione **(41)**.

$^{1}$H NMR and $^{13}$C NMR spectrum of product **40** and **41** have depicted below (Figure 77 and 78).

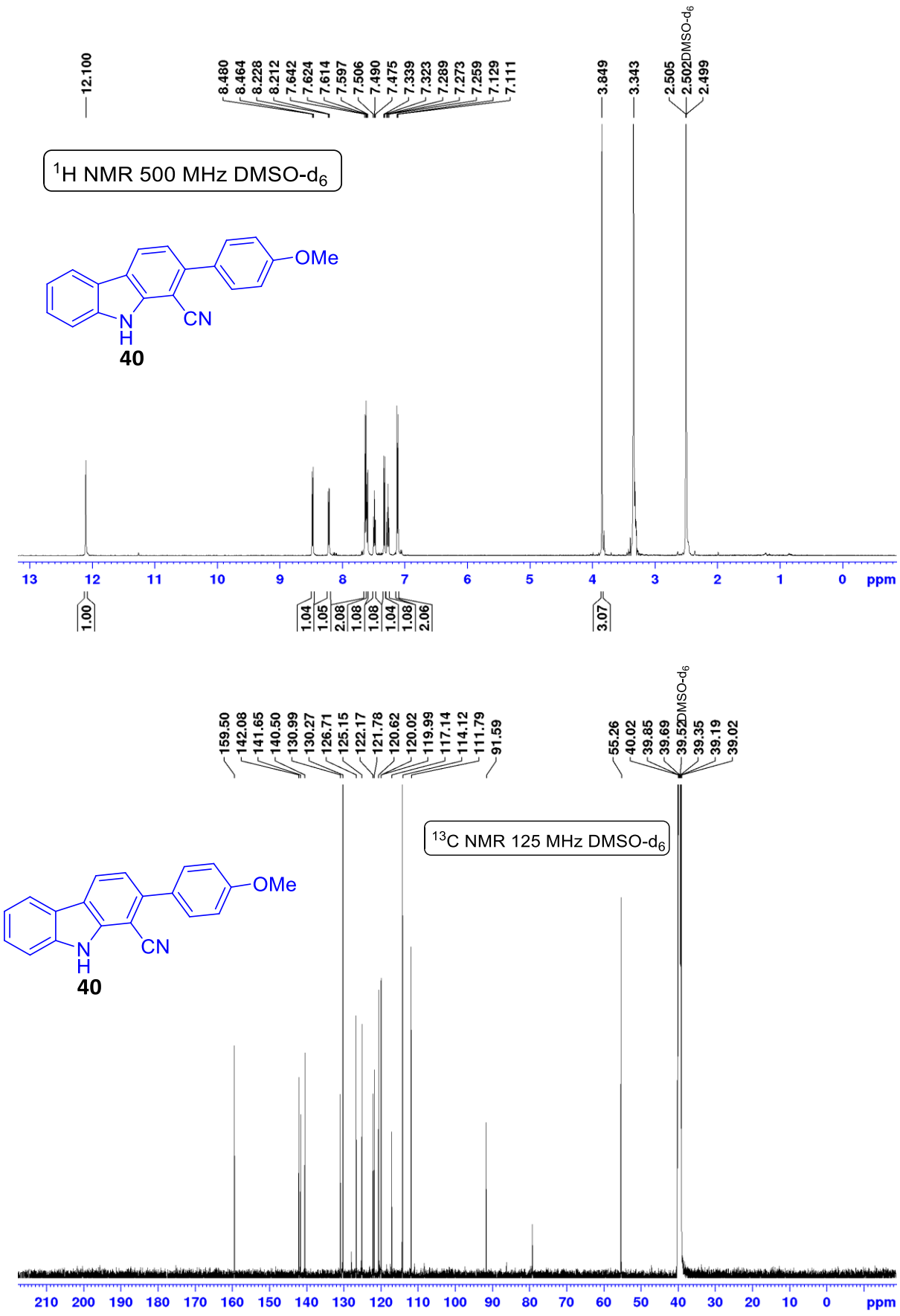



**Figure 77:** $^{1}H$ NMR and $^{13}C$ NMR spectrum of product **40**.

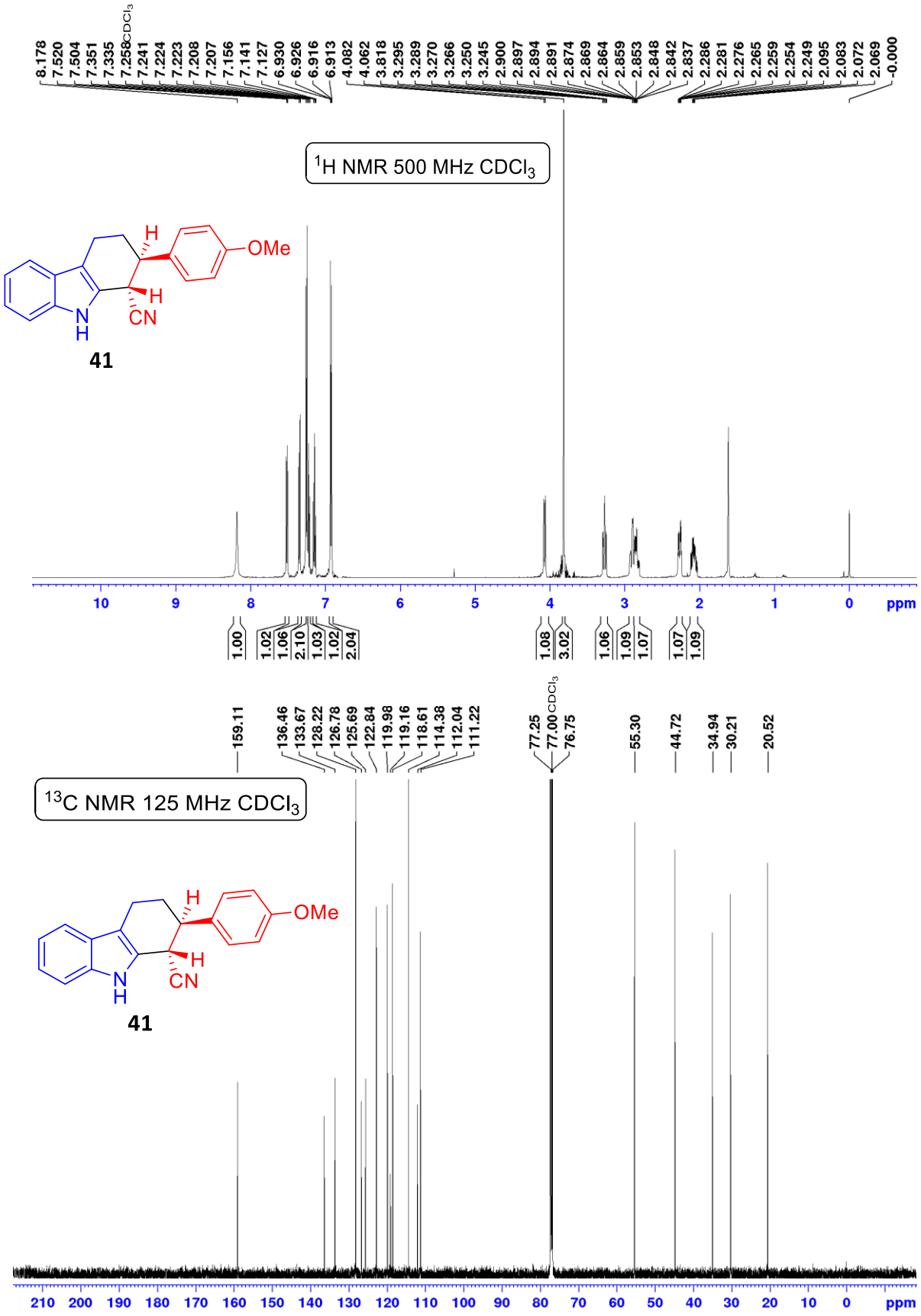
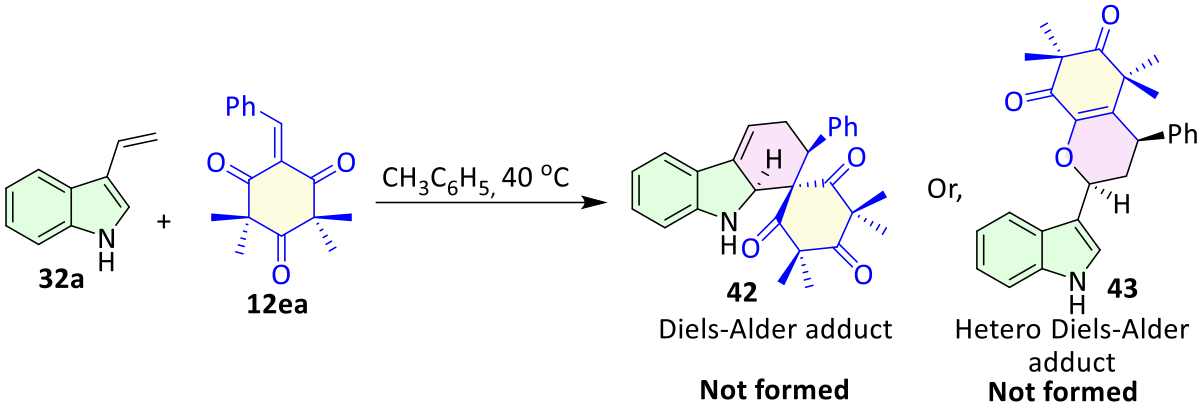



**Figure 78:** $^{1}$H NMR and $^{13}$C NMR spectrum of product **41**.

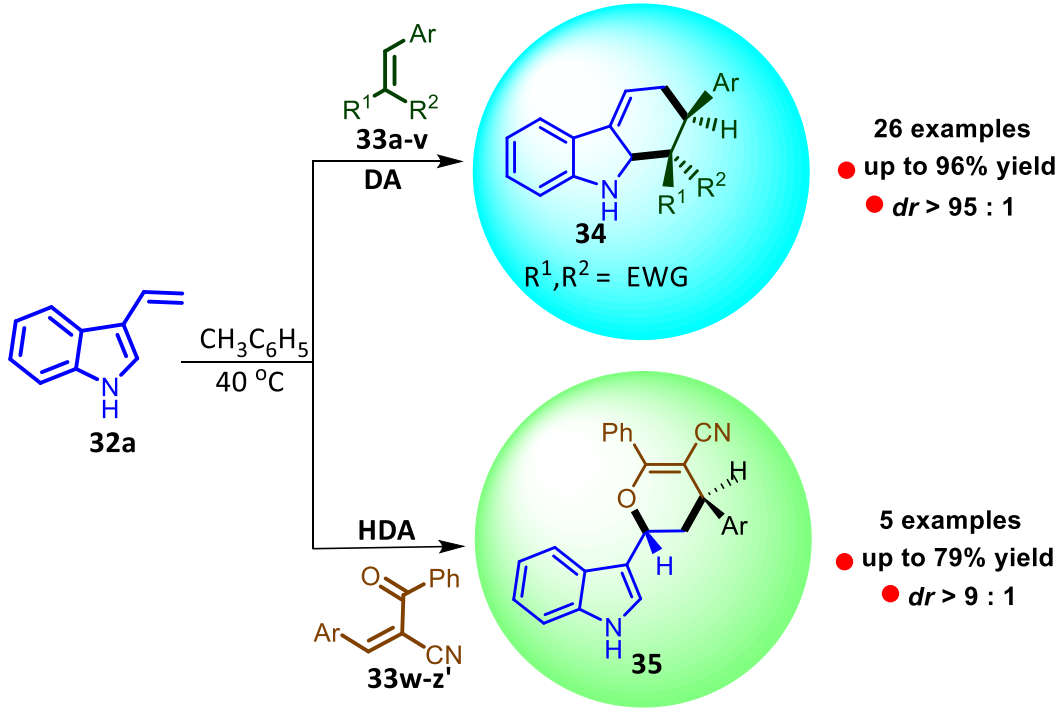
### 6.2.6 *An Unsuccessful Attempt to Use Alkylidene Syncarpic Acid as a Partner*

The reaction between 3-vinyl indole **32a** and alkylidene syncarpic acid **12ea** in toluene solvent at 40 °C did not produced any product, and starting materials were recovered with 95% yield (Scheme 34). Even longer reaction time and reflux condition also showed similar result.




**Scheme 34:** An unsuccessful try to perform reaction between **32a** and **12ea**.

## 6.3 Conclusions:




In conclusion, we have disclosed the opportunity of 3-vinyl indole as a diene as well as dienophile source depends on choosing the reaction partner and a suitable pathway for the diastereoselective preparation of 1-aminotetrahydrocarbazole derivatives with good to excellent yield and a convenient reaction condition for the preparation of biologically active 3-pyranyl indole derivatives with good yield and diastereoselectivity.

# 7. Experimental Section

## *General Methods:*

The $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS (δ = 0) for $^{1}H$ NMR and relative to the central $CDCl_3$ resonance (δ = 77.0) for $^{13}C$ NMR. In the $^{13}C$ NMR spectra, the nature of the carbons (C, CH, $CH_2$, or $CH_3$) was determined by recording the DEPT-135 experiment, and was given in parentheses. The coupling constants *J* were given in hertz. Column chromatography was performed using Acme's 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 a JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonius MACH 3 diffractometer using graphite monochromated, Mo Kα (λ = 0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ = 0.71073 Å). For thin-layer chromatography, silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of 1.5 g $KMnO_4$, 10 g $K_2CO_3$, and 1.25 mL 10% NaOH in 200 mL water.

## *1. General Experimental Procedures for One-pot Knoevenagel and [4+2]-Cycloaddition as a Platform to Calliviminones*

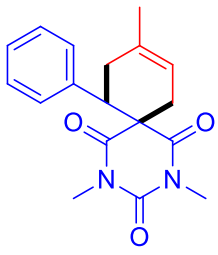
**Procedure-A:** *(S)-Proline catalyzed Knoevenagel condensation followed by Diels-Alder reaction in sequential one-pot manner:* In an ordinary glass vial with inner cap, equipped with a magnetic stirring bar, 1.0 equiv. of 1,3-diketones or active methylene compound **1** (0.3 mmol) and 1.0 equiv. of aldehyde **2** (0.3 mmol) were added to 1.0 mL of DCM (0.3 M), and then the catalyst (*S*)-proline (0.015 mmol, 1.73 mg, 5 mol %) was added, the resulting reaction mixture was stirred at ambient temperature for 1 to 2 hours. The reaction mixture was turned to yellow color and the formation of Knoevenagel intermediate was confirmed by TLC. Then DCM was removed from the reaction mixture by reduced pressure and 1.0 mL of $CH_3CN$ (0.3 M) was added to the same. Then the reaction mixture was charged with 1.0 equiv. of diene **4** (0.3 mmol) and stirred at 80 °C (oil bath) for 6-12 h. The completion of the reaction was further confirmed

by TLC. The pure Diels-Alder adducts (**5** + **6**/**7**) were obtained by silica gel column chromatography using ethyl acetate and hexane as eluents.

**Procedure-B:** *Procedure for the Synthesis of Product* ***8dj:*** In an ordinary glass vial equipped with a magnetic stirring bar, 1 equiv. of cyclohexane-1,3-dione **1d** (5 mmol, 560.7 mg) and 4-cyanobenzaldehyde **2j** (5 mmol, 665.7 mg) were added in 2.0 ml of DCM (2.5 M) and then the catalyst (*S*)-proline (0.25 mmol, 28.8 mg, 5 mol %) was added, the resulting reaction mixture was stirred at ambient temperature for half an hour. The product was precipitated after reaction completion. Then the resultant precipitate was filtered to afford the raw product (48%). Further recrystallization from ethanol afforded the pure product **8dj** (40.5%, 684 mg) and the product was fully characterized by spectroscopic data.

**Procedure-C:** *Procedure for the Synthesis of Product* ***5dja*** *from the bis-Product* ***8dj:*** An ordinary glass vial with inner cap, equipped with a magnetic stirring bar, was charged with 1 equiv. of compound **8dj** (0.3 mmol, 101.2 mg) and 1.0 mL of $CH_3CN$ (0.3 M). To the reaction mixture, 1 equiv. of isoprene **4a** (0.9 mmol, 61.3 mg) was added and then it was stirred at 80 °C (oil bath) for 48 h. The completion of the reaction was confirmed by TLC. The pure regioisomeric mixture of product **5dja** and product **6dja** (ratio = 4.0:1) was obtained by silica gel column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0) as colorless liquid (31%, 28.6 mg).

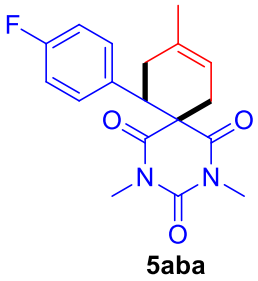
**2,4,9-Trimethyl-11-phenyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aaa):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and isolated as a white solid. Mp.: 232-235 °C. Yield: 90% (84.3 mg). IR (Neat): $\nu_{max}$ 2971, 2909, 1744, 1670, 1493, 1444, 1375, 1280, 1162, 1110, 1030, 999, 911 and 749 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *rr* = 7.7:1, major isomer): δ 7.25-7.24 (3H, m), 6.99-6.97 (2H, m), 5.52 (1H, br s, olefinic-*H*), 3.41 (1H, dd, *J* = 12.0, 5.0 Hz), 3.14 (3H, s, N-C*H*$_3$), 3.10 (1H, br s), 2.93 (3H, s, N-C*H*$_3$), 2.69 (1H, br t, *J* = 15.0 Hz), 2.39 (1H, td, *J* = 18.0, 2.0 Hz), 2.13 (1H, dd, *J* = 17.5, 4.5 Hz), 1.81 (3H, s, olefinic-C*H*$_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 7.7:1, major isomer): δ 172.2 (C, N-*C*=O), 169.8 (C, N-*C*=O), 150.3 (C, N-*C*=O), 138.5 (C), 132.8 (C), 128.4 (2 x CH), 128.2 (CH), 127.4 (2 x CH), 117.0 (CH), 54.4 (C), 49.2 (CH), 32.8 ($CH_2$), 32.7 ($CH_2$), 28.3 ($CH_3$), 28.0 ($CH_3$),



**5aaa**

23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{20}N_2O_3Na$ 335.1371; Found 335.1373.

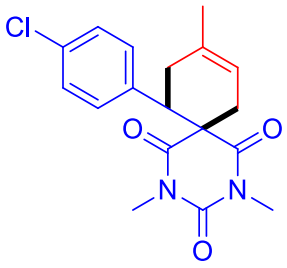
**11-(4-Fluorophenyl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aba):**



**5aba**

The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and isolated as a white solid. Mp.:178-181 °C. Yield: 85% (84.2 mg). IR (Neat): $\nu_{max}$ 2911, 1745, 1674, 1605, 1510, 1448, 1419, 1379, 1227, 1163, 1113, 1056, 837 and 752 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, *rr* = 6.3:1, major isomer): δ 6.99-6.94 (4H, m), 5.51 (1H, br s, olefinic-*H*), 3.44 (1H, dd, *J* = 12.4, 4.8 Hz), 3.16 (3H, s, N-C*H*$_3$), 3.08 (1H, br d, *J* = 18.8 Hz), 2.98 (3H, s, N-C*H*$_3$), 2.67 (1H, t, *J* = 14.8 Hz), 2.39 (1H, tt, *J* = 18.0, 2.0 Hz), 2.12 (1H, dd, *J* = 17.6, 4.8 Hz), 1.81 (3H, s, olefinic-C*H*$_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 6.3:1, major isomer): δ 172.1 (C, N-*C*=O), 169.6 (C, N-*C*=O), 162.3 (C, *C*-F, d, *J* = 246 Hz), 150.2 (C, N-*C*=O), 134.5 (C, d, *J* = 3.0 Hz), 132.8 (C), 129.0 (2 x CH, d, *J* = 8.0 Hz), 116.8 (CH), 115.3 (2 x CH, d, *J* = 21.0 Hz), 54.2 (C), 48.0 (CH), 33.1 ($CH_2$), 33.0 ($CH_2$), 28.4 ($CH_3$), 28.0 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{19}FN_2O_3Na$ 353.1277; Found 353.1278.

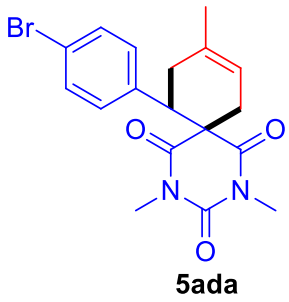
**11-(4-Chlorophenyl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aca):**



**5aca**

The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated colorless liquid. Yield: 81% (84.3 mg). IR (Neat): $\nu_{max}$ 2911, 1742, 1675, 1491, 1447, 1419, 1378, 1280, 1113, 1093, 1054, 1013, 829 and 753 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *rr* = 5.3:1, major isomer): δ 7.22 (2H, d, *J* = 8.5 Hz), 6.95 (2H, d, *J* = 8.5 Hz), 5.50 (1H, br s), 3.44 (1H, dd, *J* = 12.5, 5.0 Hz), 3.17 (3H, s), 3.06 (1H, br d, *J* = 18.5 Hz), 2.99 (3H, s), 2.68 (1H, br t, *J* = 13.5 Hz), 2.39 (1H, br d, *J* = 18.0 Hz), 2.11 (1H, dd, *J* = 17.5, 4.5 Hz), 1.81 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 5.3:1, major isomer): δ 172.1 (C, N-*C*=O), 169.7 (C, N-*C*=O), 150.3 (C, N-*C*=O), 137.4 (C), 134.0 (C), 133.0 (C), 129.0 (2 x CH), 128.6 (2 x CH), 116.8 (CH), 54.0 (C), 48.0 (CH), 33.5 ($CH_2$), 33.0 ($CH_2$), 28.5 ($CH_3$), 28.1 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{19}ClN_2O_3Na$ 369.0982; Found 369.0983.

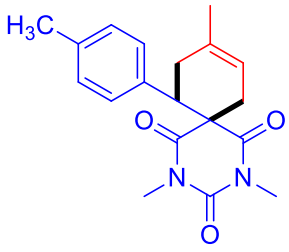
**11-(4-Bromophenyl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5ada):**



**5ada**

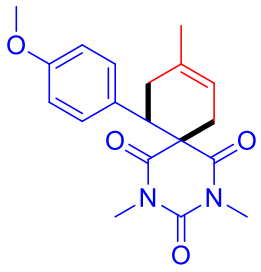
The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 67%, (78.6 mg). IR (Neat): $\nu_{max}$ 2922, 2360, 1744, 1677, 1448, 1420, 1378, 1280, 1114, 1009, 825 and 753 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz, *rr* = 8.3:1, major isomer): δ 7.39 (2H, br d, *J* = 8.0 Hz), 6.90 (2H, br d, *J* = 8.4 Hz), 5.51 (1H, br s), 3.45 (1H, dd, *J* = 12.0, 4.8 Hz), 3.19 (3H, s), 3.06 (1H, m), 3.02 (3H, s), 2.69 (1H, br t, *J* = 16.4 Hz), 2.40 (1H, td, *J* = 18.0, 2.4 Hz), 2.13 (1H, dd, *J* = 17.2, 4.8 Hz), 1.82 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 8.3:1, major isomer): δ 172.1 (C, N-*C*=O), 169.6 (C, N-*C*=O), 150.3 (C, N-*C*=O), 138.0 (C), 133.0 (C), 131.6 (2 x CH), 129.3 (2 x CH), 122.1 (C), 116.7 (CH), 54.0 (C), 48.0 (CH), 33.6 ($CH_2$), 33.0 ($CH_2$), 28.5 ($CH_3$), 28.1 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOS) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{19}BrN_2O_3Na$ 413.0477, Found 413.0478.

**2,4,9-Trimethyl-11-(*p*-tolyl)-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aea):** 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 as colorless liquid. Yield: 86% (84.2 mg). IR (Neat): $\nu_{max}$ 2914, 2360, 1744, 1671, 1513, 1445, 1418 1377, 1337, 1280, 1114, 1055, 916, 817 and 752 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz, *rr* = 6.7:1, major isomer): δ 7.04 (2H, d, *J* = 8.0 Hz), 6.85 (2H, d, *J* = 8.0 Hz), 5.51 (1H, br s), 3.37 (1H, dd, *J* = 12.5, 5.0 Hz), 3.14 (3H, s), 3.12-3.08 (1H, m), 2.94 (3H, s), 2.66 (1H, br dt, *J* = 14.5, 1.0 Hz), 2.40-2.35 (1H, m), 2.29 (3H, s), 2.09 (1H, dd, *J* = 17.5, 4.5 Hz), 1.80 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 6.7:1, major isomer): δ 172.2 (C, N-*C*=O), 169.8 (C, N-*C*=O), 150.3 (C, N-*C*=O), 137.8 (C), 135.4 (C), 132.8 (C), 128.9 (2 x CH), 127.2 (2 x CH), 116.9 (CH), 54.3 (C), 48.8 (CH), 32.8 (2 x $CH_2$), 28.3 ($CH_3$), 27.9 ($CH_3$), 23.2 ($CH_3$), 20.9 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{22}N_2O_3Na$ 349.1528; Found 349.1529.



**5aea**

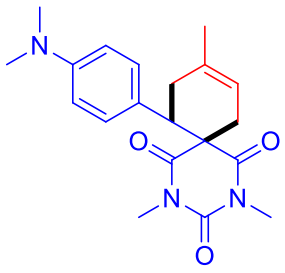
**11-(4-Methoxyphenyl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione**



**5afa**

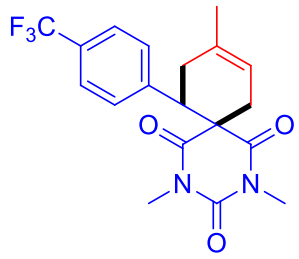
**(5afa):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0 : 9.0 to 2.0 : 8.0), and was isolated as colorless liquid. Yield: 81% (83.2 mg). IR (Neat): $\nu_{max}$ 2909, 1742, 1670, 1610, 1512, 1445, 1418, 1378, 1304, 1251, 1179, 1115, 1031, 833 and 750 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz, *rr* = 7.1:1, major isomer): δ 6.90 (2H, br d, *J* = 9.0 Hz), 6.76 (2H, br d, *J* = 9.0 Hz), 5.51 (1H, br s), 3.76 (3H, s), 3.38 (1H, dd, *J* = 12.0, 4.5 Hz), 3.16 (3H, s), 3.09 (1H, br d, *J* = 18.5 Hz), 2.97 (3H, s), 2.65 (1H, br dt, *J* = 15.0, 1.0 Hz), 2.38 (1H, br qd, *J* = 18.0, 1.5 Hz), 2.10 (1H, dd, *J* = 17.5, 4.5 Hz), 1.80 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 7.1:1, major isomer): δ 172.4 (C, N-*C*=O), 169.9 (C, N-*C*=O), 159.3 (C), 150.4 (C, N-*C*=O), 133.0 (C), 130.4 (C), 128.5 (2 x CH), 116.9 (CH), 113.7 (2 x CH), 55.2 ($CH_3$, O*C*$H_3$), 54.5 (C), 48.4 (CH), 33.0 ($CH_2$), 32.9 ($CH_2$), 28.5 ($CH_3$), 28.0 ($CH_3$), 23.3 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{22}N_2O_4Na$ 365.1477; Found 365.1478.

**11-(4-(Dimethylamino)phenyl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aga):** 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 as colorless liquid. Yield: 72% (76.8 mg). IR (Neat): $\nu_{max}$ 2959, 2926, 2858, 1713, 1462, 1331, 1243, 1175, 1124, 1045, 1024, 933, 836 and 752 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz, *rr* = 8.0:1, major isomer): δ 6.82 (2H, d, *J* = 9.0 Hz), 6.56 (2H, d, *J* = 9.0 Hz), 5.50 (1H, br s), 3.32 (1H, dd, *J* = 12.0, 5.0 Hz), 3.15 (3H, s), 3.10 (1H, br d, *J* = 17.5 Hz), 2.97 (3H, s), 2.90 (6H, s), 2.63 (1H, t, *J* = 15.0 Hz), 2.37 (1H, td, *J* = 18.0, 2.5 Hz), 2.07 (1H, dd, *J* = 17.5, 4.5 Hz), 1.79 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 8.0:1, major isomer): δ 172.6 (C, N-*C*=O), 170.1 (C, N-*C*=O), 150.5 (C, N-*C*=O), 150.2 (C), 133.0 (C), 128.0 (2 x CH), 125.6 (C), 117.0 (CH), 112.0 (2 x CH), 54.8 (C), 48.6 (CH), 40.3 (2 x $CH_3$), 33.0 ($CH_2$), 32.7 ($CH_2$), 28.4 ($CH_3$), 28.0 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{20}H_{25}N_3O_3NH_4$ 373.2234; Found 373.2236.



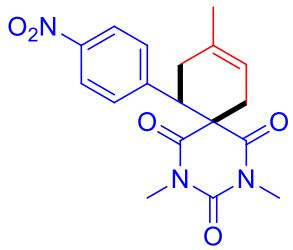
**5aga**

**2,4,9-Trimethyl-11-(4-(trifluoromethyl)phenyl)-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aha):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 78% (89.0 mg). IR (Neat): $\nu_{max}$ 2913, 2360, 1746, 1673, 1619, 1446, 1419, 1378, 1323, 1165, 1116, 1068, 1017, 840, 796 and 754 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, *rr* = 4.0:1, major isomer): δ 7.52 (2H, d, *J* = 8.0 Hz), 7.16 (2H, d, *J* = 8.0 Hz), 5.51 (1H, br s), 3.56 (1H, dd, *J* = 12.0, 5.2 Hz), 3.19 (3H, s), 3.06 (1H, br d, *J* = 19.6 Hz), 2.98 (3H, s), 2.76 (1H, br dt, *J* = 16.4, 1.2 Hz), 2.42 (1H, qd, *J* = 17.6, 1.6 Hz), 2.15 (1H, dd, *J* = 17.6, 4.8 Hz), 1.82 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 4.0:1, major isomer): δ 171.9 (C, N-*C*=O), 169.5 (C, N-*C*=O), 150.2 (C, N-*C*=O), 143.2 (C), 133.0 (C), 130.4 (C, q, *J* = 32.5 Hz), 128.2 (2 x CH), 125.4 (2 x CH, q, *J* = 4.0 Hz), 123.8 (C, q, *J* = 271.0 Hz, *C*$F_3$), 116.6 (CH), 53.8 (C), 48.0 (CH), 33.9 ($CH_2$), 33.0 ($CH_2$), 28.5 ($CH_3$), 28.1 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{19}F_3N_2O_3Na$ 403.1245; Found 403.1246.



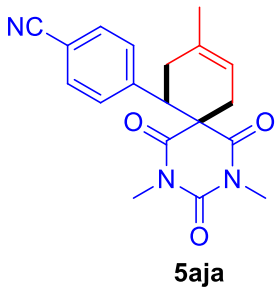
**5aha**

**2,4,9-Trimethyl-11-(4-nitrophenyl)-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aia):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as a white solid. Mp.: 263-266 °C. Yield: 78% (83.6 mg). IR (Neat): $\nu_{max}$ 2920, 1746, 1675, 1521, 1446, 1419, 1378, 1347, 1315, 1282, 1113, 859, 754 and 698 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *rr* = 5.0:1, major isomer): δ 8.12 (2H, d, *J* = 9.0 Hz), 7.24 (2H, d, *J* = 9.0 Hz), 5.52 (1H, br s), 3.65 (1H, dd, *J* = 12.0, 5.0 Hz), 3.20 (3H, s), 3.06 (1H, br d, *J* = 19.6 Hz), 3.02 (3H, s), 2.80 (1H, br t, *J* = 14.0 Hz), 2.44 (1H, qd, *J* = 17.5, 1.5 Hz), 2.18 (1H, dd, *J* = 17.0, 5.0 Hz), 1.83 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 5.0:1, major isomer): δ 171.7 (C, *C*=O), 169.3 (C, *C*=O), 150.1 (C, *C*=O), 147.5 (C, *C*-$NO_2$), 146.8 (C), 133.0 (C), 128.9 (2 x CH), 123.6 (2 x CH), 116.4 (CH), 53.6 (C), 47.5 (CH), 34.3 ($CH_2$), 33.1 ($CH_2$), 28.6 ($CH_3$), 28.3 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{19}N_3O_5Na$ 380.1222; Found 380.1222.



**5aia**

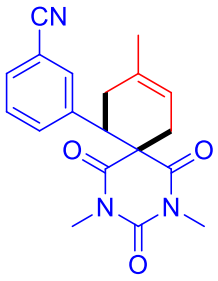
**4-(2,4,9-Trimethyl-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7-yl)benzonitrile (5aja):**



**5aja**

The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 88% (89.1 mg). IR (Neat): $\nu_{max}$ 2969, 2228, 2110, 1739, 1676, 1446, 1420, 1377, 1281, 1216, 1114, 838 and 754 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz, *rr* = 5.3:1, major isomer): δ 7.55 (2H, br d, *J* = 8.4 Hz), 7.16 (2H, br d, *J* = 8.4 Hz), 5.50 (1H, br s), 3.56 (1H, dd, *J* = 12.0, 4.8 Hz), 3.19 (3H, s), 3.03 (1H, br d, *J* = 18.5 Hz), 3.01 (3H, s), 2.75 (1H, br t, *J* = 14.0 Hz), 2.42 (1H, qd, *J* = 18.0, 1.6 Hz), 2.15 (1H, dd, *J* = 17.2, 4.8 Hz), 1.82 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 5.3:1, major isomer): δ 171.8 (C, *C*=O), 169.4 (C, *C*=O), 150.2 (C, *C*=O), 144.7 (C), 133.0 (C), 132.2 (2 x CH), 128.7 (2 x CH), 118.2 (C), 116.5 (CH), 112.2 (C, *C*N), 53.7 (C), 48.0 (CH), 34.1 ($CH_2$), 32.9 ($CH_2$), 28.6 ($CH_3$), 28.3 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{19}N_3O_3Na$ 360.1324; Found 360.1322.

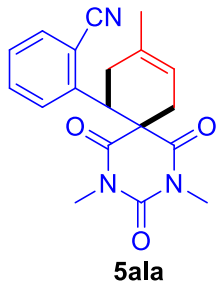
**3-(2,4,9-Trimethyl-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7-yl)benzonitrile (5aka):**



**5aka**

The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 66% (66.8 mg). IR (Neat): $\nu_{max}$ 2918, 2360, 2230, 1741, 1672, 1419, 1377, 1280, 1113, 1054, 913, 804 and 755 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz, *rr* = 6.0:1, major isomer): δ 7.56 (1H, td, *J* = 7.6, 1.2 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 7.35 (1H, br s), 7.29 (1H, td, *J* = 7.6, 1.2 Hz), 5.51 (1H, br s), 3.54 (1H, dd, *J* = 12.4, 5.2 Hz), 3.19 (3H, s), 3.03 (1H, br d, *J* = 18.0 Hz), 3.02 (3H, s), 2.74 (1H, m), 2.42 (1H, qd, *J* = 17.6, 1.6 Hz), 2.16 (1H, dd, *J* = 17.2, 4.8 Hz), 1.82 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 6.0:1, major isomer): δ 171.7 (C, *C*=O), 169.3 (C, *C*=O), 150.2 (C, *C*=O), 140.7 (C), 132.8 (C), 132.2 (CH), 131.8 (CH), 131.4 (CH), 129.3 (CH), 118.1 (C), 116.6 (CH), 112.7 (C, *C*N), 53.8 (C), 47.6 (CH), 33.8 ($CH_2$), 32.8 ($CH_2$), 28.5 ($CH_3$), 28.2 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}N_3O_3H$ 338.1505; Found 338.1506.

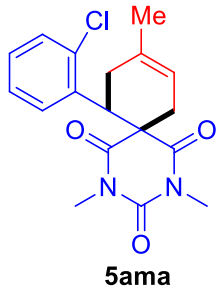
**2-(2,4,9-Trimethyl-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7-yl)benzonitrile (5ala):**



**5ala**

The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated colorless liquid. Yield: 41% (41.6 mg). IR (Neat): $\nu_{max}$ 2964, 2913, 2224, 1744, 1677, 1446, 1419, 1379, 1280, 1115 and 755 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *rr* = 4.5:1, major isomer): δ 7.64 (1H, br d, *J* = 7.5 Hz), 7.51 (1H, br t, *J* = 7.5 Hz), 7.36 (1H, br t, *J* = 7.5 Hz), 7.17 (1H, br d, *J* = 8.0 Hz), 5.51 (1H, s, olefinic-*H*), 4.07 (1H, dd, *J* = 10.5, 4.5 Hz), 3.26 (3H, br s), 3.10 (1H, br t, *J* = 18.0 Hz), 3.05 (3H, br s), 2.70 (1H, br t, *J* = 16.0 Hz), 2.46 (1H, br d, *J* = 18.0 Hz), 2.25 (1H, br dd, *J* = 17.5, 5.0 Hz), 1.82 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 4.5:1, major isomer): δ 170.9 (C, *C*=O), 169.7 (C, *C*=O), 150.5 (C, *C*=O), 143.5 (C), 133.5 (CH), 133.3 (C), 132.9 (CH), 128.4 (CH), 126.9 (CH), 117.2 (C), 116.6 (CH), 113.5 (C, *C*≡N), 53.1 (C), 45.5 (CH), 34.6 ($CH_2$), 34.5 ($CH_2$), 28.8 ($CH_3$), 28.4 ($CH_3$), 23.0 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}N_3O_3H$ 338.1505; Found 338.1504.

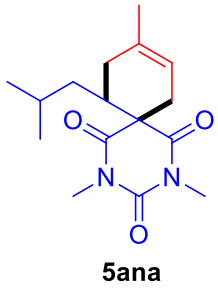
**11-(2-Chlorophenyl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5ama):**



**5ama**

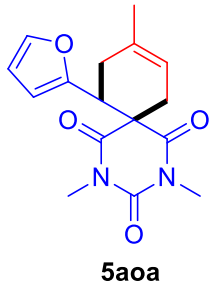
The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated colorless liquid. Yield: 70% (73.9 mg). IR (Neat): $\nu_{max}$ 2964, 2908, 2862, 1745, 1676, 1598, 1440, 1417, 1377, 1279, 1162, 1109, 1037, 1004, 851, 754 and 698 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *rr* = 5.3:1, major isomer): δ 7.35 (1H, br t, *J* = 5.0 Hz), 7.18-7.17 (2H, m), 6.98 (1H, br t, *J* = 5.0 Hz), 5.55 (1H, br s), 4.17 (1H, dd, *J* = 11.5, 4.5 Hz), 3.21 (1H, br d, *J* = 9.0 Hz), 3.20 (3H, s), 3.02 (3H, s), 2.57 (1H, br t, *J* = 14.0 Hz), 2.42 (1H, br d, *J* = 18.0 Hz), 2.13 (1H, br dd, *J* = 17.5, 4.5 Hz), 1.80 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 5.3:1, major isomer): δ 171.0 (C, N-*C*=O), 169.9 (C, N-*C*=O), 150.5 (C, N-*C*=O), 136.8 (C), 134.3 (C), 132.5 (C), 129.9 (CH), 129.0 (CH), 127.7 (CH), 126.6 (CH), 117.2 (CH), 53.1 (C), 43.4 (CH), 33.8 ($CH_2$), 32.7 ($CH_2$), 28.8 ($CH_3$), 28.1 ($CH_3$), 23.0 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{19}ClN_2O_3Na$ 369.0982; Found 369.0982.

**11-Isobutyl-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5ana):** 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 as colorless liquid. Yield: 71% (62.3 mg). IR (Neat): $\nu_{max}$ 2956, 1745, 1671, 1444, 1415, 1362, 1266, 1161, 1115, 1049, 1006, 847, 788, 756 and 733 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, *rr* = 9.0:1, major isomer): δ 5.34 (1H, s), 3.33 (3H, s), 3.28 (3H, s), 2.72 (1H, dd, *J* = 17.6, 1.6 Hz), 2.51-2.44 (1H, m), 2.34 (1H, dd, *J* = 17.6, 4.0 Hz), 2.16-2.06 (2H, m), 1.75 (3H, s), 1.70-1.64 (1H, m), 1.10 (1H, dt, *J* = 11.2, 3.6 Hz), 0.85 (3H, d, *J* = 6.4 Hz), 0.82 (3H, d, *J* = 6.8 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 9.0:1, major isomer): δ 173.0 (C, N-*C*=O), 170.0 (C, N-*C*=O), 151.2 (C, N-*C*=O), 133.4 (C), 115.3 (CH), 53.1 (C), 41.0 ($CH_2$), 38.0 (CH), 34.5 ($CH_2$), 32.6 ($CH_2$), 28.7 ($CH_3$), 28.2 ($CH_3$), 24.7 (CH), 24.0 ($CH_3$), 23.2 ($CH_3$), 20.6 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{24}N_2O_3H$ 293.1865; Found 293.1862.



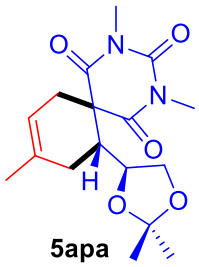
**5ana**

**11-(Furan-2-yl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aoa):** 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 as a white solid. Mp.: 249-251 °C. Yield: 83% (75.3 mg). IR (Neat): $\nu_{max}$ 2963, 2921, 2851, 1745, 1670, 1446, 1418, 1375, 1321, 1278, 1147, 1111, 1055, 1011, 960, 885, 852, 796, 741 and 599 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *rr* = 20.0:1, major isomer): δ 7.24 (1H, br d, *J* = 3.5 Hz), 6.26 (1H, dd, *J* = 3.0, 2.0 Hz), 6.03 (1H, d, *J* = 3.5 Hz), 5.48 (1H, br s), 3.60 (1H, dd, *J* = 12.0, 5.0 Hz), 3.17 (3H, s), 3.16 (3H, s), 3.02 (1H, br d, *J* = 18.0 Hz), 2.62 (1H, br t, *J* = 15.0 Hz), 2.38 (1H, br d, *J* = 18.0 Hz), 2.19 (1H, dd, *J* = 17.5, 5.0 Hz), 1.80 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 20.0:1, major isomer): δ 172.3 (C, N-*C*=O), 169.5 (C, N-*C*=O), 153.2 (C, N-*C*=O), 150.8 (C), 142.2 (CH), 132.3 (C), 116.8 (CH), 110.5 (CH), 107.0 (CH), 53.0 (C), 42.0 (CH), 32.7 ($CH_2$), 31.5 ($CH_2$), 28.8 ($CH_3$), 28.3 ($CH_3$), 23.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{18}N_2O_4Na$ 325.1164; Found 325.1166.



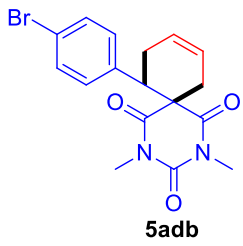
**5aoa**

**(*R*)-11-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,4,9-trimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5apa):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and isolated as a white solid. Mp.: 248-251 °C. Yield: 65% (65.6 mg). $[\alpha]_D^{25}$ = +87.8° (*c* = 0.632, $CHCl_3$, >99% *ee* and 11:1 *dr*); IR (Neat): $\nu_{max}$ 2977, 2915, 1743, 1669, 1515, 1441, 1413, 1367, 1267, 1220, 1154, 1114, 1048, 921, 860, 795, 752, 732, 511 and 470 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, *dr* = 11.0:1, major isomer): δ 5.38 (1H, br s), 3.97 (1H, dt, *J* = 6.4, 3.2 Hz), 3.89 (1H, dd, *J* = 8.4, 6.4 Hz), 3.72 (1H, dd, *J* = 8.4, 6.8 Hz), 3.35 (3H, s), 3.23 (3H, s), 2.85 (1H, br d, *J* = 18.4 Hz), 2.57 (1H, ddd, *J* = 12.0, 4.8, 3.2 Hz), 2.38 (1H, br t, *J* = 17.2 Hz), 2.30 (1H, br d, *J* = 17.6 Hz), 1.97 (1H, dd, *J* = 17.2, 4.8 Hz), 1.79 (3H, s), 1.31 (3H, s), 1.21 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 11.0:1, major isomer): δ 173.2 (C, N-*C*=O), 169.6 (C, N-*C*=O), 151.3 (C, N-*C*=O), 133.3 (C), 116.0 (CH), 109.2 (C), 74.7 (CH), 66.3 ($CH_2$), 50.7 (C), 43.9 (CH), 35.2 ($CH_2$), 28.7 ($CH_3$), 28.4 ($CH_3$), 26.9 ($CH_2$), 25.8 ($CH_3$), 24.8 ($CH_3$), 23.3 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{24}N_2O_5Na$ 359.1583; Found 359.1580.



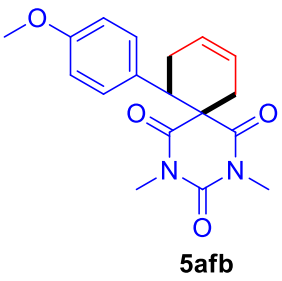
**5apa**

**11-(4-Bromophenyl)-2,4-dimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5adb):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 82% (92.8 mg). IR (Neat): $\nu_{max}$ 3025, 2908, 1744, 1675, 1448, 1420, 1376, 1280, 1113, 1075, 1009, 849, 823 and 754 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.38 (2H, td, *J* = 8.4, 1.2 Hz), 6.87 (2H, td, *J* = 8.4, 1.2 Hz), 5.98-5.93 (1H, m), 5.86-5.82 (1H, m), 3.38 (1H, dd, *J* = 12.0, 4.8 Hz), 3.18 (3H, s), 3.12-3.06 (1H, m), 2.99 (3H, s), 2.75-2.67 (1H, m), 2.41 (1H, quintet of d, *J* = 18.0, 2.0 Hz), 2.28 (1H, td, *J* = 18.0, 5.2 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135): δ 171.9 (C, N-*C*=O), 169.6 (C, N-*C*=O), 150.2 (C, N-*C*=O), 137.8 (C), 131.6 (2 x CH), 129.2 (2 x CH), 125.5 (CH), 123.1 (CH), 122.2 (C), 54.2 (C), 47.7 (CH), 32.9 ($CH_2$), 28.5 ($CH_3$), 28.2 ($CH_3$), 28.1 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{17}BrN_2O_3Na$ 399.0320; Found 399.0326.



**5adb**

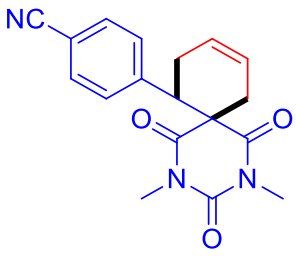
**11-(4-Methoxyphenyl)-2,4-dimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5afb):**



**5afb**

The titled 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 as colorless liquid. Yield: 72% (70.9 mg). IR (Neat): $\nu_{max}$ 3030, 2910, 2836, 2360, 1743, 1668, 1610, 1511, 1448, 1416, 1373, 1330, 1250, 1178, 1113, 1031, 830, 752, 736 and 651 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 6.88 (2H, td, *J* = 8.5, 1.2 Hz), 6.77 (2H, td, *J* = 8.5, 1.2 Hz), 5.96-5.92 (1H, m), 5.86-5.83 (1H, m), 3.76 (3H, s), 3.33 (1H, dd, *J* = 12.0, 5.0 Hz), 3.16 (3H, s), 3.15-3.08 (1H, m), 2.97 (3H, s), 2.72-2.65 (1H, m), 2.43-2.37 (1H, quintet of d, *J* = 18.0, 2.0 Hz), 2.27 (1H, br td, *J* = 18.0, 5.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135): δ 172.2 (C, N-*C*=O), 169.9 (C, N-*C*=O), 159.4 (C), 150.4 (C, N-*C*=O), 130.4 (C), 128.5 (2 x CH), 125.6 (CH), 123.3 (CH), 113.8 (2 x CH), 55.2 ($CH_3$), 54.9 (C), 48.0 (CH), 32.5 ($CH_2$), 28.5 ($CH_3$), 28.2 ($CH_2$), 28.1 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{20}N_2O_4Na$ 351.1321, Found 351.1321.

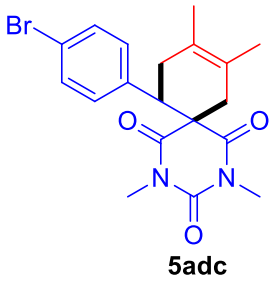
**4-(2,4-Dimethyl-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7-yl)benzonitrile (5ajb):** The



**5ajb**

title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 84% (81.4 mg). IR (Neat): $\nu_{max}$ 3031, 2920, 2855, 2228, 1745, 1670, 1607, 1449, 1418, 1374, 1280, 1113, 1055, 1011, 913, 852, 833 and 751 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz): δ 7.57 (2H, br d, *J* = 8.0 Hz), 7.15 (2H, br d, *J* = 8.4 Hz), 6.00-5.95 (1H, m), 5.86-5.83 (1H, m), 3.50 (1H, dd, *J* = 12.0, 5.2 Hz), 3.19 (3H, s), 3.10-3.05 (1H, m), 2.99 (3H, s), 2.83-2.74 (1H, m), 2.45 (1H, quintet of d, *J* = 18.4, 2.4 Hz), 2.32 (1H, td, *J* = 17.6, 5.2 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135): δ 171.5 (C, N-*C*=O), 169.3 (C, N-*C*=O), 150.1 (C, N-*C*=O), 144.5 (C), 132.2 (2 x CH), 128.6 (2 x CH), 125.3 (CH), 122.9 (CH), 118.2 (C), 112.2 (C, *C*N), 54.0 (C), 47.7 (CH), 33.3 ($CH_2$), 28.5 ($CH_3$), 28.2 ($CH_3$), 28.0 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{17}N_3O_3H$ 324.1348; Found 324.1348.

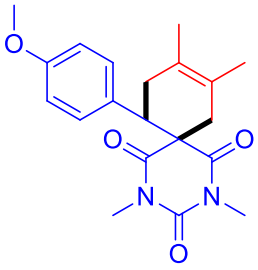
**11-(4-Bromophenyl)-2,4,8,9-tetramethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione**



**5adc**

**(5adc):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as a white solid. Mp.: 244-247 °C. Yield: 70% (85.1 mg). IR (Neat): $\nu_{max}$ 2909, 2859, 2831, 1738, 1675, 1446, 1419, 1374, 1280, 1240, 1099, 1053, 1009, 838, 819 and 754cm$^{-1}$. $^{1}$H NMR ($CDCl_3$, 500 MHz): δ 7.37 (2H, br d, *J* = 8.5 Hz), 6.87 (2H, br d, *J* = 8.0 Hz), 3.38 (1H, dd, *J* = 12.0, 4.5 Hz), 3.16 (3H, s), 3.04-2.99 (1H, m), 3.00 (3H, s), 2.70 (1H, br t, *J* = 15.0 Hz), 2.23 (1H, d, *J* = 17.5 Hz), 2.09 (1H, dd, *J* = 17.0, 4.5 Hz), 1.75 (3H, s), 1.72 (3H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135): δ 172.0 (C, N-*C*=O), 169.6 (C, N-*C*=O), 150.3 (C, N-*C*=O), 137.9 (C), 131.5 (2 x CH), 129.2 (2 x CH), 124.6 (C), 122.0 (C), 121.7 (C), 55.4 (C), 48.4 (CH), 38.7 ($CH_2$), 34.4 ($CH_2$), 28.5 ($CH_3$), 28.1 ($CH_3$), 18.9 ($CH_3$), 18.3 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}N_2O_3BrH$ 405.0814; Found 405.0814.

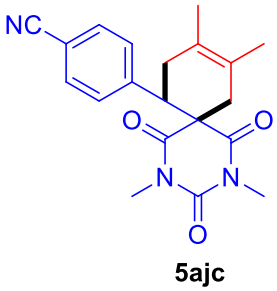
**11-(4-Methoxyphenyl)-2,4,8,9-tetramethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione**



**5afc**

**(5afc):** 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 as colorless liquid. Yield: 75% (80.2 mg). IR (Neat): $\nu_{max}$ 2999, 2910, 2837, 1742, 1674, 1610, 1512, 1447, 1418, 1376, 1250, 1179, 1134, 1033, 839 and 752 cm$^{-1}$. $^{1}$H NMR ($CDCl_3$, 500 MHz): δ 6.88 (2H, br d, *J* = 9.0 Hz), 6.76 (2H, br d, *J* = 9.0 Hz), 3.76 (3H, s), 3.33 (1H, dd, *J* = 12.5, 5.0 Hz), 3.14 (3H, s), 3.06 (1H, br d, *J* = 17.5 Hz), 2.96 (3H, s), 2.67 (1H, t, *J* = 14.5 Hz), 2.22 (1H, d, *J* = 18.0 Hz), 2.07 (1H, dd, *J* = 17.0, 4.0 Hz), 1.74 (3H, s), 1.72 (3H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135): δ 172.3 (C, N-*C*=O), 169.9 (C, N-*C*=O), 159.2 (C, *C*-OMe), 150.4 (C, N-*C*=O), 130.4 (C), 128.3 (2 x CH), 124.6 (C), 121.8 (C), 113.6 (2 x CH), 56.0 (C), 55.1 ($CH_3$, O*C*$H_3$), 48.7 (CH), 38.1 ($CH_2$), 34.4 ($CH_2$), 28.3 ($CH_3$), 27.9 ($CH_3$), 18.9 ($CH_3$), 18.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{24}N_2O_4H$ 357.1814; Found 357.1814.

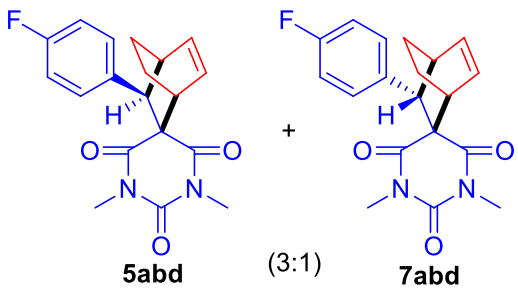
**4-(2,4,9,10-Tetramethyl-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7yl)benzonitrile**



**5ajc**

**(5ajc):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as white solid. Mp.: 320 °C. Yield: 71% (74.8 mg). IR (Neat): $\nu_{max}$ 2911, 2856, 2228, 1745, 1672, 1608, 1504, 1446, 1418, 1376, 1282, 1133, 1100, 1058, 879, 848 and 754 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz): δ 7.55 (2H, d, *J* = 8.0 Hz), 7.15 (2H, d, *J* = 8.4 Hz), 3.51 (1H, dd, *J* = 12.0, 4.8 Hz), 3.17 (3H, s), 3.04-2.99 (1H, m), 3.00 (3H, s), 2.77 (1H, br t, *J* = 15.2 Hz), 2.27 (1H, br d, *J* = 17.6 Hz), 2.13 (1H, br dd, *J* = 17.2, 4.4 Hz), 1.76 (3H, s), 1.72 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135): δ 171.6 (C, N-*C*=O), 169.3 (C, N-*C*=O), 150.1 (C, N-*C*=O), 144.6 (C), 132.1 (2 x CH), 128.5 (2 x CH), 124.5 (C), 121.6 (C), 118.2 (C), 112.0 (C, *C*N), 55.1 (C), 48.4 (CH), 39.0 ($CH_2$), 34.1 ($CH_2$), 28.5 ($CH_3$), 28.1 ($CH_3$), 18.8 ($CH_3$), 18.3 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{21}N_3O_3H$ 352.1661; Found 352.1661.

**(1*R**,3*R**,4*S**)-3-(4-Fluorophenyl)-1',3'-dimethyl-2'*H*-spiro[bicyclo[2.2.2]octane-2,5'-pyrimidin]-5-ene-2',4',6'(1'*H*,3'*H*)-trione (5abd) and (1*R**,3*S**,4*S**)-3-(4-Fluorophenyl)-1',3'-dimethyl-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidine]-2',4',6'(3'*H*)-trione**

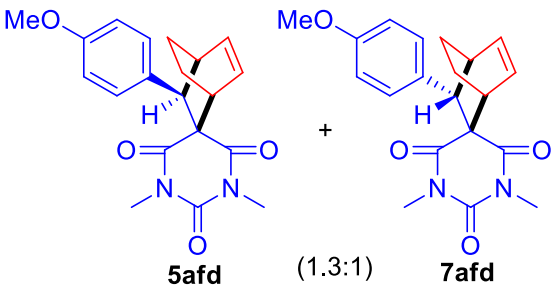


**5abd** (3:1) **7abd**

**(7abd):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as white solid. Mp.: 261-263 °C. Yield: 71% (72.9 mg). IR (Neat): $\nu_{max}$ 3059, 2947, 2875, 1746, 1677, 1509, 1415, 1361, 1222, 1160, 1107, 1025, 841 and 757 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz, *dr* = 3.0:1, major isomer): δ 7.04-6.99 (2H, m), 6.92-6.87 (2H, m), 6.71 (1H, t, *J* = 7.2 Hz), 6.17 (1H, t, *J* = 7.2 Hz), 4.25 (1H, s), 3.39 (3H, s), 3.01-2.99 (1H, m), 2.94 (3H, s), 2.90-2.88 (1H, m), 2.10-2.03 (1H, m), 1.90-1.83 (1H, m), 1.37 (1H, tt, *J* = 12.0, 3.2 Hz), 1.26 (1H, tt, *J* = 12.0, 3.2 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 3.0:1, major isomer): δ 171.5 (C, N-*C*=O), 167.2 (C, N-*C*=O), 161.2 (C, d, *J* = 243.0 Hz, *C*-F), 151.1 (C, N-*C*=O), 137.6 (C, d, *J* = 3.0 Hz), 133.8 (CH), 130.5 (CH), 129.3 (2 x CH, d, *J* = 7.0 Hz), 114.8 (2 x CH, d, *J* = 21.0 Hz), 63.4 (C), 49.8 (CH), 42.0 (CH), 34.9 (CH), 29.6 ($CH_3$), 28.7 ($CH_3$), 25.9 ($CH_2$), 20.6 ($CH_2$). $^{1}H$ NMR ($CDCl_3$, 400 MHz, *dr* = 3.0:1, minor isomer): δ 6.99-6.97 (2H, m), 6.94-6.92 (2H, m), 6.63 (1H, t, *J* = 7.2 Hz), 6.12

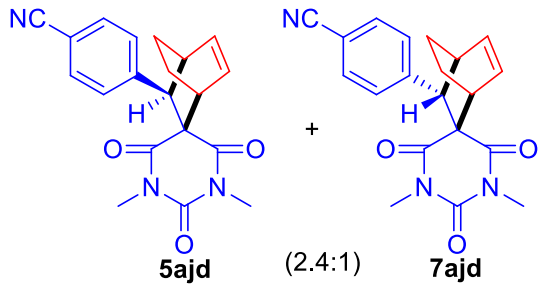
(1H, t, *J* = 7.2 Hz), 4.08 (1H, s), 3.38 (3H, s), 3.21-3.20 (1H, m), 3.14 (3H, s), 2.77-2.76 (1H, m), 2.40-2.34 (1H, m), 1.72-1.67 (1H, m), 1.42-1.35 (2H, m). $^{13}$C NMR ($CDCl_3$, DEPT-135, *dr* = 3.0:1, minor isomer): δ 171.6 (C, N-*C*=O), 168.1 (C, N-*C*=O), 160.8 (C, d, *J* = 243.0 Hz, *C*-F), 151.1 (C, N-*C*=O), 137.6 (C, d, *J* = 3.0 Hz), 137.3 (CH), 129.2 (CH), 128.0 (2 x CH, d, *J* = 7.0 Hz), 114.98 (2 x CH, d, *J* = 21.0 Hz), 59.8 (C), 44.8 (CH), 42.5 (CH), 31.8 (CH), 29.8 ($CH_3$), 28.8 ($CH_3$), 23.7 ($CH_2$), 16.8 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}FN_2O_3H$ 343.1458; Found 343.1458.

**(1*R**,3*R**,4*S**)-3-(4-Methoxyphenyl)-1',3'-dimethyl-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidine]-2',4',6'(3'*H*)-trione (5afd) and (1*R**,3*S**,4*S**)-3-(4-Methoxyphenyl)-1',3'-dimethyl-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidine]-2',4',6'(3'*H*)-trione (7afd):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid.



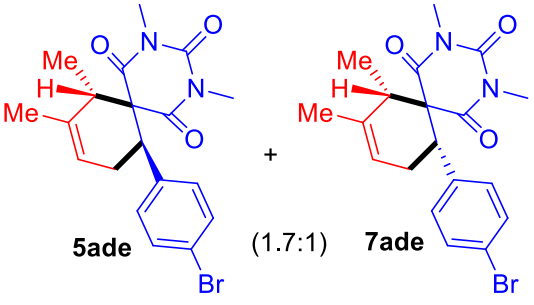

Yield: 72% (76.6 mg). IR (Neat): $\nu_{max}$ 3050, 2943, 2830, 1744, 1673, 1610, 1511, 1441, 1414, 1358, 1246, 1179, 1114,1031, 946, 833, 755 and 692 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz, *dr* = 1.3:1, major isomer): δ 6.98 (2H, d, *J* = 8.5 Hz), 6.74 (2H, d, *J* = 8.5 Hz), 6.64 (1H, t, *J* = 7.0 Hz), 6.26 (1H, t, *J* = 7.0 Hz), 4.05 (1H, s), 3.74 (3H, s), 3.37 (3H, s), 2.96-2.95 (1H, m), 2.91-2.90 (1H, m), 2.85 (3H, s), 2.25-2.19 (1H, m), 1.86-1.81 (1H, m), 1.27-1.21 (2H, m). $^{13}$C NMR ($CDCl_3$, DEPT-135, *dr* = 1.3:1, major isomer): δ 171.7 (C, N-*C*=O), 167.4 (C, N-*C*=O), 158.0 (C), 151.1 (C, N-*C*=O), 133.6 (C), 132.6 (CH), 131.6 (CH), 128.7 (2 x CH), 113.3 (2 x CH), 63.3 (C), 55.0 ($CH_3$), 51.6 (CH), 40.6 (CH), 35.3 (CH), 29.3 ($CH_3$), 28.4 ($CH_3$), 25.9 ($CH_2$), 20.7 ($CH_2$); $^1$H NMR ($CDCl_3$, 500 MHz, *dr* = 1.3:1, minor isomer): δ 6.94 (2H, d, *J* = 9.0 Hz), 6.76 (2H, d, *J* = 8.5 Hz), 6.61 (1H, t, *J* = 7.5 Hz), 6.11 (1H, t, *J* = 7.0 Hz), 4.03 (1H, s), 3.75 (3H, s), 3.37 (3H, s), 3.19 (1H, br s), 3.12 (3H, s), 2.75-2.74 (1H, m), 2.42-2.37 (1H, m), 1.75-1.70 (1H, m), 1.40-1.34 (2H, m). $^{13}$C NMR ($CDCl_3$, DEPT-135, *dr* = 1.3:1, minor isomer) δ 171.6 (C, N-*C*=O), 168.0 (C, N-*C*=O), 157.3 (C), 151.1 (C, N-*C*=O), 137.1 (CH), 133.6 (C), 129.2 (CH), 127.5 (2 x CH), 113.5 (2 x CH), 59.5 (C), 54.9 ($CH_3$), 45.2 (CH), 42.1 (CH), 32.0 (CH), 29.6 ($CH_3$), 28.6 ($CH_3$), 23.6 ($CH_2$), 16.8 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}N_2O_4H$ 355.1658; Found 355.1658.

**4-((1*R**,3*R**,4*S**)-1',3'-Dimethyl-2',4',6'-trioxo-2',3',4',6'-tetrahydro-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidin]-3-yl)benzonitrile (5ajd) and 4-((1*R**,3*S**,4*S**)-1',3'-Dimethyl-2',4',6'-trioxo-2',3',4',6'-tetrahydro-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidin]-3-yl)benzonitrile (7ajd):** The titled



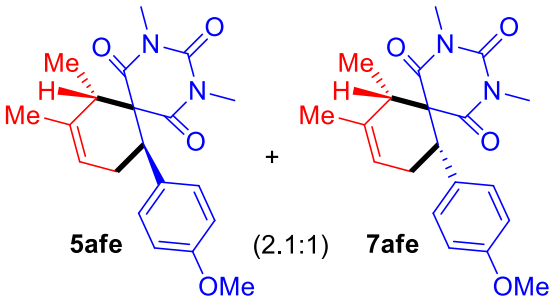

compound was prepared by following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as white solid. Mp.: 303-306 °C. Yield: 86% (90.1 mg). IR (Neat): $\nu_{max}$ 3056, 2947, 2875, 2225, 1735, 1673, 1607, 1441, 1415, 1364, 1262, 1111, 1026, 945, 848, 755 and 732 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, *dr* = 2.4:1, major isomer): δ 7.49 (2H, d, *J* = 8.4 Hz), 7.16 (2H, d, *J* = 8.4 Hz), 6.78 (1H, t, *J* = 7.2 Hz), 6.08 (1H, dt, *J* = 7.4, 0.8 Hz), 4.46 (1H, s), 3.42 (3H, s), 3.09-3.07 (1H, m), 3.01 (3H, s), 2.91-2.89 (1H, m), 1.90-1.88 (2H, m), 1.37-1.26 (2H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 2.4:1, major isomer): δ 170.9 (C, N-*C*=O), 166.9 (C, N-*C*=O), 151.0 (C, N-*C*=O), 148.0 (C), 134.7 (CH), 131.6 (2 x CH), 129.4 (CH), 128.6 (2 x CH), 118.9 (C), 109.7 (C, *C*N), 63.7 (C), 48.6 (CH), 43.3 (CH), 33.8 (CH), 29.8 ($CH_3$), 28.8 ($CH_3$), 25.5 ($CH_2$), 20.4 ($CH_2$). $^1H$ NMR ($CDCl_3$, 400 MHz, *dr* = 2.4:1, minor isomer): δ 7.54 (2H, d, *J* = 8.4 Hz), 7.13 (2H, d, *J* = 8.4 Hz), 6.63 (1H, t, *J* = 7.6 Hz), 6.14 (1H, t, *J* = 7.2 Hz), 4.15 (1H, s), 3.39 (3H, s), 3.26-3.24 (1H, m), 3.15 (3H, s), 2.83-2.80 (1H, m), 2.35-2.29 (2H, m), 1.42-1.37 (2H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 2.4:1, minor isomer) δ 171.2 (C, N-*C*=O), 168.2 (C, N-*C*=O), 150.9 (C, N-*C*=O), 148.0 (C), 137.0 (CH), 131.9 (2 x CH), 129.3 (CH), 127.4 (2 x CH), 118.9 (C), 109.5 (C, *C*N), 60.3 (C), 45.0 (CH), 42.9 (CH), 31.2 (CH), 29.9 ($CH_3$), 28.9 ($CH_3$), 23.5 ($CH_2$), 16.6 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{20}H_{19}N_3O_3NH_4$ 367.1770; Found 367.1770.

**(7*S**,11*R**)-11-(4-Bromophenyl)-2,4,7,8-tetramethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5ade) and (7*S**,11*S**)-11-(4-Bromophenyl)-2,4,7,8-tetramethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (7ade):** The titled compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as a white solid. Mp.: 312-315 °C. Yield: 83% (100.9 mg). IR (Neat): $\nu_{max}$ 3020,



1677, 1445, 1375, 1264, 1215, 1077, 1011, 823, 745 and 667 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, *dr* = 1.7 :1, major isomer): δ 7.35 (2H, d, *J* = 8.0 Hz), 7.17 (2H, d, *J* = 8.5 Hz), 5.65 (1H, br s), 3.55 (1H, dd, *J* = 9.5, 7.0 Hz), 3.23 (3H, s), 3.20 (3H, s), 2.83 (1H, dd, *J* = 16.5, 10.0 Hz), 2.48 (1H, q, *J* = 7.0 Hz), 2.38 (1H, br d, *J* = 18.0 Hz), 1.77 (3H, s), 1.08 (3H, d, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 1.7 :1, major isomer): δ 169.9 (C, N-*C*=O), 169.1 (C, N-*C*=O), 150.9 (C, N-*C*=O), 140.3 (C, *C*-Br), 132.4 (C), 131.3 (2 x CH), 131.0 (2 x CH), 122.0 (CH), 120.7 (C), 59.1 (C), 42.1 (CH), 40.2 (CH), 31.3 ($CH_2$), 28.7 ($CH_3$), 28.6 ($CH_3$), 22.3 ($CH_3$), 16.5 ($CH_3$). $^1H$ NMR ($CDCl_3$, 400 MHz, *dr* = 1.7 :1, minor isomer): δ 7.36 (2H, d, *J* = 8.0 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 5.65 (1H, br s), 3.46 (1H, dd, *J* = 12.0, 5.0 Hz), 3.29 (1H, br s), 3.19 (3H, s), 3.01 (3H, s), 2.73 (1H, br t, *J* = 15.2 Hz), 2.21 (1H, m), 1.77 (3H, s), 0.94 (3H, d, *J* = 7.5 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 1.7 :1, minor isomer): δ 172.1 (C, N-*C*=O), 167.7 (C, N-*C*=O), 150.2 (C, N-*C*=O), 138.0 (C, *C*-Br), 133.4 (C), 131.5 (2 x CH), 129.1 (2 x CH), 121.9 (C), 121.0 (CH), 61.0 (C), 48.7 (CH), 41.1 (CH), 28.8 ($CH_2$), 28.4 ($CH_3$), 27.8 ($CH_3$), 21.1 ($CH_3$), 14.1 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}BrN_2O_3H$ 405.0814; Found 405.0807.

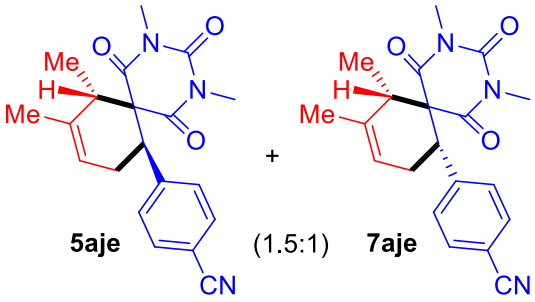
**(7*S**,11*R**)-11-(4-Methoxyphenyl)-2,4,7,8-tetramethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5afe) and (7*S**,11*S**)-11-(4-Methoxyphenyl)-2,4,7,8-tetramethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (7afe):** The title compound was prepared following



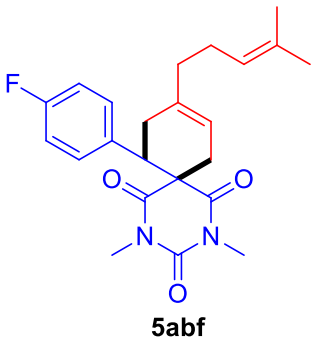

the procedure **A**, purified by column chromatography using EtOAc/hexane (1.0 : 9.0 to 2.0 : 8.0), and was isolated as colorless liquid. Yield: 78% (83.4 mg). IR (Neat): $\nu_{max}$ 2965, 1746, 1674, 1610, 1511, 1442, 1417, 1362, 1247, 1218, 1180, 1065, 1033, 831 and 749 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *dr* = 2.1:1, major isomer): δ 7.15 (2H, br d, *J* = 8.5 Hz), 6.76 (2H, br d, *J* = 8.5 Hz), 5.67 (1H, br s), 3.75 (3H, s), 3.49 (1H, dd, *J* = 9.0, 6.5 Hz), 3.21 (3H, s), 3.20 (3H, s), 2.80-2.75 (1H, m), 2.56 (1H, q, *J* = 7.0 Hz), 2.40-2.36 (1H, m), 1.79 (3H, s), 1.09 (3H, d, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 2.1:1, major isomer): δ 170.1 (C, N-*C*=O), 169.5 (C, N-*C*=O), 158.5 (C, *C*-OMe), 151.1 (C, N-*C*=O), 133.1 (C), 133.0 (C), 130.0 (2 x CH), 122.0 (CH), 113.6 (2 x CH), 59.9 (C), 55.0 ($CH_3$), 41.7 (CH), 40.9 (CH), 31.2 ($CH_2$), 28.6 ($CH_3$), 28.5 ($CH_3$), 22.1 ($CH_3$), 16.2 ($CH_3$); $^1H$ NMR ($CDCl_3$, 500 MHz, *dr* = 2.1:1, minor isomer): δ 6.88 (2H, d, *J* = 8.5 Hz), 6.75 (2H, d, *J* = 8.5 Hz), 5.63 (1H, m), 3.75 (3H, s),

3.42 (1H, dd, *J* = 12.0, 5.0 Hz), 3.35-3.31 (1H, m), 3.17 (3H, s), 2.99 (3H, s), 2.72-2.68 (1H, m), 2.21 (1H, td, *J* = 17.5, 5.0 Hz), 1.76 (3H, s), 0.94 (3H, d, *J* = 7.0 Hz). $^{13}$C NMR ($CDCl_3$, DEPT-135, *dr* = 2.1:1, minor isomer): δ 172.4 (C, N-*C*=O), 168.0 (C, N-*C*=O), 159.2 (C, *C*-OMe), 150.4 (C, N-*C*=O), 133.5 (C), 130.7 (C), 128.4 (2 x CH), 120.9 (CH), 113.7 (2 x CH), 61.7 (C), 55.1 ($CH_3$), 49.0 (CH), 40.7 (CH), 29.0 ($CH_2$), 28.4 ($CH_3$), 27.7 ($CH_3$), 21.1 ($CH_3$), 14.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{24}N_2O_4H$ 357.1814; Found 357.1812.

**4-((7*R**,11*S**)-2,4,10,11-Tetramethyl-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7-yl)benzonitrile (5aje) and 4-((7*S**,11*S**)-2,4,10,11-Tetramethyl-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7-yl)benzonitrile (7aje):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as white solid. Mp.: 320 °C. Yield: 85% (89.6 mg). IR (Neat): $\nu_{max}$ 2967, 2917, 2228, 1745, 1670, 1607, 1417, 1373, 1338, 1278, 1121, 1064, 914, 836, 753 and 732 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz, *dr* = 1.5:1, major isomer): δ 7.53 (2H, d, *J* = 8.5 Hz), 7.44 (2H, d, *J* = 8.0 Hz), 5.66 (1H, s), 3.67 (1H, dd, *J* = 10.0, 7.0 Hz), 3.26 (3H, s), 3.20 (3H, s), 2.92-2.87 (1H, m), 2.48 (1H, q, *J* = 7.0 Hz), 2.40 (1H, br d, *J* = 17.5 Hz), 1.77 (3H, s), 1.10 (3H, d, *J* = 7.0 Hz). $^{13}$C NMR ($CDCl_3$, DEPT-135, *dr* = 1.5:1, major isomer): δ 169.7 (C, N-*C*=O), 169.0 (C, N-*C*=O), 150.7 (C, N-*C*=O), 147.1 (C), 132.3 (C), 131.9 (2 x CH), 130.1 (2 x CH), 121.8 (CH), 118.5 (C), 110.8 (C, *C*N), 58.8 (C), 43.0 (CH), 41.3 (CH), 31.3 ($CH_2$), 28.7 ($CH_3$), 28.6 ($CH_3$), 22.2 ($CH_3$), 16.6 ($CH_3$). $^1$H NMR ($CDCl_3$, 500 MHz, *dr* = 1.5:1, minor isomer): δ 7.55 (2H, d, *J* = 8.5 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 5.66 (1H, s), 3.57 (1H, dd, *J* = 12.0, 5.0 Hz), 3.31-3.28 (1H, m), 3.20 (3H, s), 3.01 (3H, s), 2.82-2.76 (1H, m), 2.28-2.23 (1H, m), 1.77 (3H, s), 0.95 (3H, d, *J* = 7.5 Hz). $^{13}$C NMR ($CDCl_3$, DEPT-135, *dr* = 1.5:1, minor isomer): δ 171.7 (C, N-*C*=O), 167.5 (C, N-*C*=O), 150.0 (C, N-*C*=O), 144.6 (C), 133.4 (C), 132.1 (2 x CH), 128.3 (2 x CH), 120.4 (CH), 118.0 (C), 112.0 (C, *C*N), 60.7 (C), 49.0 (CH), 40.1 (CH), 28.6 ($CH_2$), 28.4 ($CH_3$), 27.8 ($CH_3$), 21.0 ($CH_3$), 13.9 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{21}N_3O_3H$ 352.1661; Found 352.1660.

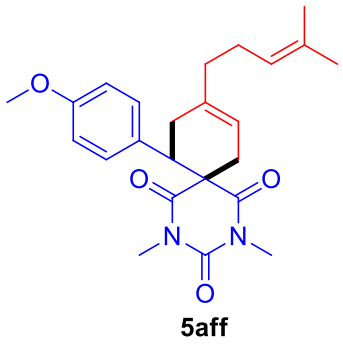


**11-(4-Fluorophenyl)-2,4-dimethyl-9-(4-methylpent-3-en-1-yl)-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5abf):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 70% (83.7 mg). IR (Neat): $\nu_{max}$ 2967, 2914, 2853, 1745, 1671, 1605, 1509, 1447, 1418, 1375, 1328, 1280, 1226, 1162, 1110, 1055, 1014, 914, 835, 752, 732 and 532 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *rr* = 4.3:1, major isomer): δ 6.99-6.92 (4H, m), 5.52 (1H, br s), 5.15 (1H, br s), 3.40 (1H, dd, *J* = 12.5, 4.5 Hz), 3.16 (3H, s), 3.09 (1H, d, *J* = 18.0 Hz), 2.97 (3H, s), 2.68 (1H, t, *J* = 14.5 Hz), 2.41 (1H, dd, *J* = 18.0, 3.0 Hz), 2.17-2.09 (5H, m), 1.70 (3H, s), 1.62 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 4.3:1, major isomer): δ 172.1 (C, N-*C*=O), 169.5 (C, N-*C*=O), 162.2 (C, d, *J* = 246.25 Hz, *C*-F), 150.2 (C, N-*C*=O), 136.5 (C), 134.6 (C, d, *J* = 3.75 Hz), 131.4 (C), 129.0 (2 x CH, d, *J* = 7.5 Hz), 123.9 (CH), 116.5 (CH), 115.2 (2 x CH, d, *J* = 21.25 Hz), 54.4 (C), 48.1 (CH), 37.1 ($CH_2$), 33.0 ($CH_2$), 31.4 ($CH_2$), 28.3 ($CH_3$), 27.9 ($CH_3$), 26.2 ($CH_2$), 25.5 ($CH_3$), 17.6 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + K]^+$ Calcd for $C_{23}H_{27}FN_2O_3K$ 437.1643; Found 437.1643.



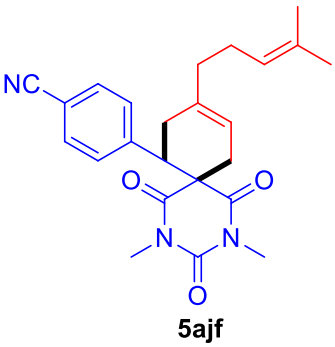
**5abf**

**11-(4-Methoxyphenyl)-2,4-dimethyl-9-(4-methylpent-3-en-1-yl)-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5aff):** The titled 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 as a white solid. Mp.: 159-161 °C. Yield: 71% (87.4 mg). IR (Neat): $\nu_{max}$ 3019, 1674, 1611, 1513, 1380, 1215, 1179, 1114, 1034, 833, 744 and 667 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, *rr* = 10.0:1, major isomer): δ 6.91 (2H, td, *J* = 8.8, 2.8 Hz), 6.78 (2H, td, *J* = 8.8, 2.8 Hz), 5.53 (1H, br s), 5.16 (1H, m), 3.77 (3H, s), 3.36 (1H, dd, *J* = 12.0, 4.4 Hz), 3.17 (3H, s), 3.14-3.09 (1H, m), 2.98 (3H, s), 2.67 (1H, br t, *J* = 15.6 Hz), 2.41 (1H, dd, *J* = 18.0, 4.4 Hz), 2.18-2.08 (5H, m), 1.71 (3H, s), 1.63 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 10.0:1, major isomer): δ 172.4 (C, N-*C*=O), 169.9 (C, N-*C*=O), 159.4 (C, *C*-OMe), 150.4 (C, N-*C*=O), 136.7 (C), 131.6 (C), 130.6 (C), 128.5 (2 x CH), 124.1 (CH), 116.6 (CH), 113.7 (2 x CH), 55.2 ($CH_3$), 54.8 (C), 48.5 (CH), 37.3 ($CH_2$), 32.9 ($CH_2$), 31.4 ($CH_2$), 28.4 ($CH_3$), 28.0 ($CH_3$), 26.3 ($CH_2$), 25.7 ($CH_3$), 17.7 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{30}N_2O_4H$ 411.2284; Found 411.2278.



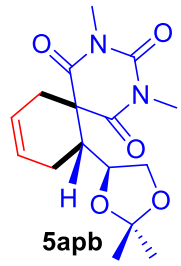
**5aff**

**4-(2,4-Dimethyl-9-(4-methylpent-3-en-1-yl)-1,3,5-trioxo-2,4-diazaspiro[5.5]undec-9-en-7-yl)benzonitrile (5ajf):** The titled compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 74% (90.0 mg). IR (Neat): $\nu_{max}$ 3020, 2225, 1679, 1421, 1379, 1214, 1113, 909, 744 and 667 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *rr* = 5.8:1, major isomer): δ 7.57 (2H, d, *J* = 8.0 Hz), 7.17 (2H, d, *J* = 8.5 Hz), 5.52 (1H, br s), 5.15 (1H, br s), 3.52 (1H, dd, *J* = 12.5, 5.0 Hz), 3.18 (3H, s), 3.05 (1H, br d, *J* = 18.0 Hz), 3.00 (3H, s), 2.76 (1H, br t, *J* = 14.5 Hz), 2.46 (1H, dd, *J* = 18.0, 3.5 Hz), 2.20-2.09 (5H, m), 1.70 (3H, s), 1.62 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 5.8:1, major isomer): δ 171.6 (C, N-*C*=O), 169.1 (C, N-*C*=O), 150.0 (C, N-*C*=O), 144.6 (C), 136.3 (C), 132.0 (2 x CH), 131.5 (C), 128.4 (2 x CH), 123.7 (CH), 118.0 (C), 116.1 (CH), 111.9 (C, *C*N), 53.7 (C), 48.0 (CH), 37.0 ($CH_2$), 33.6 ($CH_2$), 31.1 ($CH_2$), 28.3 ($CH_3$), 28.0 ($CH_3$), 26.1 ($CH_2$), 25.5 ($CH_3$), 17.5 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{27}N_3O_3H$ 406.2131; Found 406.2125.



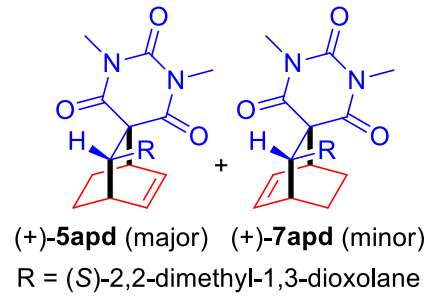
5ajf

**(*R*)-11-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,4-dimethyl-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5apb):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and isolated as a white solid. Mp.: 214-216 °C. Yield: 32% (30.9 mg). $[\alpha]_D^{25}$ = +42.5° (*c* = 0.136, $CHCl_3$, >99% *ee* and 12.5:1 *dr*); IR (Neat): $\nu_{max}$ 3031, 2979, 2912, 2850, 1742, 1671, 1518, 1444, 1415, 1369, 1317, 1266, 1205, 1153, 1115, 1047, 971, 953, 890, 848, 755, 663 and 513 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, *dr* = 12.5:1, major isomer): δ 5.92-5.89 (1H, m), 5.73-5.70 (1H, m), 3.97 (1H, dt, *J* = 6.5, 2.5 Hz), 3.90 (1H, dd, *J* = 8.5, 6.5 Hz), 3.71 (1H, dd, *J* = 8.5, 6.5 Hz), 3.36 (3H, s), 3.24 (3H, s), 2.89 (1H, br d, *J* = 18.0 Hz), 2.52-2.48 (1H, m), 2.46-2.39 (1H, m), 2.36-2.31 (1H, m), 2.15 (1H, td, *J* = 17.5, 5.0 Hz), 1.30 (3H, s), 1.21 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 12.5:1, major isomer): δ 173.0 (C, N-*C*=O), 169.7 (C, N-*C*=O), 151.3 (C, N-*C*=O), 125.9 (CH), 122.3 (CH), 109.3 (C), 74.7 (CH), 66.3 ($CH_2$), 51.1 (C), 43.7 (CH), 34.7 ($CH_2$), 28.8 ($CH_3$), 28.5 ($CH_3$), 25.8 ($CH_3$), 24.8 ($CH_3$), 22.0 ($CH_2$); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{22}N_2O_5Na$ 345.1426; Found 345.1429.

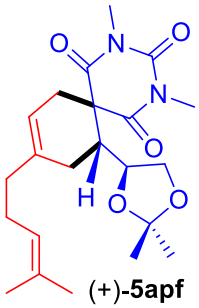


5apb

**(1*R*,3*R*,4*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1',3'-dimethyl-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidine]-2',4',6'(3'*H*)-trione (5apd) and (1*R*,3*S*,4*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1',3'-dimethyl-1'*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,5'-pyrimidine]-2',4',6'(3'*H*)-trione (7apd):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and isolated as a white solid. Mp.: 301-302 °C. Yield: 40% (41.8 mg). $[\alpha]_D^{25}$ = +11.8° (*c* = 0.265, $CHCl_3$, >99% *ee* and 1.6:1 *dr*); IR (Neat): $\nu_{max}$ 3053, 2986, 2950, 2875, 1747, 1677, 1512, 1436, 1416, 1366, 1246, 1208, 1150, 1105, 1063, 1022, 942, 855, 789, 753, 735, 695, 607, 511 and 485 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, *dr* = 1.6:1, major isomer): δ 6.58-6.53 (1H, m), 5.97 (1H, dt, *J* = 7.4, 0.8 Hz), 4.92 (1H, td, *J* = 10.0, 6.4 Hz), 3.82 (1H, dd, *J* = 7.6, 6.4 Hz), 3.31 (3H, s), 3.29 (3H, s), 3.11-3.04 (3H, m), 3.00-2.98 (1H, m), 2.07-2.02 (1H, m), 1.41 (3H, s), 1.36 (3H, s), 1.20-1.12 (3H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 1.6:1, major isomer): δ 170.6 (C, N-*C*=O), 169.9 (C, N-*C*=O), 151.1 (C, N-*C*=O), 137.4 (CH), 128.1 (CH), 109.0 (C), 73.8 (CH), 68.6 ($CH_2$), 57.1 (C), 45.9 (CH), 43.4 (CH), 31.2 (CH), 29.7 ($CH_3$), 29.0 ($CH_3$), 26.8 ($CH_3$), 25.6 ($CH_3$), 23.2 ($CH_2$), 15.7 ($CH_2$). $^1H$ NMR ($CDCl_3$, 400 MHz, *dr* = 1.6:1, minor isomer): δ 6.58-6.53 (1H, m), 6.04 (1H, dt, *J* = 7.4, 0.8 Hz), 4.53 (1H, td, *J* = 10.0, 6.4 Hz), 3.69 (1H, dd, *J* = 8.0, 6.4 Hz), 3.35 (3H, s), 3.24 (3H, s), 2.77-2.73 (3H, m), 2.69-2.68 (1H, m), 1.82-1.76 (1H, m), 1.69-1.56 (3H, m), 1.43 (3H, s), 1.33 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 1.6:1, minor isomer): δ 170.5 (C, N-*C*=O), 169.2 (C, N-*C*=O), 151.1 (C, N-*C*=O), 135.7 (CH), 129.4 (CH), 108.8 (C), 76.9 (CH), 67.9 ($CH_2$), 60.4 (C), 49.6 (CH), 43.7 (CH), 32.2 (CH), 29.6 ($CH_3$), 29.0 ($CH_3$), 26.9 ($CH_3$), 25.3 ($CH_3$), 23.4 ($CH_2$), 21.2 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_5Na$ 371.1583; Found 371.1585.

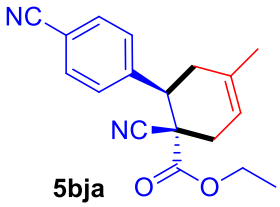



**(*R*)-11-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,4-dimethyl-9-(4-methylpent-3-en-1-yl)-2,4-diazaspiro[5.5]undec-8-ene-1,3,5-trione (5apf):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and isolated as colorless liquid. Yield: 52% (63.1 mg). $[\alpha]_D^{25}$ = +35.3° (*c* = 0.447, $CHCl_3$, >99% *ee* and 8.3:1 *dr*); IR (Neat): $\nu_{max}$ 2983, 2964, 2912, 2853, 1747, 1672, 1450, 1418, 1373, 1264, 1153, 1112, 1053, 907, 726, 647 and 473 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500



MHz, *dr* = 8.3:1, major isomer): δ 5.40 (1H, br s), 5.14 (1H, dt, *J* = 6.0, 1.5 Hz), 3.97 (1H, dt, *J* = 6.5, 3.0 Hz), 3.89 (1H, dd, *J* = 8.5, 7.0 Hz), 3.71 (1H, dd, *J* = 8.5, 7.0 Hz), 3.35 (3H, s), 3.24 (3H, s), 2.87 (1H, d, *J* = 18.0 Hz), 2.54 (1H, td, *J* = 12.0, 3.0 Hz), 2.40 (1H, d, *J* = 16.0 Hz), 2.33 (1H, dd, *J* = 18.0, 4.5 Hz), 2.16 - 2.13 (2H, m), 2.09 (2H, t, *J* = 7.5 Hz), 2.00 (1H, dd, *J* = 17.0, 4.5 Hz), 1.70 (3H, s), 1.62 (3H, s), 1.31 (3H, s), 1.21 (3H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, *dr* = 8.3:1, major isomer): δ 173.2 (C, N-*C*=O), 169.6 (C, N-*C*=O), 151.3 (C, N-*C*=O), 136.9 (C), 131.5 (C), 124.1 (CH), 115.6 (CH), 109.2 (C), 74.7 (CH), 66.3 ($CH_2$), 50.8 (C), 44.0 (CH), 37.3 ($CH_2$), 35.0 ($CH_2$), 28.7 ($CH_3$), 28.4 ($CH_3$), 26.3 ($CH_2$), 25.8 ($CH_3$), 25.7 ($CH_3$), 25.2 ($CH_2$), 24.8 ($CH_3$), 17.7 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{32}N_2O_5Na$ 427.2209; Found 427.2209.

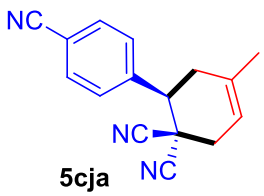
**Ethyl (1*R**,2*S**)-2,4'-dicyano-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate**



**5bja**

**(5bja):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 69% (60.9 mg). IR (Neat): $\nu_{max}$ 2976, 2921, 2856, 2228, 1738, 1609, 1444, 1368, 1260, 1231, 1082, 1035, and 844 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz, *rr* = 6.0:1, major isomer): δ 7.64 (2H, br d, *J* = 7.0 Hz), 7.55 (2H, br d, *J* = 8.0 Hz), 5.49 (1H, br s), 3.98 (2H, q, *J* = 7.0 Hz), 3.37 (1H, dd, *J* = 12.0, 4.0 Hz), 2.91-2.87 (1H, m), 2.70-2.63 (2H, m), 2.30-2.26 (1H, m), 1.80 (3H, s), 0.97 (3H, t, *J* = 7.2 Hz). $^{13}$C NMR ($CDCl_3$, DEPT-135, *rr* = 6.0:1, major isomer): δ 168.0 (C, O-*C*=O), 144.5 (C), 134.1 (C), 132.2 (2 x CH), 129.0 (2 x CH), 118.3 (C), 117.8 (C, *C*≡N), 115.9 (CH), 111.8 (C, *C*≡N), 62.6 ($CH_2$), 48.6 (C), 45.7 (CH), 35.1 ($CH_2$), 34.5 ($CH_2$), 22.8 ($CH_3$), 13.5 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{18}N_2O_2Na$ 317.1266; Found 317.1263.

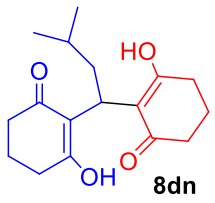
**5-Methyl-3,6-dihydro-[1,1'-biphenyl]-2,2,4'(1*H*)-tricarbonitrile (5cja):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as a white solid. Mp.: 266-268 °C. Yield: 81% (60.1 mg). IR (Neat): 2935, 2856, 2223, 2163, 1674, 1607, 1505, 1428, 1376, 1338, 1296, 1219, 1088, 1019, 868, 840, 803, 672, 564 and 547 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz, *rr* = 12.5:1, major isomer): δ 7.73 (2H, d, *J* = 8.0 Hz), 7.59 (2H, d, *J* = 8.5 Hz), 5.48 (1H, br s), 3.34 (1H, dd, *J* = 10.5, 5.0 Hz), 2.91 (2H, br s), 2.71-2.65 (1H, m), 2.42 (1H, dd, *J* = 18.5,



**5cja**

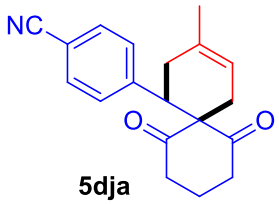
5.0 Hz), 1.83 (3H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, *rr* = 12.5:1, major isomer): δ 142.3 (C), 135.2 (C), 132.8 (2 x CH), 129.0 (2 x CH), 118.1 (C), 115.0 (C, *C*≡N), 114.6 (CH), 114.1 (C, *C*≡N), 113.1 (C, *C*≡N), 46.1 (CH), 36.3 (C), 35.7 ($CH_2$), 33.1 ($CH_2$), 22.9 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{13}N_3Na$ 270.1007; Found 270.1008.

**2,2'-(3-methylbutane-1,1-diyl)bis(3-hydroxycyclohex-2-en-1-one) (8dn):** The title compound was prepared following the procedure **B**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as a white solid. Mp.: 207-209 °C. Yield: 30% (439 mg). IR (Neat): $\nu_{max}$ 2947, 2867, 2578, 1571, 1454, 1368, 1264, 1126, 1095, 1023, 899, 835 and 766 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz): δ 12.92 (1H, s, O*H*), 12.11 (1H, br s, O*H*), 3.98 (1H, t, *J* = 8.0 Hz), 2.52-2.48 (4H, m), 2.35-2.28 (4H, m), 1.93-1.91 (2H, m), 1.87-1.78 (4H, m), 1.40-1.31 (1H, m), 0.83 (3H, d, *J* = 6.5 Hz), 0.82 (3H, d, *J* = 6.5 Hz). $^{13}$C NMR ($CDCl_3$, DEPT-135): δ 191.4 (2 x C, *C*=O), 191.0 (2 x C, =*C*-OH), 117.9 (2 x C), 38.0 ($CH_2$), 33.5 (2 x $CH_2$), 32.7 (2 x $CH_2$), 27.6 (CH), 26.9 (CH), 22.4 (2 x $CH_3$), 19.9 (2 x $CH_2$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{24}O_4H$ 293.1753; Found 293.1753.



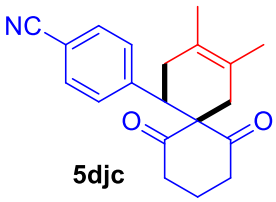
**8dn**

**4-(3-Methyl-7,11-dioxospiro[5.5]undec-3-en-1-yl)-benzonitrile (5dja):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 45% (39.6 mg). IR (Neat): $\nu_{max}$ 2970, 2916, 2846, 2258, 2226, 1725, 1692, 1606, 1504, 1427, 1312, 1206, 1022, 910, 836, 727 and 563 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz, *rr* = 7.1:1, major isomer): δ 7.54 (2H, td, *J* = 8.5, 1.2 Hz), 7.33 (2H, td, *J* = 8.5, 1.2 Hz), 5.43-5.41 (1H, m), 3.61 (1H, dd, *J* = 9.5, 6.0 Hz), 2.75-2.65 (2H, m), 2.58-2.46 (3H, m), 2.41-2.36 (1H, m), 2.32-2.26 (1H, m), 2.20 (1H, dd, *J* = 17.5, 6.0 Hz), 1.87-1.77 (1H, m), 1.75 (3H, s), 1.68-1.61 (1H, m). $^{13}$C NMR ($CDCl_3$, DEPT-135, *rr* = 7.1:1, major isomer): δ 210.0 (C, *C*=O), 208.5 (C, *C*=O), 147.4 (C), 133.8 (C), 132.1 (2 x CH), 129.9 (2 x CH), 118.7 (C), 116.4 (CH), 110.9 (C, *C*N), 66.5 (C), 44.9 (CH), 39.4 ($CH_2$), 38.8 ($CH_2$), 34.7 ($CH_2$), 32.2 ($CH_2$), 23.1 ($CH_3$), 16.9 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}NO_2H$ 294.1494; Found 294.1494.



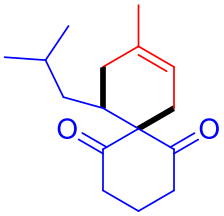
**5dja**

**4-(3,4-Dimethyl-7,11-dioxospiro[5.5]undec-3-en-1-yl)benzonitrile (5djc):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Mp.: 202-205 °C. Yield: 56% (51.6 mg). IR (Neat): $\nu_{max}$ 3019, 2228, 1725, 1693, 1607, 1504, 1430, 1313, 1214, 1118, 1023, 837, 745, 663 and 564 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 7.50 (2H, d, *J* = 8.5 Hz), 7.28 (2H, d, *J* = 12.0 Hz), 3.57 (1H, dd, *J* = 8.5, 6.0 Hz), 2.65 - 2.60 (2H, m), 2.56 - 2.47 (2H, m), 2.39 - 2.35 (2H, m), 2.25 - 2.18 (2H, m), 1.81 - 1.74 (2H, m), 1.67 (3H, s), 1.67 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135): δ 209.5 (C, *C*=O), 208.4 (C, *C*=O), 147.3 (C), 132.1 (2 x CH), 129.7 (2 x CH), 124.6 (C), 122.0 (C), 118.7 (C), 110.9 (C, *C*N), 68.1 (C), 45.2 (CH), 39.5 ($CH_2$), 38.6 ($CH_2$), 36.3 ($CH_2$), 36.0 ($CH_2$), 18.7 (2 x $CH_3$), 17.1 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{21}NO_2H$ 308.1651, Found 308.1647.



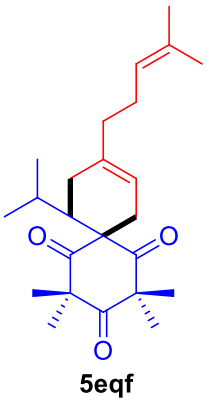
5djc

**11-isobutyl-9-methylspiro[5.5]undec-8-ene-1,5-dione (5dna):** The title compound was prepared following the procedure **C**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated colorless liquid. Yield: 40% (29.5 mg). This DA products **5dna/6dna** obtained along with unreacted starting material of **8dn** (52.5 mg, 60%) as inseparable mixture. Yields based on NMR calculation of isolated pure mixture of products. IR (Neat): $\nu_{max}$ 2951, 2875, 1726, 1694, 1581, 1456, 1366, 1269, 1195, 1138, 915, 732 and 582 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz, *rr* = 5.6:1, major isomer): δ 5.40 (1H, s, olefinic-*H*), 2.99-2.92 (1H, m), 2.81-2.75 (1H, m), 2.60-2.40 (5H, m), 2.17 (1H, br d, *J* = 17.5 Hz), 2.12-2.07 (1H, m), 1.97-1.90 (2H, m), 1.73-1.66 (1H, m), 1.62 (3H, s), 1.31-1.25 (1H, m), 0.88 (3H, d, *J* = 6.5 Hz), 0.87 (3H, d, *J* = 6.5 Hz), 0.76-0.71 (1H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 5.6:1, major isomer): δ 208.1 (C, *C*=O), 207.8 (C, *C*=O), 128.9 (C), 118.5 (CH), 70.8 (C), 38.1 ($CH_2$), 37.6 ($CH_2$), 37.4 (CH), 37.0 ($CH_2$), 31.0 ($CH_2$), 25.3 (CH), 24.1 ($CH_2$), 24.0 ($CH_3$), 23.4 ($CH_3$), 21.3 ($CH_3$), 18.4 ($CH_2$). LCMS *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{24}O_2Na$ 271.1674; Found 271.200. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{24}O_2H$ 249.1855, Found 249.1852.



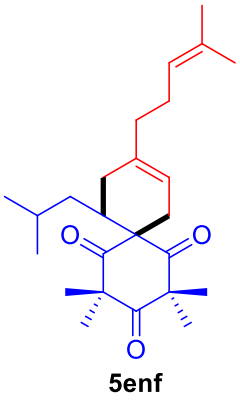
5dna

**11-isopropyl-2,2,4,4-tetramethyl-9-(4-methylpent-3-en-1-yl)spiro[5.5]undec-8-ene-1,3,5-trione [Calliviminone-A; 5eqf]:** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 35% (39.1 mg). IR (Neat): $\nu_{max}$ 2924, 1696, 1465, 1380, 1271, 1204, 1106, 1068, 1046 and 852 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz, *rr* = 6.0:1, major isomer): δ 5.26 (1H, br s), 5.06 (1H, tt, *J* = 6.8, 1.2 Hz), 2.49 (1H, br dd, *J* = 17.6, 3.2 Hz), 2.26-2.17 (3H, m), 2.14-2.05 (3H, m), 2.00-1.95 (3H, m), 1.67 (3H, s), 1.60 (3H, s), 1.41 (3H, s), 1.39 (3H, s), 1.38 (3H, s), 1.34 (3H, s), 0.89 (3H, d, *J* = 6.8 Hz), 0.84 (3H, d, *J* = 6.8 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 6.0:1, major isomer): δ 212.9 (C, *C*=O), 208.7 (C, *C*=O), 208.5 (C, *C*=O), 138.1 (C), 131.5 (C), 124.1 (CH), 115.3 (CH), 67.0 (C), 56.7 (C), 56.4 (C), 41.2 (CH), 37.1 ($CH_2$), 31.2 ($CH_2$), 30.1 (CH), 27.7 ($CH_2$), 26.22 ($CH_3$), 26.17 ($CH_2$), 25.9 ($CH_3$), 25.7 ($CH_3$), 25.0 ($CH_3$), 24.8 ($CH_3$), 24.1 ($CH_3$), 19.0 ($CH_3$), 17.7 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{36}O_3H$ 373.2743; Found 373.2741.



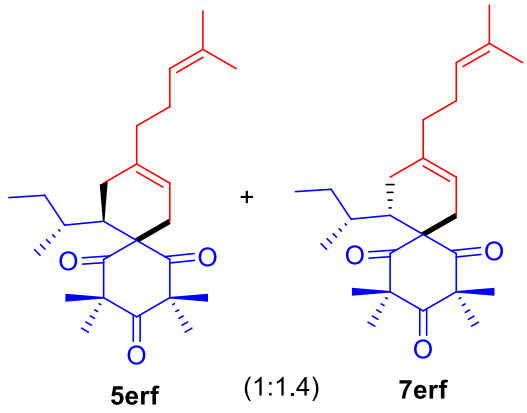
**5eqf**

**11-isobutyl-2,2,4,4-tetramethyl-9-(4-methylpent-3-en-1-yl)spiro[5.5]undec-8-ene-1,3,5-trione [Calliviminone-E; 5enf]:** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 51% (59.1 mg). IR (Neat): $\nu_{max}$ 2922, 2852, 1699, 1656, 1618, 1464, 1380, 1275, 1172, 1046, 999, 848 and 773 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz, *rr* = 8.3:1, major isomer): δ 5.31 (1H, br s), 5.04 (1H, tt, *J* = 6.8, 1.2 Hz), 2.50 (1H, br dd, *J* = 18.0, 2.0 Hz), 2.31 (1H, dq, *J* = 6.0, 2.4 Hz), 2.19-2.16 (1H, m), 2.14-2.08 (2H, m), 2.06-2.01 (2H, m), 1.99-1.92 (3H, m), 1.67 (3H, s), 1.59 (3H, s), 1.43 (1H, d, *J* = 9.6 Hz), 1.39 (3H, s), 1.39 (3H, s), 1.37 (3H, s), 1.33 (3H, s), 0.87 (3H, d, *J* = 6.4 Hz), 0.85 (3H, d, *J* = 6.4 Hz), 0.83-0.79 (1H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 8.3:1, major isomer): δ 212.8 (C, *C*=O), 208.1 (C, *C*=O), 208.0 (C, *C*=O), 136.5 (C), 131.4 (C), 123.9 (CH), 115.8 (CH), 67.5 (C), 56.7 (C), 56.1 (C), 39.0 ($CH_2$), 37.1 ($CH_2$), 33.8 (CH), 30.5 ($CH_2$), 29.4 ($CH_2$), 26.3 ($CH_2$), 26.0 ($CH_3$), 25.8 ($CH_3$), 25.6 (CH), 25.4 ($CH_3$), 24.9 ($CH_3$), 24.24 ($CH_3$), 24.21 ($CH_3$), 20.8 ($CH_3$), 17.7 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{38}O_3H$ 387.2899; Found 387.2896.

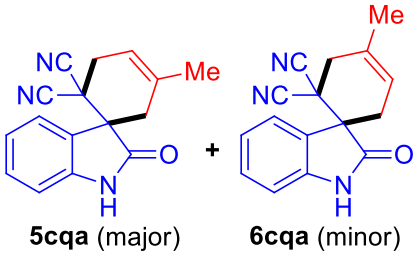


**5enf**

**(*R**)-11-((*R**)-*sec*-Butyl)-2,2,4,4-tetramethyl-9-(4-methylpent-3-en-1-yl)spiro[5.5]undec-8-ene-1,3,5-trione [Calliviminone-G; 5erf] and (*S**)-11-((*R**)-*sec*-Butyl)-2,2,4,4-tetramethyl-9-(4-methylpent-3-en-1-yl)spiro[5.5]undec-8-ene-1,3,5-trione [Calliviminone-H; 7erf]:** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as colorless liquid. Yield: 35% (40.6 mg). IR (Neat): $\nu_{max}$ 2925, 2854, 1700, 1463, 1380, 1215, 756 and 668 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz, *dr* = 1.4:1, major isomer): δ 5.27 (1H, br s), 5.08-5.04 (1H, m), 2.50 (1H, dd, *J* = 18.0, 4.5 Hz), 2.30-2.26 (2H, m), 2.12-2.07 (3H, m), 1.98-1.89 (3H, m), 1.67 (3H, s), 1.60 (3H, s), 1.49-1.44 (1H, m), 1.42 (3H, s), 1.39 (3H, s), 1.39 (3H, s), 1.34 (3H, s), 1.33-1.32 (1H, m), 1.27-1.23 (1H, m), 0.85 (3H, t, *J* = 7.5 Hz), 0.80 (3H, d, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 1.4:1, major isomer): δ 212.6 (C, *C*=O), 208.9 (C, *C*=O), 208.4 (C, *C*=O), 137.9 (C), 131.5 (C), 124.1 (CH), 115.5 (CH), 66.7 (C), 56.73 (C), 56.70 (C), 40.4 (CH), 37.1 ($CH_2$), 36.4 (CH), 31.2 ($CH_2$), 30.7 ($CH_2$), 27.2 ($CH_2$), 26.2 ($CH_3$), 26.2 ($CH_2$), 25.7 ($CH_3$), 25.5 ($CH_3$), 24.8 ($CH_3$), 19.7 ($CH_3$), 17.7 ($CH_3$), 15.3 ($CH_3$), 12.1 ($CH_3$). $^{1}H$ NMR ($CDCl_3$, 500 MHz, *dr* = 1.4:1, minor isomer): δ 5.21 (1H, br s), 5.08-5.04 (1H, m), 2.41 (1H, dd, *J* = 17.5, 5.0 Hz), 2.24-2.22 (2H, m), 2.18-2.16 (3H, m), 1.98-1.89 (3H, m), 1.67 (3H, s), 1.61 (3H, s), 1.49-1.44 (1H, m), 1.42 (3H, s), 1.39 (3H, s), 1.39 (3H, s), 1.37-1.36 (1H, m), 1.35 (3H, s), 1.27-1.23 (1H, m), 0.85 (3H, t, *J* = 7.5 Hz), 0.82 (3H, d, *J* = 7.5 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *dr* = 1.4:1, minor isomer): δ 212.7 (C, *C*=O), 209.1 (C, *C*=O), 208.6 (C, *C*=O), 139.1 (C), 131.5 (C), 124.0 (CH), 114.5 (CH), 66.1 (C), 56.76 (C), 56.6 (C), 41.2 (CH), 37.6 (CH), 37.0 ($CH_2$), 32.6 ($CH_2$), 29.1 ($CH_2$), 26.4 ($CH_3$), 26.2 ($CH_2$), 25.9 ($CH_3$), 25.5 ($CH_2$), 25.3 ($CH_3$), 24.6 ($CH_3$), 24.6 ($CH_3$), 17.7 ($CH_3$), 15.3 ($CH_3$), 12.2 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{38}O_3H$ 387.2899; Found 387.2892.



**3-Methyl-2'-oxospiro[cyclohex[3]ene-1,3'-indoline]-6,6-dicarbonitrile (5cqa) and 4-Methyl-2'-oxospiro[cyclohex[3]ene-1,3'-indoline]-6,6-dicarbonitrile (6cqa):** The title compound was prepared following the procedure **A**, purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0), and was isolated as a white solid. Mp.: 320 °C. Yield: 61% (48.2 mg). IR (Neat): $\nu_{max}$ 3053, 2947, 2878, 1746, 1676, 1603, 1509, 1443, 1415, 1361, 1222, 1160, 1107 and 757 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz, *rr* = 3.3:1, major isomer): δ 8.23 (1H, br s), 7.44 (1H, d, *J* = 8.0 Hz), 7.37 (1H, dt, *J* = 7.5, 1.5 Hz), 7.13 (1H, t, *J* = 7.5 Hz), 7.01 (1H, d, *J* = 7.5 Hz), 5.64-5.61 (1H, m), 3.28 (1H, md, *J* = 17.5 Hz), 2.98 (1H, md, *J* = 17.5 Hz), 2.72 (1H, d, *J* = 18.5 Hz), 2.40 (1H, d, *J* = 18.5 Hz), 1.84 (3H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 3.3:1, major isomer): δ 175.1 (C, *C*=O), 140.6 (C), 133.3 (C), 130.6 (CH), 127.1 (C), 124.8 (CH), 123.6 (CH), 115.1 (CH), 113.8 (C, *C*N), 113.5 (C, *C*N), 110.7 (CH), 49.5 (C), 36.2 (C), 34.7 ($CH_2$), 32.8 ($CH_2$), 23.2 ($CH_3$). $^{1}H$ NMR ($CDCl_3$, 500 MHz, *rr* = 3.3:1, minor isomer): δ 8.32 (1H, br s), 7.41-7.36 (2H, m), 7.13 (1H, t, *J* = 7.5 Hz), 7.01 (1H, d, *J* = 7.5 Hz), 5.69 (1H, br s), 3.22 (1H, d, *J* = 17.5 Hz), 2.86 (1H, d, *J* = 17.5 Hz), 2.78 (1H, d, *J* = 18.5 Hz), 2.55 (1H, d, *J* = 18.5 Hz), 1.91 (3H, br s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, *rr* = 3.3:1, minor isomer): δ 175.2 (C, *C*=O), 140.6 (C), 130.6 (CH), 128.7 (C), 127.2 (C), 124.7 (CH), 123.6 (CH), 119.0 (CH), 113.8 (C, *C*N), 113.4 (C, *C*N), 110.7 (CH), 48.7 (C), 36.9 (C), 36.7 ($CH_2$), 30.6 ($CH_2$), 22.7 ($CH_3$). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{13}N_3ONa$ 286.0956; Found 286.0956.

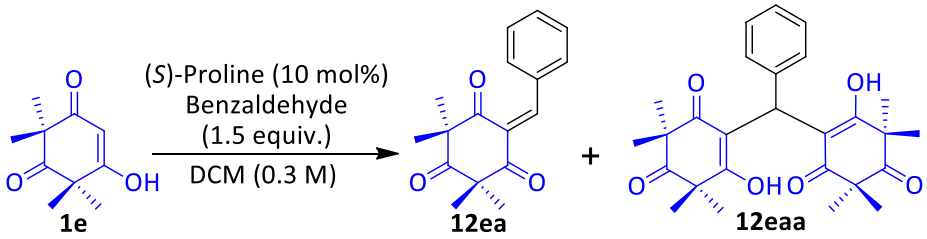



**5cqa** (major) **6cqa** (minor)

## *2. General Experimental Procedures for Organocatalytic Reductive Alkylation of Syncarpic Acid: Formal Total Synthesis of Monomeric Phloroglucinol Natural Products*

**Procedure A**: **General procedure for the synthesis of 4-alkyl-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (5):** To an ordinary glass vial with inner cap, equipped with a magnetic stirring bar, containing a solution of 0.3 mmol (54.7 mg) of syncarpic acid **1e** in acetonitrile (1.0 mL, 0.3 M), 0.45 mmol (1.5 equiv.) of aldehyde **2**, 0.33 mmol (83.6 mg) of Hantzsch ester **3** (for aromatic aldehyde) or 0.9 mmol (228.0 mg) of Hantzsch ester **3** (for aliphatic aldehyde), 0.03 mmol (10 mol%, 3.21 mg) benzylamine **10b** were added under nitrogen atmosphere. The resulting reaction mixture was stirred at 80 $^{o}$C for 6-16 h. The completion of the reaction was confirmed by TLC. The pure alkylated syncarpic acids **11** were obtained by silica gel column chromatography using ethyl acetate and hexane as eluents. When aliphatic aldehydes were used, in most of cases, final product contained a small amount of diethyl-2,6-dimethylpyridine-3,5-dicarboxylate which is the byproduct of **9**. In this case, a further flash column was done by using DCM: hexane (95:5) as eluents to obtain pure alkylated syncarpic acids **11**.

**Procedure B**: **Procedure for synthesis of Knoevenagel adduct (12ea) and bis-product (12eaa):**




In an ordinary glass vial equipped with a magnetic stirring bar, syncarpic acid **1e** (0.3 mmol, 54.7mg) and benzaldehyde **2a** (0.45 mmol, 47.8 mg) were added in 1.0 ml of DCM (0.3 M) and then catalyst (*S*)-proline (0.03 mmol, 3.45 mg, 10 mol%) was added, the resulting mixture was stirred at ambient temperature for 2.5 hours. The completion of the reaction was confirmed by TLC. The pure Knoevenagel product **12ea** was obtained by silica gel column chromatography using EtOAc/hexane (1.0 : 9.0 to 1.2 : 8.8) as white solid (41%, 33 mg). When

the same reaction mixture was allowed to stirred at ambient temperature for 5.5 h, Knoevenagel product **12ea** was slowly disappeared and bis-product **12eaa** was formed. The completion of the reaction was confirmed by TLC. The pure bis-product **12eaa** was obtained by silica gel column chromatography using EtOAc/hexane (2.0 : 8.0 to 2.2 : 7.8) as white solid (31%, 39 mg).

**Procedure C**: **Procedure for synthesis of 2-benzyl-4,4,6,6-tetramethyl-2-(3-oxobutyl) cyclohexane-1,3,5-trione (14):** An ordinary glass vial equipped with a magnetic stirring bar was charged with 4-benzyl syncarpic acid **11ea** (0.3 mmol, 81.7 mg), triethylamine (0.3 mmol, 30.4 mg) and methyl vinyl ketone **13** (0.9 mmol, 63.1 mg). The resulting mixture was stirred at ambient temperature for 15 hours. The completion of the reaction was confirmed by TLC. The pure product **14** was obtained by silica gel column chromatography using EtOAc/hexane (0.5 : 9.5 to 0.8 : 9.2) as a white solid (92%, 94 mg).

**Procedure D**: **General procedure for synthesis of 2-benzyl-2-(3-hydroxybutyl)-4,4,6,6-tetramethylcyclohexane-1,3,5-trione (15):** An ordinary glass vial equipped with a magnetic stirring bar was charged with Michael adduct **14** (0.3 mmol, 102.7 mg), $NaBH_4$ (0.36 mmol, 13.6 mg) in methanol (0.1M). The resulting mixture was stirred at ambient temperature for 12 hours. The completion of the reaction was confirmed by TLC. The pure product **15** was obtained by silica gel column chromatography using EtOAc/hexane (1.7 : 8.3 to 1.8 : 8.2) as a white solid (62%, 43 mg).

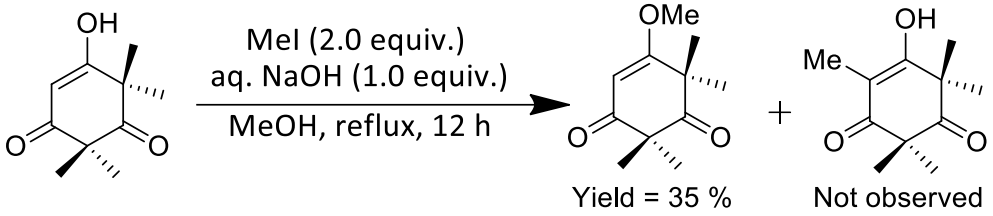
**Procedure E**: **General procedure for the oxidation of 4-alkylated syncarpic acids:** In a 10 mL round bottomed flask, 4-alkylated syncarpic acid (0.2 mmol) in THF (0.2 M) was stirred under the supply of oxygen through $O_2$ balloon for respective times. The completion of the reaction was confirmed by TLC. The pure product **16ea** was obtained by silica gel column chromatography using EtOAc/hexane as a white solid.

**Procedure F**: **General procedure for the triflation of 4-alkylated syncarpic acids:** In a 10 mL oven dried round bottomed flask was taken 4-alkylsyncarpic acid **11eq**/**11ex** (0.3 mmol, 75.7 mg) and DMAP (0.1 mmol, 12.82 mg) in DCM (0.03 M) and cooled to 0 $^oC$. To this $(^iPr)_2EtN$ (1.5 mmol, 193.9 mg) and triflic anhydride (0.54 mmol, 152.9 mg) were added respectively and allowed to stir for 1 h at 0 $^oC$ followed by 3 h at 25 $^oC$. The reaction mixture was diluted with DCM and washed with saturated aq. $NH_4Cl$. The organic layer was separated

and dried ($Na_2SO_4$), and concentrated, Pure product **17**/**21** were obtained by coloumn chromatography using EtOAc/hexane as white solid.

**Procedure G**: **General procedure for the de-triflation of 4-alkylated syncarpic acid triflates 11/15:** In a 10 mL oven dried round bottomed flask was taken 4-alkylsyncarpic acid triflate **17**/**21** (0.2 mmol, 76.9 mg) and dissolved in dry DMF (0.2 M). To this, $Pd(OAc)_2$ (0.0052 mmol, 1.56 mg), dppp (0.0052 mmol, 2.14 mg), PHMS (1.2 mmol, 305.5 mg) were added and allowed to stir at 80 $^oC$ for 12 h. The completion of the reaction was confirmed by TLC. The pure product **18/22** was obtained by silica gel column chromatography using EtOAc/hexane as a white solid.

**Procedure H**: **Procedure for the methylation of syncarpic acid:**



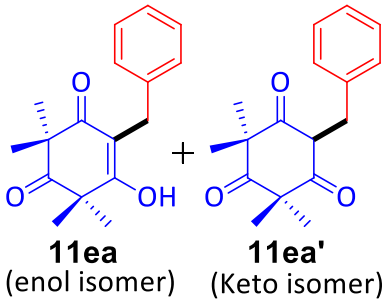

In a 10 mL oven dried round bottomed flask was taken syncarpic acid **1e** (0.3 mmol, 54.7 mg) and dissolved in methanol (0.3 M). To this, aq. NaOH (1 M, 0.3 ml), MeI (0.6 mmol, 85.2 mg) were added and allowed to stir at reflux for 12 h. The completion of the reaction was confirmed by TLC. The pure *O*-methylated syncarpic acid was obtained by silica gel column chromatography using EtOAc/hexane (1.2 : 8.8 to 1.0 : 9.0) as a white solid (35%, 21.0 mg).

***General Observations during the Recording of NMR Samples:***

(1) A mixture of keto-isomer (minor) and enol-isomer (major) have observed in the NMR spectra of 4-aryl-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione **5** in $CDCl_3$, but only enol-isomer has observed when $CD_3OD$ has used as a reference solvent. Therefore, $CD_3OD$ has used for the recording NMR spectra of **11**.

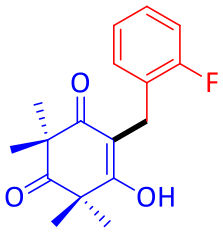
(2) Due to the enol-enol tautomerism of 4-Aryl-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione **11**, $^{13}C$ NMR resulted in the poor resolution of two 1,3-dicarbonyl carbon (2 x C=O) and adjacent to that two quaternary carbons (2 x C) even after more than 2000 scans in the $CDCl_3$ or $CD_3OD$ as reference solvent for NMR.

**4-Benzyl-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11ea):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.2 : 8.8), and isolated as a white solid. Mp.: 88-90 °C. Yield: 91% (74 mg). IR (Neat): $\nu_{max}$ 2980, 2939, 1714, 1586, 1469, 1393, 1317, 1261, 1180, 1073, 1040, 977, 748, 700, 649, 600, 492 and 453 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, 2:1 ratio, major enol isomer): δ 7.32 (2H, t, *J* = 6.8 Hz), 7.26-7.18 (3H, m), 5.99 (1H, br s, O-*H*), 3.81 (2H, s), 1.40 (12H, s). $^{13}C$ NMR ($CDCl_3$, 100 MHz, DEPT-135, 1.75:1 ratio, major enol isomer) δ 212.6 (C, *C*=O), 138.4 (C), 129.2 (2 x CH), 129.1 (CH), 127.9 (2 x CH), 111.8 (C), 77.2 (2 x C), 28.6 ($CH_2$), 24.7 (4 x $CH_3$). $^1H$ NMR ($CDCl_3$, 400 MHz, 2:1 ratio, minor keto isomer): δ 7.26-7.18 (5H, m), 3.94 (1H, t, *J* = 5.6 Hz), 3.31 (2H, d, *J* = 5.6 Hz), 1.33 (6H, s), 1.22 (6H, s). $^{13}C$ NMR ($CDCl_3$, 100 MHz, DEPT-135, 1.75:1 ratio, minor keto isomer): δ 210.7 (C, *C*=O), 204.3 (C, 2 x *C*=O), 139.1 (C), 128.5 (CH, 2 x *C*H), 127.0 (CH, 2 x *C*H), 126.5 (CH), 63.3 (CH), 58.4 (C, 2 x *C*), 29.0 ($CH_2$), 22.9 ($CH_3$, 2 x *C*$H_3$), 22.3 ($CH_3$, 2 x *C*$H_3$). $^1H$ NMR ($CD_3OD$, 500 MHz, only enol isomer): δ 7.22-7.18 (4H, m), 7.13-7.09 (1H, m), 3.72 (2H, s, C$H_2$), 1.36 (12H, s, 4 x C$H_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 100 MHz, only enol isomer): δ 215.1 (2 x C, *C*=O), 142.1 (C), 129.3 (CH, 4 x *C*H), 126.8 (CH), 113.6 (C), 52.8 (2 x C, br s), 29.5 ($CH_2$), 25.2 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{21}O_3$ 273.1491; Found : 273.1493.



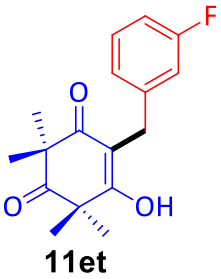
**11ea** (enol isomer) **11ea'** (Keto isomer)

**4-(2-Fluorobenzyl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11es):** The title 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 white solid. Mp.: 108-110 °C. Yield: 76% (66 mg). IR (Neat): $\nu_{max}$ 3270, 2982, 2937, 2869, 2167, 1714, 1600, 1489, 1456, 1386, 1365, 1228, 1179, 1094, 1046, 1006, 980, 755, 643, 564 and 538 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 7.14 (1H, q, *J* = 7.0 Hz), 7.07 (1H, t, *J* = 7.5 Hz), 7.00 (2H, q, *J* = 7.0 Hz), 3.74 (2H, s, C$H_2$), 1.37 (12H, s, 4 x C$H_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.7 (C, *C*=O), 162.7 (C, *C*-F, d, *J* = 242.5 Hz), 130.5 (CH, d, *J* = 5.0 Hz), 128.6 (CH, d, *J* = 7.5 Hz), 128.4 (C, d, *J* = 16.25 Hz), 125.0 (CH, d, *J* = 3.75 Hz), 115.9 (CH, d, *J* = 21.25 Hz), 111.5 (C), 52.8 (C, 2 x *C*, br s), 25.3 ($CH_3$, 4 x *C*$H_3$), 22.8 ($CH_2$, d, *J* = 3.75 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}FO_3$ 291.1396; Found : 291.1396.



**11es**

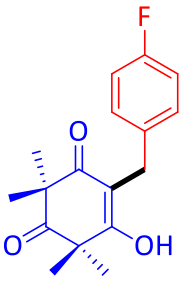
**4-(3-Fluorobenzyl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11et):** The



**11et**

title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.2 : 8.8), and isolated as a white solid. Mp.: 104-106 °C. Yield: 71% (62 mg). IR (Neat): $\nu_{max}$ 3288, 2983, 2167, 1715, 1590, 1450, 1387, 1364, 1182, 1046, 1004, 776 and 538 $cm^{-1}$. $^{1}H$ NMR ($CD_3OD$, 500 MHz): δ 7.21 (1H, q, *J* = 7.5 Hz), 7.02 (1H, d, *J* = 7.5 Hz), 6.91 (1H, d, *J* = 10.0 Hz), 6.84 (1H, d, *J* = 8.5 Hz), 3.72 (2H, s, C*H*$_2$), 1.36 (12H, s, 4 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.6 (C, *C*=O), 164.4 (C, *C*-F, d, *J* = 241.25 Hz), 145.1 (C, d, *J* = 7.5 Hz), 130.8 (CH, d, *J* = 8.75 Hz), 125.2 (CH, d, *J* = 2.5 Hz), 116.0 (CH, d, *J* = 21.25 Hz), 113.4 (CH, d, *J* = 21.25 Hz), 113.2 (C), 52.7 (C, 2 x *C*, br s), 29.4 ($CH_2$), 25.2 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}FO_3$ 291.1396; Found : 291.1394.

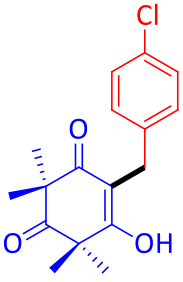
**4-(4-Fluorobenzyl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11eb):** The



**11eb**

title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.2 : 8.8), and isolated as a white solid. Mp.: 102-106 °C. Yield: 92% (80 mg). IR (Neat): $\nu_{max}$ 3264, 2983, 2939, 2878, 2167, 2008, 1713, 1600, 1507, 1469, 1386, 1354, 1220, 1180, 1093, 1046, 1005, 981, 887, 828, 576 and 530 $cm^{-1}$. $^{1}H$ NMR ($CD_3OD$, 500 MHz): δ 7.20 (2H, dd, *J* = 5.5, 8.5 Hz), 6.92 (2H, t, *J* = 8.5 Hz), 3.69 (2H, s, C*H*$_2$), 1.35 (12H, s, 4 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.6 (C, *C*=O), 162.7 (C, *C*-F, d, *J* = 240.0 Hz), 138.0 (C), 130.9 (CH, 2 x *C*H, d, *J* = 7.0 Hz), 115.7 (CH, 2 x *C*H, d, *J* = 21.0 Hz), 113.7 (C), 49.8 (C, 2 x *C*, br s), 28.8 ($CH_2$), 25.2 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}FO_3$ 291.1396; Found : 291.1395.

**4-(4-Chlorobenzyl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11ec):** The

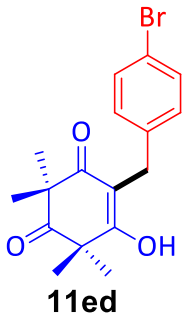


**11ec**

title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 2.0 : 8.0), and isolated as a white solid. Mp.: 108-110 °C. Yield: 72% (66 mg). IR (Neat): $\nu_{max}$ 3317, 2981, 2918, 2356, 2242, 2040, 1708, 1610, 1490, 1468, 1388, 1365, 1310, 1182, 1093, 1042, 1004, 982, 886, 820, 785, 728, 653, 608 and 581 $cm^{-1}$. $^{1}H$ NMR (DMSO-$d_6$, 500 MHz): δ 7.28 (2H, d, *J* = 8.0 Hz), 7.17 (2H, d, *J* = 8.5 Hz), 3.65 (2H, s, C*H*$_2$), 1.30 (12H, s, 4 x C*H*$_3$). $^{13}C$ NMR (DMSO-$d_6$, DEPT-135, 125

MHz): δ 212.8 (C, *C*=O), 140.0 (C), 130.0 (C), 129.7 (CH, 2 x *C*H), 128.0 (CH, 2 x *C*H), 110.8 (C), 27.7 ($CH_2$), 24.4 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}ClO_3$ 307.1101; Found : 307.1103.

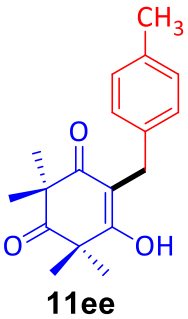
**4-(4-Bromobenzyl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11ed):** The



11ed

title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.2 : 8.8), and isolated as a white solid. Mp.: 104-106 °C. Yield: 56% (59 mg). IR (Neat): $\nu_{max}$ 3408, 2984, 2928, 2861, 2216, 1708, 1609, 1488, 1468, 1383, 1260, 1069, 1012, 813, 727, 607 and 581 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 7.35 (2H, d, *J* = 8.0 Hz), 7.12 (2H, d, *J* = 8.5 Hz), 3.67 (2H, s, C*H*$_2$), 1.35 (12H, s, 4 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.6 (C, *C*=O), 141.6 (C), 132.3 (CH, 2 x *C*H), 131.3 (CH, 2 x *C*H), 120.4 (C), 113.3 (C), 50.0 (C, 2 x *C*, br s), 29.1 ($CH_2$), 25.2 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}BrO_3$ 351.0596; Found : 351.0595.

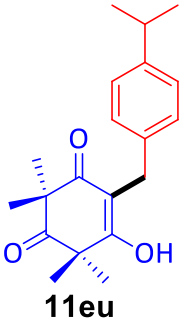
**5-Hydroxy-2,2,6,6-tetramethyl-4-(4-methylbenzyl)cyclohex-4-ene-1,3-dione (11ee):** The



11ee

title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 2.0 : 8.0), and isolated as a white solid. Mp.: 102-104 °C. Yield: 84% (72 mg). IR (Neat): $\nu_{max}$ 3318, 2980, 2928, 2875, 1713, 1595, 1512, 1468, 1384, 1353, 1281, 1176, 1107, 1046, 1004, 904, 885, 782 and 579 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 7.09 (2H, d, *J* = 8.0 Hz), 7.03 (2H, d, *J* = 8.0 Hz), 3.69 (2H, s, C*H*$_2$), 2.27 (3H, s, C*H*$_3$), 1.37 (12H, s, 4 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.8 (C, *C*=O), 138.9 (C), 136.3 (C), 129.9 (CH, 2 x *C*H), 129.2 (CH, 2 x *C*H), 113.8 (C), 51.1 (C, 2 x *C*, br s), 29.0 ($CH_2$), 25.3 ($CH_3$, 4 x *C*$H_3$), 21.2 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{23}O_3$ 287.1647; Found : 287.1648.

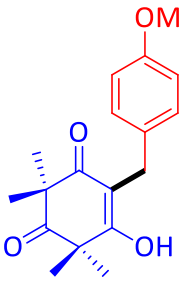
**5-Hydroxy-4-(4-isopropylbenzyl)-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11eu):**



**11eu**

The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 1.8 : 8.2), and isolated as a white solid. Mp.: 98-100 °C. Yield: 76% (72 mg). IR (Neat): $\nu_{max}$ 3405, 2986, 2958, 2252, 2168, 1712, 1645, 1382, 1217, 1049, 1023, 1001, 822, 753 and 535 $cm^{-1}$. $^{1}H$ NMR ($CD_3OD$, 500 MHz): δ 7.09 (4H, q, *J* = 8.5 Hz), 3.69 (2H, s, C*H*$_2$), 2.82 (1H, p, *J* = 7.0 Hz), 1.36 (12H, s, 4 x C*H*$_3$), 1.20 (6H, d, *J* = 7.0 Hz, 2 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.8 (C, *C*=O), 147.5 (C), 139.3 (C), 129.2 (CH, 2 x *C*H), 127.2 (CH, 2 x *C*H), 113.7 (C), 52.7 (C, 2 x *C*, br s), 35.1 (CH), 29.1 ($CH_2$), 25.3 ($CH_3$, 4 x *C*$H_3$), 24.7 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{27}O_3$ 315.1960; Found : 315.1959.

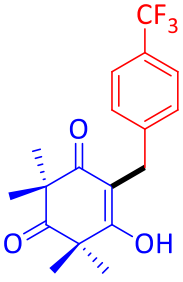
**5-Hydroxy-4-(4-methoxybenzyl)-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11ef):** The



**11ef**

title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 2.0 : 8.0), and isolated as a white solid. Mp.: 116-118 °C. Yield: 81% (73 mg). IR (Neat): $\nu_{max}$ 3455, 2985, 2937, 2856, 1700, 1608, 1511, 1463, 1382, 1248, 1178, 1109, 1031, 898, 856, 735, 701 and 589 $cm^{-1}$. $^{1}H$ NMR ($CD_3OD$, 500 MHz): δ 7.11 (2H, d, *J* = 8.5 Hz), 6.77 (2H, d, *J* = 8.5 Hz), 3.72 (3H, s, O-C*H*$_3$), 3.65 (2H, s, C*H*$_2$), 1.35 (12H, s, 4 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.8 (C, *C*=O), 159.3 (C), 134.0 (C), 130.2 (CH, 2 x *C*H), 114.7 (CH, 2 x *C*H), 114.0 (C), 55.7 ($CH_3$, O-*C*$H_3$), 52.7 (C, 2 x *C*, br s), 28.6 ($CH_2$), 25.2 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{22}O_4Na$ 303.1596; Found : 303.1596.

**5-Hydroxy-2,2,6,6-tetramethyl-4-(4-(trifluoromethyl)benzyl)cyclohex-4-ene-1,3-dione**

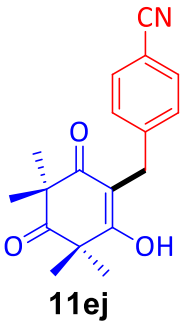


**11eh**

**(11eh):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 2.0 : 8.0), and isolated as a white solid. Mp.: 118-120 °C. Yield: 88% (90 mg). IR (Neat): $\nu_{max}$ 3342, 2981, 2167, 1711, 1615, 1471, 1386, 1325, 1163, 1122, 1067, 1018, 801, 698, 566 and 488 $cm^{-1}$. $^{1}H$ NMR ($CD_3OD$, 500 MHz): δ 7.51 (2H, d, *J* = 7.5 Hz), 7.38 (2H, d, *J* = 7.5 Hz), 3.79 (2H, s, C*H*$_2$), 1.36 (12H, s, 4 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 100 MHz): δ 214.5 (C, *C*=O), 147.0 (C), 129.9 (CH, 2 x *C*H), 129.1 (C, q, *J* = 31.0 Hz), 126.07 (C, *C*$F_3$, q, *J* = 268.0 Hz), 126.11 (CH, 2 x *C*H, d,

*J* = 3.0 Hz), 113.0 (C), 52.7 (C, 2 x *C*, br s), 29.6 ($CH_2$), 25.2 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}F_3O_4$ 341.1365; Found : 341.1364.

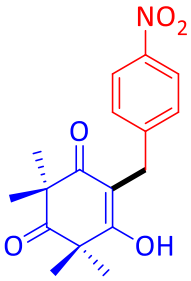
**4-((2-Hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-en-1-yl)methyl)benzonitrile**



**11ej**

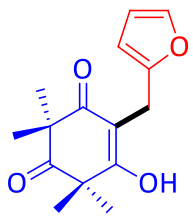
**(11ej):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 2.0 : 8.0), and isolated as a white solid. Mp.: 120-122 °C. Yield: 71% (63 mg). IR (Neat): $\nu_{max}$ 3445, 2980, 2939, 2252, 2165, 2127, 1734, 1648, 1375, 1217, 1024, 821, 748, 664, 622 and 530 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 7.58 (2H, d, *J* = 8.5 Hz), 7.38 (2H, d, *J* = 8.5 Hz), 3.79 (2H, s, C$H_2$), 1.36 (12H, s, 4 x C$H_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.5 (C, *C*=O), 148.6 (C), 133.2 (CH, 2 x *C*H), 130.4 (CH, 2 x *C*H), 120.1 (C), 112.6 (C), 110.5 (C), 52.7 (C, 2 x *C*, br s), 30.0 ($CH_2$), 25.2 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}NO_3$ 298.1443; Found : 298.1447.

**5-Hydroxy-2,2,6,6-tetramethyl-4-(4-nitrobenzyl)cyclohex-4-ene-1,3-dione (11ei):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.2 : 8.8), and isolated as a white solid. Mp.: 124-126 °C. Yield: 74% (70 mg). IR (Neat): $\nu_{max}$ 3314, 2982, 2502, 2360, 2167, 2006, 1713, 1598, 1515, 1469, 1386, 1343, 1181, 1109, 1046, 1005, 981, 857, 809, 737, 697, 637 and 567 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 8.11 (2H, d, *J* = 9.0 Hz), 7.43 (2H, d, *J* = 9.0 Hz), 3.83 (2H, s, C$H_2$), 1.36 (12H, s, 4 x C$H_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.5 (C, *C*=O), 150.7 (C), 147.8 (C), 130.4 (CH, 2 x *C*H), 124.4 (CH, 2 x *C*H), 112.6 (C), 52.8 (C, 2 x *C*, br s), 29.9 ($CH_2$), 25.2 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}NO_5$ 318.1341; Found : 318.1340.



**11ei**

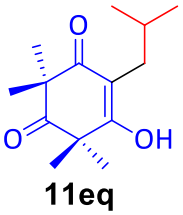
**4-(Furan-2-ylmethyl)-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11eo):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.2 : 8.8), and isolated as a yellowish solid. Mp.: 122-124 °C. Yield: 94% (74 mg). IR (Neat): $\nu_{max}$ 3142, 2985, 2936, 2168, 2006, 1703, 1568, 1510, 1457, 1394, 1358, 1212, 1151, 1050, 1016, 939, 887, 792, 749, 652 and 573 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 7.30 (1H, d, *J* = 1.0 Hz), 6.24 (1H, dd, *J* = 3.0, 2.0 Hz), 5.89 (1H,



**11eo**

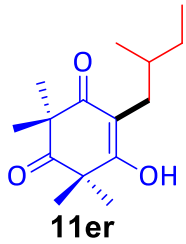
dd, *J* = 3.0, 1.0 Hz), 3.73 (2H, s, C*H*$_2$), 1.37 (12H, s, 4 x C*H*$_3$). $^{13}$C NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.7 (C, *C*=O), 155.2 (C), 142.0 (CH), 111.3 (CH), 110.3 (C), 105.8 (CH), 52.8 (C, 2 x *C*, br s), 25.3 ($CH_3$, 4 x *C*$H_3$), 22.8 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{19}O_4$ 263.1283; Found : 263.1283.

**5-Hydroxy-4-isobutyl-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11eq):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.0 : 9.0), and isolated as a white solid. Mp.: 80-82 °C. Yield: 91% (65 mg). IR (Neat): $\nu_{max}$ 3234, 2984, 2961, 2920, 2871, 2428, 2156, 1707, 1586, 1461, 1390, 1361, 1303, 1282, 1223, 1175, 1095, 1045, 959, 919, 865, 813, 739 and 644 cm$^{-1}$. $^1$H NMR ($CD_3OD$, 500 MHz): δ 2.27 (2H, d, *J* = 7.5 Hz, C*H*$_2$), 1.74 (1H, sept, *J* = 7.0 Hz), 1.35 (12H, s, 4 x C*H*$_3$), 0.88 (6H, d, *J* = 6.5 Hz, 2 x C*H*$_3$). $^{13}$C NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 215.0 (C, *C*=O), 113.2 (C), 52.8 (C, 2 x C, br s), 32.4 ($CH_2$), 29.0 (CH), 25.4 ($CH_3$, 4 x *C*$H_3$), 22.8 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{22}O_3Na$ 261.1467; Found : 261.1469.



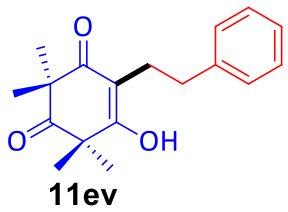
11eq

**5-Hydroxy-4-isobutyl-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11er):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.0 : 9.0), and isolated as a white solid. Mp.: 78-80 °C. Yield: 86% (65 mg). IR (Neat): $\nu_{max}$ 3328, 2960, 2930, 2874, 2187, 2147, 2048, 1708, 1596, 1463, 1383, 1364, 1277, 1212, 1168, 1103, 1045, 1008, 949, 896, 779, 693, 639 and 569 cm$^{-1}$. $^1$H NMR ($CD_3OD$, 500 MHz): δ 2.36 (1H, dd, *J* = 13.5, 6.5 Hz), 2.22 (1H, dd, *J* = 13.5, 8.0 Hz), 1.55-1.50 (1H, m), 1.43-1.28 (1H, m), 1.35 (12H, s, 4 x C*H*$_3$), 1.24-1.10 (1H, m), 0.90 (3H, t, *J* = 7.5 Hz, C*H*$_3$), 0.83 (3H, d, *J* = 6.5 Hz, C*H*$_3$). $^{13}$C NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 215.0 (C, *C*=O), 113.2 (C), 35.5 (CH), 30.9 ($CH_2$), 30.6 ($CH_2$), 25.4 ($CH_3$, 4 x *C*$H_3$), 19.2 ($CH_3$), 12.2 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{25}O_3$ 253.1804; Found : 253.1805.



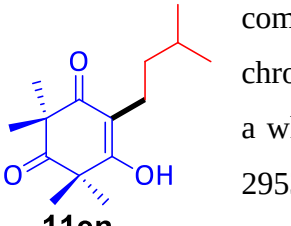
11er

**5-Hydroxy-2,2,6,6-tetramethyl-4-phenethylcyclohex-4-ene-1,3-dione (11ev):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.8 : 9.2 to 1.0 : 9.0), and isolated as a white solid. Mp.: 88-90 °C. Yield: 88% (76 mg). IR (Neat): $\nu_{max}$ 3301, 3026, 2981, 2936, 2875, 2167, 2042, 2007, 1711, 1597, 1495, 1455, 1386, 1365, 1217, 1175, 1048, 1014, 899, 832, 746, 699 and 568 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 7.25-7.18 (4H, m), 7.14-7.10 (1H, m), 2.68 (4H, s, C*H*$_2$), 1.28 (12H, s, 4 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 215.1 (C, *C*=O), 143.3 (C), 129.9 (CH, 2 x *C*H), 129.2 (CH, 2 x *C*H), 126.9 (CH), 113.2 (C), 52.6 (C, 2 x *C*, br s), 35.3 ($CH_2$), 25.6 ($CH_2$), 25.3 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{23}O_3$ 287.1647; Found : 287.1648.



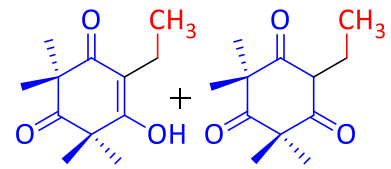
11ev

**5-Hydroxy-4-isopentyl-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11en):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.7 : 9.3 to 1.0 : 9.0), and isolated as a white solid. Mp.: 66-68 °C. Yield: 92% (70 mg). IR (Neat): $\nu_{max}$ 3297, 2953, 2870, 1712, 1593, 1468, 1385, 1365, 1295, 1205, 1169, 1109, 1043, 1000, 902, 830, 640 and 531 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 2.36 (2H, t, *J* = 8.0 Hz, C*H*$_2$), 1.55 (1H, sept, *J* = 6.5 Hz), 1.34 (12H, s, 4 x C*H*$_3$), 1.23-1.19 (2H, m, C*H*$_2$), 0.92 (6H, d, *J* = 6.5 Hz, 2 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 215.1 (C, *C*=O), 114.6 (C), 52.8 (C, 2 x *C*, br s), 38.9 ($CH_2$), 29.5 (CH), 25.3 ($CH_3$, 4 x *C*$H_3$), 23.2 ($CH_3$, 2 x *C*$H_3$), 22.0 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{25}O_3$ 253.1804; Found : 253.1804.



11en

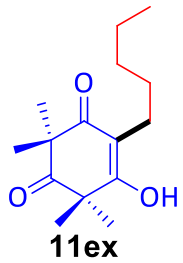
**4-Ethyl-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (11ew):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.8 : 9.2 to 1.1 : 8.9), and isolated as a white solid. Mp.: 84-86 °C. Yield: 85% (54 mg). IR (Neat): $\nu_{max}$ 3374, 2981, 2932, 2872, 2168, 2043, 2010, 1710, 1599, 1464, 1384, 1369, 1217, 1173, 1060, 879, 641 and 529 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, 2:1 ratio, major keto isomer): δ 3.50 (1H, t, *J* = 6.0 Hz), 1.97 (2H, p, *J* = 7.5 Hz), 1.37 (6H, s, 2 x C*H*$_3$), 1.28 (6H, s, 2 x C*H*$_3$), 0.97 (3H, dt, *J* = 7.5, 1.0 Hz, C*H*$_3$). $^{13}C$ NMR ($CDCl_3$, 125 MHz, DEPT-135, 2:1 ratio, major keto isomer) δ 210.8 (C, *C*=O), 205.4 (2 x C, *C*=O), 62.0 (CH), 58.4 (2 x C), 22.9 ($CH_3$, 2 x *C*$H_3$),



11ew (enol isomer) 11ew' (Keto isomer)

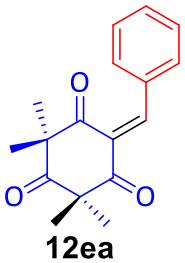
22.3 ($CH_3$, 2 x $CH_3$), 17.7 ($CH_2$), 12.9 ($CH_3$). $^1$H NMR ($CDCl_3$, 500 MHz, 2:1 ratio, minor enol isomer): δ 5.91 (1H, br s, O-*H*), 2.38 (2H, q, *J* = 7.5 Hz, C*H*$_2$), 1.38 (12H, s, 4 x C*H*$_3$), 1.00 (3H, dt, *J* = 7.5, 1.0 Hz, C*H*$_3$). $^{13}$C NMR ($CDCl_3$, 125 MHz, DEPT-135, 2:1 ratio, minor enol isomer): δ 212.9 (C, *C*=O), 113.9 (C), 77.2 (C, 2 x *C*), 24.7 ($CH_3$), 16.1 ($CH_2$), 11.8 ($CH_3$, 4 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{19}O_3$ 211.1334; Found : 211.1334.

**5-Hydroxy-2,2,6,6-tetramethyl-4-pentylcyclohex-4-ene-1,3-dione (11ex):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 0.8 : 9.2), and isolated as a white solid. Mp.: 58-60 °C. Yield: 95% (72 mg). IR (Neat): $\nu_{max}$ 3298, 2951, 2929, 2871, 2167, 2008, 1715, 1595, 1468, 1385, 1366, 1226, 1171, 1106, 1043, 641 and 538 cm$^{-1}$. $^1$H NMR ($CD_3OD$, 500 MHz): δ 2.35 (2H, t, *J* = 7.0 Hz), 1.39-1.32 (6H, m), 1.34 (12H, s, 4 x C*H*$_3$), 0.90 (3H, t, *J* = 6.5 Hz, C*H*$_3$). $^{13}$C NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 215.0 (C, *C*=O), 114.2 (C), 52.6 (C, 2 x *C*, br s), 32.9 ($CH_2$), 29.5 ($CH_2$), 25.4 ($CH_3$, 4 x *C*$H_3$), 23.8 ($CH_2$, 2 x *C*$H_2$), 14.6 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{25}O_3$ 253.1804; Found : 253.1806.



**11ex**

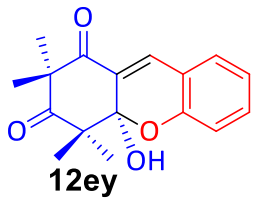
**6-Benzylidene-2,2,4,4-tetramethylcyclohexane-1,3,5-trione (12ea):** The title compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (1.0 : 9.0 to 1.2 : 8.8), and isolated as a white solid. Mp.: 124-126 °C. Yield: 41% (33 mg). IR (Neat): $\nu_{max}$ 3298, 2951, 2929, 2871, 2167, 2008, 1715, 1595, 1468, 1385, 1366, 1226, 1171, 1106, 1043, 641 and 538 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.07 (1H, s), 7.81 (2H, d, *J* = 7.2 Hz), 7.51-7.47 (1H, m), 7.47-7.41 (2H, m), 1.39 (6H, s, 2 x C*H*$_3$), 1.38 (6H, s, 2 x C*H*$_3$). $^{13}$C NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 208.6 (C, *C*=O), 200.3 (C, *C*=O), 196.2 (C, *C*=O), 150.2 (CH), 132.6 (C), 132.5 (CH), 132.2 (CH, 2 x C*H*), 130.8 (C), 128.7 (CH, 2 x C*H*), 58.9 (C), 58.7 (C), 22.3 ($CH_3$, 2 x *C*$H_3$), 21.9 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{19}O_3$ 271.1334; Found : 271.1334.



**12ea**

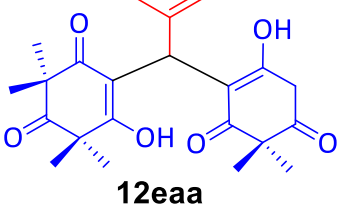
**(±)-4a-Hydroxy-2,2,4,4-tetramethyl-4,4a-dihydro-1*H*-xanthene-1,3(2*H*)-dione (12ey):** The title compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (2.0 : 8.0 to 3.0 : 7.0), and isolated as a white solid. Mp.: 146-148 °C. Yield: 33% (28 mg). IR (Neat): $\nu_{max}$ 3422, 3385, 2980, 2937, 2178, 2037, 2016, 1979, 1717, 1675, 1605, 1563, 1457, 1378, 1300, 1264, 1235, 1152, 1089, 1037, 987, 944, 850,

718, 660 and 588 $cm^{-1}$. $^{1}H$ NMR ($CD_3OD$, 500 MHz): δ 7.80 (1H, s), 7.48 (1H, d, *J* = 7.5 Hz), 7.41 (1H, t, *J* = 8.5 Hz), 7.07 (2H, dd, *J* = 11.5, 7.5 Hz), 1.45 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 1.34 (3H, s, C*H*$_3$), 1.08 (3H, s, C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.1 (C, *C*=O), 200.6 (C, *C*=O), 154.4 (C, *C*-OH), 134.0 (CH), 133.4 (CH), 131.2 (CH), 128.5 (C), 123.4 (CH), 120.9 (C), 118.3 (CH), 98.7 (C), 55.6 (C), 55.5 (C), 27.4 ($CH_3$), 24.8 ($CH_3$), 23.8 ($CH_3$), 15.8 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{18}O_4Na$ 309.1103; Found : 309.1103.



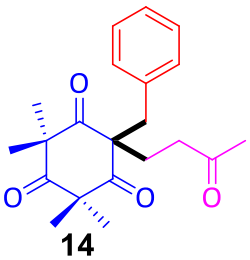
**12ey**

**5-Hydroxy-4-((2-hydroxy-5,5-dimethyl-4,6-dioxocyclohex-1-en-1-yl)-(phenyl)methyl)-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (12eaa):** The title compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.0 : 8.0 to 2.2 : 7.8), and isolated as a white solid. Mp.: 154-158 °C. Yield: 31% (39 mg). IR (Neat): $\nu_{max}$ 2981, 2938, 2878, 2020, 1997, 1719, 1672, 1631, 1466, 1380, 1350, 1157, 1088, 1033, 937, 840, 805, 699 and 591 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 7.26-7.23 (4H, m), 7.17-7.14 (1H, m), 5.02 (1H, s), 1.61 (6H, s), 1.52 (6H, s), 1.33 (6H, s), 1.10 (6H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 210.8 (C, 2 x *C*=O), 196.6 (C, 2 x *C*=O), 163.7 (C, 2 x *C*), 142.9 (C), 128.5 (CH, 2 x *C*H), 127.9 (CH, 2 x *C*H), 127.0 (CH), 113.3 (C, 2 x *C*), 56.5 (C, 2 x *C*), 47.0 (C, 2 x *C*), 33.4 (CH), 24.81 ($CH_3$, 2 x *C*$H_3$), 24.76 ($CH_3$, 2 x *C*$H_3$), 24.7 ($CH_3$, 2 x *C*$H_3$), 22.6 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + K]^+$ calcd for $C_{27}H_{32}O_6K$ 491.1836; Found : 491.1838.



**12eaa**

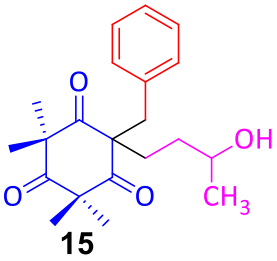
**2-Benzyl-4,4,6,6-tetramethyl-2-(3-oxobutyl)cyclohexane-1,3,5-trione (14):** The title compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 0.8 : 9.2), and isolated as a white solid. Mp.: 76-78 °C. Yield: 92% (94 mg). IR (Neat): $\nu_{max}$ 3361, 2980, 2936, 2869, 2618, 1715, 1584, 1494, 1469, 1385, 1353, 1312, 1180, 1047, 1002, 826, 732, 697, 641 and 584 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 7.20-7.15 (3H, m), 7.10 (2H, dd, *J* = 8.5, 2.0 Hz), 3.19 (2H, s), 2.46 (3H, t, *J* = 7.5 Hz), 2.14 (3H, s, C*H*$_3$), 2.00 (2H, t, *J* = 7.5 Hz), 1.31 (6H, s, 2 x C*H*$_3$), 0.90 (6H, s, 2 x C*H*$_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 210.4 (C, *C*=O), 208.8 (C, 2 x *C*=O), 206.3 (C, *C*=O), 136.5 (C), 131.2 (CH, 2 x *C*H), 128.2 (CH, 2 x *C*H), 127.1 (CH), 66.7 (C), 57.4 (C,



**14**

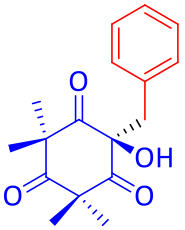
2 x *C*), 38.2 ($CH_2$), 37.4 ($CH_2$), 31.3 ($CH_2$), 30.0 ($CH_3$), 24.5 ($CH_3$, 2 x *C*$H_3$), 22.9 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{27}O_4$ 343.1909; Found : 343.1908.

**2-Benzyl-2-(3-hydroxybutyl)-4,4,6,6-tetramethylcyclohexane-1,3,5-trione (15):** The title compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.7 : 8.3 to 1.8 : 8.2), and isolated as a gummy colourless liquid. Yield: 62% (43 mg). IR (Neat): $\nu_{max}$ 3522, 3040, 2977, 2937, 2875, 2360, 2345, 1694, 1584, 1495, 1455, 1381, 1259, 1066, 1034, 999, 974, 885, 851, 804, 740, 703, 616 and 550 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz): δ 7.21-7.18 (1H, m), 7.18-7.17 (1H, m), 7.16-7.13 (3H, m), 3.70 (1H, sextet, *J* = 6.0 Hz), 3.29 (1H, d, *J* = 13.0 Hz), 3.21 (1H, d, *J* = 13.0 Hz), 1.95 (1H, dt, *J* = 12.5, 4.5 Hz), 1.72 (1H, dt, *J* = 12.5, 4.5 Hz), 1.47-1.36 (2H, m), 1.33 (3H, s, C*H*$_3$), 1.31 (3H, s, C*H*$_3$), 1.17 (3H, d, *J* = 6.0 Hz, C*H*$_3$), 0.95 (3H, s, C*H*$_3$), 0.86 (3H, s, C*H*$_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 210.8 (C, *C*=O), 208.8 (C, *C*=O), 208.7 (C, *C*=O), 137.0 (C), 131.3 (CH, 2 x *C*H), 128.1 (CH, 2 x *C*H), 126.9 (CH), 67.9 (C), 67.8 (CH), 57.6 (C), 57.2 (C), 38.0 ($CH_2$), 34.9 ($CH_2$), 32.8 ($CH_2$), 24.8 ($CH_3$), 24.5 ($CH_3$), 23.8 ($CH_3$), 22.8 ($CH_3$), 22.2 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{28}O_4Na$ 367.1885; Found : 367.1885.



**15**

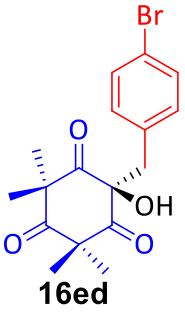
**2-Benzyl-2-hydroxy-4,4,6,6-tetramethylcyclohexane-1,3,5-trione (16ea):** The title compound was prepared following the procedure **E** and purified by column chromatography using EtOAc/hexane (1.3 : 8.7 to 1.5 : 8.5), and isolated as a yellowish white solid. Mp.: 90-92 °C. Yield: 90% (52 mg). IR (Neat): $\nu_{max}$ 3451, 3034, 2986, 2945, 2872, 1757, 1703, 1607, 1496, 1455, 1382, 1259, 1061, 736, 700 and 494 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz): δ 7.25 (2H, d, *J* = 7.0 Hz), 7.21 (2H, t, *J* = 7.0 Hz), 7.16 (1H, d, *J* = 8.0 Hz), 3.21 (2H, s, C*H*$_2$), 1.37 (6H, s, 2 x C*H*$_3$), 1.22 (6H, s, 2 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 212.1 (C, *C*=O), 208.3 (C, 2 x *C*=O), 136.6 (C), 132.2 (CH, 2 x *C*H), 129.0 (CH, 2 x *C*H), 127.7 (CH), 87.6 (C, *C*-OH), 57.4 (2 x C), 37.5 ($CH_2$), 25.0 ($CH_3$, 2 x *C*$H_3$), 24.9 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{20}O_4Na$ 311.1259; Found : 311.1259.



**16ea**

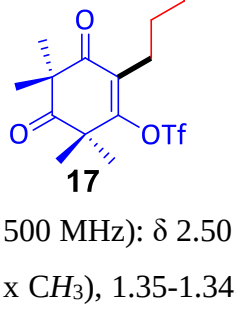
**2-(4-Bromobenzyl)-2-hydroxy-4,4,6,6-tetramethylcyclohexane-1,3,5-trione (16ed):** The title compound was prepared following the procedure **E** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 2.0 : 8.0), and isolated as a yellow solid.

Mp.: 100-102 °C. Yield: 85% (62 mg). IR (Neat): $\nu_{max}$ 3447, 2985, 2939, 2874, 1707, 1606, 1489, 1468, 1382, 1259, 1158, 1069, 1012, 898, 814 and 580 $cm^{-1}$. $^{1}H$ NMR ($CD_3OD$, 500 MHz): δ 7.36 (2H, d, *J* = 8.5 Hz), 7.20 (2H, d, *J* = 8.5 Hz), 3.18 (2H, s, C*H*$_2$), 1.38 (6H, s, 2 x C*H*$_3$), 1.23 (6H, s, 2 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 100 MHz): δ 212.0 (C, *C*=O), 208.2 (C, 2 x *C*=O), 136.2 (C), 134.1 (2 x CH), 132.0 (2 x CH), 121.5 (C), 87.5 (C, *C*-OH), 57.2 (C, 2 x *C*), 36.2 ($CH_2$), 25.0 ($CH_3$, 2 x *C*$H_3$), 24.8 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: [M + $NH_4$]$^+$ calcd for $C_{17}H_{23}BrO_4N$ 384.0810; Found : 384.0805.



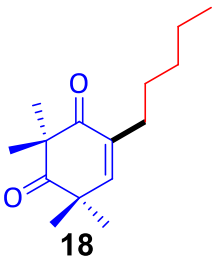
**16ed**

**4,4,6,6-Tetramethyl-3,5-dioxo-2-pentylcyclohex-1-en-1-yl trifluoromethanesulfonate (17):** The title compound was prepared following the procedure **F** and purified by column chromatography using EtOAc/hexanes (1.8 : 8.2 to 2.2 : 7.8), and isolated as a colourless liquid. Yield: 84% (97 mg). IR (Neat): $\nu_{max}$ 2964, 2923, 2853, 1729, 1690, 1646, 1604, 1465, 1405, 1282, 1242, 1224, 1160, 1029, 918, 835, 803, 697, 638 and 583 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 2.50 (2H, t, *J* = 7.5 Hz), 1.45 (6H, s, 2 x C*H*$_3$), 1.42-1.39 (1H, m), 1.37 (6H, s, 2 x C*H*$_3$), 1.35-1.34 (1H, m), 1.32 (4H, t, *J* = 3.0 Hz), 0.88 (3H, t, *J* = 7.0 Hz, C*H*$_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 208.8 (C, *C*=O), 198.3 (C, *C*=O), 161.8 (C), 131.1 (C), 118.6 (C, *C*$F_3$, q, *J* = 318.75 Hz), 56.9 (C), 49.3 (C), 31.7 ($CH_2$), 27.5 ($CH_2$), 25.6 ($CH_2$), 24.6 ($CH_3$, 2 x *C*$H_3$), 23.4 ($CH_3$, 2 x *C*$H_3$), 22.2 ($CH_2$), 13.9 ($CH_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{24}F_3O_5S$ 385.1297; Found : 385.1295.



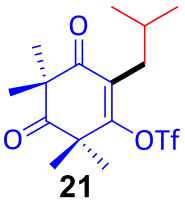
**17**

**2,2,6,6-Tetramethyl-4-pentylcyclohex-4-ene-1,3-dione (18):** The title compound was prepared following the procedure **G** and purified by column chromatography using EtOAc/hexane (0.4 : 9.6 to 0.8 : 9.2), and isolated as a colourless liquid. Yield: 82% (39 mg). IR (Neat): $\nu_{max}$ 2958, 2926, 2858, 2156, 1716, 1672, 1465, 1379, 1301, 1249, 1105, 1039, 998, 910, 729 and 580 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 6.44 (s, 1H), 2.28 (2H, dt, *J* = 7.5, 1.0 Hz), 1.42 (2H, pent, *J* = 7.0 Hz), 1.36-1.24 (4H, m), 1.32 (6H, s, 2 x C*H*$_3$), 1.30 (6H, s, 2 x C*H*$_3$), 0.89 (3H, t, *J* = 6.5 Hz, C*H*$_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz): δ 213.8 (C, *C*=O), 201.2 (C, *C*=O), 147.8 (CH), 135.8 (C), 57.2 (C), 44.9 (C), 31.5 ($CH_2$), 30.0 ($CH_2$), 28.1 ($CH_2$), 27.4 ($CH_3$, 2 x *C*$H_3$), 23.7 ($CH_3$, 2 x *C*$H_3$), 22.4 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{14}H_{24}O_2Na$ 259.1674; Found : 259.1670.



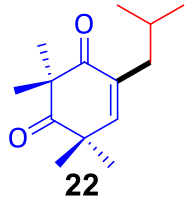
**18**

**4,4,6,6-Tetramethyl-3,5-dioxo-2-pentylcyclohex-1-en-1-yl trifluoromethanesulfonate (21):** The title compound was prepared following the procedure **F** and purified by column chromatography using EtOAc/hexane (2.0 : 8.0 to 2.2 : 7.8), and isolated as a colourless liquid. Yield: 84% (93 mg). IR (Neat): $\nu_{max}$ 2961, 2936, 2872, 1728, 1685, 1646, 1467, 1410, 1385, 1315, 1211, 1134, 1106, 1012, 930, 873, 840, 791, 760, 699 and 604 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 2.46 (2H, d, *J* = 7.5 Hz), 1.77 (1H, sept, *J* = 7.0 Hz), 1.49 (6H, s, 2 x C*H*$_3$), 1.39 (6H, s, 2 x C*H*$_3$), 0.90 (6H, d, *J* = 6.5 Hz, 2 x C*H*$_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 208.9 (C, *C*=O), 198.5 (C, *C*=O), 162.7 (C), 130.3 (C), 118.6 (C, *C*$F_3$, q, *J* = 318.75 Hz), 56.6 (C), 49.4 (C), 33.6 ($CH_2$), 27.5 (CH), 24.6 ($CH_3$, 2 x *C*$H_3$), 23.7 ($CH_3$, 2 x *C*$H_3$), 22.2 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{22}F_3O_5S$ 371.1140; Found : 371.1138.



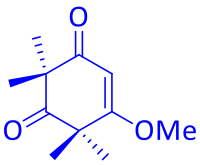
21

**4-Isobutyl-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (16):** The title compound was prepared following the procedure **G** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 0.9 : 9.1), and isolated as a colourless liquid. Yield: 84% (37 mg). IR (Neat): $\nu_{max}$ 2961, 2936, 2872, 1728, 1685, 1646, 1467, 1410, 1385, 1315, 1211, 1134, 1106, 1012, 930, 873, 840, 791, 760, 699 and 604 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 6.44 (1H, br s), 2.17 (2H, d, *J* = 6.5 Hz), 1.75 (1H, sept, *J* = 6.0 Hz), 1.33 (6H, s, 2 x C*H*$_3$), 1.31 (6H, s, 2 x C*H*$_3$), 0.89 (6H, d, *J* = 6.5 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz): δ 213.7 (C, *C*=O), 201.1 (C, *C*=O), 149.2 (CH), 134.6 (C), 57.2 (C), 44.9 (C), 39.3 ($CH_2$), 27.4 ($CH_3$, 2 x *C*$H_3$), 27.1 (CH), 23.7 ($CH_3$, 2 x *C*$H_3$), 22.3 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{23}O_2$ 223.1698; Found : 223.1699.



22

**5-Methoxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione:** The title compound was prepared following the procedure **H** and purified by column chromatography using EtOAc/hexanes (1.2 : 8.8 to 1.0 : 9.0), and isolated as a colourless liquid. Yield: 35% (21 mg). IR (Neat): $\nu_{max}$ 2984, 2935, 2353, 2014, 1708, 1607, 1468, 1383, 1233, 1175, 1061, 900, 824, 658 and 581 $cm^{-1}$. $^{1}H$ NMR ($CD_3OD$, 500 MHz): δ 5.57 (1H, s), 3.85 (3H, s, C*H*$_3$), 1.39 (6H, s, 2 x C*H*$_3$), 1.30 (6H, s, 2 x C*H*$_3$). $^{13}C$ NMR ($CD_3OD$, DEPT-135, 125 MHz): δ 214.5 (C, *C*=O), 201.8 (C, *C*=O), 181.2 (C), 99.9 (CH), 57.5 ($CH_3$), 56.3 (2 x C), 25.6 ($CH_3$, 2 x *C*$H_3$), 25.0 ($CH_3$, 2 x *C*$H_3$). HRMS (ESI-TOF) m/z: $[M + K]^+$ calcd for $C_{11}H_{16}O_3K$ 235.0737; Found : 235.0737.

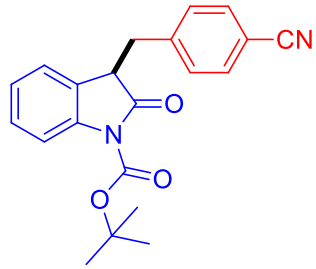


## *3. General Experimental Procedures for Organocatalytic C-H Oxidation: High-Yielding Synthesis of 3-Hydroxy-3-alkyloxindoles*

**Procedure A: General procedure for the Hantzsch ester reduction of N-protected-3-substituted-eneindolin-2-one 9:** A washed and dry 25ml RB flask equipped with a magnetic bar was charged with dry DCM (10 ml). To this, 0.3 mmol (1eq) of N-protected-3-substituted-eneindolin-2-one **24** was added followed by 0.36 mmol (1.2 eq) of Hantzsch ester. The reaction mixture was stirred for 8-12 h. The progress of the reaction was monitored by TLC analysis. Pure N-protected-3-substitued oxindole products **25** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

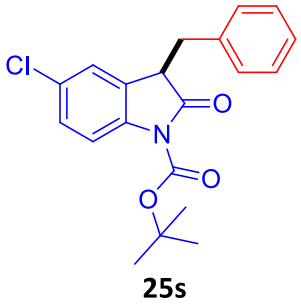
**Procedure B: General procedure for the TMG-catalyzed oxidation of N-protected-3-substituted oxindole:** An ordinary glass vial equipped with a magnetic stirring bar was charged with dry THF (1.0 mL). To this, 0.2 mmol of 3-substitued oxindole **25** was added followed by the addition of TMG (10 mol%, 2.3 mg) (**26h**) were added. The reaction mixture was stirred at 25 °C for 2-6 h. The progress of the reaction was monitored by TLC analysis. Pure 3-hydroxy-3-substitued oxindole products **27** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

***tert*-Butyl 3-(4-cyanobenzyl)-2-oxoindoline-1-carboxylate (25p):** Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 2.0 : 8.0) and was isolated as a white solid. Mp.: 137-139°C. Yield: 92% (96 mg). IR (Neat): 3019, 2984, 2931, 2231, 1789, 1760, 1732, 1607, 1464, 1370, 1350, 1294, 1251, 1216, 1146, 1093, 1059, 997, 837, 747, 665, 625, 575 and 548 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.72 (1H, d, *J* = 8.5 Hz), 7.53 (2H, d, *J* = 8.5 Hz), 7.29-7.26 (1H, m), 7.24 (2H, d, *J* = 8.5 Hz), 7.08 (1H, dt, *J* = 0.5, 7.5 Hz), 6.89 (1H, d, *J* = 7.5 Hz), 3.87 (1H, dd, *J* = 5.0, 8.0 Hz), 3.47 (1H, dd, *J* = 5.0, 14.0 Hz), 3.18 (1H, dd, *J* = 8.0, 13.5 Hz), 1.63 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 174.8 (C, *C*=O), 148.8 (C, *C*=O), 142.6 (C), 140.0 (C), 132.1 (2 x CH), 130.2 (2 x CH), 128.6 (CH), 126.2 (C), 124.1 (CH), 123.9 (CH), 118.6 (C), 115.0 (CH), 110.8 (C), 84.5 (C, *C*$Me_3$), 46.9 (CH), 37.2 ($CH_2$), 28.0 (3 x $CH_3$). HRMS m/z 371.1372 $[M + Na]^+$, calcd for $C_{21}H_{20}N_2O_3Na$ 371.1372.



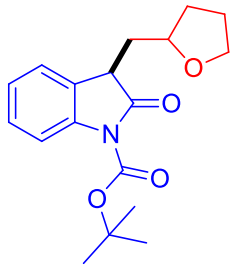
**25p**

***tert*-Butyl 3-benzyl-5-chloro-2-oxoindoline-1-carboxylate (25s):** Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1.8 : 8.2 to 2.2 : 7.8) and was isolated as a white solid. Mp.: 164-166°C. Yield: 91% (98 mg). IR (Neat): 3401, 3030, 2981, 2931, 1768, 1730, 1604, 1474, 1607, 1370, 1337, 1295, 1252, 1151, 1108, 1079, 1000, 822, 751, 700, 601 and 545 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.69 (1H, d, *J* = 8.5 Hz), 7.30-7.24 (3H, m), 7.21 (1H, dd, *J* = 8.5, 2.5 Hz), 7.14 (2H, d, *J* = 8.0 Hz), 6.71 (1H, s), 3.79 (1H, dd, *J* = 9.0, 4.5 Hz), 3.47 (1H, dd, *J* = 14.0, 5.0 Hz), 2.97 (1H, dd, *J* = 14.0, 9.0 Hz), 1.62 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 174.5 (C, *C*=O), 149.0 (C, *C*=O), 138.6 (C), 136.8 (C), 129.39 (C), 129.35 (2 x CH), 128.9 (C), 128.6 (2 x CH), 128.2 (CH), 127.1 (CH), 124.6 (CH), 116.1 (CH), 84.6 (C, *C*$Me_3$), 47.5 (CH), 37.5 ($CH_2$), 28.1 (3 x $CH_3$). HRMS m/z 380.1029 $[M + Na]^+$, calcd for $C_{20}H_{20}ClNO_3Na$ 380.1029.



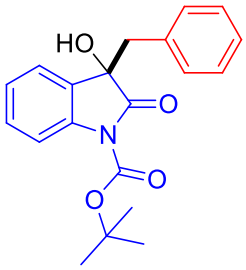
**25s**

***tert*-Butyl 2-oxo-3-((tetrahydrofuran-2-yl)methyl)indoline-1-carboxylate) (25w):** Prepared following the Pd/C reduction procedure and purified by column chromatography using EtOAc/hexane (2.0 : 8.0 to 2.5 : 7.5) and was isolated as a white solid. Mp.: 138-140°C. Yield: 87% (83 mg). IR (Neat): 3433, 2959, 2854, 1776, 1730, 1613, 1463, 1371, 1345, 1291, 1251, 1153, 1038, 917, 846 and 771 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz, *dr* = 1.2:1, major isomer) δ 7.82 (2H, dd, *J* = 6.4, 2.4 Hz), 7.14 (2H, t, *J* = 6.0 Hz), 4.10-4.05 (1H, m), 3.84-3.80 (1H, m), 3.68-3.63 (2H, m), 1.97-1.90 (4H, m), 1.639 (9H, s), 1.54-1.47 (2H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz, *dr* = 1.2:1, major isomer) δ 176.3 (C, *C*=O), 149.5 (C, *C*=O), 140.3 (C), 128.0 (CH), 127.7 (C), 124.0 (CH), 123.8 (CH), 115.0 (CH), 83.9 (C, *C*$Me_3$), 75.8 (CH), 67.3 ($CH_2$), 44.0 (CH), 37.0 ($CH_2$), 31.50 ($CH_2$), 28.13 (3 x $CH_3$), 25.5 ($CH_2$). $^{1}H$ NMR ($CDCl_3$, 400 MHz, *dr* = 1.2:1, minor isomer) δ 7.38 (1H, d, *J* = 6.0 Hz), 7.31-7.27 (3H, m), 4.19-4.14 (1H, m), 3.91 (1H, q, *J* = 6.4 Hz), 3.78-3.74 (2H, m), 2.31-2.26 (1H, m), 2.21-2.08 (3H, m), 1.89-1.82 (2H, m), 1.643 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz, *dr* = 1.2:1, minor isomer) δ 176.5 (C, *C*=O), 149.3 (C, *C*=O), 139.9 (C), 128.03 (C), 128.0 (CH), 124.6 (CH), 124.1 (CH), 114.9 (CH), 84.2 (C, *C*$Me_3$), 75.4 (CH), 67.8 ($CH_2$), 43.5 (CH), 37.4 ($CH_2$), 31.46 ($CH_2$), 28.11 (3 x $CH_3$), 25.7 ($CH_2$). HRMS m/z 318.1701 $[M + H]^+$, calcd for $C_{18}H_{24}NO_4$ 318.1705.



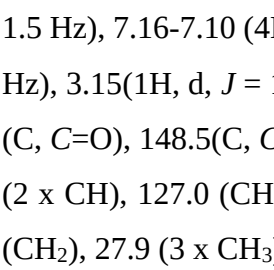
**25w**

***tert*-Butyl 3-benzyl-3-hydroxy-2-oxoindoline-1-carboxylate (27a):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 78-79 °C. Yield: 96% (65 mg). IR (Neat): 3447, 3085, 3059, 2982, 2930, 2249, 1779, 1732, 1608, 1463, 1350, 1293, 1247, 1154, 1112, 1050, 1004, 942, 849 and 751 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.60 (1H, d, *J* = 8.5 Hz), 7.26 (1H, dt, *J* = 7.8, 1.0 Hz), 7.18 (1H, dd, *J* = 7.5, 1.5 Hz), 7.16-7.10 (4H, m), 6.88 (2H, d, *J* = 7.5 Hz), 3.49 (1H, br s, O*H*), 3.27 (1H, d, *J* = 13.0 Hz), 3.15(1H, d, *J* = 12.5 Hz), 1.56 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.9 (C, *C*=O), 148.5(C, *C*=O), 139.1 (C), 133.3 (C), 130.2 (2 x CH), 129.7 (CH), 128.2 (C), 127.8 (2 x CH), 127.0 (CH), 124.5 (CH), 124.3 (CH), 114.9 (CH), 84.3 (C), 77.1 (C, *C*-OH), 45.9 ($CH_2$), 27.9 (3 x $CH_3$). HRMS m/z 362.1368 ($M + Na^+$), calcd for $C_{20}H_{21}NO_4Na$ 362.1368.



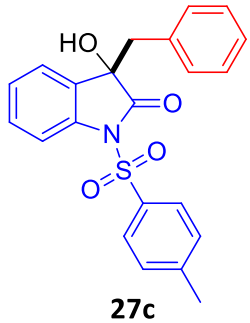
**27a**

**1-Acetyl-3-benzyl-3-hydroxyindolin-2-one (27b):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.0 : 8.0 to 2.5 : 7.5) and was isolated as a white colour gummy liquid. Yield: 91% (51 mg). IR (Neat): 3413, 3088, 3059, 3033, 2917, 1763, 1713, 1610, 1465, 1372, 1339, 1273, 1190, 1164, 1113, 1080, 1016, 989, 913, 783, 757, 701, 608, 566 and 485 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.98 (1H, d, *J* = 8.0 Hz), 7.32-7.29 (2H, m), 7.23-7.20 (1H, m), 7.16-7.09 (3H, m), 6.83 (2H, d, *J* = 7.0 Hz), 3.55-3.51 (1H, br m, O*H*), 3.29 (1H, d, *J* = 13.0 Hz), 3.18 (1H, d, *J* = 13.0 Hz), 2.46 (3H, s, COC*H*$_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 178.8 (C, *C*=O), 170.2 (C, *C*=O), 139.5 (C), 132.9 (C), 130.1 (CH), 130.0 (2 x CH), 128.4 (C), 128.0 (2 x CH), 127.4 (CH), 125.4 (CH), 124.0 (CH), 116.4 (CH), 77.4 (C, *C*-OH), 45.9 ($CH_2$), 26.1 ($CH_3$). HRMS m/z 282.1131 $[M + H]^+$, calcd for $C_{17}H_{16}NO_3$ 282.1130.



**27b**

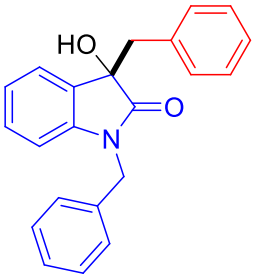
**3-Benzyl-3-hydroxy-1-tosylindolin-2-one (27c):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (3.0 : 7.0 to 3.5 : 6.5) and was isolated as a white colour gummy liquid. Yield: 90% (71 mg). IR (Neat): 3058, 2925, 1742, 1650, 1601, 1576, 1493, 1451, 1339, 1288, 1255, 1159, 1090, 990, 918, 814, 757, 700, 661, 630, 565, 546 and 509 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.91 (1H, dd, *J* = 8.25, 1.0 Hz), 7.71 (3H, d, 8.5 Hz), 7.45 (1H, dt, *J* = 8.0, 1.5 Hz), 7.35-7.27 (3H, m), 7.20 (2H, d, *J* = 8.0 Hz), 7.14 (2H, d, *J* = 7.0 Hz), 7.05 (1H, dt, *J* = 15.5, 1.0 Hz), 4.22



**27c**

(2H, s), 2.36 (3H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 201.8 (C, *C*=O), 143.8 (C), 140.6 (C), 136.7 (C), 134.9 (CH), 133.9 (C), 131.5 (CH), 129.6 (2 x CH), 129.3 (2 x CH), 128.7 (2 x CH), 127.23 (2 x CH), 127.15 (CH), 122.6 (CH), 121.8 (C), 119.4 (CH), 77.0 (C, *C*-OH), 46.4 ($CH_2$), 21.5 ($CH_3$). HRMS m/z 416.0930 $[M + Na]^+$, calcd for $C_{22}H_{19}SNO_4Na$ 416.0932.

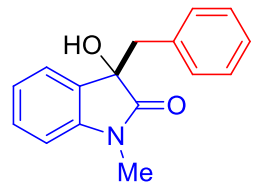
**1,3-Dibenzyl-3-hydroxyindolin-2-one (27d):** Prepared following the procedure **B** and



**27d**

purified by column chromatography using EtOAc/hexane (2.5 : 8.5 to 3.0 : 7.0) and was isolated as a white colour gummy liquid. Yield: 59% (39 mg). IR (Neat): 3373, 3085, 3062, 3033, 2922, 2851, 1703, 1614, 1493, 1468, 1436, 1353, 1298, 1285, 1199, 1170, 1112, 1079, 996, 933, 821, 781, 751, 698, 638, 584, 547, 484 and 455 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.37 (1H, m), 7.22-7.05 (8H, m), 6.94 (2H, d, *J* = 7.2 Hz), 6.71 (2H, dd, *J* = 7.6, 1.2 Hz), 6.44 (1H, d, *J* = 8.0 Hz), 5.00 (1H, d, *J* = 16.0 Hz), 4.45 (1H, d, *J* = 16.0 Hz), 3.43 (1H, d, *J* = 12.8 Hz), 3.30 (1H, d, *J* = 12.8 Hz), 3.20 (1H, s, O*H*). $^{13}$C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 177.6 (C, *C*=O), 142.7 (C), 134.9 (C), 133.8 (C), 130.4 (2 x CH), 129.8 (CH), 129.1 (C), 128.6 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 126.9 (CH), 126.6 (2 x CH), 124.4 (CH), 122.9 (CH), 109.6 (CH), 77.5 (C, *C*-OH), 44.8 ($CH_2$), 43.7 ($CH_2$). HRMS m/z 352.1316 $[M + Na]^+$, calcd for $C_{22}H_{19}NO_2Na$ 352.1313.

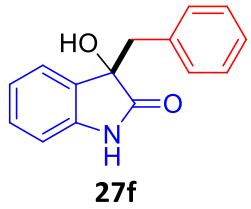
**3-Benzyl-3-hydroxy-1-methylindolin-2-one (27e):** Prepared following the procedure **B** and



**27e**

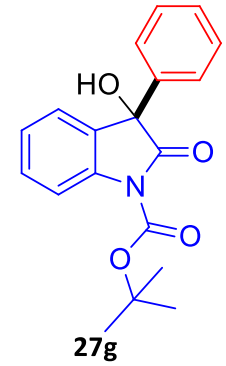
purified by column chromatography using EtOAc/hexane (2.5 : 8.5 to 3.0 : 7.0) and was isolated as a white colour gummy liquid. Yield: 56% (28 mg). IR (Neat): 3327, 3065, 3031, 2961, 2849, 1693, 1615, 1494, 1468, 1439, 1369, 1300, 1212, 1172, 1112, 1029, 1079, 752, 696, 583 and 546 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.24 (1H, d, *J* = 9.2 Hz), 7.20 (1H, d, *J* = 8.0 Hz), 7.12-7.07 (3H, m), 7.04 (1H, dt, *J* = 7.2, 0.8 Hz), 6.93 (2H, dd, *J* = 7.2, 1.6 Hz), 6.61 (1H, d, *J* = 8.0 Hz), 3.33 (1H, d, *J* = 12.8 Hz), 3.18 (1H, d, *J* = 13.2 Hz), 2.96 (3H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 177.9 (C, *C*=O), 143.1 (C), 134.0 (C), 130.2 (2 x CH), 129.6 (CH), 129.3 (C), 127.7 (2 x CH), 126.8 (CH), 124.4 (CH), 122.8 (CH), 108.1 (CH), 77.4 (C, *C*-OH), 44.9 ($CH_2$), 25.9 ($CH_3$). HRMS m/z 254.1176 $[M + H]^+$, calcd for $C_{16}H_{16}NO_2$ 254.1181.

**3-Benzyl-3-hydroxyindolin-2-one (27f):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (3.0 : 7.0 to 3.5 : 6.5) and was isolated as a white colour gummy liquid. Yield: 59% (28 mg). IR (Neat): 3345, 3147, 3090, 2921, 2850, 1706, 1626, 1474, 1358, 1291, 1219, 1181, 1113, 1083, 985, 836, 789, 756, 700, 654, 575, 542 and 497 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$ + 3 drops of $CD_3OD$, 400 MHz) δ 6.96-6.92 (2H, m), 6.89-6.84 (3H, m), 6.78 (1H, dt, *J* = 7.6, 0.8 Hz), 6.72 (2H, dd, *J* = 7.6, 1.6 Hz), 6.45 (1H, d, *J* = 8.4 Hz), 3.85 (1H, br s, O*H*), 3.05 (1H, d, *J* = 12.8 Hz), 2.91 (1H, d, *J* = 12.8 Hz). $^{13}C$ NMR ($CDCl_3$ + 3 drops of $CD_3OD$, DEPT-135, 100 MHz) δ 180.1 (C, *C*=O), 140.6 (C), 133.9 (2 x C), 129.9 (2 x CH), 129.0 (CH), 127.2 (2 x CH), 126.2 (CH), 124.2 (CH), 121.9 (CH), 109.6 (CH), 77.2 (C, *C*-OH), 43.6 ($CH_2$). HRMS m/z 262.0844 $[M + Na]^+$, calcd for $C_{15}H_{13}NO_2Na$ 262.0844.



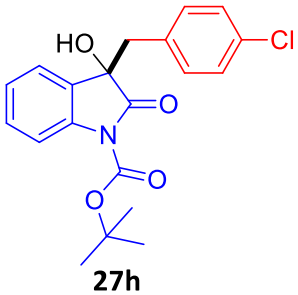
**27f**

**_tert_-Butyl 3-hydroxy-2-oxo-3-phenylindoline-1-carboxylate (27g):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.2 : 7.8 to 2.8 : 7.2) and was isolated as a white solid. Mp.: 109-110°C. Yield: 71% (46 mg). IR (Neat): 3352, 2957, 2924, 2852, 1786, 1727, 1606, 1584, 1480, 1467, 1450, 1341, 1310, 1284, 1252, 1149, 1113, 1013, 837, 773 and 698 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.94 (1H, d, *J* = 8.5 Hz), 7.40 (1H, dt, *J* = 7.75, 1.5 Hz), 7.37-7.30 (6H, m), 7.20 (1H, dt, *J* = 7.5, 1.0 Hz), 3.45 (1H, br s, O*H*), 1.63 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 175.8 (C, *C*=O), 149.0 (C, *C*=O), 139.8 (C), 139.7 (C), 130.18 (CH), 130.16 (C), 128.64 (2 x CH), 128.56 (CH), 125.5 (2 x CH), 125.3 (CH), 125.0 (CH), 115.4 (CH), 84.9 (C, *C*$Me_3$), 77.7 (C, *C*-OH), 28.0 (3 x $CH_3$). LCMS m/z 326.20 $[M + H]^+$, calcd. for $C_{19}H_{20}NO_4$ 326.3664; Anal. calcd for $C_{19}H_{19}NO_4$ (325.1314): C, 70.14; H, 5.89; N, 4.31 %. Found: C, 70.21; H, 5.87, N, 4.34 %; HRMS m/z 348.1213 $[M + Na]^+$, calcd for $C_{19}H_{19}NO_4Na$ 348.1213.



**27g**

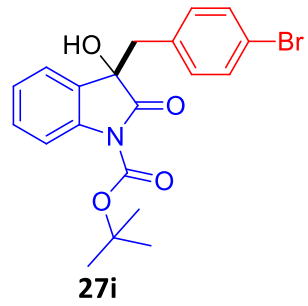
**_tert_-Butyl 3-(4-chlorobenzyl)-3-hydroxy-2-oxoindoline-1-carboxylate (27h):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.7 : 7.3 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 110-112°C. Yield: 85% (64 mg). IR (Neat): 3452, 2956, 2922, 2850, 1791, 1736, 1611, 1482, 1465, 1371, 1343, 1288, 1250, 1117, 1084, 844, 774, 755, 669, 576 and 545 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.63 (1H, d, *J* = 8.0 Hz), 7.30 (1H, dt, *J* = 7.5, 2.0 Hz), 7.20-7.14 (2H, m), 7.09 (2H, d, *J* = 8.5 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 3.30 (1H, s, O*H*), 3.23



**27h**

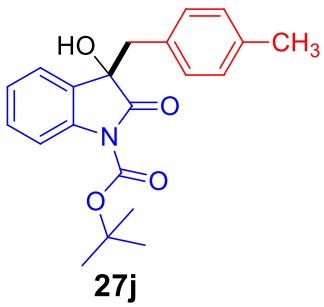
(1H, d, *J* = 13.0 Hz), 3.11 (1H, d, *J* = 13.0 Hz), 1.57 (9H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.8 (C, *C*=O), 148.4 (C, *C*=O), 139.2 (C), 133.1 (C), 131.9 (C), 131.6 (2 x CH), 130.1 (CH), 128.1 (2 x CH), 127.9 (C), 124.7 (CH), 124.3 (CH), 115.1 (CH), 84.7(C, *C*$Me_3$), 76.9 (C, *C*-OH), 45.2 ($CH_2$), 28.0 (3 x $CH_3$). LCMS m/z 374.35 $[M + H]^+$, calcd for $C_{20}H_{21}ClNO_4$ 374.1154; Anal. calcd for $C_{20}H_{20}ClNO_4$ (373.1081): C, 64.26; H, 5.39; N, 3.74 %; Found: C, 64.32; H, 5.43; N, 3.65 %.

***tert*-Butyl 3-(4-bromobenzyl)-3-hydroxy-2-oxoindoline-1-carboxylate (27i):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 125-127°C. Yield: 95% (79 mg). IR (Neat): 3444, 3031, 2976, 2919, 2852, 1776, 1731, 1611, 1478, 1466, 1371, 1345, 1288, 1250, 1147, 1112, 1047, 1004, 937, 842, 782, 748, 699, 611, 576 and 541 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.63 (1H, d, *J* = 8.0 Hz), 7.30 (1H, dt, *J* = 7.5, 2.0 Hz), 7.26-7.24 (2H, m), 7.19-7.14 (2H, m), 6.77 (2H, d, *J* = 8.5 Hz), 3.30 (1H, s, O*H*), 3.22 (1H, d, *J* = 13.0 Hz), 3.09 (1H, d, *J* = 13.0 Hz), 1.57 (9H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.7 (C, *C*=O), 148.3 (C, *C*=O), 139.1 (C), 132.3 (C), 131.9 (2 x CH), 131.0 (2 x CH), 130.0 (CH), 127.8 (C), 124.6 (CH), 124.2 (CH), 121.3 (C), 115.1 (CH), 84.7(C, *C*$Me_3$), 76.8 (C, *C*-OH), 45.2 ($CH_2$), 28.0 (3 x $CH_3$). HRMS m/z 440.0473 $[M + Na]^+$, calcd for $C_{20}H_{20}BrNO_4Na$ 440.0473.



**27i**

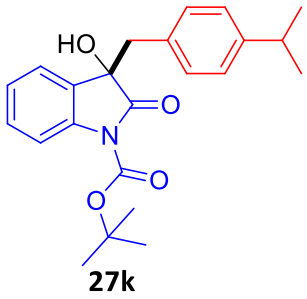
***tert*-Butyl 3-hydroxy-3-(4-methylbenzyl)-2-oxoindoline-1-carboxylate (27j):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.2 : 7.8 to 2.8 : 7.2) and was isolated as a white solid. Mp.: 112-114°C. Yield: 85% (60 mg). IR (Neat): 3447, 2978, 2922, 2852, 1776, 1731, 1680, 1512, 1479, 1468, 1371,1343, 1288, 1250, 1147, 1106, 1043, 1003, 936, 840, 814, 751, 668, 581 and 536 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.64 (1H, d, *J* = 8.0 Hz), 7.28 (1H, dt, *J* = 7.8, 1.6 Hz), 7.20 (1H, dd, *J* = 7.6, 1.6 Hz), 7.14 (1H, dt, *J* = 7.2, 0.8 Hz), 6.93 (2H, d, *J* = 7.6 Hz), 6.79 (2H, d, *J* = 8.0 Hz), 3.23 (1H, d, *J* = 12.8 Hz), 3.22 (1H, br s, O*H*), 3.11 (1H, d, *J* = 12.8 Hz), 2.24 (3H, s), 1.57 (9H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 176.9 (C, *C*=O), 148.5 (C, *C*=O), 139.2 (C), 136.6 (C), 130.1 (2 x CH), 130.0 (CH), 129.7 (C), 128.6 (2 x CH), 128.2 (C), 124.5 (CH), 124.3 (CH), 114.9 (CH), 84.3 (C, *C*$Me_3$), 77.0 (C, *C*-OH), 45.5 ($CH_2$), 27.9 (3 x $CH_3$), 21.0 ($CH_3$). LCMS m/z 354.15 ($M + H^+$), calcd



**27j**

for $C_{21}H_{24}NO_4$ 354.1750; Anal. calcd for $C_{21}H_{23}NO_4$ (353.1627): C, 71.17; H, 6.83; N, 3.95 %; Found: C, 71.26; H, 6.68; N, 3.92 %.

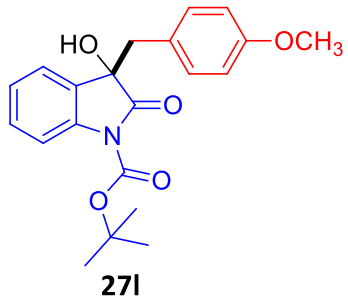
***tert*-Butyl 3-hydroxy-3-(4-isopropylbenzyl)-2-oxoindoline-1-carboxylate (27k):** Prepared



**27k**

following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.2 : 7.8 to 2.8 : 7.2) and was isolated as a white solid. Mp.: 100-104°C. Yield: 84% (64 mg). IR (Neat): 3457, 3009, 2964, 2926, 2827, 1777, 1731, 1608, 1511, 1497, 1466, 1371, 1343, 1289, 1248, 1146, 1110, 1054, 1006, 936, 841, 749, 666, 585 and 552 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.64 (1H, d, *J* = 8.0 Hz), 7.30-7.26 (1H, m), 7.19-7.13 (2H, m), 6.99 (2H, d, *J* = 7.5 Hz), 6.83 (2H, d, *J* = 8.0 Hz), 3.24 (1H, d, *J* = 13.0 Hz), 3.17 (1H, br s, O*H*), 3.10 (1H, d, *J* = 13.0 Hz), 2.80 (1H, sep, *J* = 7.0 Hz), 1.57 (9H, s), 1.17 (6H, d, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.9 (C, *C*=O), 148.5 (C, *C*=O), 147.6 (C), 139.1 (C), 130.4 (C), 130.2 (2 x CH), 129.8 (CH), 128.2 (C), 125.9 (2 x CH), 124.5 (CH), 124.3 (CH), 114.9 (CH), 84.3 (C, *C*$Me_3$), 76.9 (C, *C*-OH), 45.6 ($CH_2$), 33.6 (CH), 27.9 (3 x $CH_3$), 23.9 ($CH_3$), 23.8 ($CH_3$). LCMS m/z 381.60 [M], calcd for $C_{23}H_{27}NO_4$ 381.4648; Anal. calcd for $C_{23}H_{27}NO_4$ (381.1940): C, 72.42; H, 7.13; N, 3.67 %; Found: C, 72.53; H, 7.16; N, 3.61 %.

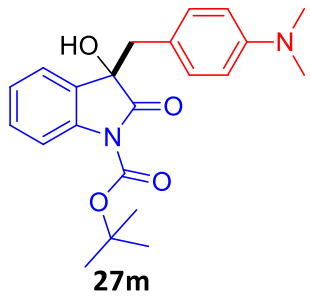
***tert*-Butyl 3-hydroxy-3-(4-methoxybenzyl)-2-oxoindoline-1-carboxylate (27l):** Prepared



**27l**

following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 2.8 : 7.2) and was isolated as a white solid. Mp.: 94-95°C. Yield: 65% (48 mg). IR (Neat): 3450, 2978, 2933, 2839, 1779, 1730, 1611, 1512, 1466, 1395, 1369, 1346, 1290, 1249, 1177, 1149, 1113, 1035, 1003, 940, 839, 756, 675, 606, 580, 564 and 542 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.62 (1H, d, *J* = 8.4 Hz), 7.28 (1H, dt, *J* = 7.6, 1.2 Hz), 7.20-7.12 (2H, m), 6.81 (2H, d, *J* = 8.8 Hz), 6.65 (2H, d, *J* = 8.4 Hz), 3.71 (3H, s, OC*H*$_3$), 3.37 (1H, br s, O*H*), 3.21 (1H, d, *J* = 13.2 Hz), 3.09 (1H, d, *J* = 12.8 Hz), 1.57 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 177.1 (C, *C*=O), 158.6 (C, *C*=O), 148.5 (C), 139.1 (C), 131.2 (2 x CH), 129.7 (CH), 128.2 (C), 125.2 (C), 124.5 (CH), 124.3 (CH), 114.9 (CH), 113.3 (2 x CH), 84.3 (C, *C*$Me_3$), 77.1 (C, *C*-OH), 55.0 ($CH_3$, O*C*$H_3$), 45.0 ($CH_2$), 27.9 (3 x $CH_3$). LCMS m/z 368.20 [M – H], calcd for $C_{21}H_{22}NO_5$ 368.4035; Anal. calcd for $C_{21}H_{23}NO_5$ (369.1576): C, 68.28; H, 6.28; N, 3.79 %; Found: C, 68.45; H, 6.25; N, 3.86 %.

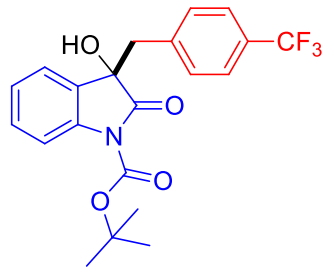
***tert*-Butyl 3-(4-(dimethylamino)benzyl)-3-hydroxy-2-oxoindoline-1-carboxylate (27m):**



**27m**

Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.8 : 7.2 to 3.2 : 6.8) and was isolated as a colourless gummy liquid. Yield: 61% (47 mg). IR (Neat): 3447, 2984, 2921, 2846, 2796, 1783, 1728, 1611, 1521, 1464, 1365, 1341, 1285, 1245, 1143, 1107, 1056, 1003, 937, 842, 811, 751, 664, 576 and 539 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.66 (1H, d, *J* = 8.0 Hz), 7.30-7.26 (1H, m), 7.19-7.12 (2H, m), 6.79 (2H, d, *J* = 8.8 Hz), 6.51 (2H, d, *J* = 8.8 Hz), 3.17 (1H, d, *J* = 13.2 Hz), 3.11 (1H, br s, O*H*), 3.03 (1H, d, *J* = 13.2 Hz), 2.86 (6H, s) 1.58 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 177.1 (C, *C*=O), 149.6 (C, *C*=O), 148.6 (C), 139.2 (C), 130.9 (2 x CH), 129.6 (CH), 128.5 (C), 124.4 (CH), 124.3 (CH), 120.8 (C), 114.9 (CH), 112.1 (2 x CH), 84.2 (C), 77.0 (C, *C*-OH), 45.0 ($CH_2$), 40.5 (2 x $CH_3$, N(*C*$H_3$)$_2$), 28.0 (3 x $CH_3$). LCMS m/z 383.40 $[M + H]^+$, calcd for $C_{22}H_{27}N_2O_4$ 383.4608; Anal. calcd for $C_{22}H_{27}N_2O_4$ (382.1893): C, 69.09; H, 6.85; N, 7.32 %; Found: C, 69.21; H, 7.05; N, 7.27 %.

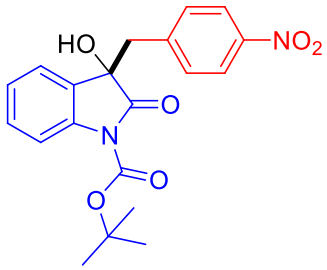
***tert*-Butyl 3-hydroxy-2-oxo-3-(4-(trifluoromethyl)benzyl)indoline-1-carboxylate (27n):**



**27n**

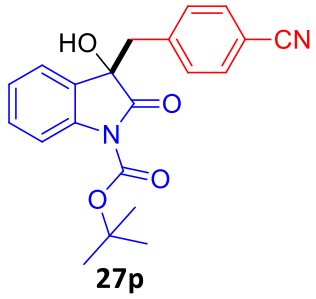
Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 94-96°C. Yield: 91% (74 mg). IR (Neat): 3446, 2981, 2925, 2859, 1793, 1737, 1610, 1479, 1469, 1369, 1343, 1290, 1249, 1147, 1124, 1067, 1019, 938, 842, 755 and 599 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 7.63 (1H, d, *J* = 8.0 Hz), 7.40 (2H, d, *J* = 8.4 Hz), 7.35-7.30 (1H, m), 7.22-7.16 (2H, m), 7.03 (2H, d, *J* = 8.0 Hz), 3.40 (1H, br s, O*H*), 3.38 (1H, d, *J* = 12.8 Hz), 3.21 (1H, d, *J* = 12.8 Hz), 1.57 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 176.7 (C, *C*=O), 148.3 (C, *C*=O), 139.0 (C), 137.5 (C), 130.6 (2 x CH), 130.2 (CH), 129.4 (C, q, *J* = 32.0 Hz), 127.7 (C), 125.1 (C, $CF_3$, q, *J* = 270.0 Hz), 124.7 (2 x CH, q, *J* = 4.0 Hz), 124.2 (2 x CH), 115.1 (CH), 84.7 (C, *C*$Me_3$), 76.9 (C, *C*-OH), 45.6 ($CH_2$), 27.9 (3 x $CH_3$). LCMS m/z 406.25 [M – H], calcd. for $C_{21}H_{19}F_3NO_4$ 406.3751; Anal. calcd. for $C_{21}H_{20}F_3NO_4$ (407.1344): C, 64.81; H, 4.95; N, 3.44; Found: C, 64.72; H, 4.92; N, 3.48 %.

***tert*-Butyl 3-hydroxy-3-(4-nitrobenzyl)-2-oxoindoline-1-carboxylate (27o):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 98-100°C. Yield: 90% (69 mg). IR (Neat): $\nu_{max}$ 3356, 2961, 2921, 2852, 1786, 1716, 1607, 1519, 1465, 1347, 1291, 1251, 1151, 1115, 856, 757 and 698 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.01(2H, d, *J* = 8.5 Hz), 7.66 (1H, d, *J* = 8.5 Hz), 7.33 (1H, dt, *J* = 7.5, 2.0 Hz), 7.19-7.15 (2H, m), 7.12 (2H, d, *J* = 9.0 Hz), 3.37 (1H, d, *J* = 13.0 Hz), 3.24 (1H, d, *J* = 13.0 Hz), 3.09 (1H, br s, O*H*), 1.58 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.2 (C, *C*=O), 148.3 (C, *C*=O), 147.2 (C), 141.2 (C), 139.1 (C), 131.2 (2 x CH), 130.4 (CH), 127.3 (C), 124.8 (CH), 124.2 (CH), 123.0 (2 x CH), 115.2 (CH), 85.0 (C), 76.6 (C, *C*-OH), 45.4 ($CH_2$), 28.0 (3 x $CH_3$). LCMS m/z 385.25 $[M + H]^+$, calcd for $C_{20}H_{21}N_2O_6$ 385.1400; Anal. calcd for $C_{20}H_{20}N_2O_6$ (384.1321): C, 62.49; H, 5.24; N, 7.29 %. Found: C, 62.51; H, 5.26, N, 8.07 %.



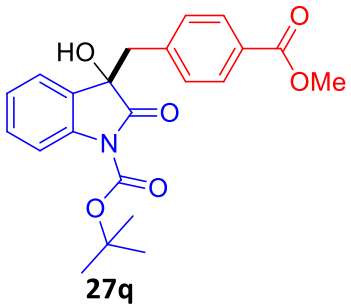
**27o**

***tert*-Butyl 3-(4-cyanobenzyl)-3-hydroxy-2-oxoindoline-1-carboxylate (27p):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 62-64°C. Yield: 88% (64 mg). IR (Neat): 3434, 2975, 2923, 2850, 2232, 1777, 1727, 1607, 1509, 1479, 1465, 1371, 1342, 1285, 1248, 1116, 1043, 1003, 936, 840, 745, 668, 579 and 555 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.63 (1H, d, *J* = 10.5 Hz), 7.43 (2H, d, *J* = 10.0 Hz), 7.31 (1H, dt, *J* = 9.5, 2.5 Hz), 7.18-7.12 (2H, m), 7.04 (2H, d, *J* = 10.0 Hz), 3.51 (1H, br s, O*H*), 3.32 (1H, d, *J* = 16.0 Hz), 3.18 (1H, d, *J* = 16.0 Hz), 1.57 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.4 (C, *C*=O), 148.2 (C, *C*=O), 139.1 (C), 138.9 (C), 131.6 (2 x CH), 131.1 (2 x CH), 130.2 (CH), 127.5 (C), 124.7 (CH), 124.2 (CH), 118.6 (C), 115.1 (CH), 111.0 (C), 84.9 (C, *C*$Me_3$), 76.7 (C, *C*-OH), 45.6 ($CH_2$), 27.9 (3 x $CH_3$). LCMS m/z 363.30 [M-H], calcd for $C_{21}H_{19}N_2O_4$ 363.3866; Anal. calcd for $C_{21}H_{20}N_2O_4$ (364.1423): C, 69.22; H, 5.53; N, 7.69 %; Found: C, 69.15; H, 5.58; N, 7.61 %.



**27p**

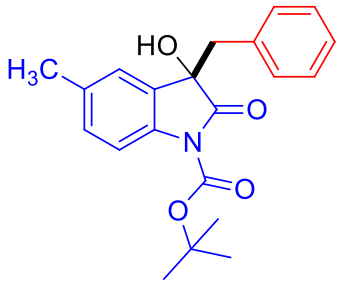
***tert*-Butyl 3-hydroxy-3-(4-(methoxycarbonyl)benzyl)-2-oxoindoline-1-carboxylate (27q):**



**27q**

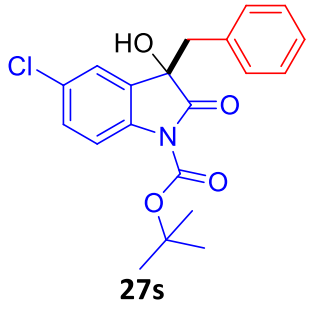
Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.6 : 7.4 to 3.0 : 7.0) and was isolated as a colourless gummy liquid. Yield: 87% (69 mg). IR (Neat): 3452, 2981, 2953, 2931, 1778, 1722, 1610, 1467, 1437, 1281, 1251, 1149, 1111, 1049, 939, 863, 842 and 753 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 7.78 (2H, d, *J* = 8.0 Hz), 7.60 (1H, d, *J* = 8.4 Hz), 7.29-7.25 (1H, m), 7.17-7.11 (2H, m), 6.98 (2H, d, *J* = 8.0 Hz), 3.86 (3H, s), 3.63 (1H, br s, O*H*), 3.33 (1H, d, *J* = 12.8 Hz), 3.20 (1H, d, *J* = 12.8 Hz), 1.55 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 176.6 (C, *C*=O), 166.9 (C, *C*=O), 148.4 (C, *C*=O), 139.0 (C), 138.8 (C), 130.3 (2 x CH), 130.0 (CH), 129.1 (2 x CH), 128.8 (C), 127.8 (C), 124.6 (CH), 124.2 (CH), 115.0 (CH), 84.5 (C, *C*$Me_3$), 76.9 (C, *C*-OH), 52.0 ($CH_3$, O*C*$H_3$), 45.7 ($CH_2$), 27.9 (3 x $CH_3$). HRMS m/z 420.1420 $[M + Na]^+$, calcd for $C_{22}H_{23}NO_6Na$ 420.1423.

***tert*-Butyl 3-benzyl-3-hydroxy-5-methyl-2-oxoindoline-1-carboxylate (27r):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 98-100°C. Yield: 87% (62 mg). IR (Neat): 3451, 3033, 2980, 2925, 2855, 1777, 1732, 1600, 1490, 1454, 1370, 1337, 1281, 1249, 1153, 1125, 937, 820, 767, 700 and 551 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.51 (1H, d, *J* = 8.0 Hz), 7.19-7.13 (3H, m), 7.09 (1H, dd, *J* = 8.0, 1.0 Hz), 6.99 (1H, s), 6.92 (2H, dd, J = 8.0, 1.5 Hz), 3.25 (1H, d, *J* = 13.0 Hz), 3.13 (1H, d, *J* = 13.0 Hz), 2.79 (1H, br s, O*H*), 2.32 (3H, s), 1.57 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.8 (C, *C*=O), 148.6 (C, *C*=O), 136.9 (C), 134.3 (2 x C), 133.3 (C), 130.4 (CH), 130.3 (2 x CH), 127.9 (2 x CH), 127.1 (CH), 124.8 (CH), 114.8 (CH), 84.2 (C, *C*$Me_3$), 76.7 (C, *C*-OH), 46.1 ($CH_2$), 28.0 (3 x $CH_3$), 21.0 ($CH_3$). HRMS m/z 376.1524 $[M + Na]^+$, calcd for $C_{21}H_{23}NO_4Na$ 376.1525.



**27r**

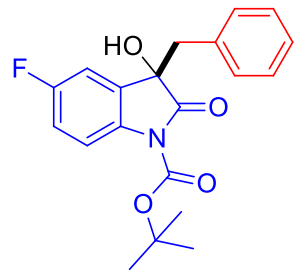
***tert*-Butyl 3-benzyl-5-chloro-3-hydroxy-2-oxoindoline-1-carboxylate (27s):** Prepared



**27s**

following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 143-145°C. Yield: 92% (69 mg). IR (Neat): 3453, 3031, 2981, 2930, 1779, 1732, 1610, 1480, 1467, 1348, 1290, 1252, 1149, 1049, 939, 842, 784, 751, 700, 575, 541 and 508 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.60 (1H, d, *J* = 9.0 Hz), 7.26 (1H, dd, *J* = 8.5, 2.5 Hz), 7.21-7.14 (4H, m), 6.92 (2H, dd, *J* = 8.0, 1.5 Hz), 3.24 (1H, d, *J* = 13.0 Hz), 3.14 (1H, d, *J* = 13.0 Hz), 2.82 (1H, s, O*H*), 1.57 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.1 (C, *C*=O), 148.3 (C, *C*=O), 137.7 (C), 132.7 (C), 130.2 (2 x CH), 130.1 (C), 129.9 (CH), 129.8 (C), 128.1 (2 x CH), 127.4 (CH), 124.6 (CH), 116.3 (CH), 84.8 (C, *C*$Me_3$), 76.96 (C, *C*-OH), 46.2 ($CH_2$), 28.0 (3 x $CH_3$). HRMS m/z 396.0995 $[M + Na]^+$, calcd for $C_{20}H_{20}ClNO_4Na$ 396.0979.

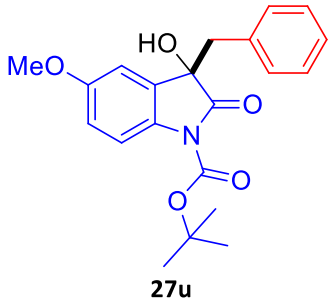
***tert*-Butyl 3-benzyl-5-fluoro-3-hydroxy-2-oxoindoline-1-carboxylate (27t):** Prepared



**27t**

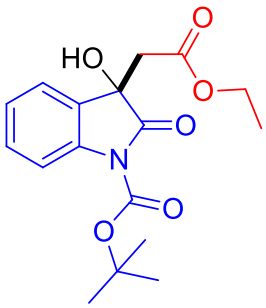
following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.7 : 7.3 to 3.2 : 6.8) and was isolated as a white solid. Mp.: 125-128°C. Yield: 85% (61 mg). IR (Neat): 3445, 2978, 2955, 2924, 2851, 1779, 1733, 1484, 1371, 1344, 1297, 1267, 1148, 776, 740 and 701 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.63 (1H, dd, *J* = 9.0, 2.5 Hz), 7.19-7.14 (3H, m), 6.98 (1H, dt, *J* = 9.0, 2.5 Hz), 6.93 (2H, dd, *J* = 8.0, 1.5 Hz), 6.90 (1H, dd, *J* = 7.5, 2.5 Hz), 3.25 (1H, d, *J* = 13.0 Hz), 3.15 (1H, d, *J* = 13.0 Hz), 3.05 (1H, br s, O*H*), 1.57 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 Hz) δ 176.5 (C, *C*=O), 159.8 (C, *C*-F, d, *J* = 243.75 Hz), 148.4 (C, *C*=O), 135.1 (C, d, *J* = 2.5 Hz), 132.8 (C), 130.2 (2 x CH), 129.9 (C, d, *J* = 8.75 Hz), 128.0 (2 x CH), 127.3 (CH), 116.4 (CH, d, *J* = 3.75 Hz), 116.3 (CH, d, *J* = 11.25 Hz), 111.8 (CH, d, *J* = 25.0 Hz), 84.6 (C, *C*$Me_3$), 77.1 (C, *C*-OH), 46.1 ($CH_2$), 28.0 (3 x $CH_3$). HRMS m/z 380.1276 $[M + Na]^+$, calcd for $C_{20}H_{20}FNO_4Na$ 380.1274.

***tert*-Butyl 3-benzyl-3-hydroxy-5-methoxy-2-oxoindoline-1-carboxylate (27u):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.6 : 7.4 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 102-104°C. Yield: 92% (68 mg). IR (Neat): 3445, 2980, 2937, 2837, 1776, 1730, 1601, 1487, 1370, 1337, 1277, 1248, 1152, 1123, 1040, 1013, 936, 846, 774, 740, 701, 617 and 557 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.57 (1H, d, *J* = 8.8 Hz), 7.19-7.14 (3H, m), 6.96 (2H, dd, *J* = 7.6, 1.6 Hz), 6.81 (1H, dd, *J* = 8.8, 2.8 Hz), 6.66 (1H, d, *J* = 2.8 Hz), 3.73 (3H, s, OC*H*$_3$), 3.27 (1H, d, *J* = 13.2 Hz), 3.10 (1H, d, *J* = 12.8 Hz), 2.85 (1H, br s, O*H*), 1.58 (9H, s). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 176.8 (C, *C*=O), 156.8 (C, *C*=O), 148.6 (C), 133.3 (C), 132.4 (C), 130.4 (2 x CH), 129.1 (C), 128.0 (2 x CH), 127.2 (CH), 116.1 (CH), 115.5 (CH), 109.9 (CH), 84.2 (C, *C*Me$_3$), 77.1 (C, *C*-OH), 55.6 ($CH_3$, O*C*H$_3$), 46.0 ($CH_2$), 28.0 (3 x $CH_3$). HRMS m/z 392.1476 $[M + Na]^+$, calcd for $C_{21}H_{23}NO_5Na$ 392.1474.



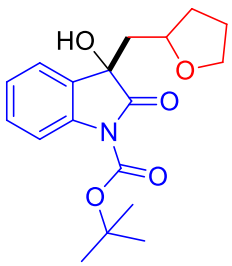
**27u**

***tert*-Butyl 3-(2-ethoxy-2-oxoethyl)-3-hydroxy-2-oxoindoline-1-carboxylate (27v):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.2 : 7.8 to 2.5 : 7.5) and was isolated as a white colour gummy liquid. Yield: 80% (54 mg). IR (Neat): 3443, 2977, 2925, 2854, 1776, 1727, 1643, 1609, 1530,1469, 1370, 1345, 1290, 1249, 1148, 1090, 1027, 1004, 942, 842, 753 and 683 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.87 (1H, d, *J* = 8.0 Hz), 7.42 (1H, dd, *J* = 7.5, 1.0 Hz), 7.38 (1H, dt, *J* = 8.0, 1.5 Hz), 7.20 (1H, dt, *J* = 7.5, 1.0 Hz), 4.24 (1H, s, O*H*), 4.11 (2H, q, *J* = 7.0 Hz), 3.04 (1H, d, *J* = 16.0 Hz), 2.91 (1H, d, *J* = 15.5 Hz), 1.64 (9H, s), 1.18 (3H, t, *J* = 7.5 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 174.8 (C, *C*=O), 169.9 (C, *C*=O), 149.0 (C, *C*=O), 139.8 (C), 130.5 (CH), 128.0 (C), 125.0 (CH), 123.7 (CH), 115.5 (CH), 84.7 (C, *C*Me$_3$), 77.3 (C, *C*-OH), 61.3 ($CH_2$), 41.8 ($CH_2$), 28.1 (3 x $CH_3$), 13.9 ($CH_3$). HRMS m/z 358.1267 $[M + Na]^+$, calcd for $C_{17}H_{21}NO_6Na$ 358.1267.



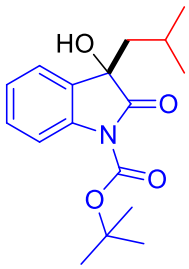
**27v**

***tert*-Butyl 3-hydroxy-2-oxo-3-((tetrahydrofuran-2-yl)methyl)indoline-1-carboxylate (27w):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.1 : 7.9 to 2.5 : 7.5) and was isolated as a white colour gummy liquid. Yield: 86% (57 mg). IR (Neat): 3322, 2955, 2920, 2852, 1778, 1727, 1613, 1460, 1440, 1370, 1348, 1297, 1252, 1190, 1152, 1065, 1036, 965, 926, 844, 771 and 562 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz, *dr* = 4.3:1, major isomer) δ 7.83 (1H, d, *J* = 8.5 Hz), 7.40 (1H, dd, *J* = 2.5, 1.0 Hz), 7.34 (1H, dt, *J* = 8.0, 1.0 Hz), 7.19 (1H, dt, *J* = 7.5, 0.5 Hz), 5.28 (1H, s), 4.46-4.41 (1H, m), 3.98-3.92 (1H, m), 3.86-3.82 (1H, m), 2.15 (1H, dd, *J* = 14.5, 11.0 Hz), 1.96-1.83 (3H, m), (1H, br s, O*H*), 1.63 (9H, s), 1.58-1.43 (2H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz, *dr* = 4.3:1, major isomer) δ 176.3 (C, *C*=O), 149.3 (C, *C*=O), 139.0 (C), 130.0 (C), 129.7 (CH), 124.7 (CH), 123.5 (CH), 115.2 (CH), 84.2 (C, *C*$Me_3$), 75.5 (C, *C*-OH), 74.7 (CH), 68.2 ($CH_2$), 43.4 ($CH_2$), 32.2 ($CH_2$), 28.1 (3 x $CH_3$), 25.0 ($CH_2$). LCMS m/z 332.20 [M – H], calcd for $C_{18}H_{22}NO_5$ 332.3710; Anal. calcd for $C_{18}H_{23}NO_5$ (333.1576): C, 64.85; H, 6.95; N, 4.20 %; Found: C, 64.92; H, 7.06; N, 4.28 %.



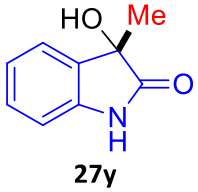
**27w**

***tert*-Butyl 3-hydroxy-3-isobutyl-2-oxoindoline-1-carboxylate (27x):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.5 : 7.5 to 2.8 : 7.2) and was isolated as a white colour gummy liquid. Yield: 65% (40 mg). IR (Neat): 3480, 2964, 2932, 2870, 1761, 1734, 1608, 1522, 1481, 1468, 1368, 1349, 1289, 1249, 1152, 1099, 840, 772, 752 and 588 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 7.85 (1H, d, *J* = 8.0 Hz), 7.40 (1H, dd, *J* = 5.0, 1.0 Hz), 7.37 (1H, dt, *J* = 8.0, 1.0 Hz), 7.21 (1H, dt, *J* = 7.5, 1.0 Hz), 2.80 (1H, d, *J* = 4.0 Hz), 1.95 (2H, d, *J* = 6.0 Hz), 1.64 (9H, s), 1.44 (1H, hep, *J* = 6.5 Hz), 0.80 (3H, d, *J* = 6.5 Hz), 0.74 (3H, d, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 177.1 (C, *C*=O), 149.0 (C, *C*=O), 139.5 (C), 129.9 (CH), 128.9 (C), 124.8 (CH), 124.2 (CH), 115.3 (CH), 84.6 (C), 76.2 (C, *C*-OH), 47.8 ($CH_2$), 28.1 (3 x $CH_3$), 24.1(CH), 23.8 ($CH_3$), 23.5 ($CH_3$). LCMS m/z 306.20 $[M + H]^+$, calcd for $C_{17}H_{24}NO_4$ 306.3768; Anal. calcd for $C_{17}H_{23}NO_4$ (305.1627): C, 66.86; H, 7.59; N, 4.59 %; Found: C, 66.98; H, 7.65; N, 4.52 %.



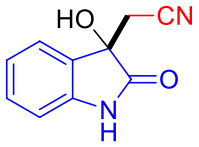
**27x**

**3-hydroxy-3-methylindolin-2-one (27y):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.8 : 7.2 to 3.0 : 7.0) and was isolated as a white colour gummy liquid. Yield: 85% (28 mg). IR (Neat): 3445, 2978, 2930, 2851, 2228, 1786, 1763, 1730, 1607, 1480, 1465, 1370, 1347, 1288, 1251, 1146, 1093, 1056, 1002, 935, 840, 754, 678 and 578 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$ + 3 drops of DMSO-$d_6$, 400 MHz) δ 9.41 (1H, s, N*H*), 7.19 (1H, d, *J* = 7.2 Hz), 7.03 (1H, dt, *J* = 7.6, 1.2 Hz), 6.84 (1H, dt, *J* = 7.6, 0.8 Hz), 6.70 (1H, d, *J* = 7.6 Hz), 4.99 (1H, s, O*H*), 1.39 (3H, s). $^{13}C$ NMR ($CDCl_3$+ 3 drops of DMSO-$d_6$, DEPT-135, 100 MHz) δ 180.5 (C, *C*=O), 140.4 (C), 132.7 (C), 128.6 (CH), 123.1 (CH), 121.9 (CH), 109.8 (CH), 73.1 (C, *C*-OH), 24.3 ($CH_3$). HRMS m/z 186.0532 $[M + Na]^+$, calcd for $C_9H_9NO_2Na$ 186.0531.



**27y**

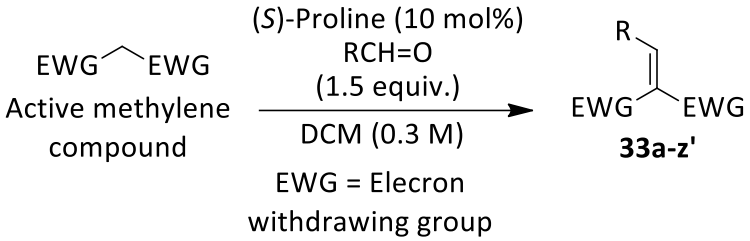
**2-(3-hydroxy-2-oxoindolin-3-yl)acetonitrile (27z):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane (2.6 : 7.4 to 3.0 : 7.0) and was isolated as a white solid. Mp.: 108-110°C. Yield: 91% (34 mg). IR (Neat): 3305, 2921, 2852, 1727, 1610, 1514, 1463, 1370, 1288, 1251, 1156, 980, 836, 771 and 508 $cm^{-1}$. $^{1}H$ NMR (DMSO-$d_6$, 500 MHz) δ 10.54 (1H, s, N*H*), 7.46 (1H, d, *J* = 7.0 Hz), 7.29 (1H, dt, *J* = 7.75, 1.0 Hz), 7.04 (1H, t, *J* = 7.5 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 6.59 (1H, s, O*H*), 3.04 (1H, d, *J* = 16.5 Hz), 2.95 (1H, d, *J* = 16.5 Hz). $^{13}C$ NMR (DMSO-$d_6$, DEPT-135, 125 MHz) δ 176.7 (C, *C*=O), 141.6 (C), 130.0 (CH), 129.8 (C), 124.1 (CH), 122.0 (CH), 117.1 (C, *C*N), 110.0 (CH), 72.0 (C, *C*-OH), 26.1 ($CH_2$). HRMS m/z 211.0484 $[M + Na]^+$, calcd for $C_{10}H_8N_2O_2Na$ 211.0483.



**27z**

## *4. General Experimental Procedures for Self-Induced [4+2]-Cycloadditon Reaction to Access Bioactive Tetrahydro-carbazoles Scaffolds*

**Procedure A**: **General procedure for the synthesis of Knoevenagel adduct (33):** To an ordinary glass vial with inner cap, equipped with a magnetic stirring bar, containing a solution of 0.3 mmol of active methylene compound in DCM (1.0 mL, 0.3 M), 0.45 mmol (1.5 equiv.) of aldehyde and 10 mol% (3.5 mg) of *L*-proline were added. The resulting reaction mixture was stirred at room temperature for 6-8 h. The completion of the reaction was confirmed by TLC. The pure Knoevenagel adducts **33a-z'** were obtained by silica gel column chromatography using ethyl acetate and hexane as eluents.




**Procedure B**: **Procedure for synthesis of Diels-Alder adduct (34aa/ba):** In an ordinary glass vial equipped with a magnetic stirring bar, 3-vinylindole **32a/32b** (0.2 mmol, 28.6 mg) and Knoevenagel adduct **33a** (0.24 mmol) were added in 1.0 ml of toluene (0.2 M), the resulting reaction mixture was stirred at 40 $^{o}$C for 16/32 h. The completion of the reaction was confirmed by TLC. The pure Diels-Alder product **34aa**/**3ab** was obtained by silica gel column chromatography using EtOAc/hexane as an eluent, in the form of white solid (**34aa**, 85%, 64 mg) or (**34ap**, 42%, 31 mg).

**Procedure C**: **General procedure for synthesis of 2-aryl-tetrahydro-1*H*-carbazole-1-carboxylate (36):** In an ordinary glass vial equipped with a magnetic stirring bar, 3-vinylindole **32a** (0.2 mmol, 28.6 mg) and Knoevenagel adduct **33** (0.24 mmol) were added in 1.0 ml of toluene (0.2 M), the resulting reaction mixture was stirred at 40 $^{o}$C for 16-36 h. The completion of the reaction was confirmed by TLC. After completion of the reaction 1.0 ml of acetone was added to the reaction mixture at 0 $^{o}$C, then 0.2 ml of 4 M HCl was added to it. Resulting reaction mixture was stirred for 0.5 h. A mini workup was done using 5 ml of ethyl acetate, organic layer was separated and dried using sodium sulphate. Pure compounds **36aa-av'** were obtained by silica gel column chromatography using EtOAc/hexane as an eluent.

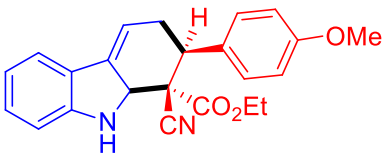
**Procedure D**: **General procedure for synthesis of hetero Diels-Alder adduct (4):** In an ordinary glass vial equipped with a magnetic stirring bar, 3-vinylindole **32a** (0.2 mmol, 28.6 mg) and Knoevenagel adduct **33w-z'** (0.24 mmol) were added in 1.0 ml of toluene (0.2 M), the resulting reaction mixture was stirred at 40 $^{o}$C for 16-22 h. The completion of the reaction was confirmed by TLC. The pure hetero Diels-Alder products **35aw-az'** were obtained by silica gel column chromatography using EtOAc/hexane as an eluent, in the form of white solid.

**Procedure E**: **Procedure for the hydroxylation of 34aa:** In a 10 mL round bottomed flask containing a magnetic stirring bar, compound **34aa** (0.2 mmol, 75 mg) was dissolved in DCM (5 ml). *m*-CPBA (0.24 mmol, 41.4 mg) was added to it at 0 $^{o}$C. Resulting reaction mixture was stirred at room temperature (25 $^{o}$C) for 0.5 h. The completion of the reaction was confirmed by TLC. The pure product **39** was obtained by silica gel column chromatography using EtOAc/hexane (2.5/7.5) as a white solid (56%, 44 mg).

**Procedure F**: **Procedure for the synthesis of 2-(4-Methoxyphenyl)-9*H*-carbazole-1-carbonitrile (40):** In a 25 mL oven dried round bottomed flask was taken compound **39** (0.1 mmol, 39 mg) and K$^{t}$OBu (0.15 mmol, 17 mg) in THF (10 ml) and refluxed for 6 h. The completion of the reaction was confirmed by TLC. After the completion of reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate, concentrated under vacuum. The residue was purified by flash chromatography on silica gel EtOAc/hexane (1/9) as a white solid (64%, 25 mg)

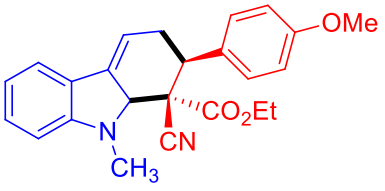
**Procedure G**: **Procedure for the decarboxylation of 36aa:** In a 10 mL oven dried round bottomed flask was taken compound **36aa** (0.1 mmol, 37.5 mg) and dissolved in Methanol (8 ml). To this, NaOH (0.3 mmol, 12 mg) was added and allowed to stir at refluxed condition for 2 h. The completion of the reaction was confirmed by TLC. The pure product **41** was obtained by silica gel column chromatography using EtOAc/hexane (1/9) as a white solid (61%, 19 mg).

**Ethyl-1-cyano-2-(4-methoxyphenyl)-2,3,9,9a-tetrahydro-1*H*-carbazole-1-carboxylate (34aa):** Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0) and isolated as a white solid). Mp.: 131-133 °C. Yield: 85% (64 mg). IR (Neat): $\nu_{max}$ 3267, 2922, 2851, 1719, 1666, 1612, 1586, 1513, 1455, 1367, 1250, 1174, 1115, 1089, 1028, 834, 742, 653, and 624 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.36 (2H, d, *J* = 9.0 Hz), 7.31 (1H, br d, *J* = 7.5 Hz), 7.08 (1H, dt, *J* = 8.0, 1.0 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 6.80 (1H, dt, *J* = 7.5, 0.5 Hz), 6.72 (1H, d, *J* = 8.0 Hz), 6.05 (1H, q, *J* = 4.0 Hz), 5.09 (1H, br s), 4.13 (1H, br s), 3.99 - 3.92 (2H, m), 3.79 (3H, s), 3.44 (1H, dd, *J* = 11.5, 6.0 Hz), 3.01 - 2.93 (1H, m), 2.72 (1H, pd, *J* = 19.5, 4.0 Hz), 0.88 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 168.0 (C, *C*=O), 159.6 (C), 151.9 (C), 136.0 (C), 129.8 (C), 129.5 (CH), 129.3 (2 x CH), 126.7 (C), 120.7 (CH), 120.3 (CH), 115.7 (C, *C*N), 115.5 (CH), 114.0 (2 x CH), 111.4 (CH), 66.4 (CH), 62.7 ($CH_2$), 55.3 (CH), 55.1 (C), 46.3 ($CH_3$), 32.3 ($CH_2$), 13.5 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{22}N_2O_3H$ 375.1709; Found: 375.1705.



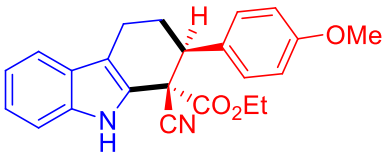
**34aa**

**Ethyl-1-cyano-2-(4-methoxyphenyl)-9-methyl-2,3,9,9a-tetrahydro-1*H*-carbazole-1-carboxylate (34ba):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.3 : 9.7 to 0.8 : 9.2) and isolated as a white solid). Mp.: 125-128 °C. Yield: 56% (43.5 mg). IR (Neat): $\nu_{max}$ 3478, 2977, 2835, 2360, 2339, 2161, 2023, 1737, 1609, 1513, 1470, 1368, 1305, 1259, 1226, 1179, 1116, 1083, 1060, 1031, 832, 750 and 668 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.37 (2H, d, *J* = 9.0 Hz), 7.30 (1H, d, *J* = 7.0 Hz), 7.15 (1H, t, *J* = 7.5 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 6.78 (1H, t, *J* = 7.5 Hz), 6.62 (1H, d, *J* = 8.0 Hz), 6.08 (1H, q, *J* = 3.5 Hz), 4.58 (1H, q, *J* = 3.5 Hz), 4.04 - 3.96 (2H, m), 3.80 (3H, s), 3.66 (1H, t, *J* = 4.5 Hz), 3.49 (1H, dd, *J* = 12.0, 6.0 Hz), 2.97 - 2.90 (1H, m), 2.71 (3H, s), 0.96 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 168.1 (C, *C*=O), 159.6 (C), 154.3 (C), 135.2 (C), 129.6 (3 x CH), 126.5 (C), 120.2 (CH), 119.5 (CH), 115.9 (CH), 115.5 (C, *C*N), 114.8 (C), 114.0 (2 x CH), 109.3 (CH), 73.4 (CH), 62.7 ($CH_2$), 55.3 (CH), 54.0 (C), 46.6 ($CH_3$), 35.7 ($CH_3$), 32.0 ($CH_2$), 13.6 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{24}N_2O_3H$ 389.1865; Found: 389.1866.



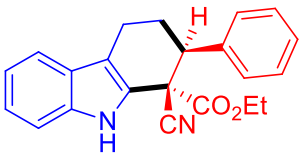
**34ba**

**Ethyl-1-cyano-2-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazole-1-carboxylate (36aa):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.8 : 9.2 to 1.2 : 8.8) and isolated as a white solid. Mp.: 125-127°C. Yield: 86% (64 mg). IR (Neat): $\nu_{max}$ 3358, 2932, 2846, 2158, 1741, 1611, 1512, 1454, 1366, 1299, 1249, 1214, 1181, 1076, 1036, 834 and 746 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.08 (1H, br s), 7.55 (1H, d, *J* = 7.6 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 7.32 (1H, t, *J* = 8.0 Hz), 7.24 (1H, q, *J* = 8.0 Hz), 7.15 (1H, t, *J* = 7.2 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 4.30 – 4.24 (2H, m), 3.84 (1H, d, *J* = 1.6 Hz), 3.81 (3H, s), 3.04 (1H, ddd, *J* = 16.0, 5.2, 2.0 Hz), 2.90 (1H, ddd, *J* = 16.0, 11.2, 5.6 Hz), 2.50 (1H, dq, *J* = 13.2, 5.2 Hz), 2.24 (1H, td, *J* = 13.6, 2.8 Hz), 1.24 (3H, t, *J* = 7.2 Hz).$^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 166.7 (C, *C*=O), 159.4 (C), 136.8 (C), 131.1 (C), 129.6 (2 x CH), 126.5 (C), 125.7 (C), 123.6 (CH), 120.1 (CH), 119.1 (CH), 116.6 (C, *C*N), 113.9 (2 x CH), 113.7 (C), 111.4 (CH), 63.6 ($CH_2$), 55.2 (*C*$H_3$, OMe), 52.3 (C), 46.6 (CH), 27.1 ($CH_2$), 20.8 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{22}N_2O_3H$ 375.1708, Found 375.1709.



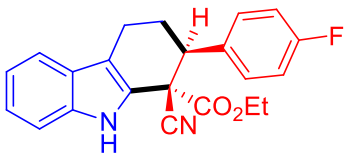
**36aa**

**Ethyl-1-cyano-2-phenyl-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ab):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.8 : 9.2 to 1.2 : 8.8) and isolated as a white solid. Mp.: 135-137 °C. Yield: 83% (58 mg). IR (Neat): $\nu_{max}$ 3371, 2924, 2851, 2181, 1742, 1603, 1493, 1453, 1367, 1244, 1214, 1157, 1037, 853, 745, and 702 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.11 (1H, br s), 7.55 (1H, d, *J* = 8.0 Hz), 7.43 (1H, dd, *J* = 10.0, 2.0 Hz), 7.39-7.34 (3H, m), 7.30 (1H, d, *J* = 8.4 Hz), 7.24 (1H, dt, *J* = 6.4, 1.2 Hz), 7.15 (1H, dt, *J* = 8.0, 0.8 Hz), 4.29-4.20 (2H, m), 3.86 (1H, dd, *J* = 12.8, 2.4 Hz), 3.04 (1H, ddd, *J* = 16.0, 5.6, 2.4 Hz), 2.95 – 2.87 (1H, m), 2.59-2.50 (1H, m) 2.28 (1H, pd, *J* = 13.6, 2.0 Hz), 1.20 (3H, t, *J* = 6.8 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 166.6 (C, *C*=O), 138.9 (C), 136.8 (C), 128.6 (4 x CH), 128.2 (CH), 126.5 (C), 125.6 (C), 123.6 (CH), 120.1 (CH), 119.1 (CH), 116.6 (C, *C*N), 113.7 (C), 111.4 (CH), 63.6 ($CH_2$), 52.0 (C), 47.4 (CH), 26.9 ($CH_2$), 20.8 ($CH_2$), 13.9 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{20}N_2O_2Na$ 367.1422, Found 367.1423.



**36ab**

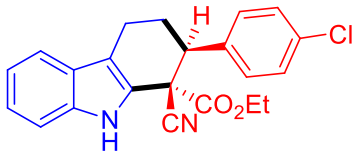
**Ethyl-1-cyano-2-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ac):**




**36ac**

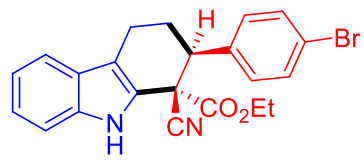
Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0) and isolated as a white solid. Mp.: 162-164 °C. Yield: 88% (64 mg). IR (Neat): $\nu_{max}$ 3368, 2933, 2849, 2242, 1741, 1605, 1510, 1452, 1367, 1298, 1235, 1162, 1037, 1013, 839 and 745 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.06 (1H, br s), 7.55 (1H, d, *J* = 8.0 Hz), 7.42 (2H, dd, *J* = 8.5, 5.5 Hz), 7.33 (1H, d, *J* = 8.5 Hz), 7.25 (1H, t, *J* = 8.0 Hz), 7.16 (1H, t, *J* = 7.5 Hz), 7.06 (2H, d, *J* = 8.5 Hz), 4.31-4.23 (2H, m), 3.87 (1H, d, *J* = 11.0 Hz), 3.04 (1H, ddd, *J* = 16.0, 5.0, 1.5 Hz), 2.94-2.88 (1H, m), 2.49 (1H, dq, *J* = 13.0, 4.0 Hz), 2.25 (1H, td, *J* = 13.5, 2.5 Hz), 1.25 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 166.4 (C, *C*=O), 162.6 (C, *C*F, d, *J* = 245.0 Hz), 136.7 (C), 134.8 (C, d, *J* = 2.5 Hz), 130.3 (2 x CH, d, *J* = 8.75 Hz), 126.4 (C), 125.3 (C), 123.7 (CH), 120.2 (CH), 119.1 (CH), 116.4 (C, *C*N), 115.6 (CH), 115.4 (CH), 113.7 (C), 111.4 (CH), 63.8 ($CH_2$), 51.9 (C), 46.5 (CH), 27.0 ($CH_2$), 20.8 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{19}FN_2O_2H$ 363.1508, Found 363.1508.

**Ethyl-2-(4-chlorophenyl)-1-cyano-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ad):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.0 : 9.0) and isolated as a white solid. Mp.: 149-151 °C. Yield: 81% (62 mg). IR (Neat): $\nu_{max}$ 3340, 2918, 2849, 2022, 1742, 1493, 1453, 1413, 1299, 1244, 1215, 1093, 1038, 1014, 834 and 747 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.01 (1H, br s), 7.56 (1H, d, *J* = 8.0 Hz), 7.40-7.33 (4H, m), 7.29-7.25 (2H, m), 7.17 (1H, dt, *J* = 7.2, 0.8 Hz), 4.35-4.24 (2H, m), 3.87 (1H, dd, *J* = 12.4, 2.0 Hz), 3.04 (1H, ddd, *J* = 16.0, 5.2, 2.4 Hz), 2.91 (1H, ddd, *J* = 16.4, 10.8, 5.6 Hz), 2.54-2.43 (1H, m), 2.25 (1H, qd, *J* = 14.0, 2.4 Hz), 1.29 (3H, t, *J* = 7.2 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 166.3 (C, *C*=O), 137.5 (C), 136.7 (C), 134.2 (C), 130.0 (2 x CH), 128.8 (2 x CH), 126.5 (C), 125.2 (C), 123.8 (CH), 120.3 (CH), 119.2 (CH), 116.3 (C, *C*N), 113.8 (C), 111.4 (CH), 63.9 ($CH_2$), 51.7 (C), 46.5 (CH), 26.9 ($CH_2$), 20.7 ($CH_2$), 14.1 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{19}ClN_2O_2Na$ 401.1032, Found 401.1036.



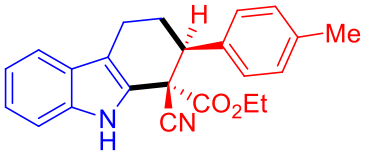

**36ad**

**Ethyl-2-(4-bromophenyl)-1-cyano-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ae):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.2 : 8.8) and isolated as a white solid. Mp.: 139-141 °C. Yield: 77% (66 mg). IR (Neat): $\nu_{max}$ 3367, 2926, 2850, 2022, 1741, 1489, 1453, 1299, 1243, 1214, 1076, 1037, 1010, 831 and 746 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.06 (1H, br s), 7.56 (1H, d, *J* = 8.0 Hz), 7.50 (2H, d, *J* = 8.4 Hz), 7.35 -7.31 (3H, m), 7.26 (1H, t, *J* = 8.0 Hz), 7.16 (1H, t, *J* = 8.0 Hz), 4.34-4.23 (2H, m), 3.85 (1H, dd, *J* = 12.4, 2.0 Hz), 3.04 (1H, ddd, *J* = 16.0, 5.2, 2.4 Hz), 2.91 (1H, ddd, *J* = 16.4, 11.2, 5.6 Hz), 2.48 (1H, ddd, *J* = 24.8, 13.2, 5.6 Hz), 2.24 (1H, pd, *J* = 8.8, 2.8 Hz), 1.27 (3H, t, *J* = 7.2 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 166.3 (C, *C*=O), 138.0 (C), 136.7 (C), 131.7 (2 x CH), 130.4 (2 x CH), 126.4 (C), 125.2 (C), 123.8 (CH), 122.3 (C), 120.3 (CH), 119.1 (CH), 116.3 (C, *C*N), 113.7 (C), 111.4 (CH), 63.9 ($CH_2$), 51.6 (C), 46.5 (CH), 26.8 ($CH_2$), 20.7 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{19}BrN_2O_2H$ 423.0708, Found 423.0708.



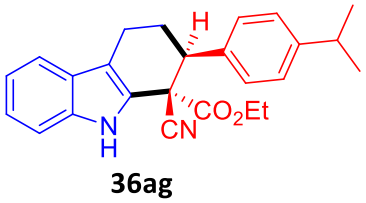
**36ae**

**Ethyl-1-cyano-2-(*p*-tolyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36af):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.7 : 9.3 to 1.2 : 8.8) and isolated as a white solid. Mp.: 116-118 °C. Yield: 87% (62 mg). IR (Neat): $\nu_{max}$ 3358, 2923, 2856, 1709, 1588, 1455, 1366, 1302, 1220, 820 and 746 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.06 (1H, br s), 7.55 (1H, d, *J* = 7.5 Hz), 7.32-7.31 (3H, m), 7.25 (1H, t, *J* = 7.0 Hz), 7.16 (3H, dd, *J* = 14.0, 7.5 Hz), 4.32-4.19 (2H, m), 3.84 (1H, d, *J* = 11.5 Hz), 3.04 (1H, br dd, *J* = 16.0, 3.0 Hz), 2.91 (1H, ddd, *J* = 16.0, 11.0, 5.0 Hz), 2.51 (1H, dq, *J* = 212.5, 5.0 Hz), 2.36 (3H, s), 2.56 (1H, td, *J* = 13.5, 2.5 Hz), 1.24 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 166.7 (C, *C*=O), 137.9 (C), 136.8 (C), 136.0 (C), 129.3 (2 x CH), 128.4 (2 x CH), 126.5 (C), 125.7 (C), 123.6 (CH), 120.1 (CH), 119.1 (CH), 116.6 (C, *C*N), 113.8 (C), 111.4 (CH), 63.6 ($CH_2$), 52.1 (C), 47.0 (CH), 27.0 ($CH_2$), 21.1 ($CH_3$), 20.8 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{22}N_2O_2H$ 359.1759, Found 359.1759.



**36af**

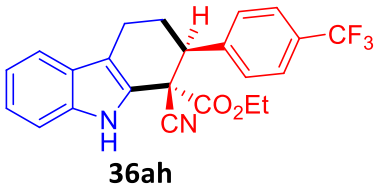
**Ethyl-1-cyano-2-(4-isopropylphenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ag):** Prepared by following the procedure **C** and purified by column chromatography using



**36ag**

EtOAc/hexane (0.5 : 9.5 to 0.8 : 9.2) and isolated as a white solid. Mp.: 121-123 °C. Yield: 82% (64 mg). IR (Neat): $\nu_{max}$ 3385, 2959, 2235, 1748, 1621, 1452, 1365, 1301, 1240, 1215, 1157, 1078, 1005, 975, 835 and 743 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.05 (1H, br s), 7.55 (1H, d, *J* = 8.0 Hz), 7.35 (2H, d, *J* = 8.0 Hz), 7.32 (1H, d, *J* = 8.0 Hz), 7.25 (1H, dd, *J* = 7.0, 1.0 Hz), 7.22 (2H, d, *J* = 8.0 Hz), 7.15 (1H, t, *J* = 7.0 Hz), 4.30-4.19 (2H, m), 3.83 (1H, dd, *J* = 12.5, 2.0 Hz), 3.04 (1H, ddd, *J* = 16.0, 3.0, 2.0 Hz), 2.94-2.87 (2H, m), 2.52 (1H, ddd, *J* = 24.5, 13.5, 5.5 Hz), 2.27 (1H, td, *J* = 13.5, 2.5 Hz), 1.26 (6H, d, *J* = 7.0 Hz), 1.20 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 166.7 (C, *C*=O), 148.8 (C), 136.8 (C), 136.3 (C), 128.5 (2 x CH), 126.6 (2 x CH), 126.5 (C), 125.8 (C), 123.6 (CH), 120.1 (CH), 119.1 (CH), 116.7 (C, *C*N), 113.8 (C), 111.4 (CH), 63.6 ($CH_2$), 52.1 (C), 47.1 (CH), 33.8 (CH), 27.0 ($CH_2$), 23.92 ($CH_3$), 23.88 ($CH_3$), 20.9 ($CH_2$), 13.9 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{26}N_2O_2H$ 387.2073, Found 387.2072.

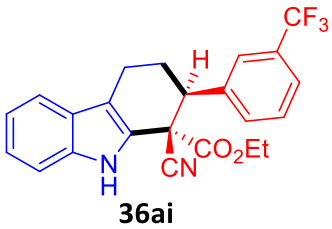
**Ethyl-1-cyano-2-(4-(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ah):** Prepared by following the procedure **C** and purified by column chromatography using



**36ah**

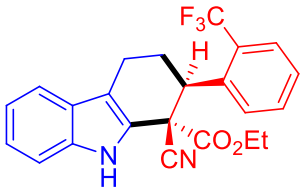
EtOAc/hexane (0.8 : 9.2 to 1.4 : 8.6) and isolated as a white solid. Mp.: 140-142 °C. Yield: 84% (70 mg). IR (Neat): $\nu_{max}$ 3367, 2924, 2853, 1743, 1619, 1455, 1325, 1244, 1168, 1128, 1069, 1017, 847 and 744 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.11 (1H, br s), 7.64 (2H, d, *J* = 8.5 Hz), 7.57 (3H, t, *J* = 6.5 Hz), 7.34 (1H, d, *J* = 8.5 Hz), 7.27 (1H, dt, *J* = 7.0, 1.0 Hz), 7.17 (1H, dt, *J* = 8.0, 1.0 Hz), 4.33-4.22 (2H, m), 3.95 (1H, dd, *J* = 12.5, 2.5 Hz), 3.05 (1H, ddd, *J* = 16.0, 5.0, 2.0 Hz), 2.93 (1H, ddd, *J* = 16.0, 11.0, 5.5 Hz), 2.53 (1H, dq, *J* = 13.5, 5.5 Hz), 2.27 (1H, pd, *J* = 13.5, 2.5 Hz), 1.25 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 166.1 (C, *C*=O), 143.0 (C), 136.7 (C), 130.4 (C, q, *J* = 32.5 Hz), 129.2 (2 x CH), 126.4 (C), 125.5 (CH, q, *J* = 3.75 Hz), 125.0 (C), 124.0 (C, *C*$F_3$, q, *J* = 270.0 Hz), 123.8 (2 x CH), 120.3 (CH), 119.2 (CH), 116.3 (C, *C*N), 113.7 (C), 111.5 (CH), 63.9 ($CH_2$), 51.4 (C), 46.8 (CH), 26.8 ($CH_2$), 20.6 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{19}F_3N_2O_2H$ 413.1477, Found 413.1477.

**Ethyl-1-cyano-2-(3-(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ai):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.7 : 9.3 to 1.2 : 8.8) and isolated as a white solid. Mp.: 136-138 °C. Yield: 71% (58 mg). IR (Neat): $\nu_{max}$ 3367, 2923, 2852, 1742, 1493, 1452, 1331, 1299, 1247, 1215, 1166, 1126, 1075, 1038, 903, 807 and 746 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.15 (1H, br s), 7.71 (1H, d, *J* = 7.6 Hz), 7.65-7.61 (2H, m), 7.56-7.50 (2H, m), 7.32 (1H, td, *J* = 8.0, 0.8 Hz), 7.25 (1H, dt, *J* = 7.2, 1.2 Hz), 7.16 (1H, dt, *J* = 7.2, 1.2 Hz), 4.33-4.18 (2H, m), 3.94 (1H, dd, *J* = 12.8, 2.4 Hz), 3.06 (1H, ddd, *J* = 16.4, 5.6, 2.4 Hz), 2.92 (1H, ddd, *J* = 16.4, 11.2, 5.2 Hz), 2.60-2.49 (1H, m), 2.28 (1H, pd, *J* = 13.6, 2.4 Hz), 1.22 (3H, t, *J* = 6.8 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 166.3 (C, *C*=O), 140.0 (C), 136.8 (C), 131.7 (CH), 130.8 (C, q, *J* = 32 Hz), 129.2 (CH), 126.4 (C), 126.0 (CH, q, *J* = 3.0 Hz), 125.08 (CH, q, *J* = 4.0 Hz), 125.06 (C), 124.00 (C, *C*$F_3$, q, *J* = 271.0 Hz), 123.8 (CH), 120.3 (CH), 119.1 (CH), 116.2 (C, *C*N), 113.6 (C), 111.5 (CH), 64.0 ($CH_2$), 51.8 (C), 46.9 (CH), 26.8 ($CH_2$), 20.7 ($CH_2$), 13.8 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{19}F_3N_2O_2H$ 413.1477, Found 413.1477.



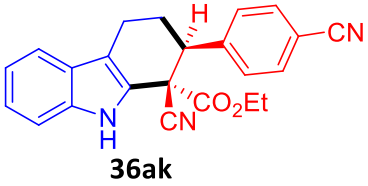
**36ai**

**Ethyl-1-cyano-2-(2-(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36aj):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.6 : 9.4 to 1.0 : 9.0) and isolated as a white solid. Mp.: 134-136 °C. Yield: 68% (56 mg). IR (Neat): $\nu_{max}$ 3377, 2958, 2243, 1748, 1492, 1453, 1311, 1230, 1208, 1156, 1108, 1036, 1012, 769 and 735 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.27 (1H, br s), 7.86 (1H, d, *J* = 8.0 Hz), 7.72 (1H, d, *J* = 7.5 Hz), 7.58-7.53 (2H, m), 7.45-7.40 (2H, m), 7.29 (1H, dt, *J* = 7.5, 1.0 Hz), 7.18 (1H, dt, *J* = 8.0, 1.0 Hz), 4.26 (1H, dd, *J* = 8.5, 3.0 Hz), 4.23-4.12 (2H, m), 2.99-2.87 (2H, m), 2.43-2.37 (1H, m), 2.35-2.30 (1H, m), 1.10 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 166.0 (C, *C*=O), 138.4 (C), 137.0 (C), 132.3 (CH), 128.7 (CH), 128.6 (C, q, *J* = 30.0 Hz), 127.8 (CH), 126.4 (C), 126.3 (CH, q, *J* = 6.25 Hz), 125.5 (C), 124.4 (C, *C*$F_3$, q, *J* = 272.5 Hz), 123.8 (CH), 120.2 (CH), 119.2 (CH), 117.3 (C, *C*N), 114.1 (C), 111.5 (CH), 63.6 ($CH_2$), 49.2 (C), 41.8 (CH, d, *J* = 1.25 Hz), 28.2 ($CH_2$), 19.2 ($CH_2$), 13.6 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{19}F_3N_2O_2Na$ 435.1296, Found 435.1299.



**36aj**

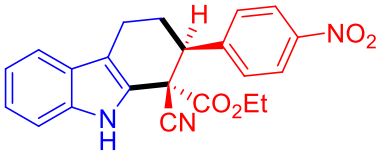
**Ethyl-1-cyano-2-(4-cyanophenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ak):**




**36ak**

Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.8 : 9.2 to 1.4 : 8.6) and isolated as a white solid. Mp.: 154-156 °C. Yield: 78% (58 mg). IR (Neat): $\nu_{max}$ 3347, 2930, 2851, 2229, 1742, 1609, 1505, 1452, 1418, 1367, 1299, 1242, 1216, 1098, 1037, 1014, 844 and 747 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.09 (1H, br s), 7.68 (2H, d, *J* = 8.4 Hz), 7.59-7.56 (3H, m), 7.37 (1H, d, *J* = 8.0 Hz), 7.29 (1H, d, *J* = 7.2 Hz), 7.18 (1H, t, *J* = 7.6 Hz), 4.36-4.26 (2H, m), 3.96 (1H, d, *J* = 11.2 Hz), 3.08-3.03 (1H, m), 2.93 (1H, ddd, *J* = 16.4, 10.8, 5.6 Hz), 2.51 (1H, ddd, *J* = 24.4, 12.8, 5.6 Hz), 2.27 (1H, td, *J* = 13.2, 2.0 Hz), 1.29 (3H, t, *J* = 7.2 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 165.9 (C, *C*=O), 144.2 (C), 136.7 (C), 132.3 (2 x CH), 129.6 (2 x CH), 126.2 (C), 124.6 (C), 123.8 (CH), 120.3 (CH), 119.1 (CH), 118.5 (C, *C*N), 116.1 (C, *C*N), 113.6 (C), 112.1 (C), 111.5 (CH), 64.0 ($CH_2$), 51.1 (C), 46.8 (CH), 26.6 ($CH_2$), 20.5 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{19}N_3O_2H$ 370.1555, Found 370.1555.

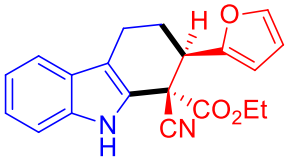
**Ethyl-1-cyano-2-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36al):**




**36al**

Prepared by 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 white solid. Mp.: 147-149 °C. Yield: 71% (56 mg). IR (Neat): $\nu_{max}$ 3381, 2923, 2851, 1741, 1601, 1521, 1452, 1347, 1299, 1262, 1216, 1110, 1037, 1013, 857, 745 and 702 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 8.22 (2H, d, *J* = 9.0 Hz), 8.18 (1H, br s), 7.63 (2H, d, *J* = 8.5 Hz), 7.56 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 8.5 Hz), 7.27 (1H, d, *J* = 7.5 Hz), 7.17 (1H, t, *J* = 8.0 Hz), 4.36-4.24 (2H, m), 4.02 (1H, dd, *J* = 12.5, 2.0 Hz), 3.05 (1H, qd, *J* = 16.5, 2.5 Hz), 2.93 (1H, ddd, *J* = 16.5, 11.0, 5.5 Hz), 2.52 (1H, dq, *J* = 13.5, 5.5 Hz), 2.28 (1H, pd, *J* = 13.5, 3.0 Hz), 1.27 (3H, t, *J* = 7.5 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 165.8 (C, *C*=O), 147.7 (C), 146.2 (C), 136.7 (C), 129.8 (2 x CH), 126.3 (C), 124.5 (C), 123.9 (CH), 123.7 (2 x CH), 120.4 (CH), 119.1 (CH), 116.1 (C, *C*N), 113.6 (C), 111.5 (CH), 64.1 ($CH_2$), 51.1 (C), 46.5 (CH), 26.7 ($CH_2$), 20.5 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{19}N_3O_4H$ 390.1454, Found 390.1453.

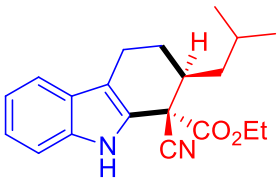
**Ethyl-1-cyano-2-(furan-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36am):**




**36am**

Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (1.5 : 8.5 to 1.8 : 8.2) and isolated as a white solid. Mp.: 156-158 °C. Yield: 61% (42 mg). IR (Neat): $\nu_{max}$ 3372, 2927, 2851, 2158, 1741, 1621, 1503, 1452, 1368, 1298, 1242, 1203, 1038, 1011, 936 and 742 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.09 (1H, br s), 7.54 (1H, d, *J* = 8.0 Hz), 7.40 (1H, d, *J* = 1.0 Hz), 7.34 (1H, d, *J* = 8.5 Hz), 7.26 (1H, dt, *J* = 7.5, 1.0 Hz), 7.15 (1H, dt, *J* = 7.5, 0.5 Hz), 6.39 (1H, dd, *J* = 3.5, 2.0 Hz), 6.37 (1H, d, *J* = 3.5 Hz), 4.46-4.33 (2H, m), 4.07 (1H, dd, *J* = 12.5, 2.5 Hz), 3.04 (1H, ddd, *J* = 16.0, 5.0, 2.0 Hz), 2.90 (1H, ddd, *J* = 16.5, 11.5, 5.5 Hz), 2.47 (1H, pd, *J* = 13.5, 2.5 Hz), 2.38-2.30 (1H, m), 1.36 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 166.6 (C, *C*=O), 153.0 (C), 142.2 (CH), 136.7 (C), 126.5 (C), 124.6 (C), 123.7 (CH), 120.2 (CH), 119.1 (CH), 116.0 (C, *C*N), 113.6 (C), 111.4 (CH), 110.5 (CH), 107.6 (CH), 63.9 ($CH_2$), 50.4 (C), 41.3 (CH), 24.6 ($CH_2$), 20.2 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{18}N_2O_3Na$ 357.1215, Found 357.1213.

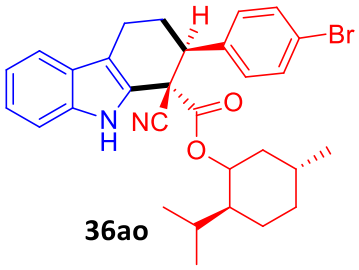
**Ethyl-1-cyano-2-isobutyl-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36an):**




**36an**

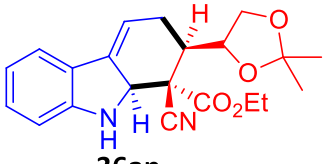
Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 0.8 : 9.2) and isolated as a colorless liquid. Yield: 62% (40 mg). IR (Neat): $\nu_{max}$ 2960, 2872, 1731, 1624, 1467, 1390, 1369, 1280, 1253, 1170, 1096, 1072, 1047, 857 and 760 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.04 (1H, br s), 7.52 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.24 (1H, dt, *J* = 7.0, 1.0 Hz), 7.13 (1H, dt, *J* = 7.5, 0.5 Hz), 4.44-4.30 (2H, m), 2.90 (1H, qd, *J* = 16.0, 2.5 Hz), 2.73 (1H, qd, *J* = 16.0, 5.5 Hz), 2.65 (1H, td, *J* = 11.0, 2.5 Hz), 2.18 (1H, pd, *J* = 14.0, 3.0 Hz), 1.83-1.77 (1H, m), 1.76-1.70 (1H, m), 1.66 (1H, ddd, *J* = 13.5, 10.5, 4.0 Hz), 1.37 (3H, t, *J* = 7.0 Hz), 1.33-1.30 (1H, m), 1.00 (3H, d, *J* = 6.5 Hz), 0.95 (3H, d, *J* = 6.5 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 167.0 (C, *C*=O), 136.5 (C), 126.6 (C), 125.1 (C), 123.5 (CH), 120.1 (CH), 119.1 (CH), 116.6 (C, *C*N), 114.0 (C), 111.3 (CH), 63.7 ($CH_2$), 50.8 (C), 41.4 ($CH_2$), 38.9 (CH), 25.5 (CH), 25.3 ($CH_2$), 23.9 ($CH_3$), 21.5 ($CH_3$), 20.2 ($CH_2$), 14.1 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}N_2O_2H$ 325.1916, Found 325.1918.

**2-Isopropyl-5-methylcyclohexyl-2-(4-bromophenyl)-1-cyano-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (36ao):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0) and isolated as a white solid. Mp.: 170-172 °C. Yield: 65% (70 mg). IR (Neat): $\nu_{max}$ 3401, 2956, 2869, 2246, 1732, 1490, 1449, 1368, 1301, 1253, 1218, 1075, 1010, 981, 946, 824, and 742 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, major isomer, *dr* = 0.8:1) δ 7.86 (1H, s), 7.56 (1H, d, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 8.4 Hz), 7.36-7.32 (3H, m), 7.28 (1H, d, *J* = 6.8 Hz), 7.17 (1H, dd, *J* =8.0, 7.2 Hz), 4.83-4.74 (1H, m), 3.90 (1H, dd, *J* =12.4, 2.0 Hz), 3.07-2.88 (2H, m), 2.53-2.42 (1H, m), 2.26-2.17 (2H, m), 1.72-1.64 (3H, m), 1.51-1.39 (2H, m), 1.30-1.15 (3H, m), 0.96 (3H, d, *J* = 6.8 Hz), 0.93 (3H, d, *J* = 7.2 Hz), 0.89 (3H, d, *J* = 6.4 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz, major isomer, *dr* = 0.8:1) δ 165.5 (C, *C*=O), 138.0 (C), 136.6 (C), 131.67 (2 x CH), 130.5 (2 x CH), 126.5 (C), 125.53 (C), 122.2 (C), 120.3 (CH), 119.14 (CH), 116.3 (C), 113.6 (C), 111.3 (2 x CH), 78.7 (CH), 51.9 (C), 46.7 (CH), 46.6 (CH), 40.8 ($CH_2$), 33.9 ($CH_2$), 31.5 (CH), 26.6 ($CH_2$), 25.7 (CH), 23.1 ($CH_2$), 22.0 ($CH_3$), 20.8 ($CH_2$), 20.6 ($CH_2$), 15.9 ($CH_3$). $^1H$ NMR ($CDCl_3$, 400 MHz, minor isomer, *dr* = 0.8:1) δ 7.88 (1H, s), 7.56 (1H, d, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 8.4 Hz), 7.36-7.32 (3H, m), 7.28 (1H, d, *J* = 6.8 Hz), 7.17 (1H, dd, *J* =8.0, 7.2 Hz), 4.83-4.74 (1H, m), 3.84 (1H, dd, *J* =12.4, 2.0 Hz), 3.07-2.88 (2H, m), 2.53-2.42 (1H, m), 2.09-2.05 (2H, m), 1.81-1.77 (3H, m), 1.51-1.39 (2H, m), 1.05-0.99 (3H, m), 0.79 (3H, d, *J* = 6.8 Hz), 0.68 (3H, d, *J* = 6.8 Hz), 0.51 (3H, d, *J* = 6.8 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz, minor isomer, *dr* = 0.8:1) δ 166.0 (C, *C*=O), 138.1 (C), 136.7 (C), 131.7 (2 x CH), 130.4 (2 x CH), 126.5 (C), 125.5 (C), 123.8 (CH), 122.2 (C), 120.3 (CH), 116.5 (C), 113.8 (C), 111.3 (2 x CH), 78.9 (CH), 77.2 (CH), 51.3 (C), 46.1 (CH), 40.1 ($CH_2$), 33.8 ($CH_2$), 31.4 (CH), 27.1 ($CH_2$), 26.4 (CH), 22.9 ($CH_2$), 21.8 ($CH_3$), 20.9 ($CH_3$), 20.4 ($CH_3$), 15.8 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{30}H_{33}N_2O_2BrNa$ 555.1623, Found 555.1622.



**36ao**

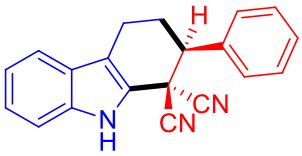
**Ethyl-1-cyano-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,3,9,9a-tetrahydro-1*H*-carbazole-1-carboxylate (36ap):** Prepared by following the procedure **B** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0) and isolated as a white solid. Mp.: 115-117 °C. Yield: 42% (30 mg). IR (Neat): $\nu_{max}$ 3349, 2985, 2935, 2249, 1736, 1609, 1468, 1371, 1253, 1227, 1153, 1063, 911, 857 and 737 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, major



**36ap**

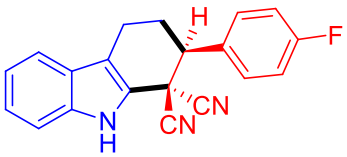
isomer, *dr* = 7.1:1) δ 7.29 (1H, d, *J* = 7.0 Hz), 7.08 (1H, dt, *J* = 8.0, 1.0 Hz), 6.79 (1H, dt, *J* = 7.5, 0.5 Hz), 6.71 (1H, d, *J* = 8.0 Hz), 5.98 (1H, q, *J* = 4.0 Hz), 4.90 (1H, dt, *J* = 9.0, 3.5 Hz), 4.38 (2H, dq, *J* = 7.0, 2.0 Hz), 4.23 (1H, q, *J* = 6.5 Hz), 4.06 (1H, d, *J* = 5.5 Hz), 3.98 (1H, dd, *J* = 8.5, 6.0 Hz), 3.66 (1H, dd, *J* = 8.0, 7.0 Hz), 2.71-2.68 (2H, m), 2.57-2.52 (1H, m), 1.44 (3H, s), 1.42 (3H, t, *J* = 7.5 Hz), 1.36 (3H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz, major isomer, *dr* = 7.1:1) δ 168.8 (C, *C*=O), 151.5 (C), 135.7 (C), 129.5 (CH), 126.5 (C), 120.7 (CH), 120.4 (CH), 114.8 (C, *C*N), 114.7 (CH), 111.5 (CH), 109.3 (C), 75.8 (CH), 67.3 ($CH_2$), 66.8 (CH), 63.5 ($CH_2$), 52.5 (CH), 42.9 (CH), 26.6 ($CH_2$), 26.3 ($CH_3$), 25.2 ($CH_3$), 14.1 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}N_2O_4H$ 369.1814, Found 369.1816.

**2-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarbonitrile (36aq):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.7 : 9.3 to 1.2 : 8.8) and isolated as a white solid. Mp.: 118-120 °C. Yield: 84% (50 mg). IR (Neat): $\nu_{max}$ 3363, 3064, 2904, 2162, 2033, 1978, 1604, 1464, 1421, 1324, 1233, 1086, 893, 826, 755, 698, 672 and 635 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.33 (1H, br s), 7.57 (1H, d, *J* = 8.0 Hz), 7.54-7.52 (1H, m), 7.49-7.43 (3H, m), 7.39 (1H, d, *J* = 8.4 Hz), 7.32 (1H, dt, *J* = 7.2, 0.8 Hz), 7.20 (1H, dt, *J* = 7.6, 0.8 Hz), 3.62 (1H, dd, *J* = 12.4, 2.0 Hz), 3.09 (1H, ddd, *J* = 16.4, 5.2, 2.0 Hz), 2.91 (1H, qd, *J* = 16.4, 5.6 Hz), 2.57 (1H, dq, *J* = 14.0, 5.6 Hz), 2.40 (1H, pd, *J* = 14.0, 2.4 Hz). $^{13}$C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 137.0 (C), 136.6 (C), 129.2 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 126.0 (C),124.6 (CH), 121.7 (C), 120.7 (CH), 119.4 (CH), 114.12 (C, *C*N), 114.08 (C, *C*N), 112.7 (C), 111.8 (CH), 49.4 (CH), 39.5 (C), 25.9 ($CH_2$), 20.5 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{15}N_3Na$ 320.1164, Found 320.1164.



**36aq**

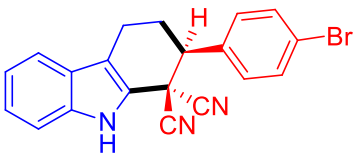
**2-(4-Fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarbonitrile (36ar):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.8 : 9.2 to 1.3 : 8.7) and isolated as a white solid. Mp.: 130-132 °C. Yield: 86% (54 mg). IR (Neat): $\nu_{max}$ 3360, 2922, 2851, 2017, 1719, 1606, 1512, 1453, 1357, 1301, 1232, 1162, 1103, 1014, 886, 837, 802, 746 and 679 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz) δ 8.32 (1H, br s), 7.58 (1H, d, *J* = 8.0 Hz), 7.52 (2H, dd, *J* = 8.5, 5.0 Hz), 7.42 (1H, d, *J* = 8.0 Hz), 7.34 (1H, dt, *J* = 7.0, 1.0 Hz), 7.21 (1H, dt, *J* = 7.5, 1.0 Hz), 7.17 (2H, t, *J* = 8.5 Hz),



**36ar**

3.64 (1H, dd, *J* = 12.5, 2.0 Hz), 3.11 (1H, ddd, *J* = 16.5, 5.5, 2.0 Hz), 2.94 (1H, ddd, *J* = 16.5, 11.0, 5.5 Hz), 2.59-2.50 (1H, m), 2.42-2.37 (1H, m). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 163.2 (C, *C*F, d, *J* = 247.5 Hz), 137.0 (C), 132.5 (C, d, *J* = 2.5 Hz), 130.4 (2 x CH, d, *J* = 8.75 Hz), 126.0 (C), 124.7 (CH), 121.4 (C), 120.8 (CH), 119.4 (CH), 116.1 (CH), 116.0 (CH), 114.1 (C, *C*N), 114.0 (C, *C*N), 112.6 (C), 111.8 (CH), 48.8 (CH), 39.6 (C), 26.1 ($CH_2$), 20.5 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}N_3FH$ 316.1249, Found 316.1250.

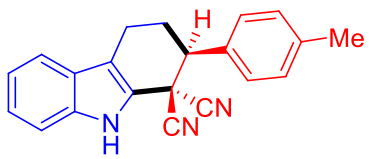
**2-(4-Bromophenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarbonitrile (36as):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.7 : 9.3 to 1.2 : 8.8) and isolated as a white solid. Mp.: 127-129 °C. Yield: 82% (62 mg).



**36as**

IR (Neat): $\nu_{max}$ 3313, 2932, 1709, 1656, 1620, 1489, 1471, 1450, 1408, 1325, 1198, 1075, 1009, 939, 824, 749, 679 and 616 cm$^{-1}$. $^1$H NMR ($CDCl_3$ + 1 drop DMSO-$d_6$, 500 MHz) δ 11.42 (1H, br s), 7.59 (2H, d, *J* = 8.5 Hz), 7.54 (1H, d, *J* = 8.0 Hz), 7.44 (3H, t, *J* = 8.0 Hz), 7.26 (1H, dt, *J* = 7.5, 1.0 Hz), 7.13 (1H, dt, *J* = 7.5, 1.0 Hz), 3.65 (1H, d, *J* = 12.0 Hz), 3.08 (1H, dd, *J* = 16.0, 4.5 Hz), 2.93 (1H, qd, *J* = 16.5, 5.0 Hz), 2.49 (1H, dq, *J* = 13.5, 5.0 Hz), 2.35 (1H, td, *J* = 13.0, 2.0 Hz). $^{13}$C NMR ($CDCl_3$ + 1 drop DMSO-$d_6$, DEPT-135, 125 MHz) δ 136.9 (C), 135.6 (C), 131.4 (2 x CH), 130.0 (2 x CH), 125.1 (C), 123.2 (CH), 122.6 (C), 121.2 (C), 119.3 (CH), 118.5 (CH), 113.8 (C), 112.5 (C), 112.0 (C), 111.6 (CH), 48.5 (CH), 38.7 (C), 25.5 ($CH_2$), 20.0 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}N_3BrH$ 376.0449, Found 376.0448.

**2-(*p*-Tolyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarbonitrile (36at):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0) and isolated as a white solid. Mp.: 98-100 °C. Yield: 84% (52 mg).

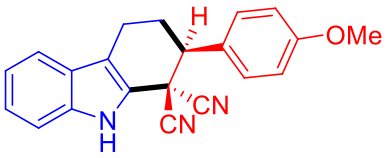


**36at**

IR (Neat): $\nu_{max}$ 3330, 3059, 2921, 2851, 2253, 2188, 2155, 1976, 1720, 1515, 1453, 1347, 1303, 1265, 1217, 1172, 1155, 1078, 1023, 887, 817, 749 and 682 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz) δ 8.37 (1H, br s), 7.56 (1H, d, *J* = 8.0 Hz), 7.41 (2H, d, *J* = 7.5 Hz), 7.38 (1H, d, *J* = 8.5 Hz), 7.31 (1H, dt, *J* = 8.0, 1.0 Hz), 7.27 (2H, d, *J* = 8.0 Hz), 7.20 (1H, dt, *J* = 8.0, 1.0 Hz), 3.59 (1H, dd, *J* = 12.5, 2.0 Hz), 3.08 (1H, ddd, *J* = 16.5, 5.0, 1.5 Hz), 2.90 (1H, qd, *J* = 16.0, 6.0 Hz), 2.54 (1H, dq, *J* = 14.0, 5.5 Hz), 2.40 (3H, s), 2.38-2.35 (1H, m). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 139.1 (C), 137.0 (C), 133.7 (C), 129.7 (2

x CH), 128.5 (2 x CH), 126.0 (C), 124.5(CH), 121.7 (C), 120.7 (CH), 119.4 (CH), 114.2 (C, *C*N), 114.1 (C, *C*N), 112.8 (C), 111.8 (CH), 49.2 (CH), 39.7 (C), 26.0 ($CH_2$), 21.2 ($CH_3$), 20.5 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{17}N_3Na$ 334.1320, Found 334.1322.

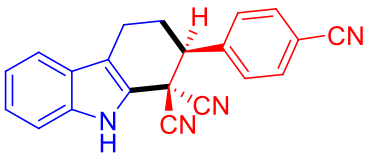
**2-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarbonitrile (36au):**



**36au**

Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.8 : 9.2 to 1.2 : 8.8) and isolated as a white solid. Mp.: 117-119 °C. Yield: 79% (52 mg). IR (Neat): $\nu_{max}$ 3731, 3627, 3029, 2851, 2360, 2340, 2222, 2041, 1737, 1604, 1569, 1511, 1446, 1369, 1318, 1277, 1237, 1182, 1154, 1021, 936, 833, 668, 610 and 571 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.31 (1H, br s), 7.57 (1H, d, *J* = 8.0 Hz), 7.46 (2H, d, *J* = 8.5 Hz), 7.43 (1H, d, *J* = 8.5 Hz), 7.33 (1H, t, *J* = 7.0 Hz), 7.21 (1H, t, *J* = 7.5 Hz), 6.99 (2H, d, *J* = 8.5 Hz), 3.85 (3H, s), 3.61 (1H, dd, *J* = 12.5, 2.0 Hz), 3.10 (1H, ddd, *J* = 16.5, 5.5, 2.0 Hz), 2.93 (1H, qd, *J* = 16.5, 5.5 Hz), 2.55 (1H, dq, *J* = 6.5, 5.5 Hz), 2.41-2.37 (1H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 160.2 (C), 137.0 (C), 129.8 (2 x CH), 128.7 (C), 126.0 (C), 124.5 (CH), 121.8 (C), 120.7 (CH), 119.4 (CH), 114.4 (2 x CH), 114.2 (C, *C*N), 114.1 (C, *C*N), 112.8 (C), 111.8 (CH), 55.3 ($CH_3$), 48.9 (CH), 39.8 (C), 26.1 ($CH_2$), 20.6 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{17}N_3ONa$ 350.1269, Found 350.1265.

**2-(4-Cyanophenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarbonitrile (36av):** Prepared by following the procedure **C** and purified by column chromatography using EtOAc/hexane (0.7 : 9.3 to 1.2 : 8.8) and isolated as a white solid. Mp.: 133-135 °C. Yield: 72% (46 mg).

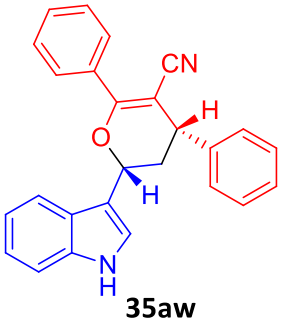


**36av**

IR (Neat): $\nu_{max}$ 3330, 2921, 2851, 2230, 2036, 1739, 1610, 1455, 1374, 1302, 1218, 1096, 841, 746 and 595 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ + 1 drop DMSO-$d_6$, 400 MHz) δ 11.36 (1H, br s), 7.78 (2H, d, *J* = 8.4 Hz), 7.69 (2H, d, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 7.6 Hz), 7.46 (1H, t, *J* = 8.0 Hz), 7.28 (1H, t, *J* = 8.4 Hz), 7.15 (1H, t, *J* = 8.8 Hz), 3.75 (1H, d, *J* = 12.4 Hz), 3.11 (1H, qd, *J* = 16.4, 2.0 Hz), 2.95 (1H, qd, *J* = 16.4, 5.6 Hz), 2.60-2.53 (1H, m), 2.42-2.36 (1H, m). $^{13}C$ NMR ($CDCl_3$ + 1 drop DMSO-$d_6$, DEPT-135, 125 MHz) δ 141.9 (C), 137.3 (C), 132.3 (2 x CH), 129.5 (2 x CH), 125.4 (C), 123.7 (CH), 121.1 (C), 119.8 (CH), 118.8 (CH), 118.0 (C), 113.8 (C), 112.8 (C, *C*N), 112.5 (C, *C*N), 112.4 (C, *C*N), 112.0 (CH),

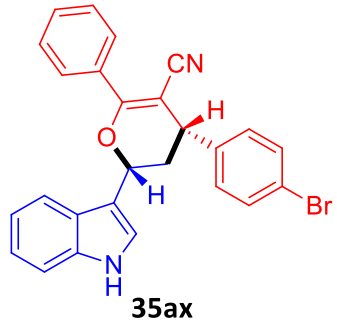
49.3 (CH), 38.7 (C), 25.7 ($CH_2$), 20.2 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{14}N_4Na$ 345.1116, Found 345.1117.

**2-(1*H*-indol-3-yl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (35aw):** Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.0 : 9.0 to 1.5 : 8.5) and isolated as a white solid. Mp.: 170-172 °C. Yield: 74% (56 mg). IR (Neat): $\nu_{max}$ 3408, 3059, 2926, 2201, 1598, 1573, 1492, 1455, 1353, 1278, 1230, 1152, 1128, 1099, 1078, 1030, 1008, 950, 908, 854, 732, 697 and 648 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, major isomer, *dr* = 6.7 :1) δ 8.23 (1H, br s), 7.84 (2H, dd, *J* = 7.5, 1.0 Hz), 7.76 (1H, d, *J* = 7.5 Hz), 7.44-7.39 (6H, m), 7.37 (2H, d, *J* = 8.5 Hz), 7.33-7.31 (1H, m), 7.24 (1H, dt, *J* = 7.5, 1.0 Hz), 7.19 (2H, t, *J* = 7.0 Hz), 5.62 (1H, d, *J* = 11.5 Hz), 4.05 (1H, dd, *J* = 11.5, 6.5 Hz), 2.67 (1H, dd, *J* = 14.0, 6.5 Hz), 2.46 (1H, q, *J* = 12.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz, major isomer, *dr* = 6.7 :1) δ 166.9 (C), 141.5 (C), 136.4 (C), 133.2 (C), 130.9 (CH), 129.0 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.63 (2 x CH), 127.60 (CH), 125.8 (C), 122.7 (CH), 122.2 (CH), 120.3 (CH), 119.9 (C), 119.1 (CH), 114.5 (C), 111.5 (CH), 88.2 (C), 74.4 (CH), 42.3 (CH), 37.8 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{20}N_2ONa$ 399.1473, Found 399.1475.



35aw

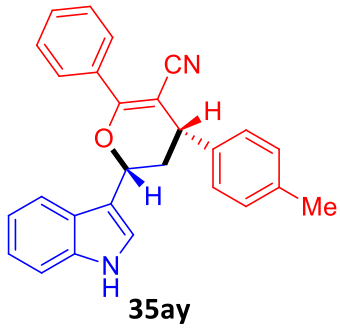
**4-(4-Bromophenyl)-2-(1*H*-indol-3-yl)-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (35ax):** Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.2 : 8.8 to 1.6 : 8.4) and isolated as a white solid. Mp.: 185-187 °C. Yield: 79% (72 mg). IR (Neat): $\nu_{max}$ 3379, 3053, 2951, 2205, 1604, 1571, 1554, 1487, 1460, 1441, 1404, 1355, 1275, 1241, 1212, 1179, 1150, 1129, 1074, 1029, 1010, 965, 947, 928, 854, 827, 773, 751, 700, 665, 652, 627, 606, 587 and 570 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, major isomer, *dr* = 1.1 : 1) δ 8.22 (1H, br s), 7.84 (2H, d, *J* = 7.0 Hz), 7.57 (1H, d, *J* = 8.0 Hz), 7.53 (2H, d, *J* = 3.5 Hz), 7.46-7.44 (2H, m), 7.39-7.37 (2H, m), 7.28 (4H, d, *J* = 8.5 Hz), 7.18-7.16 (1H, m), 5.63 (1H, d, *J* = 10.5 Hz), 4.03 (1H, dd, *J* = 11.5, 6.5 Hz), 2.67 (1H, ddd, *J* = 14.0, 6.5, 1.5 Hz), 2.41 (1H, q, *J* = 12.0 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz, major isomer, *dr* = 1.1 : 1) δ 167.0 (C), 136.38 (C), 136.35 (C), 133.0 (C), 132.0 (2 x CH), 130.9 (CH), 129.4 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 125.5 (C), 122.75 (CH), 122.1 (CH), 121.36 (C),



35ax

119.7 (C, *C*N), 119.1 (2 x CH), 114.3 (C), 111.6 (CH), 84.1 (C), 70.2 (CH), 39.5 (CH), 35.3 ($CH_2$). $^1$H NMR ($CDCl_3$, 500 MHz, minor isomer, *dr* = 1.1 : 1) δ 8.17 (1H, br s), 7.88 (2H, d, *J* = 6.5 Hz), 7.74 (1H, d, *J* = 8.0 Hz), 7.55 (2H, d, *J* = 4.0 Hz), 7.43-7.40 (4H, m), 7.24-7.23 (2H, m), 7.20 (2H, d, *J* = 7.5 Hz), 7.14-7.13 (1H, m), 5.39 (1H, dd, *J* = 11.0, 2.0 Hz), 3.99 (1H, dd, *J* = 5.5, 2.5 Hz), 2.77-2.71 (1H, m), 2.32 (1H, td, *J* = 14.0, 2.0 Hz). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz, minor isomer, *dr* = 1.1 : 1) δ 167.2 (C), 141.5 (C), 140.5 (C), 133.1 (C), 132.2 (2 x CH), 131.0 (CH), 129.8 (2 x CH), 128.38 (2 x CH), 128.36 (2 x CH), 125.7 (C), 122.8 (CH), 122.2 (CH), 121.44 (C), 120.4 (CH), 120.3 (CH), 119.7 (C, *C*N), 114.4 (C), 111.5 (CH), 87.5 (C), 74.3 (CH), 41.8 (CH), 37.6 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{29}BrN_2ONa$ 477.0578, Found 477.0568.

**2-(1*H*-indol-3-yl)-6-phenyl-4-(p-tolyl)-3,4-dihydro-2*H*-pyran-5-carbonitrile (35ay):**

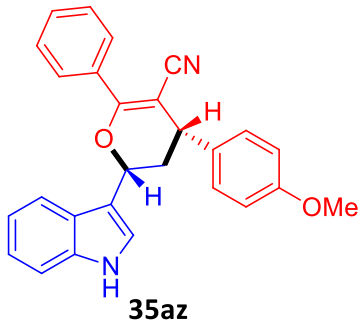


**35ay**

Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.1 : 8.9 to 1.5 : 8.5) and isolated as a white solid. Mp.: 167-169 °C. Yield: 73% (58 mg). IR (Neat): $\nu_{max}$ 3700, 3058, 2921, 2358, 2263, 2201, 1696, 1597, 1512, 1492, 1449, 1394, 1331, 1277, 1216, 1182, 1153, 1129, 1102, 1078, 1030, 1005, 950, 927, 857, 825, 751, 689, and 668 $cm^{-1}$. $^1$H NMR (DMSO, 500 MHz, major isomer, *dr* = 9.1 : 1) δ 11.21 (1H, s), 7.76 (1H, d, *J* = 8.0, Hz), 7.74 (2H, dd, *J* = 7.5, 1.5 Hz), 7.51-7.46 (4H, m), 7.40 (1H, d, *J* = 8.0 Hz), 7.35 (2H, d, *J* = 8.0 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 7.13 (1H, t, *J* = 7.5 Hz), 7.06 (1H, t, *J* = 7.5 Hz), 5.74 (1H, d, *J* = 12.0 Hz), 4.11 (1H, dd, *J* = 11.5, 6.5 Hz), 2.57 (1H, q, *J* = 6.5 Hz), 2.38 (1H, q, *J* = 11.5 Hz), 2.33 (3H, s). $^{13}$C NMR ($CDCl_3$, DEPT-135, 125 MHz, major isomer, *dr* = 9.1 : 1) δ 166.4 (C), 139.1 (C), 136.3 (C), 136.2 (C), 133.5 (C), 130.7 (CH), 129.3 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.6 (2 x CH), 125.9 (C), 124.0 (CH), 121.4 (CH), 119.8 (C), 119.1 (CH), 118.8 (CH), 112.9 (C), 111.7 (CH), 88.1 (C), 74.2 (CH), 36.8 ($CH_2$), 30.6 (CH), 20.6 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{22}N_2OH$ 391.1810, Found 391.1816.

**2-(1*H*-indol-3-yl)-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (35az):** Prepared by following the procedure **D** and purified by column chromatography using EtOAc/hexane (1.3 : 8.7 to 1.8 : 8.2) and isolated as a white solid. Mp.: 161-163 °C. Yield: 78% (64 mg). IR (Neat): $\nu_{max}$ 3405, 3058, 2927, 2360, 2340, 2201, 1705, 1608, 1578, 1510, 1493, 1457, 1443, 1354, 1278, 1249, 1178, 1153, 1129, 1109, 1078, 1032, 1010, 965, 909, 856,

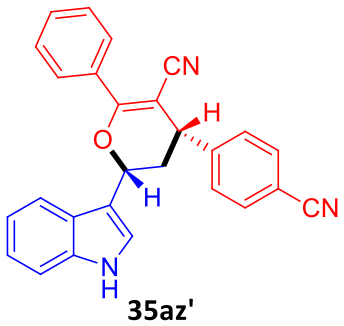
833, 773, 736, 696, 668 and 649 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz, major isomer, *dr* = 1.6 : 1)



**35az**

δ 8.17 (1H, br s), 7.89 (2H, dd, *J* = 7.2, 1.2 Hz), 7.59 (1H, d, *J* = 7.6 Hz), 7.47-7.44 (2H, m), 7.42-7.36 (3H, m), 7.33-7.30 (2H, m), 7.24-7.20 (1H, m), 7.18-7.12 (2H, m), 6.94 (2H, d, *J* = 8.4 Hz), 5.43 (1H, dd, *J* = 10.8, 1.6 Hz), 4.04-3.98 (1H, m), 3.82 (3H, s), 2.74-2.64 (1H, m), 2.33 (1H, td, *J* = 14.0, 2.4 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz, major isomer, *dr* = 1.6 : 1) δ 166.5 (C), 158.8 (C), 136.4 (C), 134.6 (C), 133.4 (C), 130.7 (CH), 129.1 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (C), 122.7 (CH), 122.1 (CH), 120.6 (C), 120.2 (CH), 119.2 (CH), 114.7 (C), 114.3 (2 x CH), 111.5 (CH), 84.9 (C), 70.1 (CH), 55.3 (CH), 39.2 ($CH_3$) 35.6 ($CH_2$). $^1H$ NMR ($CDCl_3$, 400 MHz, minor isomer, *dr* = 1.6 : 1) δ 8.22 (1H, br s), 7.84 (2H, dd, *J* = 7.6, 1.6 Hz), 7.76 (1H, d, *J* = 7.6 Hz), 7.47-7.44 (1H, m), 7.42-7.36 (3H, m), 7.33-7.30 (3H, m), 7.24-7.20 (1H, m), 7.18-7.12 (2H, m), 6.94 (2H, d, *J* = 8.4 Hz), 5.63 (1H, d, *J* = 11.2 Hz), 4.04-3.98 (1H, m), 3.82 (3H, s), 2.74-2.64 (1H, m), 2.49-2.40 (1H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 100 MHz, minor isomer, *dr* = 1.6 : 1) δ 166.6 (C), 159.0 (C), 136.4 (C), 133.5 (C), 133.3 (C), 130.8 (CH), 128.7 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 125.8 (C), 122.7 (CH), 122.2 (CH), 120.3 (CH), 120.0 (C), 119.2 (CH), 114.7 (C), 114.4 (2 x CH), 111.5 (CH), 88.5 (C), 74.4 (CH), 55.3 (CH), 41.5 ($CH_3$) 37.7 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{27}H_{23}N_2O_2Na$ 429.1579, Found 429.1578.

**4-(4-Cyanophenyl)-2-(1H-indol-3-yl)-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (35az'):** Prepared by following the procedure **D** and purified by column chromatography using

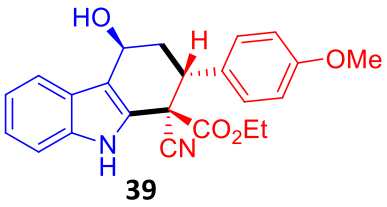


**35az'**

EtOAc/hexane (1.4 : 8.6 to 2.0 : 8.0) and isolated as a white solid. Mp.: 176-178 °C. Yield: 71% (57 mg). IR (Neat): $\nu_{max}$ 3322, 3059, 2203, 1736, 1662, 1625, 1486, 1458, 1405, 1338, 1278, 1254, 1150, 1102, 1073, 1030, 1010, 883, 855, 827, 772, 740, 696 and 671 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz, major isomer, *dr* = 7.7 : 1) δ 8.22 (1H, br s), 7.84 (2H, dd, *J* = 8.0, 1.5 Hz), 7.74 (1H, d, *J* = 8.0 Hz), 7.54 (2H, d, *J* = 8.5 Hz), 7.45-7.39 (4H, m), 7.28 (3H, d, *J* = 8.5 Hz), 7.24 (1H, d, *J* = 2.5 Hz), 7.20 (1H, dt, *J* = 7.5, 1.0 Hz), 5.63 (1H, dd, *J* = 12.0, 1.5 Hz), 4.04 (1H, dd, *J* = 11.5, 6.5 Hz), 2.67 (1H, ddd, *J* = 14.0, 6.5, 1.5 Hz), 2.42 (1H, q, *J* = 11.5 Hz). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz, major isomer, *dr* = 7.7 : 1) δ 167.2 (C), 140.6 (C), 136.4 (C), 133.1 (C), 132.2 (2 x CH), 131.0 (CH), 129.4 (3 x

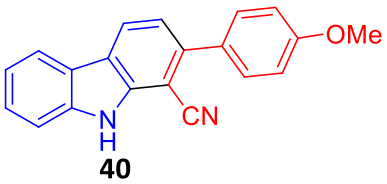
CH), 128.41 (C), 128.4 (3 x CH), 125.8 (C), 122.9 (CH), 122.2 (CH), 121.5 (C), 120.4 (CH), 119.7 (C), 119.1 (CH), 114.5 (C), 111.6 (CH), 87.6 (C), 74.4 (CH), 41.9 (CH), 37.7 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{19}N_3OH$ 402.1606, Found 402.1605.

**Ethyl-1-cyano-4-hydroxy-2-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (39):** Prepared by following the procedure **E** and purified by column chromatography using EtOAc/hexane (2.0 : 8.0 to 2.5 : 7.5) and isolated as a white solid. Mp.: 166-168 °C. Yield: 56% (44 mg). IR (Neat): $\nu_{max}$ 3432, 3253, 2929, 1719, 1613, 1514, 1369, 1285, 1258, 1177, 1158, 1045, 841, 742 and 614 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz) δ 11.47 (1H, s), 7.64 (1H, d, *J* = 8.0 Hz), 7.37 (1H, d, *J* = 8.0 Hz), 7.25 (2H, d, *J* = 8.5 Hz), 7.18 (1H, dt, *J* = 9.0, 1.0 Hz), 7.09 (1H, t, *J* = 7.0 Hz), 6.97 (2H, d, *J* = 8.5 Hz), 5.32 (1H, d, *J* = 5.0 Hz), 5.11 (1H, s), 4.22 (2H, dq, *J* = 7.0, 1.0 Hz), 4.08 (1H, d, *J* = 11.5 Hz), 3.78 (3H, s), 2.60 (1H, dt, *J* = 14.0, 4.0 Hz), 2.08 (1H, d, *J* = 14.0 Hz), 1.14 (3H, t, *J* = 7.0 Hz). $^{13}C$ NMR (DMSO-$d_6$, DEPT-135, 125 MHz) δ 166.6 (C, *C*=O), 159.1 (C), 136.8 (C), 130.4 (C), 129.5 (2 x CH), 127.8 (C), 125.5 (C), 122.8 (CH), 119.5 (CH), 119.3 (CH), 116.4 (C), 114.5 (C), 113.9 (2 x CH), 111.7 (CH), 63.1 ($CH_2$), 59.2 (CH), 55.1 (CH), 52.8 (C), 42.2 ($CH_3$), 36.5 ($CH_2$), 13.9 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{22}N_2O_4Na$ 413.1477, Found 413.1477.



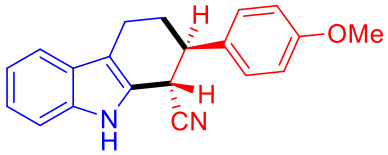
**39**

**2-(4-Methoxyphenyl)-9*H*-carbazole-1-carbonitrile (40):** Prepared by following the procedure **F** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0) and isolated as a white solid. Mp.: 170-172 °C. Yield: 64% (25 mg). IR (Neat) $\nu_{max}$: 3401, 3259, 2921, 2852, 2227, 2026, 1604, 1459, 1253, 1179, 1034, 839 and 740 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz) δ 12.10 (1H, s), 8.47 (1H, d, *J* = 8.0 Hz), 8.22 (1H, d, *J* = 8.0 Hz), 7.63 (2H, d, *J* = 9.0 Hz), 7.61 (1H, d, *J* = 8.5 Hz), 7.49 (1H, t, *J* = 8.0 Hz), 7.33 (1H, d, *J* = 8.0 Hz), 7.27 (1H, t, *J* = 8.0 Hz), 7.12 (2H, d, *J* = 9.0 Hz), 3.85 (3H, s). $^{13}C$ NMR (DMSO-$d_6$, DEPT-135, 125 MHz) δ 159.5 (C), 142.1 (C), 141.7 (C), 140.5 (C), 131.0 (C), 130.3 (2 x CH), 126.7 (CH), 125.2 (CH), 122.2 (C), 121.8 (C), 120.6 (CH), 120.02 (CH), 120.0 (CH), 117.1 (C), 114.1 (2 x CH), 111.8 (CH), 91.6 (C), 55.3 ($CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{14}N_2ONa$ 321.1004, Found 321.0998.



**40**

**2-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carbonitrile (41):** Prepared by following the procedure **G** and purified by column chromatography using EtOAc/hexane (0.5 : 9.5 to 1.0 : 9.0) and isolated as a white solid. Mp.: 159-161 °C. Yield: 61% (19 mg). IR (Neat): $\nu_{max}$ 3387, 3352, 2929, 2845, 2244, 1612, 1513, 1460, 1302, 1279, 1247, 1179, 1033, 909, 829 and 740 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 8.18 (1H, s), 7.51 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.25 (2H, d, *J* = 8.5 Hz), 7.22 (1H, dd, *J* = 8.0, 0.5 Hz), 7.14 (1H, t, *J* = 8.0 Hz), 6.92 (2H, d, *J* = 8.5 Hz), 4.07 (1H, d, *J* = 10.0 Hz), 3.82 (3H, s), 3.27 (1H, dt, *J* = 12.5, 3.0 Hz), 2.93 – 2.89 (1H, m), 2.87-2.82 (1H, m) 2.27 (1H, pd, *J* = 13.0, 2.5 Hz), 2.12-2.03 (1H, m). $^{13}C$ NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 159.1 (C), 136.5 (C), 133.7 (C), 128.2 (2 x CH), 126.8 (C), 125.7 (C), 122.8 (CH), 120.0 (CH), 119.2 (C), 118.6 (CH), 114.4 (2 x CH), 112.0 (C), 111.2 (CH), 55.3 ($CH_3$), 44.7 (CH), 34.9 (CH), 30.2 ($CH_2$), 20.5 ($CH_2$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}N_2OH$ 303.1497, Found 303.1498.




**41**

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# ABOUT THE AUTHOR

*The author,* ***Mr. Pritam Roy*** *was born on 13th June 1993 in Barasat, West Bengal. After his initial schooling at Nabapalli Boys' High School, Barasat, he obtained his B.Sc. Chemistry (Honours) degree in 2014 from Sri Chaitanya College for Science and Arts, Habra, affiliated to West Bengal State University. Thereafter, he obtained his M.Sc. degree in general chemistry in 2016 from University of Hyderabad. During his M.Sc., he worked as a "Summer Project Fellow" at Food Technology Department, Jadavpur University, Kolkata during 15-5-2015 to 10-7-2015 and "M.Sc. Project Student" at School of Chemistry, University of Hyderabad under the supervision of Prof. D. B. Ramachary, during 02-01-2016 to 15-06-2016. He qualified in NET (JRF) in 2015 conducted by Council of Scientific and Industrial Research (CSIR), India. He also qualified in GATE 2016, conducted by Indian Institute of Technology (IIT). 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 6th August 2016 onwards. His major research focus is on "****Development of Direct Organocatalytic Reactions on Syncarpic Acid: Scope and Applications****" with the objective of asymmetric organocatalysis.*

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

1. One-Pot Knoevenagel and [4+2] Cycloaddition as a Platform for Calliviminones. **Pritam Roy**, S. Rehana Anjum, D. B. Ramachary, Org. Lett. **2020**, *22*, 2897.

2. Organocatalytic Reductive Alkylation of Syncarpic Acid: Formal Total Synthesis of Monomeric Phloroglucinol Natural Products. **Pritam Roy**, A. Vamshi Krishna, D. B. Ramachary, *Manuscript submitted for publication.*

3. Organocatalytic C-H Oxidation: High-Yielding Synthesis of 3-Hydroxy-3-alkyloxindoles. **Pritam Roy**, D. B. Ramachary, *Manuscript under preparation.*

4. Self-Induced [4+2]-Cycloaddition Reaction to Access Bioactive Tetrahydro-carbazoles Scaffolds. **Pritam Roy**, S. Rehana Anjum, D. B. Ramachary, *Manuscript under preparation*.

## ❖ Other publications as a co-author during the PhD work:

1. Catalytic Ynone–Amidine Formal [4 + 2]-Cycloaddition for the Regioselective Synthesis of Tricyclic Azepines. T. Prabhakar Reddy, Jagjeet Gujral, **Pritam Roy**, D. B. Ramachary, *Org. Lett.* **2020**, *22*, 9653.

## ❖ Presentations and conferences attended:

1. "**Best Oral Presentation Award**" in ChemFest 2021. (National Level) (Sponsored by American Chemical Society). Title of the talk: *One-Pot Knoevenagel and [4+2] Cycloaddition as a Platform for Calliviminones.*
2. "**Best Oral Presentation Award**" in XVII-JNOST 2022. (National Level) (Sponsored by Royal Society of Chemistry). Title of the talk: *One-Pot Knoevenagel and [4+2] Cycloaddition as a Platform for Calliviminones.*
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5. Attened and volunteered ChemFest 2017, 2018 and 2019 organized by School of Chemistry, University of Hyderabad, Hyderabad.
6. Attened and volunteered *Theoretical Chemistry Symposium (TCS)* 2016 affiliated by School of Chemistry, University of Hyderabad, Hyderabad. Topic: Muti-State Problem in Quantum and Statistical Mechanics.
7. Attended Nobel Symposium 2021 organized by University of Hyderabad.

# Development of Direct Organocatalytic Reactions on Syncarpic Acid: Scope and Applications

*by* Pritam Roy

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