Intramolecular Morita Baylis Hillman (IMBH) Reaction

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Reg. No. MS14067

A dissertation submitted for the partial fullfilment of BS-MS dual degree in science

Indian Institute of Science Education and Research Mohali
April 26, 2019

Certificate of Examination

This is to certify that the dissertation titled "***Intramolecular Morita Baylis Hillman (IMBH) Reaction***" submitted by Ms. Shivangi (Reg. No. MS14067) for the partial fulfilment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

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Dated: April 26, 2019

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. S. S. V. Ramasastry at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussion. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Shivangi
(Candidate)
Dated: April 26, 2019

In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. S. S. V. Ramasastry
(Supervisor)

Acknowledgments

It is my privilege to express my sincere gratitude to my supervisor, Dr. S. S. V. Ramasastry for his guidance and invaluable discussion throughout the work. Additionally, I am very thankful to him for exposing me to this interesting field of research.

I am extremely thankful to all my lab-members for their help in learning the experimental techniques, which benefited me during the course of the project. I am thankful to DST, New Delhi for inspire fellowship. Also, I would like to acknowledge all the faculty members of Department of Chemical Sciences for their constant support. I am thankful to library, IR, NMR, X-ray and HRMS facilities of IISER-Mohali.

Last but not the least; I would like to acknowledge my family for always standing behind me with their love and support.

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Abbreviations

δ	Chemical shift in ppm
d	Doublet
dd	Doublet of doublet
dt	Doublet of triplet
EtOAc	Ethyl acetate
HRMS	High resolution mass spectroscopy
HPLC	High Performance Liquid Chromatography
IR	Infra-red
M. P.	Melting point
m	Multiplet
NMR	Nuclear magnetic resonance
ppm	Parts per million
PEG	Polyethylene glycol
s	Singlet
TLC	Thin layer chromatography
t	Triplet
td	Triplet of doublet
q	Quartet

Abstract

An efficient strategy for the synthesis of cycloheptannulated arenes and heteroarenes *via* an Intramolecular Baylis Hillman Reaction (IMBH) has been developed; also efforts have been made in order to develop the enantioselective version of the reaction.

Introduction

Strategies for synthesis of seven-membered rings

The motivation for developing methods for the formation of seven-membered rings derives from the occurrence of these frameworks in biologically active natural products. It is well known that few straight-chain cyclization methods are implied to form seven membered rings but they usually result in low yields. Other strategy developed to form seven membered rings is to use more accessible smaller rings (three to six) as starting points in order to form medium-rings via ring expansion. Here, few biologically active natural products which involve seven membered rings as their basic framework are presented. Also, few important strategies in order to build such important frameworks and approach towards seven membered ring formations are discussed.

Natural products containing seven-membered rings

Seven-membered rings are found throughout the variety of natural products, but certainly predominate within the terpenoid families, and to a lesser extent in alkaloids. **Figure 1-4**, represent some important natural products which have captured synthetic interest in last few decades.

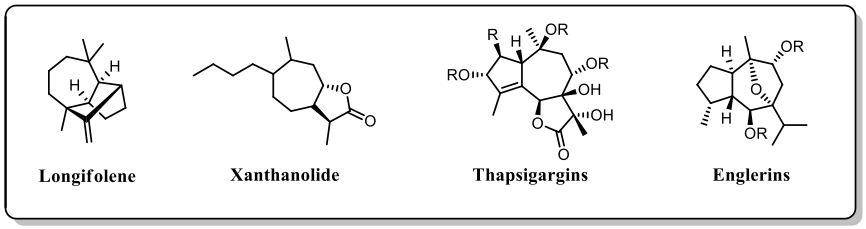


Figure 1: Sesquiterpenoid based natural products.[1]

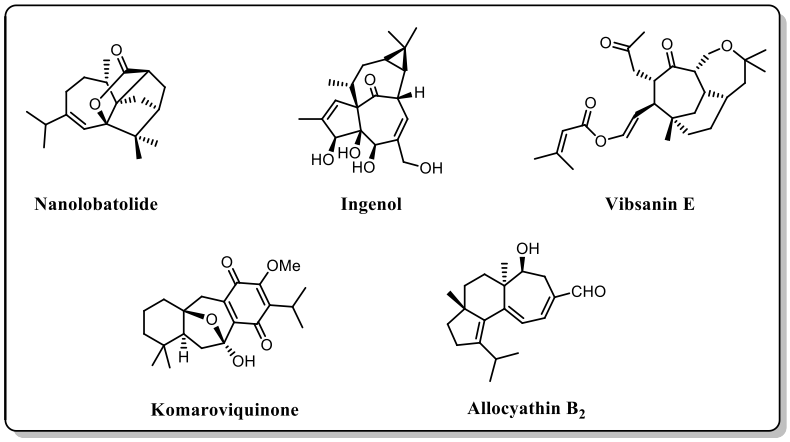


Figure 2: Diterpenoid based natural products.[2]

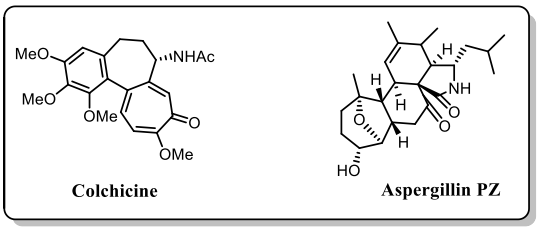


Figure 3: Alkaloid based natural products.[3]

Some other natural products of our interest included (–)-Allocolchcine, Tenuifolin, Metasequirine B, (a*R*,7*R*)-Dihydroisosubamol, Reticuol, (–)-Androbiphenyline, (–)-Colchibiphenyline, Subavenoside which possess dibenzocycloheptane framework. Their impressive pharmacological properties and complex molecular architectures have inspired several research groups to contribute significantly to their synthesis.

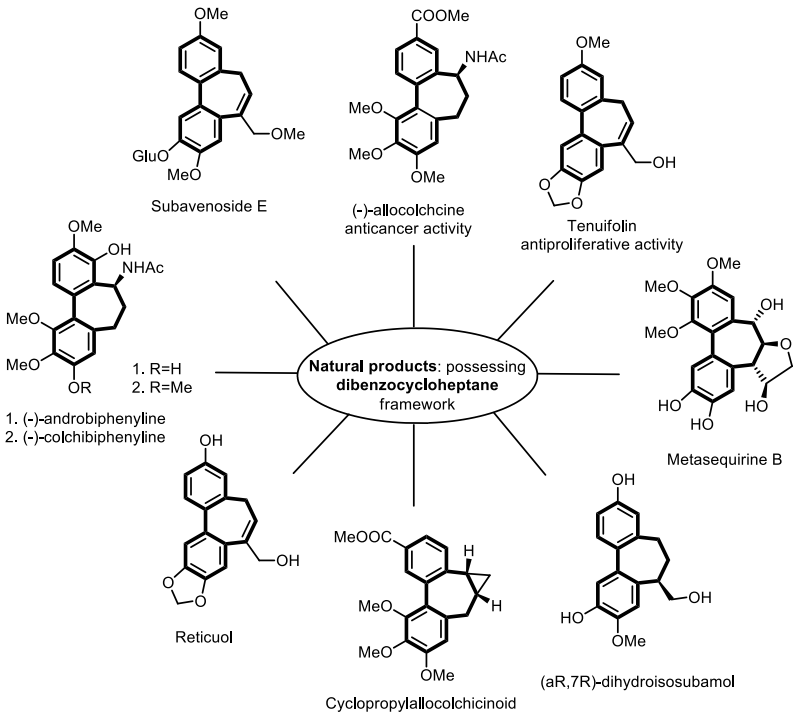


Figure 4: Natural products possessing dibenzocycloheptane framework.

Synthetic methodologies for the formation of seven-membered rings

One of the common strategy is the cyclization of a substrate containing reactive centres at 1,7-positions, taking Baldwin's rules[4] in consideration. Generally, all possible forms of seven member ring closure are favoured, but the synthesis of suitable acyclic substrates with appropriate X and Y groups (Figure 5) account to be the major difficulty.

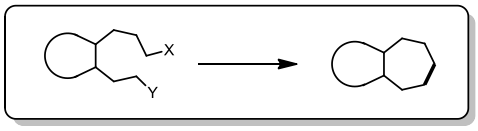


Figure 5: Cyclization and annulation ring closures

The presence of another preformed ring leads to even further restraints on the cyclization process. This approach consists of different strategies including free radical cyclization, ring-closing metathesis (RCM) and cross-coupling methodologies. Also, high transition state energies and entropy factors do not support this type of cyclization. Seven membered rings can also be synthesized *via* (4+3) and (5+2) cycloaddition, pericyclic and transition metal catalyzed reactions (Figure 6). The strategies involving (4+3)[5]and (5+2)[6] cycloadditions have also been studied recently.

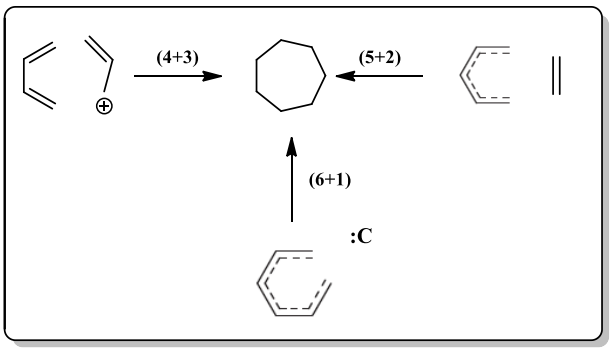
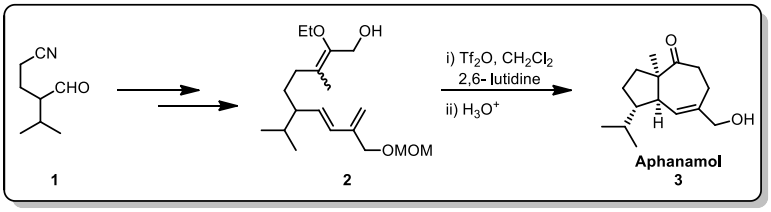


Figure 6: (x+y) cycloaddition strategies

- ***Cycloaddition methodologies***

  Here, cycloaddition approach to form seven membered rings is discussed. Harmata *et al.*[7] provides an early example of the (4+3) cycloaddition towards the synthesis of a natural product Aphanamol **3**, an isodaucane sesquiterpene. A very simple starting material **1** was subjected to triflation followed by in situ cycloaddition to furnish Aphanamol (Scheme 1).

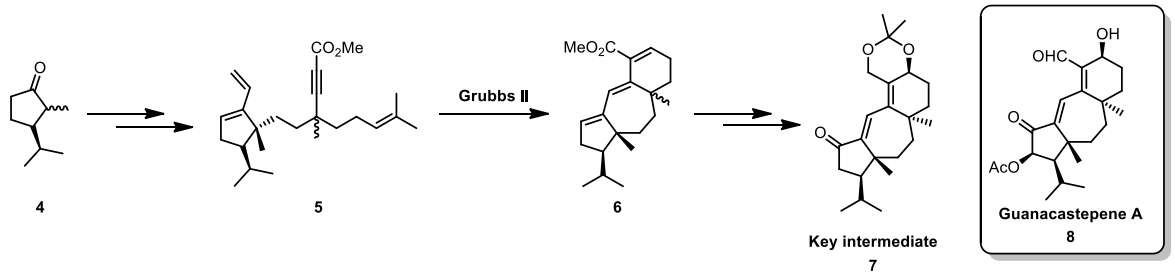


Scheme 1: Harmata's synthesis of Aphanamol.

- ***Cyclization by RCM***

The metathesis reaction is now very common for the formation of carbon–carbon double bonds and therefore the corresponding single bonds. In the present context, we present the RCM reactions which have been widely used to create cyclic compounds such as seven membered rings in total synthesis.

In 2004, Boyer *et al.*[8] presented an approach towards the total synthesis of Guanacastepenes which included the construction of seven membered ring *via* ring closing metathesis (Scheme 2). Reaction of a monocyclic precursor **5** with the 2nd generation Grubbs catalyst (Grubbs II) furnished the tricyclic intermediate **7** for the synthesis of Guanacastepenes.



Scheme 2: RCM approach to synthesize an intermediate in total synthesis of Guanacastepene.

- ***One-carbon ring expansion methodologies***

This methodology involves the ring expansion of five- and six-membered precursors by two- and one-carbon atom respectively by suitable insertion sequences. The two general approaches involve cyclopropanation of a cyclohexene followed by cleavage of the intercyclic C-C bond, or nucleophilic addition to cyclohexanone and then Wagner–Meerwein-type rearrangement, led to formation of seven membered rings, as shown in Figure 7.

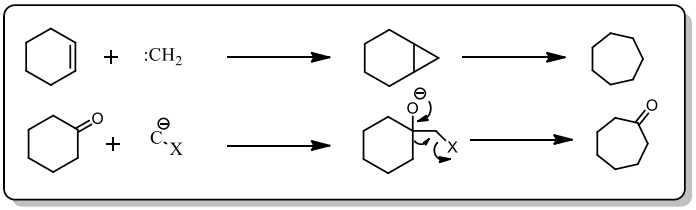
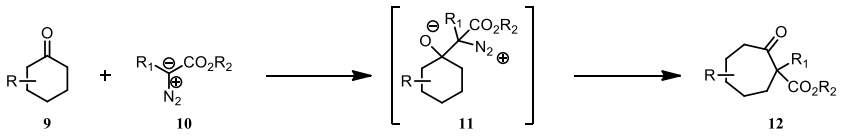


Figure 7: Ring expansion methodologies

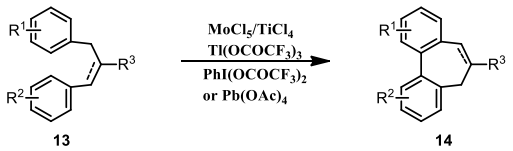
In this context, the Maruoka *et al.*[9] has made significant contributions to synthesize seven-membered rings, by using tertiary diazoacetates **10**. The addition of these tertiary diazoacetates **10** to cyclohexanones **9,** generate the Tiffeneau–Demjanov intermediate **11** which after in situ rearrangement provides a disubstituted cycloheptanones **12**, as presented in scheme 3.



Scheme 3: Diazoacetate ring expansion

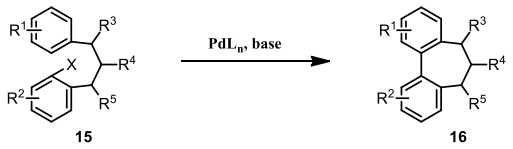
- ***Some other strategies employed to form seven membered rings***

One-pot synthesis of dibenzocycloheptane derivatives **14** *via* oxidative biaryl coupling (scheme 4).[10]



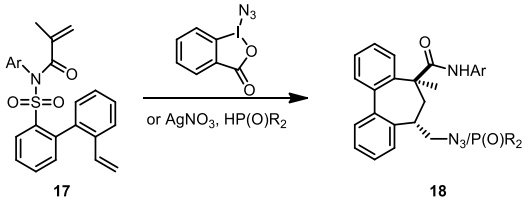
Scheme 4: Oxidative biaryl coupling.

Synthesis of dibenzocycloheptane derivatives **16** *via* base mediated C-X biaryl coupling by using Palladium as a catalyst (scheme 5).[11]



Scheme 5: Palladium catalysed biaryl coupling.

Nevado's work of forming dibenzocycloheptane **18** *via* aryl-heterofunctionalization of activated alkenes **17** (scheme 6).[12]



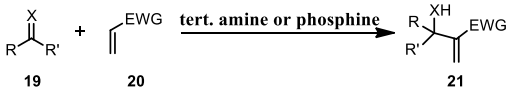
Scheme 6: Aryl-heterofunctionalization of activated alkenes.

The Challenges to Synthesis Seven-membered ring

The chemistry of all carbon atom seven-membered rings is different from the immediate neighbours and therefore not fully explored. The common rings containing three to six carbon atoms have been widely studied for at least a century. Also medium sized rings from 8 up to 12 are also extensively studied. The intermediate seven-membered ring is very flexible with several different conformations of similar energies and very low energy barriers between them. This situation leads to difficulties on predicting reactivity of such kind of systems. There are some solutions available to synthesize six-membered rings *via* Robinson annulation[13], the Diels–Alder reaction[14], and cyclization reactions, however no such universal reactions for seven-membered ring have been reported. Hence, there are no obvious, simple, and excellent methods, to synthesize seven membered rings.

Intramolecular Morita-Baylis-Hillman (IMBH) Reaction to Synthesize Seven-membered Ring

One of the most important reactions in organic chemistry is the carbon−carbon bond forming reaction and therefore has been a fascinating area in organic synthesis. Among these carbon-carbon bond forming reactions, the Morita Baylis Hillman (MBH) reaction has become one of the most useful reactions with enormous synthetic utility. The classical MBH reaction can be broadly defined as the formation of α-methylene-β-hydroxycarbonyl compounds by addition of α,β-unsaturated carbonyl compounds to aldehydes, catalyzed by tertiary amine or phosphine (Scheme 7).



19 **20** **21**

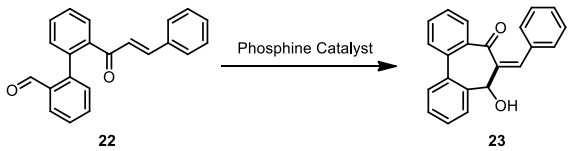
R = aryl, alkyl, heteroaryl, etc.: R' = H, CO_2R", alkyl, etc.
X = O, NCO_2R", NSO_2Ar, etc.
EWG = COR", CHO, CN, CO_2R", $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh, etc.

Scheme 7: General MBH reaction.

Instead of aldehydes, if imines are employed in the reaction, this process is commonly referred to as aza-Morita Baylis Hillman (aza-MBH) reaction. The origin of MBH reaction

date back to 1968 to a pioneering report presented by Morita (phosphine-catalyzed reaction)[15] and then Baylis and Hillman described a similar amine-catalyzed reaction in 1972.[16] Though this reaction is promising and fascinating, unfortunately, it has been ignored by organic chemists for almost a decade after its discovery. Interestingly, there are no reports encountered where MBH reaction has been used to obtain seven membered rings. Recently our group reported an IMBH reaction of biaryl ynone-aldehyde system, led to formation of cyclohepta fused arenes.[17]

Here, a strategy to synthesize seven membered rings *via* phosphine catalysed IMBH reaction of biaryl enone-aldehyde systems **22** has been developed (Scheme 8). An enantioselective version of the same was also tried. To our delight, 92% enantiomeric excess was obtained, but the yield of reactions was not quite satisfactory.



22 23

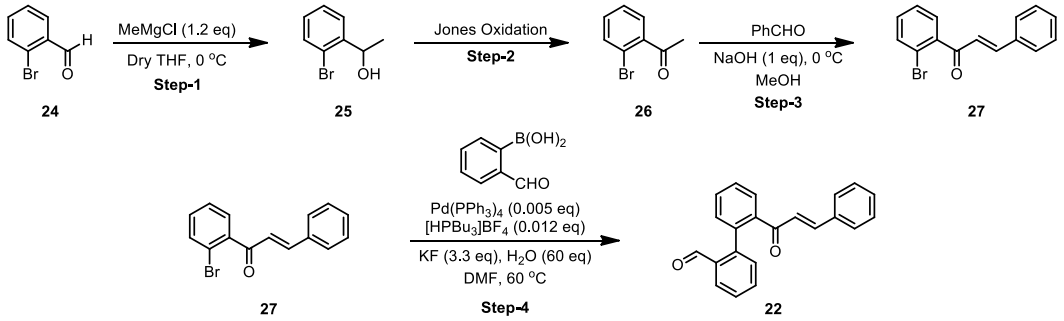
Scheme 8: IMBH reaction of biaryl enone-aldehydes **22**.

So, the synthesis of a seven membered ring *via* phosphine catalysed Intramolecular Morita-Baylis-Hillman reaction of biaryl enone-aldehyde systems has been developed.

Results and Discussion

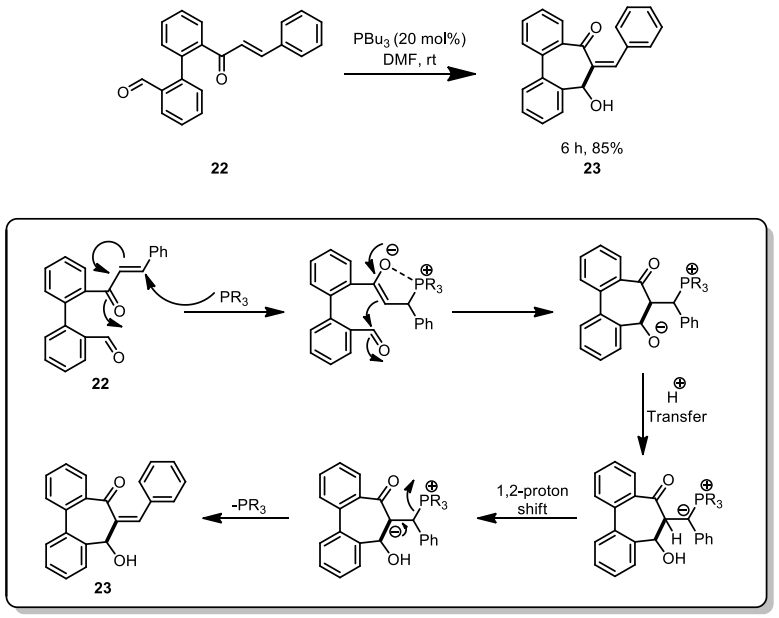
With the desire to access the cycloheptannulated arenes *via* IMBH reaction, we initiated studies to synthesize the proposed starting material **22** bearing enone and aldehyde moiety in a biaryl system, Scheme 9.

At the outset, the enone-aldehydes **22A-22I** were synthesized from the corresponding 2-bromo enones **28** and 2-formylboronic acid *via* Suzuki coupling in good to excellent yields (Scheme 9).



Scheme 9. General approach towards the synthesis of biaryl enone-aldehyde **22**.

The starting material **22** was screened with various catalysts (amines or phosphines) and solvent combinations to obtain the cycloheptannulated product **23**. The desired product was obtained with PBu_3 (20 mol%) in DMF at room temperature with 85% yield, Scheme 10.

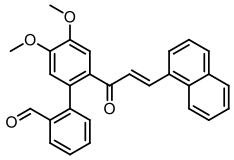
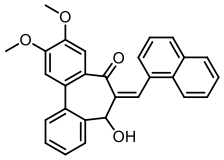
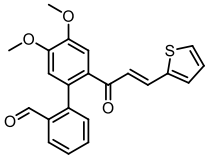
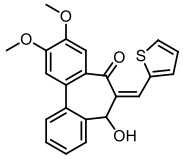
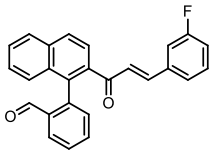
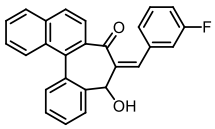
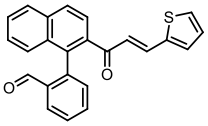
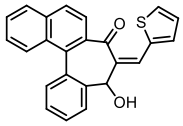
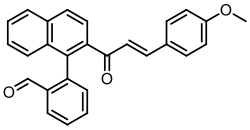
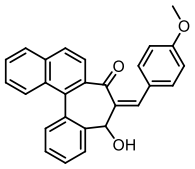
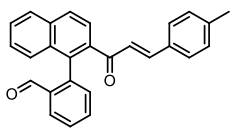
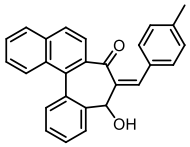


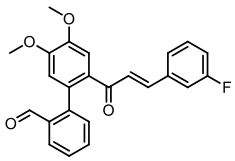
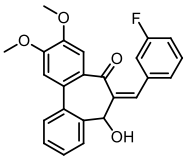
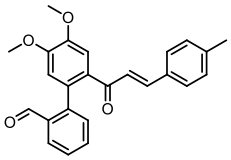
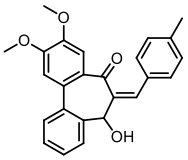
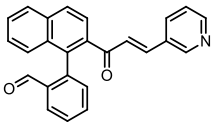
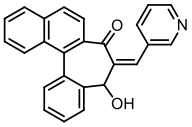
Scheme 10. Optimized condition and mechanism involved for the synthesis of cycloheptannulated product, **23**.

With the optimized conditions for **23** in hand, we proceeded to evaluate the substrate scope, Table 1. Clearly, a wide range of electronically and structurally diverse substituents across the aryl ring were well-tolerated and generated the **29A-29I** in moderate to good yields.

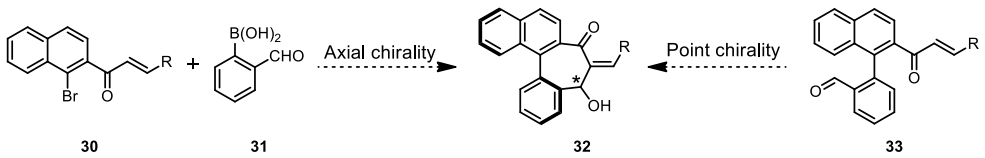
28 **29**

Table 1. Substrate scope for cycloheptannulated product.

Entry	Starting material	Product	Time	Yield(%)
1.	 **28A**	 **29A**	2 hr	84%
2.	 **28B**	 **29B**	6 hr	85%
3.	 **28C**	 **29C**	3 hr	86%
4.	 **28D**	 **29D**	5 hr	70%
5.	 **28E**	 **29E**	6 hr	75%
6.	 **28F**	 **29F**	3 hr	89%

Entry	Starting material	Product	Time	Yield(%)
7.	 **28G**	 **29G**	4 hr	86%
8.	 **28H**	 **29H**	4 hr	83%
9.	 **28I**	 **29I**	2 hr	88%

After successfully establishing a new method for the synthesis of cyclohepta fused arenes, development of the enantioselective version of the same was focused. Two different schemes were designed in order to achieve chirality in our product *via* axial chirality or point chirality.

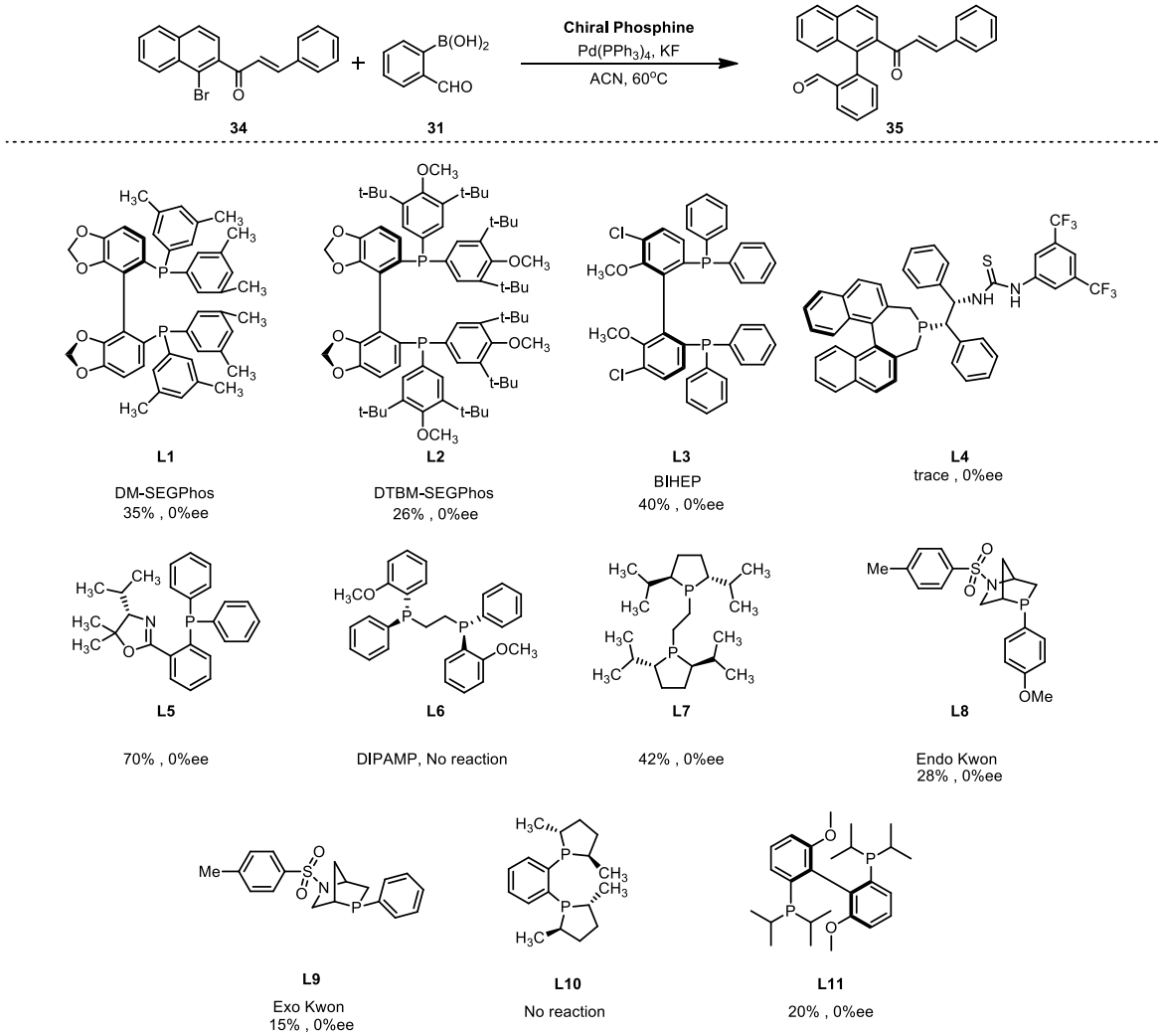


30 **31** **32** **33**

Scheme 11. Axial Chirality and Point Chirality

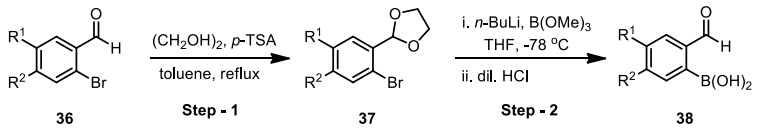
Axial Chirality via Atroposelective Suzuki Coupling

In the optimized condition for the racemic Suzuki coupling, the salt ($[HPBu_3]BF_4$) used in the reaction was replaced by some phosphine ligands like SPhos and XPhos and the product was still obtained in very good yields. So our approach was to replace the ligands with some chiral ligands in order to achieve chirality in the product.

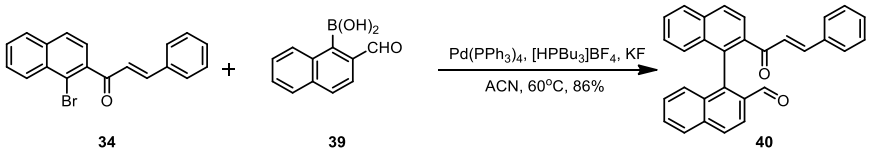


Scheme 12. Brief screening of chiral ligands **(L1-L11).**

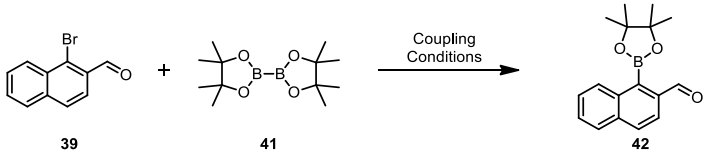
Since, no enantiomeric excess with employing chiral catalysts in napthyl-phenyl enone-aldehyde **35** was achieved, the substrate was modified to napthyl-napthyl enone-aldehyde (Scheme 14) in order to achieve axial chirality. However, the formation of napthyl boronic acid **39**, required for coupling was the major problem. Usually scheme 13 was followed to prepare several boronic acids but in this case the yield was very poor. Therefore, to achieve the boronic acid in good yields, a different strategy was opted (Scheme 15). Boronic ester **42** from bis(pinacolato) boron **41** was prepared instead of boronic acid for which several conditions were screened, however product **42** did not form.



Scheme 13: General scheme for boronic acids preparation**.**



Scheme 14: Suzuki coupling for preparation of 42.



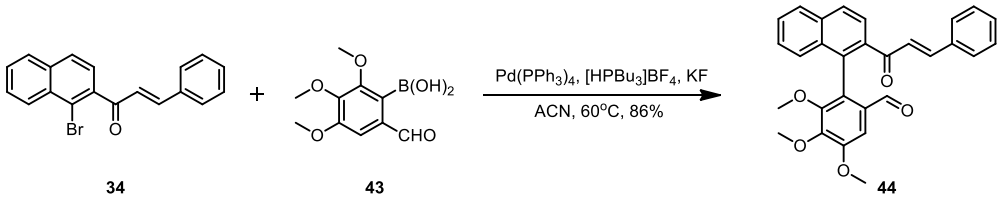
Scheme 15: Boronic ester preparation

Table 2: Screening of different catalysts to obtain boronic ester.

S. No.	Catalyst	Salt	Solvent	Temp.
1.	$Pd(PPh_3)_2Cl_2$	NaOAc	PEG	130 °C
2.	$Pd(PPh_3)_2Cl_2$	NaOAc	1,4 dioxane	130 °C
3.	$Pd(PPh_3)_2Cl_2$	KOAc	PEG	130 °C
5.	$Pd(acac)_2$	KOAc	PEG	130 °C
6.	$Pd(PPh_3)_4$	KOAc	PEG	130 °C
7.	$Pd(PPh_3)_2Cl_2$	KOAc	Dry toluene	100 °C
8.	$Pd(PPh_3)_2Cl_2$	KOAc	Dry 1,4 dioxane	130 °C
9.	$Pd(PPh_3)_2Cl_2$	KOAc	Dry THF	60 °C
10.	$Pd(PPh_3)_2Cl_2$	KOAc	Dry DMF	130 °C
11.	$Pd(acac)_2$	KOAc	Dry DMF	130 °C
12.	$Pd(PPh_3)_4$	KOAc	Dry DMF	130 °C

After the failed attempt to prepare boronic ester **42**, boronic acid *via* scheme 13 was prepared in very low yield. However, the final reaction of **34** and boronic acid in order to achieve **40** did not work.

Another scheme was designed by modifying the substrate. Boronic acid **43** was prepared according to Scheme 16. However, the final reaction of **34** and boronic acid in order to achieve **44** did not work.

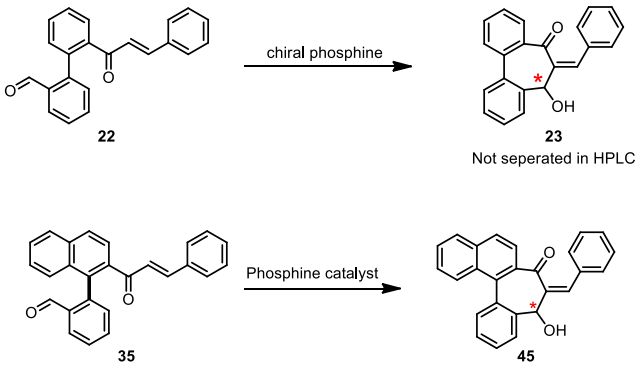


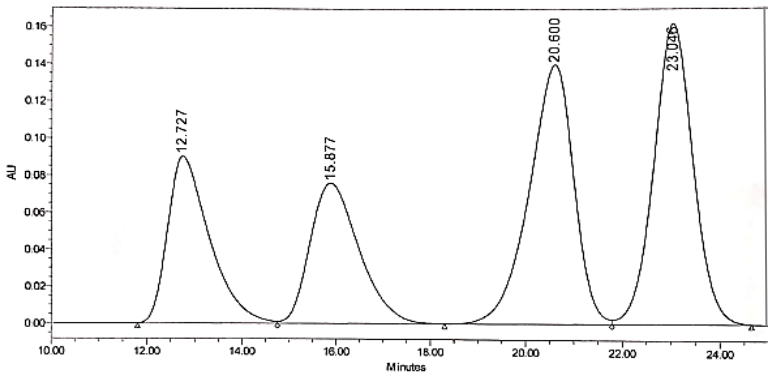
Scheme 16: Suzuki coupling for preparation of **44**.

After the various failed attempts in order to achieve axial chirality, efforts were directed to achieve point chirality.

Development of an enantioselective IMBH reaction

After achieving a practical, general and highly efficient IMBH reaction for the synthesis of cycloheptannulated arenes from biaryl enone-aldehydes, an asymmetric organocatalytic version was undertaken. Despite significant advancements in the area of asymmetric nucleophilic organocatalysis, only a handful of enantioselective IMBH reactions are reported so far. Towards this, the study with **22** as a model substrate was initiated, in order to obtain the HPLC condition but the MBH product **23** was not separated in the HPLC**.** Substrate was modified to **35** and with which four peaks were observed in HPLC (two for the axial and two for point chirality), Scheme 17.



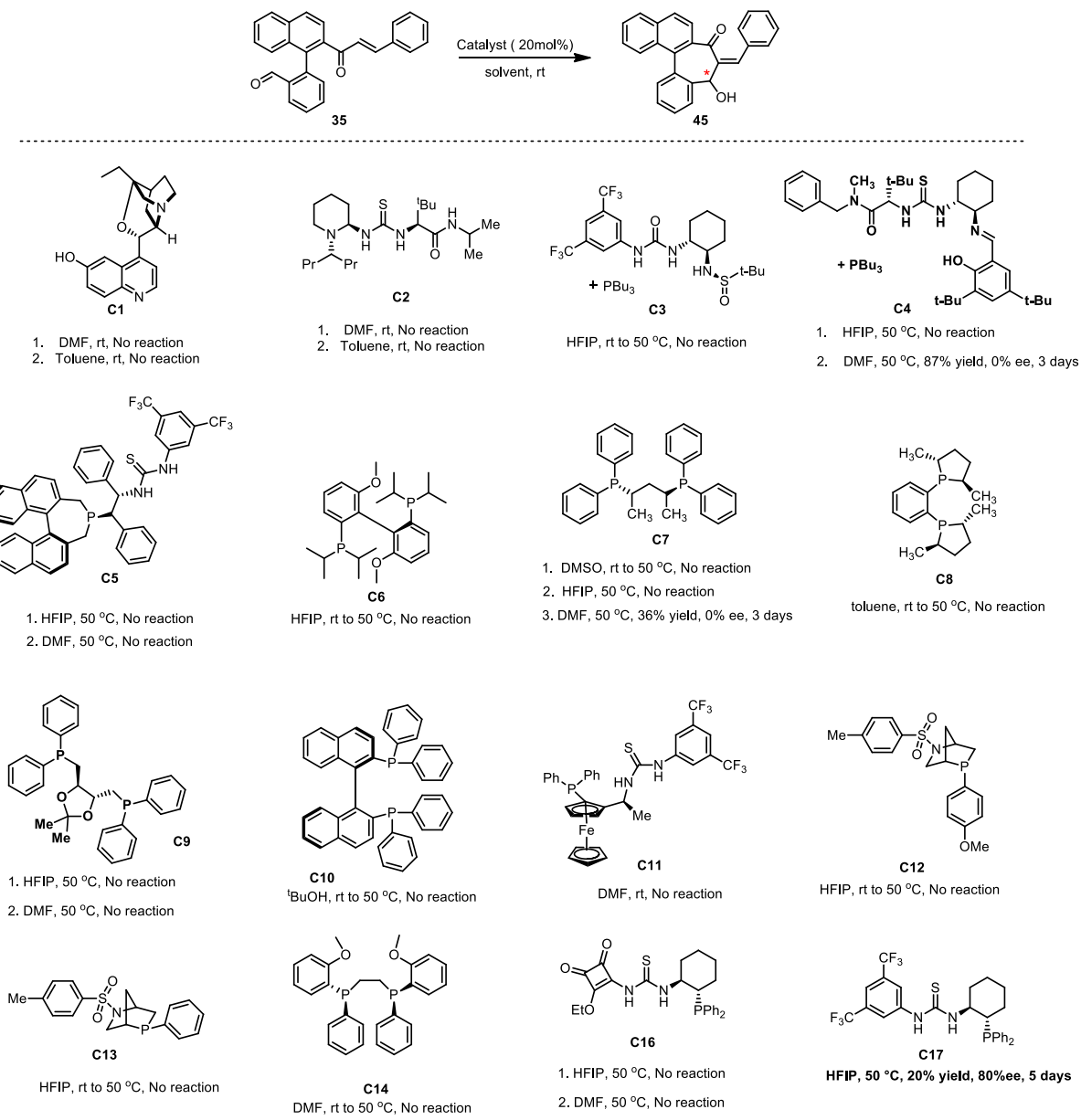


	RT	Area	% Area	Height
1	12.727	5579883	19.18	90895
2	15.877	5576750	19.17	76870
3	20.600	8981269	30.87	139758
4	23.046	8958410	30.79	161165

Scheme 17. HPLC condition for **45**.

After obtaining the HPLC condition in our hand, screening of different chiral phosphines was initiated. Various catalyst, ligand and solvent combinations were evaluated. The initial reactions were tried with various amines such as β-isocupreidine **C1** (β -ICD)[18] but they failed to promote the IMBH reaction. Further, Jacobsen's bifunctional amine-thiourea catalyst **C2** was also unsuccessful.[19] Another combination of chiral amine ligands **C3-C4** with different nucleophiles were also tried but no product was observed. Further, phosphepine[20] based bifunctional catalyst **C5** were tested in different solvents, but no product was observed even after prolonged reaction time, Scheme 18. Bidentate phosphines **C6-C9** also failed to deliver the product in various solvents. Few other catalysts **C10-C14** were also tried but no product formation was observed. Recent advancements in the dramatic influence of fluorinated alcohols encouraged us to consider the fluorinated solvents.[21] Therefore, all the phosphines were investigated using 2,2,2-trifluoroethanol (TFE), trifluorotoluene (TFT) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).

Surprisingly, bifunctional thiourea **C17** afforded the desired product **45** only in HFIP with 20% yield and 80% ee. With the initial success in HFIP, we verified the outcome of a different class of bifunctional catalysts. Interestingly, no product was observed with any of the bifunctional catalysts in toluene, DMF or even in the fluorinated solvents such as TFE or TFT. Further, screenings were carried out in order to improve the yields of **45** (Table-3). With the bifunctional thiourea catalyst **C17** in our hand, few other solvents were screened but all the efforts directed to improve the yields of **45** were met with no considerable success. However, addition of a few equivalents of water with HFIP solvent provided an increase in the enantiomeric excess upto 92%.



Scheme 18. Brief screening of chiral phosphines for the enantioselective synthesis of **45.**

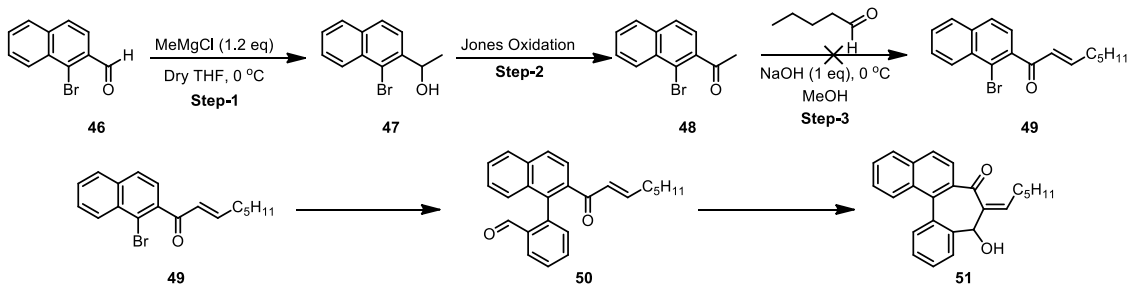
Table 3: Screening of different solvents for C17

S.No.	Catalyst (20 mol%)	Solvent	Time (days)	Temp.	Yield(%)	ee(%)
1.	C17	DMF	5	rt to 50 °C	No reaction	-
2.	C17	DMSO	5	rt to 50 °C	No reaction	-
3.	C17	Toluene	5	rt to 50 °C	No reaction	-
4.	C17	MeCN	5	rt to 50 °C	No reaction	-
5.	C17	^{t}BuOH	5	rt to 50 °C	No reaction	-
6.	C17	TFE	5	rt to 50 °C	No reaction	-
7.	C17	TFT	5	rt to 50 °C	No reaction	-
8.	C17	HFIP	5	rt	trace	-
9.	C17	HFIP	5	40 °C	10	-
10.	C17	HFIP	5	50 °C	20	80
11.	**C17**	**HFIP+5eq. H_2O**	**5**	**50 °C**	**20**	**92**
12.	C17	HFIP+50eq. H_2O	5	50 °C	20	-

Since, these were unsuccessful, therefore, as part of our attempts to improve the efficiency of the formation of **45** from **35**, few more modifications were tried.

1. **Replacing the aryl group of enone with an alkyl group.**

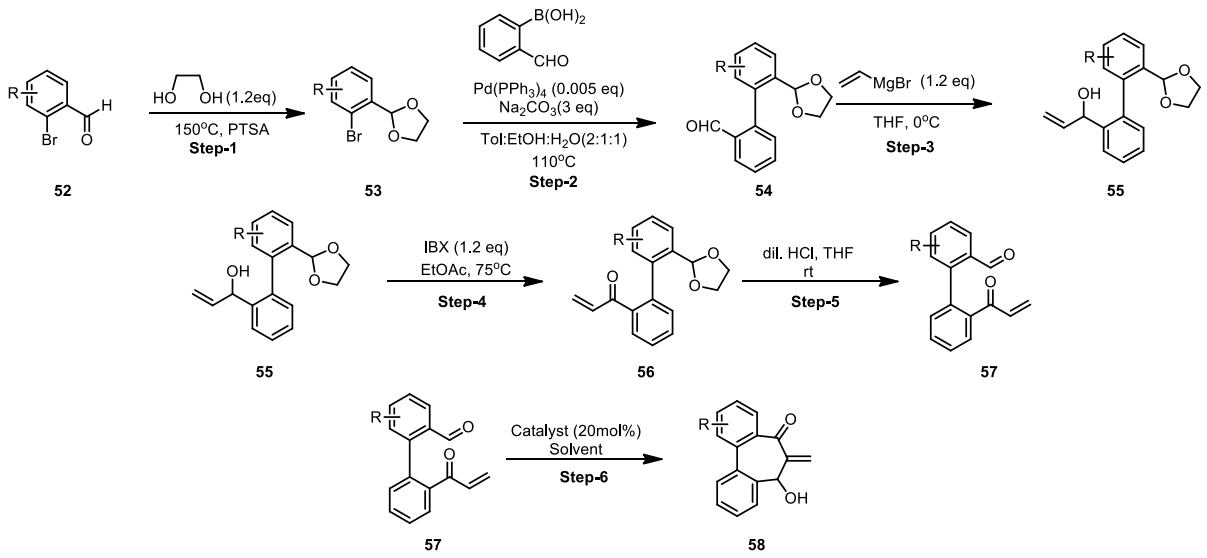
   The steric hindrance provided by the aryl group of the enone was considered to be the reason of very low yields, therefore another Scheme was designed where Step 3 was modified and instead of performing the aldol reaction with benzaldehyde, it was done with veraldehyde in order to obtain a less hindered environment for more facile attack of phosphine catalyst (Scheme 18). However, the aldol reaction of **48** with veraldehyde resulted in many products (as observed on TLC plate) and could not be isolated. Therefore, an attempt towards the formation of less hindered substrate was unsuccessful.



Scheme 19. New substrate design to improve yield.

2. Unsubstituted biaryl enone-aldehydes:

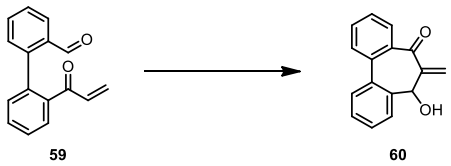
Another scheme 20 was designed in order to increase the yields of the final reaction.



Scheme 20. General scheme for unsubstituted biaryl enone-aldehydes **57**.

It is well known in literature that unsubstituted systems are highly reactive. This study was based on three different types of unsubstituted systems where R= H, Me, Ph.

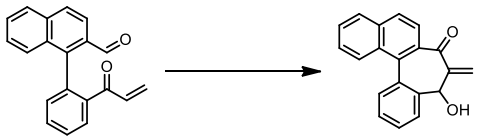
When, R= H



Scheme 21. Unsubstituted biaryl system, when R = H.

After the preparation of starting material as mentioned in scheme 18, various catalysts were screened to get the product. The system **59** being highly reactive, the final reaction with different phosphine catalyst was finished in less than 15 min. However, the product **60** formed was highly unstable and decomposed even after purification. Then we moved to another substrate and similar screening was carried out to obtain the product.

When, R= Ph



61 62

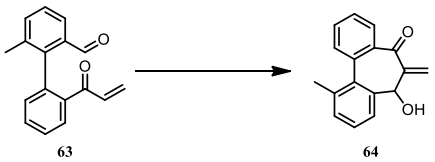
Scheme 22. Unsubstituted biaryl system, when R = Ph.

Table 4: Screening of different catalysts

S. No.	Catalyst	Solvent	Time	Temp	Result	Yield
1.	PBu_3	Toluene	30 min	rt	decomposed	-
2.	PMe_3	Toluene	30 min	rt	decomposed	-
3.	PPh_3	Toluene	30 min	rt	Multiple spots	-
4.	PCy_3	Toluene	30 min	rt	Multiple spots	-
5.	DBU	Toluene	30 min	rt	Multiple spots	-
6.	PPh_3	DMF	30 min	rt	3 spots	-
7.	PPh_3	DCM	30 min	rt	Multiple spots	-
8.	PPh_3	HFIP	30 min	rt	No reaction	-
9.	PPh_3	Toluene	30 min	-10°C to rt	Multiple spots	-
10.	PPh_3	DMF	30 min	-10°C to rt	Multiple spots	-
11.	PPh_3	DCM	30 min	-10°C to rt	Multiple spots	-
12.	DBU	Toluene	30 min	-10°C to rt	Multiple spots	-
13.	PPh_3	DMF	24 hrs	-10°C to rt	3 spots	-
14.	PPh_3	DMF	24 hrs	rt	3 spots	-
15.	$P(tolyl)_3$	DMF	24 hrs	rt	Multiple spots	-
16.	$P(\text{ -OMe})_3$	DMF	24 hrs	rt	Multiple spots	-
17.	PPh_3	Toluene	24 hrs	rt	Multiple spots	-
18.	PPh_3	THF	1 hr	rt	Product formed	72%
19.	DMAP	DMF	1 hr	rt	Product formed	80%
20.	DMAP	DMSO	1 hr	rt	Product formed	70%
21.	DABCO	MeCN:H_2O (1:1)	1 hr	rt	Product formed	75%
22.	DABCO	1,4dioxane:H_2O (1:1)	1 hr	rt	Product formed	78%
23.	**3-quinidine**	**Toluene**	**1 hr**	**rt**	Product formed	**85%**

After the optimized condition in our hand, the product was injected to HPLC to obtain the racemic condition before the chiral screening was started. However, peaks were not separated in HPLC. After this unsuccessful attempt, another unsubstituted system was designed.

When, R= Me**,**



63 64

Scheme 23. Unsubstituted biaryl system, when R = Me.

Table 5: Screening of different catalysts

S. No.	Catalyst	Solvent	Time	Temp	Yield
1.	PPh_3	THF	1 hr	rt	85%
2.	DMAP	DMF	1 hr	rt	72%
3.	DMAP	DMSO	1 hr	rt	70%
4.	DABCO	MeCN:H_2O (1:1)	1 hr	rt	78%
5.	DABCO	1,4dioxane:H_2O (1:1)	1 hr	rt	82%
6.	**3-quinidine**	**Toluene**	**1 hr**	**rt**	**88%**

After the optimized condition **6**, in our hand, the product was injected to HPLC to obtain the racemic condition before the chiral screening was started.

HPLC condition : Chiralpak IA, 5% 2-Propanol/Hexane, 1mL/min

The chiral screening for substrate **64** is yet to be done.

Summary

In conclusion, we have demonstrated an Intramolecular Morita-Baylis-Hillman (IMBH) reaction of unexplored biaryl enone-aldehydes to access cycloheptannulated arenes in excellent yields has been developed. Further, an enantioselective version also was tried by employing bifunctional thiourea catalyst in hexafluoroisopropanol, however yield of the reaction was very low.

Experimental methods

General experimental methods: All the starting compounds and catalysts employed in this study were procured from Sigma-Aldrich and were used without further purification. For thin layer chromatography (TLC), silica aluminium foils with fluorescent indicator 254 nm (from Aldrich) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Column chromatography was performed using SD Fine silica gel 100-200 mesh (approximately 15–20 g per 1 g of the crude product). Dry THF was obtained by distillation over sodium and stored over sodium wire. IR spectra were recorded on a Perkin–Elmer FT IR spectrometer as thin films or KBr pellet, as indicated, with ν_{max} in inverse centimetres. Melting points were recorded on a digital melting point apparatus Stuart SMP30 and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz BrukerBiospinAvance III FT-NMR spectrometer. NMR shifts are reported as delta (δ) units in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). The following abbreviations are utilized to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Proton chemical shifts are given in δ relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$.Carbon chemical shifts are internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.1 ppm). High-resolution mass spectra were recorded on a Waters QTOF mass spectrometer. Enantiomeric excess was determined by using Waters Chiral HPLC.

Procedure A: Preparation of biaryl enon-aldehyde systems. (22A-22I).[22]

All the biaryl enone-aldehyde systems (**22A-22I**) employed in this study were prepared following a four-step protocol starting from 2-bromobenzaldehyde **24**. Addition of methyl magnesuim chloride to 2-bromobenzaldehyde **24** afforded 2-bromo alcohol **25** which upon Jones oxidation generated the 2-bromo ketone **26**. Further addition of corresponding aldehydes to 2-bromo ketone **26** furnished aldol products **27A-27I.** Further reaction of different aldol products with boronic acid under Suzuki coupling conditions resulted in biaryl enon-aldehyde substrates **22A-22I** (Scheme 9).

Representative procedure for step-I (Scheme 9): An oven dried round bottom flask was charged with 2-bromobenzaldehyde **24** (1.0 mmol), 5 mL dry THF and placed at 0^{o}C. Methyl

magnesium chloride (3.0 M in THF, 1.2mmol) was added drop wise at the same temperature and stirred for 1h. Upon completion, the reaction mixture was quenched by adding dil. HCl (1 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20-30% EtOAc/hexane) to afford **25** in 95% yield.

Representative procedure for step-II (Scheme 9): Alcohol **25** (1 mmol) was dissolved in Acetone (5 mL), and Jones reagent (CrO_3: H_2O: H_2SO_4, 1:3:1) was added dropwise. The resulting mixture was stirred at room temperature until alcohol **25** disappeared as monitored by TLC. Acetone in the reaction mixture was concentrated under reduced pressure and then the mixture was filtered through celite pad. The residue was washed with ethyl acetate (3×2 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10-20% EtOAc/hexane) to afford **26** in 90% yield.

Representative procedure for step-III (Scheme 9): A round bottom flask was charged with the mixture of **26** (1 mmol) and corresponding aldehydes (1 mmol) to prepare different aldol products**,** 5 mL MeOH and placed at 0^oC. Then, NaOH (1.2 mmol) was grinded and added in small amounts to the reaction mixture. The resulting mixture was stirred at room temperature until both the starting materials disappeared as monitored by TLC. Methanol in the reaction mixture was concentrated under reduced pressure. The residue was washed with ethyl acetate (3×2 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10-20% EtOAc/hexane) to afford **27** in 80-90% yield.

Representative procedure for step-IV (Scheme 9): $Pd(PPh_3)_4$ (0.005 mmol), $[HP(^{t}Bu)_3]BF_4$ (0.012 mmol), aryl halide (1.0 mmol), boronic acid (2.0 mmol), KF (3.3 mmol) and H_2O (60.0 mmol) were added to a sealed tube. The reaction tube was degassed with nitrogen and then MeCN (2.0 mL) was added using a syringe, and the resulting solution was stirred at 60 °C for 9-10 h. After the reaction was completed (TLC), the reaction was quenched with saturated aq. NH_4Cl solution and extracted using ethyl acetate. The organic extracts were combined dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography using 10-20% EtOAc/hexane as eluent to afford biaryl-enone aldehydes **22A-22I**.

General procedure-B: Evaluating the substrate scope (Table 1)

An oven dried 5 mL glass vial was charged with **28** (1 mmol), DMF (1.0 mL) and tributylphosphine (0.02 mmol) at room temperature (rt) and stirring continued until **29** disappeared as monitored by TLC. Then the reaction was quenched with water and extracted using ethyl acetate. The organic extracts were combined and dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel flash chromatography using 20-30% EtOAc/hexane as eluent, to afford **29**.

General procedure-C: Screening of reaction parameters (Scheme-12).

$Pd(PPh_3)_4$ (0.005 mmol), chiral ligand **(L1-L12)** (0.012 mmol), aryl halide **34** (1.0 mmol), boronic acid **31** (2.0 mmol), KF (3.3 mmol) and H_2O (60.0 mmol) were added to a sealed tube. The reaction tube was degassed with nitrogen and then MeCN (2.0 mL) was added using a syringe, and the resulting solution was stirred at 60 °C for 9-10 h. Reaction was monitored by TLC.

General procedure-D: Synthesis of 2-formyl boronic acids (Scheme-13).

All 2-formyl boronic acids (**38**) were synthesized according to reported literature.[23]

General procedure-H: Screening of reaction parameters (Scheme-18).

An oven dried 5 mL glass vial was charged with **35** (1 mmol), different solvents (1.0 mL) and chiral catalyst (**C1-C17**) (0.02 mmol) at different temperatures and stirring continued until **45** started forming as monitored by TLC. Crude reaction mixture was used to determine enantiomeric excess.

General procedure-I: Screening of reaction parameters (Table-3).

An oven dried 5 mL glass vial was charged with **35** (1 mmol), different solvents (1.0 mL) and chiral catalyst **C17** (0.02 mmol) at different temperatures and stirring continued until **45** started forming as monitored by TLC. Crude reaction mixture was used to determine enantiomeric excess.

General procedure-J: Preparation of unsubstituted biaryl enone-aldehyde systems.

All the three unsubstituted biaryl enone-aldehyde systems employed in this study were prepared following a five-step protocol starting from 2-bromobenzaldehyde (**52**). Step-1 involved the protection of corresponding benzaldehydes, followed by Suzuki coupling in

step-2. Addition of vinyl magnesuim bromide to coupling products (**54**) was done in Step-3. IBX oxidation in step 4 followed by deprotection afforded the starting materials (**57**). (Scheme 20).

Representative procedure for step-I and STEP-II (Scheme 20): Products **53** and **54** were synthesized according to reported literature.[22]

Representative procedure for step-III (Scheme 20): An oven dried round bottom flask was charged with **54** (1.0 mmol), 5 mL dry THF and placed at 0^{o}C. Vinyl magnesium bromide (1.0 M in THF, 1.5mmol) was added drop wise at the same temperature and stirred for 1h. Upon completion, the reaction mixture was quenched by adding dil. HCl (1 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20-30% EtOAc/hexane) to afford **55** in 95% yield.

Representative procedure for step-IV (Scheme 20): An oven dried round bottom flask was charged with **55** (1.0 mmol), IBX (1.5 mmol) was dissolved in EtOAc (4.0 mL) with vigorous stirring for approximately 3 hr at 75°C. The reaction was monitored by TLC until complete consumption of starting material was observed. The mixture was filtered through celite pad. The residue was washed with EtOAc (2x5 mL), the organic phase was washed with water, dried over anhydrous Na_2SO_4, and concentrated. Final purification was done by column chromatography (silica gel) to furnish the desired product **56**.

Representative procedure for step-V (Scheme 20): An oven dried round bottom flask was charged with **56** (1.0 mmol) was dissolved in THF (4.0 mL). To which dil. HCl was added drop wise for few minutes for approximately half hour at room temperature. The reaction was monitored by TLC until complete consumption of starting material was observed. The mixture was extracted with EtOAc (2x5 mL), the organic phase was washed with water, dried over anhydrous Na_2SO_4, and concentrated. Final purification was done by column chromatography (silica gel) to furnish the desired product **57**.

General procedure-K: Screening of reaction parameters (Scheme 21-23).

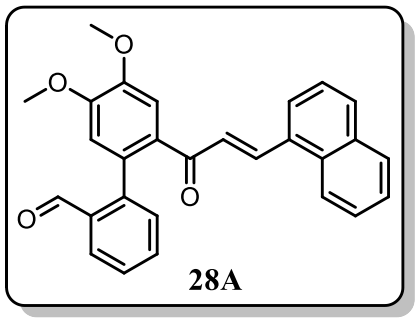
Starting materials were prepared according to general procedure-J. An oven dried 5 mL glass vial was charged with unsubstituted enone-aldehydes **57** (1 mmol), different solvents (1.0 mL) and catalysts (0.02 mmol) at various temperatures and stirring continued until starting material disappeared as monitored by TLC. Then the reaction was quenched with water and extracted using ethyl acetate. The organic extracts were combined and dried over anhydrous

Na_2SO_4 and concentrated. The crude product was purified by silica gel flash chromatography using 20-30% EtOAc/hexane as eluent, to afford the final MBH product.

Spectroscopic data of all new compounds reported in this study

(*E*)-4',5'-Dimethoxy-2'-(3-(naphthalen-1-yl)acryloyl)-[1,1'-biphenyl]-2-carbaldehyde (28A).

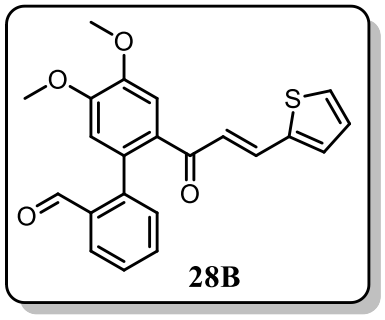
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow oil. **IR (thin film, neat):** ν_{max}/cm^{-1} 3004, 2962, 2940, 2849, 1694, 1652, 1597, 1572, 1351, 1235, 1022, 732. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.01 (s, 1H), 8.31 (d, *J* = 15.5 Hz, 1H), 8.06-8.02 (m, 2H), 7.86-7.84 (m, 2H), 7.63 (dt, *J* = 7.4 Hz, 1.2 Hz, 1H), 7.56-7.50 (m, 3H), 7.46 (s, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.24, 1H), 6.84 (s, 1H), 6.72 (d, *J* = 15.4 Hz, 1H), 4.04 (s, 3H), 3.97(s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.3, 191.5, 150.9, 148.7, 144.3, 140.4, 134.4, 133.6, 132.9, 131.8, 131.5, 131.1, 130.7, 128.7, 128.3, 128.0, 126.9, 126.2, 125.2, 125.0, 123.3, 114.2, 111.9, 56.2. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{22}O_4$ $(M+H)^+$: 445.1415. Found: 445.1398.



28A

(*E*)-4',5'-Dimethoxy-2'-(3-(thiophen-2-yl)acryloyl)-[1,1'-biphenyl]-2-carbaldehyde (28B).

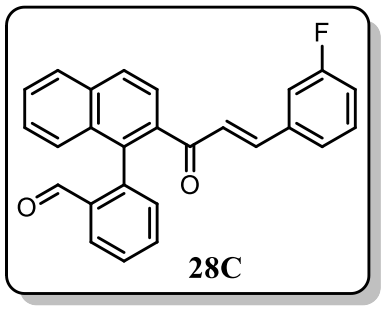
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow oil. **IR (thin film, neat):** ν_{max}/cm^{-1} 3012, 2962, 2936, 2845, 1693, 1651, 1596, 1515, 1391, 1235, 1021, 776. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.01 (d, *J* = 7.8Hz, 1H), 7.61 (dt, *J* = 7.5 Hz, 1.1 Hz, 2H), 7.54 (d, *J* = 15.4Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.38-7.35 (m, 2H), 7.31-7.28 (m, 1H), 7.11(d, *J* = 3.4 Hz,1H), 7.00-6.97 (m, 1H), 6.81 (s, 1H), 6.37 (d, *J* = 15.4 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 191.8, 191.5, 150.8, 148.7, 144.1, 140.0, 135.8, 134.3, 133.5, 132.8, 131.8, 131.3, 131.06, 131.01, 128.8, 128.4, 128.2, 128.0, 124.5, 114.1, 111.8, 56.25. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{18}O_4S$ $(M+Na)^+$: 401.0823. Found: 401.0817.



28B

(*E*)-2-(2-(3-(3-Fluorophenyl)acryloyl)naphthalen-1-yl)benzaldehyde (28C).

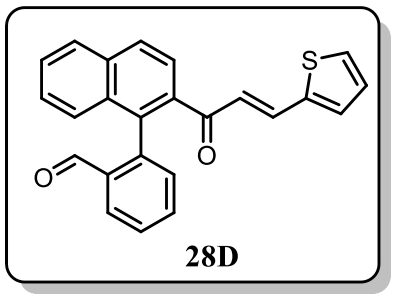
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow oil. **IR (thin film, neat):** ν_{max}/cm^{-1} 3065, 2955, 2928, 2852, 1697, 1650, 1598, 1582, 1242, 971, 765. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.69 (s, 1H), 8.10 (dd, *J* = 7.7 Hz, 0.9 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.67 (dt, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.64-7.56 (m ,2H), 7.48 (dt, *J* = 7.0 Hz, 1.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 16.6 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.34-7.29 (m, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.09-7.04 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.1, 191.3, 162.9 (d, *J* = 245.5 Hz, 1C), 143.8 (d, *J* = 2.4 Hz, 1C), 141.0, 137.3, 136 (d, *J* = 7.6 Hz, 1C), 135.4, 134.8, 134.0, 133.6, 132.8, 131.9, 130.4 (d, *J* = 8.1 Hz, 1C), 128.8 (d, *J* = 4.9 Hz, 2C), 128.3, 127.9, 127.5 (d, *J* = 6.4 Hz, 1C), 127.3, 126.9, 124.4 (d, *J* = 2.6 Hz, 1C), 124.3 (2C), 117.5 (d, *J* = 21.2 Hz, 1C), 114.4 (d, *J* = 21.8 Hz, 1C). **^{19}F NMR (376.5 MHz, $CDCl_3$):** δ -112.3. **HRMS (ESI):** *m/z* calcd for $C_{26}H_{17}FO_2$ $(M+Na)^+$: 403.1110. Found: 403.1127.



28C

(*E*)-2-(2-(3-(Thiophen-2-yl)acryloyl)naphthalen-1-yl)benzaldehyde (28D).

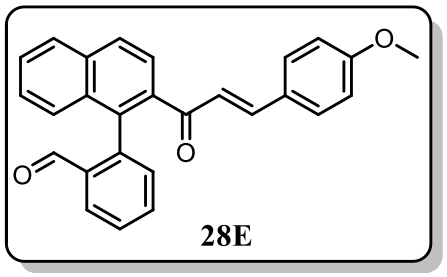
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow solid. **M.P** = 197.5-199.0 °C. **IR (thin film, neat):** ν_{max}/cm^{-1} 3060, 2925, 2850, 2749, 1697, 1651, 1594, 1583, 1270, 1073, 732. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.69 (s, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.62-7.56 (m ,2H), 7.52-7.46 (m, 2H), 7.42-7.35 (m, 3H), 7.17 (d, *J* = 3.0 Hz, 1H), 7.03 (t, *J* = 4.8Hz, 1H), 6.60 (d, *J* = 15.6 Hz,1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.8, 191.4, 141.1, 139.7, 137.68, 137.62, 135.4, 134.6, 134.0, 133.7, 132.9, 132.1, 131.8, 129.3, 128.8, 128.7, 128.34, 128.30, 127.8, 127.5 (2C), 126.8, 125.1, 124.4. **HRMS (ESI):** *m/z* calcd for $C_{24}H_{16}O_2S$ $(M+Na)^+$: 391.0768. Found: 391.0770.



28D

(*E*)-2-(2-(3-(4-Methoxyphenyl)acryloyl)naphthalen-1-yl)benzaldehyde (28E).

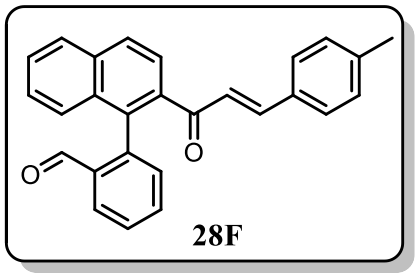
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow oil. **IR (thin film, neat):** ν_{max}/cm^{-1} 3008, 2966, 2936, 2841, 1694, 1634, 1597, 1572, 1337, 1251, 1028, 735. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.69 (s, 1H), 8.09 (d, *J* = 7.8 Hz , 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.67-7.54 (m, 3H) 7.47 (t, *J* = 8.1 Hz, 1H), 7.42-7.28 (m, 5H), 6.87 (d, *J* = 8.3 Hz ,2H), 6.69 (d, *J* = 15.9 Hz, 1H), 3.84 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.7, 191.5, 161.8, 145.7, 141.2, 137.9, 135.3, 134.3, 133.8, 133.6, 132.9, 131.8, 130.2 (2C), 128.68, 128.65, 128.3, 127.6, 127.4, 127.3, 136.9, 126.8, 124.4, 124.3, 114.4 (2C), 55.4. **HRMS (ESI):** *m/z* calcd for $C_{27}H_{20}O_3$ $(M+Na)^+$: 415.1310. Found: 415.1295.



28E

(*E*)-2-(2-(3-(*p*-Tolyl)acryloyl)naphthalen-1-yl)benzaldehyde (28F).

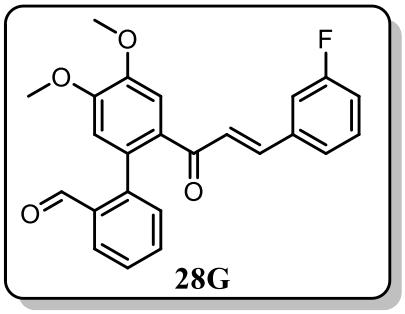
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow oil. **IR (thin film, neat):** ν_{max}/cm^{-1} 3027, 3059, 2923, 2848, 1694, 1644, 1596, 1568, 1337, 1261, 1051, 753. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.70 (s, 1H), 8.10 (dd , *J* = 7.6 Hz, 0.8 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.67-7.54 (m, 3H), 7.48 (dt, *J* = 0.8 Hz , 8.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.38-7.33 (m, 2H), 7.29-7.27 (m ,2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* =16.0 Hz, 1H), 2.37 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.7, 191.4, 145.9, 141.3, 141.2, 137.8, 135.4, 134.4, 133.9, 133.6, 133.4, 132.9, 131.8, 131.7, 131.5, 129.6, 128.7, 128.6, 128.4, 128.3, 127.7, 127.5, 127.4, 126.8, 125.5, 124.4, 21.5. **HRMS (ESI):** *m/z* calcd for $C_{27}H_{20}O_2$ $(M+Na)^+$: 399.1361. Found: 399.1351.



28F

(*E*)-2'-(3-(3-Fluorophenyl)acryloyl)-4',5'-dimethoxy-[1,1'-biphenyl]-2-carbaldehyde (28G).

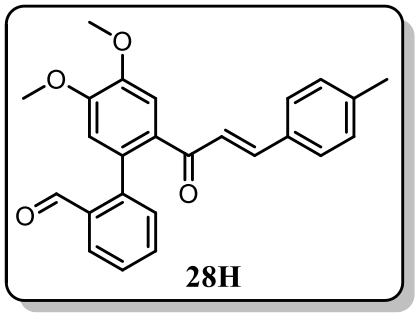
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow oil. **IR (thin film, neat):** ν_{max}/cm^{-1} 3061, 3004, 2970, 2940, 1693, 1661, 1596, 1516, 1267, 1021, 733. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.93 (s, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 9.3 Hz, 3H), 7.28-7.22 (m, 1H), 7.03-6.97 (m, 2H), 6.82 (s, 2H), 6.54 (d, *J* = 15.7 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.0, 191.4, 162.8 (d, *J* = 245.3 Hz, 1C), 151.1, 148.8, 144.1, 141.9, 136.8 (d, *J* = 7.6 Hz, 1C), 134.4, 133.5, 132.5, 131.3 (d, *J* = 15.1 Hz, 2C), 130.3 (d, *J* = 8.1 Hz, 1C), 128.4, 128.1, 126.7, 124.3 (d, *J* = 2.4 Hz, 1C), 117.1 (d, *J* = 21.2 Hz, 1C), 114.2, 114.0 (d, *J* = 4.1 Hz, 1C), 111.9, 56.2 (2C). **^{19}F NMR (376.5 MHz, $CDCl_3$):** δ -112.5. **HRMS (ESI):** *m/z* calcd for $C_{24}H_{19}FO_4$ $(M+Na)^+$: 413.1165. Found: 413.1146.



28G

(*E*)-4',5'-Dimethoxy-2'-(3-(*p*-tolyl)acryloyl)-[1,1'-biphenyl]-2-carbaldehyde (28H).

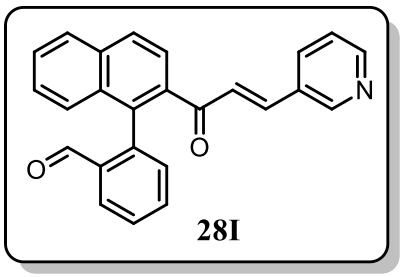
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow oil. **IR (thin film, neat):** ν_{max}/cm^{-1} 3004, 2970, 2940, 2852, 1693, 1658, 1597, 1567, 1390, 1235, 1022, 814, 733. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.98 (s, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47(t, J = 7.5 Hz, 1H), 7.41-7.35 (m,3H), 7.14-7.09 (m,4H), 6.82(s, 1H), 6.56 (d, J = 15.7 Hz,1H), 4.02 (s,3H), 3.95 (s,3H), 2.34(s,3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.7, 191.5, 150.7, 148.7, 144.3, 143.9, 141.0, 134.3, 133.4, 132.9, 131.7, 131.3, 130.8, 129.5 (2C), 128.3, 128.2 (2C), 127.9, 124.7, 114.1, 111.8, 56.2 (2C), 21.4. **HRMS (ESI):** *m/z* calcd for $C_{25}H_{22}O_4$ $(M+Na)^+$: 409.1415. Found: 409.1444.



28H

(*E*)-2-(2-(3-(Pyridin-3-yl)acryloyl)naphthalen-1-yl)benzaldehyde (28I).

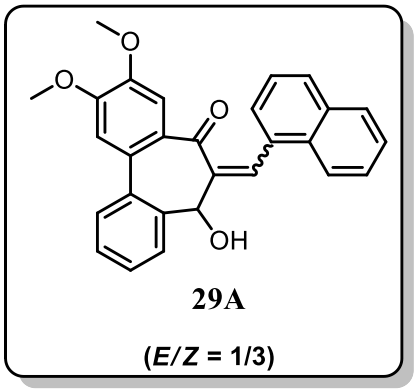
This compound was prepared following the general procedure A (Scheme 9) and was isolated as yellow oil. **IR (thin film, neat):** ν_{max}/cm^{-1} 2925, 2875, 1714, 1660, 1590, 1515, 1106, 825. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.68 (s, 1H), 8.59 (s, 2H), 8.08 (t, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.73-7.67 (m, 2H), 7.64-7.57 (m, 2H), 7.49 (t, *J* = 8.2 Hz, 1H), 7.44-7.33 (m, 4H), 8.08 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.5, 191.3, 150.0, 148.7, 140.9, 140.5, 137.0, 135.5, 135.3, 135.0, 134.2, 133.7, 132.7, 131.9, 130.6, 128.96, 128.92, 128.3, 128.1, 127.8, 127.6, 126.9, 124.3, 124.1, 124.0. **HRMS (ESI):** *m/z* calcd for $C_{25}H_{17}NO_2$ $(M+H)^+$: 364.1337. Found: 364.1320.



28I

7-Hydroxy-2,3-dimethoxy-6-(naphthalen-1-ylmethylene)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (29A). (major isomer)

This compound was isolated as yellow oil. Following the general procedure B, 50 mg of **28A** afforded 42 mg of **29A** (84% yield). **IR (thin film, neat):** ν_{max}/cm^{-1} 3493, 3058, 2962, 2929, 1651, 1588, 1517, 1395, 1269, 1021, 784. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.38 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.60-7.55 (m, 4H), 7.50-7.42 (m, 3H), 7.40-7.34 (m, 1H), 7.25 (d, *J* = 7.3 Hz, 1H), 7.02 (s, 2H), 5.75 (d, *J* = 5.9Hz, 1H), 4.04 (s, 3H), 4.03 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.4, 152.5, 148.7, 143.4, 138.7, 134.2, 133.4, 132.7, 132.6, 131.6, 131.1, 130.8, 129.2, 128.7, 128.5, 128.1, 127.9, 126.7, 126.5, 125.1, 124.3, 112.8, 112.2, 72.1, 56.17, 56.12, 29.7, 14. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{22}O_4$ $(M+H)^+$: 423.1596. Found: 423.1578.

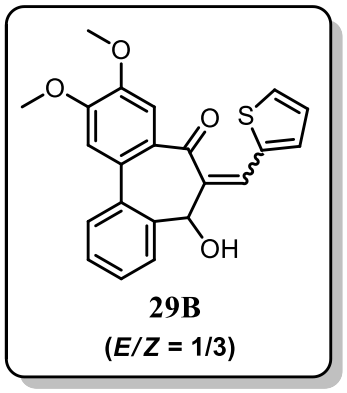


29A

(*E*/*Z* = 1/3)

7-Hydroxy-2,3-dimethoxy-6-(thiophen-2-ylmethylene)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (29B). (major isomer)

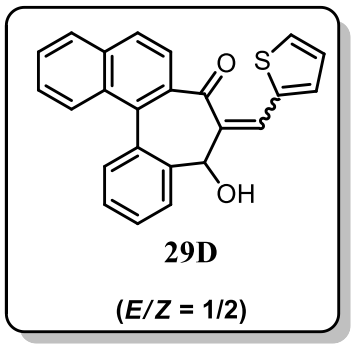
This compound was isolated as yellow oil. Following the general procedure B, 50 mg of **28B** afforded 42.5 mg of **29B** (85% yield). **IR (thin film, neat):** ν_{max}/cm^{-1} 3429, 3012, 2966, 2849, 1640, 1601, 1557, 1354, 1269, 1021, 731. **^{1}H NMR (400 MHz, $(CD_3)_2SO$):** δ 7.71 (d, J = 7.0 Hz, 1H), 7.59 (s, 1H), 7.54 (s, 1H), 7.50-7.48 (m, 2H), 7.47-7.43 (m, 2H), 7.41-7.36 (m, 1H), 7.11-7.09 (m, 1H), 6.98 (s, 1H), 5.71 (s, 1H), 4.017 (s, 3H), 4.013 (s, 3H), 2.66 (s, 1H). **^{13}C NMR (100 MHz, $(CD_3)_2SO$):** δ 190.6, 152.5, 148.8, 142.2, 140.0, 138.7, 138.4, 137.2, 136.4, 133.2, 130.7, 129.6, 129.5, 128.6, 128.2, 127.6, 112.9, 112.7, 112.4, 112.2, 56.2, 56.0. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{18}O_4S$ $(M+H)^+$: 379.1004. Found: 379.1016.



29B
(***E*/*Z*** **= 1/3)**

9-Hydroxy-8-(thiophen-2-ylmethylene)-8,9-dihydro-7*H*-benzo[6,7]cyclohepta[1,2-*a*]naphthalen-7-one (29D). (major isomer)

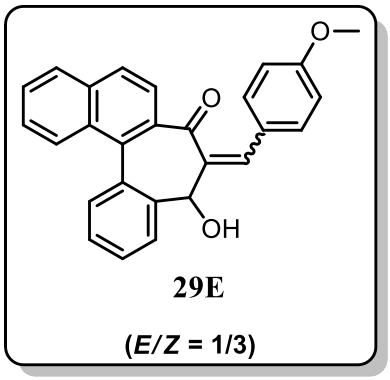
This compound was isolated as yellow oil. Following the general procedure B, 50 mg of **28D** afforded 44 mg of **29D** (88% yield). **M.P** = 136.2-137.3 °C. **IR (thin film, neat):** ν_{max}/cm^{-1} 3436, 3024, 2960, 2935, 1650, 1601, 1584, 1356, 1269, 1022, 783. **^{1}H NMR (400 MHz, $(CD_3)_2SO$):** δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 2H), 7.58 (s, 1H), 7.46-7.43 (m, 2H), 7.38-7.29 (m, 4H), 7.21-7.18 (m, 1H) ,7.00-6.98 (m,1H), 5.63 (s,1H), 5.58 (d, *J* = 2.8 Hz, 1H). **^{13}C NMR (100 MHz, $(CD_3)_2SO$):** δ 193.0, 143.3, 139.5, 138.2, 137.0, 136.7, 135.5, 134.5, 134.2, 132.0, 130.8, 130.2, 129.3, 128.9, 128.6, 128.2, 127.9, 127.7, 127.5, 127.1, 126.7, 125.1, 122.7, 70.0 **HRMS (ESI):** *m/z* calcd for $C_{24}H_{16}O_2S$ $(M+H)^+$: 369.0949. Found: 369.0934.



29D
(***E*/*Z*** **= 1/2)**

9-Hydroxy-8-(4-methoxybenzylidene)-8,9-dihydro-7H-benzo[6,7]cyclohepta[1,2-*a*]naphthalen-7-one (29E). (major isomer)

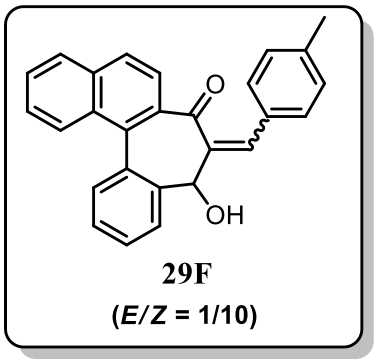
This compound was isolated as yellow oil. Following the general procedure B, 50 mg of **28E** afforded 37.5 mg of **29E** (75% yield). **IR (thin film, neat):** ν_{max}/cm^{-1} 3438, 2924, 2854, 1651, 1604, 1509, 1338, 1247, 1033, 822 **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.96-7.93 (m, 2H), 7.81-7.74 (m, 3H), 7.63-7.57 (m, 4H), 7.43 (t, *J* = 7.36 Hz, 1H), 7.33 (t, *J* = 7.36 Hz, 1H), 7.26 (t, *J* = 6.9 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 5.95 (d, *J* = 5.5 Hz, 1H), 3.90 (s, 3H), 2.32 (d, *J* = 6.4 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.4, 160.7, 141.2, 140.0, 139.5, 137.1, 136.2, 135.7, 133.9, 132.9, 131.7, 130.8, 128.69, 128.62, 128.5, 128.4, 128.1, 127.6, 127.4, 127.1, 126.9, 126.8, 126.4, 125.1, 114.3, 71.8, 55.4. **HRMS (ESI):** *m/z* calcd for $C_{27}H_{20}O_3$ $(M+H)^+$: 393.1490. Found: 393.1476.



29E
(*E*/*Z* = 1/3)

9-Hydroxy-8-(4-methylbenzylidene)-8,9-dihydro-7H-benzo[6,7]cyclohepta[1,2-*a*]naphthalen-7-one (29F). (major isomer)

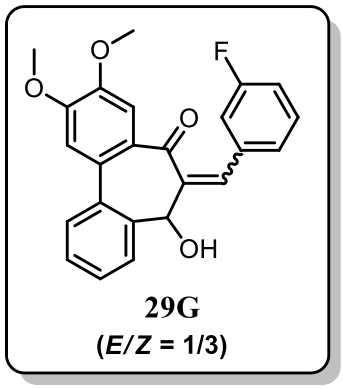
This compound was isolated as yellow oil. Following the general procedure B, 50 mg of **28F** afforded 44.5 mg of **29F** (89% yield). **IR (thin film, neat):** ν_{max}/cm^{-1} 3449, 3054, 2979, 2921, 1655, 1590, 1508, 1338, 1234, 1032, 757. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.14 (d, *J* = 8.4 Hz, 1H), 7.96-7.93 (m, 2H), 7.84 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.54-7.48 (m, 5H), 7.34-7.28 (m, 4H), 7.24 (d, *J* = 7.4 Hz, 1H), 5.94 (d, *J* = 6.6 Hz, 1H), 2.45 (s, 3H), 2.30 (d, *J* = 6.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.3, 142.1, 139.7, 139.6, 137. 0,136.4, 135.7, 134.0, 132.1, 131.7, 130.9, 130.2, 129.9, 129.5, 128.9, 128.6, 128.5, 128.4, 128.1, 127.6, 127.4, 127.4, 127.1, 126.7, 125.1, 121.7, 71.7, 21.5 **HRMS (ESI):** *m/z* calcd for $C_{27}H_{20}O_2$ $(M+H)^+$: 377.1541. Found: 377.1528.



29F
(*E*/*Z* = 1/10)

6-(3-Fluorobenzylidene)-7-hydroxy-2,3-dimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (29G). (major isomer)

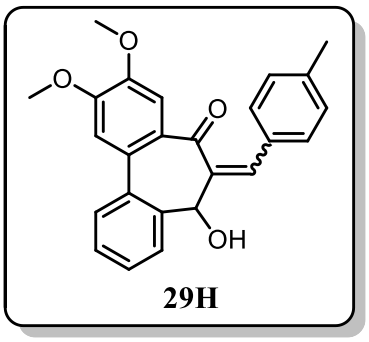
This compound was isolated as yellow oil. Following the general procedure B, 50 mg of **28G** afforded 43 mg of **29G** (86% yield). **IR (thin film, neat):** ν_{max}/cm^{-1} 3436, 3065, 2966, 2936, 1583, 1651, 1518, 1357, 1267, 1022, 754. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.82 (s, 1H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.47-7.44 (m, 3H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.23-7.10 (m, 5H), 7.00 (s, 1H), 5.86 (s, 1H), 4.02 (s, .3H), 4.00 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.36, 162.7 (d, *J* = 245.7 Hz, 1C), 152.5, 148.8, 142.6, 138.4, 138.1, 137.3 (d, *J* = 7.9 Hz, 1C), 137.1, 132.4 (d, *J* = 11.4 Hz, 1C), 131.0 (d, *J* = 11.7 Hz, 1C), 130.1 (d, *J* = 8.4 Hz, 1C), 129.3, 128.2 (2C), 125.0 (d, *J* = 2.8 Hz, 1C), 116.0 (d, *J* = 21.8 Hz, 1C), 115.7 (d, *J* = 21.0 Hz, 1C), 112.7, 112.2, 96.1, 71.6, 56.1, 56.0. **^{19}F NMR (376.5 MHz, $CDCl_3$):** δ -112.2. **HRMS (ESI):** *m/z* calcd for $C_{24}H_{19}FO_4$ $(M+H)^+$: 391.1345. Found: 391.1328.



29G
(*E*/*Z* = 1/3)

7-Hydroxy-2,3-dimethoxy-6-(4-methylbenzylidene)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (29H). (major isomer)

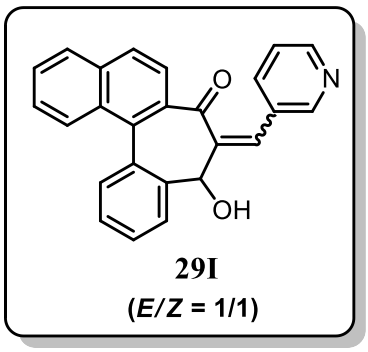
This compound was isolated as yellow oil. Following the general procedure B, 50 mg of **28H** afforded 41.5 mg of **29H** (83% yield). **IR (thin film, neat):** ν_{max}/cm^{-1} 3495, 3005, 2956, 2926, 1651, 1601, 1585, 1356, 1268, 1022, 782. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.44-7.41 (m, 2H), 7.38 (d, *J* = 7.7 Hz, 2H), 7.32-7.27 (m, 3H), 7.22 (d, *J* = 6.8 Hz, 1H), 7.60 (s, 1H), 5.96 (s, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 2.43 (s, 3H), 2.07 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 191.1, 152.3, 148.7, 141.2, 139.2, 138.8, 137.1, 132.7, 132.4, 132.1, 131.4, 130.8, 129.9, 129.5, 129.3, 129.1, 128.6, 128.1, 127.6, 112.7, 112.1, 71.6, 56.1, 56.0, 21.4. **HRMS (ESI):** *m/z* calcd for $C_{25}H_{22}O_4$ $(M+H)^+$: 387.1596. Found: 387.1579.



29H

9-Hydroxy-8-(pyridin-3-ylmethylene)-8,9-dihydro-7*H*-benzo[6,7]cyclohepta[1,2-*a*]naphthalen-7-one (29I). (major isomer)

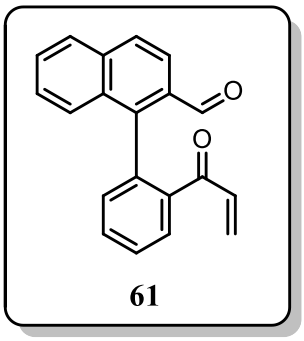
This compound was isolated as yellow oil. Following the general procedure B, 50 mg of **28I** afforded 44 mg of **29I** (88% yield). **IR (thin film, neat):** ν_{max}/cm^{-1} 2928, 2859, 1668, 1604, 1467, 1279, 761. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.77 (s, 1H), 8.60 (d, *J* = 4.6 Hz, 1H), 8.12-8.08 (m, 1H), 7.94-7.91 (m, 3H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.52-7.48 (m, 3H), 7.44-7.40 (m, 2H), 7.32 (d, *J* = 6.0 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 5.76 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.1, 149.4, 144.6, 139.1, 137.1, 136.7, 136.5, 136.0, 135.9, 134.8, 134.2, 132.3, 129.2, 128.7, 128.6, 128.48, 128.44, 128.3, 127.4, 127.7, 127.1, 126.9, 125.0, 122.2, 71.4. **HRMS (ESI):** *m/z* calcd for $C_{25}H_{17}NO_2$ $(M+H)^+$: 364.1337. Found: 364.1338



29I
(*E*/*Z* = 1/1)

1-(2-Acryloylphenyl)-2-naphthaldehyde (61).

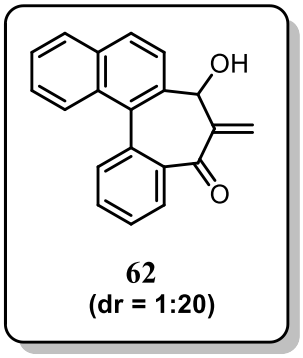
This compound was isolated as yellow oil following the general procedure J. (82% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ. 9.87, (s, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.96-7.91 (m, 2H), 7.84-7.82 (m, 1H), 7.69-7.66 (m, 2H), 7.62-7.58 (m, 1H), 7.47-7.43 (m, 3H), 6.45-6.38 (m, 1H), 6.01 (dd, *J* = 1.2 Hz, 17.3 Hz, 1H), 6.01 (dd, *J* = 1.2 Hz, 10.5 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.9, 191.9, 144.3, 139.8, 135.9, 134.88, 134.80, 132.5, 132.4, 131.4 (2C), 130.8, 128.77, 128.73, 128.6, 128.5, 128.3, 127.1, 127.0, 122.1.



61

7-Hydroxy-8-methylene-7*H*-benzo[6,7]cyclohepta[1,2-*a*]naphthalen-9(8*H*)-one (62).

This compound was isolated as white semi-solid following the general procedure J. (85% yield). **^{1}H NMR (400 MHz, $(CD_3)_2SO$):** δ 8.05 (d, *J* = 8.6 Hz, 1H), 8.00-7.98 (m, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.80-7.76 (m, 2H), 7.70 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.66-7.64 (m, 1H), 7.62-7.59 (m,1H), 7.70 (dt, *J* = 7.1 Hz, 1.8 Hz, 2H), 6.34 (d, *J* = 4.3 Hz, 1H), 6.07 (t, *J* = 1.7 Hz, 1H), 5.78 (d, *J* = 1.8 Hz, 1H), 5.54 (d, *J* = 4.3 Hz, 1H). **^{13}C NMR (100 MHz, $(CD_3)_2SO$):** δ 192.9, 152.4, 139.8, 138.3, 134.3, 133.5, 121.0, 131.7, 131.1, 129.64, 129.61,

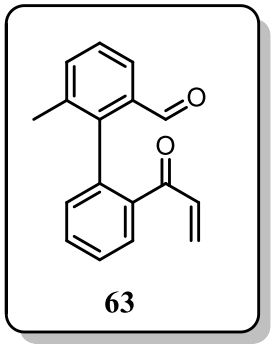


62
(dr = 1:20)

129.07, 129.05, 128.8.

2'-Acryloyl-6-methyl-[1,1'-biphenyl]-2-carbaldehyde (63).

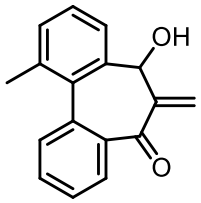
This compound was isolated as yellow oil following the general procedure J. (85% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ. 9.69 (s, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.62-7.52 (m, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.41-7.38 (m, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 6.57-6.51 (m, 1H), 6.10 (d, *J* = 17.3 Hz, 1H), 5.81 (d, *J* = 10.5 Hz, 1H), 2.04 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.1, 192.0, 143.3, 138.5, 137.3, 136.6, 135.2, 135.1, 134.3, 131.3, 131.1, 131.0, 128.7, 127.9, 127.8, 125.2, 19.9.



63

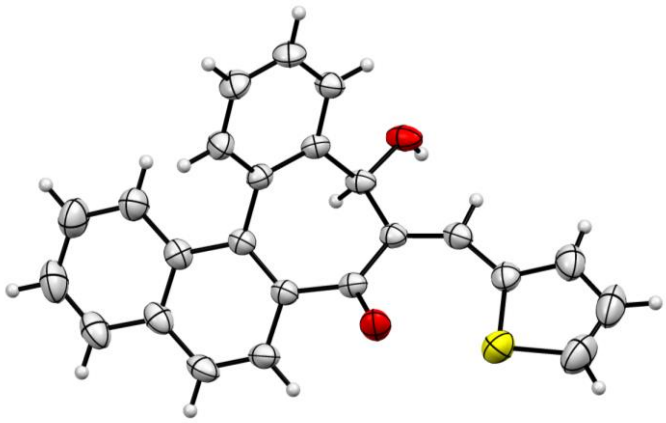
7-Hydroxy-11-methyl-6-methylene-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (64).

This compound was isolated as white semi-solid following the general scheme 16 (88% yield). **^{1}H NMR (400 MHz, $(CD_3)_2SO$):** δ 7.66 (t, *J* = 7.6 Hz, 1H), 7.59-7.48 (m, 4H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.13 (s, 1H), 6.05 (s, 1H), 5.74 (s, 1H), 5.32 (s, 1H), 2.22 (s, 3H). **^{13}C NMR (100 MHz, $(CD_3)_2SO$):** δ 193.1, 152.2, 141.2, 139.3, 135.9, 135.4, 133.2, 131.6, 131.3, 130.4, 128.7, 128.6, 128.3, 120.0, 118.5, 68.8, 21.1.



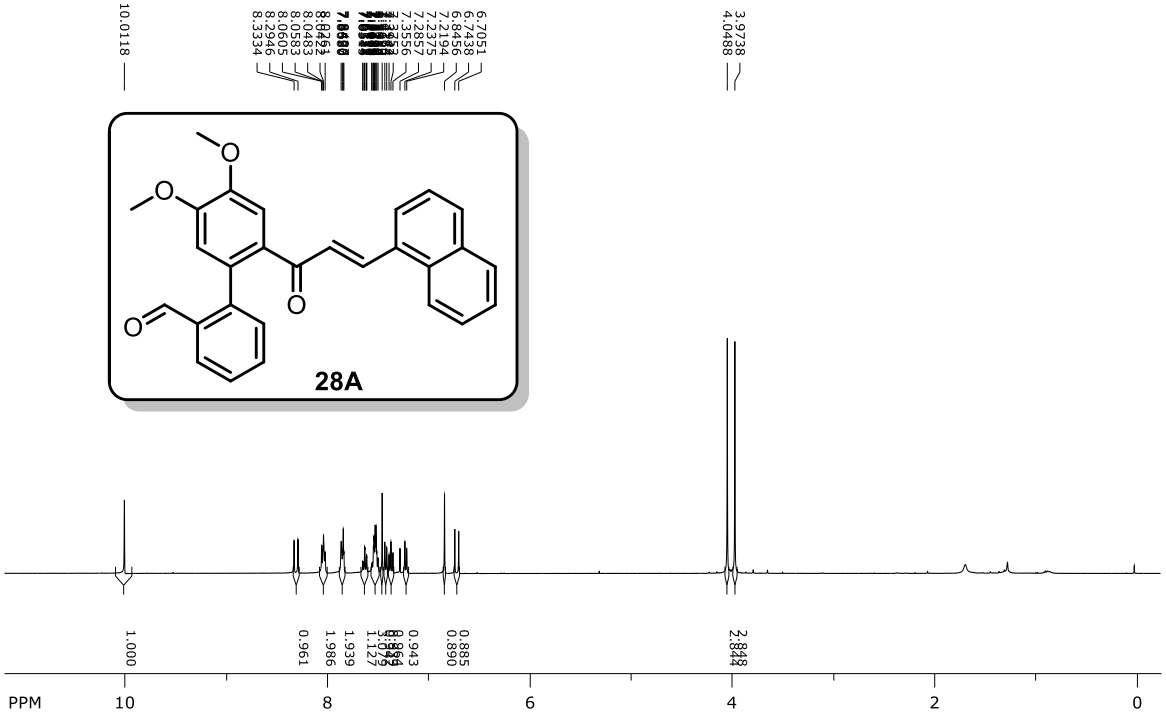
64
(dr = 1:2)

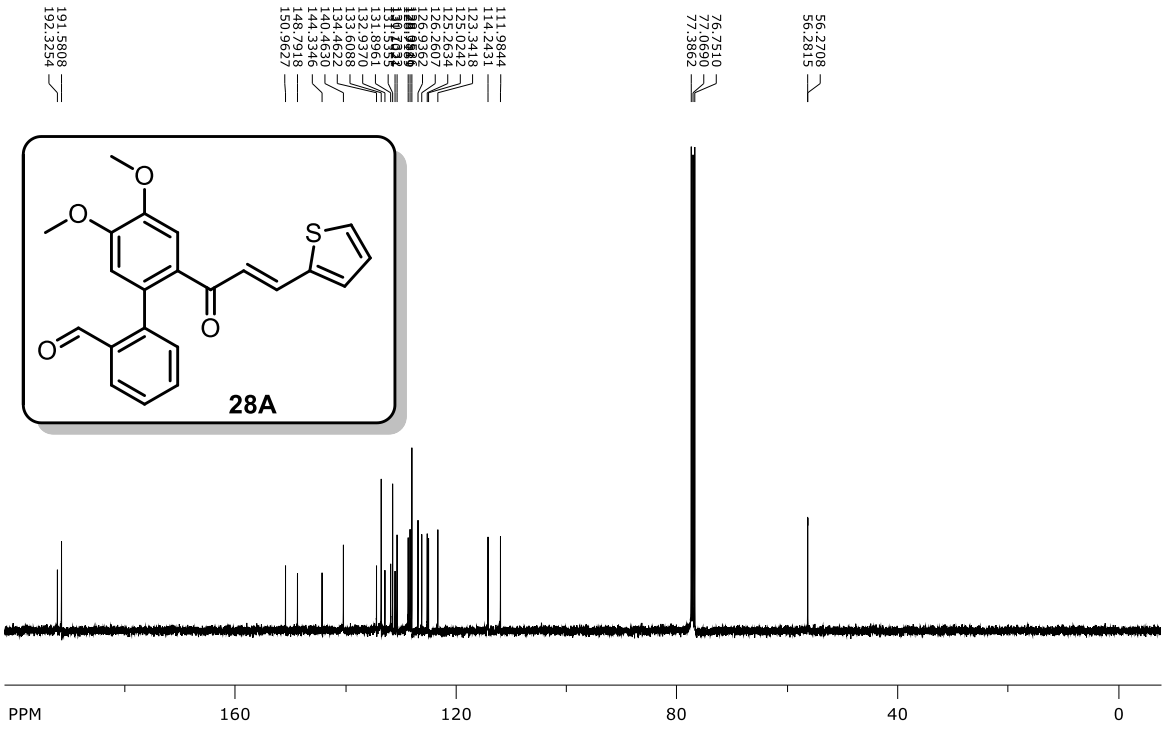
Crystal structure of 29D : Structure of the 9-hydroxy-8-(thiophen-2-ylmethylene)-8,9-dihydro-7H-benzo[6,7]cyclohepta[1,2-a]naphthalen-7-one (**29D)** was confirmed by single crystal X-ray diffraction analysis.

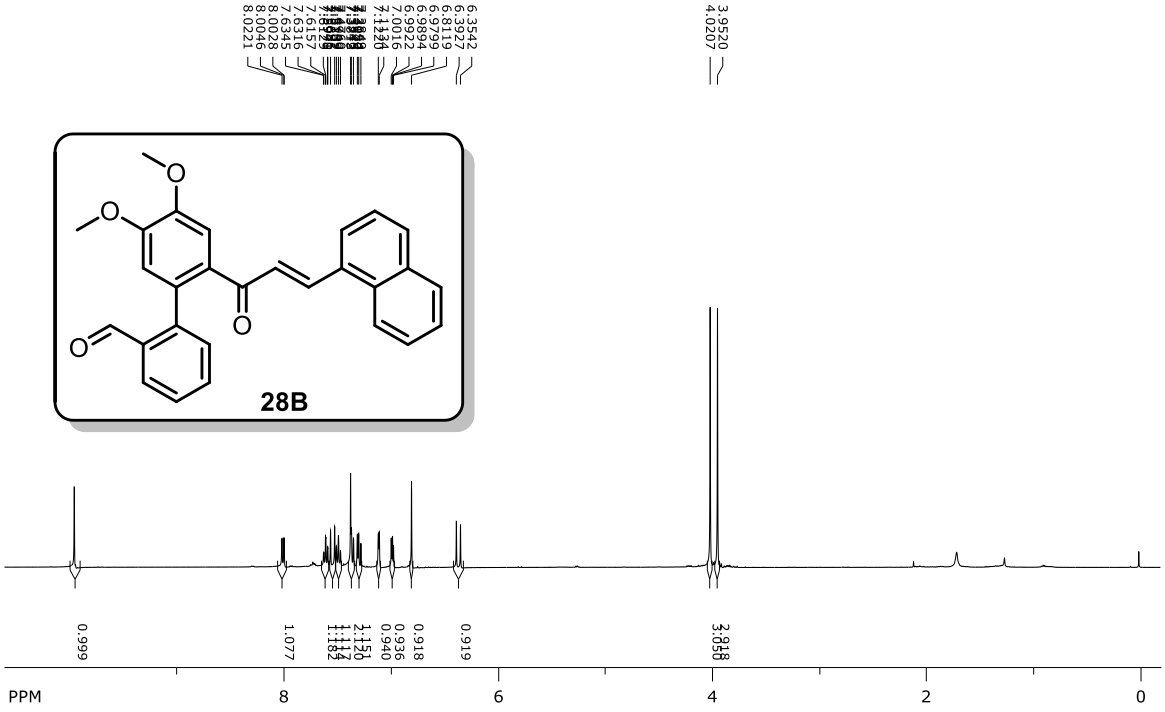


Copies of ^{1}H and ^{13}C-NMR spectra of all the new compounds reported in this study

(In general, in a ^{1}H NMR spectrum recorded in $CDCl_3$, a peak at around δ 1.6 refers to moisture in the solvent/sample and a peak at about δ 1.2 refers to oil/grease present in the sample. In a ^{13}C NMR spectrum recorded in $CDCl_3$, a peak at about δ 29.7 usually represents oil/grease)






28B
PPM
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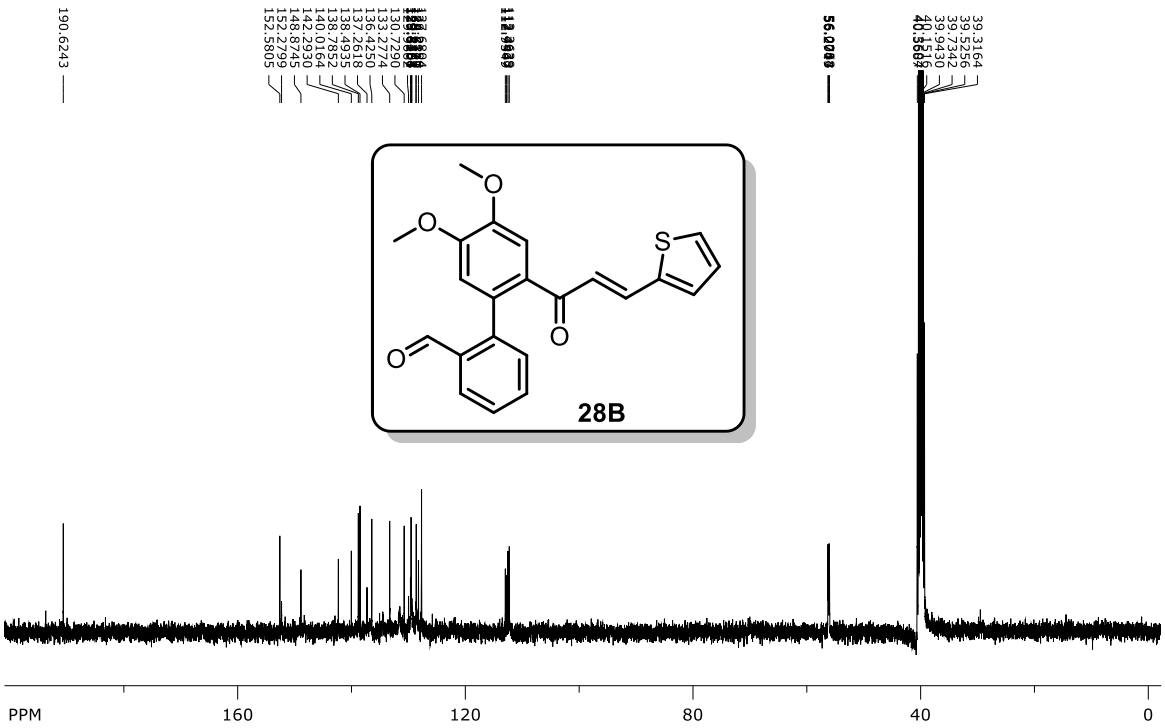
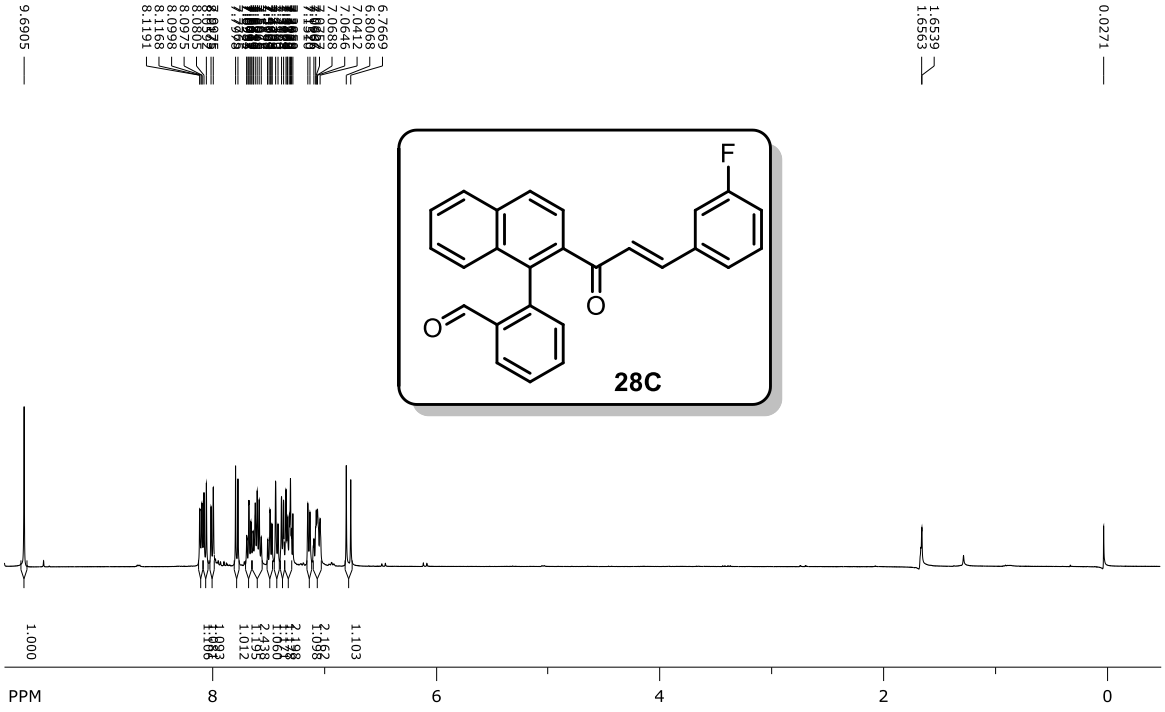
6
4
2
0


28B
PPM
160
120
80
40
0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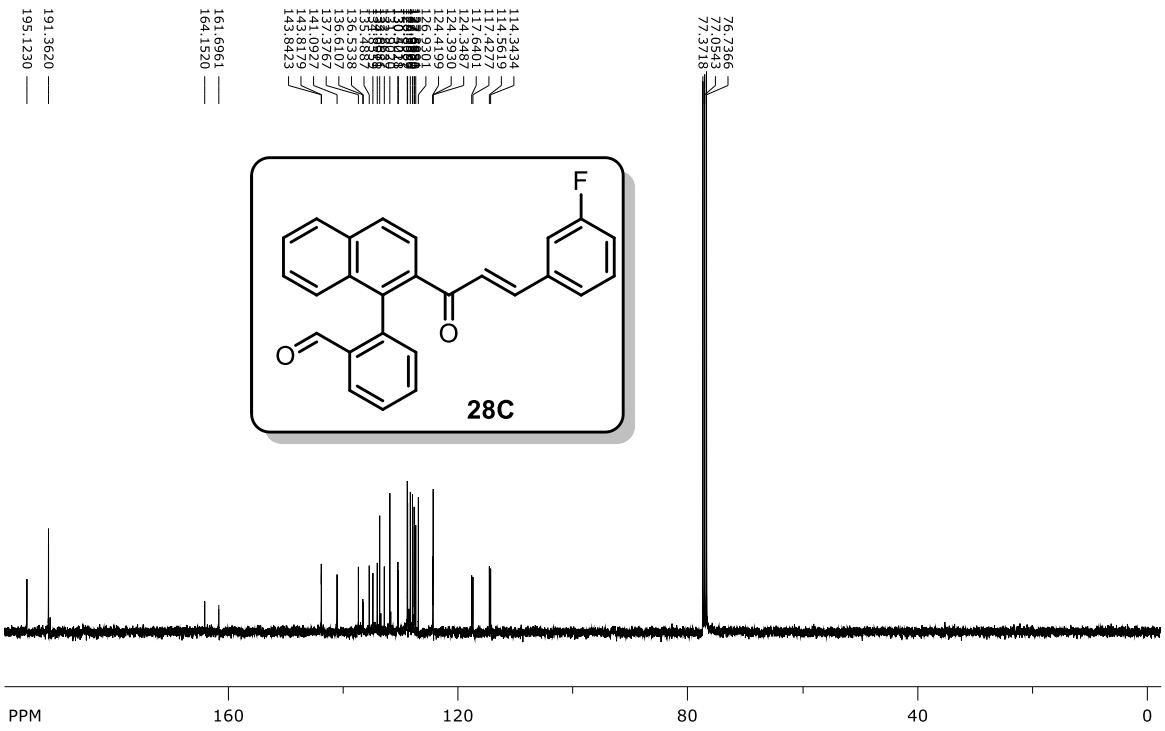
1.6563
0.0271
F
O
O
28C
1.000
1.103
PPM
8
6
4
2
0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O
28C
PPM
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120
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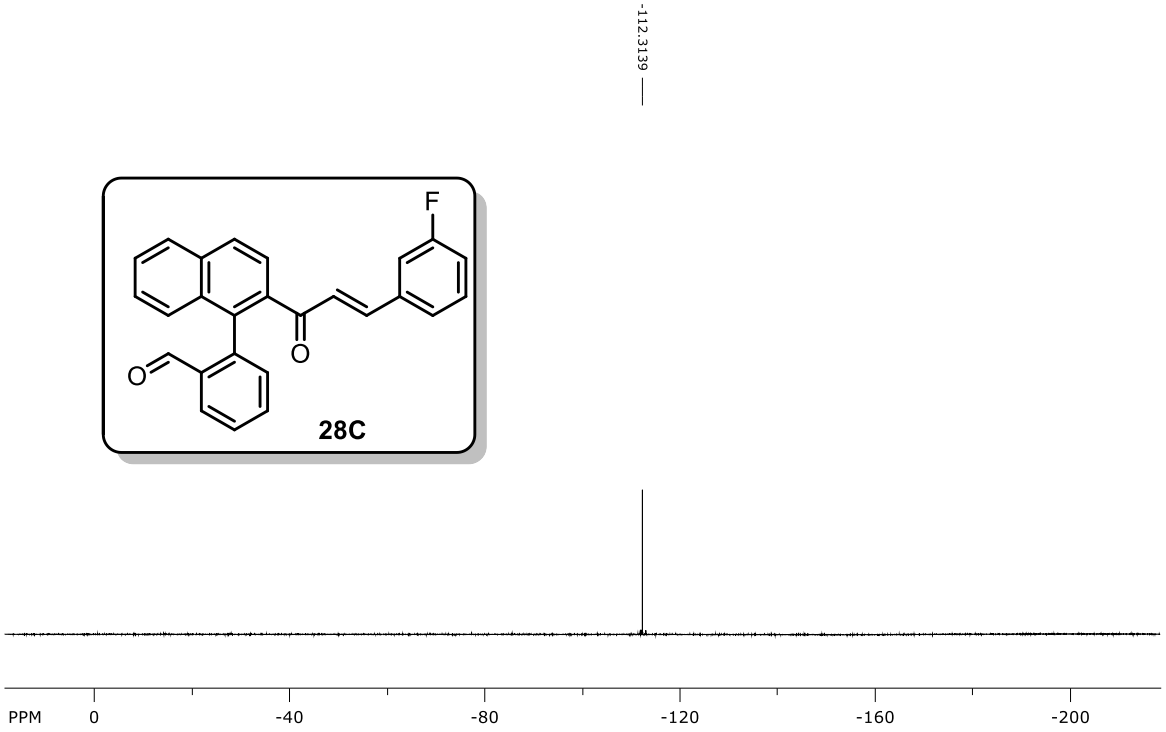
40
0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PPM
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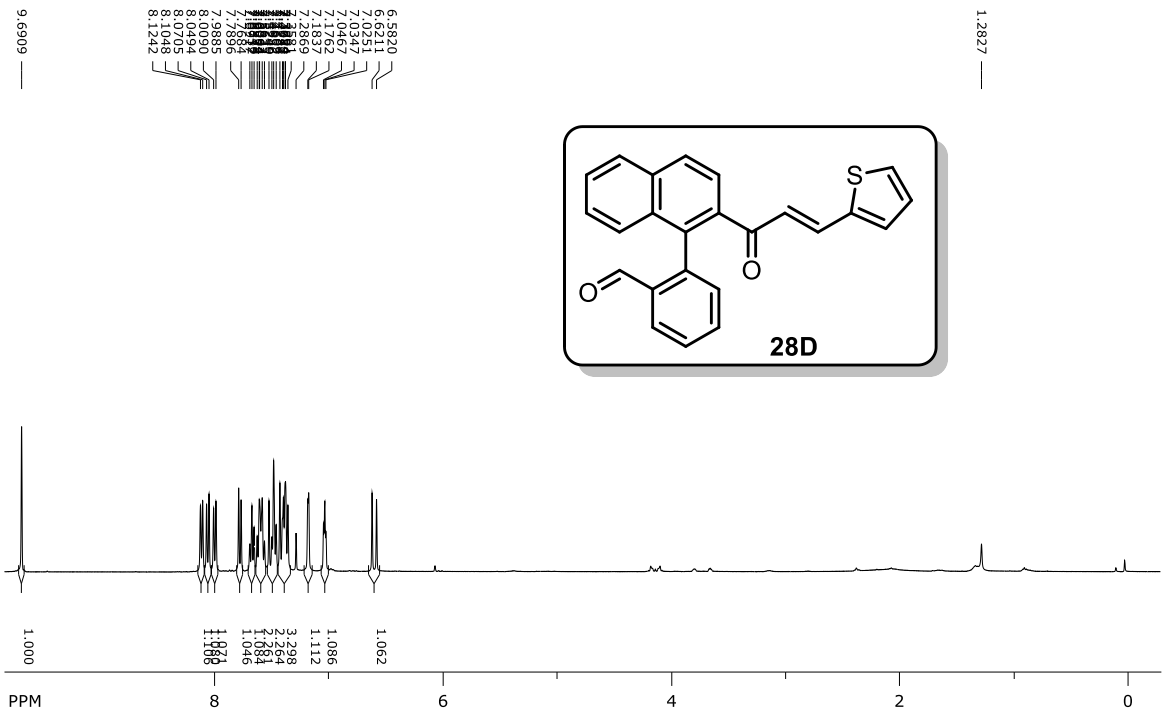
-160
-200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7.0467
7.0347
6.6211
6.5820
1.2827
S
O
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1.112
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1.046
1.062
PPM
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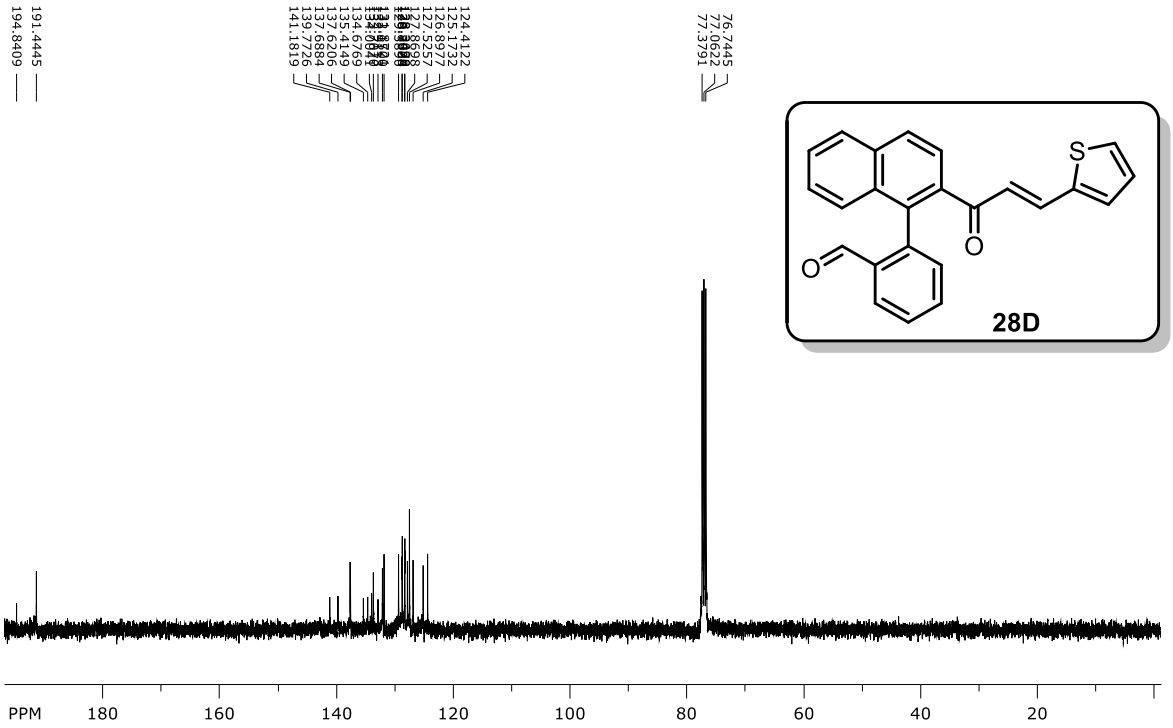
4
2
0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127.5257
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137.6206
135.4149
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139.7726
76.7445
77.0622
77.3791
S
O
O
28D
PPM
180
160
140
120
100
80
60
40
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9.693
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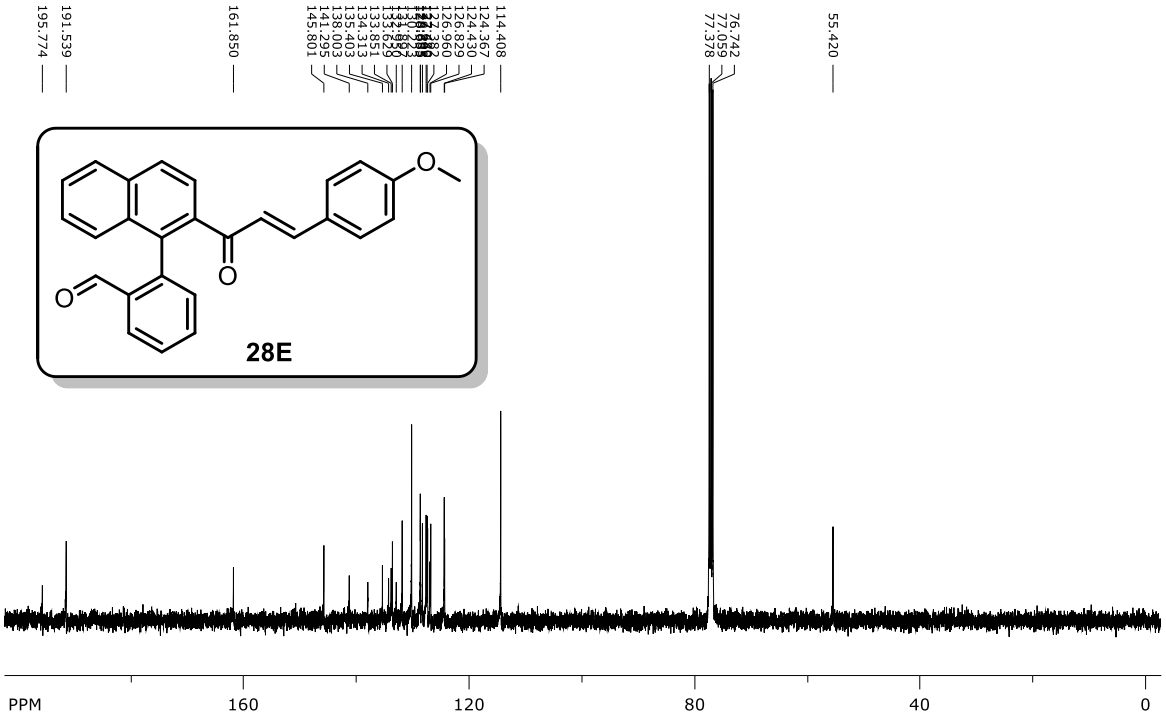
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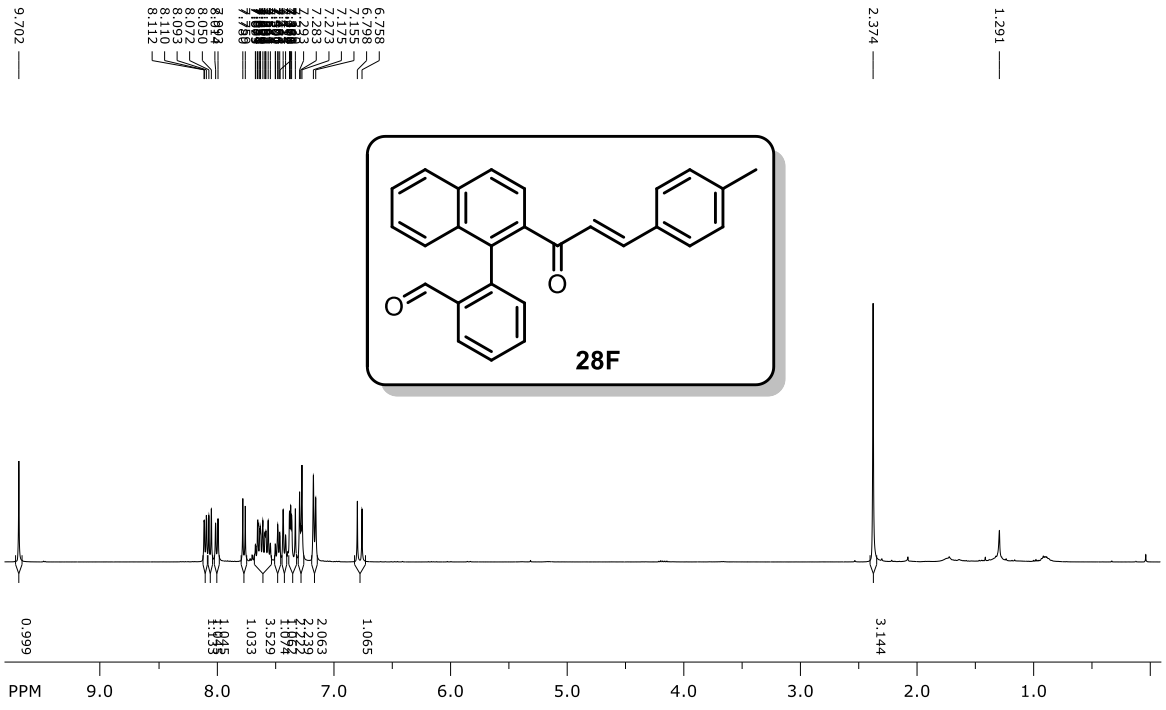
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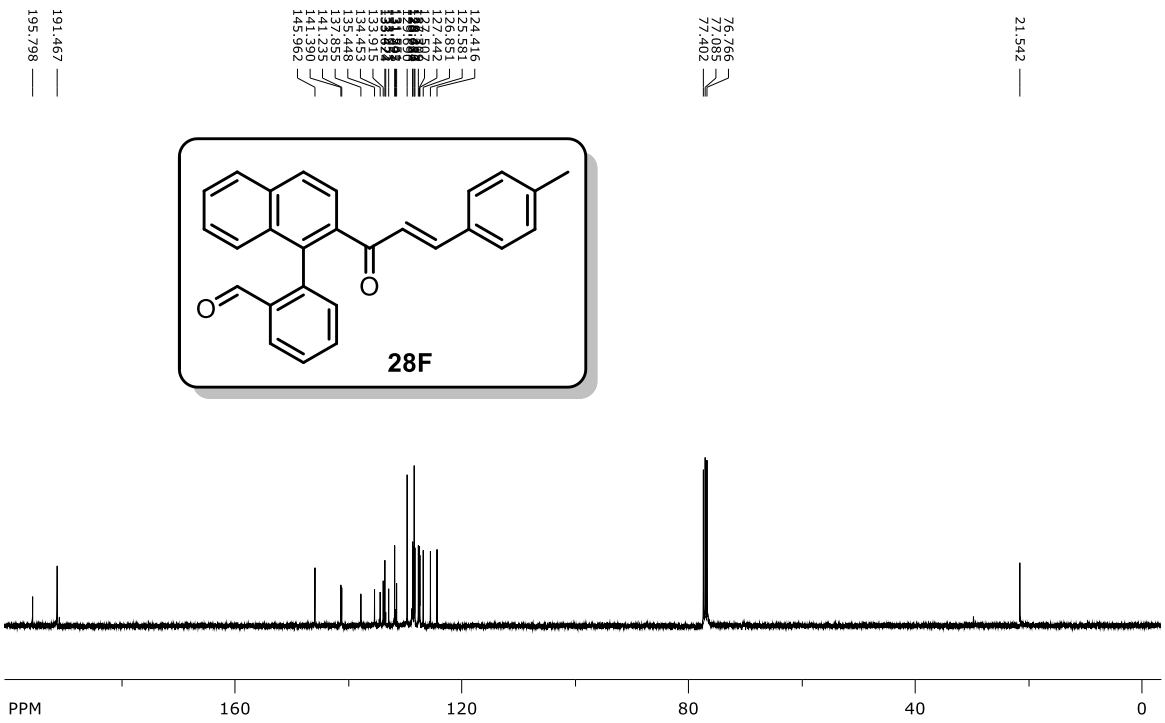
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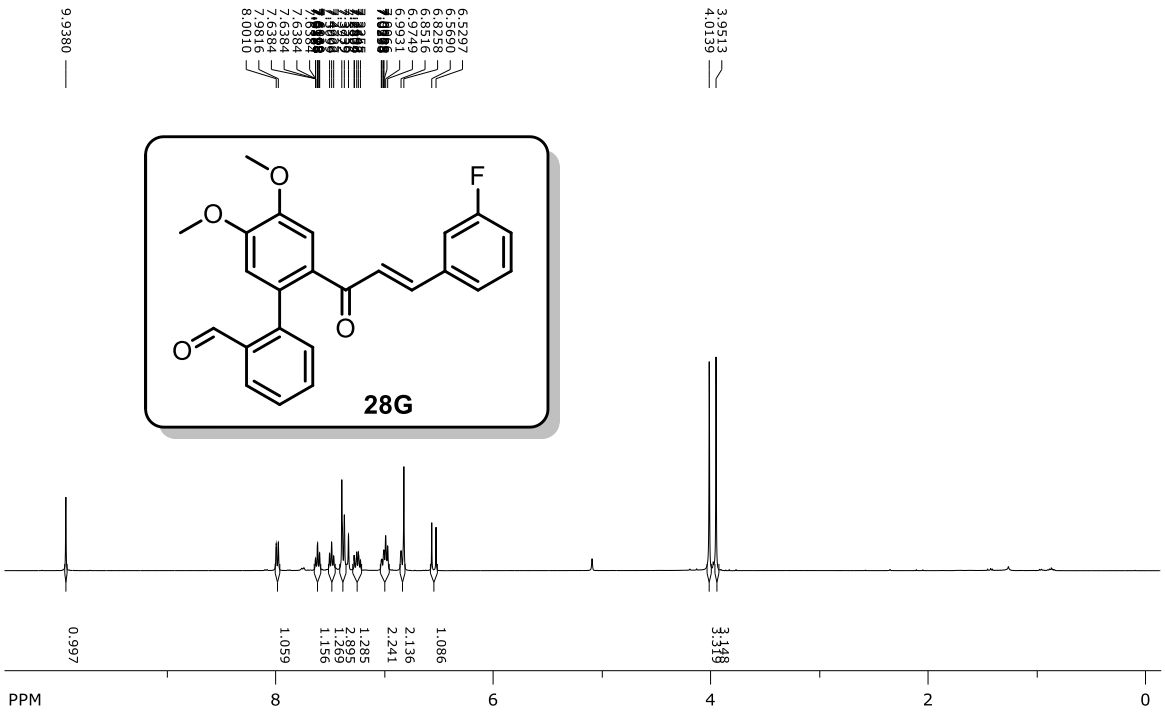
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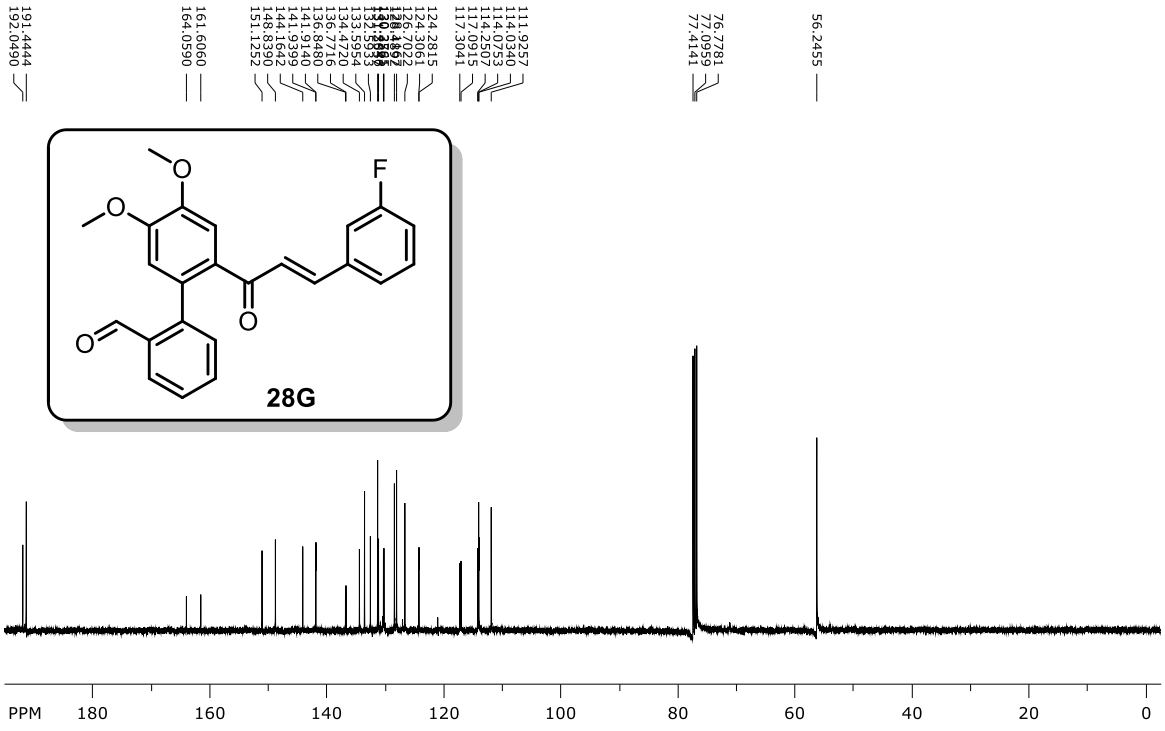
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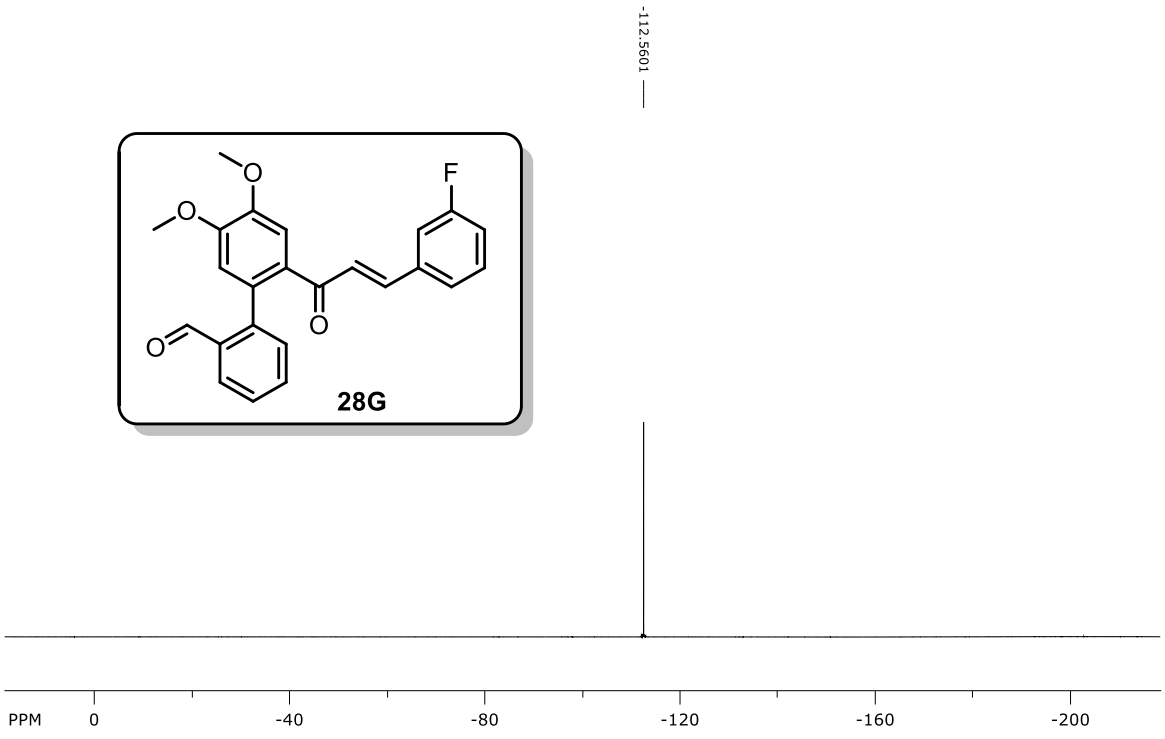
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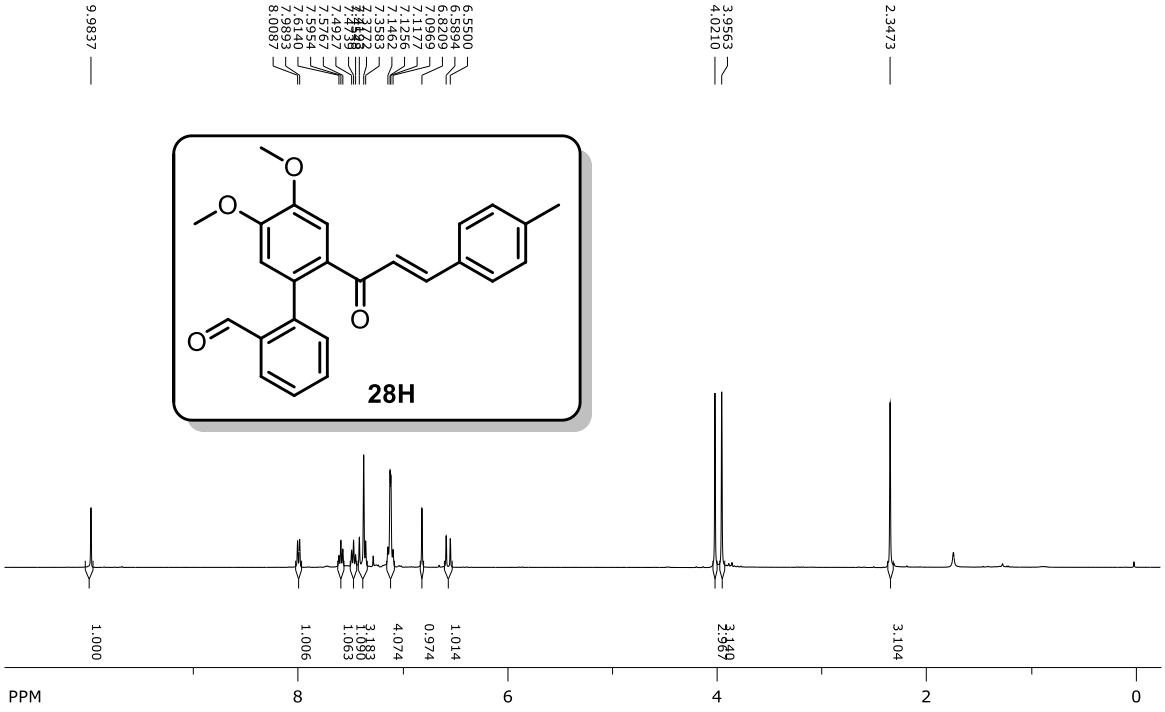
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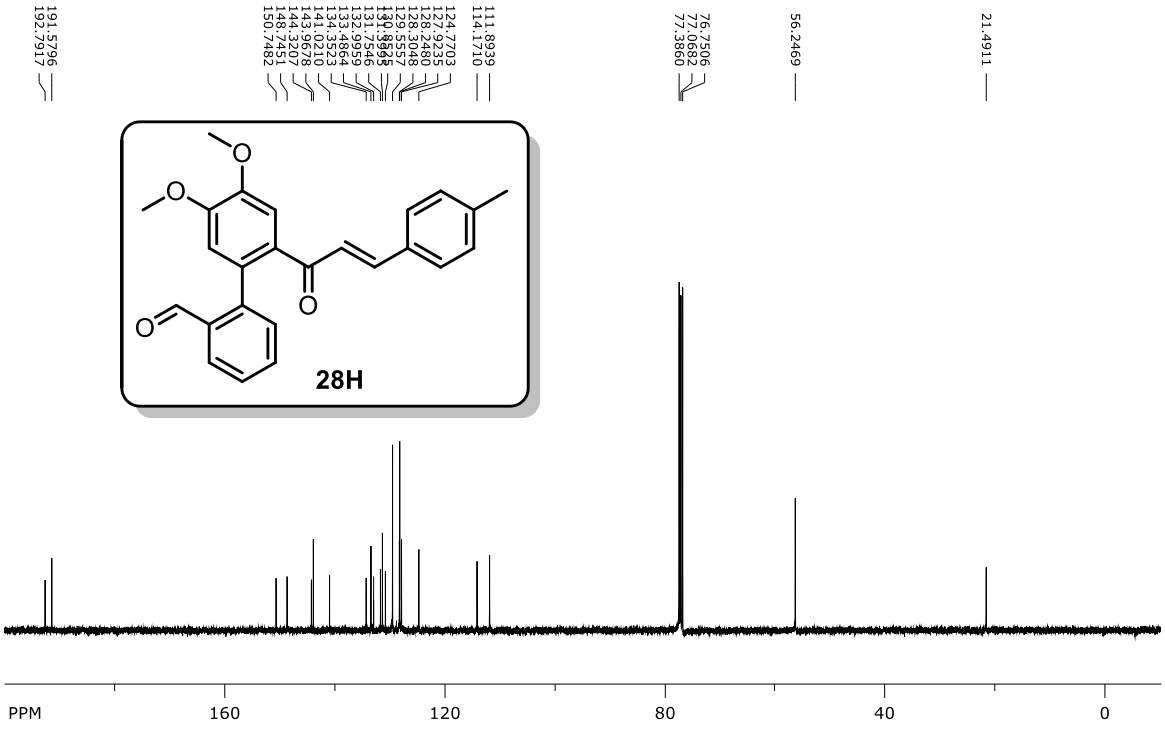
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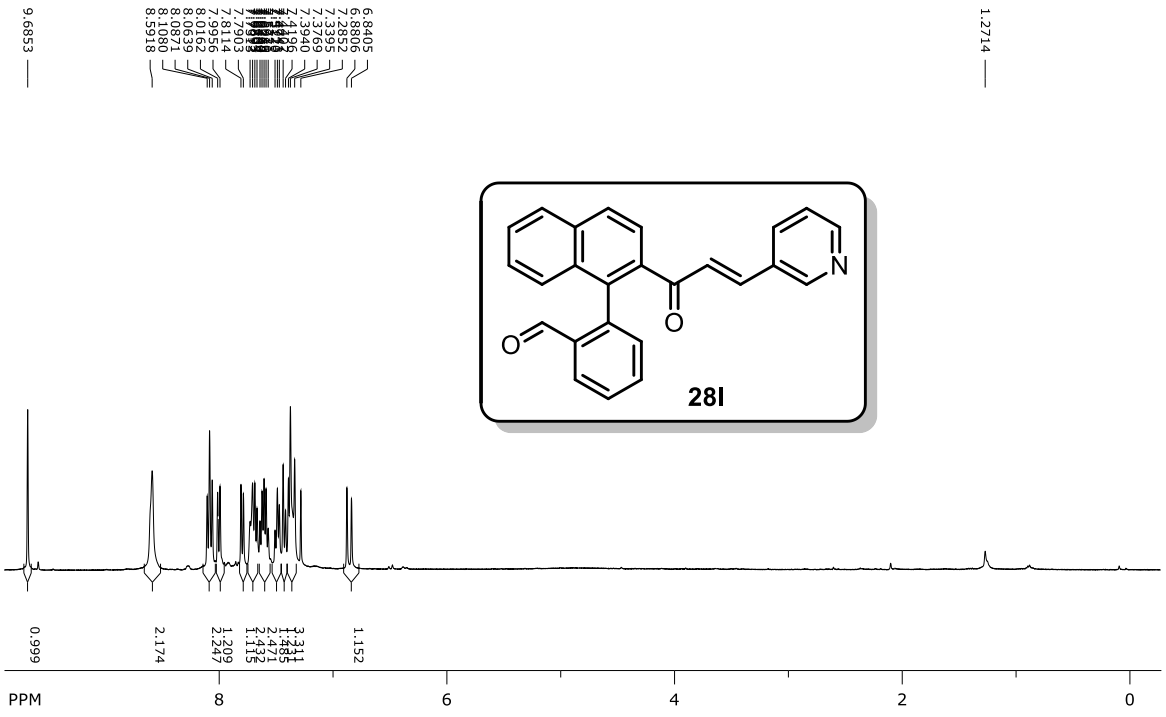
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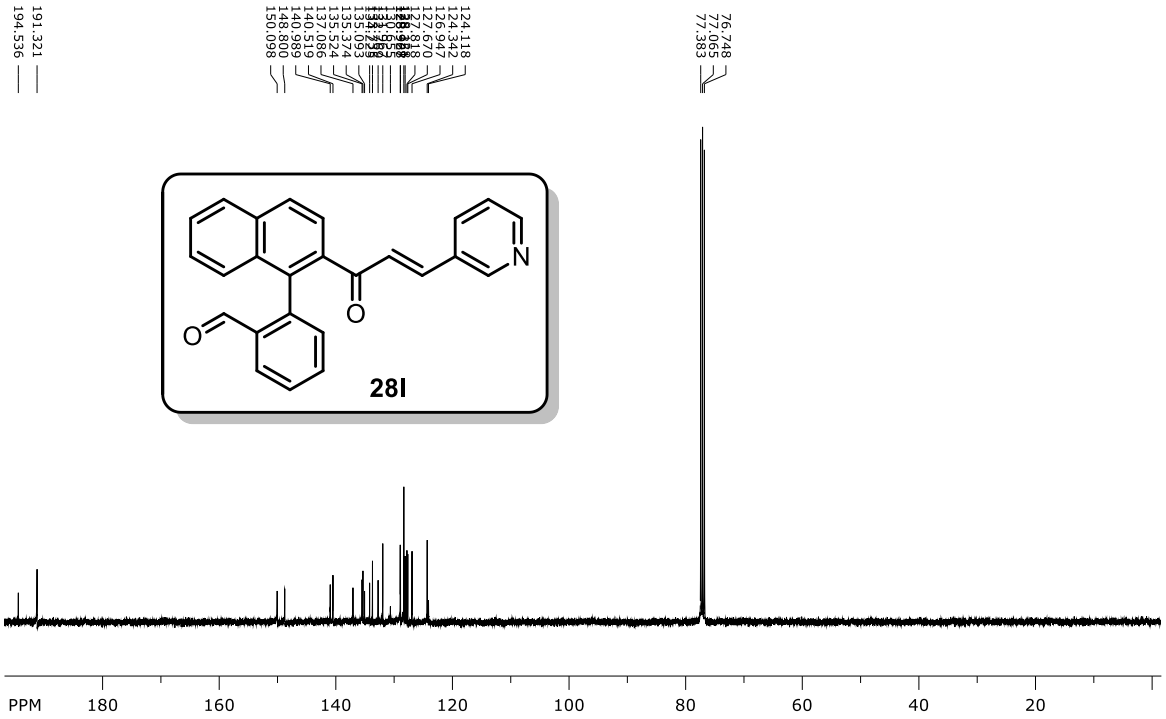
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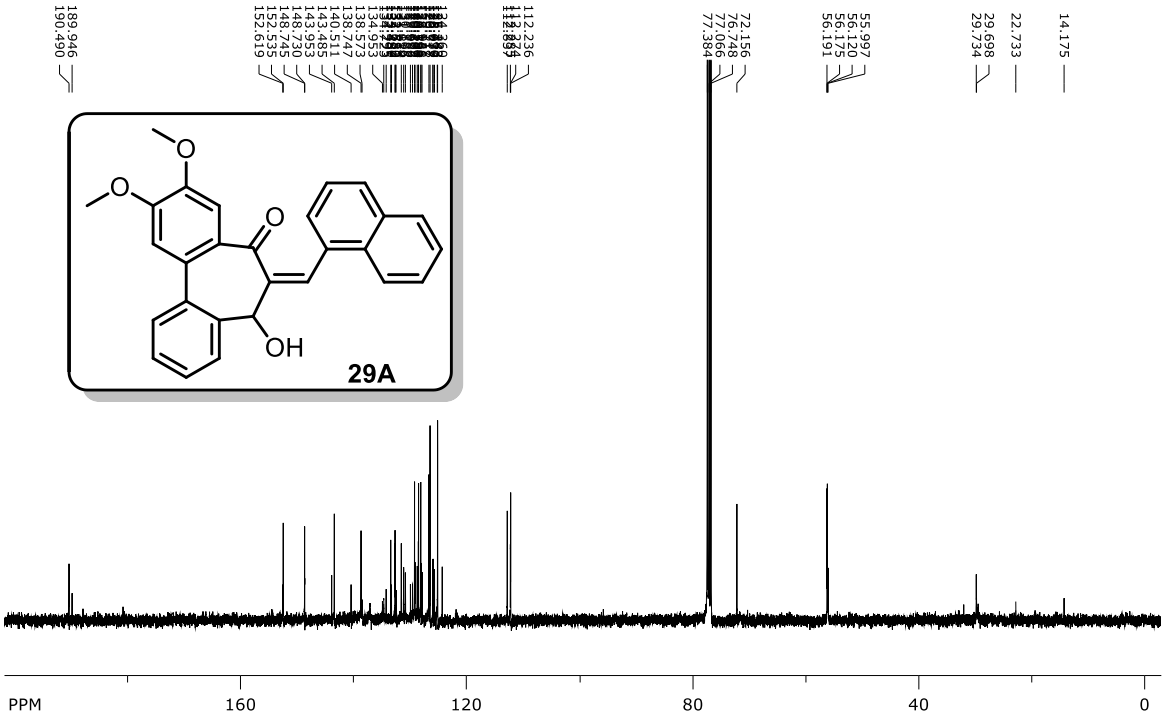
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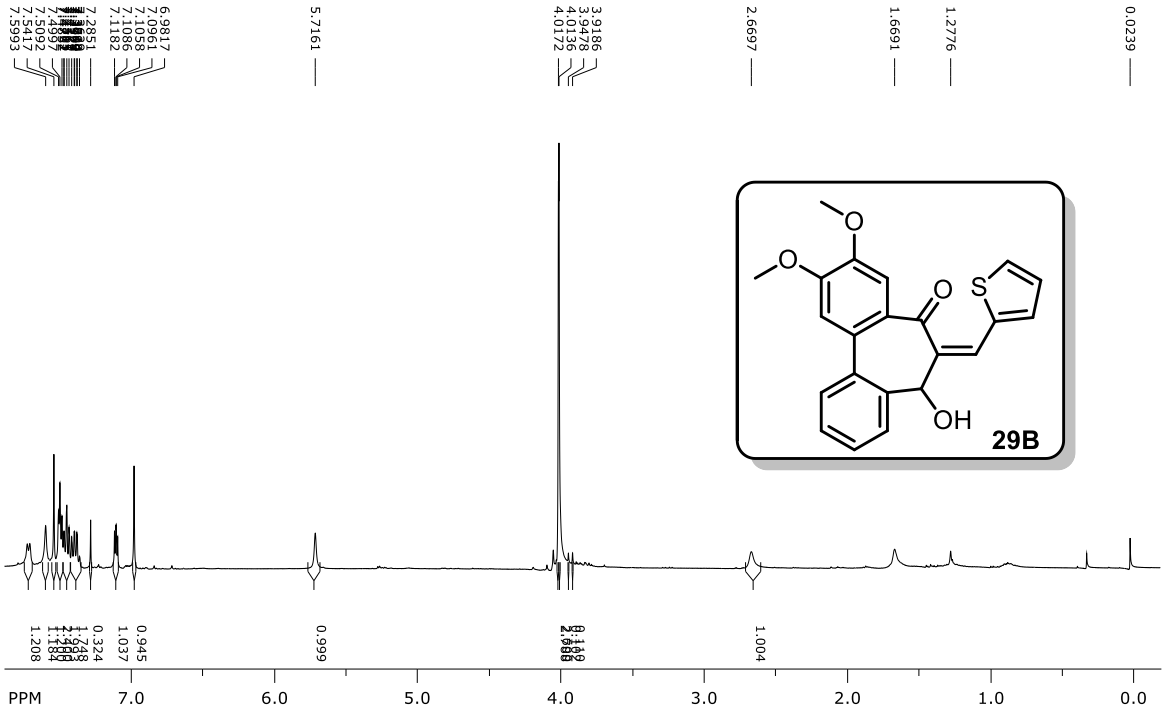
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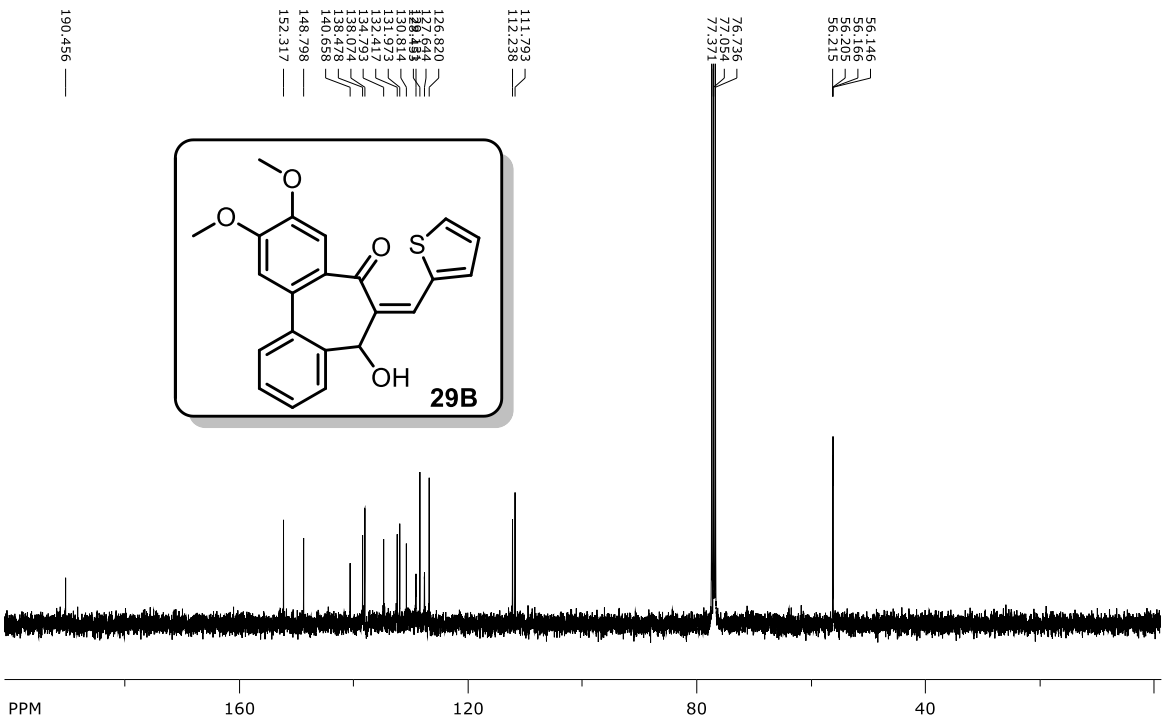
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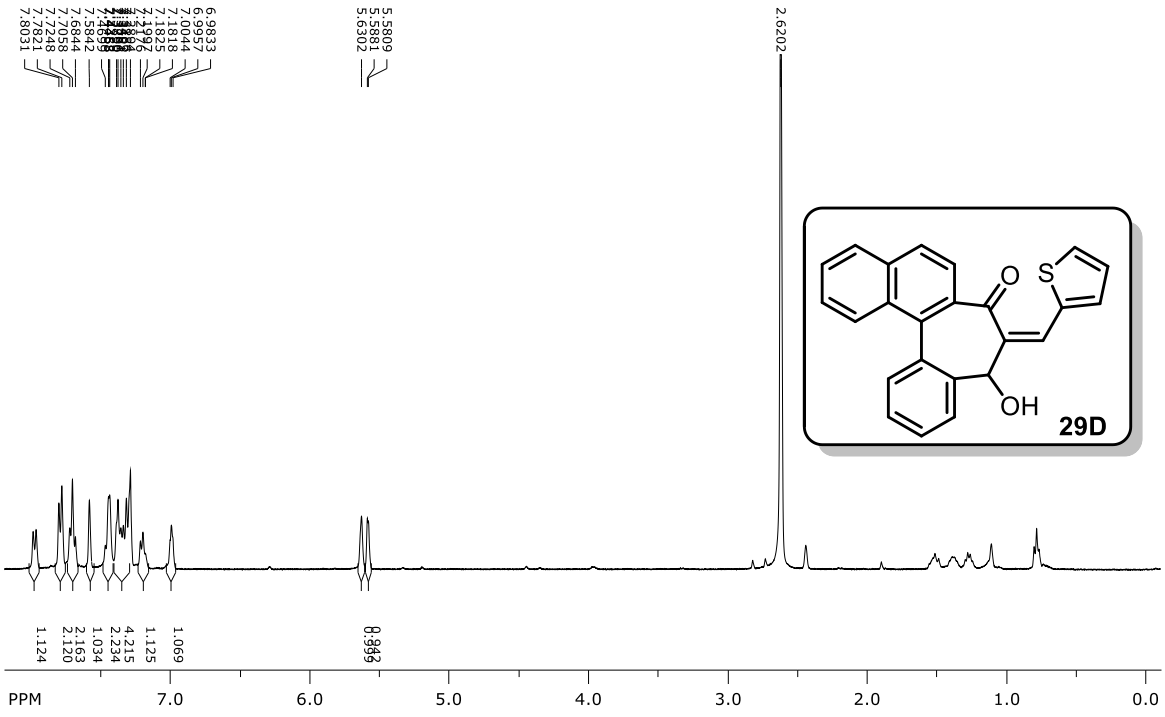
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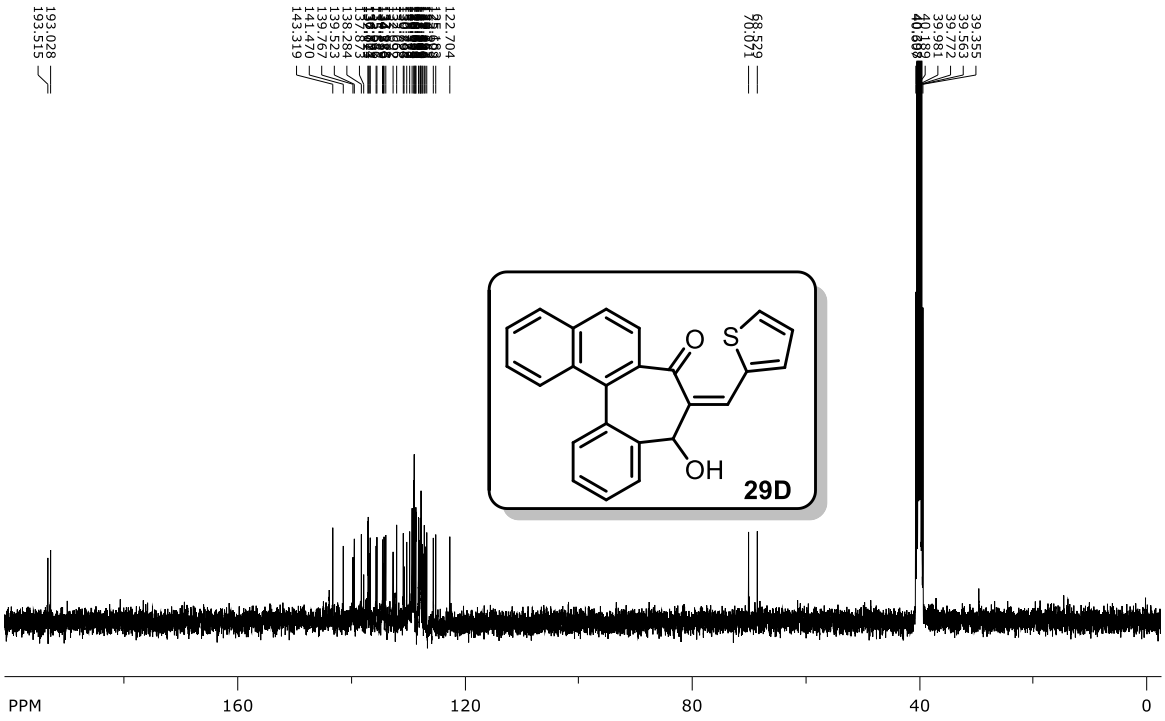
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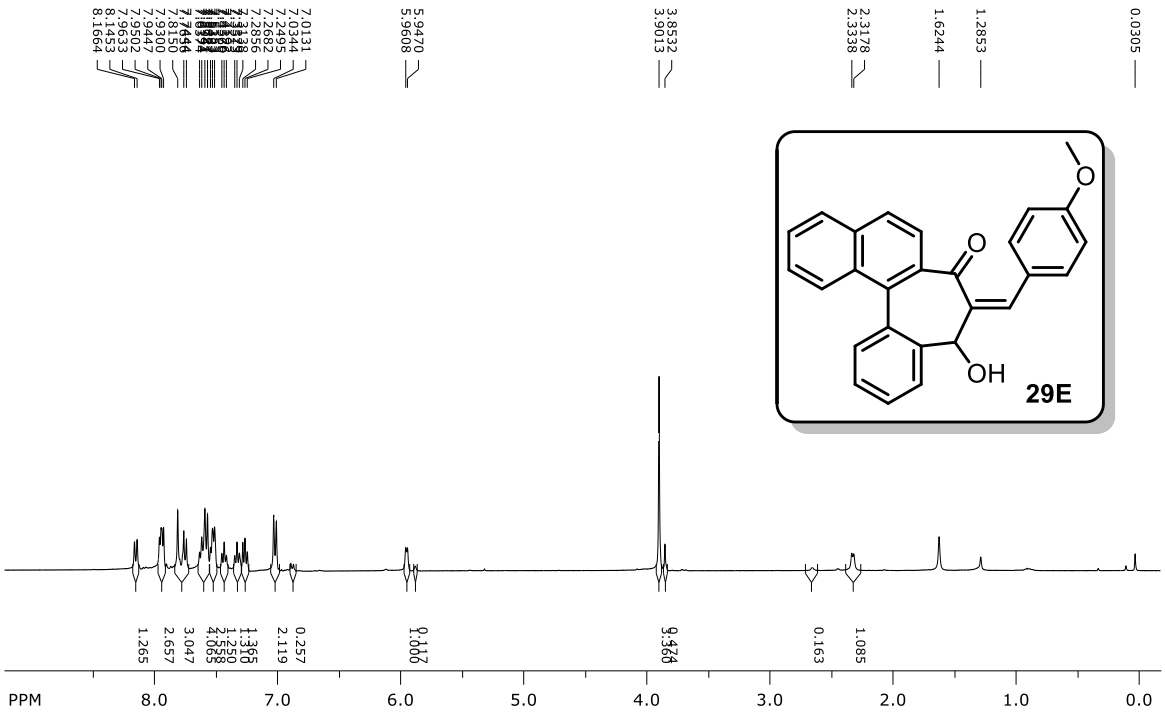
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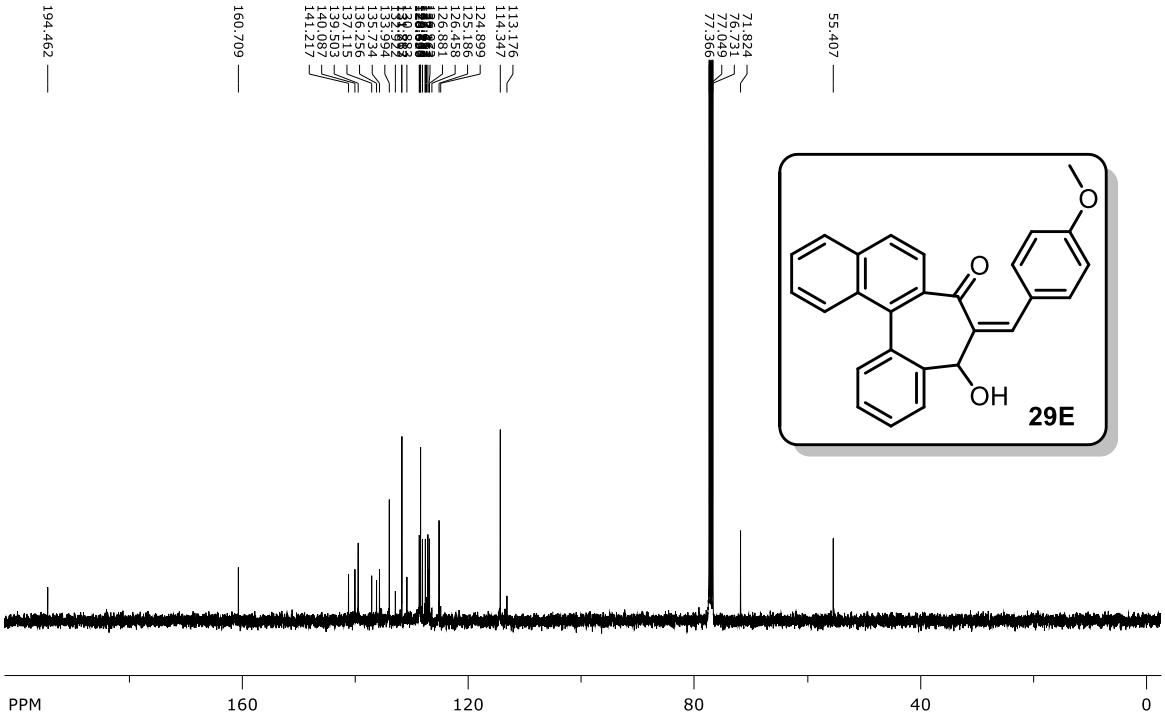
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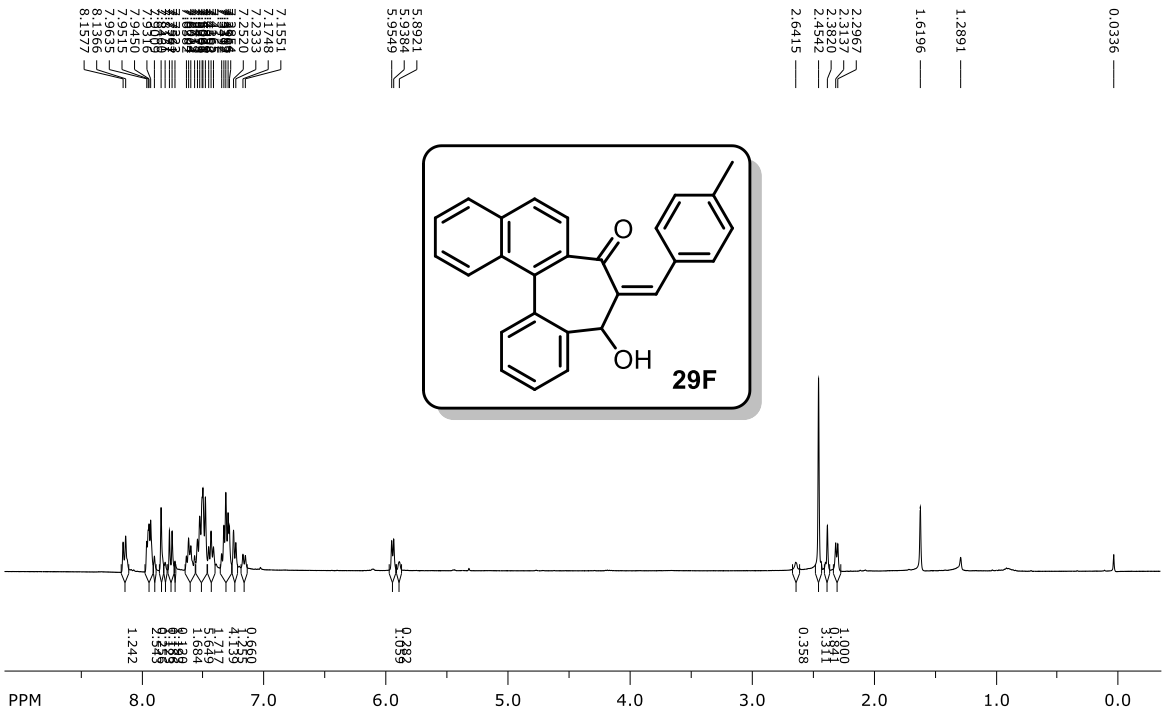
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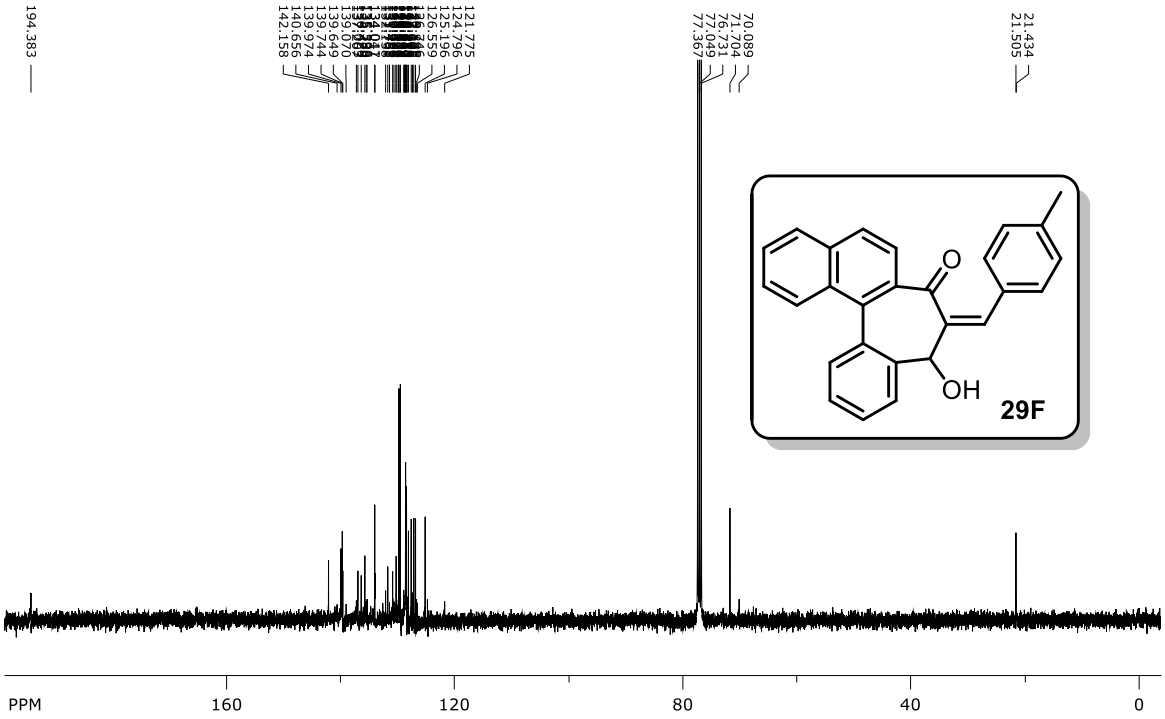
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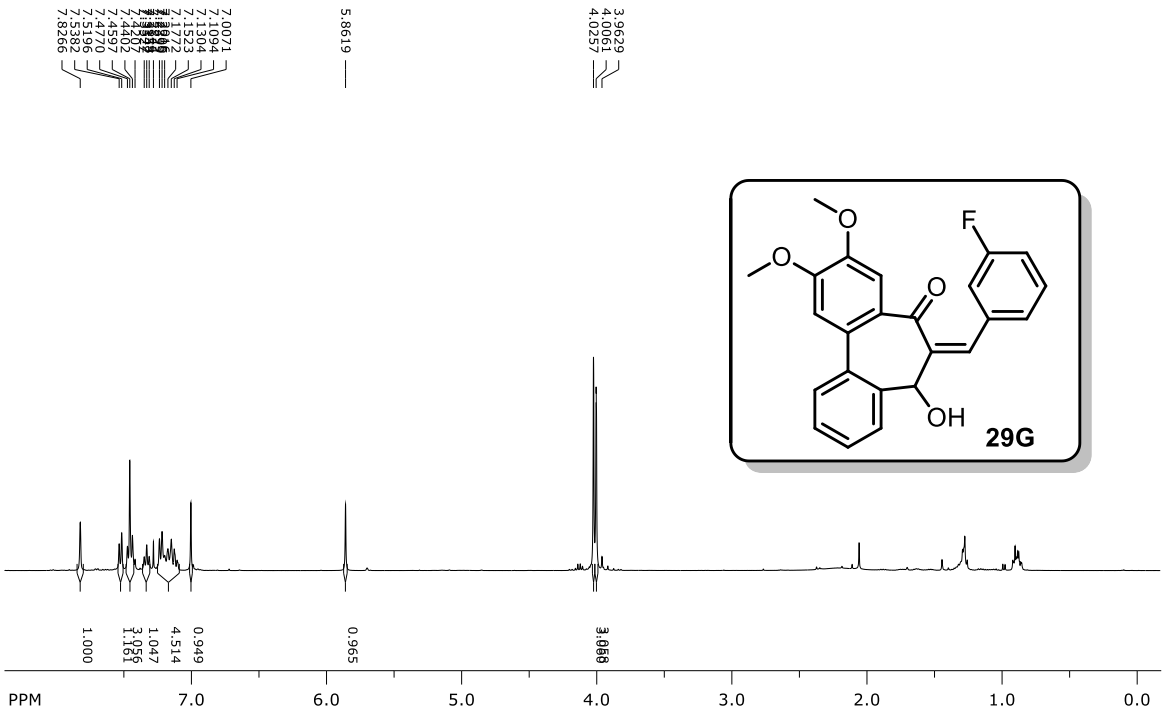
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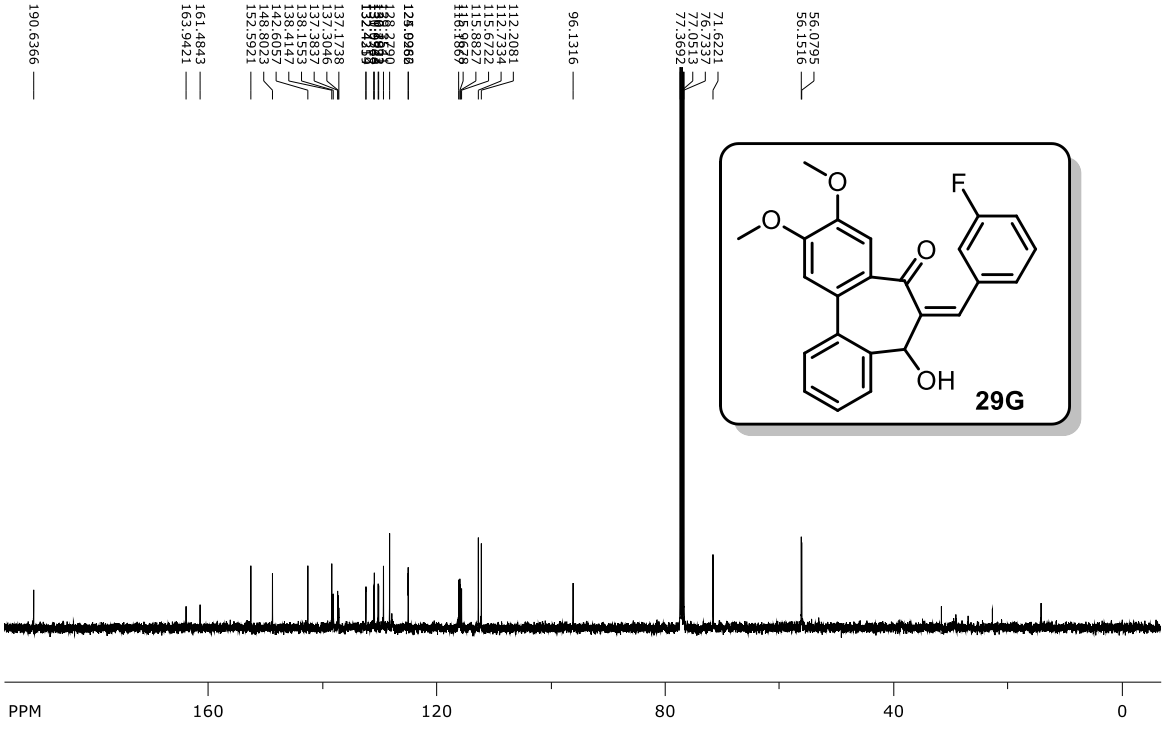
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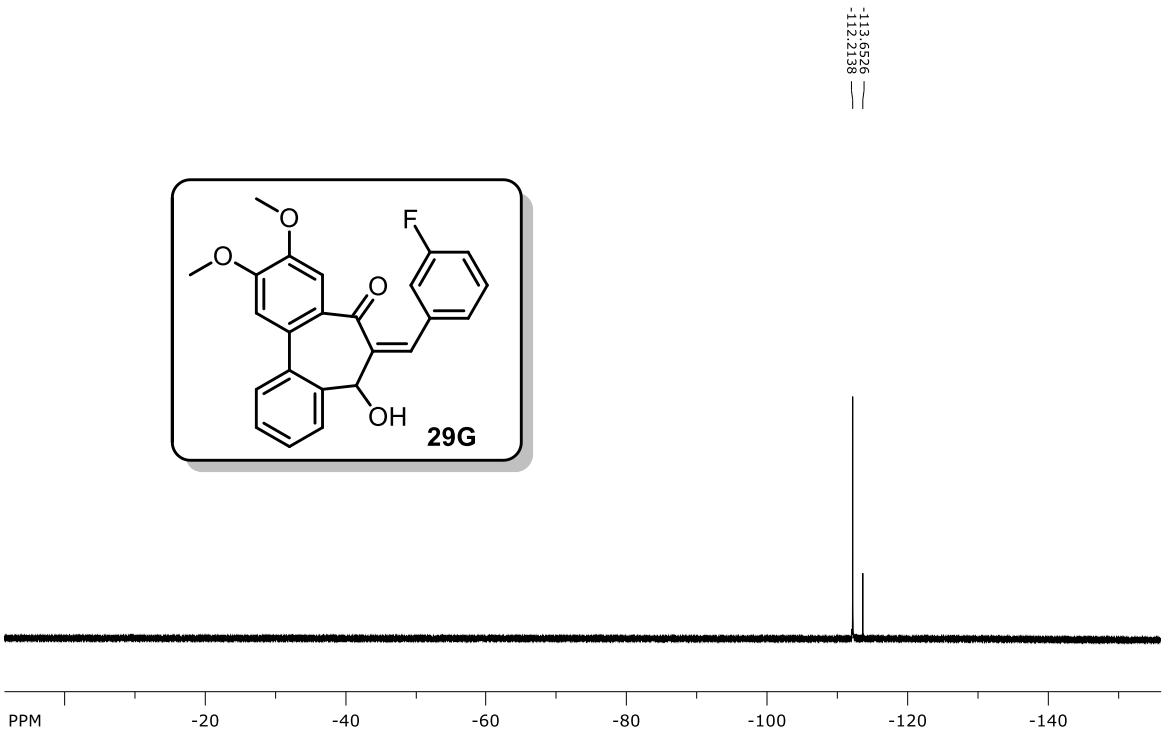
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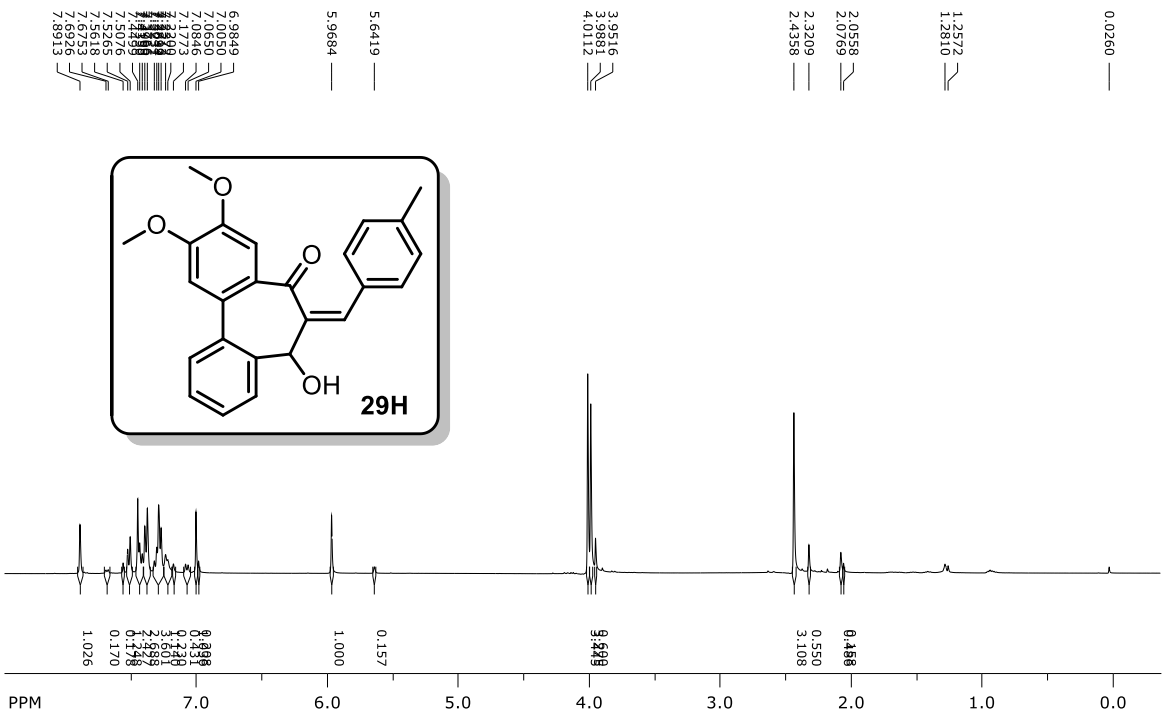
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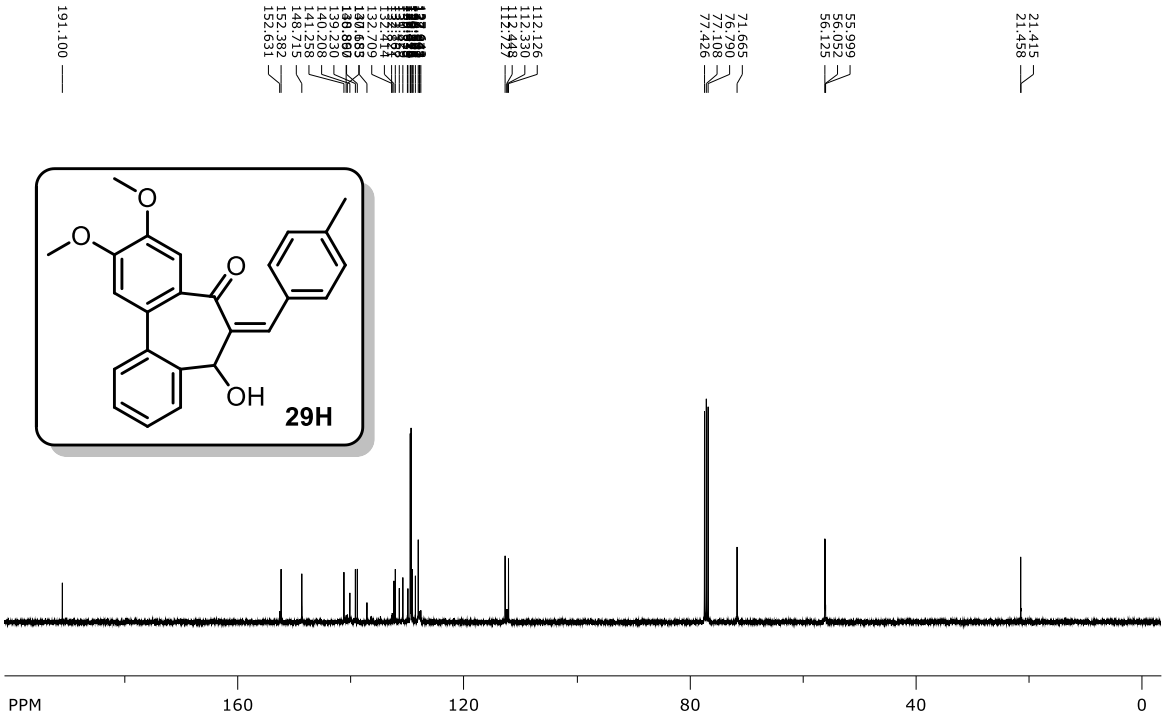
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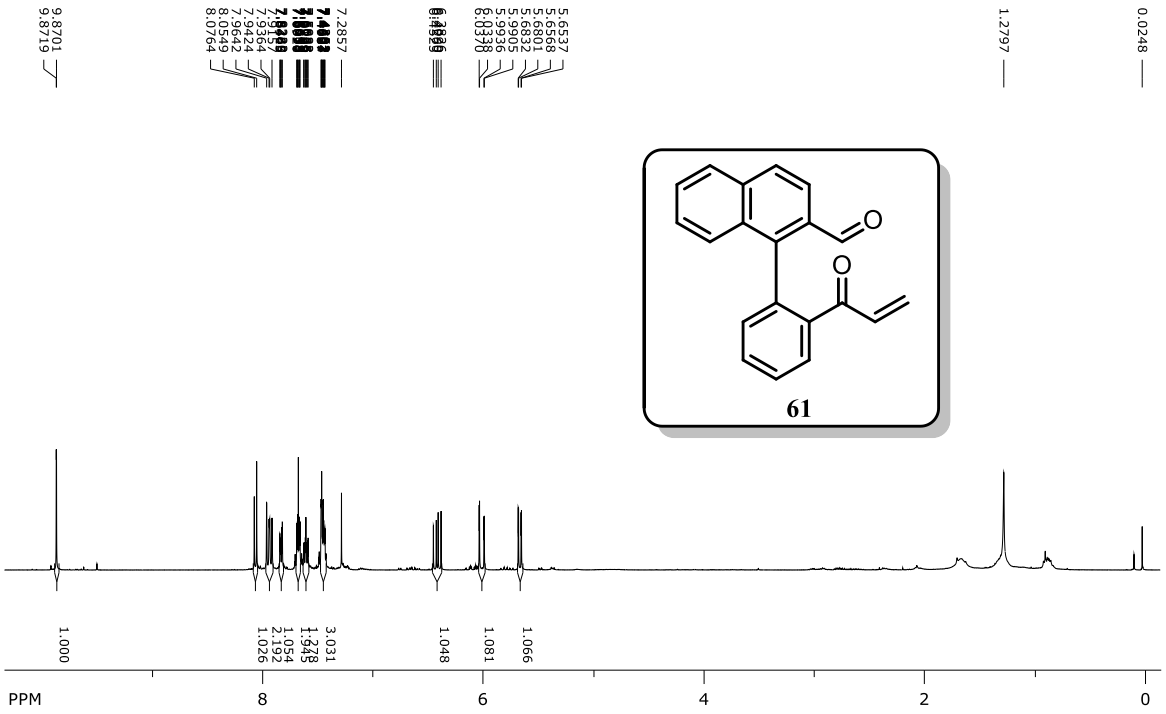
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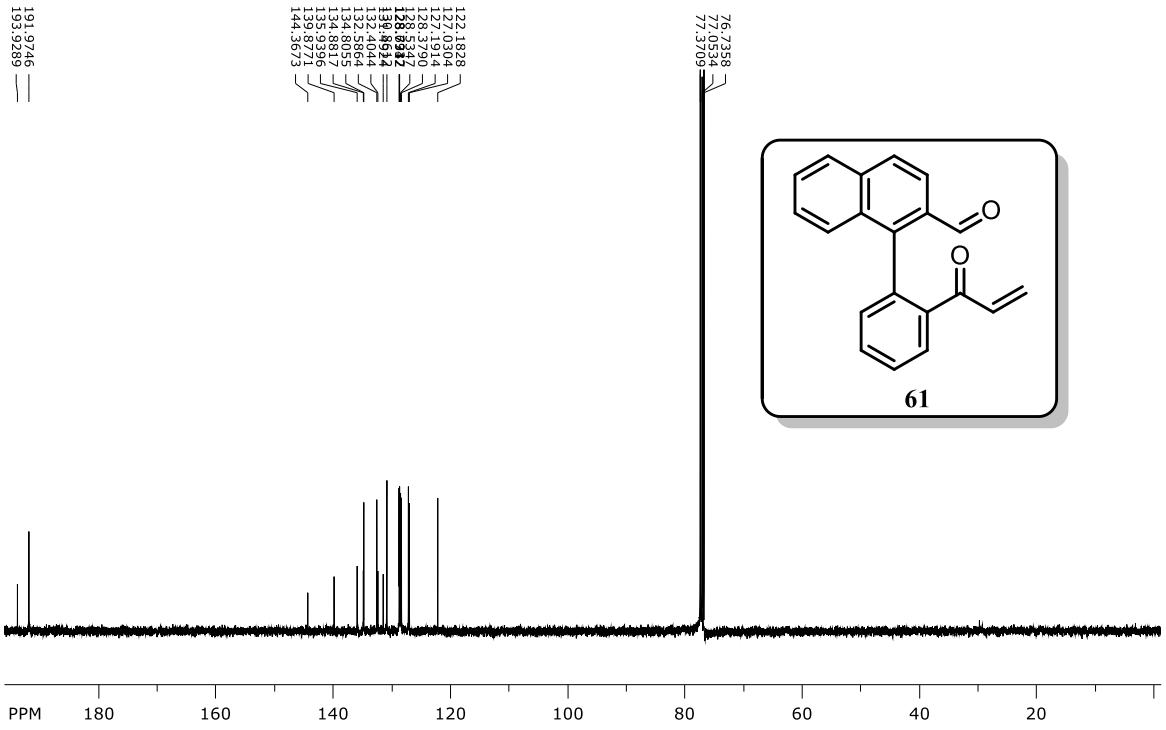
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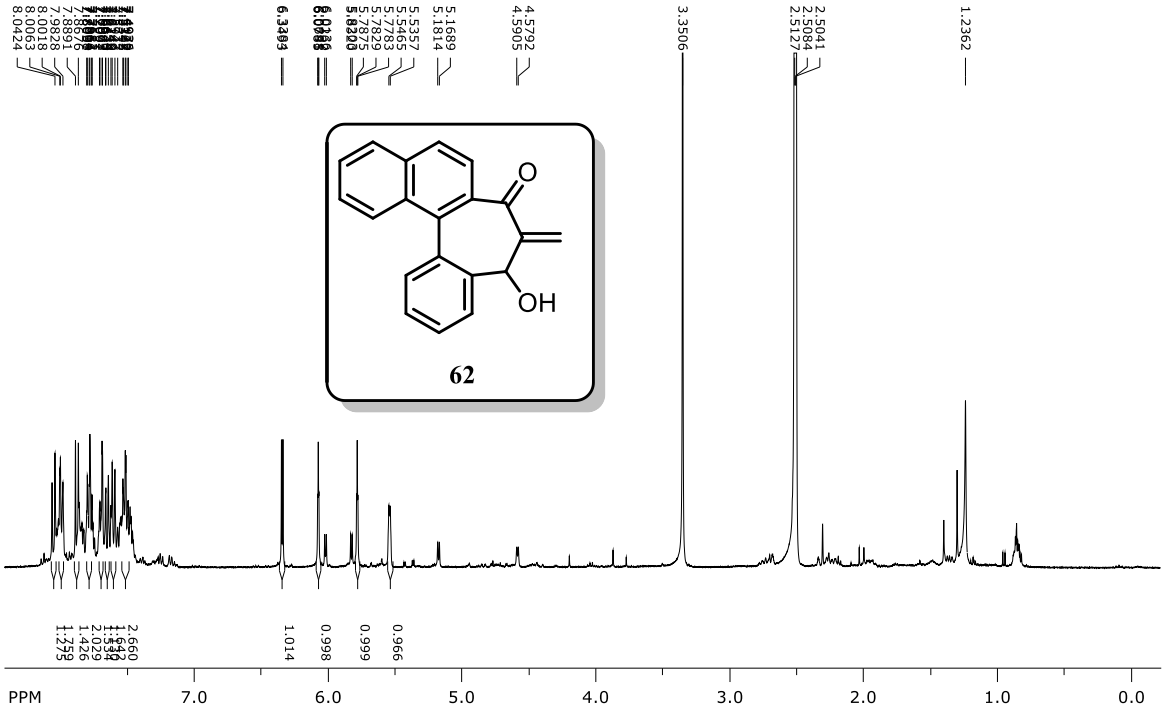
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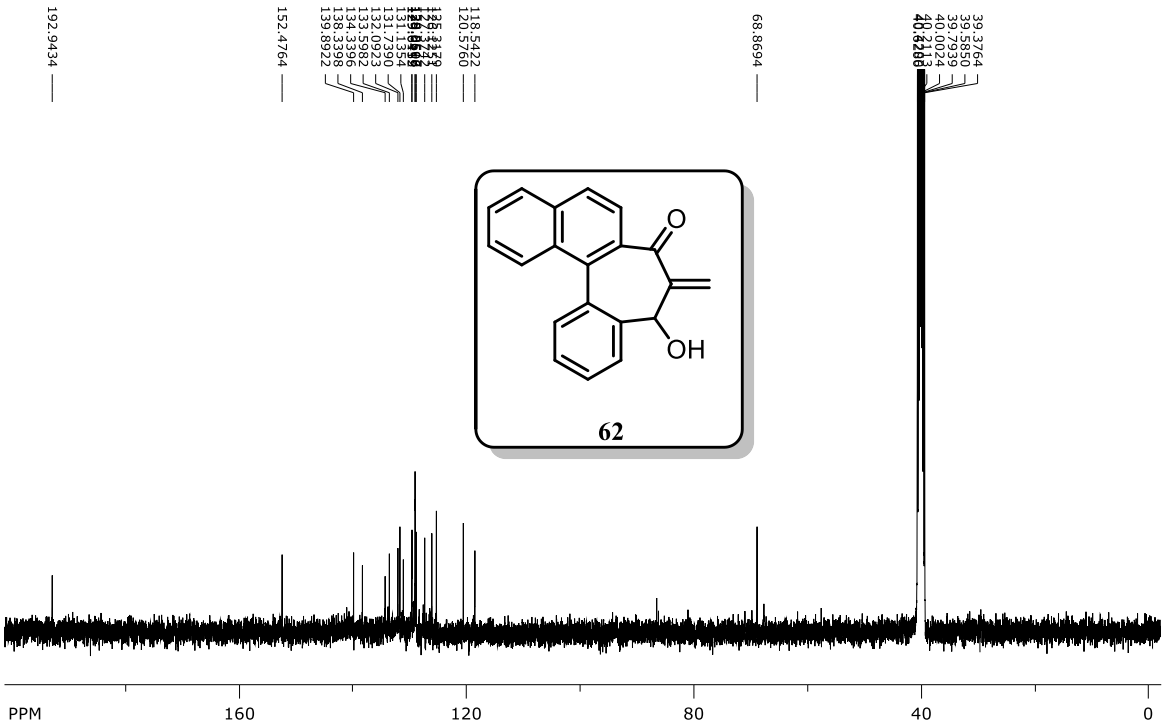
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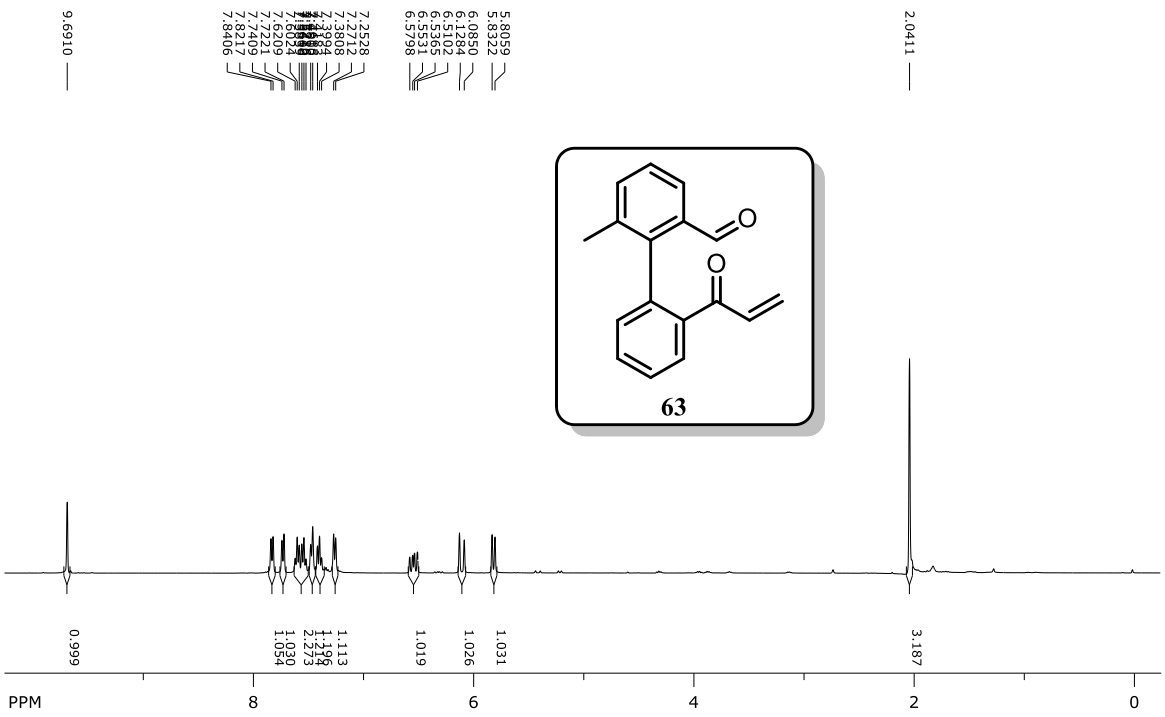
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6.1284
6.0850
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5.8332
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0.999
1.030
1.054
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6
4
2
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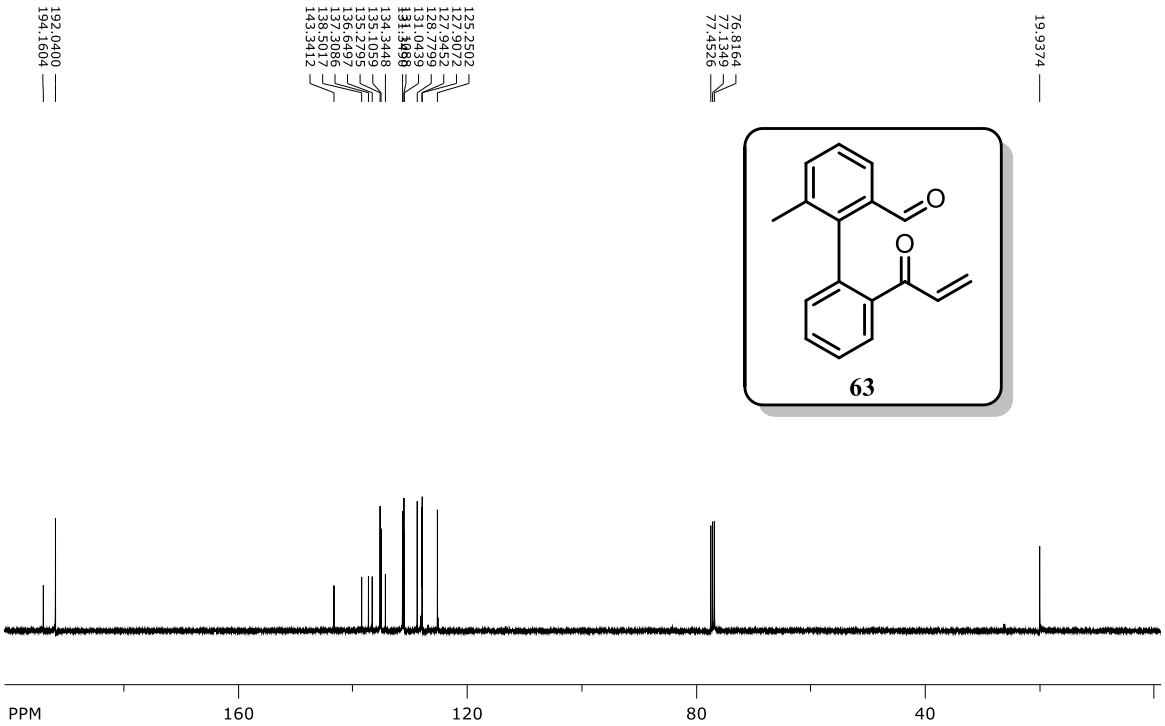
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PPM
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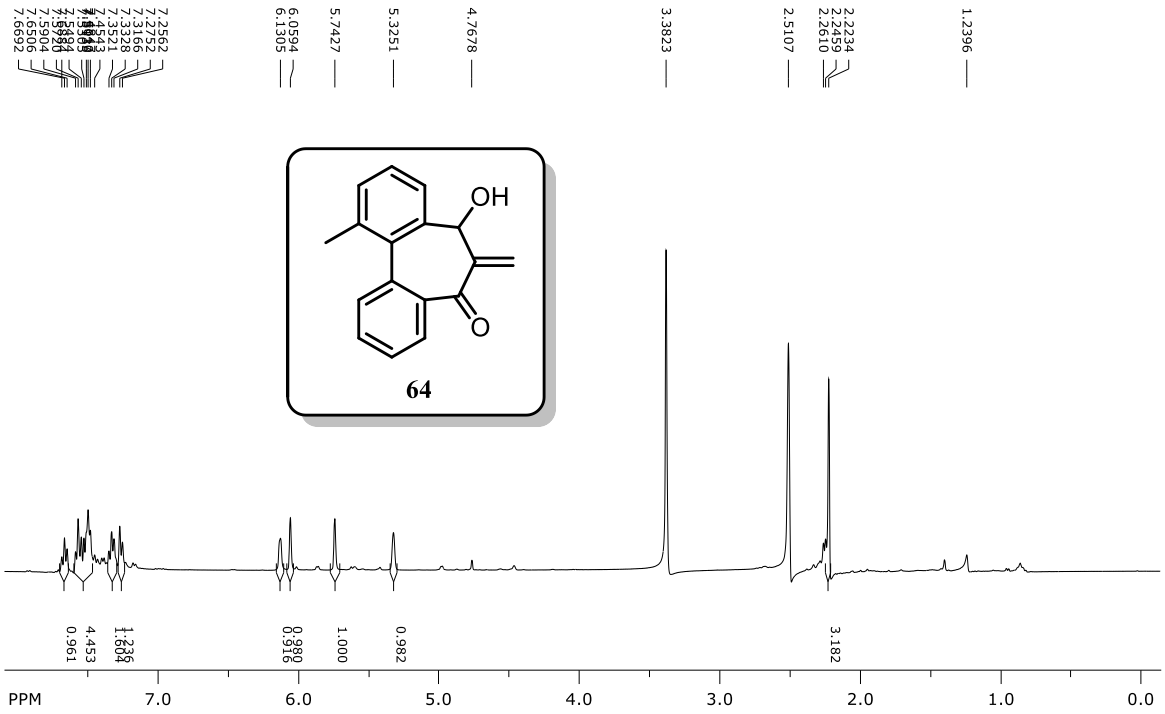
120
80
40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3.3823
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1.604
0.980
0.916
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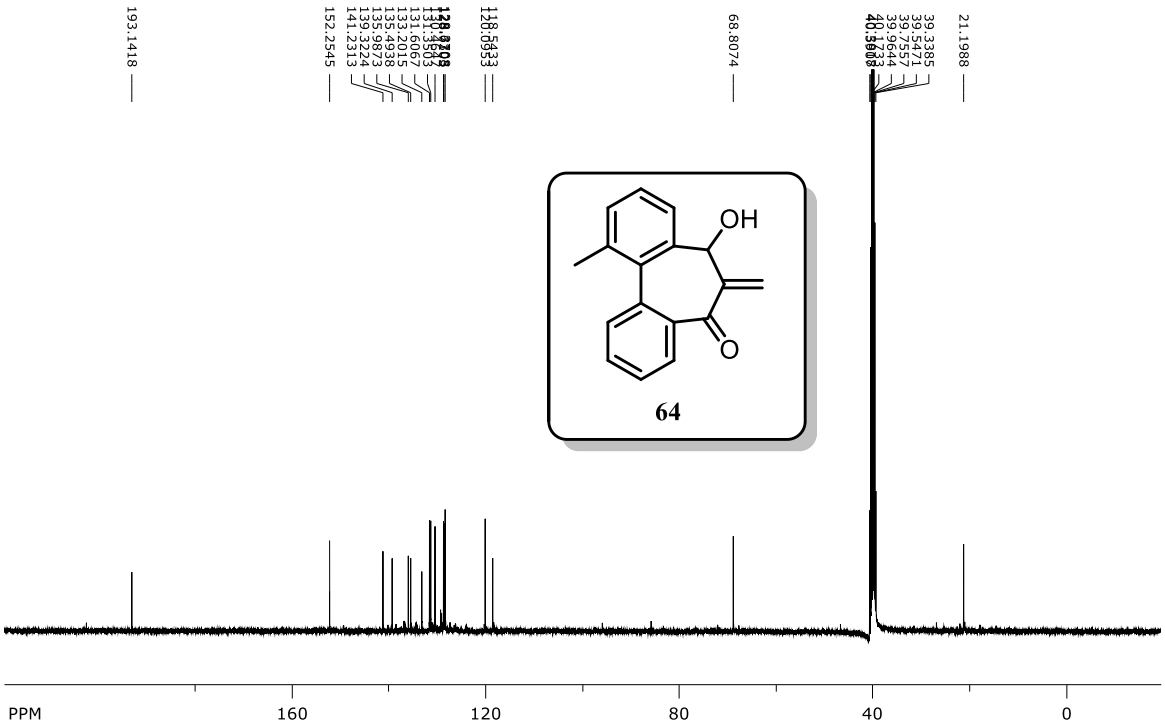
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39.7557
39.9644
21.1988
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PPM
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0

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