Synthesis of Bioactive Natural Products Cleistenolide, Isocryptolepine and Circumdatins Using Novel Methodologies

Thesis Submitted to AcSIR
For the Award of the Degree of

DOCTOR OF PHILOSOPHY
In
CHEMICAL SCIENCES

By

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Under the guidance of
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(Academy of Scientific and Innovative Research)

Division of Organic Chemistry
CSIR-National Chemical Laboratory
Pune 411 008, India

April 2018

To

My Three Lifelines

My Mother

My Wife & My Daughter

सीएसआयआर–राष्ट्रीय रासायनिक प्रयोगशाला
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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **Synthesis of Bioactive Natural Products Cleistenolide, Isocryptolepine and Circumdatins Using Novel Methodologies**, submitted by **Mr. Pankaj Shantaram Mahajan** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc. used in the thesis from other sources, have been duly cited and acknowledged.

Mr. Pankaj Shantaram Mahajan
(Research Student)

Dr. Santosh B. Mhaske
(Research Supervisor)

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled **Synthesis of Bioactive Natural Products Cleistenolide, Isocryptolepine and Circumdatins Using Novel Methodologies**, submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph. D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. Santosh B. Mhaske**, Senior Scientist, Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

April 2018
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Pankaj S. Mahajan

Contents

Abbreviation

APS	Ammonium peroxydisulfate
BHT	Butylated hydroxytoluene
BQ	Benzoquinone
BR	Beckmann rearrangement
brsm	Based on recovered starting material
DBPO	Dibenzoyl peroxide
DCE	Dichloroethane
DCM	Dichloromethane
DET	Diethyl tartarate
DIPEA	Diisopropylethylamine
DMAc	Dimethyl acetate
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMF	Dimethyl formamide
DMS	Dimethyl sulfone
DMSO	Dimethyl sulphoxide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
er	Enantiomeric ratio
EtOAc	Ethyl acetate
HOBt	Hydroxybenzotriazole
LiDBB	Lithium 4,4'-di-*ter*-butyldiphenylide
MeCN	Acetonitrile
MOC	Memory of chirality
MOM	Methoxy methyl
NBS	N-bromosuccinamide
NMO	*N*-Methylmorpholine *N*-oxide
NMP	N-Methyl-2-pyrrolidone
ODC	Oxidative decarboxylative coupling
PivOH	Pivalic acid
p-TSA	*p*-Toluene sulfonic acid
TBHP	t-Butyl hydroperoxide
TEMDA	Tetramethylethylenediamine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

General information

All reagents and solvents were used as received from commercial sources. All experiments were carried out under argon atmosphere unless otherwise noted. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for thin layer chromatography (TLC). Column chromatographic purifications were carried out on flash silica-gel (240–400 mesh) using petroleum ether and ethyl acetate as eluents unless otherwise noted. The ^{1}H, ^{13}C NMR spectra were recorded on 200/400/500 MHz, and 50/100/125 MHz NMR spectrometers, respectively in $CDCl_3$/DMSO-d_6/acetone-d_6. Chemical shifts were reported as δ values from standard peaks. Melting points recorded are uncorrected. Optical rotations were measured on ADP 220 polarimeter (Bellingham + Stanley Ltd). Chiral HPLC analysis was performed on the Shimadzu Class-VP V6.12 SP5 instrument with a UV detector. Mass spectra were taken on LC-MS (ESI) or GCMS spectrometer. HRMS were scanned on Quadrupole-Orbitrap Mass Spectrometer available at NCL, Pune.

Synopsis of the Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry

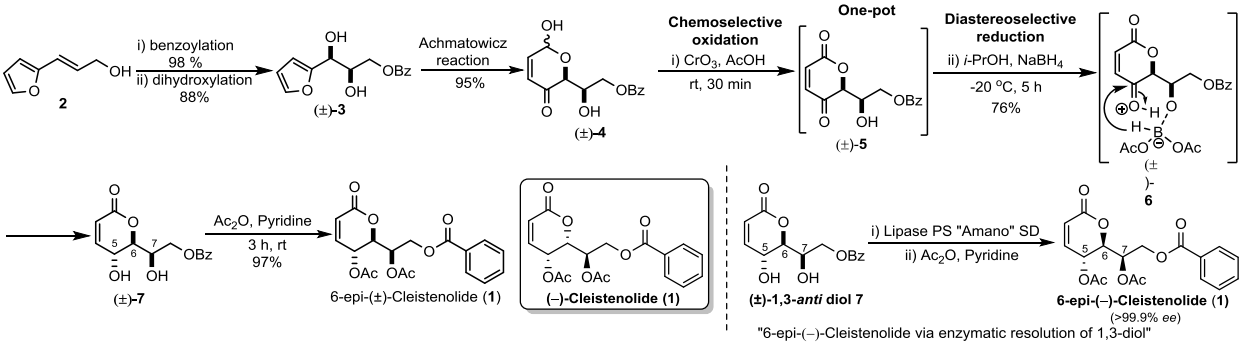
Name of the Candidate	Mr. Pankaj Shantaram Mahajan
Degree Enrolment No. and Date	Ph. D. in Chemical Sciences (10CC12A26020); August 2012
Title of the Thesis	Synthesis of Bioactive Natural Products Cleistenolide, Isocryptolepine and Circumdatins Using Novel Methodologies
Research Supervisor	Dr. Santosh B. Mhaske (AcSIR, CSIR-NCL, Pune)

Abstract

The thesis is mainly focused on the development of novel protocols/methodologies and their applications to the synthesis of bioactive molecules and natural products. The first chapter describes the protecting group free total synthesis of 6-epi-(±)-Cleistenolide and chemoenzymatic synthesis of 6-epi-(–)-Cleistenolide. The second chapter is divided into two sections. The Section-A demonstrates the development of a new reagent combination "ammonium persulfate-dimethyl sulfoxide" (APS-DMSO) for various transformations including methylene insertion between amides/aryls and Mannich reaction as well as the synthesis of thiadizole and pthalimide. The Section-B deals with development of novel radical Beckmann rearrangement and its application to the formal total synthesis of an antimalarial natural product Isocryptolepine and well-known Anticancer molecule. This work also involves development of double C–H activation for the construction of indoloquinolone scaffold. The third and the last chapter deals with the development of novel oxidative decarboxylative intramolecular radical cyclization with memory of chirality and its application to the synthesis of Circumdatin alkaloids.

Chapter 1: Protecting group free, diastereoselective, chemoenzymatic synthesis of 6-epi-Cleistenolide

The antifungal/antibacterial natural product (–)-Cleistenolide (**1**) was isolated by Nkunya *et al*. Prior eight total syntheses of (–)-Cleistenolide (**1**) utilized chiral-pool approaches involving protection and deprotection chemistry. We envisioned that the Achmatowicz reaction[1] could be useful in the synthesis of



Scheme 1: Protecting group free synthesis of 6-epi-(±)-Cleistenolide and chemoenzymatic synthesis of 6-epi-(−)-Cleistenolide

this natural product. The Achmatowicz reaction worked well on the unprotected diol substrate **3** to deliver the key intermediate hydroxypyranone **4**. One-pot chemoselective oxidation of allyl alcohol followed by *in*

situ diastereoselective reduction of ketone was developed to achieve the 1,3-*anti* diol product (±)-**7**. Further diacetylation of the diol **7** delivered 6-epi-(±)-Cleistenolide (**1**). The synthesis was achieved in five linear steps with 60% overall yield. The relative stereochemistry of the newly generated stereocenter was confirmed by 2D NMR spectroscopy. The developed approach is general, practical and protecting group-free.[2] Moreover, an enzymatic resolution of 1,3-*anti* diol intermediate (±)-**7** has also been demonstrated for the first time using enzyme Lipase PS "Amano" SD and applied to the synthesis of 6-epi-(–)-Cleistenolide (**1**, 99.9% *ee*). The absolute stereochemistry of 6-epi-(–)-Cleistenolide was confirmed by single crystal X-ray analysis (Scheme 1).[2]

Chapter 2: Novel Protocol APS-DMSO for Various Transformations: The Radical Beckmann Rearrangement and its Application in the Synthesis of Isocryptolepine via C–H Activation

This chapter is divided into two sections. The Section-A demonstrates the development of a new protocol "ammonium persulfate-dimethyl sulfoxide" (APS-DMSO) for various transformations including methylene insertion between amides/aryls and Mannich reaction as well as synthesis of thiadizole and pthalimide (17 examples).[3] The radical pathway involved in the present protocol was proved by trapping experiments. This section forms the basis for the development of APS-DMSO reagent for the Beckmann rearrangement described in the next section.

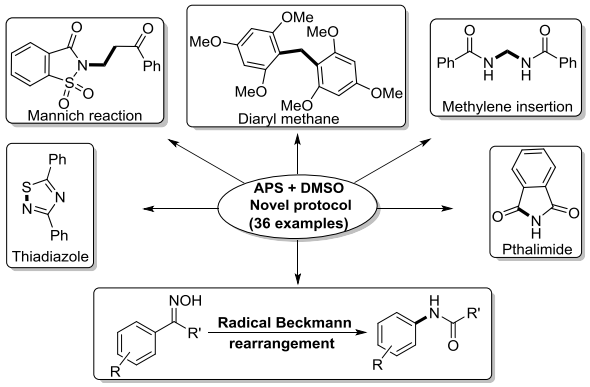
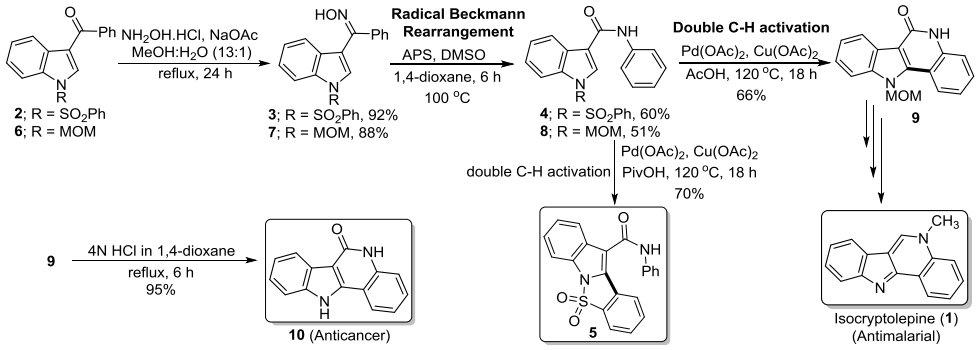


Figure 1: Applications of the developed APS-DMSO protocol[3,4]

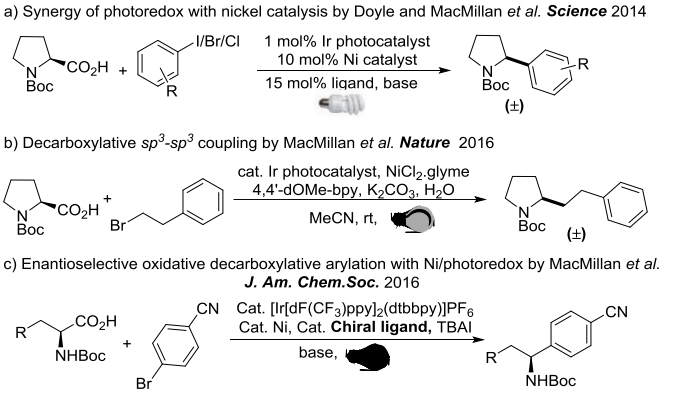
The Section-B provides the details on the development of the novel radical Beckmann rearrangement mediated by APS-DMSO (Figure 1) and its application to the synthesis of antimalarial natural product Isocryptolepine (**1**, Scheme 2).[4] Few examples of photocatalyzed radical Beckmann rearrangement are known, however with poor yields. The mild protocol developed herein worked well and tolerated a variety of functional groups (19 examples). Mechanistic aspects of the newly developed radical Beckmann



Scheme 2: Formal total synthesis of Isocryptolepine using radical Beckmann rearrangement and double C–H activation

rearrangement were studied well by radical trapping and oxygen labelling experiments. ^{18}O-Labelling experiment proved that the oxygen is internal and originates from the ketoxime.[4] The radical Beckmann rearrangement protocol was successfully applied to the synthesis of the antimalarial natural product Isocryptolepine (**1**) and an Anticancer Indoloquinolone molecule (**10**). The synthesis also features a new Pd-catalyzed intramolecular double C-H activation to construct indoloquinolone scaffold (**9**, Scheme 2).[4]

Chapter 3: Development of an Intramolecular Oxidative Decarboxylative Radical Cyclization via Memory of Chirality and its Application to Circumdatin Alkaloids



Scheme 3: Known decarboxylative coupling of amino acids using photocatalyst

Oxidative decarboxylative coupling (ODC) reactions of amino acids always provide racemic products as the generated radical is labile and achiral (Scheme 3). The chiral product is possible with ODC only in the

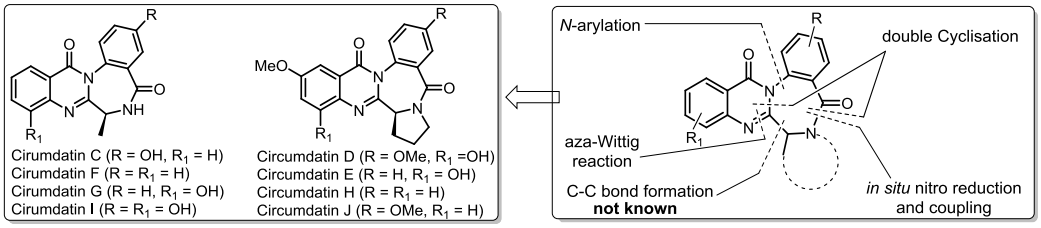
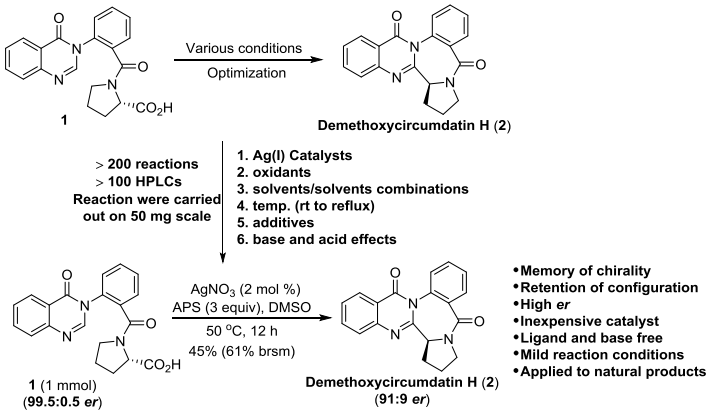


Figure 2: Circumdatin alkaloids and C–N bond formation strategies used for their synthesis

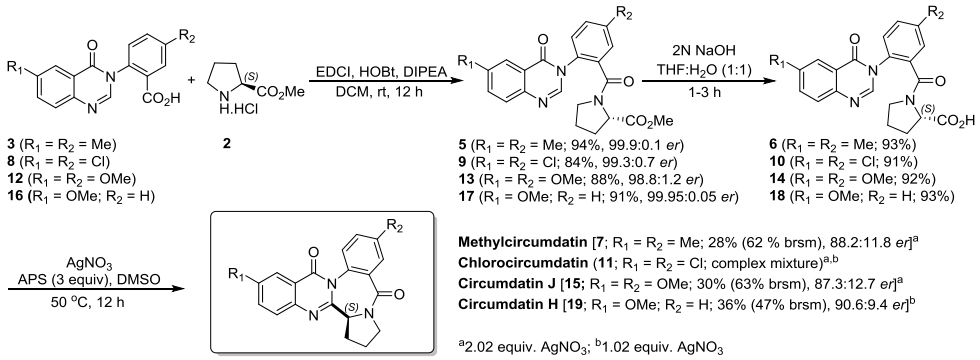
presence of chiral ligand and expensive photocatalysts (Scheme 3). We envisioned an intramolecular ODC of amino acids to provide a chiral product via memory of chirality (MOC). We selected bioactive Circumdatin alkaloids (Figure 2) as a rigid scaffold wherein, amino acids can be used as a precursor for the ODC via MOC. Circumdatin alkaloids have always been achieved via C–N bond forming reactions; however, C-C bond coupling has never been explored (Figure 2). A novel oxidative-decarboxylative-



Scheme 4: Optimization of the ODC via MOC

intramolecular (Csp^3-Csp^2) radical cyclization protocol was first optimized for Demethoxycircumdatin H (Scheme 4). The novel protocol utilizes Ag (I) and APS for decarboxylative coupling and delivers requisite stereochemistry with retention of the configuration (Scheme 4).

The developed protocol was then applied on the substrates **6**, **10**, **14** and **18** (Scheme 5) to obtain Circumdatin alkaloids Circumdatin J, Circumdatin H and their analogues (**7**, **11**, **15** and **19**) with ~90:10 er.[5] Radical trapping experiment proved the formation of a chiral monoradical.



Scheme 5: Synthesis of Circumdatin alkaloids utilizing ODC via MOC

In summary, the present desertion describes development of novel methodologies and their applications to the synthesis of bioactive molecules and natural products.

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1. **Mahajan**, **P. S.;** Humne, V. T.; Mhaske, S. B. *Curr. Org. Chem.* **2017**, *21*, 503.
2. **Mahajan**, **P. S.;** Gonnade, R. G.; Mhaske, S. B. *Eur. J. Org. Chem.* **2014**, 8049.
3. **Mahajan**, **P. S.;** Tanpure, S. D.; More, N. A.; Gajbhiye, J. M.; Mhaske, S. B. *RSC Adv.* **2015**, *5*, 101641.
4. **Mahajan**, **P. S.;** Humne, V. T.; Tanpure, S. D.; Mhaske, S. B. *Org. Lett.* **2016**, *18*, 3450.
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Chapter 1

Protecting-Group-free, Diastereoselective, Chemoenzymatic Synthesis of 6-epi-Cleistenolide

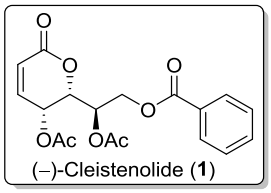
Mahajan, P. S.; Gonnade, R. G.; Mhaske, S. B. *Eur. J. Org. Chem.* **2014**, 8049.

Protecting-Group-Free, Diastereoselective, Chemoenzymatic Synthesis of 6-epi-Cleistenolide

1.1 Abstract

The chapter discloses the protecting-group-free total synthesis of 6-epi-(±)-cleistenolide. The Achmatowicz reaction, one-pot chemoselective oxidation and diastereoselective reduction are the key features of the total synthesis. Moreover, an enzymatic resolution of the 1,3-*anti*-diol using Lipase PS "Amano" SD has been achieved for the first time and applied to the chemoenzymatic synthesis of 6-epi-(–)-cleistenolide. An extensive study was performed to determine the stereochemistry of the natural product epimer.

1.2 Introduction



(–)-Cleistenolide (**1**)


Cleistochlamys kirkii Oliver plant

Figure 1: (–)-Cleistenolide (**1**) and *Cleistochlamys kirkii* Oliver plant

The natural product (–)-cleistenolide (**1**) was isolated from *Cleistochlamys kirkii* Oliver plant species (Figure 1) found in Tanzania and Mozambique. The plant extracts of the *Cleistochlamys kirkii* are traditionally useful in the treatment of rheumatism, wound infections and tuberculosis.[1] The natural product (–)-cleistenolide (**1**) bears *in vitro* antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis* and also shows antifungal activity against *Candida albicans*.[1a] Structurally, the natural product has three chiral centres and an α,*β*-unsaturated *δ*-lactone. (–)-Cleistenolide (**1**) resembles with some of the other biologically active natural products having *α*,*β*-unsaturated *δ*-lactone core (Figure 2).

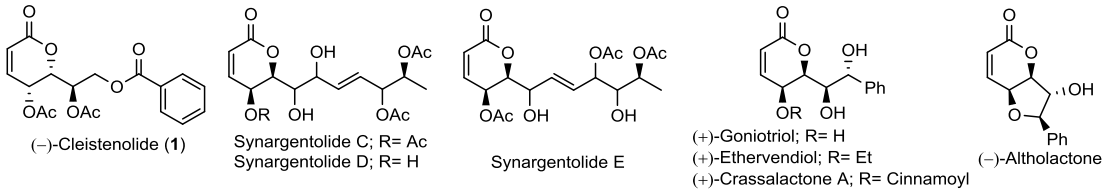
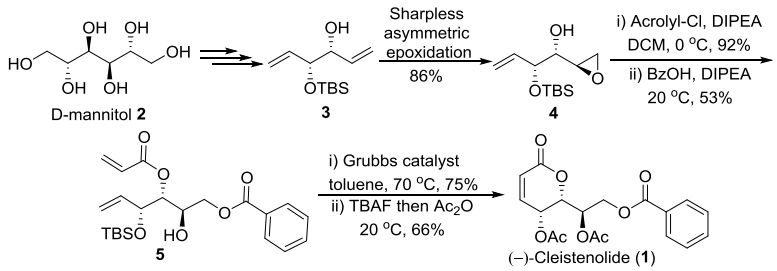


Figure 2: (–)-Cleistenolide (**1**) and natural products having α,β-unsaturated δ-lactone core

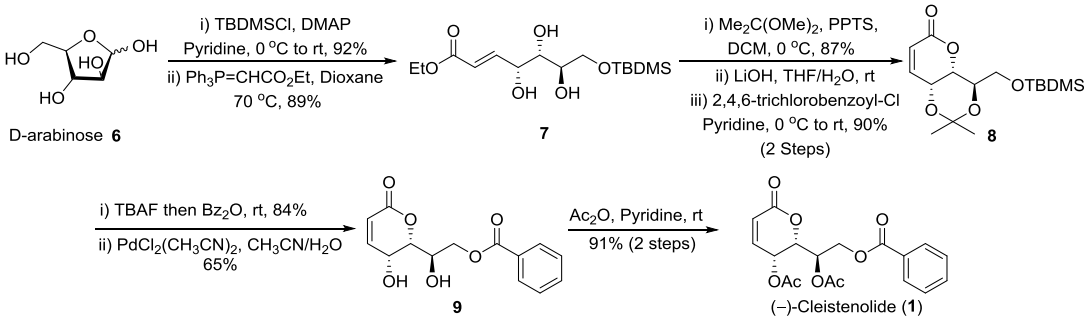
The potential pharmacological activity and fascinating structural features of (–)-cleistenolide (**1**) attracted many research groups to work on its synthesis utilizing various synthetic routes.[2] Eight prior total syntheses of (–)-cleistenolide (**1**) are summarized below.

1.3 Literature review



Scheme 1: Synthesis of (–)-cleistenolide (**1**) by Schmidt et al.[2a]

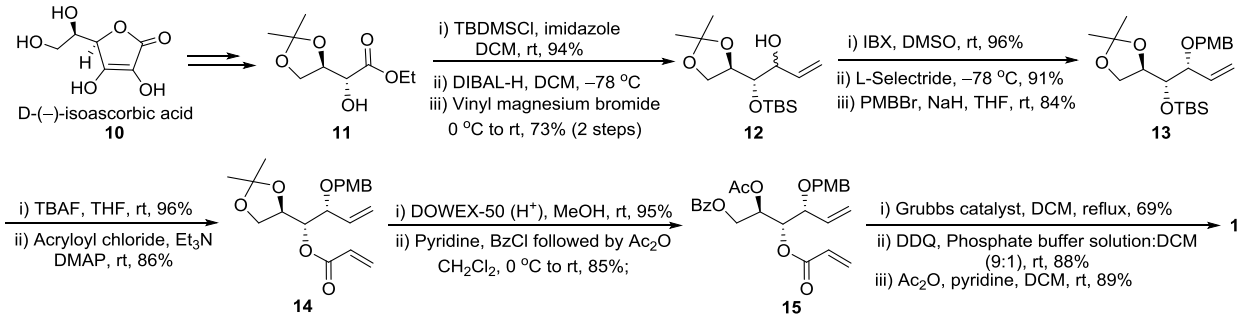
Biernat et al. applied Sharpless asymmetric epoxidation and ring closing metathesis to achieve the first total synthesis of (–)-cleistenolide (**1**) in six linear steps with 18% overall yield. The synthesis started from D-mannitol **2**. The ring closing metathesis of **5** afforded the expected lactone, which was desilylated and diacetylated to provide (–)-cleistenolide (**1**, Scheme 1). [2a]



Scheme 2: Synthesis of (–)-cleistenolide (**1**) by Linhardt et al.[2b]

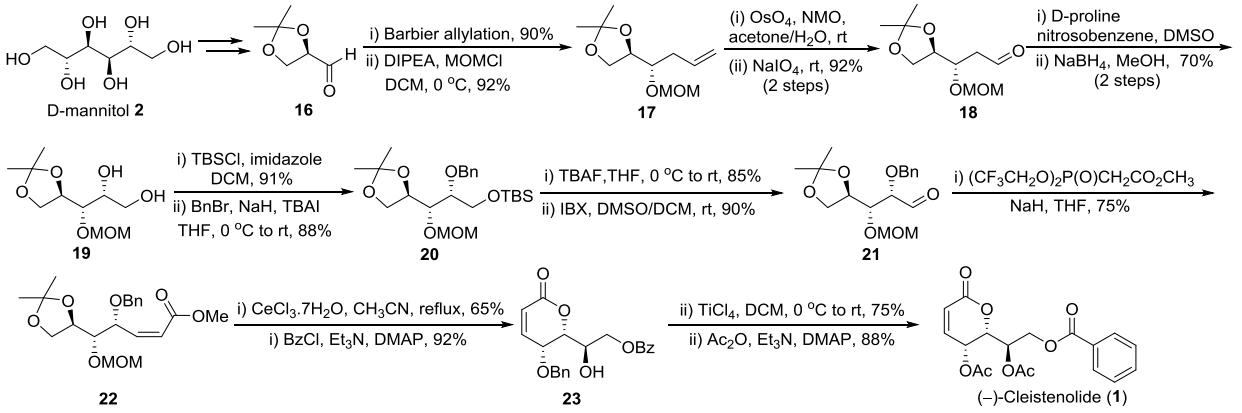
Linhardt et al. achieved the second total synthesis of (–)-cleistenolide (**1**) from D-arabinose **6** in total eight linear steps with 49% overall yield. Intramolecular Yamaguchi esterification was used as one of the key steps. Acetonide deprotection of **8** followed by diacetylation smoothly furnished the natural product (–)-cleistenolide (**1**, Scheme 2).[2b]

Venkateswarlu et al. synthesized (–)-cleistenolide (**1**) from D-(–)-isoascorbic acid (**10**) using Grignard reaction, L-selectride reduction and ring closing metathesis as important transformations (**1**, Scheme 3).[2c]



Scheme 3: Synthesis of (–)-cleistenolide (**1**) by Venkateswarlu et al.[2c]

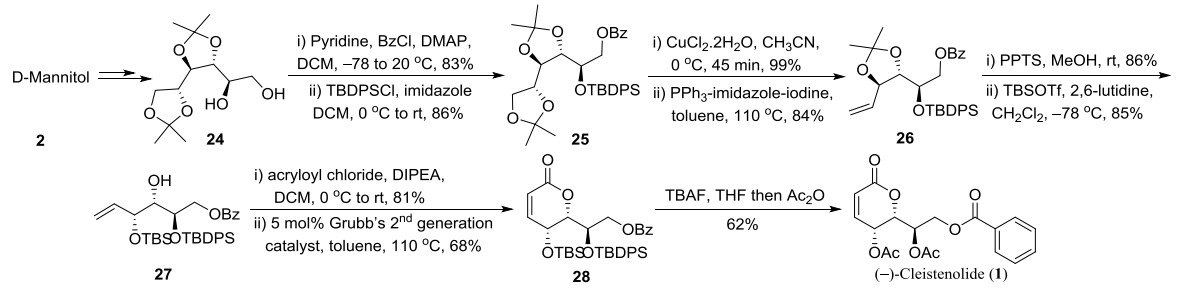
Reddy et al. achieved the total synthesis of (–)-cleistenolide (**1**) from D-mannitol **2**. Barbier allylation, Upjohn oxidation, MacMillan α-hydroxylation and the Stille-Gennari olefination are the key features of this synthesis. (**1**, Scheme 4).[2d]



Scheme 4: Synthesis of (–)-cleistenolide (**1**) by Reddy et al.[2d]

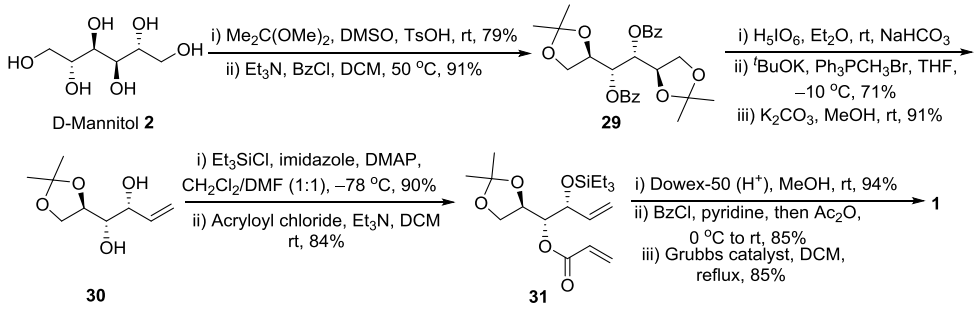
Meshram et al. synthesized (–)-cleistenolide (**1**) from the known diacetonide **24**, which was achieved from D-mannitol **2**. Copper-mediated selective deprotection of acetonide and ring

closing metathesis was utilized efficiently to obtain (–)-cleistenolide (**1**, Scheme 5).[2e]



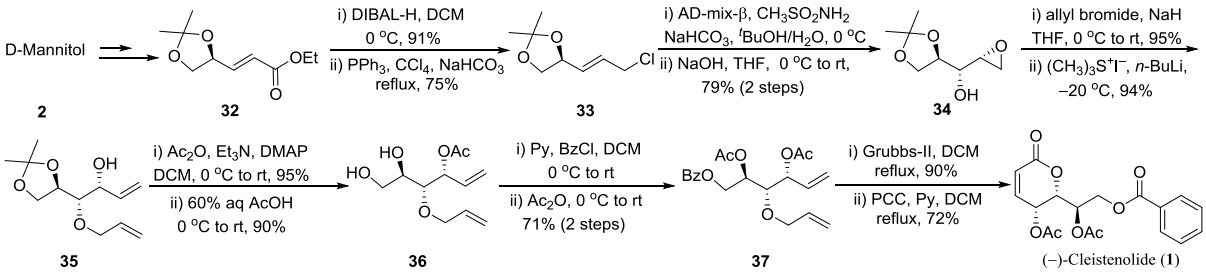
Scheme 5: Synthesis of (–)-cleistenolide (**1**) by Meshram et al.[2e]

Venkateswarlu et al. again synthesized the natural product but starting from D-mannitol **2** using Wittig reaction and ring closing metathesis more efficiently to complete the synthesis in 10-steps (Scheme 6).[2f]



Scheme 6: Synthesis of (–)-cleistenolide (**1**) by Venkateswarlu et al.[2f]

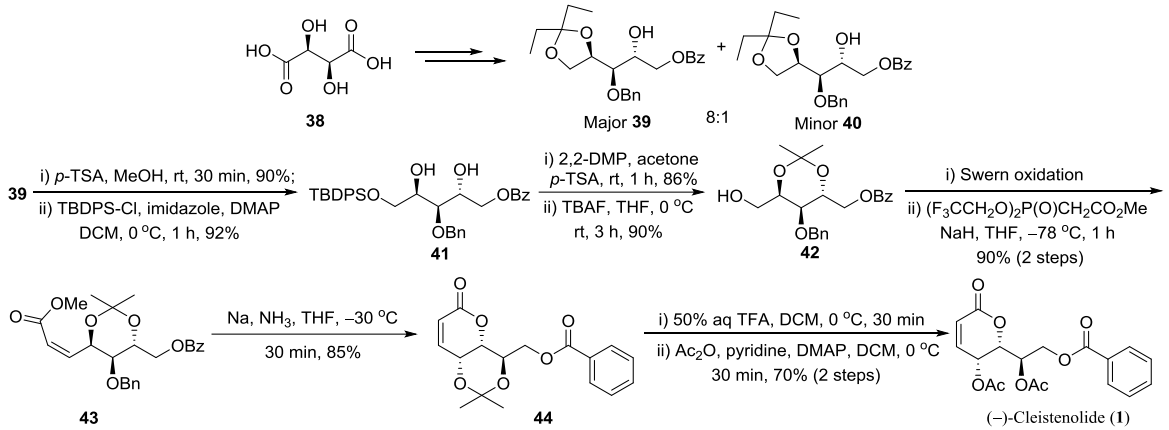
Rao et al. used D-mannitol **2** for the synthesis of (–)-cleistenolide (**1**). Sharpless asymmetric dihydroxylation, sulfur ylide-mediated epoxide opening and ring closing metathesis were applied in the synthesis of natural product (–)-cleistenolide (**1**, Scheme 7).[2g]



Scheme 7: Synthesis of (–)-cleistenolide (**1**) by Rao et al.[2g]

Narsaiah et al. synthesized (–)-cleistenolide (**1**) from D-tartaric acid **38**. The sequence of

reactions yielded **39** as a major diastereomer. The Stille–Gennari olefination and other usual transformations furnished (–)-cleistenolide (**1**, Scheme 8).[2h]



Scheme 8: Synthesis of (–)-cleistenolide (**1**) by Narsaiah et al.[2h]

The total syntheses reported so far used chiral-pool approaches,[2] which needs lots of protection-deprotection chemistry (Scheme 1-8).[2] This leads to increase in the number of steps and ultimately loss of atom economy in the natural product synthesis.[3] The strategies involved herein (Figure 3) also lack a simple and general approach to synthesize the structurally similar natural products (Figure 2). Therefore, a new protecting-group-free route for the synthesis of (−)-

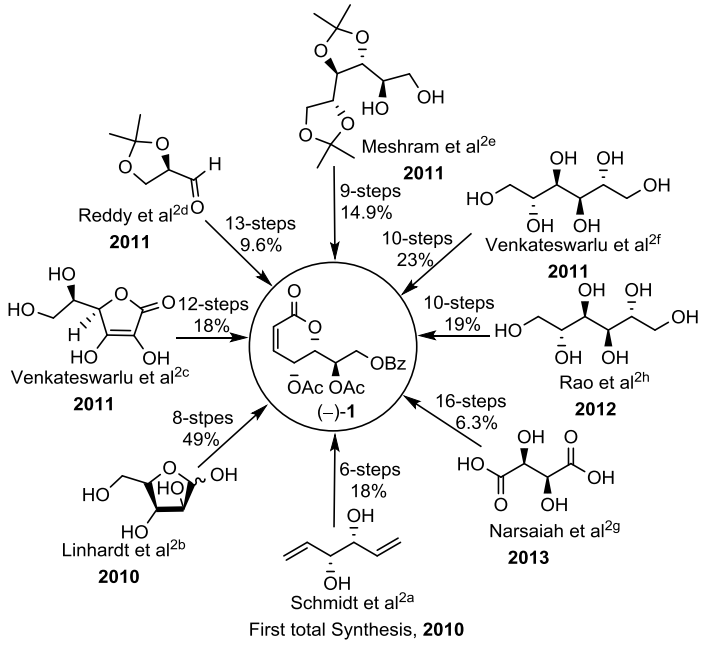
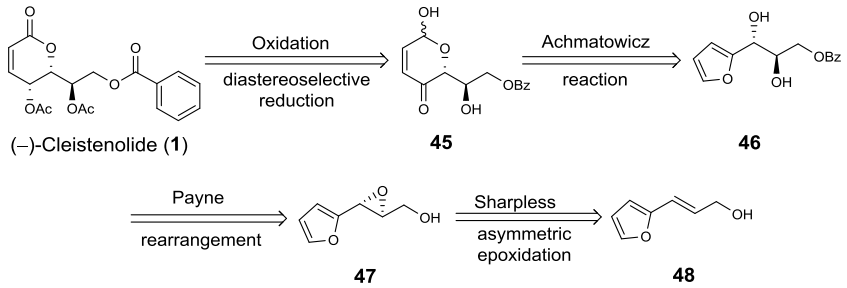


Figure 3: Previous known total syntheses of (–)-cleistenolide (**1**) [2]

cleistenolide (**1**) is desired, which would provide better yields and can be applied to structurally resembling natural products as well as their rational analogues.

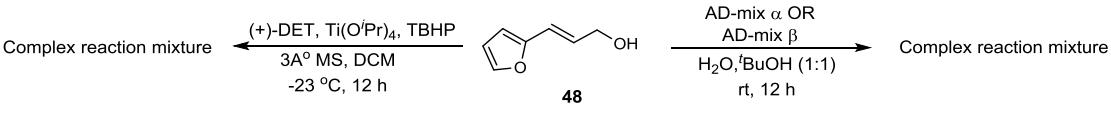
1.4 Results and discussion

We envisioned that the Achmatowicz reaction[4] could be very useful to generate hydroxy pyranone core **45** of the natural product (–)-cleistenolide (**1**). Therefore, retrosynthetic plan was designed utilizing Achmatowicz reaction and Payne rearrangement. (–)-Cleistenolide (**1**) can be achieved from the Achmatowicz reaction product hydroxy pyranone **45** upon selective oxidation of the hemiacetal followed by reduction of ketone and diacetylation. The Achmatowicz reaction product **45** could be gained from the 1,2-*trans*-diol **46**, which can be generated from the epoxide **47** using the Payne rearrangement. Sharpless asymmetric epoxidation of furyl allyl alcohol **48** should provide epoxide **47** (Scheme 9).



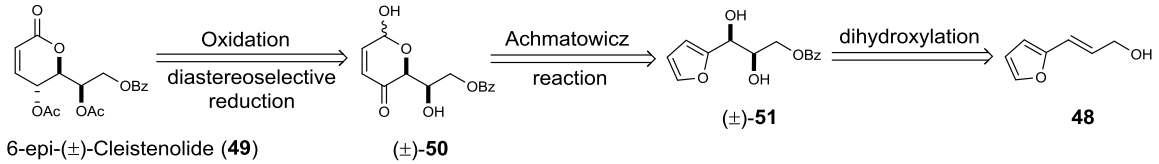
Scheme 9: Retrosynthesis of (–)-Cleistenolide (**1**)

Attempts to synthesize epoxide **47** began with the commercially available furyl allyl alcohol **48**. The allyl alcohol was subjected to the Sharpless asymmetric epoxidation, but a complex reaction mixture with the decomposition of the starting material was observed. The asymmetric dihydroxylation of the alcohol **48** also met with failure (Scheme 10). The furan moiety in the molecule **48** was not tolerant to these reactions.



Scheme 10: Attempts for asymmetric synthesis

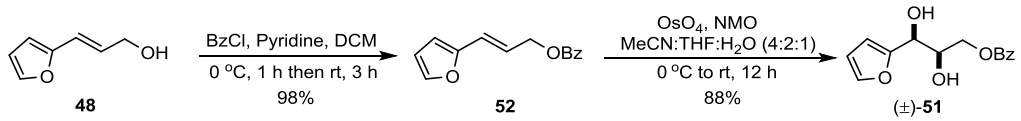
These results ended our hopes of the asymmetric synthesis starting from the alcohol **48**, hence, a new retro-synthetic route was designed for the synthesis of 6-epi-(±)-cleistenolide (**49**) utilizing the Achmatowicz reaction as a key step (Scheme 11). The 6-epimer of the natural



Scheme 11: Retrosynthetic plan for 6-epi-(±)-cleistenolide (**49**)

product **49** can be derived from the Achmatowicz reaction product (±)-**50**, which can be gained from the 1,2-*syn*-diol (±)-**51**. The allylic alcohol **48** would be a synthetic precursor to obtain the diol (±)-**51**.

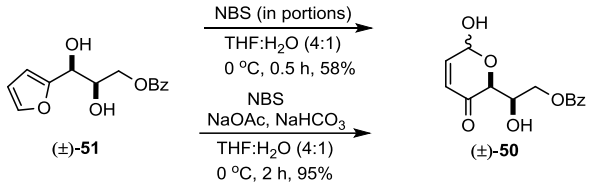
The allylic alcohol **48** was benzoylated using benzoyl chloride and pyridine in DCM to get benzoate **52** in 98% yield. Decomposition of the starting material **48** was observed when diisopropylethylamine was used as a base in DCM. The Upjohn oxidation was performed on **52** with catalytic OsO_4 and stoichiometric NMO in THF:H_2O (1:1) solvent system for 12 h to get *syn*-diol (±)-**51** in less than 60% yields. The solvent system was then changed to MeCN:THF:H_2O (2:2:1), which enhanced the yield to 74%. Finally the optimal condition MeCN:THF:H_2O (4:2:1) gave us the diol **51** in 88% yield (Scheme 12).



Scheme 12: Synthesis of 1,2-*Syn* diol (±)-**51**

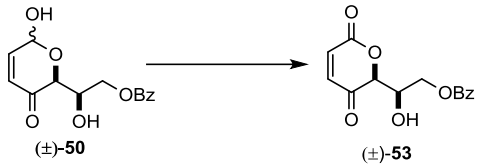
The *syn*-diol (±)-**51** was subjected to the standard Achmatowicz reaction conditions using portion-wise addition of NBS (1 equiv) in THF:H_2O (4:1) to obtain the required product hydroxy pyranone (±)-**50**. To our delight the reaction worked well to provide 58% yield in the first attempt. A drastic enhancement in the yield of the Achmatowicz reaction product pyranone (±)-**50** was achieved when NaOAc (1 equiv) and $NaHCO_3$ (2 equiv) were used along with NBS (1

equiv) in the same solvent system [THF:H_2O (4:1)]. The pyranone (±)-**50** was obtained in 95% yield (Scheme 13). Previously, O'Doherty used the similar condition for the Achmatowicz reaction on protected furyl 1,2-diol.[5] This transformation is used efficiently for the first time on an unprotected furyl 1,2-diol system.



Scheme 13: The Achmatowicz reaction on an unprotected 1,2-diol (±)-**51**

The next job was to oxidize the allylic alcohol (hemiacetal) of (±)-**50**. Therefore, various oxidizing agents were tried to achieve the lactone (±)-**53** (Table 1). MnO_2 in benzene[6] at room



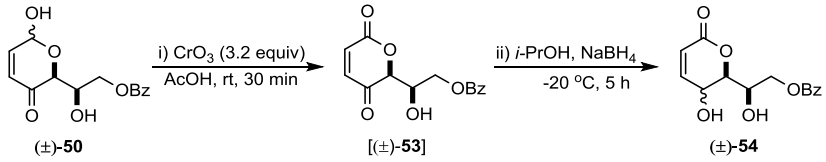
Entry	Oxidizing agents	Solvents	Reaction temp.	Reaction time	Result
1	MnO_2	benzene	rt	12 h	no reaction
2	MnO_2	benzene	reflux	4 h	decomposed
3	MnO_2	DMF	rt	12 h	no reaction
4	MnO_2	DMSO	rt	12 h	no reaction
5	DDQ	DCM	rt	6 h	no reaction
6	DDQ	DCM:dioxane(1:1)	rt	14 h	no reaction
7	PCC	DCM	rt	6 h	no reaction
8	$CrO_3.NH_4Cl$	DCM	rt	12 h	no reaction
9	DDQ	DCM:dioxane(1:1)	50 °C	14 h	decomposed
10	CrO_3, aq. H_2SO_4	acetone	0 °C	1 h	decomposed
11	DMSO, $(COCl)_2$	DCM	−78 °C	4 h	inseparable mixture
12	CrO_3	AcOH	0 °C	1 h	decomposed

Table 1: Attempts for oxidation of allylic alcohol (±)-**50**

temperature was used but the reaction did not work (Table 1, entry 1). Hence, the reaction mixture was refluxed, wherein decomposition of the starting material (±)-**50** was observed

(Table 1, entry 2). Then MnO_2 was tried in DMF and DMSO, but the reaction did not work (Table 1, entry 3-4). DDQ in dichloromethane, dioxane and dichloromethane mixture (1:1)[7] or PCC in dichloromethane at room temperature did not work (Table 1, entry 5-7). The freshly synthesized reagent $CrO_3.NH_4Cl$[8] in dichloromethane also did not work (Table 1, entry 8). The standard Jones oxidation (Table 1, entry 10) and Swern oxidation (Table 1, entry 11) ended up in either complex inseparable mixture or decomposed products. Finally, the Fieser oxidation[9] using CrO_3 (3.2 equiv) in AcOH was applied and it was observed from Thin Layered Chromatography (TLC) that the starting material was consuming and leading to a new non-polar spot (Table 1, entry 12). Isolation of the newly formed spot was tried on column chromatography with silica, alumina (Neutral, acidic, basic) but every time we failed to isolate the desired compound because of its instability. The HRMS (ESI) m/z calcd for $C_{14}H_{12}O_6Na$: 299.0526, found 299.0523 of the reaction mixture confirmed the presence of oxidized compound (±)-**53** in the reaction mixture.[9]

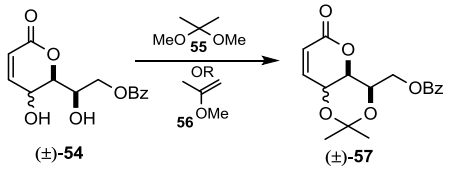
To overcome this problem we decided to reduce the unstable oxidized product (±)-**53** *in situ*. First, we confirmed the time required for complete consumption of the hydroxy pyranone (±)-**50** using CrO_3 (3.2 equiv), which was found to be 30 minutes. Isopropanol and $NaBH_4$ were added sequentially to the reaction after complete consumption of (±)-**50**. Several permutations



Entry	$NaBH_4$ (equiv)	Reaction temp (reduction)	Yields (%)
1	1.4	0 °C	20
2	1.4	−20 °C	42
3	10	−20 °C	10
4	5	−20 °C	62
5	**4**	**−20 °C**	**76**
6	3	−20 °C	68

Table 2: Optimization of two steps one-pot oxidation-reduction reactions

and combinations of equivalents of $NaBH_4$ and reaction temperature (Table 2) provided the optimized condition (Table 2, entry 5). CrO_3 (3.2 equiv) in acetic acid for 30 minutes at room temperature then cooling to −20 ^oC followed by sequential addition of isopropanol and $NaBH_4$ (4 equiv) gave 1,3-diol (±)-**54** in 76% yield (Table 2, entry 5). The spectral analysis of 1,3-diol (±)-**54** shows a single diastereomer, which confirmed that the reduction proceeds in diastereoselective fashion. To determine the relative stereochemistry of the 1,3-diol (±)-**54**, we planned to use the Rychnovsky's acetonide method.[10] Several available conditions were tried to synthesize the acetonide (±)-**57,** but we could not prepare it (Table 3).

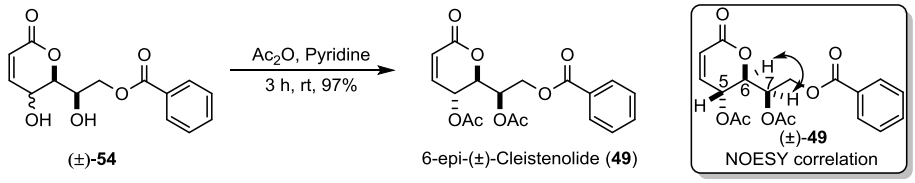


Entry	Catalyst (5 mol %)	Acetonide source (equiv)	solvent	Reaction Time (h)	temp	results
1	PTSA	**55** (2)	DCM	12	rt	no reaction
2	PTSA	**55** (200)	DCM	5	rt	no reaction
3	PTSA	**55** (2)	DMF	10	rt	no reaction
4	PTSA	**55** (2)	DMSO	10	rt	no reaction
5	CSA	**55** (400)	DMF	5	rt	no reaction
6	CSA	**55** (400)	DMSO	5	rt	no reaction
7	PTSA	**55** (200)	Acetone	5	rt	decomposed
8	PPTS	**55** (2)	DCM	12	rt	no reaction
9	PPTS	**55** (2)	DCM	5	0 ^oC	no reaction
10	PPTS	**55** (200)	DCM	5	0 ^oC to rt	no reaction
11	PPTS	**56** (200)	DCM	5	rt	no reaction
12	PPTS	**56** (200)	DCM	5	0 ^oC to rt	no reaction
13	PTSA	**55** (200)	THF	6	rt	no reaction
14	PTSA	**56**(200)	THF	6	rt	no reaction
15	CSA	**55** (200)	Pet ether	10	reflux	no reaction
17	PTSA	**55** (200)	THF	12	reflux	no reaction
18	CSA	**55** (200)	DCM	10	rt	no reaction

Table 3: Attempts to synthesize acetonide (±)-**57**

Hence, we decided to synthesize the epimer of the natural product 6-epi-(±)-cleistenolide (**49**) and determine the relative stereochemistry of the product. The 1,3-diol (±)-**54** was treated with acetic anhydride and pyridine at room temperature to furnish diacetylated product 6-epi-(±)-cleistenolide (**49**) in 97% yield (Scheme 14). Thus, the synthesis was achieved in 60% overall

yields in five linear steps from commercially available furyl allyl alcohol **48**. The relative stereochemistry of all three chiral centers of the natural product was confirmed by 2D NMR spectroscopy of 6-epi-(±)-cleistenolide (**49**). This confirmed that the diol (±)-**54** synthesized in the one-pot two-step reaction sequences has *anti* relative configuration for the 1,3-diol and the reaction proceeded diastereoselectively.



Scheme 14: Synthesis of 6-epi-(±)-cleistenolide (**49**)

The mechanism of the formation of 1,3-*anti*-diol (±)-**54** via diastereoselective reduction could be now explained. Acetic acid and $NaBH_4$ *in situ* forms $NaBH(OAc)_3$, which chelates with the free hydroxy of the pyranone (±)-**53** to form a boron-ate complex [(±)-**58**]. The boron-ate complex [(±)-**58**] then delivers the proton from the opposite side to obtain 1,3-*anti*-diol (±)-**54** via Saksena-Evans reduction (Figure 4).[11]

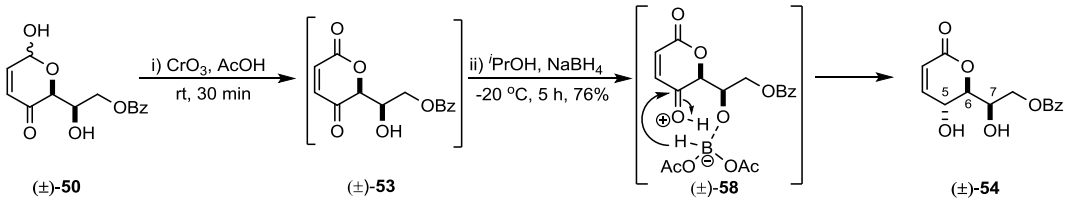
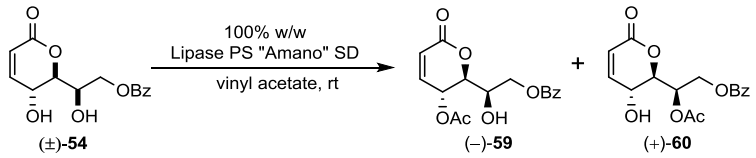


Figure 4: The mechanism for the observed diasterioselectivity in the synthesis of (±)-**54**

We realized that the intermediate 1,3-*anti*-diol (±)-**54** could furnish the enantiomerically pure 6-epimer of (±)-cleistenolide (**49**) using enzymatic resolution. Candida lipase enzymes have been used for enzymatic resolution of 1,3-diols.[12] To study the enzymatic resolution of the 1,3-*anti*-diol (±)-**54** we chose the enzyme Lipase PS "Amano" SD (100% w/w) and vinyl acetate (4 equiv) as the acyl source. The study was performed using various solvents and solvent combinations to optimize the enzymatic protocol (Table 4). The final optimized condition was

achieved, wherein *n*-hexane:benzene:acetone (2:1:1) at room temperature for 7 days (Table 4, entry 7) furnished (–)-**59** and (+)-**60** (combined) in 43% yield.



Entry	Solvent combination	Reaction time	result
1	n-hexane	7 days	no reaction
2	Pet ether	7 days	no reaction
3	benzene	7 days	no reaction
4	Pet ether: benzene (2:1)	2 days	no reaction
5	n-hexane:acetone	7 days	10%
6	n-hexane:benzene:acetone (2:1:1)	3 days	20%
7	**n-hexane:benzene:acetone (2:1:1)**	**7 days**	**43%**
8	n-hexane:benzene:acetone:phosphate buffer (2:1:1:0.5)	7 days	no reaction

Table 4: Optimization of enzymatic resolution of 1,3-diol (±)-**50**

Both the monoacylated products (–)-**59** and (+)-**60** from enzymatic resolution were separated by column chromatography. 2D NMR spectroscopy study of these enzymatically resolved products suggested that they are having same stereochemistry and the only difference is at the acylation of the alcohol (Figure 5).

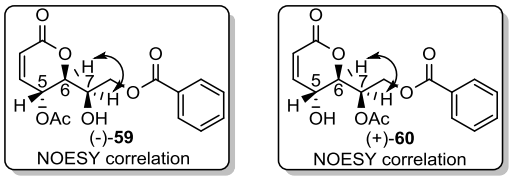
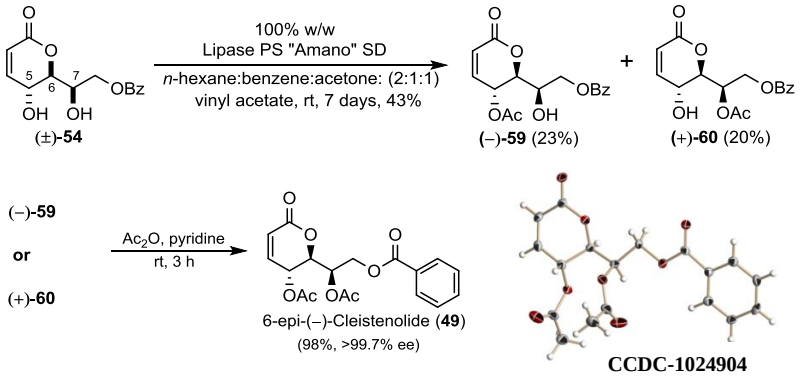


Figure 5: Enzymatically resolved products and their stereochemistry

The products (–)-**59** and (+)-**60** were acetylated separately with acetic anhydride and pyridine to get the product 6-epi-(–)cleistenolide (**49**) in 98% yield. 6-epi-(–)-Cleistenolide (**49**), which was synthesized from (–)-**59** showed 63% *ee* by chiral HPLC. The enhancement in % *ee* was achieved to >99.7% *ee* after single recrystallization, whereas 6-epi-(–)-cleistenolide (**49**) achieved from (+)-**60** gave >99.9% *ee* without any recrystallization. The stereochemistry of (–)-**59** and (+)-**60** was reconfirmed from the optical rotation and chiral HPLC of the corresponding



Scheme 15: Chemoenzymatic synthesis of 6-epi-(–)-cleistenolide (**49**)

product (–)-**49**. Hence, it was confirmed that the enzyme is very selective for only (*5R,6R,7R*) enantiomer of the 1,3-*anti*-diol (±)-**54**. The absolute stereochemistry of the 6-epi-(–)-cleistenolide (**49**) was again reconfirmed with single-crystal X-ray diffraction analysis (Scheme 15).

This work has been cited six times. This method was found useful for the synthesis of the *α,β*-unsaturated *δ*-lactone core utilizing the Achmatowicz reaction.[4,13]

1.5 Conclusions

A simple, practical, scalable and general route was developed to synthesize 6-epi-(±)-cleistenolide (**49**) using Achmatowicz reaction as a key step. It does not require special reagents or dry atmosphere. The one-pot chemoselective oxidation of allylic alcohol followed by diastereoselective 1,3-*anti* reduction of the ketone with *in situ* generated $NaBH(OAc)_3$ was achieved in high yields. For the first time, enzyme Lipase PS "Amano" SD was utilized for the resolution of 1,3-*anti* diol (±)-**54** and found selective to only one of the enantiomer. This strategy enables straight forward access to similar class of natural products and their rational analogues.

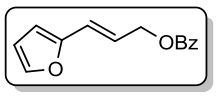
1.6 Experimental section

1.6.1 General information

Chiral HPLC analysis was performed using Kromasil 5 AmyCoat (4.6 x 250mm) column on Shimadzu Class-VP V6.12 SP5 with UV detector.

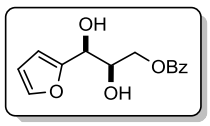
1.6.2 Synthesis and data

(*E*)-3-(Furan-2-yl)allyl benzoate (52). A two-neck round-bottom flask containing a solution of allylic alcohol **48** (500 mg, 1.03 mmol) in dichloromethane (10 mL) was cooled to 0 ^{o}C under argon atmosphere. Pyridine (0.56 mL, 5.64 mmol, 1.4 eq.) was added and the reaction mixture was stirred for 5 minutes. Finally, drop wise addition of benzoyl chloride (0.45 mL, 4.83 mmol, 1.2 eq.) over a period of 5 minutes followed by stirring the reaction at the same temperature for an hour. It was then allowed to warm to ambient temperature (30 °C) and stirred for another 3 h. After completion of the reaction, it was diluted with dichloromethane (20 mL) and the DCM layer was washed with saturated aqueous $CuSO_4$ solution. Organic layer was dried over sodium sulfate, concentrated and purified by column chromatography using ethyl acetate-petroleum ether (3:97) to provide compound **52** in 98% yield (901 mg, yellow oil).



R_f: 0.8 (1:9 Ethyl acetate:Petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): 8.09 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.38 (S, 1H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.40 (dd, *J* = 3.2, 1.7 Hz, 1H), 6.32-6.39 (m, 1H), 6.32 (d, *J* = 3.2 Hz, 1H) 4.97 (dd, *J* = 6.3, 0.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 151.8, 142.4, 133.0, 130.1, 129.7, 128.4, 122.1, 121.7, 111.4, 108.9, 65.1,; HRMS-ESI (*m/z*) calcd $(C_{14}H_{12}O_3 + Na)^{+}$: 251.0679 found: 251.0678.

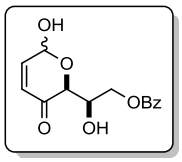
3-(Furan-2-yl)-2,3-dihydropropyl benzoate (±)-**51.** The benzoylated compound **52** (200 mg, 0.87 mmol) was taken in single-neck round-bottom flask and dissolved in a mixture of acetonirile (3 mL), THF (1.5 mL), water (0.75 mL) [4:2:1]. NMO (123 mg, 1.05 mmol, 1.2 eq.) was added and the reaction mixture was cooled to 0 ^{o}C. Finally 0.05 M solution of OsO_4 (13.36 mg, 0.052 mmol, 0.06 eq.) in *t*-butanol was added and the reaction was allowed to reach to room temperature followed by stirring for 12 h. The reaction mixture was diluted with ethyl acetate (25 mL) and ethyl acetate layer was washed twice with brine (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL). Combined organic layers were dried over sodium sulfate, concentrated and purified by column chromatography using ethyl acetate-petroleum ether (3:7) to furnish 1, 2 diol **51** in 88% yield (203 mg, thick colorless liquid).



R_f: 0.3 (1:1 Ethyl acetate:Petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 1.0 Hz, 1H), 6.41 (d, J = 3.3 Hz, 1H), 6.37 (dd, J = 3.3, 1.8 Hz, 1H), 4.80 (d, J = 5.5 Hz, 1H), 4.43-4.49 (m, 1H), 4.29-4.37 (m, 2H), 2.92 (bs, 1H), 2.85 (bs, 1H),; ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 153.0, 142.6, 133.3, 129.74, 129.69, 128.4, 110.5, 108.1, 71.9, 68.3, 65.6,; HRMS-ESI (*m/z*) calcd $(C_{14}H_{14}O_5 + Na)^{+}$: 285.0733 found: 285.0732.

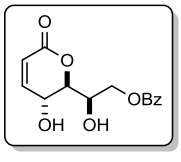
2-Hydroxy-2-(6-hydroxy-3-oxo-3,6-dihydro-2*H*-pyran-2-yl)ethyl benzoate (±)-**50**. The solution of diol **51** (100 mg, 0.38 mmol) in THF (3 mL) and water (0.75 mL) (4:1) was cooled to 0 ^{o}C, followed by addition of $NaHCO_3$ (64 mg, 0.76 mmol, 2 eq.), NaOAc (31 mg, 0.38 mmol, 1 eq.) and NBS (67 mg, 0.38, 1 eq.) sequentially. The reaction mixture was stirred at the same temperature for 2 h. After completion of reaction saturated aqueous $NaHCO_3$ (2 mL) was added and the reaction mixture was extracted with dichloromethane (10 mL) twice, dried over sodium

sulfate, concentrated and purified by column chromatography using ethyl acetate-petroleum ether (4:6) to give diol **50** in 95 % yield (101 mg, thick oil).



R_f: 0.2 (1:1 Ethyl acetate:Petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.02 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 6.89-7.00 (m, 1H), 6.20 (dd, J = 15.5, 10.5 Hz, 1H), 5.70 (dd, J = 22.2, 3.3 Hz, 1H), 4.40-4.76 (m, 4H), 2.63 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.9, 194.3, 166.81, 166.78, 146.2, 145.2, 133.4, 133.3, 129.71, 129.68, 129.5, 129.4, 128.5, 128.0, 127.8, 87.7, 87.1, 79.1, 73.5, 70.0, 68.6, 65.04, 64.9,; HRMS-ESI (*m/z*) calcd $(C_{14}H_{14}O_6 + Na)^+$: 301.0683 found: 301.0681.

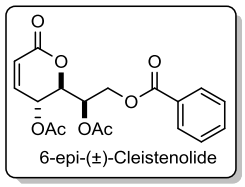
2-Hydroxy-2-(3-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)ethyl benzoate (±)-**54.** In a two-neck round-bottom flask containing a solution of compound **50** (100 mg, 0.36 mmol) in acetic acid (2mL) was added solution of chromium trioxide (114 mg, 1.15 mmol, 3.2 eq.) in acetic acid (10 mL) drop wise at room temperature and stirred for 30 minutes. Isopropanol (5 mL) was added and the reaction mixture was cooled to −20 ^{o}C. Finally, $NaBH_4$ (54 mg, 1.44 mmol, 4 eq.) was added and the stirring was continued at the same temperature for another 5 h. After completion of the reaction, solvents were evaporated and the remaining residue was dissolved in ethyl acetate (20 mL). Ethyl acetate layer was washed with brine (5 ml), dried over sodium sulfate, concentrated and purified by column chromatography using ethyl acetate-petroleum ether (1:1) to obtain 76% of 1, 3 diol **54** (76 mg, white solid).



R_f: 0.3 (6:4 Ethyl acetate:Petroleum ether); m.p. 134 ^{o}C; ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.06 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 6.97 (dd, J = 10.0, 1.5 Hz, 1H), 5.88 (dd, J = 9.8, 2.0 Hz, 1H), 5.05 (d, J = 7.0 Hz, 1H), 4.76-4.82 (m, 1H), 4.67 (d, J = 7.5 Hz, 1H), 4.56 (dd, J = 11.0, 7.3 Hz, 1H),

4.47 (dd, *J* = 11.0, 5.8 Hz, 1H), 4.42 (dd, *J* = 9.8, 1.2 Hz, 1H), 4.37 (apparent t, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, Acetone-d_6): δ 166.6, 162.8, 152.0, 134.0, 131.1, 130.3, 129.4, 119.7, 82.7, 67.3, 66.1, 62.5,; HRMS-ESI (*m/z*) calcd $(C_{14}H_{14}O_6 + Na)^+$: 301.0683 found: 301.0678.

6-epi-(±)-Cleistenolide (49). Compound (±)-**54** (20 mg, 0.072 mmol) was taken in two-neck round-bottom flask and treated with pyridine (0.75 mL) and acetic anhydride (0.5 mL). The reaction mixture was stirred at room temperature for 3 h. Solvents were evaporated and column chromatographic purification of the residue with ethyl acetate-petroleum ether (3:7) gave 6-epi-(±)-Cleistenolide (**49)** in 97% yield (25.3 mg, white solid).

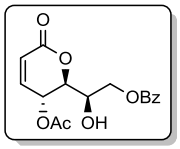


6-epi-(±)-Cleistenolide

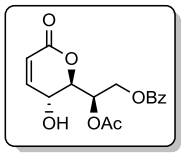
R_f: 0.6 (1:1 Ethyl acetate:Petroleum ether); m.p. 121 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 6.79 (dd, *J* = 10.0, 2.8 Hz, 1H), 6.12 (dd, *J* = 10.0, 1.7 Hz, 1H), 5.59 (dt, *J* = 6.3, 2.0 Hz, 1H), 5.52 (ddd, *J* = 7.0, 5.3, 1.9 Hz, 1H), 4.75 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.63 (dd, *J* = 11.5, 5.3 Hz, 1H), 4.58 (dd, *J* = 11.5, 7.3 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H),; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 169.7, 165.9, 160.9, 144.1, 133.4, 129.7, 129.4, 128.5, 121.9, 78.0, 67.9, 63.3, 62.4, 20.7,; HRMS-ESI (*m/z*) calcd $(C_{18}H_{18}O_8 + Na)^+$: 385.0894 found: 385.0892.

Chemoenzymatic synthesis of 6-epi-(–)-Cleistenolide-(49). The diol **50** (600 mg, 2.15 mmol) and vinyl acetate (750 mg, 8.71 mmol, 4 eq.) was dissolved in a mixture of acetone (50 mL), benzene (50 mL) and *n*-hexane (100 mL) [1:1:2]. Enzyme Lipase PS "Amano" SD (600 mg) was added and the reaction mixture was stirred at room temperature for 7 days. The reaction mixture was filtered off through celite and washed with 50 mL acetone. Combined organic layers were concentrated and the residue was purified by column chromatography using ethyl acetate-

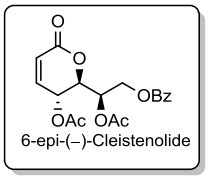
petroleum ether (2:8) to furnish monoactates (–)-**55** and (+)-**57** in 23% (159 mg, colourless oil) yield and 20% (139 mg, colourless oil) yield respectively.



(*R*)-2-((2*S*,3*R*)-3-Acetoxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-2-hydroxyethyl benzoate (–)-**59.** R_f: 0.5 (3:2 Ethyl acetate:Petroleum ether); $[\alpha]^{24}_{D}$ –8 (*c* 1, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.83 (dd, *J* = 10.0, 2.2 Hz, 1H), 6.09 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.81 (dt, *J* = 9.0, 2.2 Hz, 1H), 4.65 (dd, *J* = 11.5, 7.1 Hz, 1H), 4.57 (dd, *J* = 9.0, 1.7 Hz, 1H), 4.51 (dd, *J* = 11.5, 5.1 Hz, 1H), 4.09-4.16 (m, 1H), 2.80 (d, *J*= 7.6 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 166.5, 161.3, 144.7, 133.4, 129.8, 129.5, 128.5, 121.4, 79.2, 67.9, 65.0, 64.0, 20.8; HRMS-ESI (*m/z*) calcd $(C_{16}H_{16}O_7 + Na)^+$: 343.0788 found: 343.0785.



(*R*)-2-Acetoxy-2-((2*R*,3*R*)-3-hydroxy-6-oxo -3,6-dihydro-2*H*-pyran-2-yl) ethyl benzoate (+)-**60.** R_f: 0.4 (3:2 Ethyl acetate:Petroleum ether); $[\alpha]^{24}_{D}$ +45 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.83 (dd, *J* = 10.0, 1.5 Hz, 1H), 6.00 (dd, *J* = 10.0, 2.4 Hz, 1H), 5.56-5.51 (m, 1H), 4.72 (dd, *J* = 11.7, 7.6 Hz, 1H), 4.65 (dd, *J* = 11.7, 5.3 Hz, 1H), 4.45 (dd, *J* = 10.5, 1 Hz, 1H), 4.33 (d, *J* = 10.5 Hz, 1H), 3.56 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 165.9, 162.0, 149.6, 133.4, 129.7, 129.3, 128.5, 120.0, 80.3, 69.0, 62.7, 62.4, 20.8; HRMS-ESI (*m/z*) calcd $(C_{16}H_{16}O_7 + Na)^+$: 343.0788, found:343.0789.



6-epi-(–)-Cleistenolide (49). Compound (–)-**59** and (+)-**60** (20 mg, 0.062 mmol) were treated with pyridine (0.75 mL) and acetic anhydride (0.5 mL) at room temperature separately. The reaction mixture was stirred at room temperature for 3 h. Solvents were evaporated and column chromatographic purification of the

residue with ethyl acetate-petroleum ether (3:7) gave 6-epi-(–)-cleistenolide (**49**) in 98% yield (22.2 mg, white solid). In the case of compound (–)-**59** the *ee* of the product (–)-**49** was 63%, which enhanced to >99.7% after single recrystallization from the mixture of ethyl acetate and petroleum ether (1:8). However, in the case of compound (+)-**60** the *ee* of the product **1** was >99.9% without any recrystallization. m.p. 140 ^{o}C; $[\alpha]^{24}_{D}$ –22 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 6.79 (dd, *J* = 10.0, 2.8 Hz, 1H), 6.12 (dd, *J* = 10.0, 1.5 Hz, 1H), 5.59 (dt, *J* = 8.6, 2.0 Hz, 1H), 5.52 (ddd, *J* = 7.3, 5.2, 1.9 Hz, 1H), 4.75 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.63 (dd, *J* = 11.6, 5.2 Hz, 1H), 4.59 (dd, *J* = 11.6, 7.3 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 169.7, 165.9, 160.9, 144.2, 133.4, 129.7, 129.3, 128.5, 121.9, 77.8, 67.8, 63.2, 62.4, 20.7; HRMS-ESI (*m/z*) calcd $(C_{18}H_{18}O_8 + Na)^+$: 385.0894 found: 385.0894.

1.7 References

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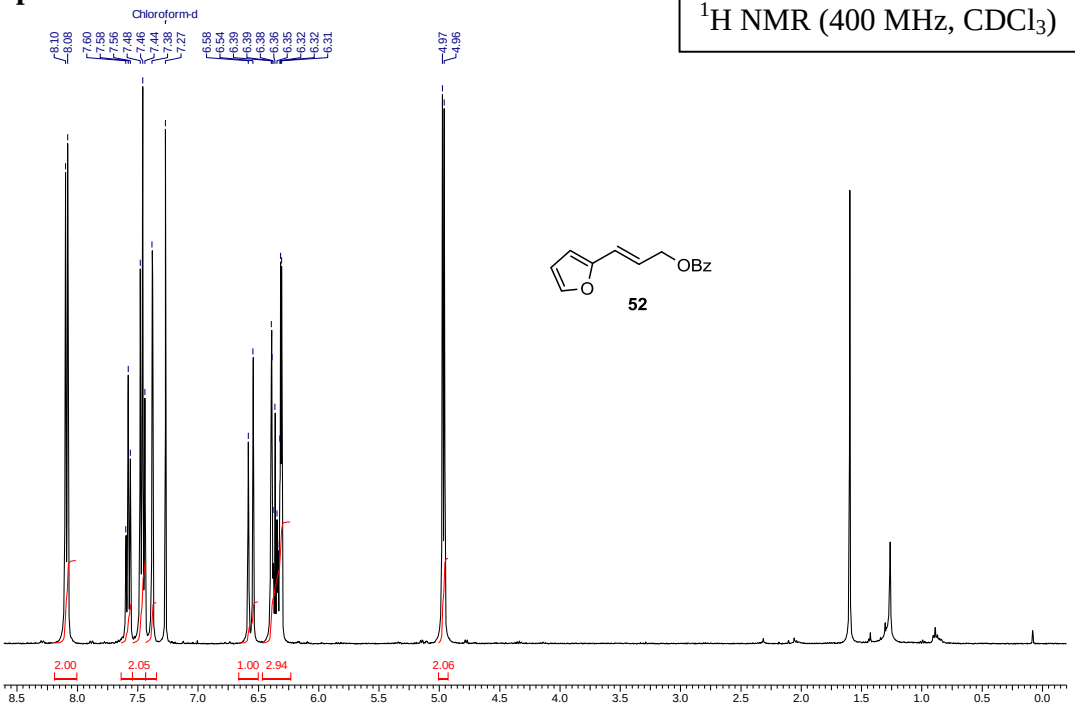
1.8 Spectra

^{1}H NMR (400 MHz, $CDCl_3$)



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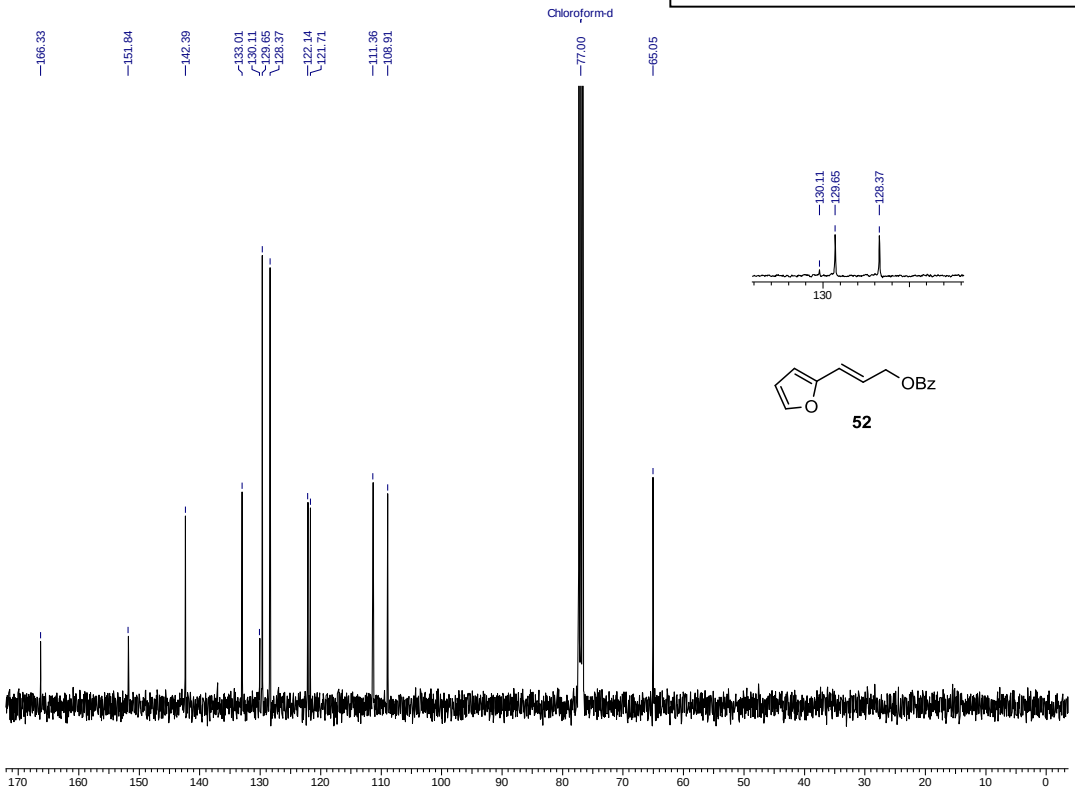

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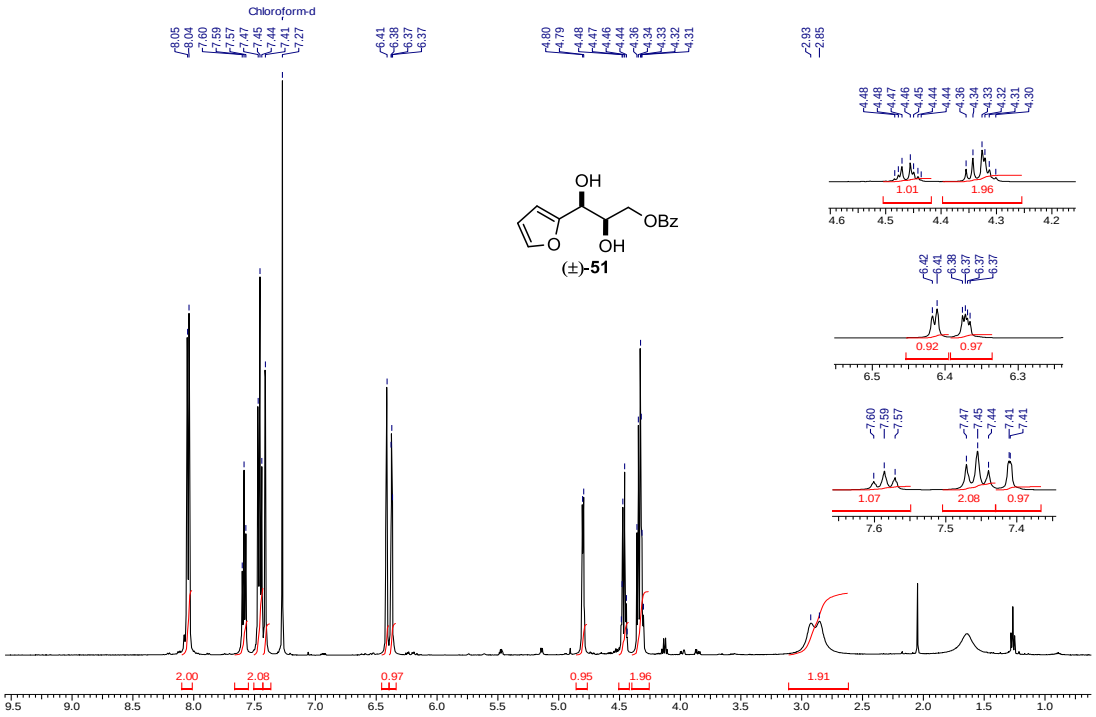

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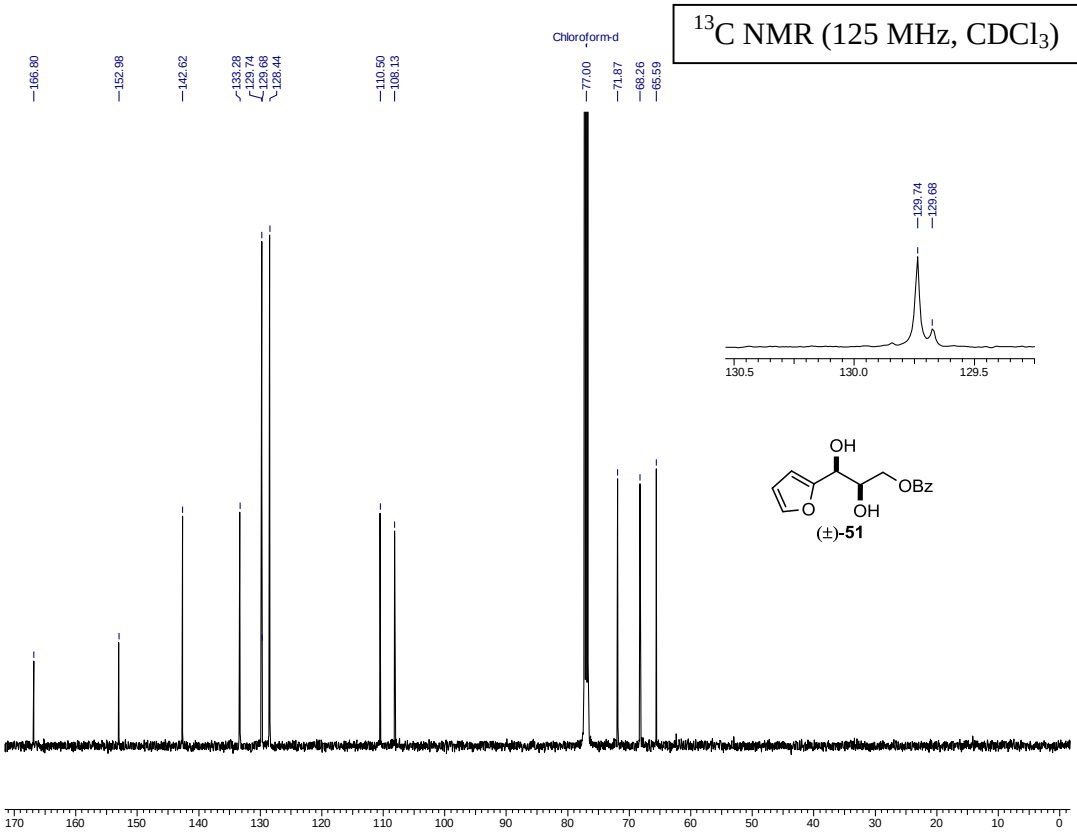

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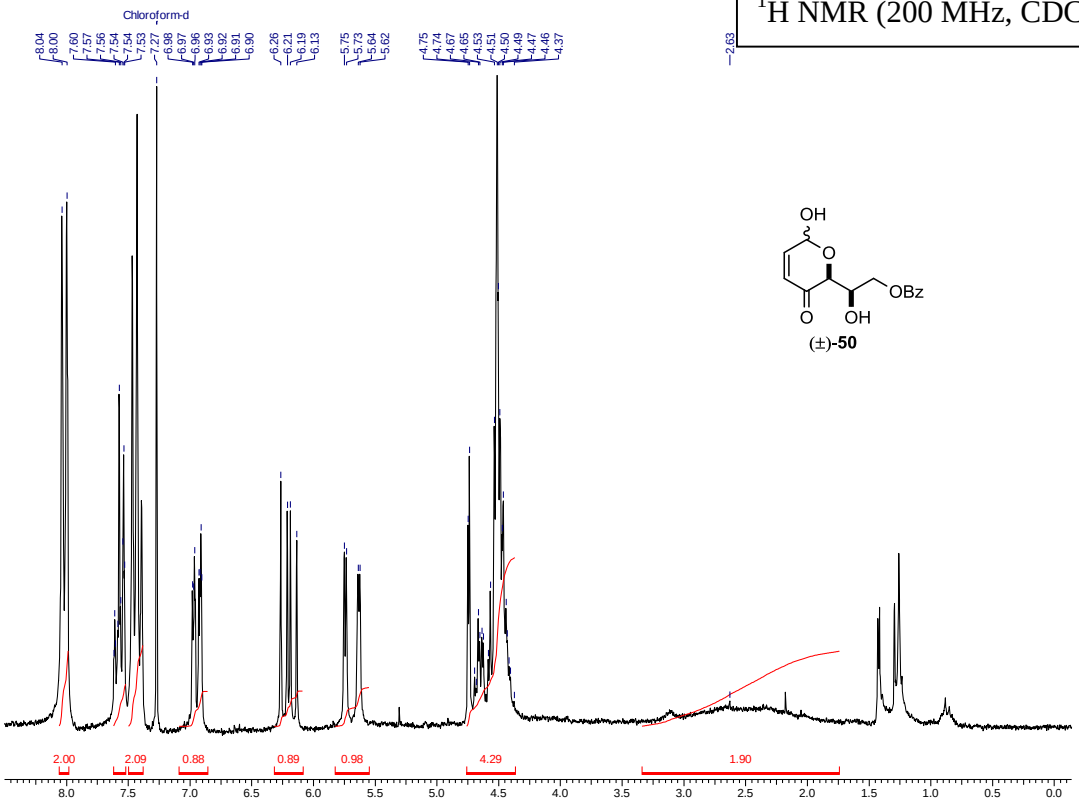

(±)-**50**

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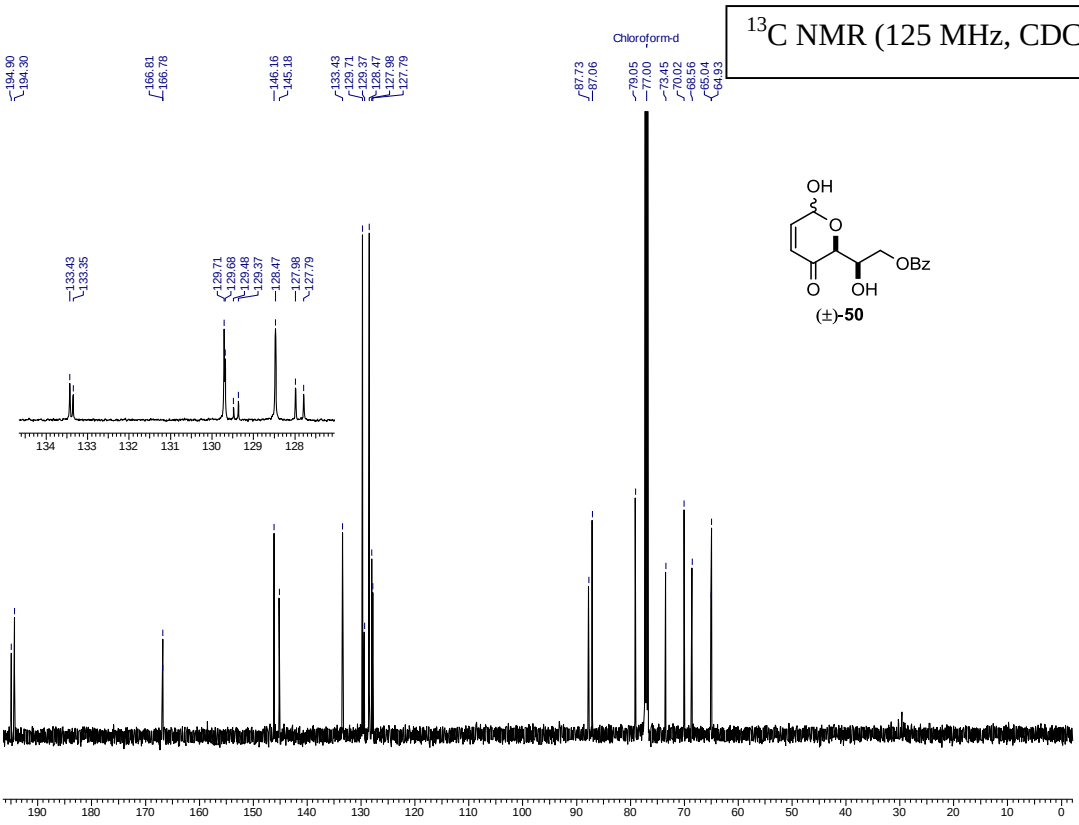

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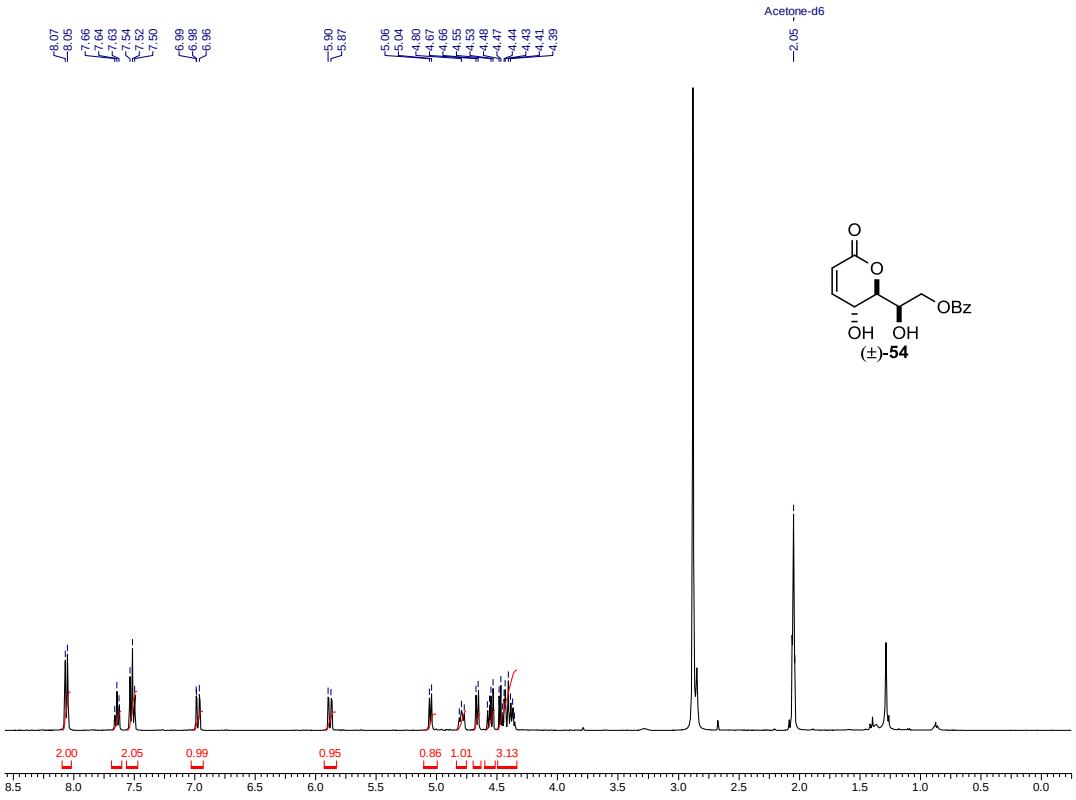

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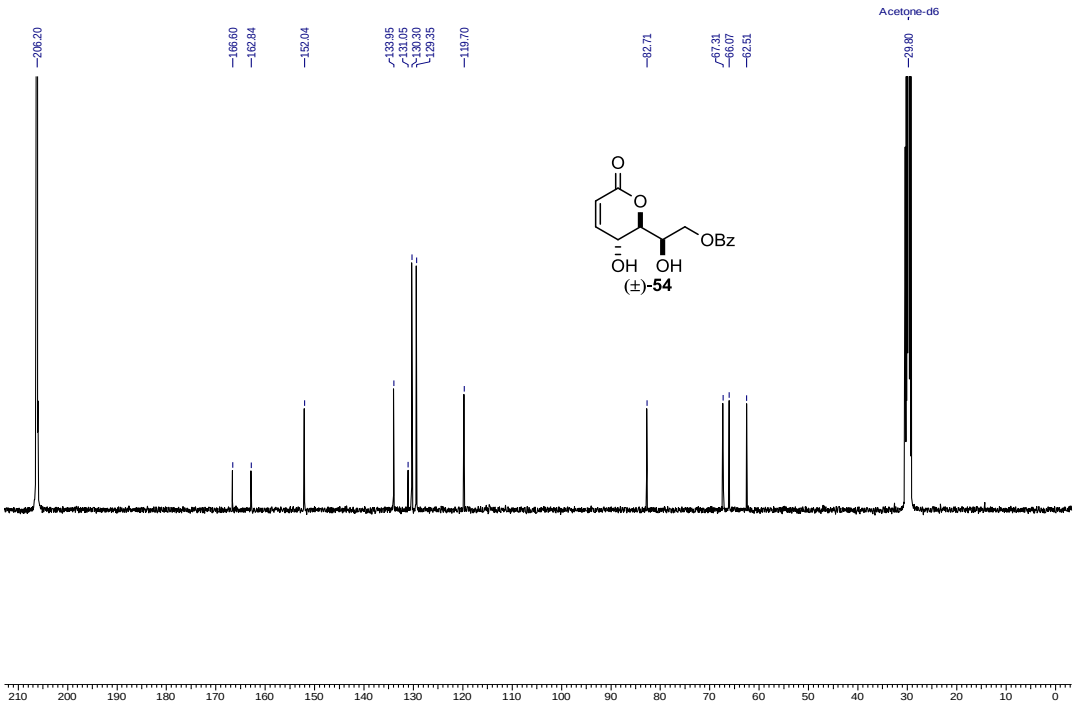

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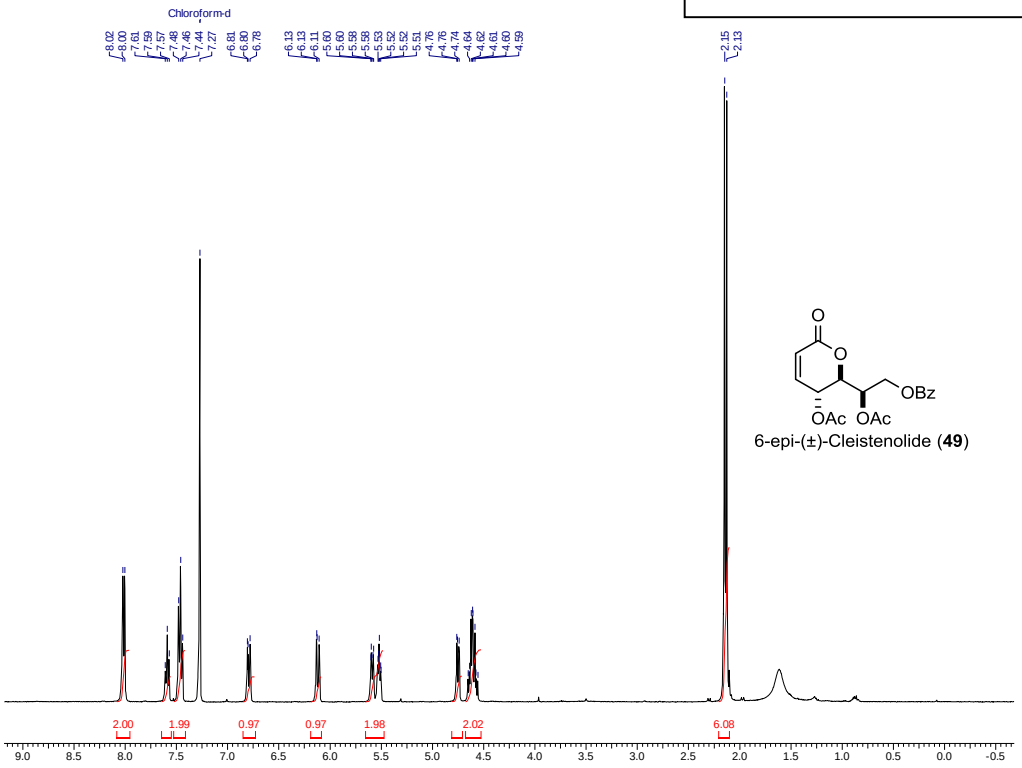

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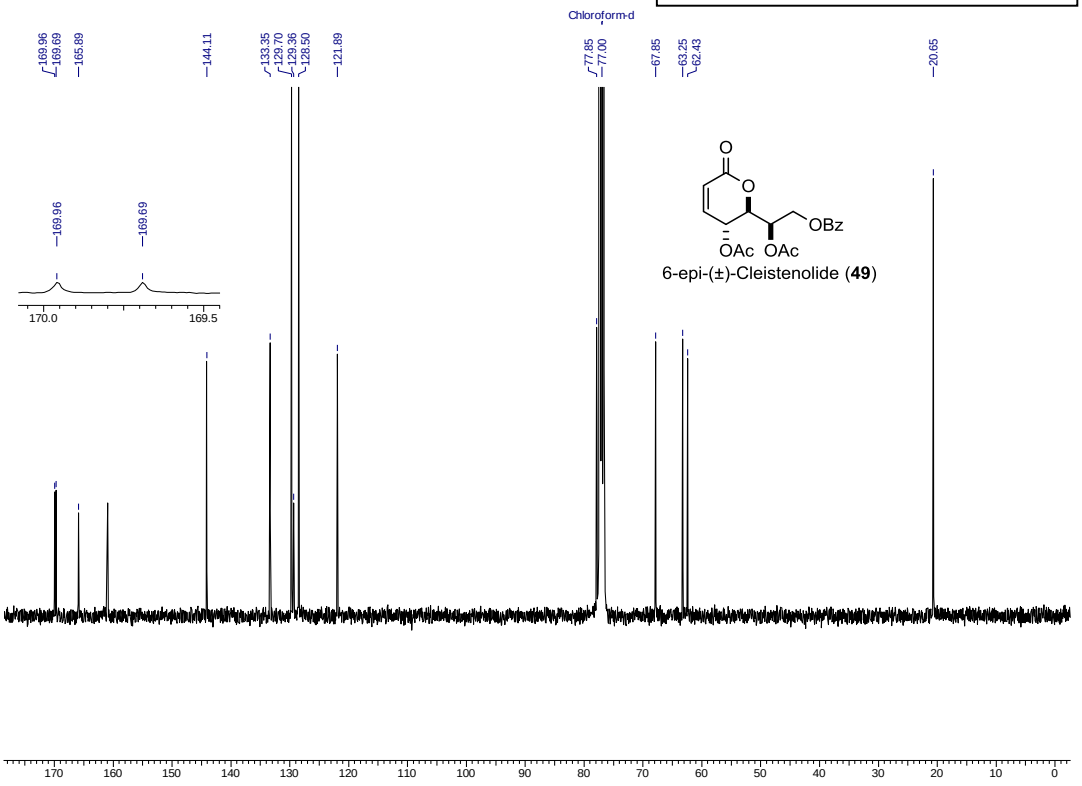

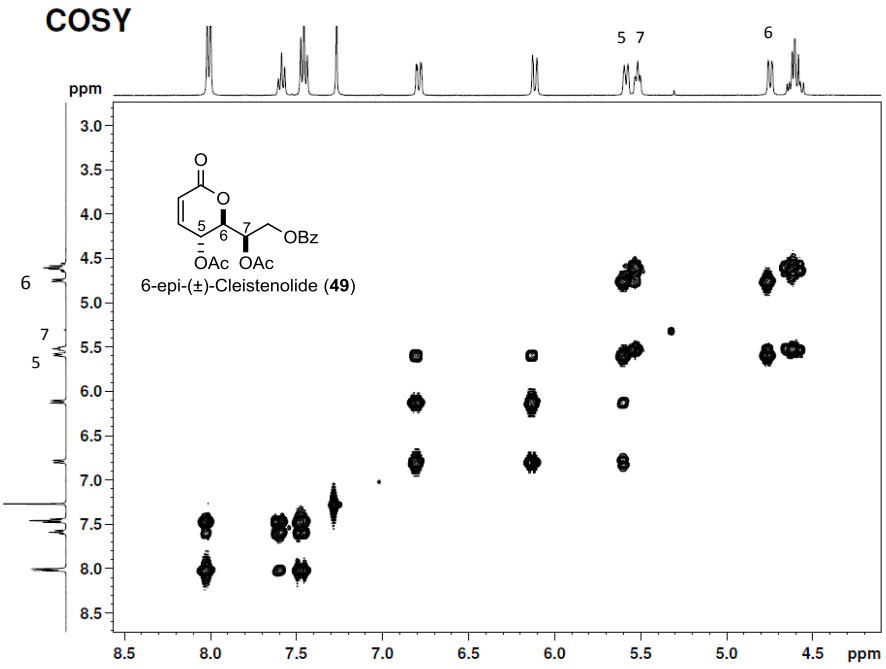
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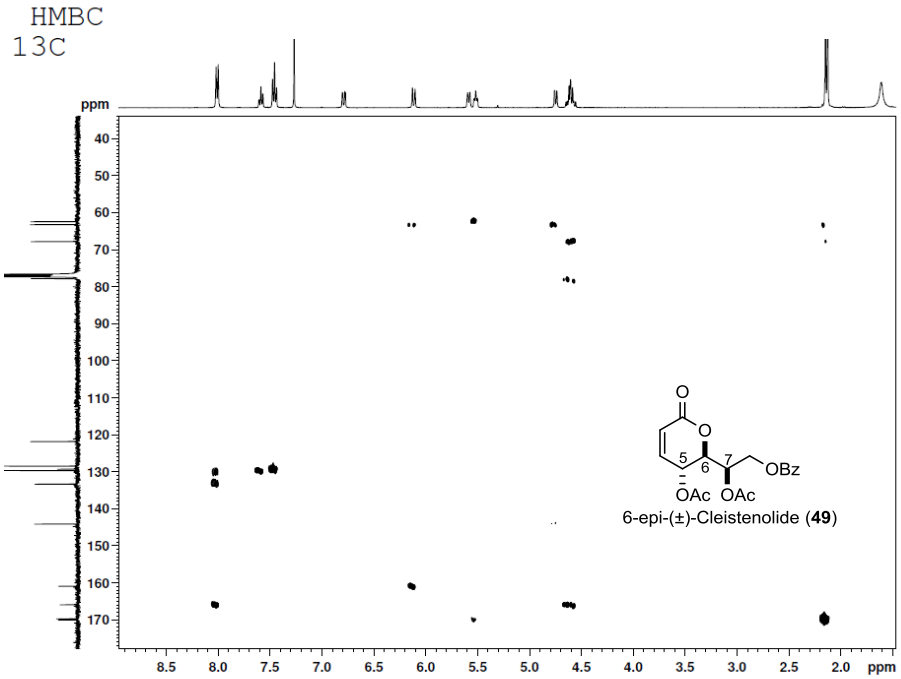
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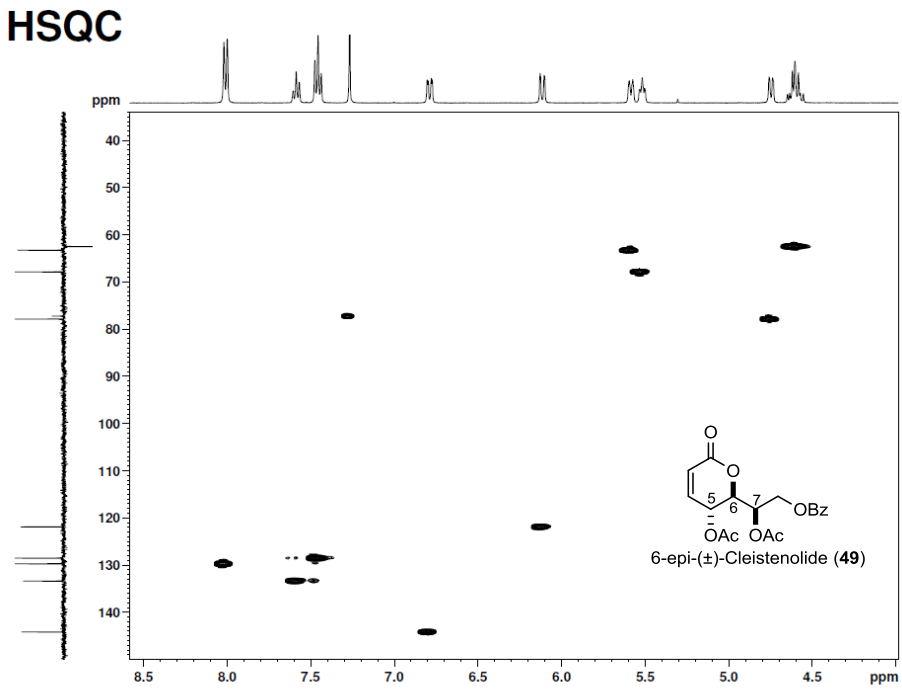
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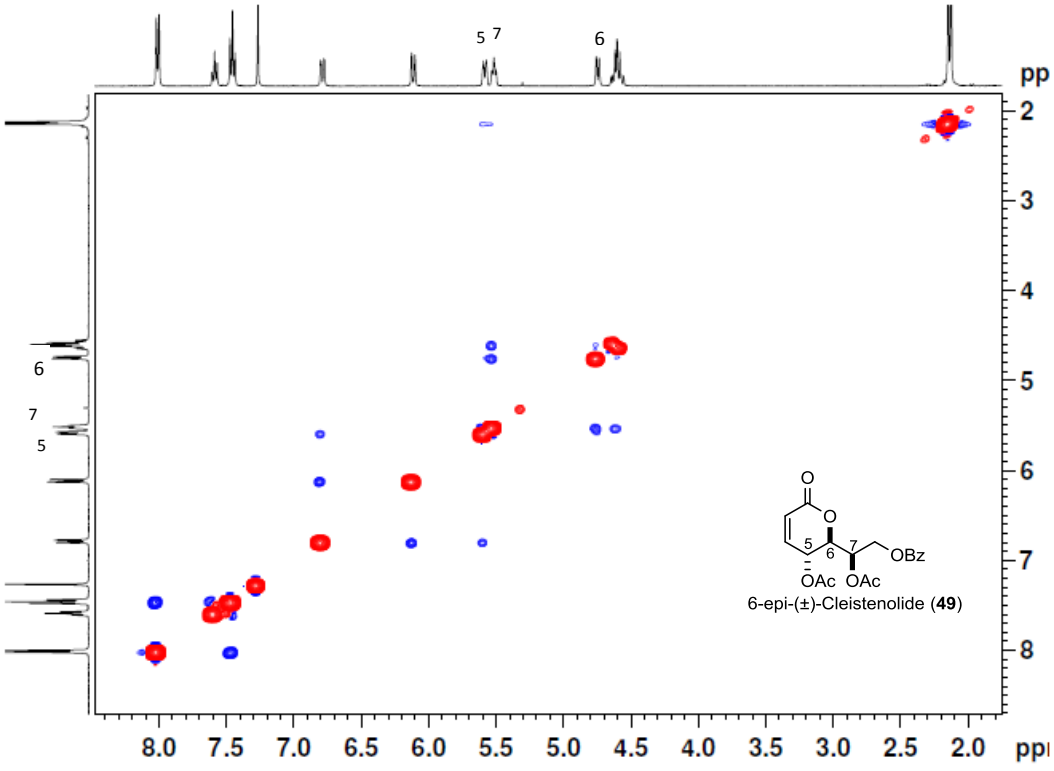
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6-epi-(±)-Cleistenolide (49)

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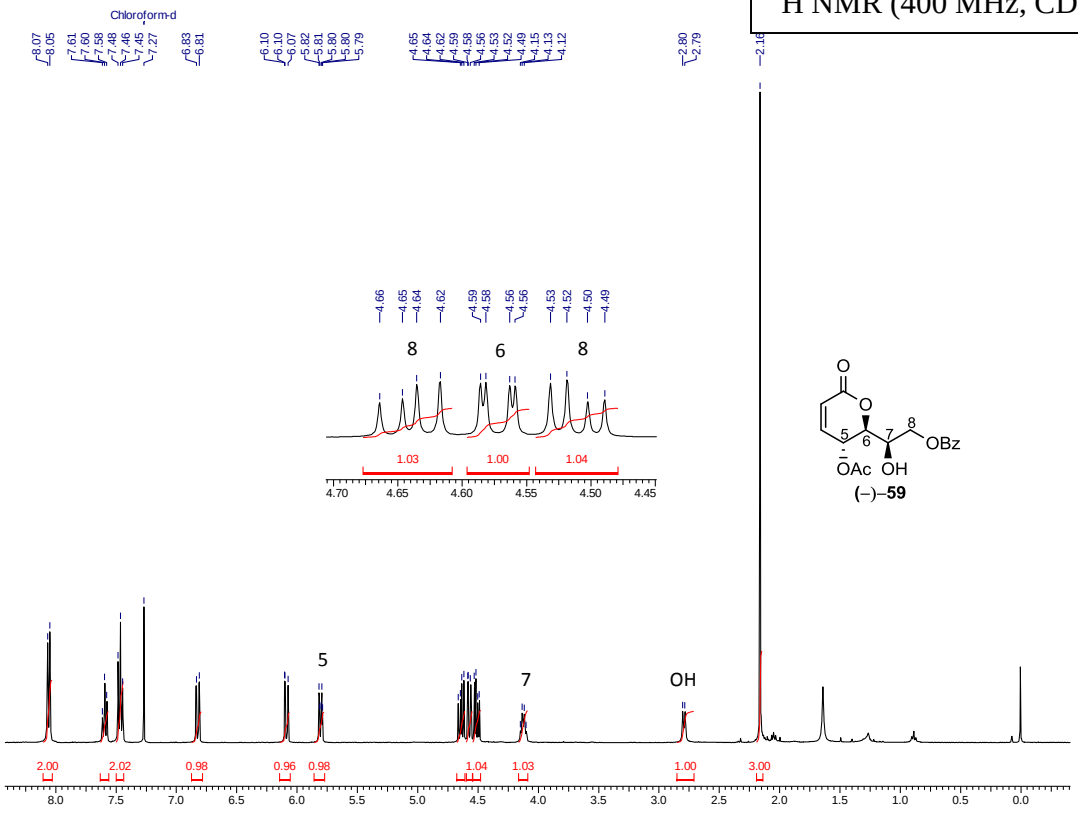

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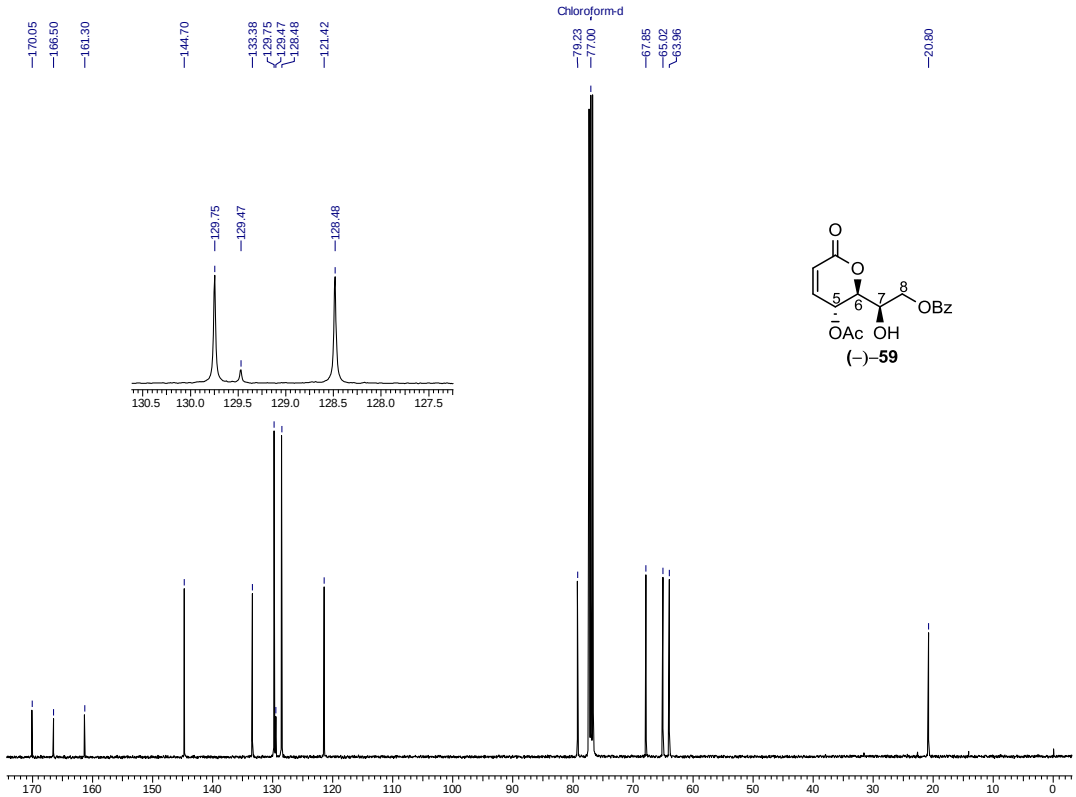

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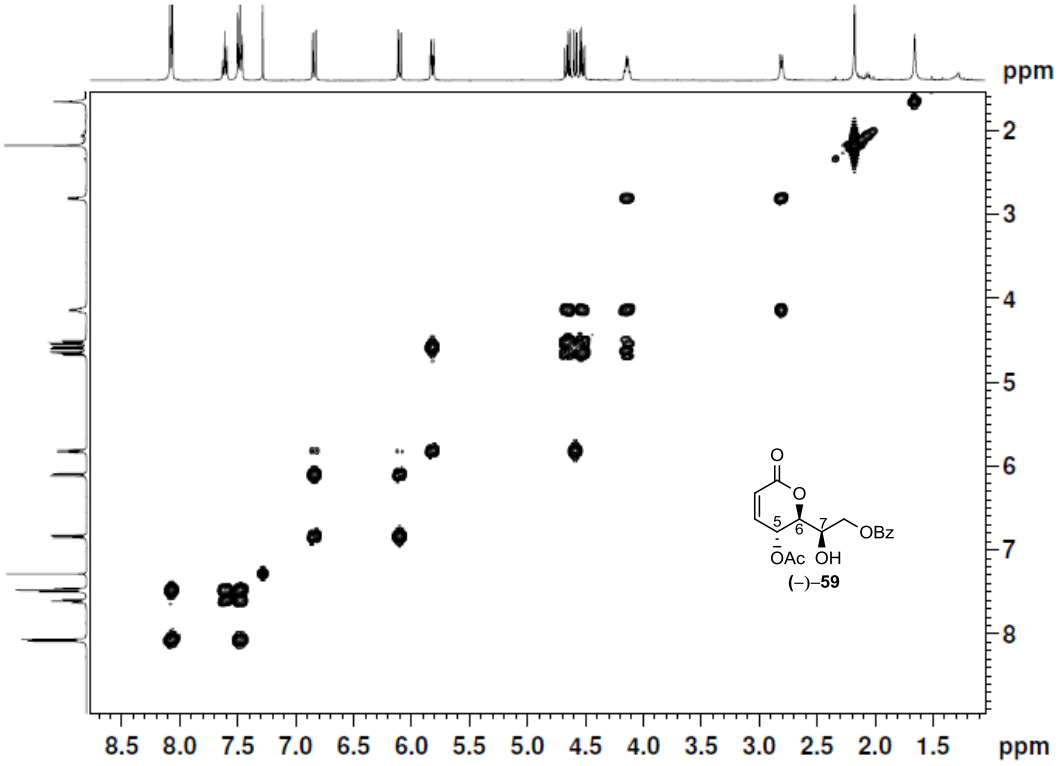
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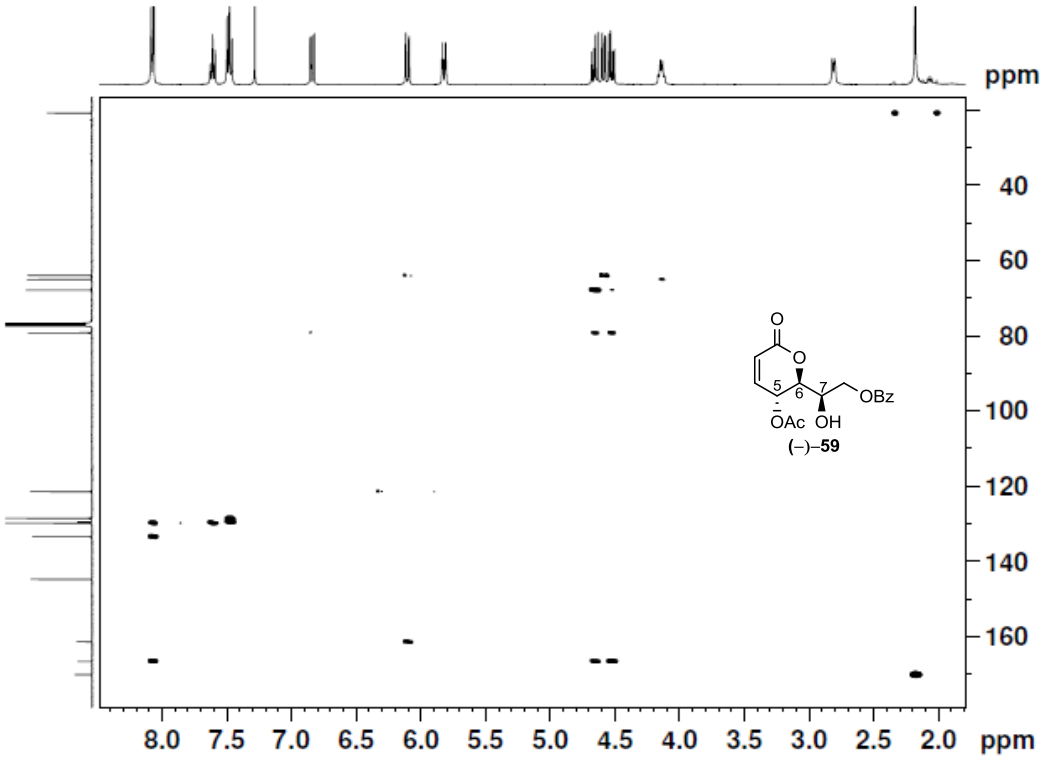
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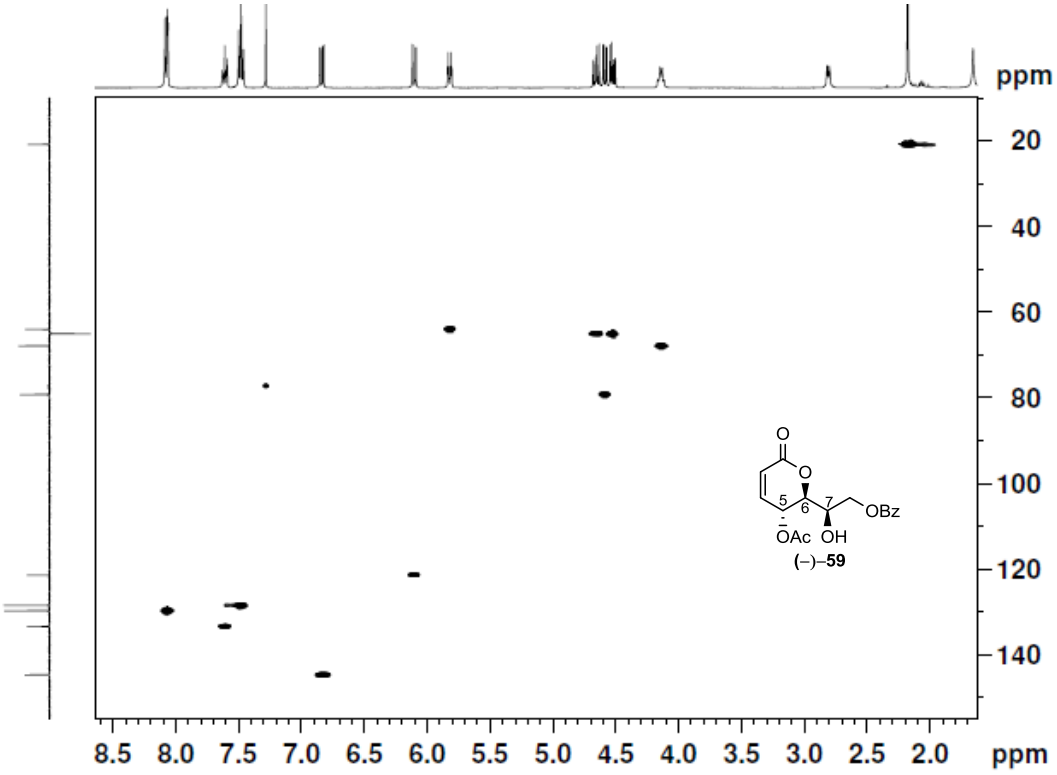
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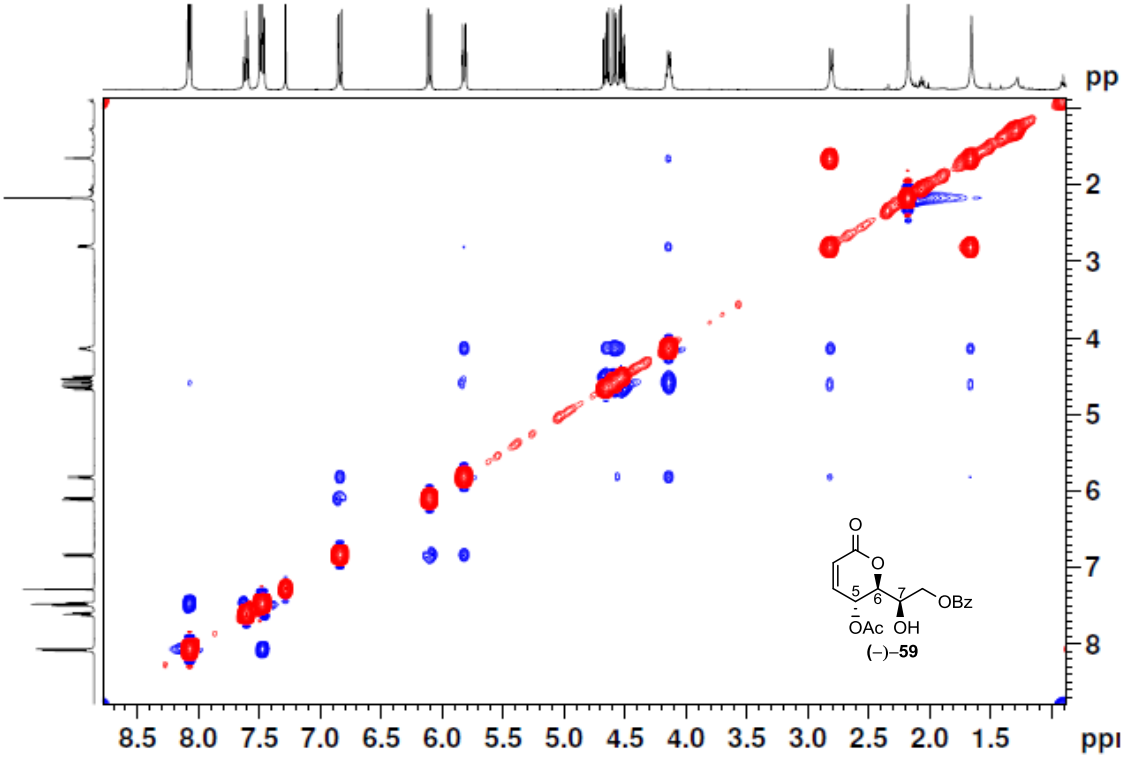
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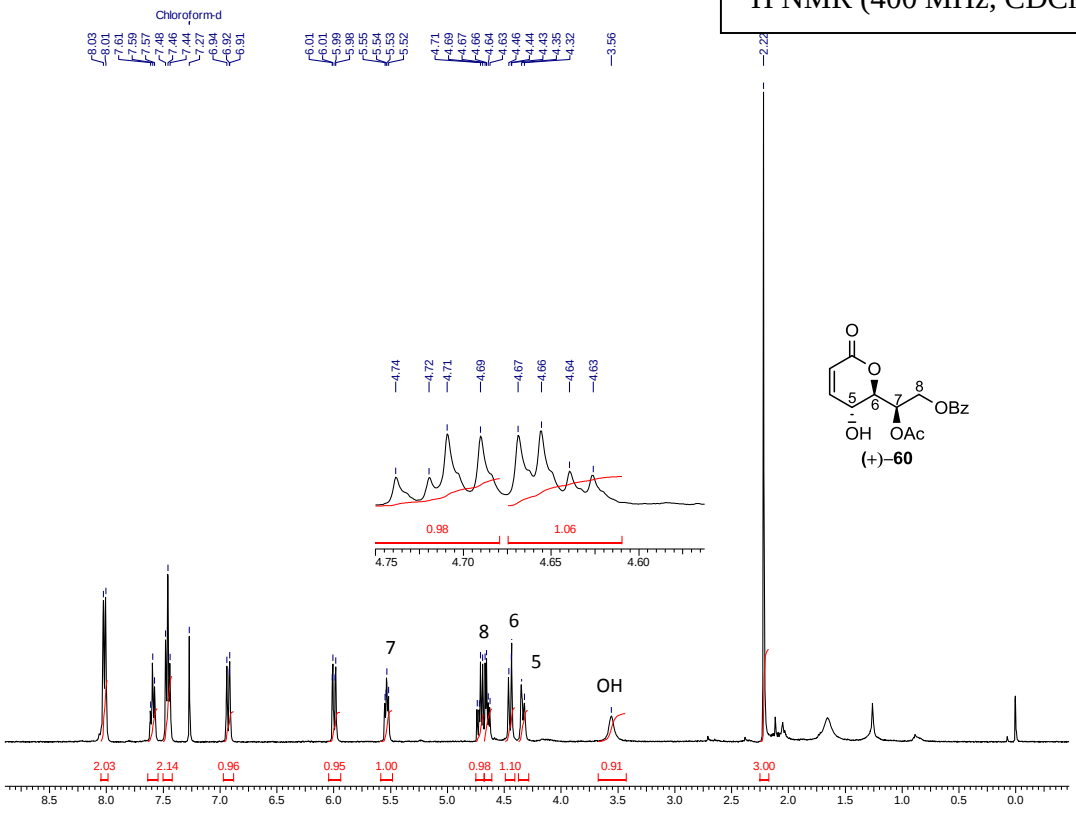

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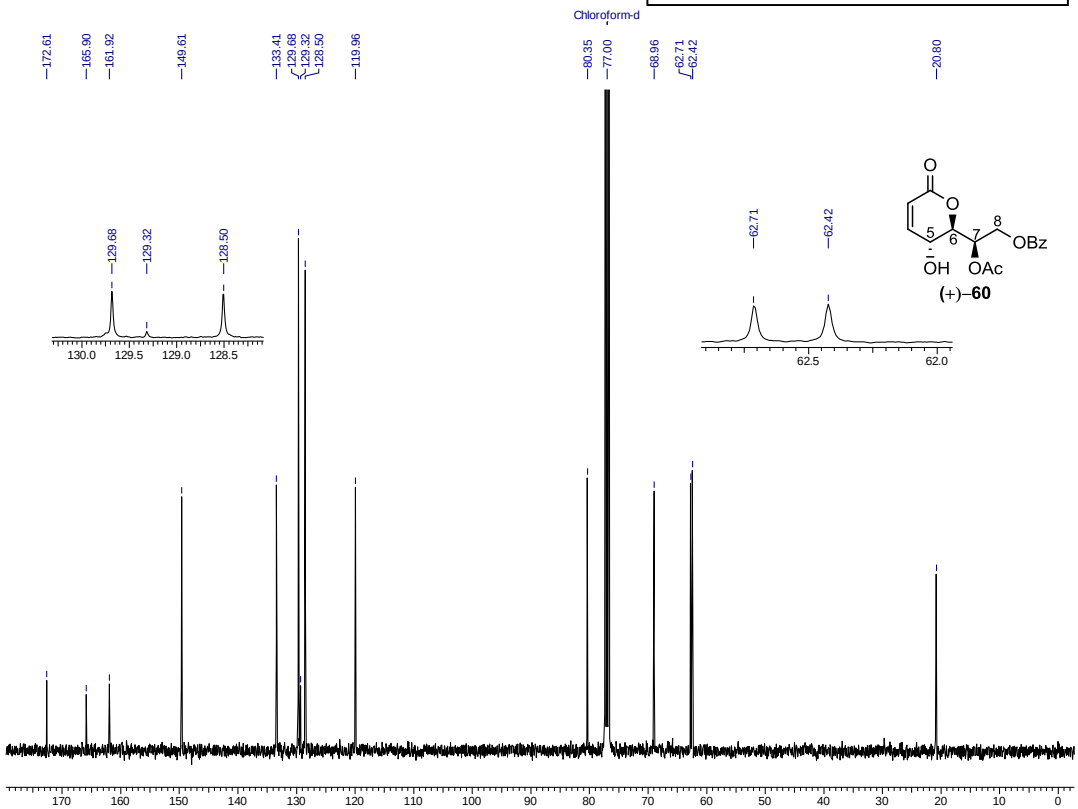

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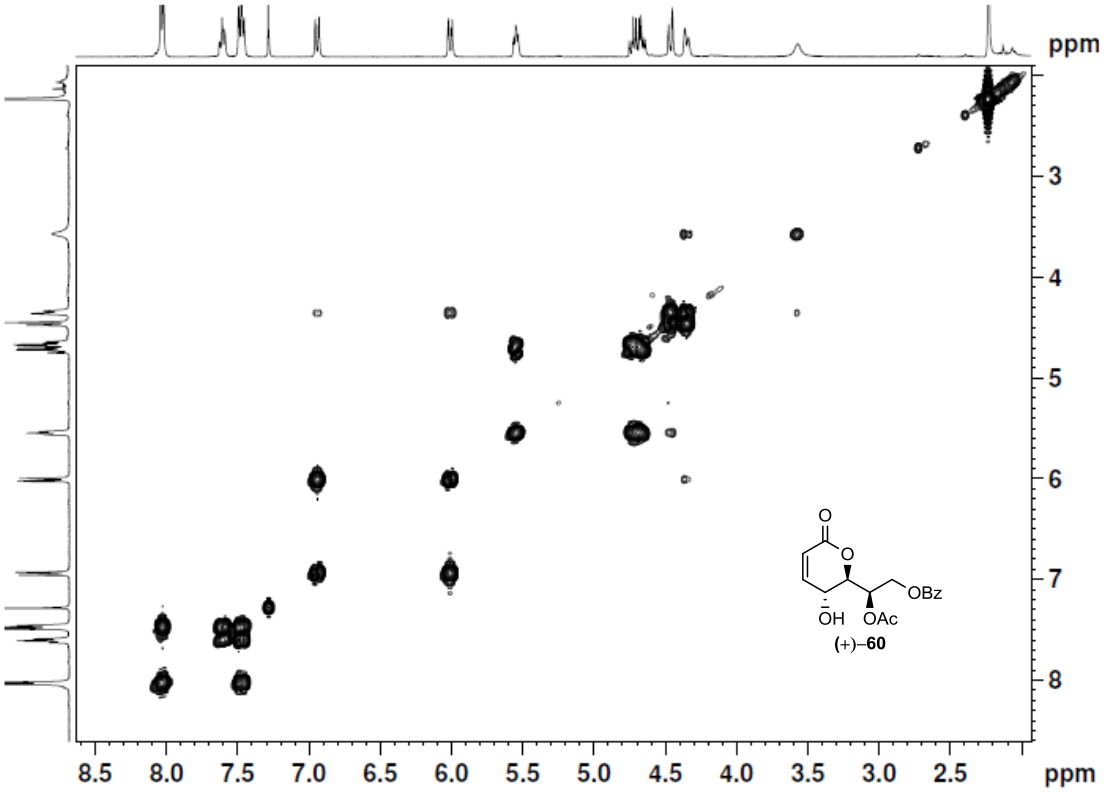
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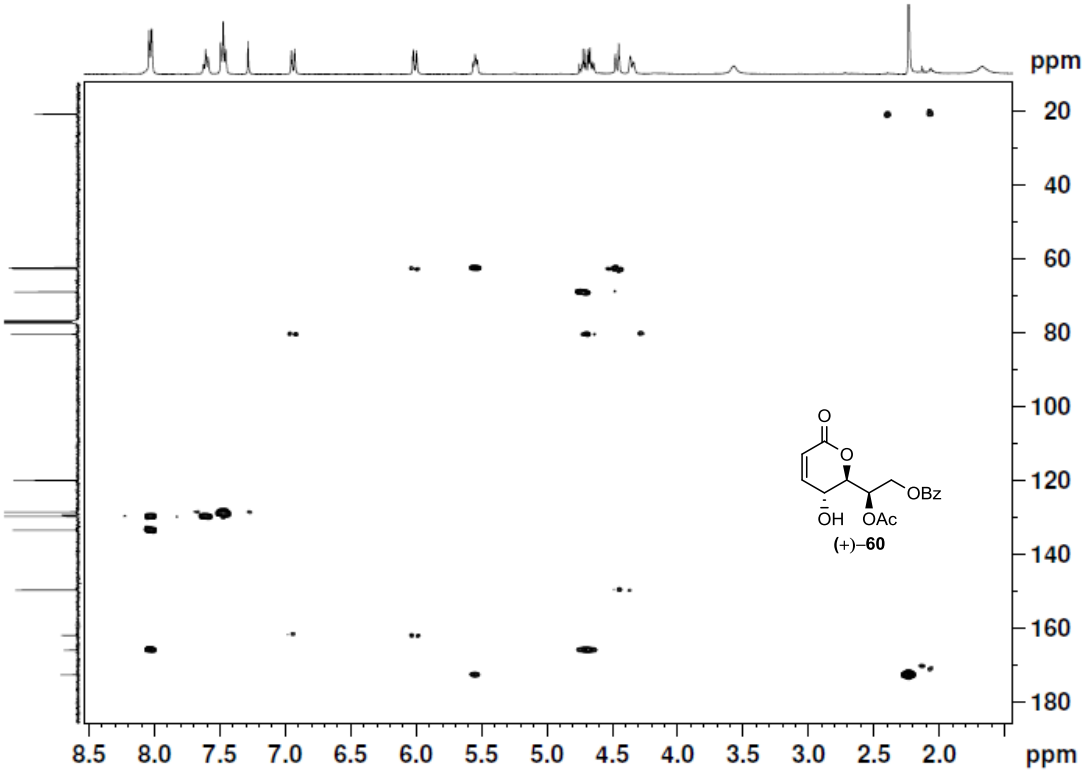
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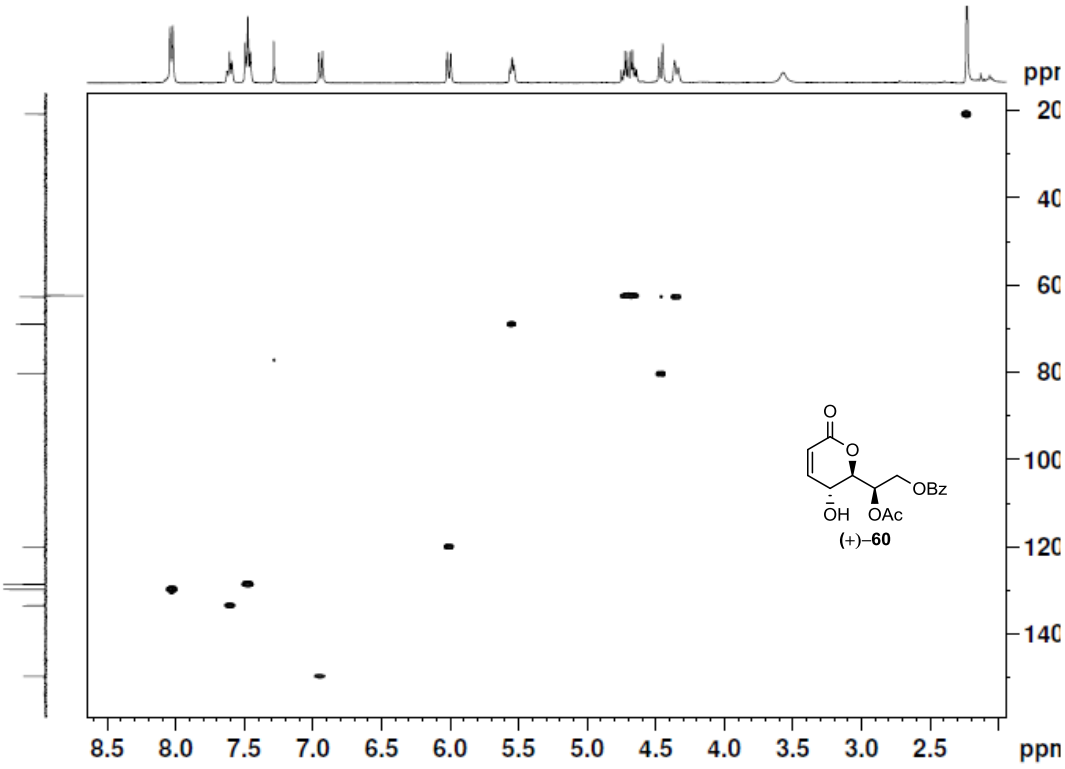
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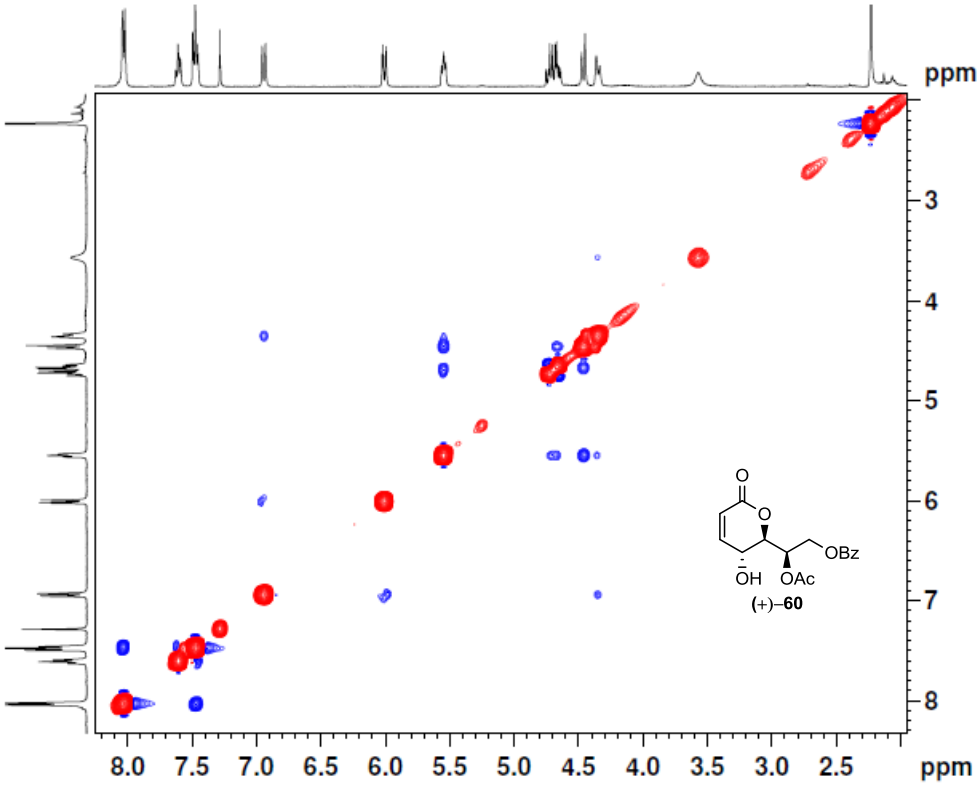
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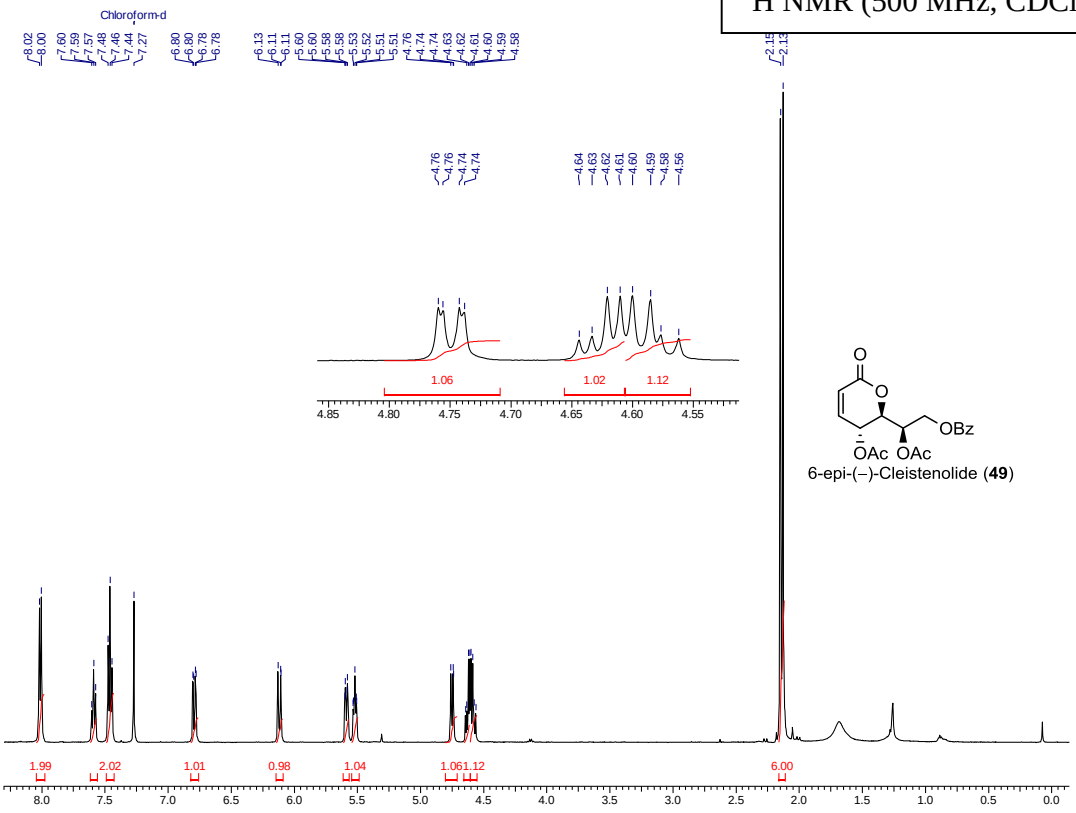

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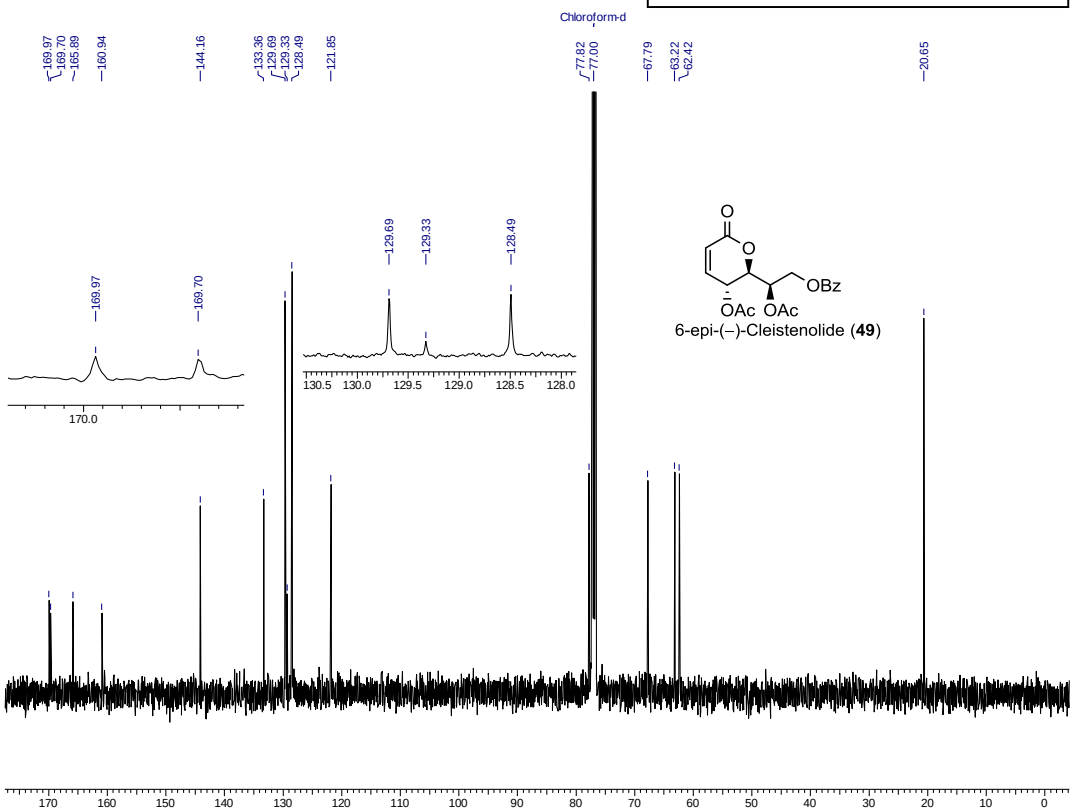
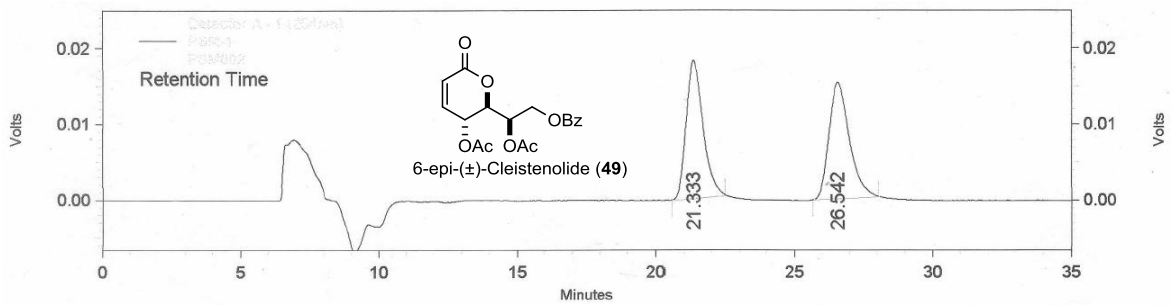


1.9 Copies of HPLC chromatograms



Detector A - 1 (254nm)

Retention Time	C Area	Area %
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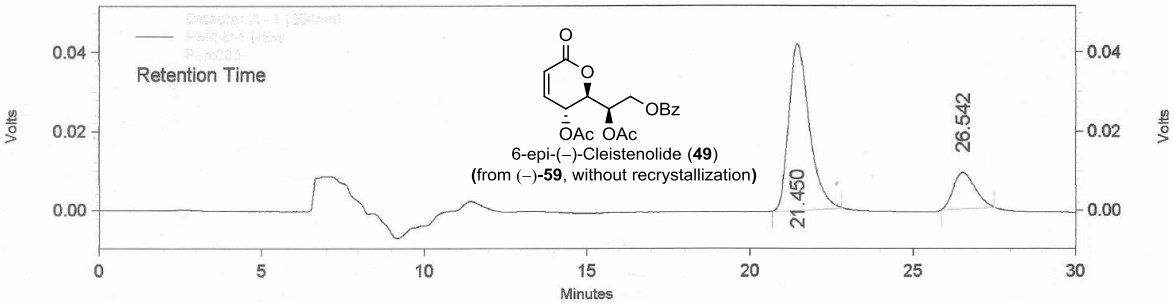
26.542	389203	50.436
Totals	771682	100.000



Detector A - 1 (254nm)

Retention Time	C Area	Area %
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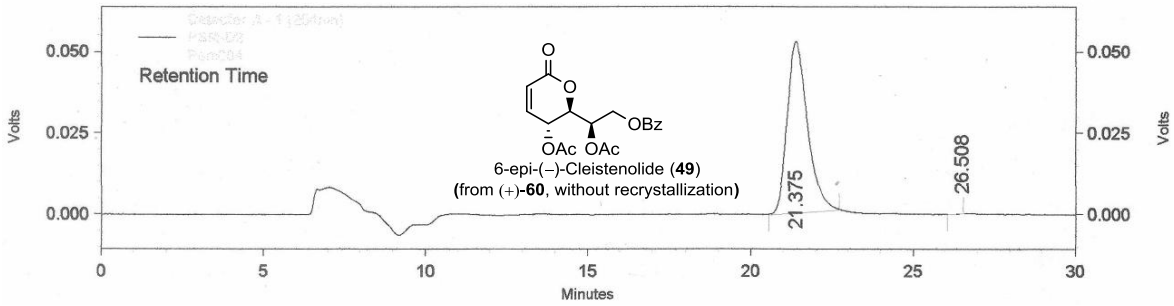
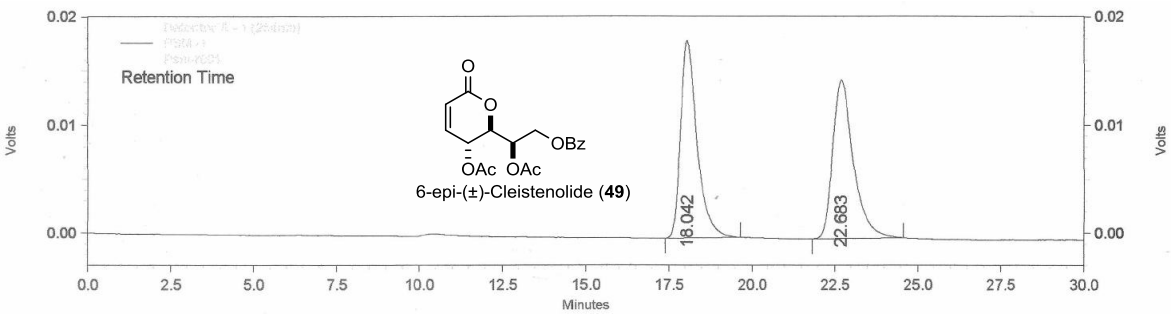
Totals	1134915	100.000



Detector A - 1 (254nm)

Retention Time	C Area	Area %
21.375	1143956	99.964
26.508	411	0.036
Totals	1144367	100.000

Column	:Kromasil 5 AmyCoat (4.6X250mm)	Flow Rate	: 0.5 ml/min (35)kgf
Mobile Phase	:IPA:n-Hexane (15:85)	Conc.	:1mg/mL
Wavelength	:254nm	Inj vol-	:20 ul



Detector A - 1 (254nm)

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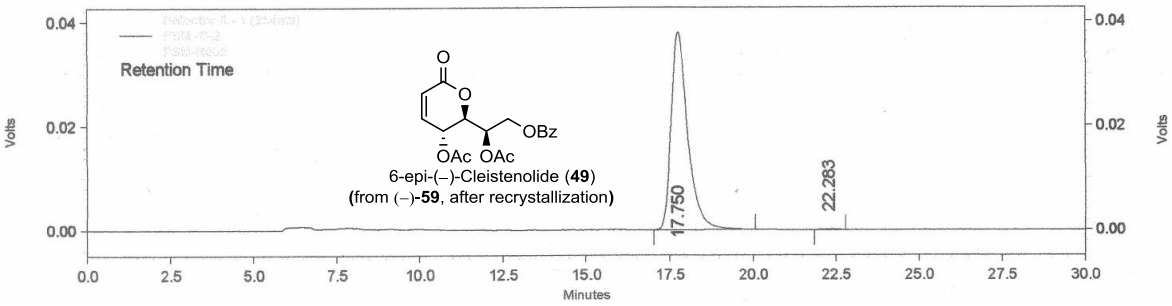
Totals		1272277	100.000



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	17.750	1320414	99.862
2	22.283	1827	0.138
Totals		1322241	100.000

Column	: Kromasil 5- AmyCoat (250mm x 4.6mm)	Flow Rate	: 0.5ml/min
Mobile Phase	:IPA:n-Hexane (20:80)	Conc.	: 1mg/2ml
Wavelength	: 254 nm	Inj vol-	: 05ul

Chapter 2

Novel Protocol APS-DMSO for Various Transformations: The Radical Beckmann Rearrangement and its Application in the Synthesis of Isocryptolepine via C–H Activation

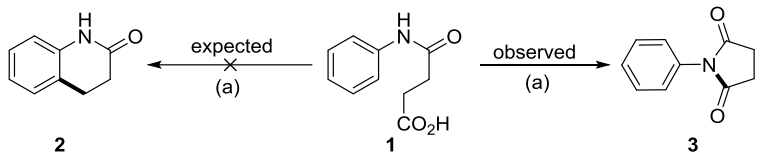
Novel Protocol APS-DMSO for Various Transformations: The Radical Beckmann Rearrangement and its Application in the Synthesis of Isocryptolepine via C–H Activation

2.1 Abstract

This chapter demonstrates the development of a new protocol "ammonium persulfate-dimethyl sulfoxide" (APS-DMSO) for various transformations including methylene insertion between amides/aryls, Mannich reaction as well as the synthesis of a thiadiazole and phthalimide. The development of APS-DMSO reagent for the radical Beckmann rearrangement is also described. Mechanistic aspects of the new protocol APS-DMSO were studied well by radical trapping and oxygen labeling experiments. The radical Beckmann rearrangement protocol was successfully applied to the synthesis of the antimalarial natural product isocryptolepine and one anticancer Indoloquinolone molecule.

2.2 Background

Generally, DMSO is used as a common solvent and ammonium peroxysulfate is used as a strong oxidant in organic synthesis. APS is a bench-top, stable and safe reagent. It is also used in hair dyes. It generates radical on heating in solutions. The combination of APS-DMSO is very often used in the C−H activation studies along with metal catalysts. While studying the intramolecular decarboxylative C−H activation on the substrate **1** using Pd-catalyst, APS, and DMSO, our research group observed the formation of cyclic imide **3** by dehydration (Scheme 1).[1]



Reaction conditions: (a) $Pd(OAc)_2$ (10 mol %), APS (2 equiv), DMSO/1,4-dioxane (5:95), 100 °C, 3 h.

Scheme 1: Attempted methodology and its outcome

The methodology was generalized for imide preparation and successfully applied in the synthesis the drug vernakalant.[1] The detailed study revealed that the combination of APS-DMSO is must for the protocol and dimethyl sulfone was identified as a side product. Also, the radical nature of the developed protocol was confirmed. These results prompted us to find more applications for the APS-DMSO protocol. Accordingly it was applied in various transformations successfully. Based on the transformations, this chapter is divided into two sections as follows.

Section A: APS-DMSO: A New Reagent in the Synthesis of Methylenebisamides and Other Applications

Section B: Development of Radical Beckmann Rearrangement and its Application to the Synthesis of Antimalarial Natural Product Isocryptolepine

2.3 References

1. Garad, D. N.; Tanpure, S. D.; Mhaske, S. B. *Beilstein J. Org. Chem.* **2015**, *11*, 1008 and references cited herein.

Chapter 2

Section A

APS-DMSO: A New Reagent in the Synthesis of Methylenebisamides and Other Applications

Mahajan, P. S.; Tanpure, S. D.; More, N. A.; Gajbhiye, J. M.; Mhaske, S. B. *RSC Adv.* **2015**, *5*, 101641.

Section A

APS-DMSO: A New Reagent in the Synthesis of Methylenebisamides and Other Applications

2A.1 Abstract

DMSO was activated using a new reagent combination (APS-DMSO). The activated DMSO is utilized as a one-carbon synthon in the synthesis of symmetrical methylenebisamides. The developed process is economical and environmentally benign. The protocol was also used for Mannich reaction, synthesis of thiadiazole, phthalimide and bis(phenyl)methane. Radical pathway of the developed protocol was proved by mechanistic studies.

2A.2 Introduction

DMSO has been activated *in situ* by various electrophiles and used for various organic transformations.[1] The Swern oxidation is the best example wherein activated DMSO is used very efficiently.[1d] DMSO has been also utilized as a reagent in the organic synthesis.[2] Other than DMSO, DMF and $CHCl_3$ are also used as reagents in the synthetic transformation. The study and investigation of these common organic solvents for their extended utility is of contemporary interest.[3] DMSO was also utilized as a one carbon source to test a new alternative for the environmentally malignant formaldehyde.[4] These reports prompted us to study and develop a new methodology using DMSO as a one carbon source in the synthesis of methylenebisamide.

2A.3 Background

Methylenebisamides are important part of peptidomimetic compounds,[5] natural products[6] and also potential key substrates in the synthesis of bioactive compounds.[7,8] Methylenebisamides are

key intermediates of *gem*-diaminoalkyl residues in the retro-inverso pseudopeptide derivatives, which are used for their structure-activity-relationship studies.[9]

Synthesis of methylenebisamides is known by using formaldehyde, strong acids and nitriles.[8,10] Other reagents such as hexamethylenetetramine[11] and DMSO[4] are used as a single carbon source and surrogate to formaldehyde. The synthesis of methylenebisamides utilizing DMSO as a methylene source resulted in low yields.[4b,c] When cyanuric chloride (2,4,6-trichloro[1,3,5]triazine) was used in combination with DMSO moderate to good yields of methylenebisamides were observed by Li et al. (Figure 1).[4a]

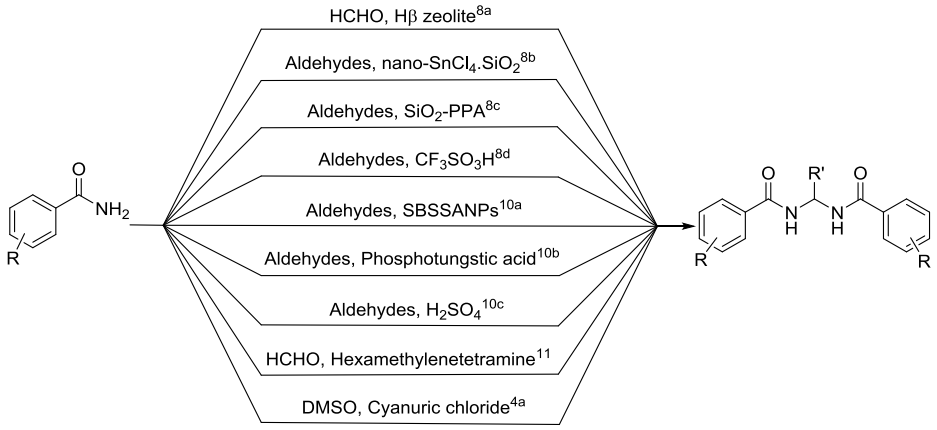
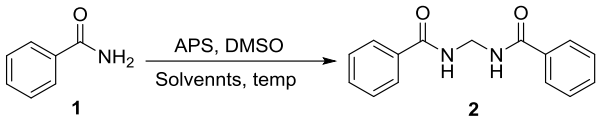


Figure 1: Routes to methylenebisamides

2A.4 Results and discussion

Our group previously used APS-DMSO protocol very successfully in the synthesis of imides.[12] Our curiosity to explore the utility of this interesting reagent combination, prompted us to test APS-DMSO protocol in the synthesis of methylenebisamides. We believed that DMSO present in our protocol (APS-DMSO) will act as methylene source and will produce the expected bisamide products. The idea was to replace harmful formaldehyde, strong acids and other corrosive/toxic reagents utilizing our mild protocol. Therefore, the investigation was started on a simple benzamide (**1**) using APS (1 equiv) and DMSO (4 equiv) in 1,4-dioxane at 100 ^{o}C (Table

1, entry 1). The reaction gave low yield, but the protocol worked at its very first trial and produced methylenebisamide **2**. In the absence of one of the reagents, the protocol did not produce any product (Table 1, entry 2,3). The excess amount of DMSO also could not furnish the product **2** (Table 1, entry 4,5). When APS (2 equiv) and DMSO (4 equiv) were used, the reaction gave 88% yield of **2** in 18 h (Table 1, entry 6). Further increase in the equivalents of APS reduced the yield to 71% (Table 1, entry 7). Increase in the equivalents of DMSO enhanced the yield and also reduced the reaction time (Table 1, entry 8,9). When DMSO (6 equiv) was used, the reaction gave quantitative yields (Table 1, entry 9). So, the optimum condition for the synthesis of methylenebisamide **2** was found to be APS (2 equiv), DMSO (6 equiv) in 1,4-dioxane at 100 ^{o}C for 6 h. Further permutations and combinations of equivalents of APS, DMSO or solvent did not show any improvement in the yield (Table 1, entry 10,11,17,18). When APS



1 **2**

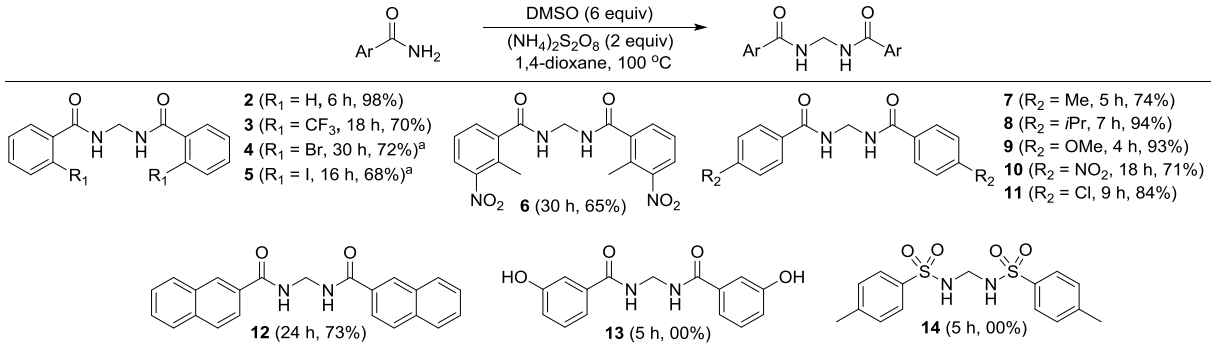
Entry[a]	**Oxidant/DMSO** (equiv)	**Solvent** (2 mL)	**Temp./time** (^{o}C h^{-1})	**Yield**[b] (%)
1	APS (1)/4	1,4-dioxane	100/18	38
2	APS (1)/−	1,4-dioxane	100/18	00
3	−/4	1,4-dioxane	100/04	00
4	APS (1)/excess	− −	100/18	trace
5	APS (2)/excess	− −	100/10	05
6	APS (2)/4	1,4-dioxane	100/18	88
7	APS (3)/4	1,4-dioxane	100/18	71
8	APS (2)/5	1,4-dioxane	100/09	94
9	**APS (2)/6**	1,4-**dioxane**	**100/06**	**98**
10	APS (1)/6	1,4-dioxane	100/12	40
11	APS (2)/10	1,4-dioxane	100/06	97
12	$K_2S_2O_8$ (2)/6	1,4-dioxane	100/06	35
13	tBuO-OtBu	1,4-dioxane	100/06	00
14	DBPO[c] (2)/6	1,4-dioxane	100/06	trace
15	$PhI(OAc)_2$ (2)/6	1,4-dioxane	100/06	trace
16	Oxone™	1,4-dioxane	100/06	17
17	APS (2)/6	toluene	111/06	58
18	APS (2)/6	water	100/06	07

[a]Reactions were performed on 50 mg scale of amide **1**. [b]Isolated yields. [c]DBPO = dibenzoyl peroxide.

Table 1: Optimization studies

was replaced with $K_2S_2O_8$, the yield was reduced to 35% (Table 1, entry 12). Other peroxides/oxidants did not give the expected product in good yields (Table 1, entry 13-16).

The substrate scope study was then planned. Various substituted aromatic benzamides were tried for the methylene insertion to form symmetrical methylenebisamides (Scheme 1). The benzamides substituted with CF_3, Br and I at the *o*-position of amide smoothly furnished the corresponding bisamides **3**-**5** respectively in good yields (Scheme 1). The *m*-NO_2 substituted benzamide was used to see the effect of an electron withdrawing substituent on the system. The protocol worked well and produced methylenebisamide **6** in 65% yield. The effect of *p*-substituted of benzamide having both electron donating as well as electron withdrawing was studied. Alkyl substitution provided bisamides **7** and **8** in good and excellent yields respectively. The *p*-methoxy substituted benzamide also furnished the corresponding bisamide **9** in excellent yield.



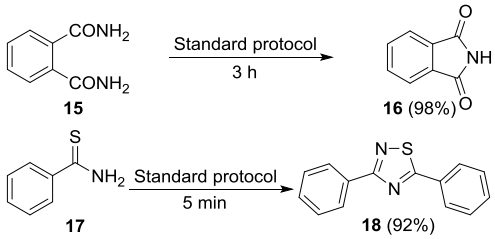
[[a]The ratio for amide:APS:DMSO = 1:3:9]

Scheme 1: Scope of aromatic amides

The *p*-NO_2 substituted benzamide, however, provided the bisamide **10** in 71% yield. The yields are similar to the *m*-NO_2 substrate. Hence, the reactivity of aromatic amides having electron donating substituents is better than that of electron withdrawing under the developed protocol. *p*-Chloro substituent on the benzamide is also tolerated and furnished the corresponding bisamide **11** in very good yield. The naphthalenyl benzamide (2-naphthamide) was chosen to see the effect

of the polyaromatic system on the protocol. The protocol furnished polyaromaticbisamide **12** in 73% yield. This shows that polyaromatic system has slight effects on the protocol hence, lower yield. Reactions on the two benzamides 3-hydroxybenzamide and *p*-toluenesulfonamide were performed, however, they remained unreactive and the corresponding bisamides **13** and **14** were not obtained (Scheme 1).

To study the reactivity of the developed protocol on a diamide, the *o*-benzyldiamide **15** was subjected to our protocol. Interestingly the phthalimide **16** was obtained in quantitative yield. The protocol worked differently and provided **16** via deaminative cyclization. The



Scheme 2: Protocol furnished different products than bisamides

protocol when applied to the benzothioamide **17**, furnished diphenylthiadiazole **18** in 92% yield (Scheme 2). The diphenylthiadiazole **18** formed via desulfurative coupling form benzothioamide **17.** This could be a simple and efficient alternative method to access thiadiazoles using our protocol.[13] Both the examples might be following the similar reaction pathway as we observed in the case of imide formation.[12]

The protocol was also tested for the heteroaromatic amides. Thiophene-2-carboxamide provided the corresponding symmetrical bisamide **19** in excellent yield. The protocol failed to give the desired bisamide **20** product from quinoline-3-carboxamide. Most probably, the basic

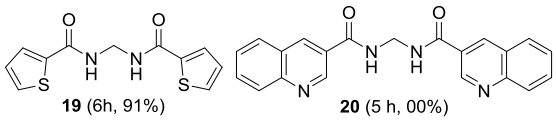


Figure 2: Heteroaromatic bisamide

quinoline nitrogen is interfering in the reaction and getting oxidized due to the powerful oxidizing agent (APS) present in the reaction (Figure 2).

The protocol was applied on the non-aromatic amides (Figure 3). The *α,β*-unsaturated amide (cinnamamide) produced the corresponding bisamide **21** in 74% yield. Other benzylic amides also furnished their corresponding arylbisamides **22**, **23** and **24** in moderate to good yields.

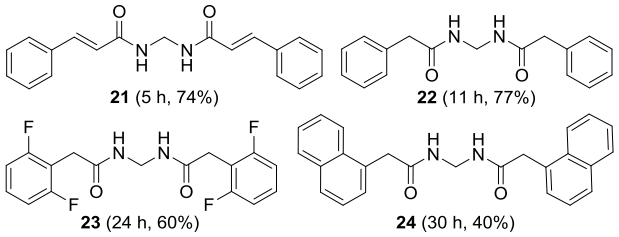


Figure 3: Cinnamide and benzylic amide provided the corresponding bisamides

The studies boosted our curiosity to test the protocol against the aliphatic amides. The protocol was performed on short as well as long chain aliphatic amides (Figure 4). Preparation of the desired bisamides **25** and **26** was not fruitful with the developed protocol and showed complex reaction mixture. The instability of the generated aliphatic radical intermediate might be the reason. Therefore, the trichloroacetamide was subjected to the protocol, but again the expected product **27** was not observed even in a trace amount. Difficulty in the synthesis of aliphatic amides (using cyanuric chloride:DMSO) was also observed by Li et al.,[4a] but the reason is obscure (Figure 4).

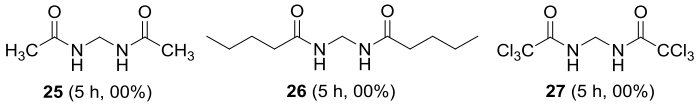
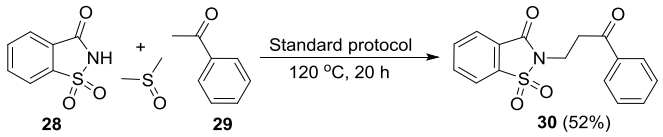


Figure 4: Protocol did not work on aliphatic amides

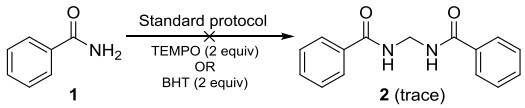
While the study was in progress a report appeared,[2e] wherein a multicomponent Mannich reaction was achieved with saccharine (**28**), ketone **29**, DMSO using $RuCl_3$ and Selectfluor®. We

performed the same reaction using our developed protocol and successfully achieved the multicomponent Mannich reaction product **30** in 52% yields (Scheme 3). Improvement in yields will be possible with the development of right protocol.



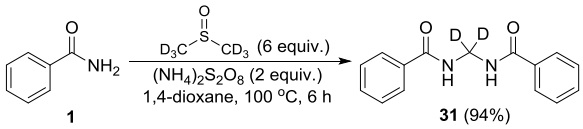
Scheme 3: Application of the protocol to a multicomponent Mannich reaction

We also studied the mechanism of our protocol. The radical trapping experiments were carried out using radical scavengers TEMPO (2 equiv) and BHT (2 equiv) in separate reactions (Scheme 4). In both the cases only trace amount of the product **2** was observed when the standard protocol was applied on the benzamide (**1**). This concludes that the protocol has a radical intermediate involved in the synthesis of methylenebisamides.



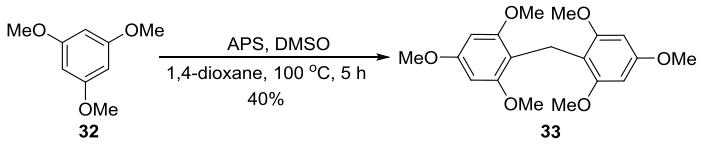
Scheme 4: Radical trapping experiment with TEMPO and BHT

The methylene source in the developed protocol was confirmed by using DMSO-d_6 in the reaction instead of DMSO (Scheme 5). The reaction of benzamide (**1**) furnished the deuterated methylenebisamide product **31**, which was confirmed by ^{1}H NMR and HRMS-ESI.



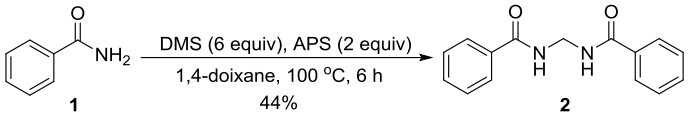
Scheme 5: Isotopic labeling experiment using DMSO-d_6

The formaldehyde equivalent formation in the reaction was reconfirmed by trapping it with 1,3,5-trimethoxybenzene (**32**) to form a methylene inserted diarylmethane product **33**. The diarylmethane class of compounds are presents in natural products,[6a,14] biologically active compounds, supramolecular architectures as well as in pharmaceuticals (Scheme 6).[14]



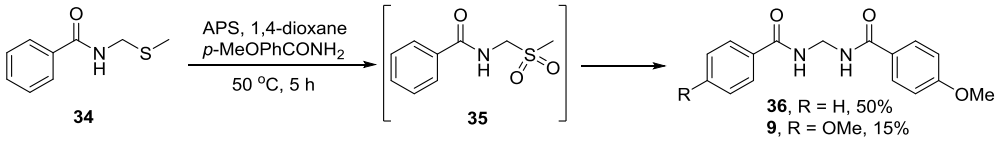
Scheme 6: Demonstration of DMSO as a surrogate for formaldehyde

In the previous imide project, formation of dimethyl sulfone (DMS) was observed,[12] which is a product of DMSO oxidation catalyzed by APS. To investigate whether DMS can generate a formaldehyde equivalent in our condition, DMS was used instead of DMSO (Scheme 7). The reaction gave moderate yields, which reconfirmed that DMSO is the major source of



Scheme 7: Reaction using dimethyl sulfone (DMS) instead of DMSO

methylene. For further evidence of formation of formaldehyde equivalent from DMSO/DMS in a developed protocol, the substrate **34** was designed.[15] The reaction of the substrate **34** was performed with *p*-methoxybenzamide in the presence of APS. The unsymmetrical methylenebisamide **36** was obtained in 50% yield along with symmetrical **9** in 15% (Scheme 8).



Scheme 8: The plausible route via the intermediate **35**

The reaction of the substrate **34** using the developed protocol and its outcome confirms the oxidation of thiol to form an intermediate **35**. Elimination of the oxidized thiol in the form of methane sulfonic acid[16a] delivers the unsymmetrical methylenebisamide **36** (Scheme 8). The reaction also produced the symmetrical methylenebisamide **9** as a minor product, which probably suggest that the formation of compound **35** and its conversion to DMS radical and benzamide (**1**) is reversible. The reaction did not produce the bisamide **2** probably because of the low

temperature of the reaction and less reactivity of the benzamide (**1**) as compared to its *p*-methoxybenzamide.

Based on the mechanistic studies (Scheme 4-8) and the literature precedence[14b,16] A plausible mechanism has been depicted in Figure 5. Combination of APS and DMSO in a heating condition forms DMS and/or DMSO radical, which forms an intermediate **A** with benzamide (**1**). Elimination of methane sulfonic acid[16a] and addition of another benzamide (**1**) furnishes the methylenebisamide (**5**).

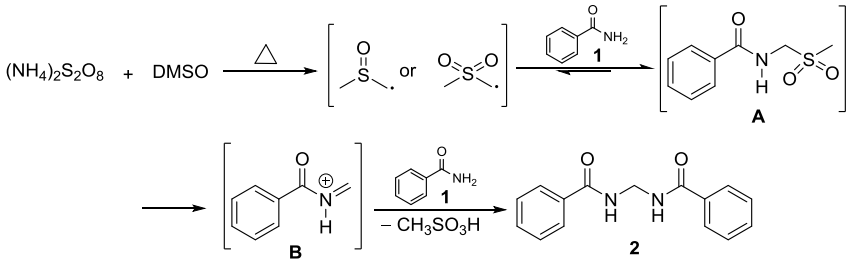


Figure 5: Plausible mechanism of methylene insertion to the benzamide

This work is cited six times, particularly for the use of DMSO in the organic transformation.[17]

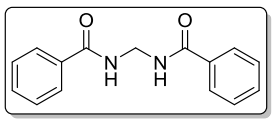
2A.5 Conclusion

An efficient and mild protocol was developed for the synthesis of methylenebisamides using bench-top reagent APS and the common organic solvent DMSO. DMSO has been utilized as a safer surrogate for the formaldehyde. Use of strong acids and any transition-metal catalysts are avoided in the synthesis of symmetrical methylenebisamides. The protocol was successfully applied to a three-component Mannich reaction and in the synthesis of bis(phenyl)methane as well as thiadiazoles. Based on mechanistic studies, radical nature of the reaction and probable mechanism of the protocol is proposed.

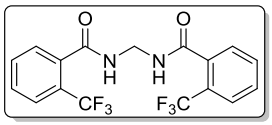
2A.6 Experimental section

2A.6.1 General procedure for the synthesis of methylenebisamides

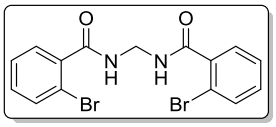
A solution of amide (50 mg, 1 equiv), ammonium persulfate [$(NH_4)_2S_2O_8$] (2 equiv) and DMSO (6 equiv) in 1,4-dioxane (2 mL) was heated at 100 ^oC in a round-bottom flask, equipped with a stirring bar and water condenser, until the reaction was complete as indicated by thin layer chromatography. After completion, the reaction mixture was filtered through a cotton plug and 1,4-dioxane was removed under vacuum. The residue was then dissolved in ethyl acetate (10 mL) and washed with warm water (4 mL) and brine (3 mL x 2). The organic layer was dried over anhydrous sodium sulfate and the crude product was purified by flash column chromatography to furnish corresponding methylenebisamides in good to excellent yields.



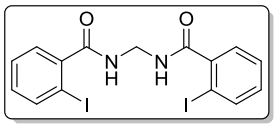
N,N'-Methylenedibenzamide (2).[4a] Reaction time: 6 h; R*f*: 0.5 (1:1, EtOAc:Pet. Ether); White solid; mp 210-212 ^oC; 51 mg, 98%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.70 (m, 6H), 7.43 (t, J = 5.9 Hz, 2H), 7.40-7.30 (m, 4H), 5.00 (t, J = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 133.4, 132.0, 128.6, 127.3, 45.7; HRMS-ESI (*m/z*) calcd $[(C_{15}H_{14}O_2N_2)+Na]^+$: 277.0947, found: 277.0946.



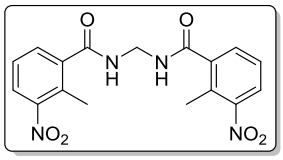
N,N'-Methylenebis(2-(trifluoromethyl)benzamide) (3). Reaction time: 18 h; R_f = 0.6 (EtOAc:Pet. Ether, 1:1). White solid; 36 mg, 70%, mp 213-215 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 9.26 (t, J = 5.6, 2H), 7.78 (d, J = 7.8, 2H), 7.74 (t, J = 7.6, 2H), 7.65 (t, J = 7.6, 2H), 7.51(d, J = 7.3, 2H), 4.69 (t, J = 5.6, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.6, 132.5, 130.0, 128.8, 125.3-126.4 (m, CF_3), 126.0, 122.6, 44.4; HRMS-ESI (m/z) calcd $[C_{17}H_{12}O_2N_2F_6+Na]^+$: 413.0695, found 413.0687.



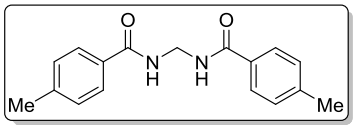
N,N'-Methylenebis(2-bromobenzamide) (4). Reaction time: 30 h; R*f*: 0.5 (1:1, EtOAc:Pet. Ether); White solid; mp 213-215 ^{o}C; 37 mg, 72%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (t, J = 5.6 Hz, 2H), 7.65 (d, J = 7.3 Hz, 2H), 7.46-7.34 (m, 6H), 4.71 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 138.7, 132.9, 131.2, 129.2, 127.7, 119.1, 44.5; HRMS-ESI (*m/z*) calcd $[(C_{15}H_{12}O_2N_2{}^{79}Br_2)+H]^+$: 410.9338, found: 410.9345.



N,N'-Methylenebis(2-iodobenzamide) (5). Reaction time: 16 h; R*f*: 0.5 (3:2, EtOAc:Pet. Ether); White solid; mp 231-233 ^{o}C; 35 mg, 68%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (t, J = 5.5 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.47-7.43 (m, 2H), 7.40-7.35 (m, 2H), 7.20-7.14 (m, 2H), 4.70 (t, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 142.4, 139.3, 131.1, 128.5, 128.1, 93.6, 44.7; HRMS-ESI (*m/z*) calcd $[(C_{15}H_{12}O_2N_2I_2)+H]^+$: 506.9061, found: 506.9056.

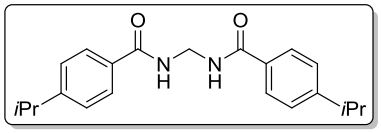


N,N'-methylenebis(2-methyl-3-nitrobenzamide) (6). Reaction time: 30 h; R*f*: 0.5 (9:1, EtOAc:Pet. Ether); White solid; mp 277-279 ^{o}C; 34 mg, 65%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (t, 5.5 Hz, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.8 Hz, 2H), 4.77 (t, J = 5.5 Hz, 2H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.1, 150.7, 140.0, 131.5, 129.1, 127.4, 124.9, 44.6, 15.6; HRMS-ESI (*m/z*) calcd $[(C_{17}H_{16}O_6N_4)+Na]^+$: 395.0962, found: 395.0960.

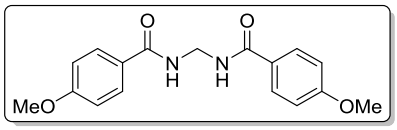


N,N'-Methylenebis(4-methylbenzamide) (7).[4a] Reaction time: 5 h; R_f = 0.5 (EtOAc:Pet. Ether, 2:3). White solid; 39 mg, 74%, mp

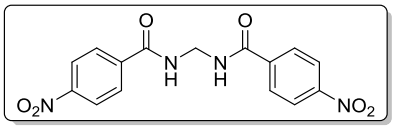
205-207 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.93 (t, J = 5.5 Hz, 2H), 7.81(d, J = 7.9 Hz, 4H), 7.26 (d, J = 7.9 Hz, 4H), 4.84 (t, J = 5.5 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.5, 141.4, 131.4, 128.9, 127.6, 45.3, 21.1; ESI-MS (m/z): 305 (M+Na).



N,N'-Methylenebis(4-isopropylbenzamide) (8).[3h] Reaction time: 7 h; R$_f$ = 0.3 (EtOAc:Pet. Ether, 1:1). White solid; 49 mg, 94%, mp 181-183 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (t, J = 5.6 Hz, 2H), 7.83 (d, J = 8.3 Hz, 4H), 7.32 (d, J = 8.3 Hz, 4H), 4.84 (t, J = 5.6 Hz, 2H), 2.98-2.87 (m, 2H), 1.20 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.6, 152.2, 131.8, 127.8, 126.4, 45.2, 33.5, 23.8; HRMS-ESI (m/z) calcd $[C_{21}H_{26}O_2N_2+Na]^+$: 361.1886, found 361.1881.

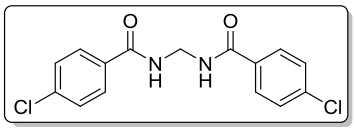


N,N'-Methylenebis(4-methoxybenzamide) (9).[4a] Reaction time: 4 h; Rf: 0.5 (13:7, EtOAc:Pet. Ether); White solid; mp 199-201 ^{o}C; 48 mg, 93%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.88 (t, J = 5.6 Hz, 2H), 7.89 (d, J = 8.8 Hz, 4H), 6.98 (d, J = 8.8 Hz, 4H), 4.82 (t, J = 5.6 Hz, 2H), 3.80 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 161.9, 129.5, 126.4, 113.6, 55.5, 45.3; HRMS-ESI (m/z) calcd $[(C_{17}H_{18}N_2O_4)+Na]^+$: 337.1159, found: 337.1156.

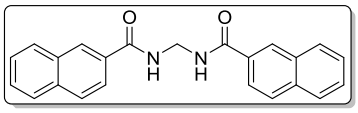


N,N'-Methylenebis(4-nitrobenzamide) (10).[4a] Reaction time: 18 h; Rf: 0.5 (7:3, EtOAc:Pet. Ether); White solid; mp 247-249 ^{o}C; 37 mg, 71%; ^{1}H NMR (500 MHz, DMSO-d_6) : δ 9.5 (bs, 2H), 8.33-8.31 (m, 4H), 8.14-8.12 (m, 4H), 4.9 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) : δ165.2, 149.3, 139.7, 129.2, 123.7, 45.5;

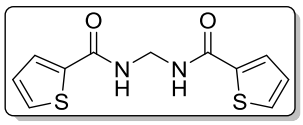
HRMS-ESI (*m/z*) calcd $[(C_{15}H_{12}O_6N_4)+Na]^+$: 367.0649, found: 367.0647.



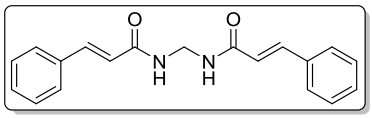
N,N'-Methylenebis(4-chlorobenzamide) (11).[4a] Reaction time: 9 h; R*f*: 0.5 (9:11, EtOAc:Pet. Ether); White solid; mp 248-250 ^oC; 44 mg, 84%; ^1H NMR (400 MHz, DMSO-d_6): δ 9.18 (t, 5.5 Hz, 2H), 7.92 (d, J = 8.6 Hz, 4H), 7.54 (d, J = 8.6 Hz, 4H), 4.84 (t, 5.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.7, 136.5, 132.9, 129.6, 128.6, 45.4; HRMS-ESI (*m/z*) calcd $[(C_{15}H_{12}O_2N_2{}^{35}Cl_2)+Na]^+$: 345.0168, found: 345.0166.



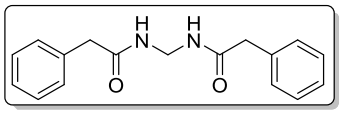
N,N'-Methylenebis(2-naphthamide) (12).[3h] Reaction time: 24 h; R*f*: 0.5 (1:1, EtOAc:Pet. Ether); White solid; mp 235-237 ^oC; 38 mg, 73%; ^1H NMR (400 MHz, DMSO-d_6): δ 9.27 (t, J = 5.4 Hz, 2H), 8.55 (s, 2H), 8.04-7.95 (m, 8H), 7.65-7.57 (m, 4H), 4.99 (t, J = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8, 134.4, 132.3, 131.5, 129.1, 128.1, 128.0, 127.9, 127.8, 126.9, 124.5, 45.5; HRMS-ESI (*m/z*) calcd $[(C_{23}H_{18}N_2O_2)+Na]^+$: 377.1260, found: 377.1266.



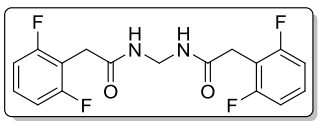
N,N'-Methylenebis(thiophene-2-carboxamide) (19).[8a] Reaction time: 6 h; R*f*: 0.6 (EtOAc:Pet. Ether, 1:1). White solid; 48 mg, 91%, mp 224-226 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 9.16 (t, J = 5.6 Hz, 2H), 7.88 (d, J = 3.7 Hz, 2H), 7.77 (d, J = 4.9 Hz, 2H), 7.14 (t, J = 4.9 Hz, 2H), 4.78 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7, 139.7, 131.5, 128.9, 128.3, 44.7; HRMS-ESI (m/z) calcd $[C_{11}H_{10}O_2N_2S_2+Na]^+$: 289.0076, found 289.0072.



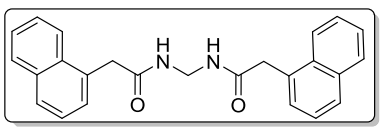
(2E,2'E)-N,N'-Methylenebis(3-phenylacrylamide) (21).[4a] Reaction time: 5 h; R*f*: 0.5 (3:2, EtOAc:Pet. Ether); White solid; mp 256-258 ^{o}C; 38 mg, 74%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (t, J = 6.1 Hz, 2H), 7.58-7.53 (m, 4H), 7.48 (d, J = 15.6 Hz, 2H), 7.45-7.36 (m, 6H), 6.69 (d, J = 15.6 Hz, 2H), 4.64 (t, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.6, 139.7, 135.0, 129.9, 129.2, 127.8, 122.0, 43.8; HRMS-ESI (*m/z*) calcd [($C_{19}H_{18}N_2O_2$)+Na]$^{+}$: 329.1260, found: 329.1259.



N,N'-Methylenebis(2-phenylacetamide) (22).[4a] Reaction time: 11 h; R*f*: 0.5 (1:1, EtOAc:Pet. Ether); White solid; mp 213-215 ^{o}C; 40 mg, 77%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.73 (t, J = 5.9 Hz, 2H), 7.30-7.19 (m, 10H), 4.38 (t, J = 5.9 Hz, 2H), 3.41 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 136.4, 129.2, 128.4, 126.6, 43.6, 42.2; HRMS-ESI (*m/z*) calcd [($C_{17}H_{18}O_2N_2$)+Na]$^{+}$; 305.1260, found: 305.1259.

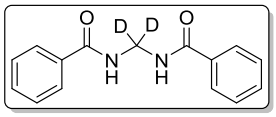


N,N'-Methylenebis(2-(2,6-difluorophenyl)acetamide) (23). Reaction time: 24 h; R*f*: 0.5 (2:3, EtOAc:Pet. Ether); White solid; mp 281-283 ^{o}C; 31 mg, 60%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (t, J = 5.9 Hz, 2H), 7.43-7.28 (m, 2H), 7.15-6.98 (m, 4H), 4.42 (t, J = 5.9 Hz, 2H), 3.52 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.8, 161.4 (dd, J_{CF} = 245.8, 8.5 Hz), 129.2 (t, J_{CF} = 10.0 Hz), 112.0 (t, J_{CF} = 20.0 Hz), 111.4 (dd, J_{CF} = 19.3, 6.9 Hz), 43.8, 28.8; HRMS-ESI (*m/z*) calcd [($C_{17}H_{14}N_2O_2F_4$)+H]$^{+}$: 355.1064, found: 355.1061.



N,N'-Methylenebis(2-(naphthalene-1-yl)acetamide) (24). Reaction time: 30 h; R*f*: 0.5 (7:3, EtOAc:Pet. Ether); White

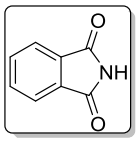
solid; mp 279-281^{o}C; 22 mg, 40%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (t, J = 6.1 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 2H), 7.59 – 7.39 (m, 8H), 4.44 (t, J = 6.1 Hz, 2H), 3.90 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 133.6, 132.8, 132.2, 128.6, 127.9, 127.3, 126.2, 125.9, 125.8, 124.6, 43.7, 39.65; HRMS-ESI (*m/z*) calcd $[(C_{25}H_{22}O_2N_2)+H]^+$: 383.1754, found: 383.1750.



N,N'-(Methylene-d$_2$)dibenzamide (31). DMSO-d_6 was used instead of DMSO. Reaction time: 6 h; R*f*: 0.5 (1:1, EtOAc:Pet. Ether); White solid; mp 224-226 ^{o}C; 50 mg, 94%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.3 Hz, 4H), 7.61 (bs, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.34 (t, 7.5 Hz, 4H); HRMS-ESI (*m/z*) calcd $[(C_{15}H_{12}{}^{2}H_2O_2N_2)+Na]^+$: 279.1073, found: 279.1078.

2A.6.2 Procedure for the synthesis of phthalimide (16)

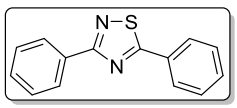
The solution of amide **15** (50 mg, 1 equiv, 0.30 mmol), ammonium persulfate $[(NH_4)_2S_2O_8]$ (138 mg, 2 equiv, 0.60 mmol) and DMSO (130 µL, 6 equiv, 1.82 mmol) in 1,4-dioxane (2 mL) was heated at 100 ^{o}C in a round bottom flask, equipped with a stirring bar and water condenser, until the reaction was complete (3 h) as indicated by thin layer chromatography. After completion, the reaction mixture was filtered through a cotton plug and 1,4-dioxane was removed under vacuum. The residue was then dissolved in ethyl acetate (10 mL) and washed with warm water (4 mL) and brine (3 mL x 2). The organic layer was dried over anhydrous sodium sulfate and the crude product was purified by flash column chromatography to furnish phthalimide (**16**) in 98% yield (44 mg).



Isoindoline-1,3-dione (16).[18] Reaction time: 3 h; R*f*: 0.5 (1:4, EtOAc:Pet. Ether); White solid; mp 237-239 ^{o}C; 44 mg, 98%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.33 (s, 1H), 7.82 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 134.5, 132.8, 123.2; GC-MS (M^{+}) : 147.0

2A.6.3 Procedure for the synthesis of diphenylthiadiazole (18)

The solution of thiamide **17** (50 mg, 1 equiv, 0.36 mmol), ammonium persulfate [$(NH_4)_2S_2O_8$] (166 mg, 2 equiv, 0.72 mmol) and DMSO (154 µL, 6 equiv, 2.16 mmol) in 1,4-dioxane (2 mL) was heated at 100 ^{o}C for 5 minutes in a round bottom flask, equipped with a stirring bar and water condenser. The reaction mixture was filtered through a cotton plug and 1,4-dioxane was removed under vacuum. The residue was then dissolved in ethyl acetate (10 mL) and washed with warm water (4 mL) and brine (3 mL x 2). The organic layer was dried over anhydrous sodium sulfate and the crude product was purified by flash column chromatography to furnish 3,5-diphenyl-1,2,4-thiadiazole (**18**) in 92% yield (40 mg).

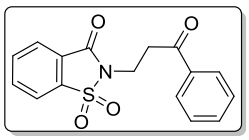


3,5-Diphenyl-1,2,4-thiadiazole (18).[19] Reaction time: 5 min; R*f*: 0.5 (1:19, EtOAc:Pet. Ether); White solid; mp 95-97 ^{o}C; 40 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, J = 7.6, 1.9 Hz, 2H), 7.98 (dd, J = 7.4, 2.1 Hz, 2H), 7.50-7.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1, 173.8, 132.8, 131.9, 130.7, 130.4, 129.3, 128.7, 128.3, 127.5; HRMS-ESI (*m/z*) calcd $[(C_{14}H_{10}N_2S)+H]^{+}$: 239.0637, found: 239.0636.

2A.6.4 Procedure for the synthesis of 2-(3-oxo-3-phenylpropyl)benzo[d]isothiazol-3(2*H*)-one 1,1-dioxide (**30**)

The solution of acetophenone (**29**, 50 mg, 1 equiv, 0.42 mmol), saccharine (**28**, 152 mg, 2 equiv,

0.83 mmol), ammonium persulfate [$(NH_4)_2S_2O_8$] (190 mg, 2 equiv, 0.83 mmol) and DMSO (177 µL, 6 equiv, 2.46 mmol) in 1,4-dioxane (2 mL) was heated for 20 h at 120 ^oC in a Schlenk tube equipped with a stirring bar. The reaction mixture was filtered through a cotton plug and 1,4-dioxane was removed under vacuum. The residue was then dissolved in ethyl acetate (10 mL) and washed with warm water (4 mL) and brine (3 mL x 2). The organic layer was dried over anhydrous sodium sulfate and the crude product was purified by flash column chromatography to furnish 2-(3-oxo-3-phenylpropyl)benzo[d]isothiazol-3(2*H*)-one 1,1-dioxide (**30**) in 52% yield (68 mg).



2-(3-Oxo-3-phenylpropyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (30).[2e] Reaction time: 20 h; R*f*: 0.5 (3:7, EtOAc:Pet. Ether); White solid; mp 137-139 ^oC; 68 mg, 52%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.98 (m, 1H), 7.92 – 7.74 (m, 5H), 7.51 (t, J = 7.7 Hz, 1H), 7.39 (t, 7.7 Hz, 2H), 4.19 (t, 7.8 Hz, 2H), 3.50 (t, 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 158.8, 137.7, 136.2, 134.8, 134.4, 133.5, 128.7, 128.0, 127.3, 125.2, 120.9, 36.8, 34.4; HRMS-ESI (*m/z*) calcd $[(C_{16}H_{13}O_4NS)+Na]^+$: 338.0457, found: 338.0452.

2A.6.5 Mechanistic aspect study

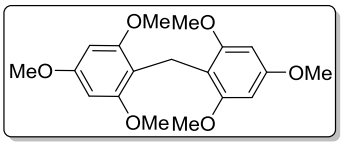
I) Procedure for Radical trapping experiment

The solution of amide **1** (50 mg, 1 equiv, 0.41 mmol), ammonium persulfate [$(NH_4)_2S_2O_8$] (188 mg, 2 equiv, 0.82 mmol), TEMPO (128 mg, 2 equiv, 0.82 mmol) and DMSO (175 µL, 6 equiv, 2.46 mmol) in 1,4-dioxane (2 mL) was heated for 24 h at 100 ^oC in a round bottom flask, equipped with a stirring bar and water condenser. Only a trace amount of product **2** was seen on

TLC. Repetition of the same reaction using BHT (145 mg, 4 equiv, 0.66 mmol) as a radical scavenger showed the same result.

II) Procedure for trapping the formaldehyde equivalent intermediate to furnish compound 33

To the solution of compound **32** (250 mg, 1.48 mmol, 1 eq) in 2 mL 1,4-dioxane added sequentially APS (628 mg, 2.97 mmol, 2 eq) and DMSO (0.64 mL, 8.91 mmol, 6 eq) and heated at 100 ^{o}C for 5 h then solvents were evaporated under vacuum and added 10 mL ethyl acetate and washing of brine was given (5 mL X 2). The organic layer was separated dried over sodium sulfate and column chromatography was done with 3:7 (ethyl acetate: petroleum ether) to give 104 mg, 40% of **33**.



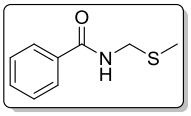
Bis(2,4,6-trimethoxyphenyl)methane (33).[20] R*f*: 0.5 (1:5, EtOAc:Pet. Ether); White solid; mp 110-112 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 4H), 3.85 (s, 2H), 3.78 (s, 6H), 3.71 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.6, 111.9, 91.1, 56.0, 55.2, 16.6; HRMS-ESI (*m/z*) calcd$[(C_{19}H_{25}O_6)+H]^+$; 349.1646, found: 349.1646.

III) Procedure using DMS instead of DMSO

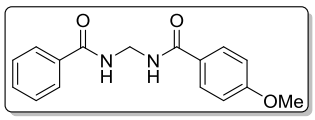
The solution of amide **1** (50 mg, 1 equiv, 0.41 mmol), ammonium persulfate $[(NH_4)_2S_2O_8]$ (188 mg, 2 equiv, 0.82 mmol), and DMS (232 mg, 6 equiv, 2.47 mmol) in 1,4-dioxane (2 mL) was heated for 6 h at 100 ^{o}C in a round bottom flask, equipped with a stirring bar and water condenser. Usual work-up followed by column chromatographic (2:3, ethyl acetate: petroleum ether) purification furnished 23 mg, 44% of **2**.

IV) Compound 35 as a plausible intermediate

The compound **34** was prepared as per the literature procedure.[15] To the solution of compound **34** (80 mg, 0.44 mmol, 1 eq) in 2 mL 1,4-dioxane added sequencially 4-methoxy benzamide (66 mg, 0.44 mmol, 1 eq), APS (50 mg, 0.22 mmol, 0.5 eq) and heated at 50 ^{o}C for 5 h then reaction mixture was directly loaded on column and purification done with 1:1 (ethylacetate: petroleum ether) to give 63 mg, 50% of **36** and 10 mg, 18% of benzamide **1** (based on ^{1}H NMR) and 10 mg, 15% of compound **9** (corresponding to 4-methoxy benzamide).



N-((Methylthio)methyl)benzamide (34).[15] R*f*: 0.3 (1:5, EtOAc:Pet. Ether); White Solid; mp 105-107 ^{o}C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84-7.78 (m, 2H), 7.58-7.41 (m, 3H), 6.49 (bs, 1H), 4.60 (d, *J* = 6.3 Hz, 2H), 2.22 (S, 3H).



N-(Benzamidomethyl)-4-methoxybenzamide (36). R*f*: 0.3 (1:1, EtOAc:Pet. Ether); White Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.3 Hz, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.74 (t, *J* = 6.1 Hz, 1H), 7.64 (t, *J* = 6.1 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* =7.3 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.04 (t, *J* = 6.1 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 168.0, 162.6, 133.5, 132.0, 129.1, 128.6, 127.2, 125.7, 113.8, 55.4, 45.6; HRMS-ESI (*m/z*) calcd[$(C_{16}H_{16}N_2O_3)$+Na]$^{+}$; 307.1053, found: 307.1046.

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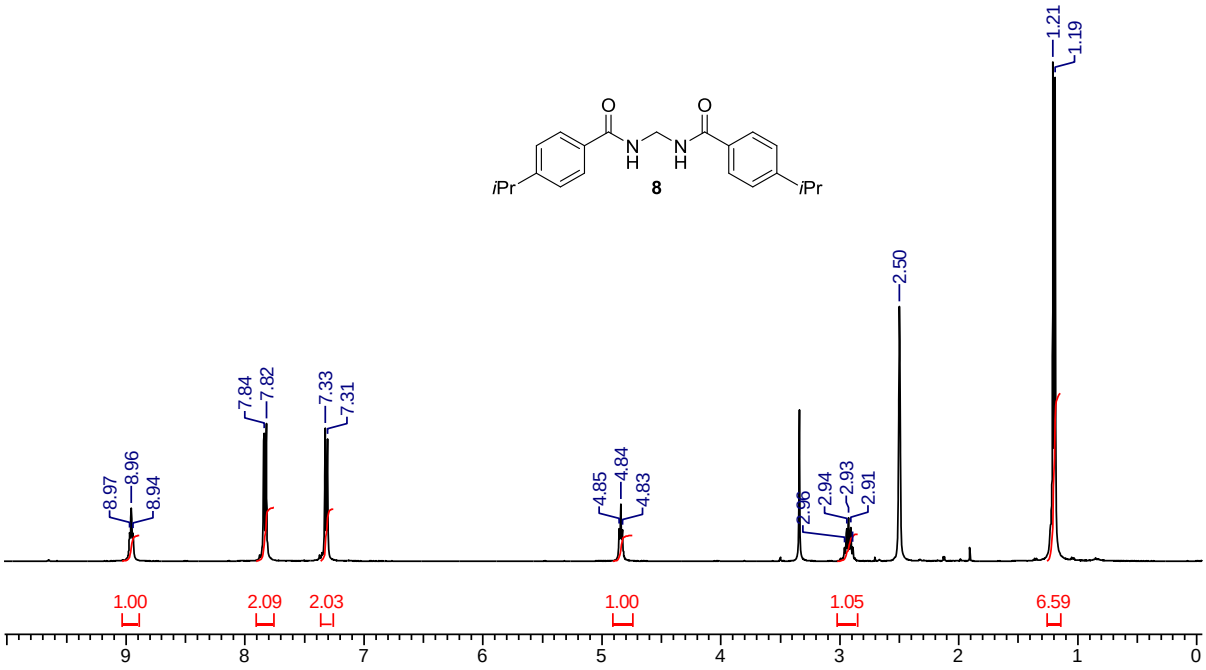
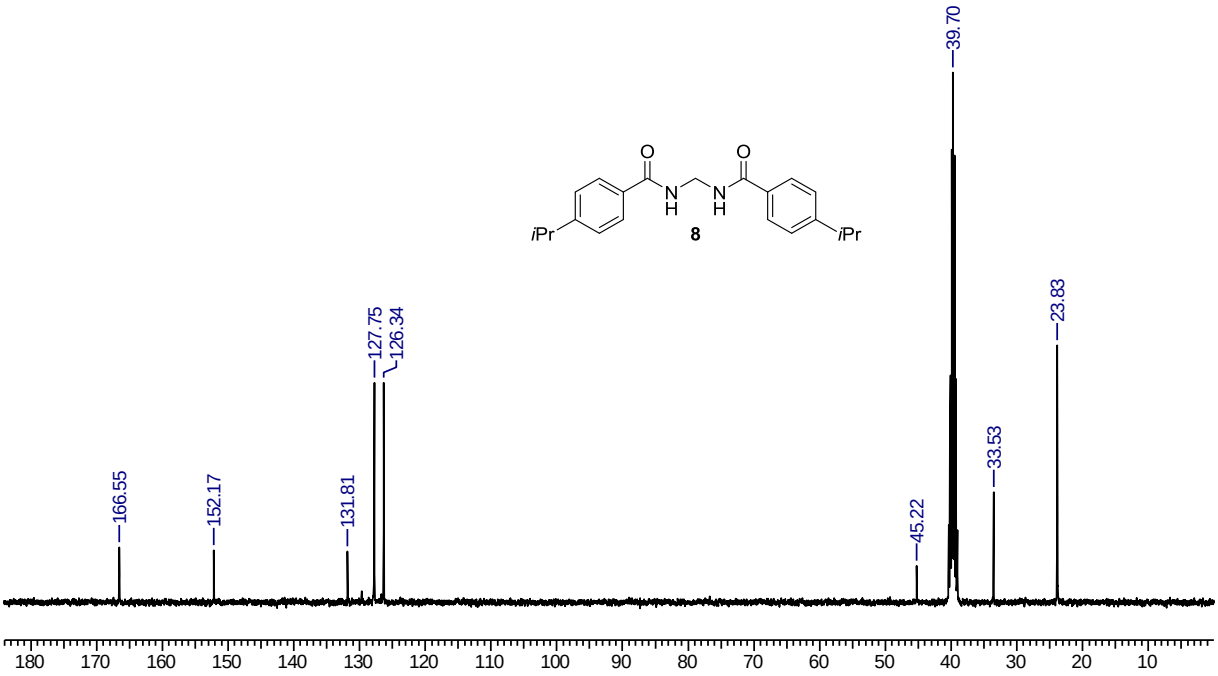
2A.8 Selected spectra

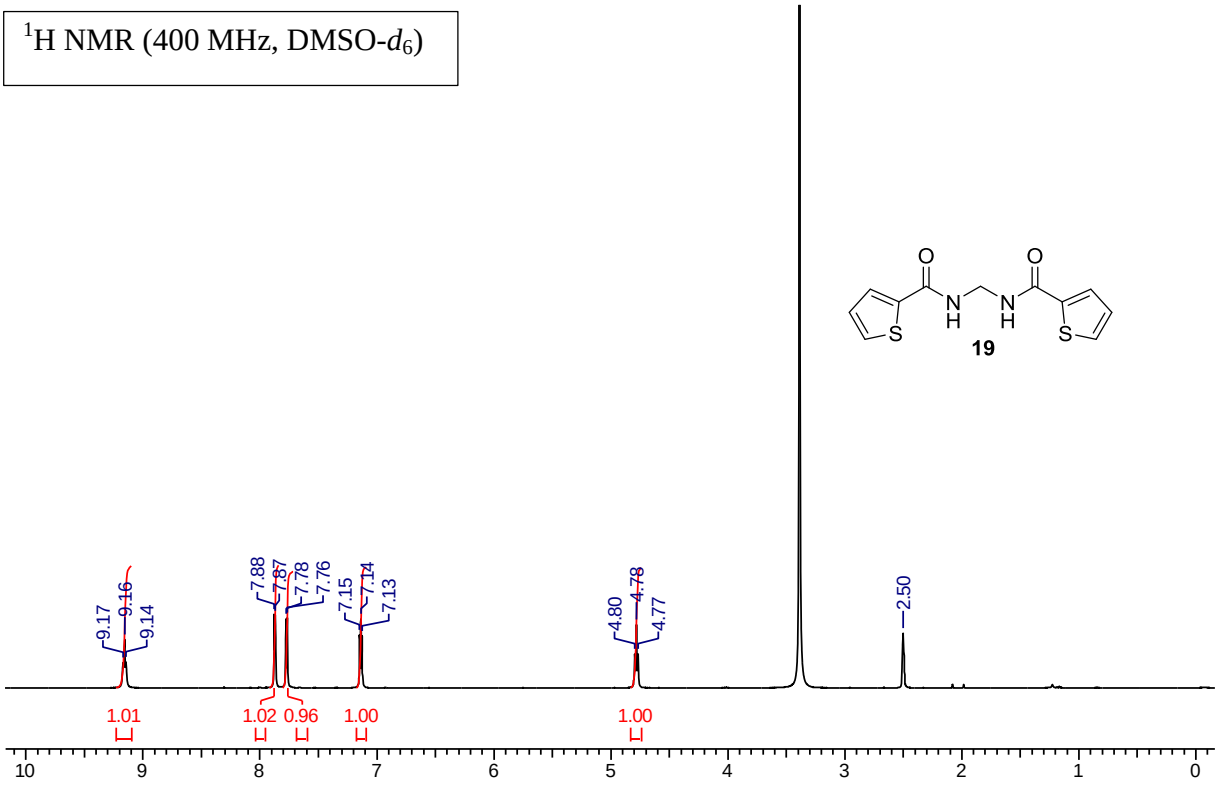
^{1}H NMR (400 MHz, DMSO-d_6)



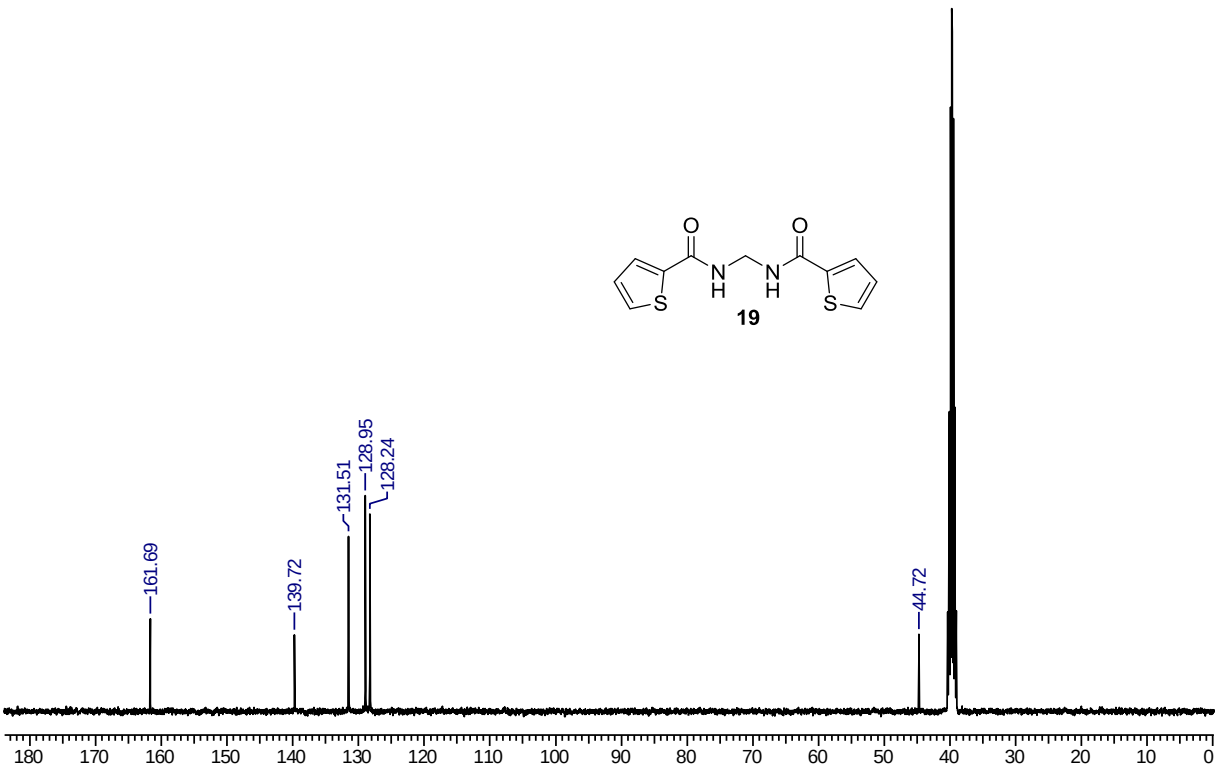
^{13}C NMR (100 MHz, DMSO-d_6)



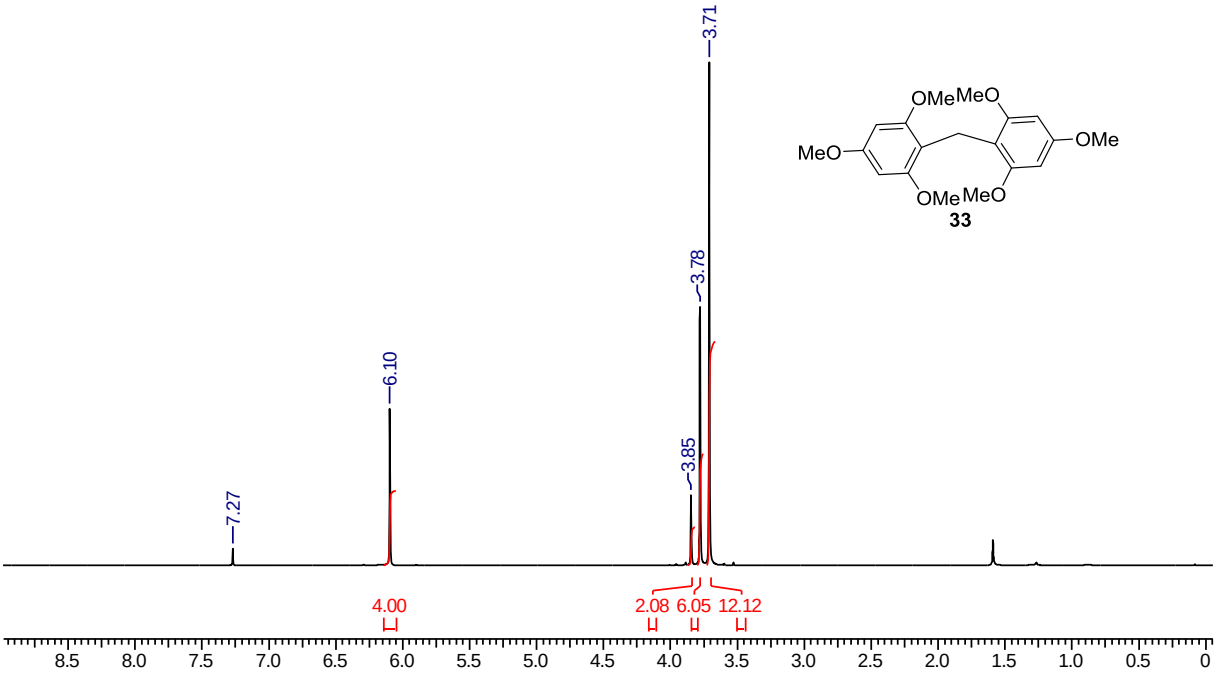
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)

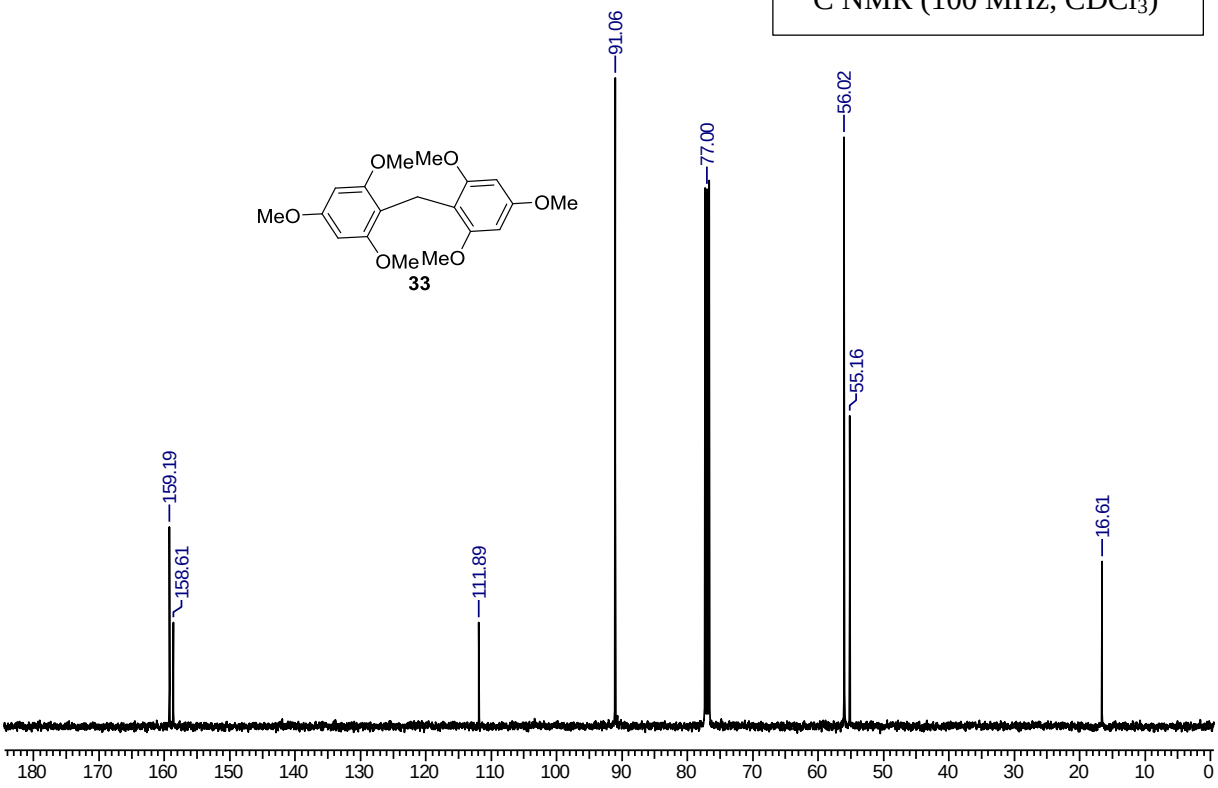


^{1}H NMR (400 MHz, $CDCl_3$)



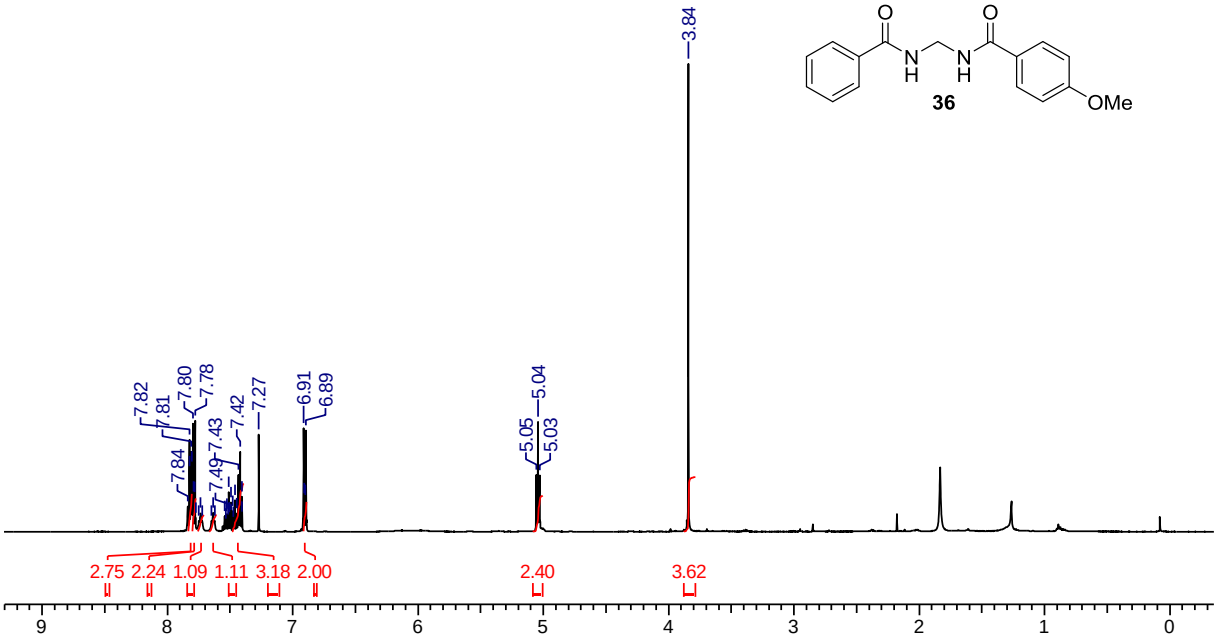
33

^{13}C NMR (100 MHz, $CDCl_3$)

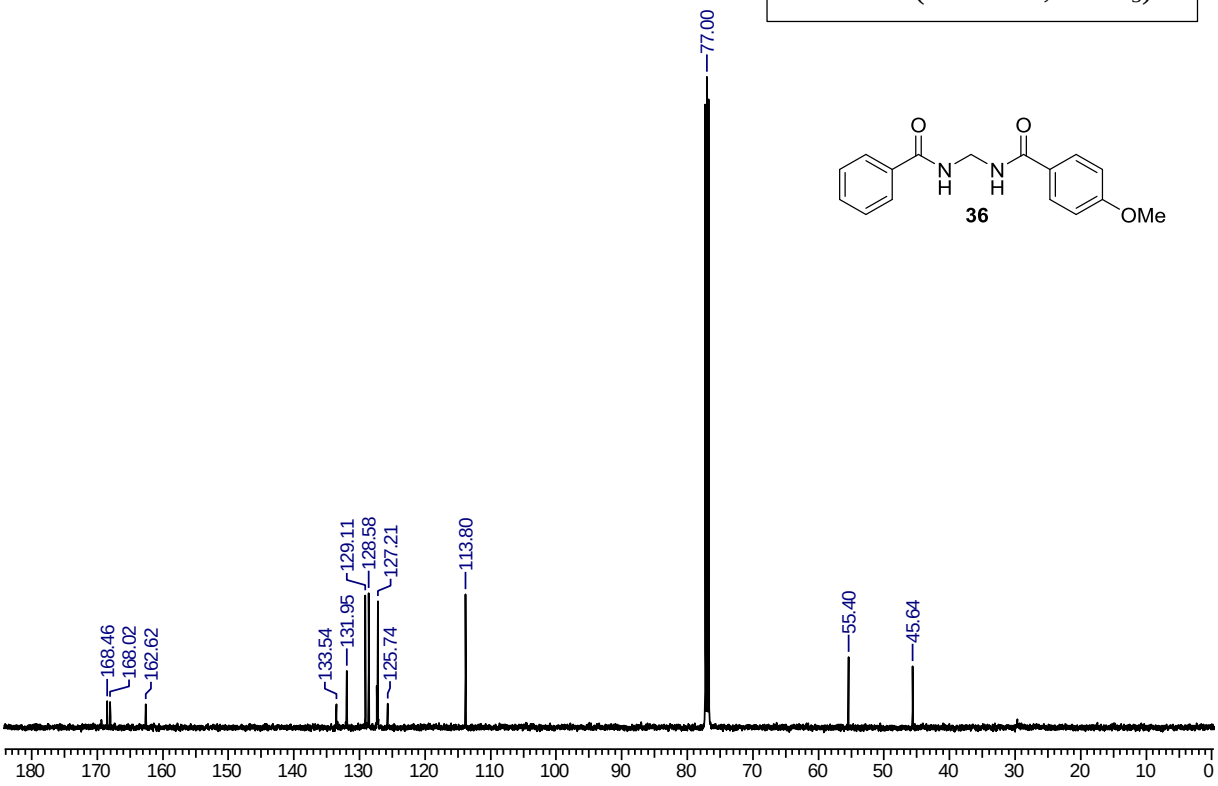


33

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)



Chapter 2

Section B

Development of Radical Beckmann Rearrangement and its Application to the Synthesis of Antimalarial Natural Product Isocryptolepine

Mahajan, P. S.; Humne, V. T.; Tanpure, S. D.; Mhaske, S. B. *Org. Lett.* **2016**, *18*, 3450.

Section B

Development of Radical Beckmann Rearrangement and its Application to the Synthesis of Antimalarial Natural Product Isocryptolepine

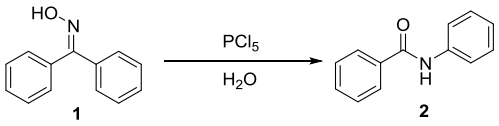
2B.1 Abstract

This section presents the development of the radical Beckmann rearrangement, its mechanistic study and successful application to the synthesis of the antimalarial natural product isocryptolepine and a known anticancer indoloquinolone molecule.

2B.2 The Beckmann rearrangement

2B.2.1 History

Beckmann Rearrangement (BR) was discovered in 1886 by the German chemist Ernst Beckmann. The reaction is typically acid-catalyzed, which delivers an amide from ketoxime via rearrangement.[1a] The BR was discovered accidently. Beckmann wanted to develop a typical method to distinguish aldehyde and ketone by their chemical reactivities. Aldoxime to nitrile conversion was known that time with phosphorous pentachloride. Beckmann tried the same experiment on benzophenone oxime **1** but after hydrolysis, he got benzanilide **2** (Scheme 1). This new rearrangement became popular in the field of organic chemistry.[1a] Many groups started



Scheme 1: BR did by Ernst Beckmann

working on this rearrangement and discovered various catalysts and reaction conditions.[1b] The mechanism of the rearrangement was uncertain therefore, chemists started looking into it using different experients.[1c] Jones described the BR as "Mona Lisa" of all the rearrangements discovered.[1d] The BR has been used in the synthesis and semi-synthesis of bioactive molecules

and natural products.[2] The BR is generally catalyzed by strong acids including Bronsted and Lewis acids. Dehydrating agents also have been used at high temperature. This ultimately limits the use of BR in the synthesis of complex and sensitive substrates.[3]

2B.2.2 Recent developments in BR

The utility of the BR[2] and limitations[3] prompted many scientists to develop and study catalytic as well as stoichiometric protocols. Some selected recent literature is presented herein (Figure 1).[4,5]

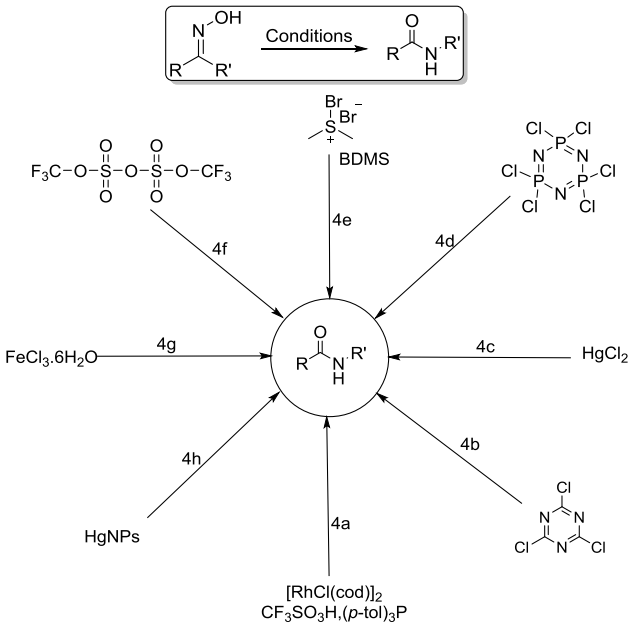
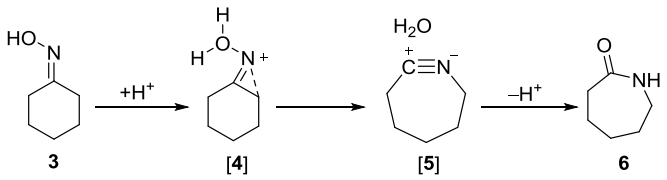


Figure 1: Recent developments in Beckmann rearrangement[4]

The BR catalyzed by $[RhCl(cod)]_2$, trifluoromethanesulfonic acid and tris(*p*-tolyl)phosphine at reflux in dichloroethane was developed by Yamaguchi[4a] Giacomelli developed the BR using cyanuric chloride at room temperature in DMF.[4b] Park developed the reaction in acetonitrile under reflux condition using catalytic mercury(II) chloride.[4c] Triphosphazene or 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC) was used as a catalyst in acetonitrile or hexafluoroisopropanol (HFIP) by Ishii for the rearrangement.[4e] Triflic

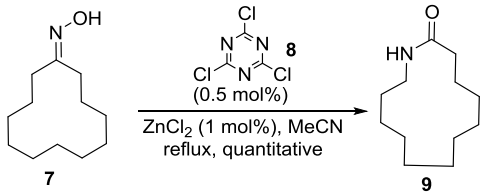
anhydride was used as a reagent for the BR in dichloromethane by Kalkhambkar at room temperature.[4f] Kapoor et al. reported the BR of *in situ* generated ketoxime from the corresponding ketone and hydroxylamine hydrochloride, which was catalyzed by $FeCl_3.6H_2O$.[4g] Bhalla used mercury nanoparticles (HgNPs) to catalyze the rearrangement.[4h]

Boero showed that supercritical water catalyzes the BR. Its application to cyclohexanone oxime **3** smoothly delivered the ε-caprolactam **6** and via the proposed intermediates **4** and **5** (Scheme 2).[5a]



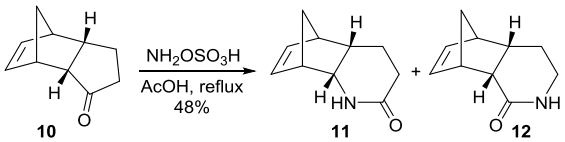
Scheme 2: Synthesis of ε-caprolactam **6** by Boero using supercritical water[5a]

Yamamoto developed the first organocatalytic BR using the catalytic combination of cyanuric chloride **8** and zinc chloride in acetonitrile. The azacyclotridecan-2-one **9** was achieved in quantitative yields, which is a synthetic precursor for nylon-12 (Scheme 3).[5b]



Scheme 3: BR developed by Yamamoto[5b]

Kotha achieved one-step BR from the ketone **10** using hydroxylamine-*O*-sulfonic acid (NH_2OSO_3H) in acetic acid. The observed ratio for **11** and **12** was 2:1 (Scheme 4).[5c]

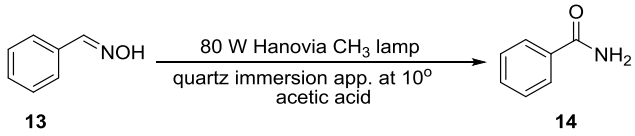


Scheme 4: BR in a single step from ketone by Kotha[5c]

2B.2.3 Radical Beckmann rearrangement

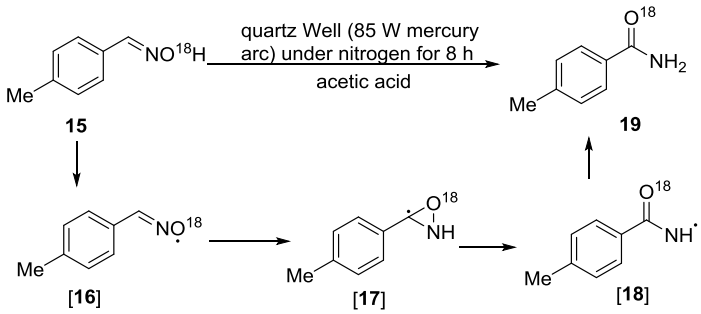
BR can also be driven by radicals, but very limited literature is available. The studies on the development of photochemical (radical) BR are presented below.[6]

The first photochemical BR was studied by de Mayo with 80W Hanovia methyl lamp in a quartz immersion apparatus at 10^{o} in acetic acid and observed the formation of benzamide **14** from benzaldoxime **13** (Scheme 5).[6a]



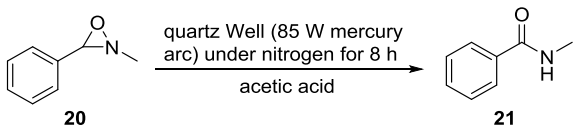
Scheme 5: Photochemical BR studied by de Mayo[6a]

The proof for internal oxygen involved in the photochemical BR was provided by O^{18} labeling experiment. The O^{18} labeled *p*-toluataldehyde oxime **15** upon irradiation gave *p*-methyl benzamide **19** with retention of the O^{18}. Hence, the mechanism was proposed via intermediate oxaziridine **17** (Scheme 6).[6a]



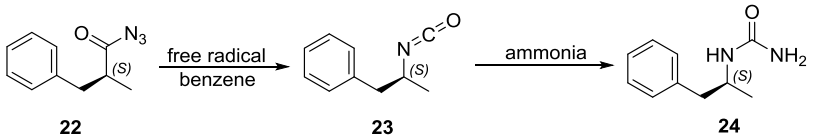
Scheme 6: Mechanism of radical BR proved with oxygen labeling by de Mayo[6a]

The mechanism of the reaction was reconfirmed by irradiating phenyl-*N*-methyl oxaziridine **20**, which gave corresponding amide **21** (Scheme 7).[6b]



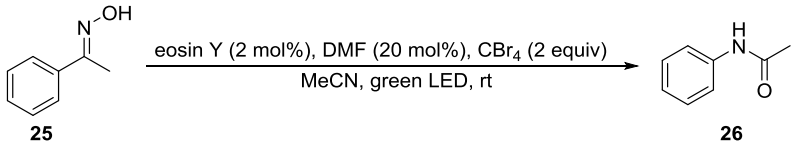
Scheme 7: Proof for the formation of oxaziridine[6b]

The investigation by Jones and Wallis performed on a chiral substrate proved that the optically active radical do exist in a radical BR.[6c] An optically active D-benzylmethylacetazide **22** produced an optically active isocyanate **23** via BR, which was then converted to its optically active urea **24** on treatment with ammonia (Scheme 8). The authors claimed that the optically active substrate produces an optically active product with retention of the configuration; therefore, radical involved in the reaction must be chiral.[6c]



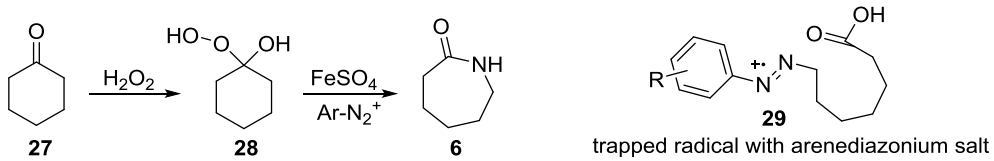
Scheme 8: BR of an optically active azide with free radical[6c]

Yadav developed a new protocol for photochemical BR using eosin Y as a catalyst. In a visible-light-mediated reaction; DMF and CBr_4 generate *in situ* Vilsmeier-Haack reagent, which catalyzed the reaction from corresponding ketoximes at room temperature (Scheme 9).[6d]



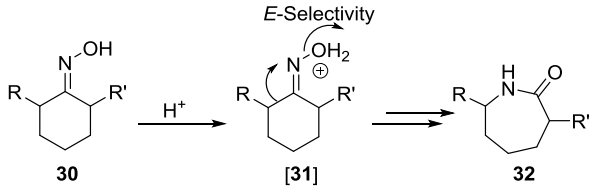
Scheme 9: Eosin Y catalyzed BR using DMF and CBr_4[6d]

Heinrich developed a new method for the radical Beckmann type rearrangement using hydroperoxides and iron(II). The author achieved ε-caprolactam **6** from cyclohexanone **27** via peroxy compound **28**. The reaction worked well on aliphatic substrates. The active radical intermediate was trapped as substrate **29** using arenediazonium salts (Scheme 10).[6e]



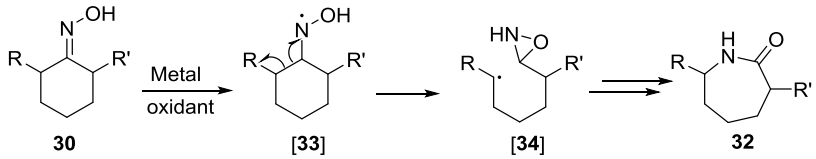
Scheme 10: Radical BR developed by Heinrich[6c]

The classical BR of ketoxime of the type **30** involves migration of a substituent from carbon to nitrogen of the type **31,** which is *anti* to the ketoxime hydroxyl (leaving group H_2O). This makes the reaction regioselective and delivers product **32** (Scheme 11). Whereas, in a radical BR



Scheme 11: Classical Beckmann rearrangement

regioselectivity of the reaction depends on the stability of the radical involved in the reaction as well as the reaction temperature. The reaction proceeds through oxaziridine **34** and give the rearranged product **32** (Scheme 12).[6e]



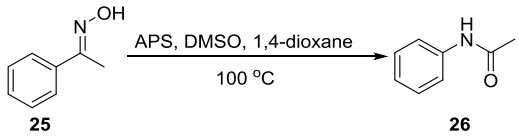
Scheme 12: Radical Beckmann rearrangement

2B.3 Results and discussion

Radical reactions are important tools in organic synthesis. Radicals have been utilized for new transformations as well as in the synthesis of complex structures efficiently. The radical reactions are chemoselective and practical, which enables very rapid access to novel scaffolds. The radical transformations in the organic synthesis were celebrated as a festival in 2017 by the American Chemical Society under the title "Radicals in Action".

The radical BR is studied photochemically in the past, but not sufficiently explored.[6] We have previously demonstrated that APS-DMSO is a useful reagent for various transformations (Section 2A). In continuation of our interest in inventing new synthetic methods we endeavoured

to develop the radical BR using APS-DMSO protocol. The protocol developed [APS (2 equiv), DMSO (6 equiv) in 1,4-dioxane at 100 ^{o}C for 3 h] for the methylene insertion was applied on the acetophenone ketoxime **25**. Interestingly, the protocol worked well and the amide was obtained in 80% yield in the first attempt (Scheme 13, table 1, entry 1). The optimization of the protocol was carried out by varying equivalents of APS and DMSO at 100 ^{o}C in 1,4-dioxane (Table 1). The optimized condition was found to be APS (1.5 equiv), DMSO (6 equiv) in 1,4-dioxane at 100 ^{o}C for 3 h (Table 1, entry 6).



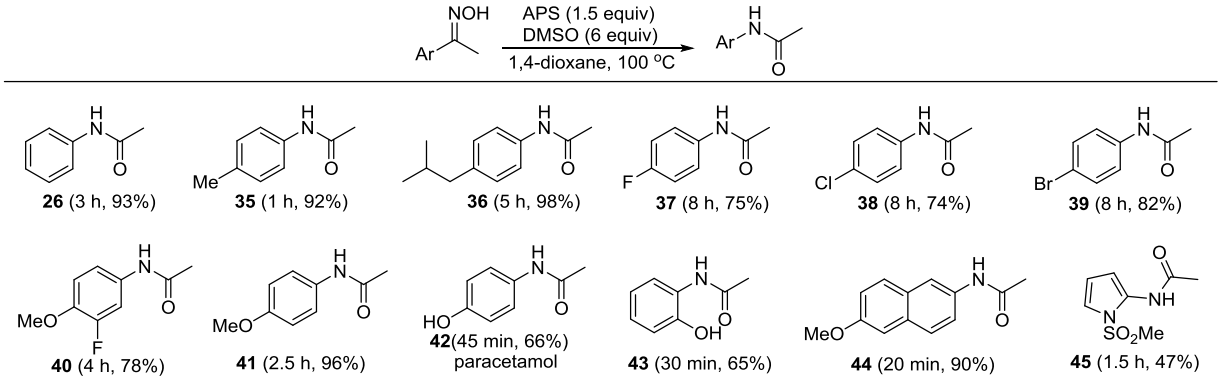
25 **26**

Scheme 13: Attempted radical BR

Entry	APS (equiv)	DMSO (equiv)	26 (% Yields)
1	2	6	80
2	3	6	72
3	5	10	76
4	2	10	72
5	4	6	82
6	**1.5**	**6**	**93**
7	1.5	8	86

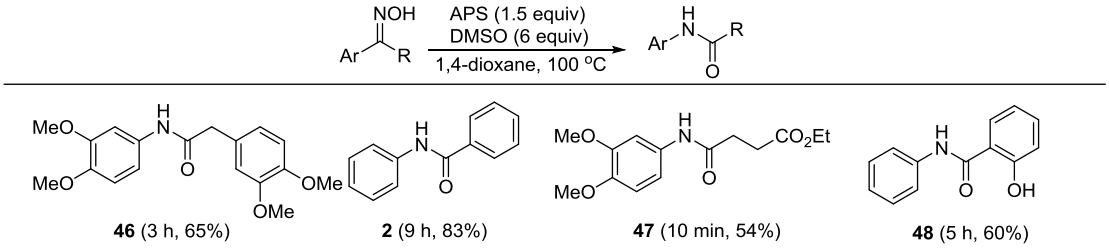
Table 1: Optimization of the radical BR

After optimization, the substrate scope and generality of the developed radical BR protocol was studied by varying aryl substituents of the ketoximes (Scheme 14). The radical BR worked well with oximes having *para* alkyl substituents (**35**, **36,** Scheme 14) as well as halogen substituents at *par*position (Scheme 14, **37**, **38**, **39**). Presence of methoxy at the *para* position also worked well (**40**, **41**). Paracetamol **42** and its regiomer **43** was achieved with in good yields; thus the free hydroxy is also tolerated. Naphthol derivative gave excellent yields for **44** in a short span of time. Heteroaromatic ketoxime of pyrrole also worked in moderate yield to deliver **45** (Scheme 14).



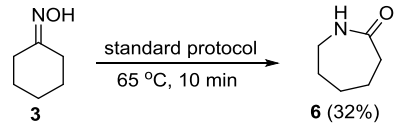
Scheme 14: Generality of the protocol on various aromatics

The study of the effect of variation in the other part (aliphatic) of the ketoxime on was also completed (Scheme 15). The replacement of methyl group by benzyl group (R = 3,4-MeO-Ph-CH_2-) provided **46** in 65% yields. Benzophenone ketoxime delivered the corresponding amide **2** in 83% yield. The extended aliphatic chain (R = EtO_2C-CH_2-CH_2-) containing substrate could only provide a moderate yield of **47**. Amide **48** was obtained in 60% from the free hydroxy substituted benzophenone ketoxime (Scheme 15).



Scheme 15: Varyingly substituted '-R'

The most important commercial applications of the BR is the synthesis of ε-caprolactam **6**, which is a synthetic precursor for the production of Nylon-6.[7] We attempted the reaction on cyclohexanoneoxime **3** to obtain the ε-caprolactam **6** using our protocol. The reaction did not work well and produced several unidentified products along with the ε-caprolactam **6** with the maximum 32% yield at 65 °C (Scheme 16). Several conditions were tested to increase the yield, but all met with failure. Oligomer formation or polymerization under our reaction condition was observed, which could be the reason behind low yield.



Scheme 16: Synthesis of ε-caprolactam

The developed radical BR protocol failed on the five ketoximes **49**-**53** (Figure 2). The two ketoximes **49** and **50** remained unreactive. The rationale behind this might be the difficulty in the migration of aromatic ring, as the substrate possesses ring strain. The ketoxime **51** having a nitro substitution on the aromatic ring did not work. The ketoxime **51** remained unreactive probably because of the the low migratory aptitude of the electron deficient aromatic ring. Amino substituted ketoxime **52** and ketoxime of pyridine **53** turned dark brown with complete consumption of the starting material and showed a very complex TLC. Tendency of basic nitrogen containing compounds to undergo oxidation in the presence of oxidizing reagents might be the cause.

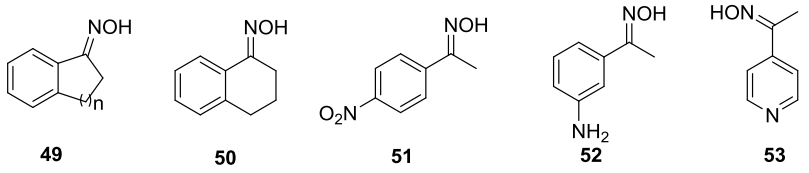
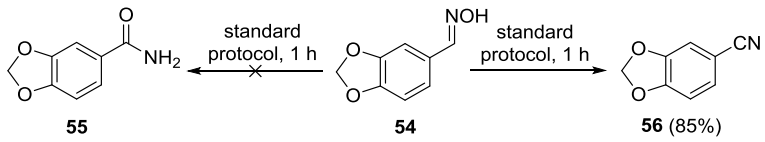


Figure 2: Developed protocol did not work with these substrates

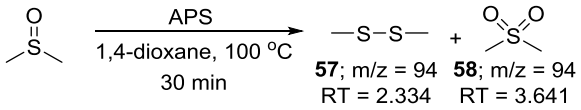
The developed protocol when applied to the aldoxime **54**, the expected product **55** was not observed, but benzonitrile **56** was obtained in very good yield (Scheme 17). Augustine also reported similar observations.[8]



Scheme 17: Aldoxime provided the corresponding benzonitrile

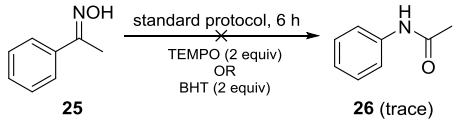
After establishing the generality of the radical BR successfully, its mechanism was studied. A blank reaction was performed without ketoxime to observe the reactive species

generated from APS and DMSO. The study was performed by GC-MS and two major reactive intermediates were found i.e. dimethyl disulfide and dimethyl sulfone, which are confirmed by GC-MS library (Scheme 18).



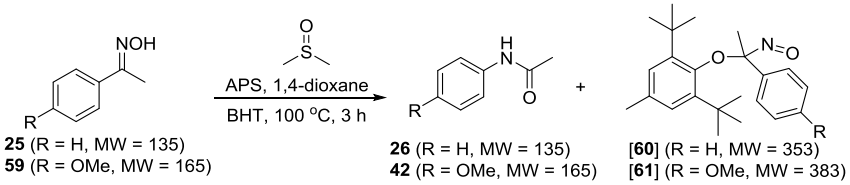
Scheme 18: Blank reaction and its outcomes

The presence of 1,2-dimethyldisulfane **57** in the reaction mixture of the blank reaction indicates formation of methanethiol from DMSO while heating.[9] The formation of **57** might be possible by radical-radical coupling of the methanethiol.[9b] To prove the radical involved in the reaction we carried out radical trapping experiments with radical scavengers TEMPO and BHT and as expected we observed trace amount of product formation (Scheme 19). These experiments confirmed that our protocol works through radical pathway.



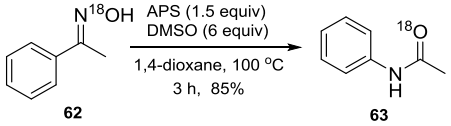
Scheme 19: Radical trapping experiments with radical scavengers

Two reactions were performed using the standard protocol in the presence of BHT (4 equiv) and the active intermediates were confirmed by ESI-HRMS of the reaction mixtures (Scheme 20). The intermediates **60** and **61** were found to be a combination of the corresponding ketoximes **25** and **59** with BHT.[9a] Isolation of the trapped intermediate was unsuccessful.



Scheme 20: Confirmation of active intermediates by trapping with BHT

It is known that the internal rearrangement of oxygen takes place in the photochemical BR.[6a,b] To confirm the source of oxygen in the product by developed radical BR protocol, the ^{18}O-enriched ketoxime **62** was synthesized.[10] The developed protocol furnished the ^{18}O-enriched acetanilide **63** with more than 50% retention of the heavy oxygen (Scheme 21). This confirmed the involvement of oxaziridine intermediate[6a,b] and its rearrangement[11] to deliver the corresponding BR products.



Scheme 21: Oxygen labeling experiment

Based on the radical trapping experiments, mechanistic studies and literature precedence[1,6a-b,9,11] the probable mechanism is depicted herein (Figure 3).

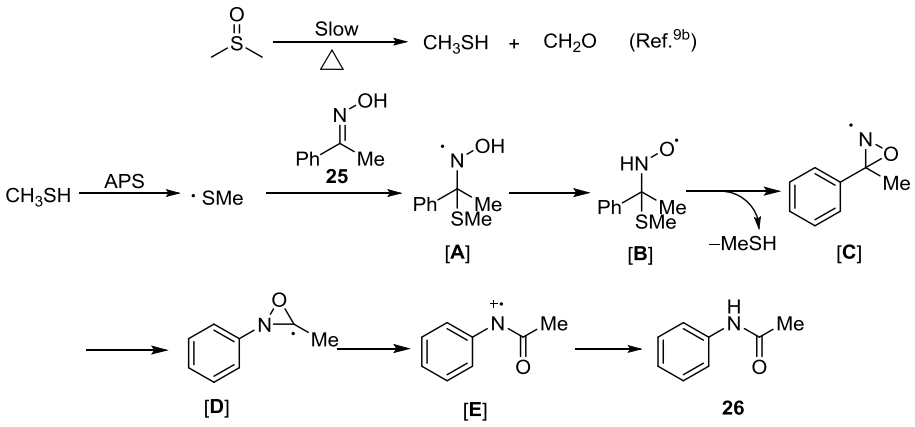


Figure 3: Mechanism for the APS-DMSO mediated radical Beckmann rearrangement

DMSO generates methanethiol radical and formaldehyde[9b] when heated in the presence of radical initiator APS. The generated sulfur radical reacts with the carbon-nitrogen double bond of the ketoxime **25** to form an intermediate **A**. 1,2 Hydride shift followed by oxygen radical cyclization generates oxaziridine **C** via elimination of methanethiol. The rearrangement of the oxaziridine then furnishes the amide **26**.

2B.4 Application of the radical BR to the synthesis of the antimalarial natural product isocryptolepine

The generality and wide scope of the developed radical BR prompted us to demonstrate its application in the synthesis of bioactive natural product. The antimalarial natural product isocryptolepine (**64**, Figure 4) was selected as a target for this purpose.

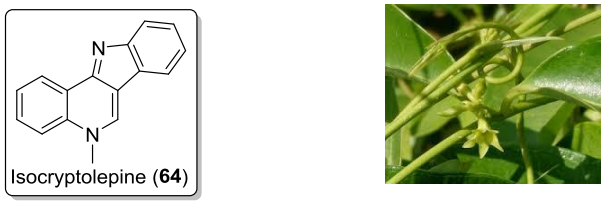


Figure 4: Antimalarial natural product isocryptolepine (**64**) and its source

The natural product isocryptolepine (**64**, Figure 4) was isolated from the roots of the plant *Cryptolepis sanguinolenia* and bears very good antimalarial activity.[12] The fascinating heterocyclic structure and antimalarial activity attracted many scientists to work on the synthesis of the natural product and its derivatives for structure-activity-relationship studies.[13] Syntheses of isocryptolepine by various approaches are summarized in Figure 5.

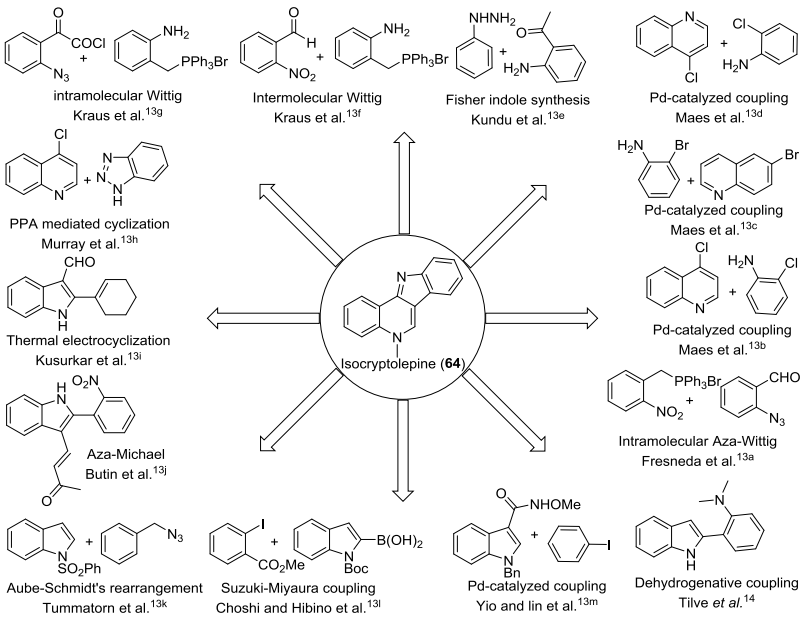
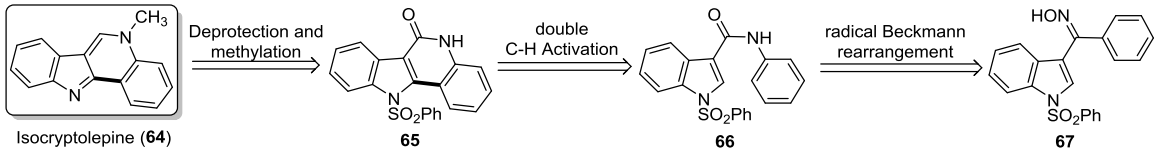


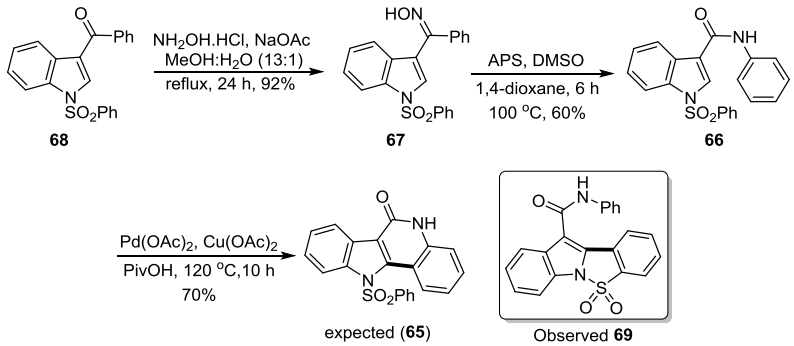
Figure 5: Isocryptolepine (**64**) and its known syntheses[13]

All the previous reported syntheses indicated that the molecule isocryptolepine (**64**) and its derivatives have high demand for their antimalarial activity and structure-activity-relationship studies. The careful study of the previously reported syntheses reveals that the BR has never been utilized in the synthesis of isocryptolepine (**64**). A new retrosynthetic route was designed for isocryptolepine (**64**), which utilizes the developed radical BR and a new intramolecular double C−H activation as key steps (Scheme 22).



Scheme 22: Retrosynthesis of isocryptolepine (**64**) using radical BR and C−H activation

Synthesis of isocryptolepine (**64**) began with the known *N*-sulfonated ketone **68**.[14] The ketone **68** was then converted to the corresponding ketoxime **67** in excellent yields (Scheme 23). The developed radical BR protocol was applied successfully on the ketoxime **67** to furnish the Beckmann reaction product **66** in 60% yields. The synthesis of such kind of amides from indole-3-carboxylic acid and aniline gives low yield[15] and the indole-3-carboxylic acid is expensive (1 g for Rs. ~1700). The double C−H activation of **66** was tried using Pd-catalyst. The reaction worked when catalytic $Pd(OAc)_2$ and stoichiometry of $Cu(OAc)_2$ was

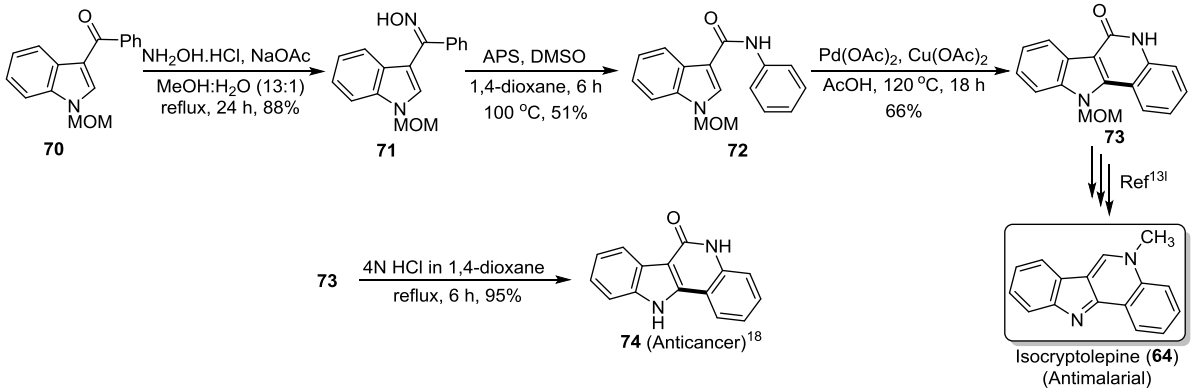


Scheme 23: Attempted synthesis of isocryptolepine (**64**) using radical BR and C−H activation

heated at 120 ^{o}C for 10 h in pivalic acid (Table 2, entry 11). The NMR study confirmed the formation of the unexpected product **69** instead of the expected indoloquinolone **65** (Scheme 23).

Such type of intramolecular oxidative double C−H activation is recently reported by Laha et al. on phenyl sulfone-protected indoles.[16]

The designed route (Scheme 24) failed to deliver the natural product isocryptolepine (**64**), but the radical BR protocol and double C−H activation worked efficiently. The protecting group (SO_2Ph) was the only hurdle in the successful synthesis of the natural product therefore, we started with the MOM protected ketone **70**, which was prepared from known 3-benzoylindole.[17] Ketone **70** was converted to the corresponding ketoxime **71** by the usual method. The developed protocol was furnished expected MOM protected indole-3-carboxamide **72** in 51% yields.



Scheme 24: Formal synthesis of isocryptolepine (**64**) using radical BR and C−H activation

The double C−H activation was achieved on **72** using our previously used conditions to obtain the MOM-protected indoloquinolone **73** (Table 2, entry 11) in 56% yields. The yield was enhanced to 66% (Table 2, entry 8) by the change in a solvent from pivalic acid to acetic acid. The synthesis of isocryptolepine (**64**) from the MOM-protected indoloquinolone **73** is reported by Choshi and Hibino.[13l] Thus, the formal total synthesis of isocryptolepine (**64**) was achieved by employing the radical BR protocol and newly developed double C-H activation. Deprotection of **73** leads to a known anticancer bioactive molecule indoloquinolinone **74**.[18] The indoloquinolinone of the class of **74** are known as effective DNA intercalators and cytotoxic against leukemia and ovarian, breast, colon and central nervous system cancer.[19]

Entry	Pd-catalyst (equiv)	oxidant/Base (equiv)	solvent	65 (%)	73 (%)
1	$Pd(OAc)_2$ (0.1)	CsOAc (2.8)	DMAc	NR	NR
2	$Pd(OAc)_2$ (0.05)	K_2CO_3 (3)	toluene	NR	NR
3	$PdCl_2$ (0.05)	$Cu(OAc)_2$ (1.2)	*p*-xylene	NR	NR
4	$Pd(TFA)_2$ (0.05)	AgOAc (3)	PivOH	NR	NR
5	$Pd(TFA)_2$ (0.05)	$AgCO_3$ (3)	PivOH	NR	NR
6	$Pd(OAc)_2$ (0.2)	BQ (0.1), Ag_2CO_3 (0.2)	DCE	NR	NR
7	$Pd(OAc)_2$ (0.15)	$Cu(OAc)_2$ (1)	AcOH	NR	53
8	$Pd(OAc)_2$ (0.2)	$Cu(OAc)_2$ (1)	AcOH	NR	66
9	$Pd(OAc)_2$ (0.05)	$Cu(OAc)_2$ (1)	AcOH	NR	25
10	$Pd(OAc)_2$ (0.1)	$Cu(OAc)_2$ (1)	AcOH	NR	46
11[a]	$Pd(OAc)_2$ (0.2)	$Cu(OAc)_2$ (1)	PivOH	70(**69**)	56

[a]Unexpected product **69** obtained

Table 2: Optimization of the C-H activation protocol on **66** and **72** at 120 ^oC on 50 mg scale

This works is appreciated well and got seven citations. It is mostly cited for the radical BR and C−H activation studies.[20]

2B.5 Conclusion

A general efficient radical BR was developed using a new APS-DMSO reagent at the mild reaction condition. The reagent is inexpensive, environmentally benign and safe to handle. It is an efficient alternative to existing noncatalytic and harsh methods. The generality of the developed protocol is demonstrated by representative examples. Radical mechanism of the developed protocol is proposed by detailed mechanistic study and literature precedent. The developed protocol was successfully applied to the synthesis of the antimalarial natural product isocryptolepine and a known anticancer indoloquinolone molecule via newly developed double C-H activation.

2B.6 Experimental section

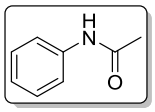
Ketoximes/aldoximes were prepared as per the known procedure.[21]

2B.6.1 General experimental procedure for the radical Beckmann rearrangement

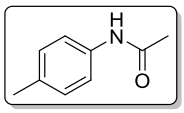
The solution of ketoxime (1 equiv), ammonium persulfate (1.5 equiv) and DMSO (6 equiv) in 1,4-dioxane (2 mL) was heated at 100 ^{o}C in a Schlenk tube under argon atmosphere until completion of the reaction as indicated by thin layer chromatography. After completion, the reaction mixture was filtered through a cotton plug and 1,4-dioxane was evaporated under vacuum. The residue was dissolved in ethyl acetate (10 mL) and washed with warm water (4 mL) and brine (3 mL x 2). The organic layer was dried over anhydrous sodium sulfate and the crude product was purified by flash column chromatography using a gradient of ethyl acetate (EtOAc) and petroleum ether (Pet. Ether) to furnish corresponding amides in good to excellent yields.

All the reactions were performed on 50 mg of ketoxime/aldoxime.

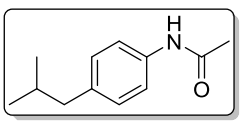
2B.6.2 Characterization Data of BR products



***N*-Phenylacetamide (26).**[22] Reaction time: 3 h; R_f = 0.3 (EtOAc:Pet. Ether, 2:3). White solid; 46.6 mg, 93%, mp 114-115 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (bs, 1H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 137.8, 128.9, 124.3, 120.0, 24.4; GC-MS (M^+) 135.

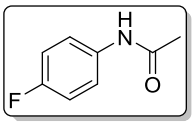


***N*-(*p*-Tolyl)acetamide (35).**[22] Reaction time: 1 h; R_f = 0.3 (EtOAc:Pet. Ether, 2:3). White solid; 46 mg, 92%, mp 151-153 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (bs, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 2.31 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 135.3, 133.9, 129.4, 120.0, 24.5, 20.8; GC-MS (M^+) 149.

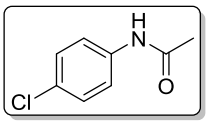


***N*-(4-Isobutylphenyl)acetamide (36)**. Reaction time: 5 h; R_f = 0.3 (EtOAc:Pet. Ether, 2:3). White solid; 49 mg, 98%, mp 127-130 ^{o}C; ^{1}H

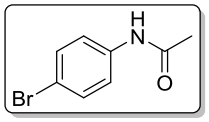
NMR (400 MHz, $CDCl_3$): δ 7.41 (bs, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 2.43 (d, J = 7.3 Hz, 2H), 2.16 (s, 3H), 1.83 (septate, 1H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 137.8, 135.5, 129.5, 119.8, 44.8, 30.2, 24.5, 22.3; HRMS-ESI (*m*/*z*) calcd $[C_{12}H_{17}ON+Na]^+$: 214.1202, found 214.1198.



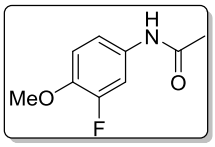
***N*-(4-Fluorophenyl)acetamide (37).**[23] Reaction time: 8 h; R_f = 0.4 (EtOAc:Pet. Ether, 2:3). White solid; 37.7 mg, 75%, mp 154-156 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (bs, 1H), 7.45 (dd, J_1 = 4.9 Hz, J_2 = 9.0 Hz, 2H), 7.00 (t, J = 8.6 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 160.6 and 158.1 (d, J = 243.5 Hz, 1C), 133.8, 121.83 and 121.76 (d, J = 7.7 Hz, 1C), 115.7 and 115.5 (d, J = 22.4 Hz, 1C), 24.3; GC-MS (M^+) 153.



***N*-(4-Chlorophenyl)acetamide (38).**[23] Reaction time: 8 h; R_f = 0.4 (EtOAc:Pet. Ether, 2:3). White solid; 37.2 mg, 74%, mp 177-180 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.2 Hz, 2H), 7.29-7.27 (m, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 136.4, 129.3, 129.0, 121.1, 24.6; GC-MS (M^+) 169.

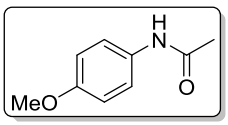


***N*-(4-Bromophenyl)acetamide (39).**[24] Reaction time: 8 h; R_f = 0.4 (EtOAc:Pet. Ether, 2:3). White solid; 41.1 mg, 82%, mp 165-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 4H), 7.35 (bs, 1H), 2018 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 136.9, 131.9, 121.3, 116.8, 24.6; GC-MS (M^+) 213.

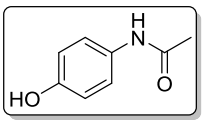


***N*-(3-Fluoro-4-methoxyphenyl)acetamide (40).** Reaction time: 4 h; R_f = 0.5 (EtOAc:Pet. Ether, 1:1). White solid; 39 mg, 78%, mp 165-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (bs, 1H), 7.41 (dd, J = 12.7, 2.2 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.89 (t, J = 9.0 Hz, 1H), 3.86 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz,

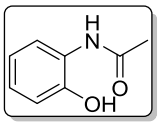
$CDCl_3$): δ 168.3, 153.2 and 150.8 (d, J = 245.1 Hz, 1C), 144.4 and 144.3 (d, J = 10.8 Hz, 1C), 131.3 and 131.2 (d, J = 9.3 Hz, 1C), 115.72 and 115.69 (d, J = 3.1 Hz, 1C), 113.62 and 113.60 (d, J = 2.3 Hz, 1C), 109.4 and 109.2 (d, J = 23.1 Hz, 1C), 56.6, 24.3; HRMS-ESI (m/z) calcd $[C_9H_{11}O_2NF]^+$: 184.0768, found 184.0767.



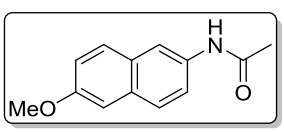
***N*-(4-Methoxyphenyl)acetamide (41).**[23] Reaction time: 2.5 h; R_f = 0.5 (EtOAc:Pet. Ether, 1:1). White solid; 48 mg, 96%, mp 130-133 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.8 Hz, 2H), 7.33 (bs, 1H), 6.85 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.3, 156.4, 130.9, 121.9, 114.1, 55.5, 24.3; GC-MS (M^+) 165.



***N*-(4-Hydroxyphenyl)acetamide (42).**[22] Reaction time: 0.75 h; R_f = 0.5 (EtOAc:Pet. Ether, 1:1). White solid; 33 mg, 66%, mp 166-168 ^oC;^1H NMR (400 MHz, Acetone-d_6): δ 8.96 (bs, 1H), 8.21 (s, 1H), 7.43 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6): 168.2, 156.1, 132.7, 121.6, 115.8, 24.0; GC-MS (M^+) 152.

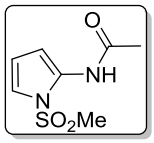


***N*-(2-Hydroxyphenyl)acetamide (43).**[25] Reaction time: 0.5 h; R_f = 0.5 (EtOAc:Pet. Ether, 1:1). White solid; 32.3 mg, 65%, mp 206-209 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 9.74 (s, 1H), 9.30 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 6.93 (t, J= 7.6 Hz, 1H), 6.85 (d, J= 7.1 Hz, 1H), 6.75 (t, J= 7.6 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2, 148.1, 126.6, 124.8, 122.6, 119.2, 116.1, 23.8; HRMS-ESI (m/z) calcd $[C_8H_{10}O_2N]^+$: 152.0706, found 152.0704.

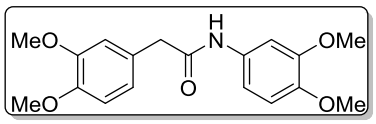


***N*-(6-Methoxynaphthalen-2-yl)acetamide (44).**[26] Reaction time: 20 min; R_f = 0.5 (EtOAc:Pet. Ether, 2:3). White solid; 45 mg, 90%, mp

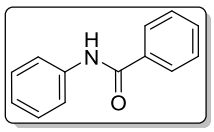
162-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.48 (bs, 1H), 7.44 (dd, J = 8.8, 2.0 Hz, 1H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 3.91 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 157.1, 133.5, 131.7, 129.1, 127.4, 120.5, 119.2, 117.1, 105.6, 55.3, 24.6; GC-MS (M^+) 215.



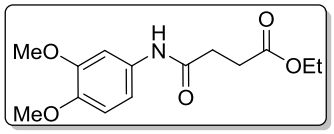
***N*-(1-(Methylsulfonyl)-1H-pyrrol-2-yl)acetamide (45)**. Reaction time: 1.5 h; R_f = 0.3 (EtOAc:Pet. Ether, 1:1). Brown solid; 23.7 mg, 47 %, mp 125-127 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (bs, 1H), 6.87 (dd, J = 1.5 Hz, 1H), 6.53 (d, J = 1.2 Hz, 1H), 6.29 (t, J = 3.4 Hz, 3.7 Hz, 1H), 3.15 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 127.3, 117.0, 112.3, 105.6, 42.2, 23.8; HRMS-ESI (*m*/*z*) calcd $[C_7H_{10}O_3N_2S+Na]^+$: 225.0304, found 225.0307.



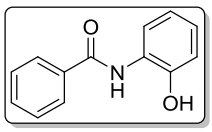
***N*,2-Bis(3,4-dimethoxyphenyl)acetamide (46).**[27] Reaction time: 03 h; R_f: 0.5 (EtOAc:Pet. Ether1:1,); Silver white Solid; 32.5 mg, 65%; mp 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.11 (s, 1H), 6.90-8.86 (m, 2H), 6.84 (s, 1H), 6.76 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 149.4, 139.3, 149.0, 148.6, 145.9, 131.2, 126.8, 121.8, 112.5, 112.7, 111.6, 104.8, 56.1, 55.9, 44.3; GC-MS (M^+) 331.



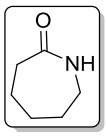
***N*-Phenylbenzamide (2).**[27] Reaction time: 5 h; R_f: 0.5 (EtOAc:Pet. Ether, 2:3); white Solid; 41.7 mg, 83%; mp 161-163 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (bs, 1H), 7.88 (d, J = 7.3 Hz, 2H), 7.66 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.0 Hz, 1H), 7.49 (t, J = 7.0, 7.6 Hz, 2H), 7.38 (t, J = 7.02, 7.3 Hz, 2H), 7.17 (t, J = 7.0, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8. 137.9, 135.0, 131.8, 129.1, 128.8, 127.0, 124.6, 120.2; GC-MS (M^+) 197.



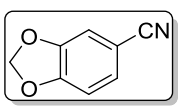
Ethyl 4-((3,4-dimethoxyphenyl)amino)-4-oxobutanoate (47). Reaction time: 10 min; R_f: 0.5 (EtOAc:Pet. Ether, 1:1); Silver white Solid; 27 mg, 54%; mp 110-113 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.34 (s, 1H), 6.86 (dd, J = 7.8, 2.2 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.75 (t, J = 6.4 Hz, 2H), 2.64 (t, J = 6.4 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 169.6, 149.0, 145.7, 131.5, 111.6, 111.2, 104.8, 60.9, 56.1, 55.9, 32.0, 29.5, 14.1; HRMS-ESI (m/z) calcd $[C_{14}H_{20}O_5N]^+$: 282.1336, found 282.1328.



***N*-(2-Hydroxyphenyl)benzamide (48)**.[28] Reaction Time: 05 h; R*f*: 0.5 (EtOAc:Pet. Ether, 1:4); White Solid; 30 mg, 60%; mp 135-137 ^oC; ^1H NMR (500 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.52 (s, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.67 (d, J = 7.6 Hz, 1H), 7.61-7.50 (m, 3H), 7.10-6.80 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.5, 149.6, 134.5, 131.9, 128.7, 127.7, 126.0, 124.4, 119.3, 116.2; GC-MS (M^+) 213.

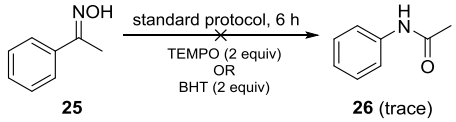


Azepan-2-one (6).[30] Reaction Time: 15 min at 65 ^oC R*f*: 0.5 (1:20, MeOH: DCM); White Solid; 16 mg, 32%; mp 68-70 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (bs, 1H), 3.25-3.15 (m, J = 2H), 2.50-2.45 (m, 2H), 1.80-1.60 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 42.9, 36.6, 30.6, 29.7, 23.2; LC-MS (M+H) 114.



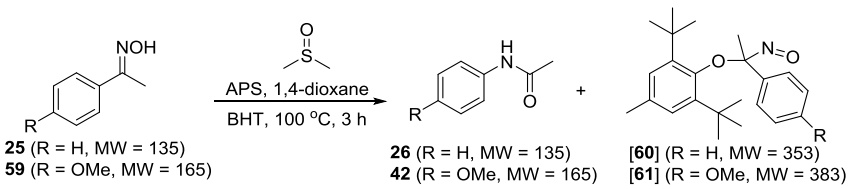
Benzo[d][1,3]dioxole-5-carbonitrile (56).[31] Reaction time: 1 h; R_f = 0.5 (EtOAc:Pet. Ether, 1:5). White solid; 38 mg, 85%, mp 94-97 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, J =8.1 Hz, 1.5 Hz, 1H), 7.04 (d, J = 1.5 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 148.0, 128.2, 118.9, 111.4, 109.1, 104.9, 102.3; LC-MS (M+Na) 170.

2B.6.3 Radical trapping experiments



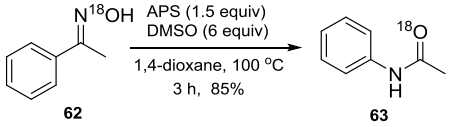
In a round bottom flask equipped with a stirring bar and water condenser, the solution of acetophenone oxime (50 mg, 1 equiv, 0.37 mmol), ammonium persulfate (168 mg, 2 equiv, 0.74 mmol), TEMPO (115 mg, 2 equiv, 0.74 mmol) and DMSO (157 µL, 6 equiv, 2.46 mmol) in 1,4-dioxane (2 mL) was heated at 100 ^{o}C for 6 h. The reaction was followed by TLC, however only a trace amount of amide **1** was observed.

The same reaction was performed in the presence of BHT (326 mg, 4 equiv, 1.47 mmol) as a radical scavenger. In this case also only a trace amount of product **1** was seen on TLC. The trapped products were detected by LC-MS and HRMS.



2B.6.4 Labelling experiment

Adapted procedure for the preparation of ^{18}O-enriched $NaNO_2$



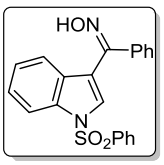
^{18}O-Labeled NH2^{18}OH was prepared to start from $H_2{}^{18}O$ and ammonia following the reported procedure.[10] It was used for the preparation of previously known ^{18}O-labelled acetophenone oxime **62**.[10b] Treatment of the oxime **62** under our standard protocol (General procedure) furnished 18O-labelled acetanilide (**63**) in 85% yield. Spectral and analytical data were in

agreement with the above reported-compound **26**. More than 50% of acetanilide (**63**) had incorporated the heavy oxygen atom (approximate calculation from the Mass spectrum). HRMS-ESI(*m*/*z*) calcd $[C_8H_9{}^{18}ON+H]^+$: 138.0799, found 138.0797.

2B.6.5 Synthesis of *N*-phenyl-1-(phenylsulfonyl)-1*H*-indole-3-carboxamide (69)

(*E*)-Phenyl(1-(phenylsulfonyl)-1*H*-indol-3-yl)methanone oxime (67)

A two necked round bottom flask containing the solution of benzoyl compound **68**[14] (1 g, 2.76 mmol, 1 equiv), $NH_2OH.HCl$ (4.8 g, 69.17 mmol, 25 equiv) and NaOAc (5 g, 60.9 mmol, 22 equiv) in MeOH:H_2O (50 mL:15 mL) was heated at 90 ^oC for 24 hours. After completion of the reaction, methanol was evaporated in vaccuo and the residue was extracted with ethyl acetate (20 mL). Organic layer was dried over sodium sulfate, concentrated and the crude product was purified by recrystallization in methanol to provide ketoxime **67** (959 mg, 92%) as a white solid.

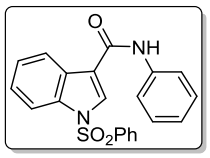


R*f* = 0.3 (EtOAc:Pet. Ether, 3:7). White solid; mp 186-187 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 11.76 (s, 1H), 8.09 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.73 (t, *J* = 7.3 Hz, 1H), 7.63 (t, *J* = 7.8, 7.3 Hz, 2H), 7.42-7.34 (m, 6H), 7.16 (t, *J* = 7.8, 7.3 Hz,, 1H), 6.96 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 148.5, 137.0, 136.4, 135.1, 134.0, 130.2, 129.3, 129.1, 128.7, 128.1, 127.3, 127.1, 125.2, 123.7, 121.9, 114.5, 113.4; HRMS-ESI (*m*/*z*) calcd $[C_{21}H_{16}O_3N_2S+H]^+$: 377.0954, found 377.0943.

N-Phenyl-1-(phenylsulfonyl)-1*H*-indole-3-carboxamide (66)[32]

The reaction mixture containing ketoxime **67** (500 mg, 1.3 mmol, 1 equiv), APS (606 mg, 2.65 mmol, 2 equiv) and DMSO (0.56 mL, 7.96 mmol, 6 equiv) in 1,4-dioxane (10 mL) was heated at 150 ^oC for 6 h in a glass tube sealed with Teflon cap. After completion of the reaction, 1,4-

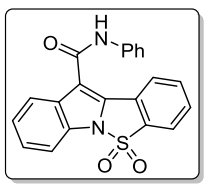
dioxane was evaporated under vacuum and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with brine (10 x 2 mL) and dried over sodium sulfate. Evaporation of ethyl acetate under vacuum followed by flash column chromatography of the residue with ethyl acetate: petroleum ether (3:7) gave (300 mg, 60%) of compound **66**.



R*f* = 0.5 (EtOAc:Pet. Ether, 3:7). White solid; mp 172-174 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.12 (d, *J* = 7.6, 1H), 8.01 (d, *J* = 8.4, 1H), 7.94 (d, *J* = 7.6, 2H), 7.80 (bs, 1H), 7.65 (d, *J* = 8.0, 2H), 7.59 (t, *J* = 7.6, 1H), 7.48 (t, *J* = 7.6, 2H), 7.43-7.35 (m, 4H), 7.17 (t, *J* = 7.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 137.62, 137.56, 135.0, 134.5, 129.6, 129.2, 127.8, 127.4, 127.0, 125.8, 124.63, 124.55, 121.7, 120.2, 118.0, 113.5; HRMS-ESI (*m*/*z*) calcd $[C_{21}H_{16}O_3N_2S+Na]^+$: 399.0774, found 399.0760.

***N*-Phenylbenzo[4,5]isothiazolo[2,3-a]indole-11-carboxamide 5,5-dioxide (69)**

Amide **66** (200 mg, 0.53 mmol, 1 equiv), palladium acetate (23 mg, 0.1 mmol, 0.2 equiv) and copper acetate (96 mg, 0.53 mmol, 1 equiv) were taken in a schlenk tube equipped with a magnetic stirring bar. It was kept under reduced pressure for some time, flushed with oxygen and kept under oxygen balloon pressure. After the addition of 1 mL of pivalic acid the reaction was heated at 120 ^{o}C for 24 h. It was then allowed to attain room temperature and ethyl acetate (15 mL) was added. The ethyl acetate layer was washed with aqueous saturated sodium bicarbonate (5 mL x 3), dried over sodium sulfate and concentrated under vacuum. Flash column chromatography using ethyl acetate: petroleum ether (3:7) yielded (140 mg, 70%) of pure compound **69**.



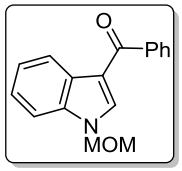
R*f* = 0.5 (EtOAc:Pet. Ether, 3:7). White solid; mp 202-207 ^{o}C; 1H NMR 400 MHz, $CDCl_3$): δ 10.71 (s, 1H), 8.31 (d, *J* = 7.8, 1H), 8.22 (d, *J* = 7.8, 1H), 7.94-790 (m, 2H), 7.81-7.76 (m, 4H), 7.55 (t, *J* = 7.8, 1H), 7.47-7.39 (m, 3H),

7.17 (t, *J* = 7.3, 1H); 13C NMR (100 MHz, $CDCl_3$): δ 161.1, 138.9, 137.5, 135.6, 132.4, 131.5, 131.1, 130.4, 129.1, 127.1, 125.8, 125.5, 124.5, 124.4, 123.4, 123.0, 120.4, 113.1, 111.5; HRMS-ESI (*m*/*z*) calcd $[C_{21}H_{14}O_3N_2S+Na]^+$: 397.0617, found 397.0606.

2B.6.7 Formal Total synthesis of Isocryptolepine (64)

(1-(Methoxymethyl)-1*H*-indol-3-yl)(phenyl)methanone (70)

In a two necked round bottom flask containing the solution of (1*H*-indol-3-yl)(phenyl)methanone (200 mg, 0.90 mmol, 1 equiv) in DMF was added NaH (65 mg, 2.7 mmol, 3 equiv) at 0 ^oC and the reaction mixture was stirred for another 10 minutes. MOM chloride (0.1 mL, 1.35 mmol, 1.5 equiv) was added and the reaction mixture was stirred at rt for 6 h. After the completion of the reaction, ice was added followed by extraction with ethyl acetate (10 mL x 2). The organic layer was washed with brine (10 mL x 2) and dried over sodium sulfate. Concentration of organic layer under vacuum followed by column chromatography ethyl acetate: petroleum ether (3:7) yielded MOM protected ketone **70** in (216 mg, 90%).

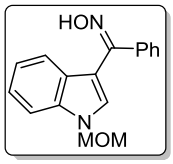


R*f* = 0.4 (EtOAc:Pet. Ether, 3:7). White solid; mp 97-99 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45-8.42 (m, 1H), 7.85 (d, *J* = 7.3 Hz, 2H), 7.66 (s, 1H), 7.60-7.55 (m, 2H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.41-7.36 (m, 2H), 5.50 (s, 2H), 3.30 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 191.1, 140.6, 136.9, 136.7, 131.4, 128.7, 128.4, 127.5, 124.2, 123.2, 122.8, 166.7, 110.3, 78.1, 56.3; HRMS-ESI (*m*/*z*) calcd $[C_{17}H_{15}O_2N+Na]^+$: 288.0995, found 288.0988.

(*E*)-(1-(Methoxymethyl)-1*H*-indol-3-yl)(phenyl)methanone oxime (71)

In a round bottom flask containing MOM ketone **70** (200 mg, 0.75 mmol, 1 equiv), hydroxylamine hydrochloride (1.3 g, 18.8 mol, 25 equiv) and sodium acetate (1.54 g, 18.8 mol,

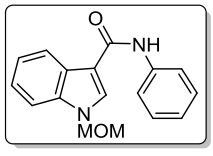
25 equiv) was added 13 mL of methanol:water (10:3) and the resulting reaction mixture was heated at 90 ^{o}C for 24 h. After completion of the reaction as indicated by thin layer chromatography, methanol was evaporated followed by the addition of ethyl acetate (20 mL). The organic layer was washed with cold water (10 mL x 2), dried over sodium sulfate and concentrated under vacuum. Flash column chromatography ethyl acetate: petroleum ether (3:7) afforded ketoxime **71** in (186 mg, 88%) yield.



R*f* = 0.3 (EtOAc:Pet. Ether, 3:7). White solid; mp 155-157 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.39 (s, 1H), 8.07 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.46-7.39 (m, 5H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.61(s, 2H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 150.3, 137.9, 135.7, 133.3, 128.8, 128.4, 128.2, 127.2, 122.0, 121.3, 120.3, 110.8, 107.0, 76.9, 55.6; HRMS-ESI (*m*/z) calcd $[C_{17}H_{16}O_2N_2+H]^+$: 281.1285, found 281.1281.

1-(Methoxymethyl)-*N*-phenyl-1*H*-indole-3-carboxamide (72)

A Schlenk tube containing ketoxime **71** (100 mg, 0.35 mmol, 1 equiv) and ammonium peroxysulfate (122 mg, 0.53 mmol, 1.5 equiv) was kept under reduced pressure and flushed with argon, followed by the addition of 1,4-dioxane (4 mL) and DMSO (0.15 mL, 2.14 mmol, 6 equiv). The reaction mixture was heated at 100 ^{o}C for 6 h. After completion of the reaction, 1,4-dioxane was evaporated and 10 mL ethyl acetate was added. The organic layer was washed with brine (5 mL X 2), dried over sodium sulfate and concentrated. Column chromatography ethyl acetate: petroleum ether (2:3) of the residue afforded (51 mg, 51%) of **72**.

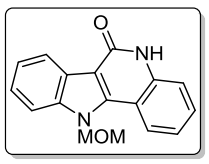


R*f* = 0.5 (EtOAc:Pet. Ether, 2:3). White solid; mp 78-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.08 (m, 1H), 7.85 (s, 1H), 7.84 (bs, 1H), 7.68(d, *J* =

8.1 Hz, 2H), 7.55-7.55 (m, 1H), 7.40-734 (m, 4H), 7.14 (t, *J* = 7.3 Hz, 1H), 5.45 (s, 2H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 138.2, 136.7, 131.5, 129.1, 125.9, 124.1, 123.4, 122.4, 120.3, 120.1, 112.5, 111.0, 78.0, 56.2; HRMS-ESI (*m*/*z*) calcd $[C_{17}H_{16}O_2N_2+Na]^+$: 303.1104, found 303.1102.

11-(Methoxymethyl)-5,11-dihydro-6*H*-indolo[3,2-c]quinolin-6-one (73)[13l]

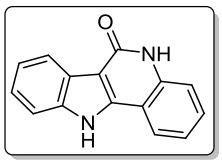
To a flame dried schlenk tube kept under oxygen balloon were added amide **72** (40 mg, 0.14 mmol, 1 eq), palladium acetate (6.5 mg, 0.02 mmol, 0.2 eq) and copper acetate (26 mg, 0.14 mmol, 1 eq). The schlenk tube was evacuated and charged with 1 mL of acetic acid under oxygen atmosphere. The reaction mixture was heated at 110 oC for 18 h. It was then allowed to come to the room temperature and ice water (5 mL) was added with stirring. The reaction mixture was extracted with ethyl acetate (10 mL X 2) and the combined organic layer was washed with aqueous saturated sodium bicarbonate (5 mL X 2). The organic layer was dried over sodium sulfate and purified by column chromatography with ethyl acetate:petroleum ether (1:1) to furnish tetracyclic amide **73** (26 mg, 66%).



R*f* = 0.3 (EtOAc:Pet. Ether, 2:3). White solid; mp 272-274 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.70 (bs, 1H), 8.67 (d, *J* = 7.3 Hz, 1H), 8.40 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 5.95 (s, 2H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 141.4, 140.1, 138.2, 129.2, 125.0, 124.3, 123.6, 122.5, 122.46, 117.2, 112.8, 109.0, 75.3, 56.3; HRMS-ESI (*m*/*z*) calcd $[C_{17}H_{15}O_2N_2+H]^+$: 279.1128, found 279.1126.

5,11-Dihydro-6*H*-indolo[3,2-c]quinolin-6-one (74)[18]

In a round bottom flask, the solution of MOM-protected amide **73** (20 mg, 0.07 mmol, 1 eq) and 4N HCl in 1,4-dioxane (1 mL) was refluxed for 6 h. After completion of the reaction as indicated by thin layered chromatography, solvent was evaporated under vacuum and ethyl acetate (10 mL) was added. The ethyl acetate layer was washed with aqueous saturated sodium bicarbonate (5 mL X 2), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography using ethyl acetate:petroleum ether (1:1) afforded (16 mg, 95%) of **74**.



R*f* = 0.4 (EtOAc:Pet. Ether, 1:1). White solid; mp 337-339 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.57 (s, 1H), 11.43 (s, 1H), 8.20 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 8.3 Hz, 1H), 7.53-7.44 (m, 2H), 7.37 (t, J = 8.1 Hz, 1H), 7.31-7.24 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1, 140.9, 138.2, 137.9, 129.4, 124.6, 124.2, 122.3, 121.7, 121.2, 120.9, 116.2, 112.2, 111.9, 106.6.

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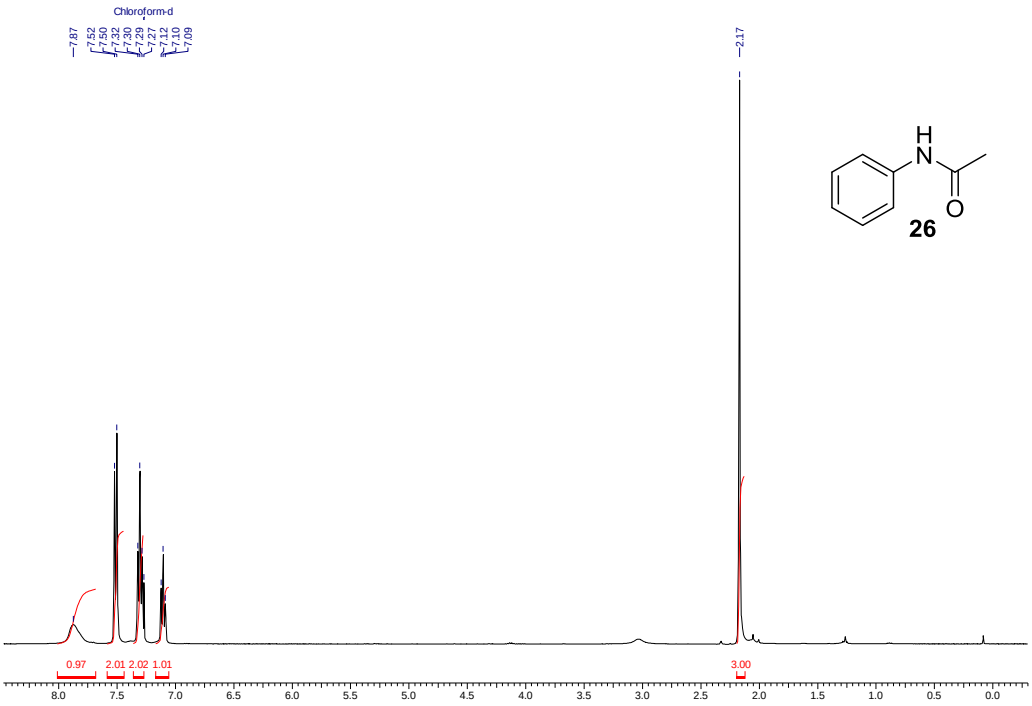
2B.8 Selected spectra

^{1}H NMR (400 MHz, $CDCl_3$)



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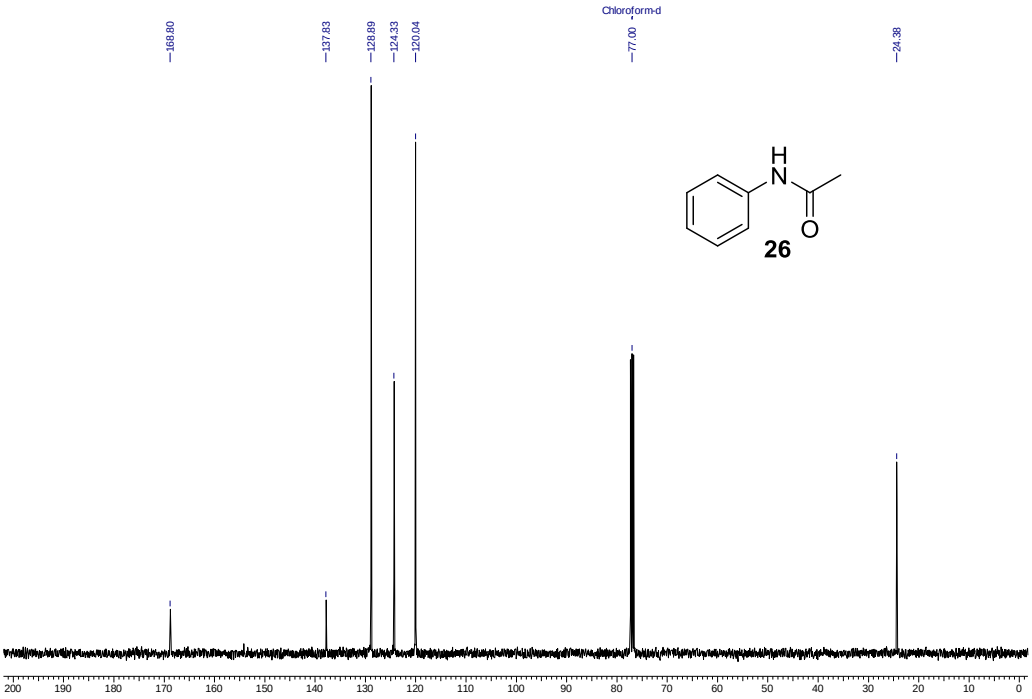

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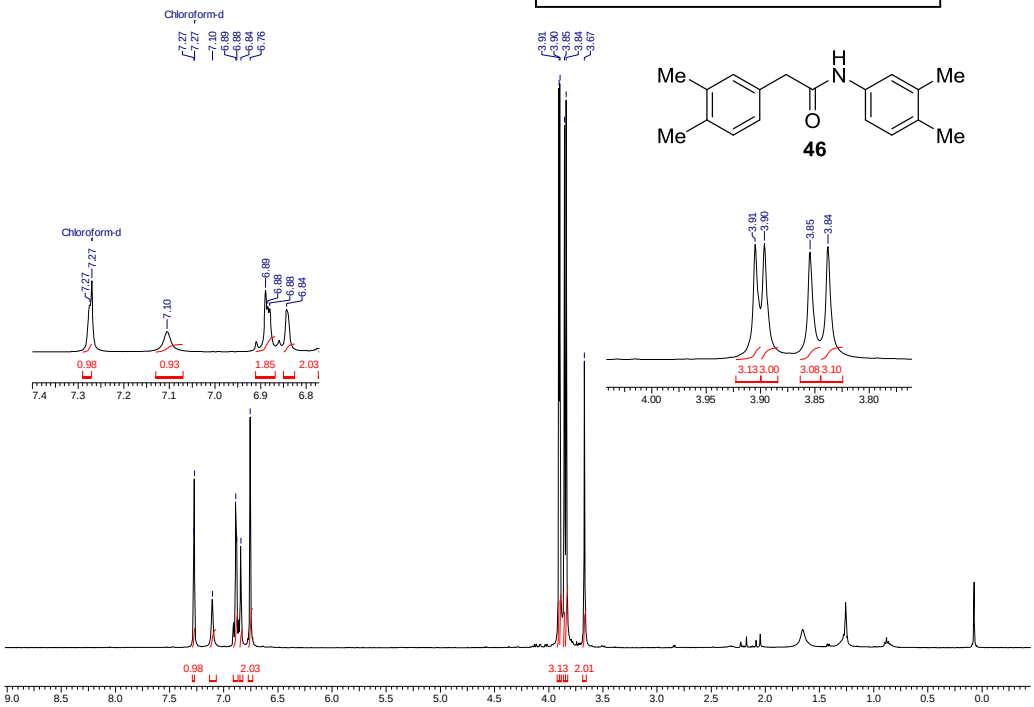

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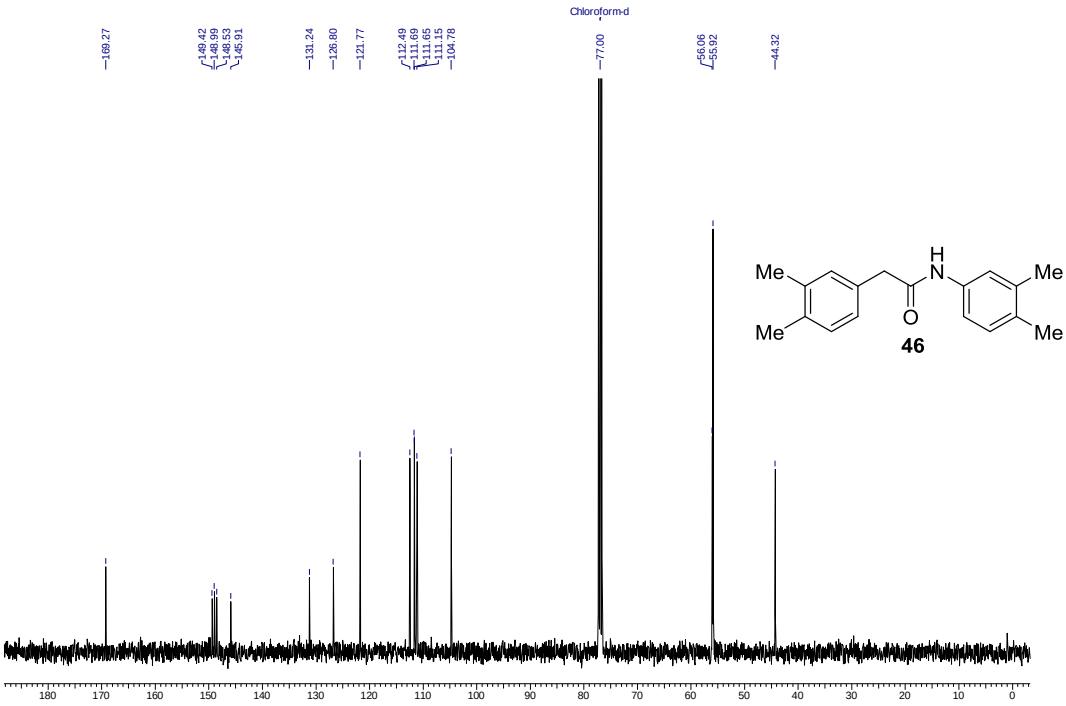

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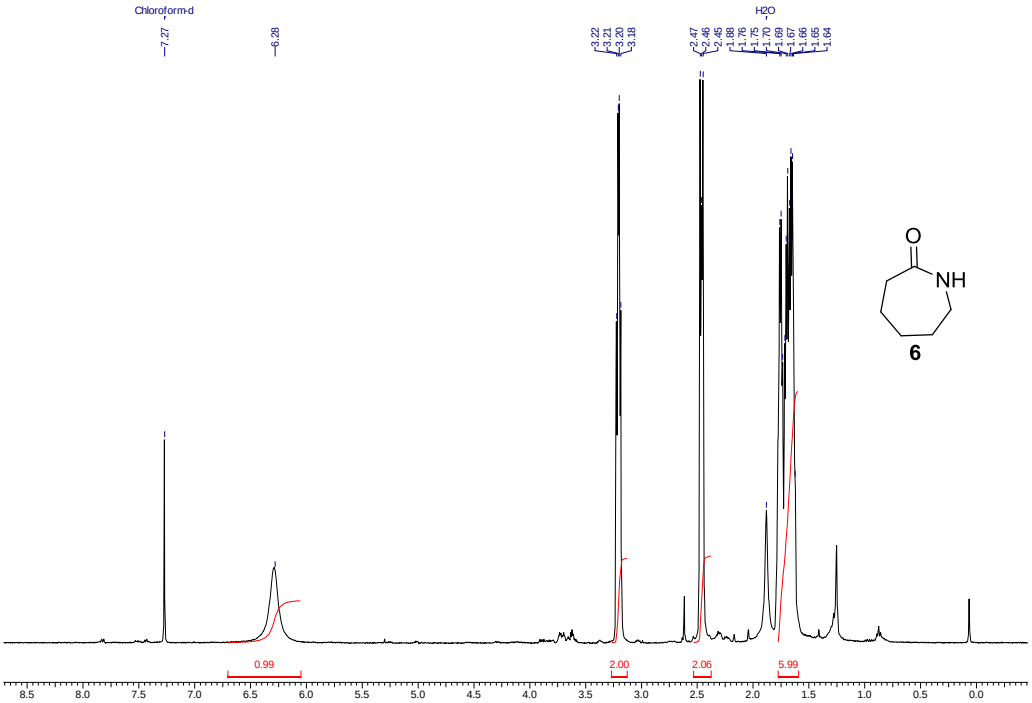

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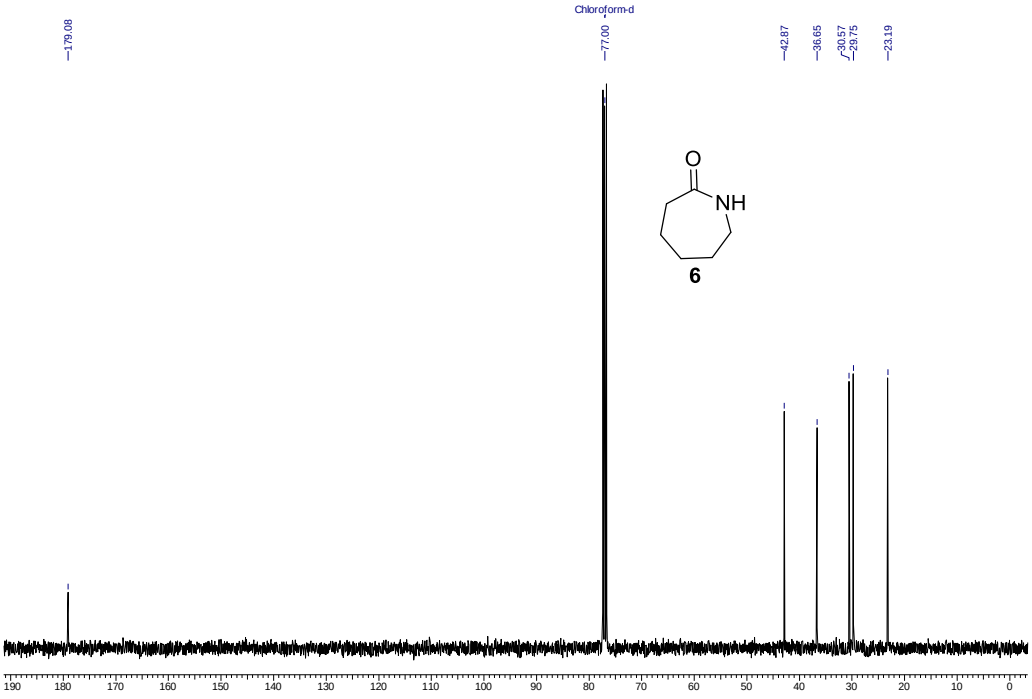

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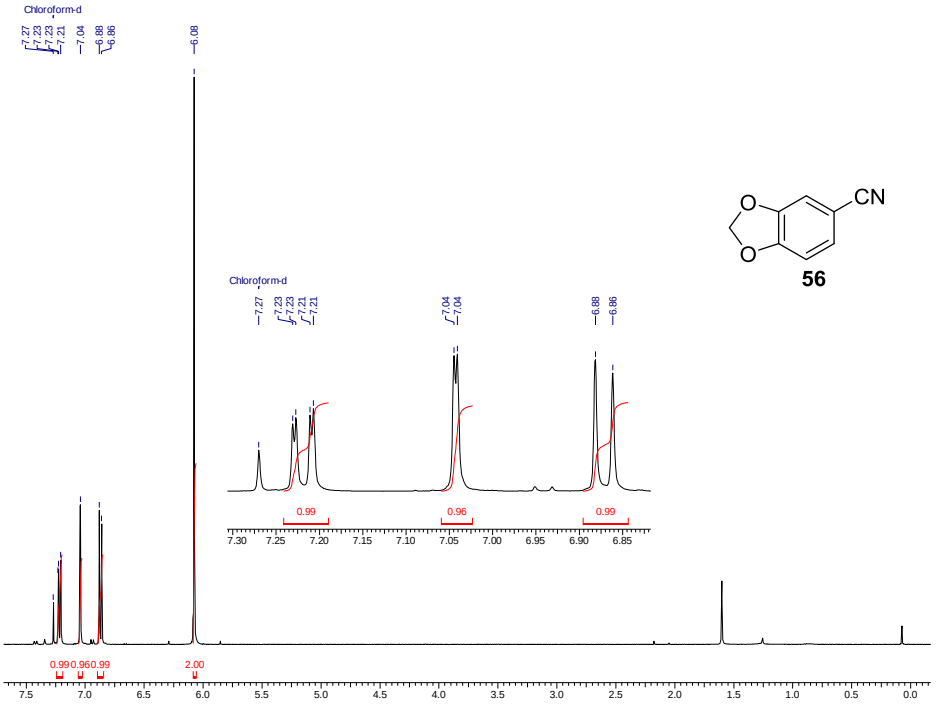

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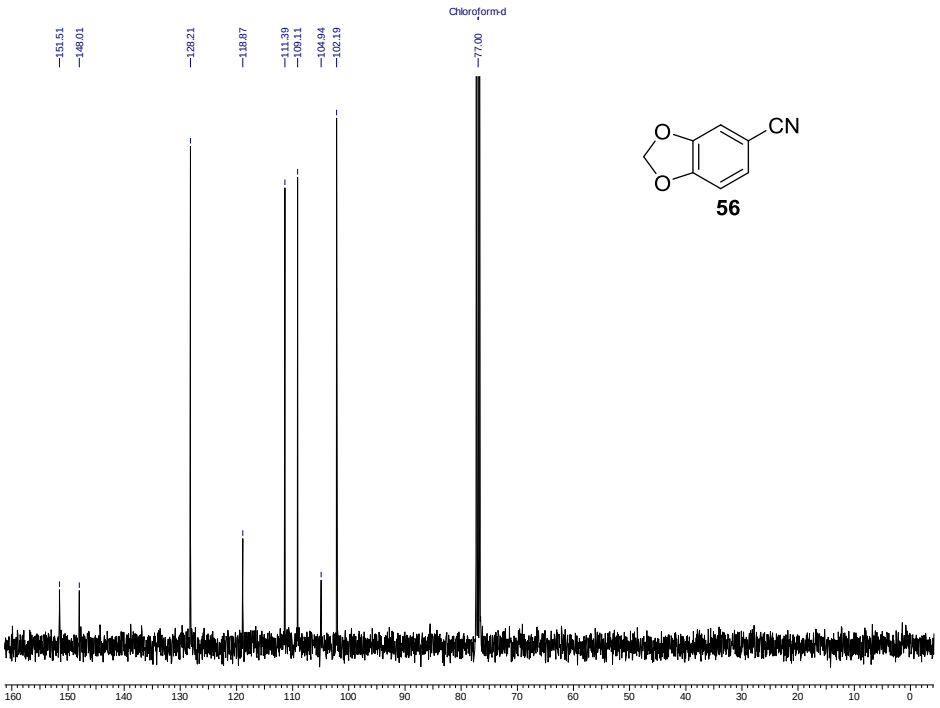

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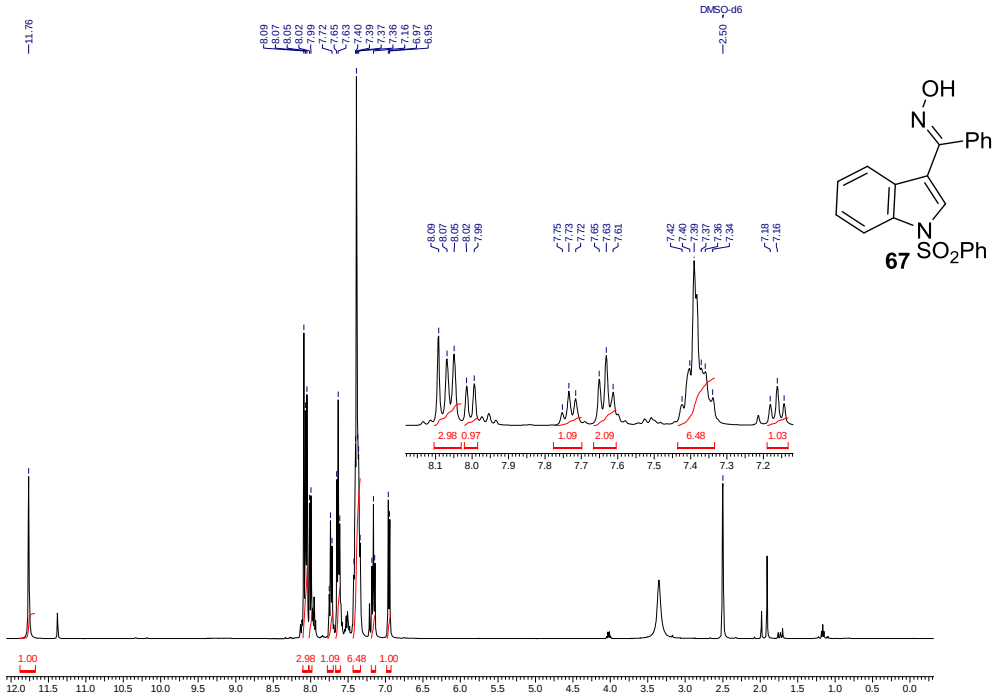

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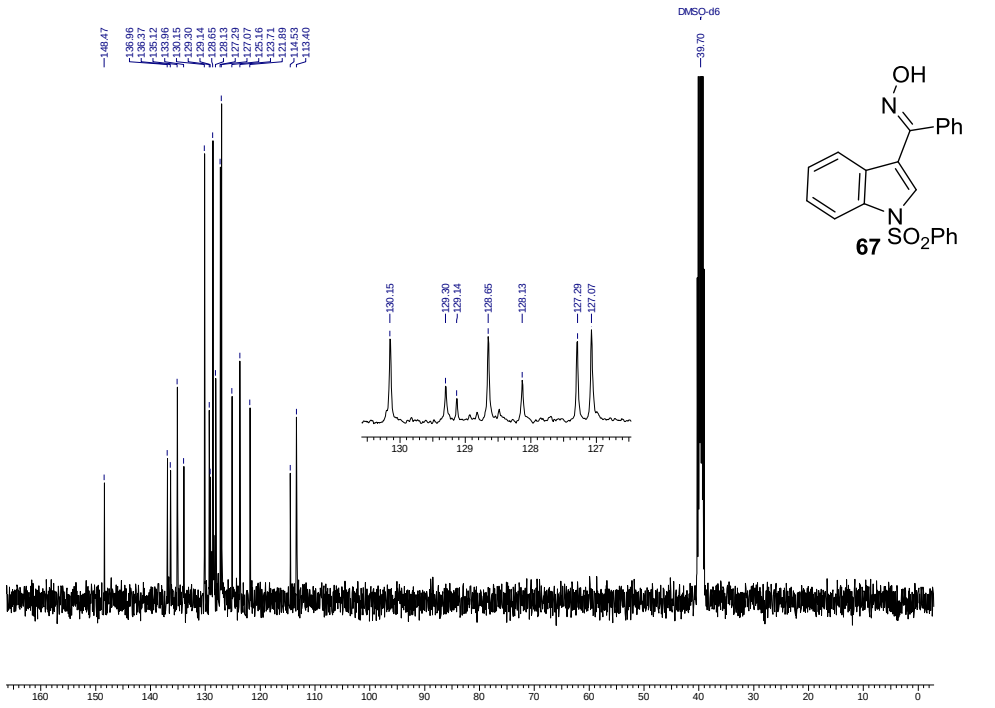

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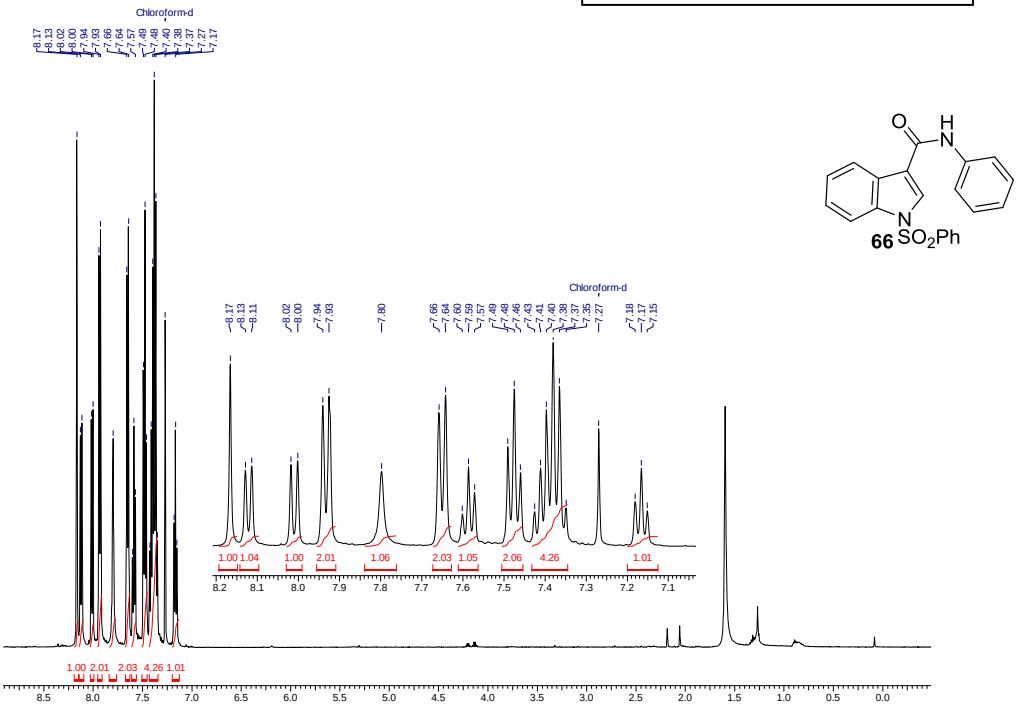

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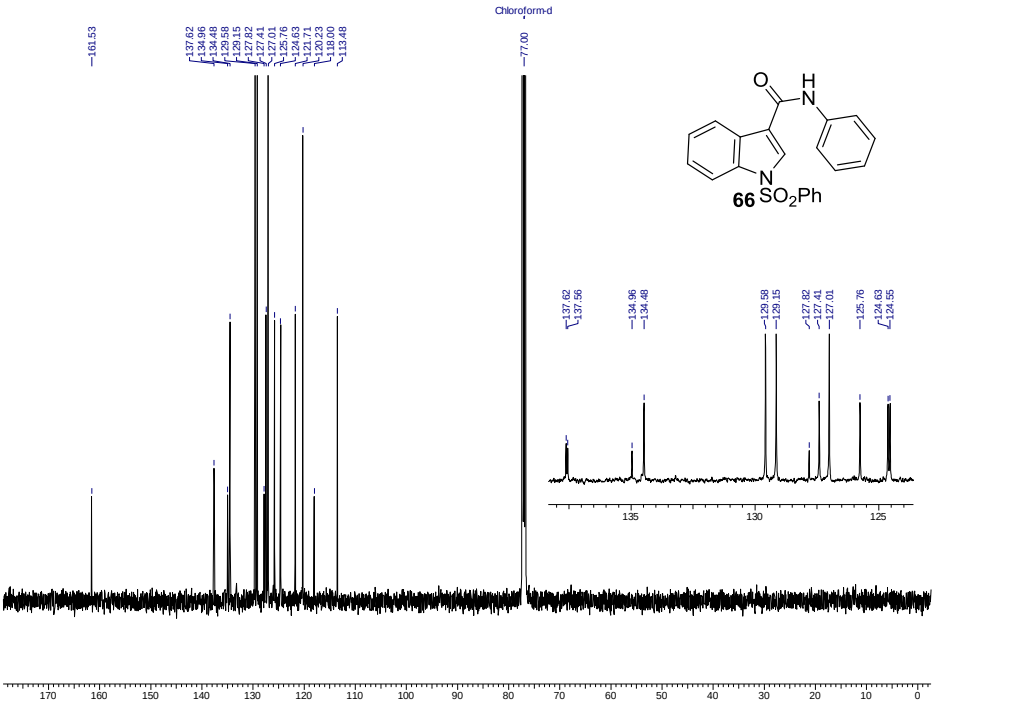

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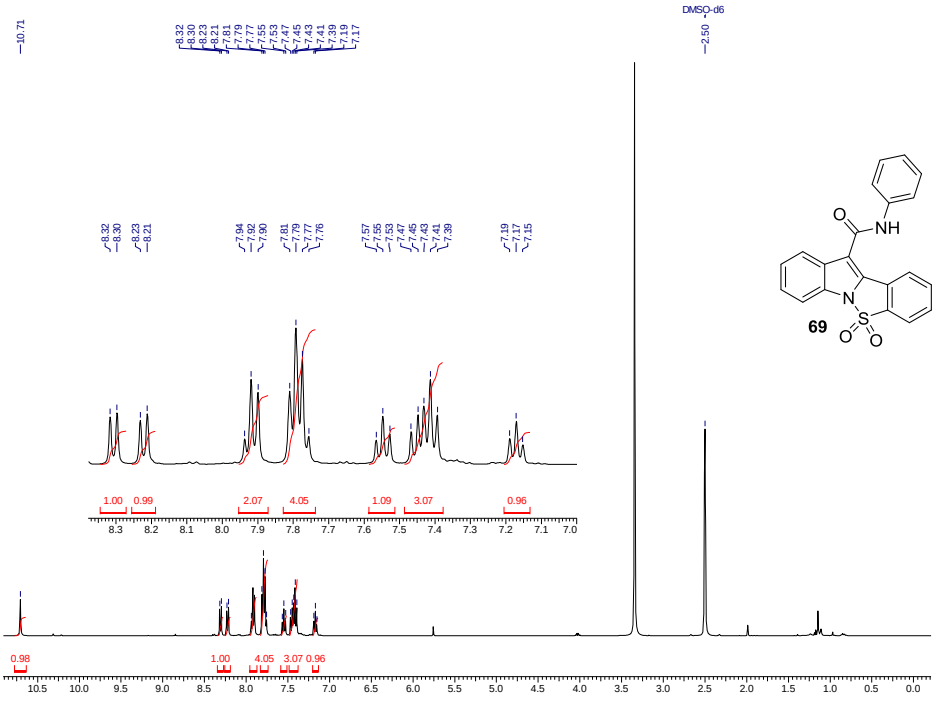

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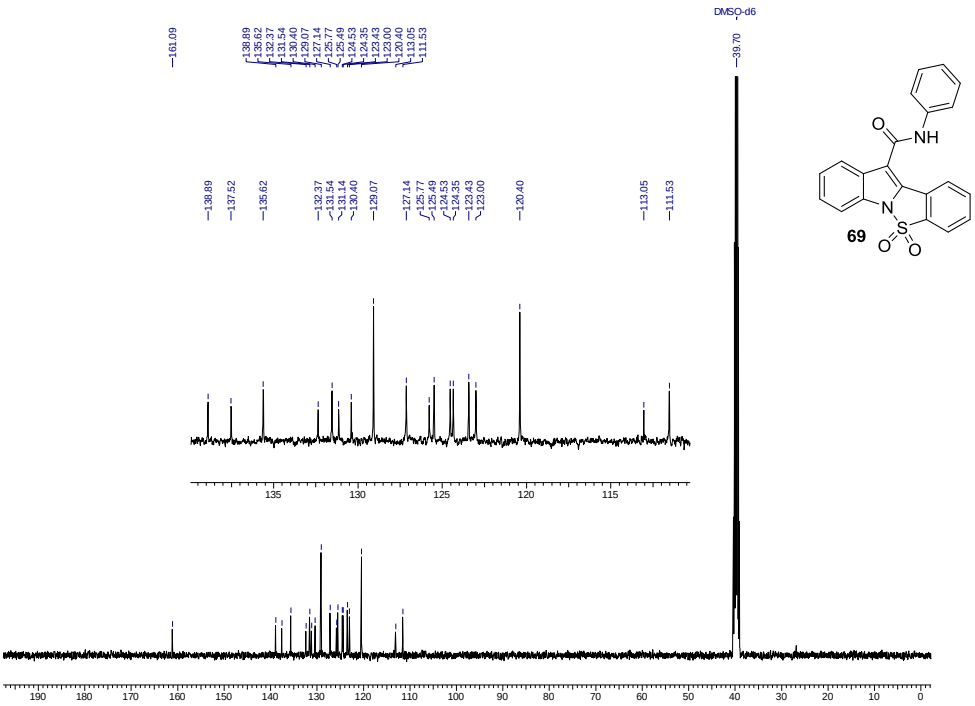

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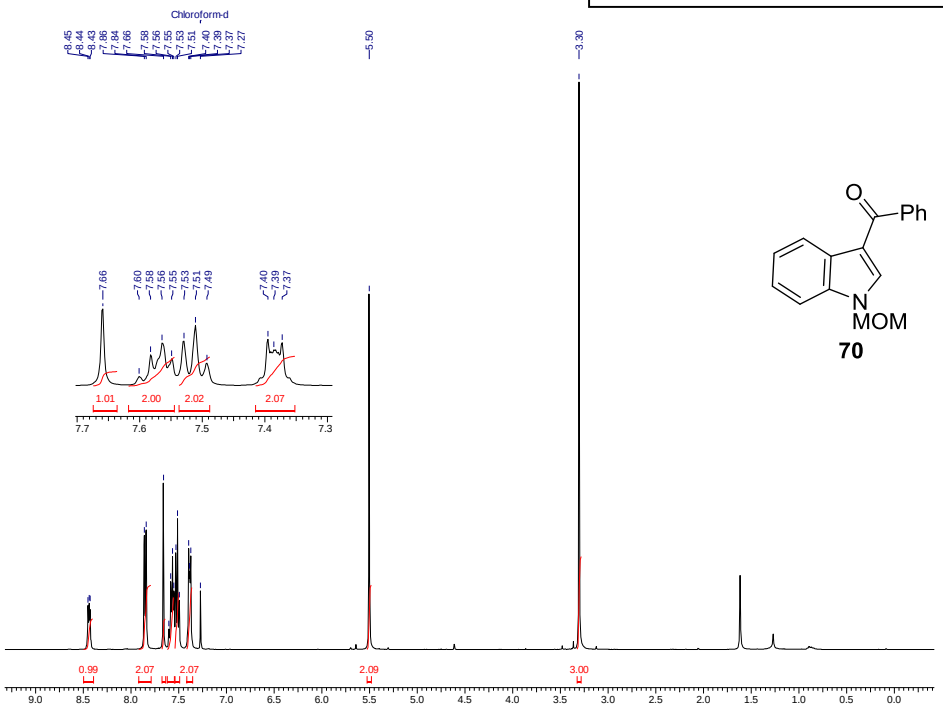

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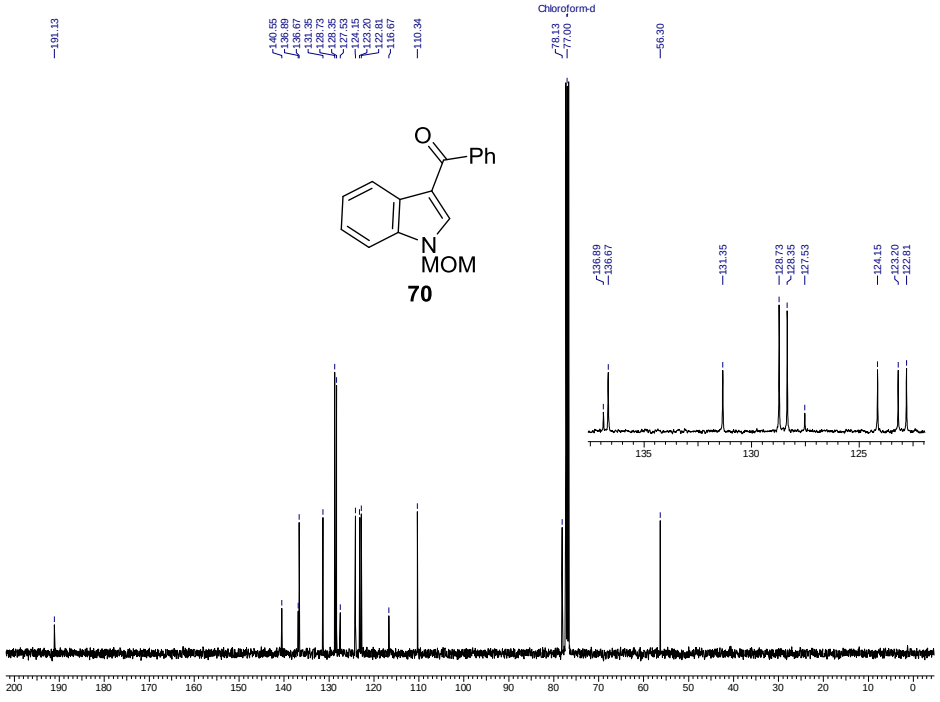

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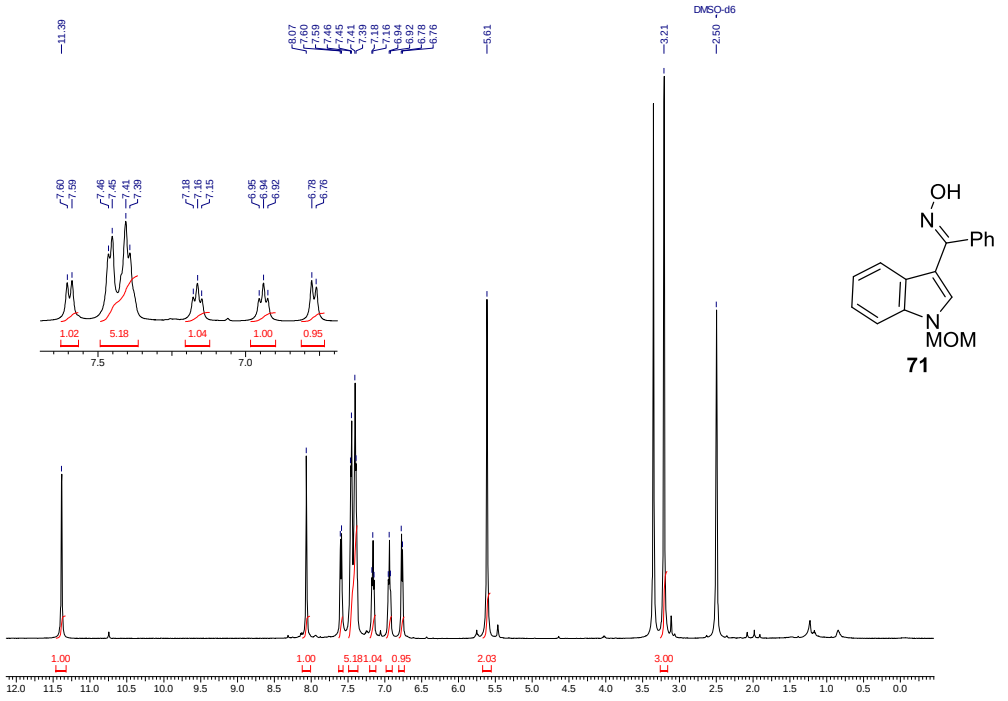

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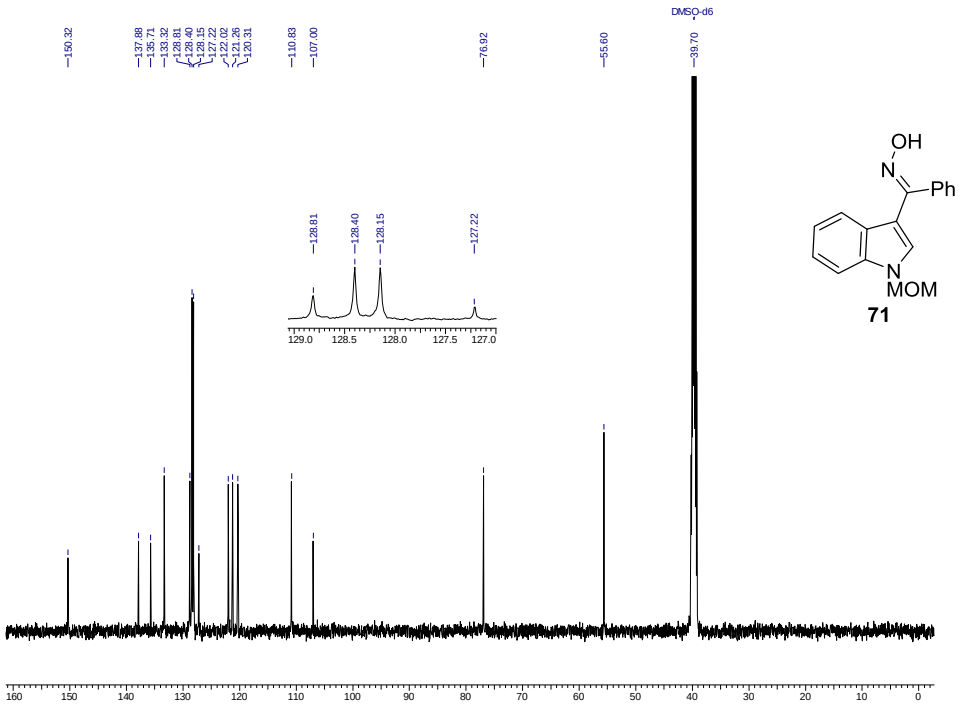

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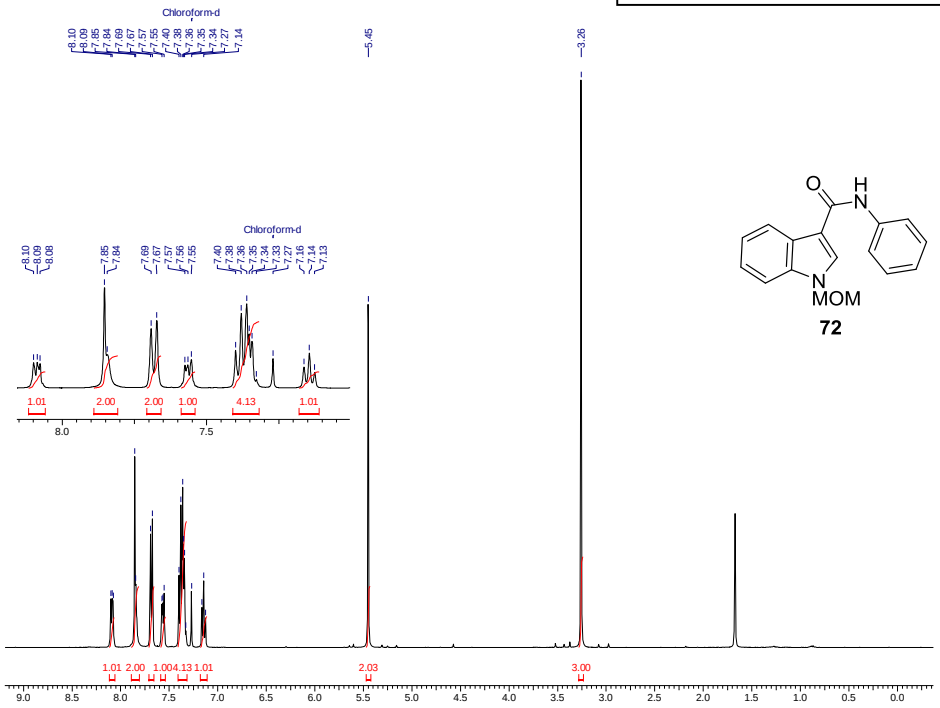

72

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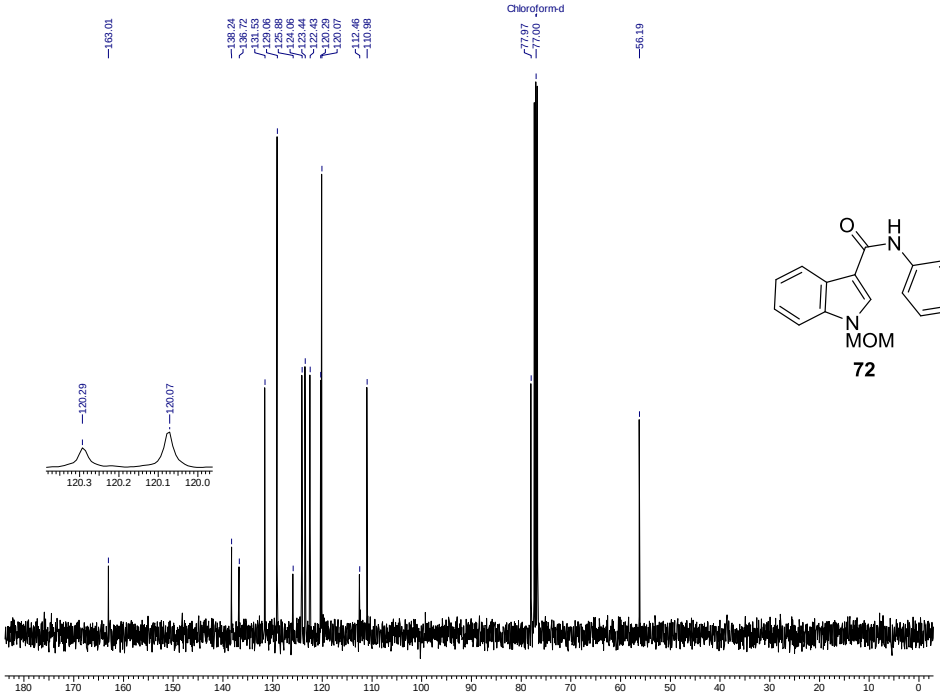

72

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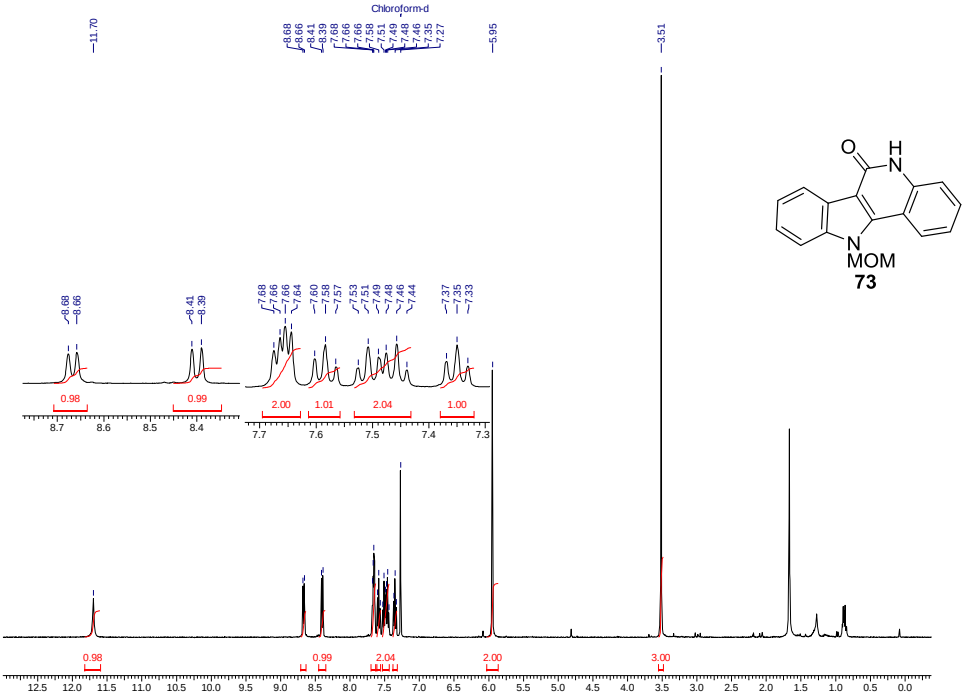

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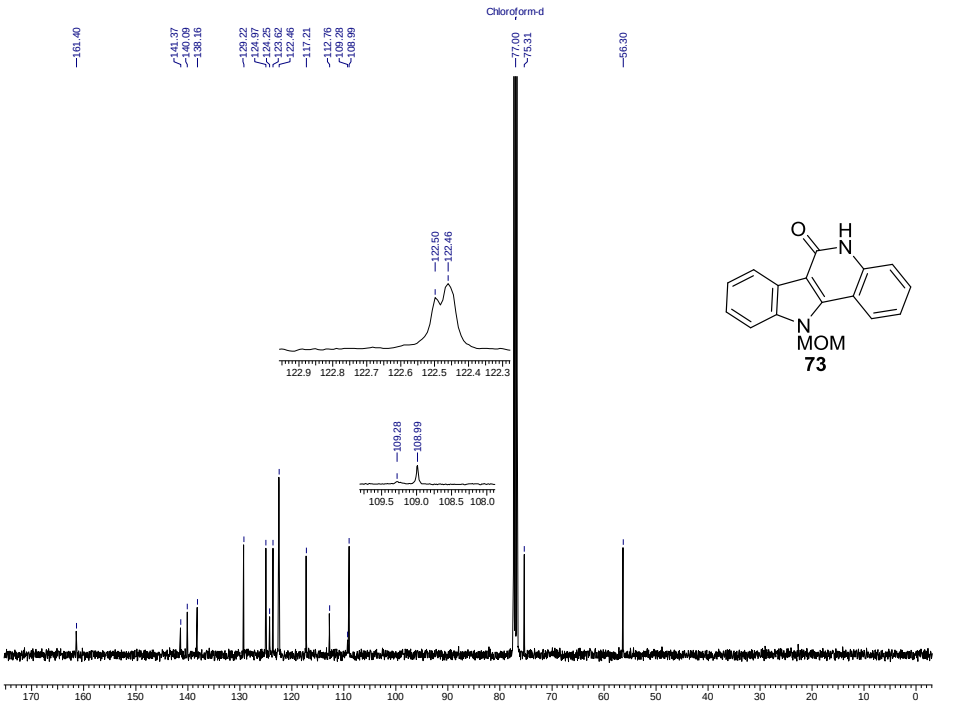

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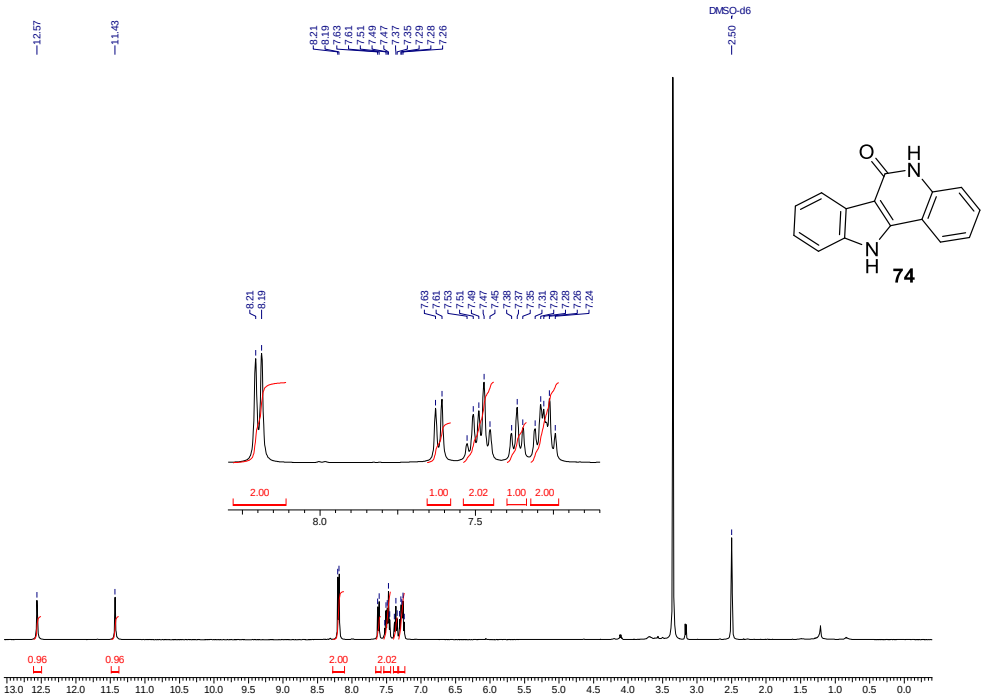

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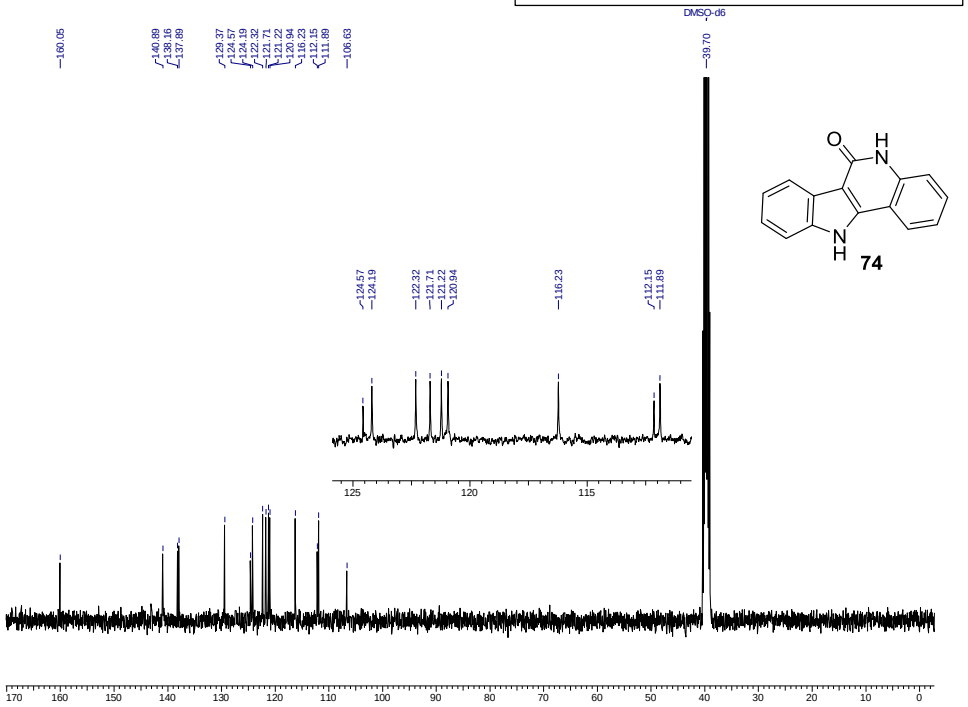

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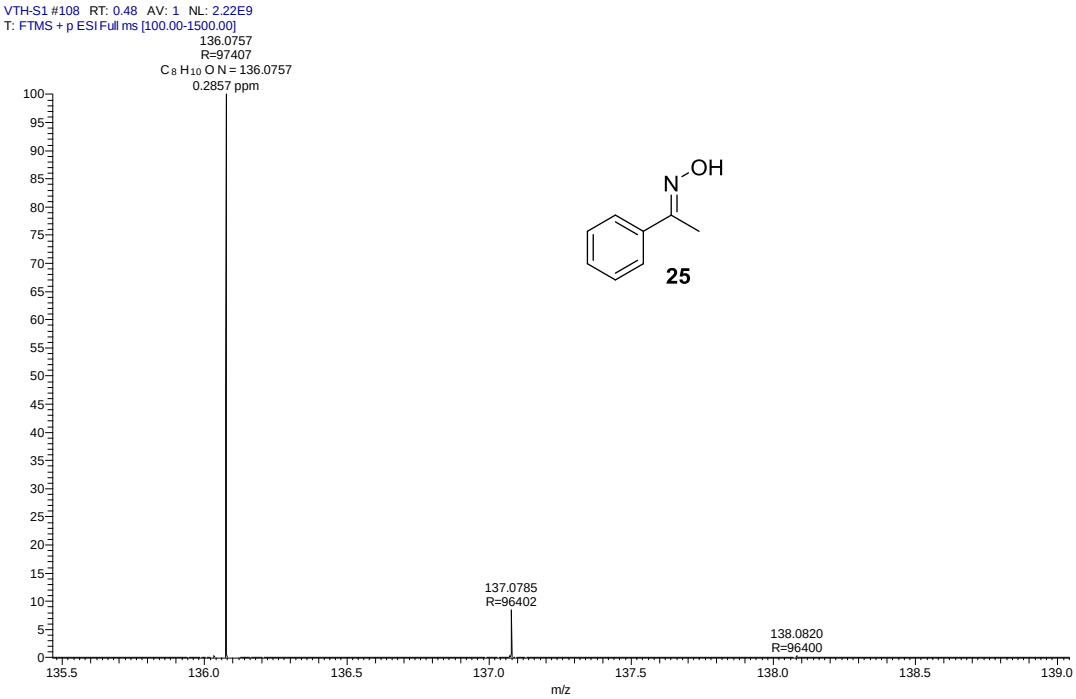

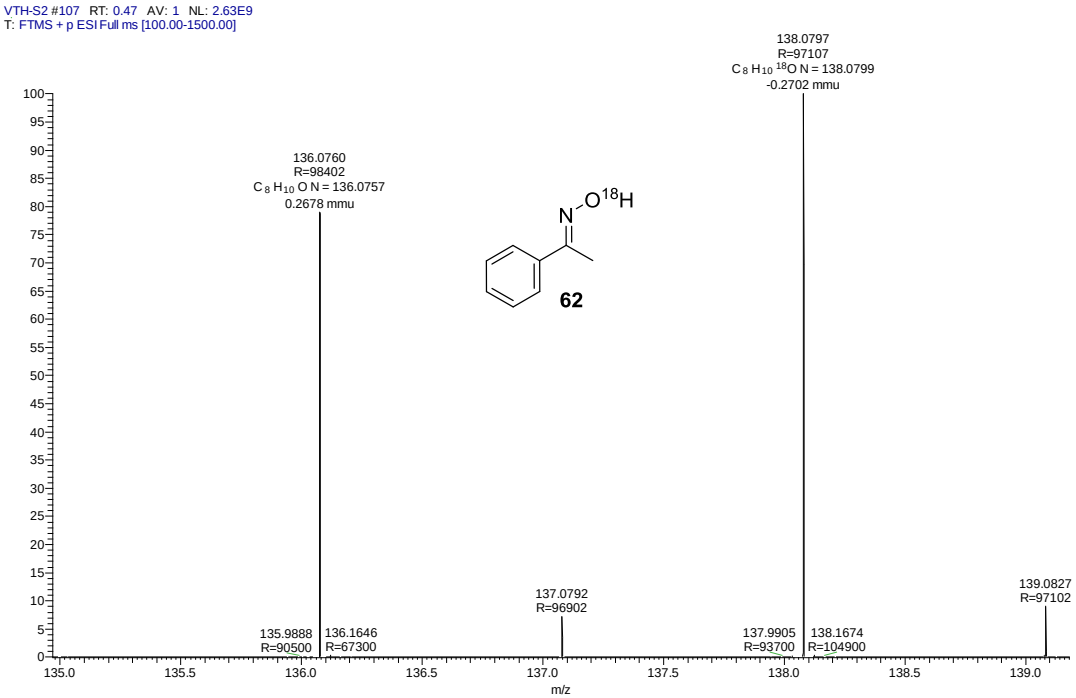

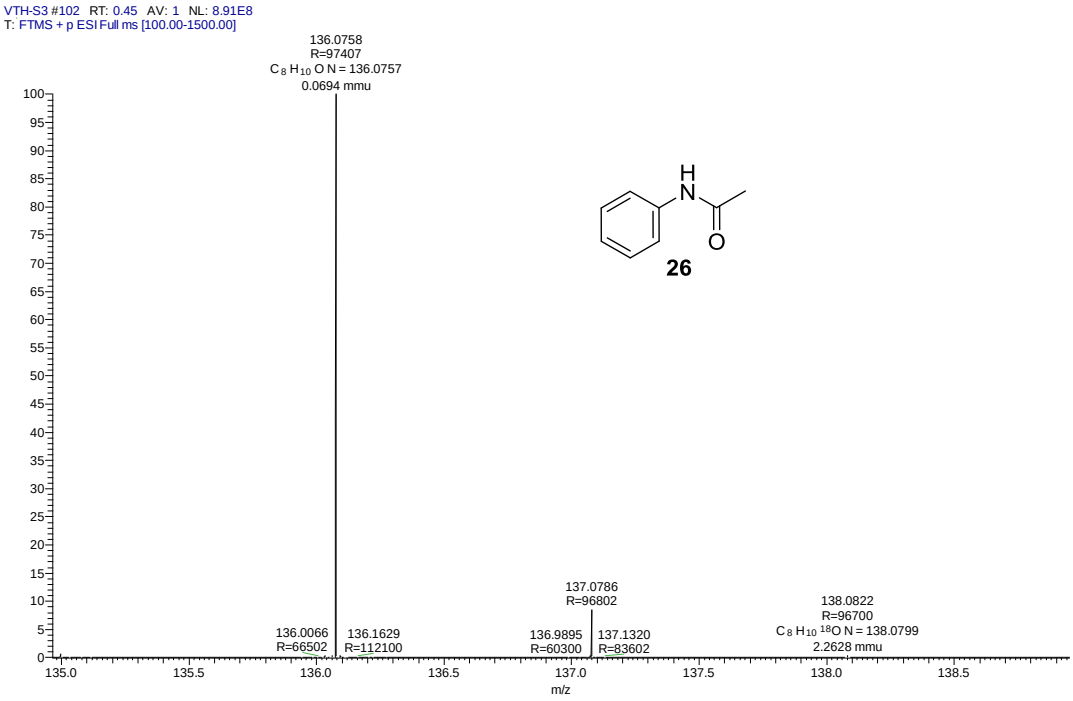
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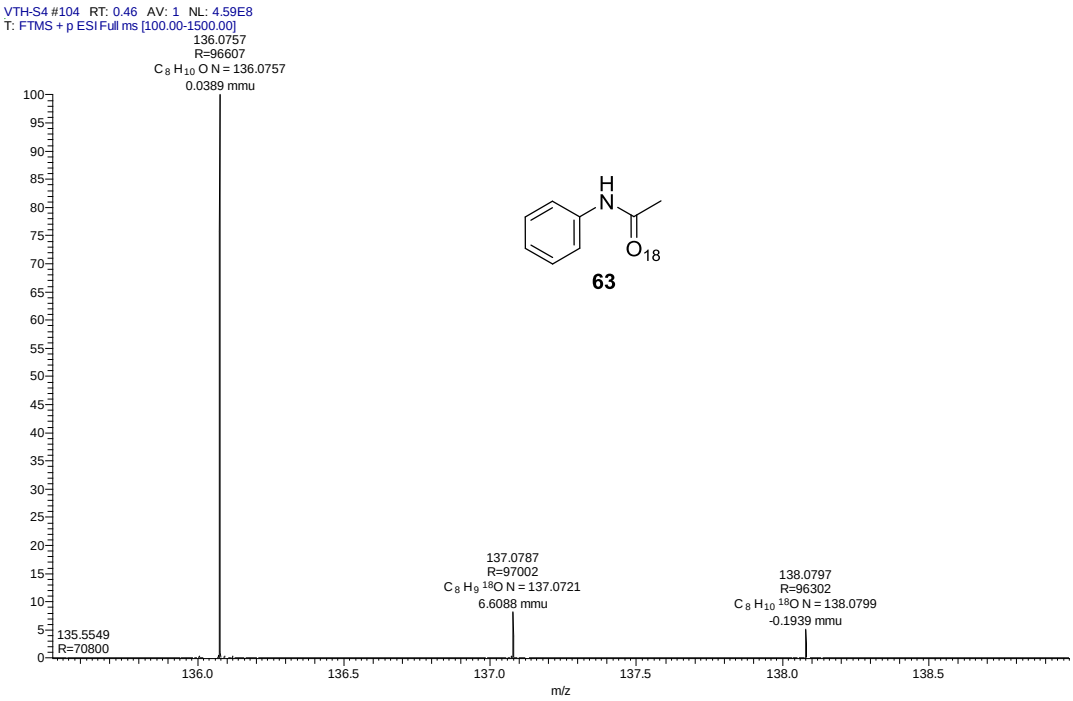
R=97407
C 8 H 10 O N = 136.0757
0.0694 mmu
137.0786
R=96802
138.0822
R=96700
C 8 H 10 18O N = 138.0799
2.2628 mmu
136.0066
R=66502
136.1629
R=112100
136.9895
R=60300
137.1320
R=83602
m/z

26


VTH-S4 #104 RT: 0.46 AV: 1 NL: 4.59E8
T: FTMS + p ESI Full ms [100.00-1500.00]
136.0757
R=96607
C 8 H 10 O N = 136.0757
0.0389 mmu
137.0787
R=97002
C 8 H 9 18O N = 137.0721
6.6088 mmu
138.0797
R=96302
C 8 H 10 18O N = 138.0799
-0.1939 mmu
135.5549
R=70800
m/z

63

Chapter 3

Development of an Intramolecular Oxidative Decarboxylative Radical Cyclization via Memory of Chirality and its Application to Circumdatin Alkaloids

Mahajan, P. S.; Mhaske, S. B. *Org. Lett.* **2018**, *20*, 2092.

Development of an Intramolecular Oxidative Decarboxylative Radical Cyclization via Memory of Chirality and its Application to Circumdatin Alkaloids

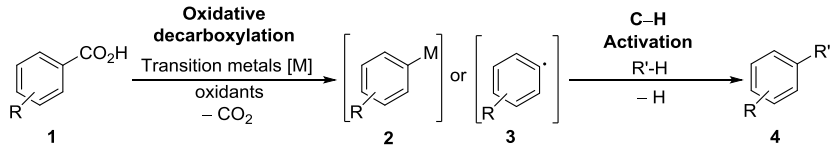
3.1 Abstract

The present chapter describes the development of a novel silver-mediated oxidative decarboxylative intramolecular C_{sp^3}–C_{sp^2} asymmetric radical coupling via memory of chirality. The developed protocol was successfully applied to the synthesis of bioactive circumdatin alkaloids and its congeners with ~90% retention of the configuration. The involvement of a chiral monoradical was confirmed by mechanistic studies and the probable mechanism is proposed.

3.2 Introduction

3.2.1 Decarboxylative coupling (DC)

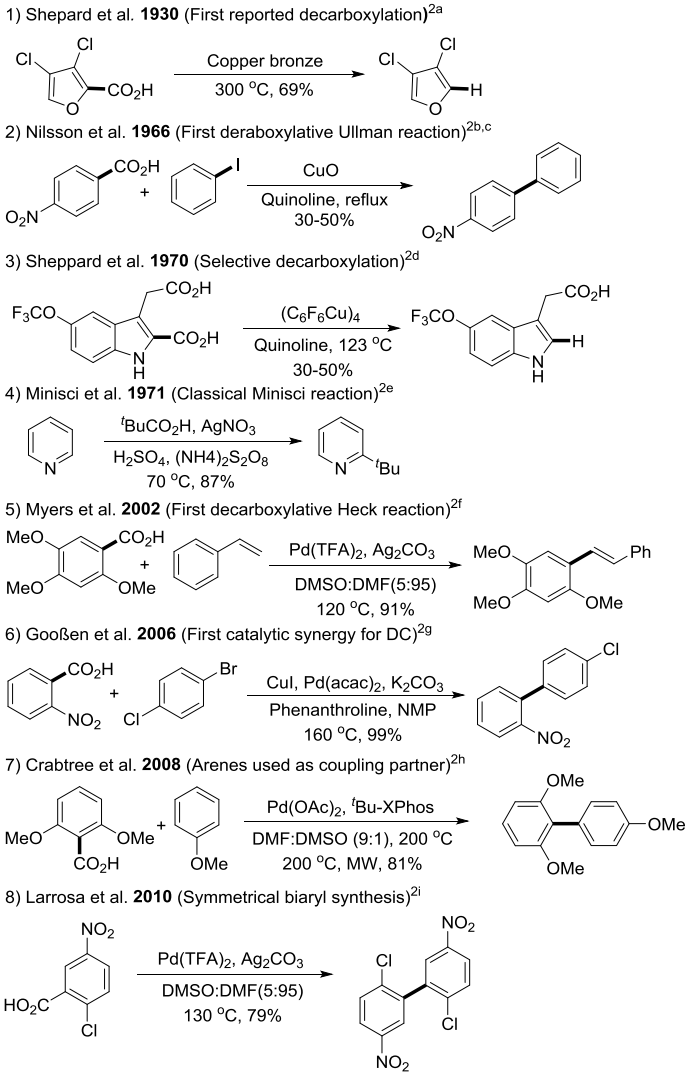
Decarboxylative coupling (DC) reactions are gaining importance because of their applications in the synthesis of novel and valuable products.[1] The starting materials for DC are stable, cheap, atom economical and easily available carboxylic acids, which are efficient alternatives to corresponding halides and organometallic reagents required for traditional cross coupling reactions.[1] Typically, the DC uses carboxylic acid as a handle and the process is a combination of decarboxylation and functionalization via activation of the C–H bond. These processes generally involve a metal catalyst, which cleaves the acid ($C–CO_2H$) group with libration of an equivalent amount of carbon dioxide ($-CO_2$) to generate a carbon radical or a C–Metal species. Mostly, transition-metals such as silver, gold, palladium, rhodium, copper etc. are used as catalysts for this transformation.[1] The carboxylic acid **1** undergoes decarboxylation to deliver a coupled product **4** via two possible intermediates **2** or **3** (Scheme 1). The redox-neutral



Scheme 1: Typical oxidative decarboxylative coupling process

decarboxylation, wherein oxidation state of the metal ion involved in the reaction does not change, forms nucleophilic intermediate **2**, whereas, in the case of oxidative decarboxylative coupling (ODC), decarboxylation is promoted by metal ion and oxidation state of the metal changes to form radical intermediate **3**.[1]

3.2.1.1 History of oxidative decarboxylative coupling (ODC)



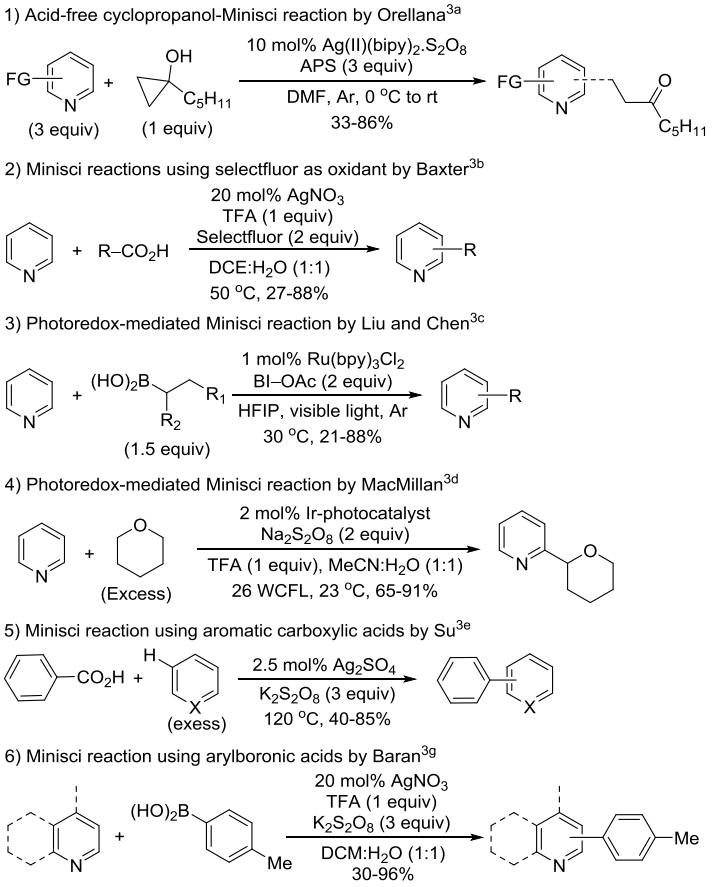
Scheme 2: History of the ODC[2]

The first decarboxylation of a carboxylic acid was observed by Shepard in 1930, when furan-2-carboxylic acid was heated in the presence of copper (Scheme 2, eq 1).[2a] The copper-mediated oxidative decarboxylation was then studied and advanced by Nilsson[2b,c] and Sheppard in 1970s[2d] (Scheme 2, eq 2,3). The classical Minisci reaction was invented[2e] in 1971, which brought the ODC to limelight (Scheme 2, eq 4). In 2002, the first Heck-type decarboxylative coupling was invented by Myers with catalytic palladium (Scheme 2, eq 5).[2f] This discovery truly inspired researchers to study and develop new ODC reactions. In 2006, direct coupling of the benzoic acid derivative with aryl halide was developed by Gooßen[2g] and showed that the catalytic amount of copper and palladium in synergy works very well than stoichiometry (Scheme 2, eq 6). Crabtree in 2008 developed the ODC reaction with carboxylic acids (C–CO_2H) and arenes (C–H) as unactivated coupling partner (Scheme 2, eq 7).[2h] Larrosa in 2010 developed an ODC wherein both the partners are acids and delivers symmetrically substituted product[2i] (Scheme 2, eq 8). After these inventions, many reports on ODC appeared in the last decade with new developments.[1]

3.2.1.2 Development and study of Minisci reaction

The classical Minisci reaction (Scheme 2, eq 4)[2e] is well studied and largely explored with several different variants.[3] Orellana used cyclopropanol as an alkylating agent in the acid-free environment with a silver-(II)-pyridine complex catalyst at a lower temperature (Scheme 3, eq 1).[3a] Baxter[3b] used selectfluor as an oxidant in combination with acid for the Minisci reaction (Scheme 3, eq 2). Liu and Chen utilized photoredox catalysis for the transformation with alkyl boronic acids in hexaflouroisopropanol (HFIP, Scheme 3, eq 3).[3c] MacMillan explored the photoredox mediated Minisci reaction utilizing Ir-photocatalyst, acid and an oxidant. The direct α-arylation of cyclic and acyclic ethers with heteroarenes is developed (Scheme 3, eq 4).[3d] Su

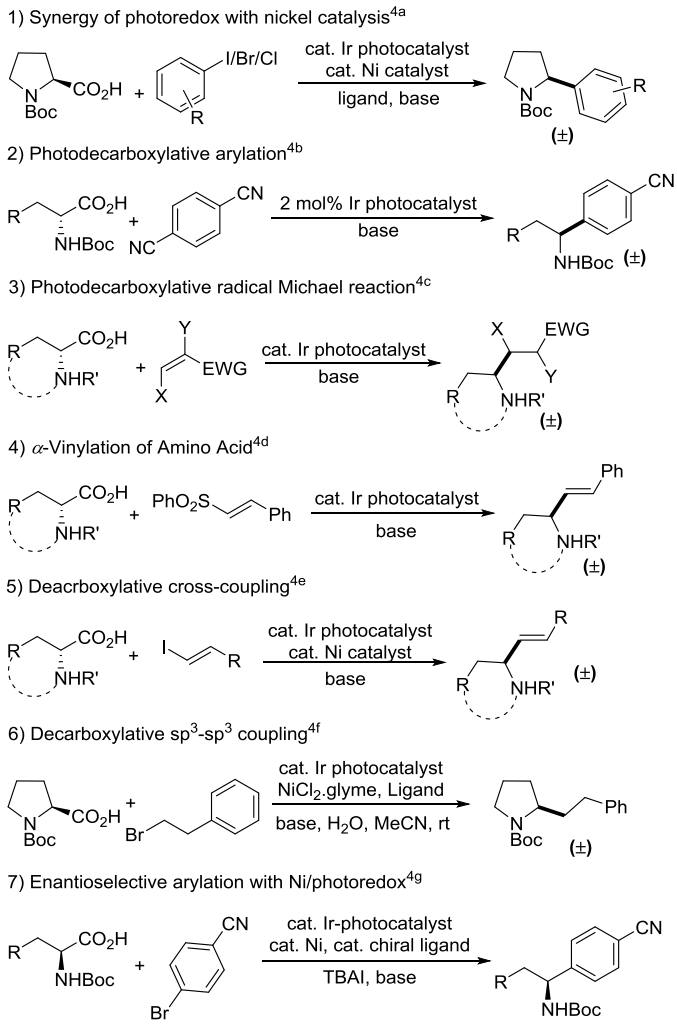
used aromatic carboxylic acids for the Minisci transformation with silver-(I) catalyst in combination with an oxidant (Scheme 3, eq 5).[3e] Several other variants are being utilized in the development and exploration of the Minisci reaction.[3f] Baran used aryl boronic acids for the same and demonstrated its utility on large scale (Scheme 3, eq 6).[3g]



Scheme 3: Exploration of Minisci reaction using different variants[3]

3.2.1.3 Photodecarboxylative coupling reactions of amino acids

Photodecarboxylative coupling reactions of amino acids and derivatives has been developed by MacMillan group using iridium photocatalysts (Scheme 4).[4] MacMillan and Doyle et al. reported a synergistic catalysis with the combination of Ir-photocatalyst and Ni-catalyst to deliver a coupled product from Boc-proline and aryl halide[4a] (Scheme 4, eq 1). MacMillan then utilized amino acid substrates to develop various methodologies such as arylation,[4b] radical



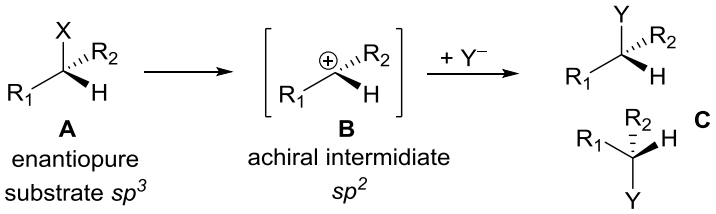
Scheme 4: Photodecarboxylative intermolecular coupling reactions of amino acids by MacMillan[5]

Michael reaction,[4c] α-vinylation,[4d] cross-coupling reaction with vinyl iodide[4e] etc. (Scheme 4, eq 2-5). Photodecarboxylative C_{sp^3}-C_{sp^3} coupling of α-amino acid and alkyl halide was achieved by MacMillan (Scheme 4, eq 6) using a synergy of Ir and Ni catalysts.[4f] However, these processes generate an achiral radical intermediate, which provides a racemic product (Scheme 4, eq 1-6). MacMillan demonstrated that the intervention of a chiral ligand could produce photodecarboxylative reaction products in good enantioselectivity[4g] (Scheme 4, eq 7). All these transformations are mediated by expensive photocatalyst. Also, to activate the coupling partner another catalyst is required along with ligands, base and additives.

We envisioned that the use of memory of chirality (MOC) in an intramolecular ODC would be an efficient way to construct various chiral scaffolds.

3.2.2 Memory of chirality (MOC)

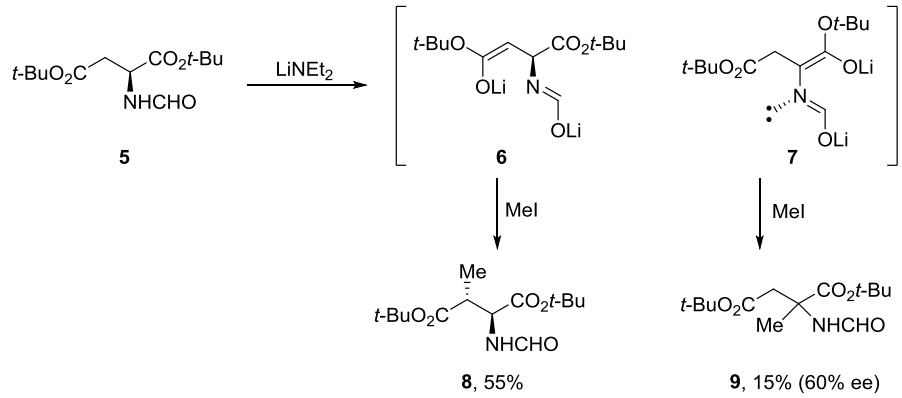
Usually an enantiopure substrate **A** having sp^3 carbon centre forms an intermediate [**B**] having a planer sp^2 carbon centre when a good leaving group X leaves via (C−X) bond fission. An external nucleophile Y^- attacks from both *alpha* and *beta* phases equally to deliver a racemic product **C**. It is hardly impossible to get an enantiopure product from such reaction (Scheme 5).



Scheme 5: Racemization of an enantiopure substrate due to trigonalization

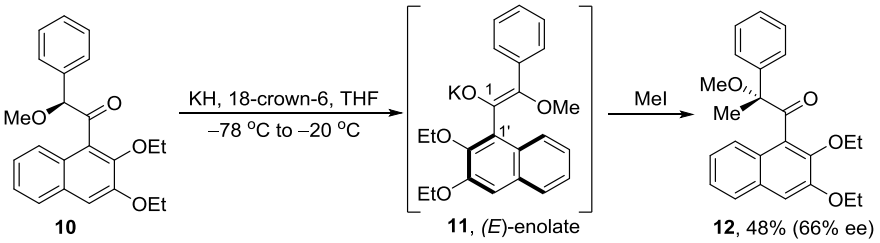
However, when the optically active substrate having sp^3 stereogenic centre delivers an optically active product without any interference of external permanent chiral reagent or catalyst via an sp^2 trigonal centre, the phenomenon is known as memory of chirality (MOC). MOC occurs when a chiral substrate results in a chiral product through a conformationally labile intermediate having no other permanent chiral features.

The memory of chirality (MOC) was first observed by Seebach et al.[5a] when they were performing methylation of α-amino acid derivative **5** using 2 equiv of lithium diethylamine. They observed an unwanted enantioselective side product **9** (Scheme 6). This is the first example, wherein the enantiopure starting material produced an enantioselective product via an enolate.[5a] Seebach proposed that the dilithium derivative intermediate [**7**] formed in the reaction with the axial chirality is responsible for the observed enantioselectivity.[5a]



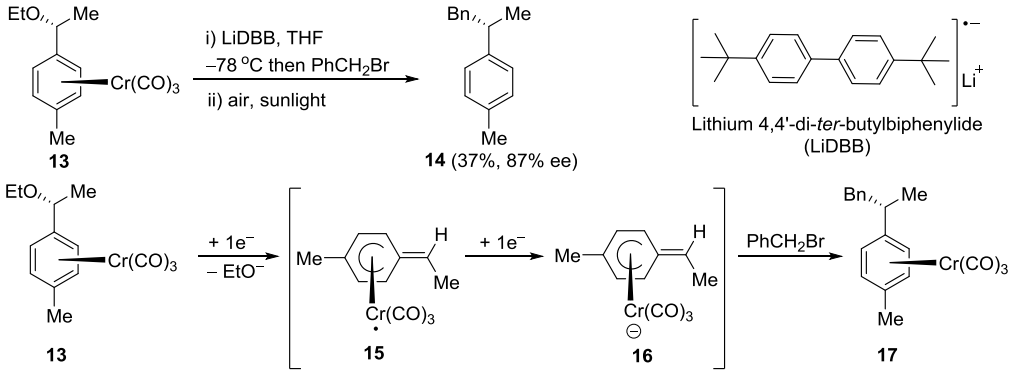
Scheme 6: MOC observed by Seebach et al.[5a]

Inspired by Seebach's results, Fuji in 1991 purposely designed a scheme with chiral naphthalenyl substrate **10** to study the chirality induction.[5b] The methylated product **12** was found chiral upon methylation. Fuji proposed that the *E*-enolate [**11**] forms during the course of reaction, wherein axial chirality about C_1–C_1' bond is preserved, which delivers the methylated enantioenriched product **12** (Scheme 7).[5b] He coined the term "memory of chirality (MOC)".



Scheme 7: Fuji's design for MOC and its outcome[5b]

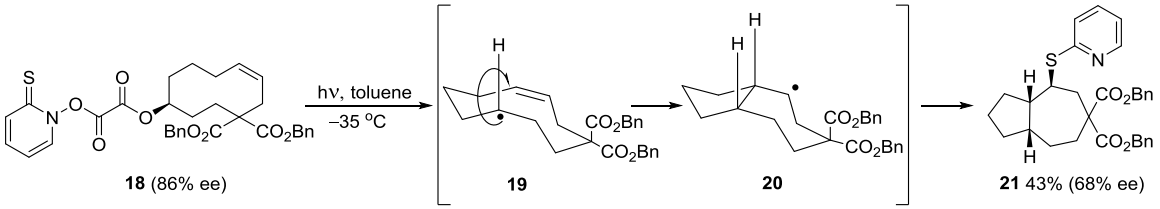
Koning utilized the arene-tricarbonylchromium complex **13** to get retention of the configuration in the benzylated product **14** (Scheme 8).[5c] The substrate **13** was treated with lithium 4,4'-di-*ter*-butyldiphenylide (LiDBB) and benzyl bromide to form **17** via intermediates [**15**] and [**16**]. Oxidative removal of $Cr(CO)_3$ from **17** furnished **14** in 37% yield (87% *ee*). The author suggested that the substrate **13** converts to the planar chiral radical intermediate [**15**] enantioselectively, which rapidly forms the configurationally stable anion [**16**] by reduction and reacts with benzyl bromide to obtain the compound **17** (Scheme 8). [5c]



13 **14** (37%, 87% ee) **15** **16** **17**

Scheme 8: Stereospecific benzylation by Koning via MOC benzylated product **14** via intermediates[5c]

Rychnovsky developed an intramolecular decarboxylative radical transannulative coupling via MOC. An enantioenriched *N*-oxypyridine-2-thione substrate **18** upon photodecarboxylation yielded bicyclo[5.3.0]decane **21** in 43% yield with 68% *ee* (Scheme 9). [5d]

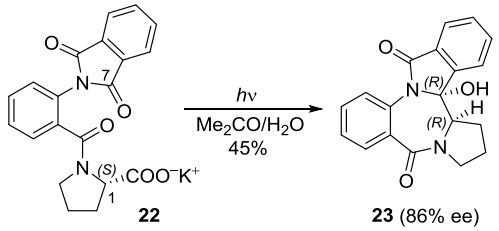


18 (86% ee) **19** **20** **21** 43% (68% ee)

Scheme 9: An intramolecular radical transannulative coupling via MOC developed by Rychnovsky[5d]

A chiral radical intermediate [**19**] formed after decarboxylation attacks on a double bond to form five-membered fused ring system and the newly generated radical was trapped by sulfur radical via radical-radical interaction to form **21**.[5d]

Griesbeck designed a proline potassium salt substrate **22**. An intramolecular phtodecarboxylative cyclization leads to the cyclized product **23** with complete inversion of the configuration (Scheme 10).[5e] The MOC observed in the formation of the product **23** is because



22 **23** (86% ee)

Scheme 10: Intramolecular photocyclization via MOC[5e]

of the non-diaryl atropisomeric 1,7-diradical intermediate and atropisomers present in the system, which restricts rotation about the central C–N single bond in the arylimide as well as the amide moiety (Scheme 10).[5e]

MOC is not fully explored as compared to the other areas of synthetic organic chemistry.[6] Examples of MOC via decarboxylative intermolecular radical coupling are rare,[6] and there are only two examples in the literature wherein MOC has been reported in the decarboxylative intramolecular radical coupling. The first example, reported by Rychnovsky utilized transannular radical cyclization via photodecarboxylative coupling (Scheme 9)[5d] and the second example reported by Griesbeck (Scheme 10).[5e]

3.3 Results and discussion

An intermolecular DC of amino acids generates an achiral radical and results in racemic products.[4] Interestingly until now oxidative decarboxylative intramolecular radical coupling via MOC is not reported in the literature. This prompted us to explore and study a new methodology for the synthesis of enantiopure compounds using the combination of ODC and MOC.

We envisioned that MOC would be possible to achieve with an intramolecular ODC of an amino acid substrate to form a new asymmetric C–C bond if the chiral radical could be trapped before racemization. For this purpose, a rigid circumdatin alkaloid scaffold was selected to study our hypothesis (Figure 1). Circumdatin class of quinazolinone alkaloids have a wide range

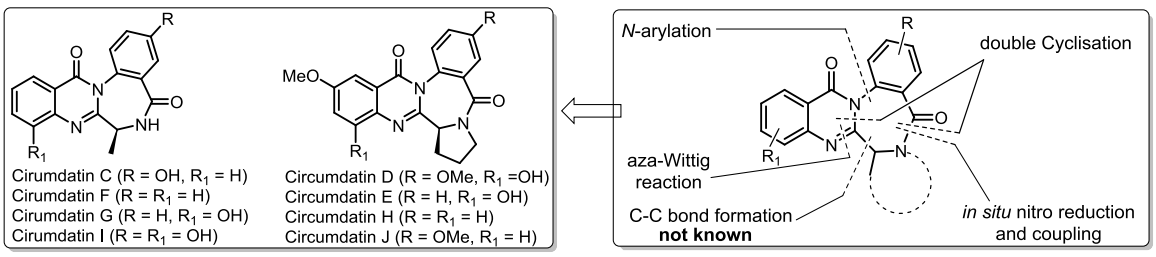
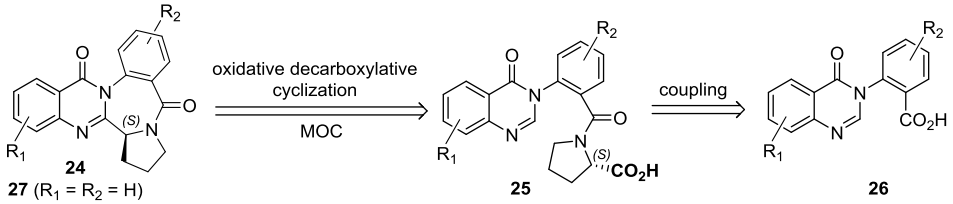


Figure 1: Bioactive circumdatin alkaloids and known strategies for their synthesis[7,8]

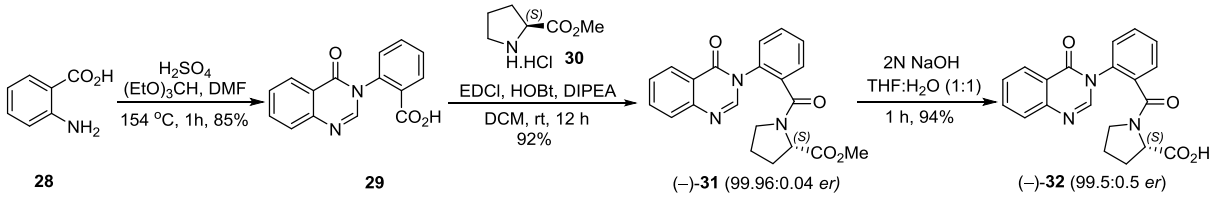
of biological properties such as hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, anti-tumor, etc.[7] They have been synthesized with C–N bond coupling/forming reactions, however, C–C bond coupling has never been utilized for their synthesis (Figure 1).[7,8]

Retrosynthetic strategy for the synthesis of the circumdatin alkaloids utilizing the oxidative decarboxylative radical cyclization via MOC was designed (Scheme 11). The circumdatin alkaloids of type **24** can be obtained from the proline substrate of type **25**, which can be obtained from the corresponding quinazolinone **26**.



Scheme 11: Retrosynthesis of circumdatin alkaloids utilizing ODC via MOC

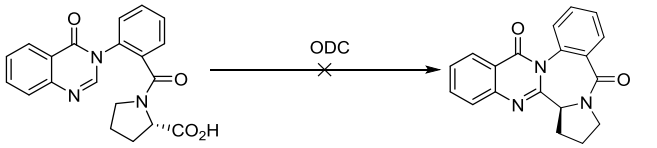
To implement the postulate, the molecule demethoxycircumdatin H (**27**, Scheme 11) was chosen for the study. The synthesis began with the anthranilic acid **28**. The quinazolinone **29** was synthesized in one step from **28** using catalytic sulfuric acid and triethyl orthoformate.[9] The enantiomerically pure proline methyl ester **30** was coupled with **29** using ECD.HCl (EDCI), HOBt, diisopropylethylamine (DIPEA) in DCM at room temperature for 12 h to get (–)-**31** in 92% yield (Scheme 12). The next job was to get proline substrate (–)-**32**, a precursor for the ODC via MOC postulate. Ester hydrolysis of (–)-**31** was achieved in the solvent combination of THF and water in 1:1 ratio and 2 equiv 2N $NaOH_{(aq.)}$ to get the proline substrate (–)-**32** in



Scheme 12: Synthesis of the proline substrate (–)-**32**

excellent yields and without loss of enantiopurity. When higher equivalents of NaOH were used, many side products were observed in the ester hydrolysis.

The proline substrate (–)-**32** was then subjected to ODC reaction (Scheme 13) using various conditions (Table 1). Various catalysts such as copper, palladium, iron were screened for the transformation along with different oxidants and bases/additives. Our APS-DMSO protocol



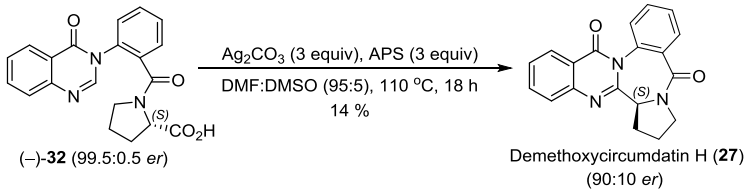
Scheme 13: Attempted ODC reactions for demethoxycircumdatin H

Entry	Catalyst	Ligand or oxidant	Additive or base	Solvent	Temp (^oC)	Reaction time (h)	27
1	$Pd(OAc)_2$	PPh_3	KO^tBu	NMP	100	16	CRM
2	$Cu(OAc)_2$	– –	Cs_2CO_3	1,4-dioxane	100	16	NR
3	$Cu(OAc)_2$	Ag_2CO_3	Cs_2CO_3	1,4-dioxane	100	16	NR
4	$Cu(OAc)_2$	Ag_2CO_3	Cs_2CO_3	1,4-dioxane	100	16	NR
5	Cs_2CO_3	APS	DMSO	1,4-dioxane	100	12	NR
6	$Cu(OAc)_2$	APS	DMSO	1,4-dioxane	100	12	NR
7	$Cu(OAc)_2$	Ag_2CO_3	KO^tBu	1,4-dioxane	100	16	NR
8	$Cu(OAc)_2$	K_3PO_4	– –	DMSO	130	12	CRM
9	CuI	– –	– –	toluene	110	16	NR
10	APS	– –	DMSO	1,4-dioxane	100	16	NR
11	$Pd(OAc)_2$	APS	DMSO	1,4-dioxane	100	16	NR
12	$Cu(OAc)_2$	– –	K_3PO_4	DMSO	40-90	6/h	NR
13	$Cu(OAc)_2$	– –	K_3PO_4	DMSO	130	18	NR
14	CuI	– –	– –	NMP	110	18	NR
15	$CuCl_2.2H_2O$	– –	pyridine	DMAc	130	18	NR
16	$CuCl.H_2O$	$K_2S_2O_8$	– –	DMAc	130	12	NR
17	I_2	TBHP	– –	DMAc	rt	12	NR
18	I_2	TBHP	– –	DMAc	110	12	NR
19	$Pd(TFA)_2$	– –	Ag_2CO_3	DMSO:DMF (5:95)	80	12	NR
20	Cu powder	$K_2S_2O_8$	$AgNO_3$	MeCN	90	12	NR
21	$Pd(OAc)_2$	CuI	LiO^tBu	DMF	130	12	NR
22	$CuSO_4.5H_2O$	O_2		DMF	90	14	NR
23	CuBr		TEMDA	toluene	120	6	NR
24	$Pd(OAc)_2$	$PhI(OAc)_2$	– –	DMAc	40	18	NR
25	$Pd(OAc)_2$	$PhI(OAc)_2$	– –	DMAc	110	12	NR
26	CuBr	$^tBuOO^tBu$	TEMDA	toluene	110	12	NR
27	$FeCl_2$	$^tBuOO^tBu$	– –	toluene	115	10	NR
28	$Cu(OAc)_2$	O_2	– –	DMSO	120	15	NR
29	– –	**APS**	**Ag_2CO_3**	**DMF:DMSO (95:5)**	**110**	**18**	**14%**

CRM: Complex reaction mixture; NR: no reaction (reaction did not work)

Table 1: Reactions tried for ODC via MOC protocol

and catalytic iodine also failed to deliver the product **27**. The known conditions for the similar transformations from the literature did not work (Table 1, entry 1-28). In one of the attempt, Ag_2CO_3 (3 equiv) and APS (3 equiv) was used in the solvent combination of DMF:DMSO (95:5) at 110 ^oC (Table 1, entry 29). To our delight, the expected product demethoxycircumdatin H (**27**) was obtained in 14% yield with 90:10 *er* (Scheme 14). The product obtained from the reaction was isolated and

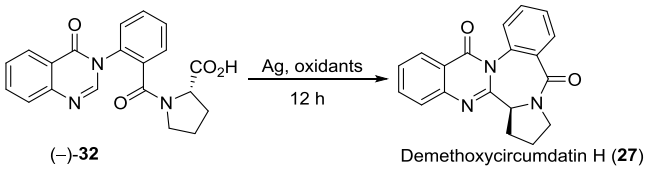


Scheme 14: Execution of the postulate

characterized. The spectral and analytical data, as well as the specific rotation, was in agreement with the literature,[8c] which confirms that the reaction proceeded via MOC with retention of the configuration. This result encouraged us to optimize the protocol further for better yields and enantiopurity of the product demethoxycircumdatin H (**27**). For this purpose, more than 200 various reaction conditions were screened with silver catalysts, solvents and solvents combinations, temperatures, oxidants, radical initiators, additives, acids and bases. The selected study is presented in table 2.

When Ag_2CO_3 (3 equiv) was replaced with $AgNO_3$ (1 equiv) slight enhancement in the yield was observed (Table 2, entry 2). Change in the ratio of the solvent combination DMSO:DMF (1:1) and use of catalytic amount of the $AgNO_3$ delivered the product in better yields and reasonable *er* (Table 2, entry 3). The solvents DMF and DMSO (Table 2, entry 4,5) were tried in the separate reactions and DMSO gave good *er* with 32% yield at 110 ^oC. Hence, it was confirmed that DMSO is the best solvent for the protocol. The effects of temperature and various mole ratios of $AgNO_3$ on the reaction were also studied (Table 2, entry 6-13). The

optimum condition found was 2 mol % $AgNO_3$ and APS (3 equiv) in DMSO at 50 ^oC for 12 h (Table 2, entry 9). Additives acids such as catalytic H_2SO_4 or TFA gave complex mixture,



(–)-**32** Demethoxycircumdatin H (**27**)

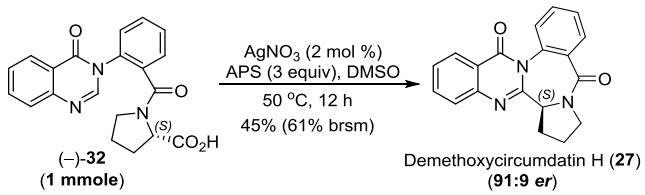
Entry[a]	**Radical initiator** (equiv)	**Solvent**	**Catalyst** (equiv)	**Temp.** (^oC)	**27** (% yield)	**27** (*er*)
1	APS (3)	DMF:DMSO (95:5)	Ag_2CO_3 (3)	110	14	90:10
2	APS (2)	DMF:DMSO (95:5)	$AgNO_3$ (1)	110	19	84:16
3	APS (3)	DMF:DMSO (1:1)	$AgNO_3$ (0.2)	110	20	87.3:12.7
4	APS (3)	DMF	$AgNO_3$ (0.2)	110	11	84.75:15.25
5	APS (3)	DMSO	$AgNO_3$ (0.2)	110	32	90.75:9.25
6	APS (3)	DMSO	$AgNO_3$ (0.2)	rt	21	91.5:8.5
7	APS (3)	DMSO	$AgNO_3$ (0.6)	rt	21	90.5:9.5
8	APS (3)	DMSO	$AgNO_3$ (0.2)	80	27	90:10
9	**APS (3)**	**DMSO**	**$AgNO_3$ (0.02)**	**50**	**41 (brsm 65%)**	**91:9**
10	APS (3)	DMSO	$AgNO_3$ (0.05)	50	40	90:10
11	APS (3)	DMSO	$AgNO_3$ (0.02), $KHSO_4$ (3)	50	21	89.8:10.2
12	APS (3)	DMSO	$AgNO_3$ (0.02), $CuSO_4.5H_2O$ (0.02)	50	11	88.8:11.2
13	APS (3)	DMSO	$AgNO_3$ (0.02), K_3PO_4 (3)	50	25	87.35:12.65
14	$K_2S_2O_8$ (3)	DMSO	$AgNO_3$ (0.02)	50	7	85:15
15	$Na_2S_2O_8$ (3)	DMSO	$AgNO_3$ (0.02)	50	7	88.4:11.6
16	APS (5)	DMSO	$AgNO_3$ (0.2)	50	29	88.3:11.7
17	APS (10)	DMSO	$AgNO_3$ (0.2)	50	27	85.9:14.1
18	APS (2)	DMSO	$AgNO_3$ (0.2)	50	23	84:16

[a]Reactions were carried out on 50 mg scale for 12 h.

Table 2: Reactions tried for ODC via MOC protocol

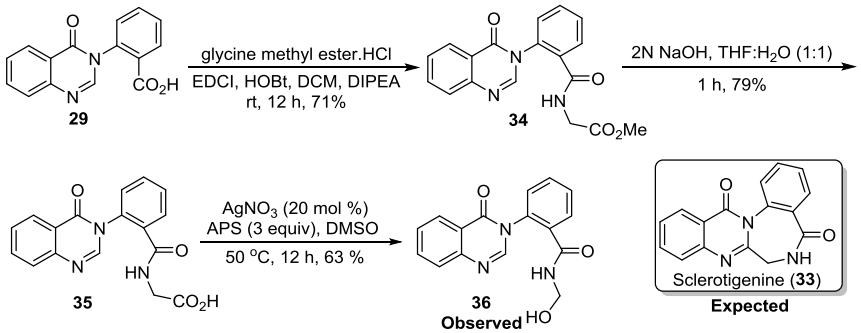
whereas addition of bases or catalytic copper did not enhance yields or enantioselectivity of the reaction (Table 2, entry 11-13). Various oxidants such as $K_2S_2O_8$, $Na_2S_2O_8$ (Table 2, entry 14-15), and H_2O_2, $^tBuOOBu^t$ gave low yields. The radical initiators such as AIBN or ceric ammonium nitrate (reaction did not work) did not provide any products. The screening provided APS as the best radical initiator (oxidant) for the developed protocol when used in 3 equiv (Table 2, entry 16-18).

The catalytic protocol on 1 mmol scale gave 45% yield (61% brsm, Scheme 15). The recovered starting material (–)-**32** from this reaction was utilized to check the reproducibility of the protocol. The reaction worked equally well providing the product **27** without loss of yield or enantioselectivity. Thus, the catalytic protocol was successfully developed and applied to the synthesis of the natural product analogue demethoxycircumdatin H (**27**).



Scheme 15: Protocol on 1 mmol scale

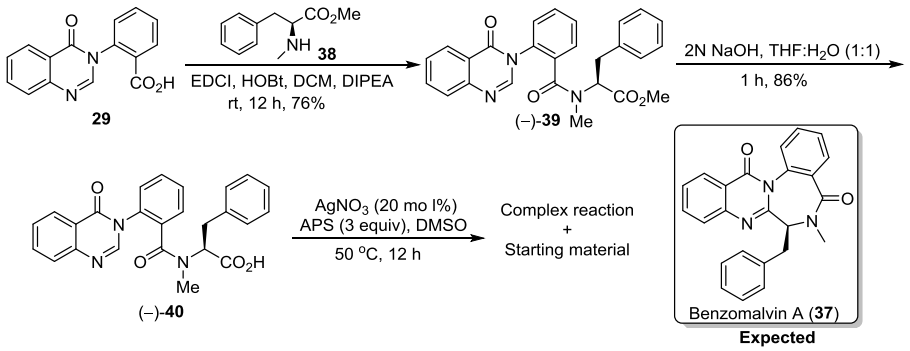
Once the protocol is set, our curiosity was to see whether it can be applied on acyclic N–H free amino acid containing substrates. Therefore, the natural product sclerotigenine (**33**, Scheme 16) was targeted. The developed sequence of reactions provided the glycine precursor **35** in good yields. The developed catalytic protocol did not work well. Therefore, the reaction was carried out with 20 mol % $AgNO_3$, but interestingly the formation of the natural product sclerotigenine (**33**) did not observe, instead we got the product alcohol **36** via decarboxylative



Scheme 16: Attempt for sclerotigenine (**33**) and its outcome

hydroxylation (Scheme 16). This protocol represents an alternative method to Barton's photodecarboxylative hydroxylation and its variations,[10] Thus, it was confirmed that the developed catalytic protocol is not suitable for amino acids with free nitrogen (-NH-). The natural product benzomalvin A (**37**, Scheme 17) was targeted wherein the nitrogen of the

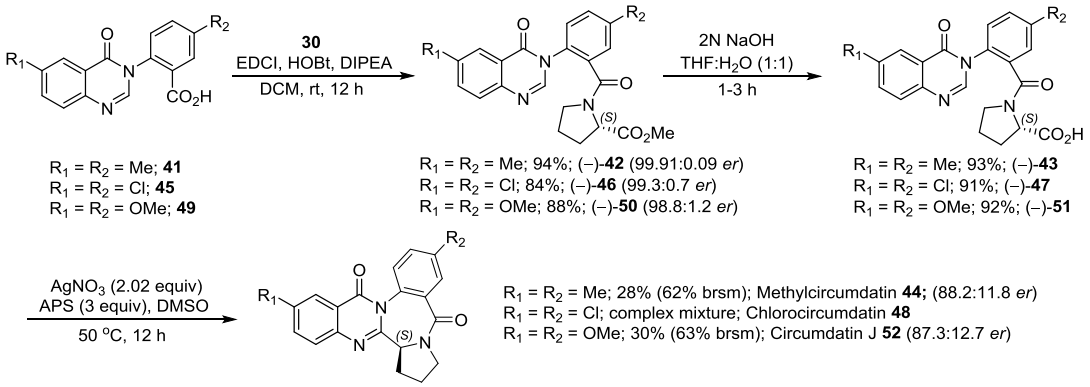
phenylalanine is fully substituted. The developed sequence for the synthesis of amino acid precursor worked well to deliver the phenylalanine substrate (–)-**40**. The developed protocol failed to deliver the natural product benzomalvin A (**37**) from the phenylalanine substrate (–)-**40**



Scheme 17: Attempt for benzomalvin A and its outcome

using 2-20 mol % of $AgNO_3$. A complex reaction mixture was observed along with some unconsumed starting material. These experiments prove that the developed protocol could be applied to only cyclic amino acid substrates, probably because of the stability of cyclic radical intermediate. Therefore, we focused on proline-based circumdatin alkaloids and their analogues.

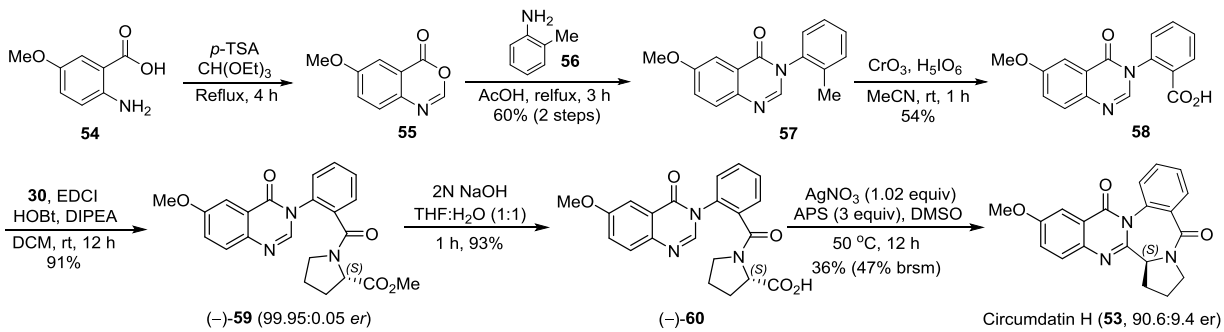
The proline-based circumdatin alkaloids and analogues were selected as the target for the synthesis utilizing the developed catalytic protocol. The proline substrates (–)-**43,** (–)-**47**, (–)-**51**, were synthesized via the developed route (Scheme 18) from the corresponding quinazolinone benzoic acids[9] **41**, **45**, **49**. The developed catalytic protocol failed to deliver the expected products; in fact, the reaction did not work at all with 2 mol % $AgNO_3$. Therefore, the protocol was again standardized for each circumdatin alkaloid (Table 3). The dimethyl substituted analog methylcircumdatin (**44**) was synthesized from the corresponding substrate (–)-**43** in 28% (62% brsm) yield with 88.2:11.8 *er* using 2.02 equiv of $AgNO_3$ (Table 3 & Scheme 18). The protocol was also applied for the synthesis of dichloro substituted analogue chlorocircimdatin (**48**, Scheme 18) but as expected the desired product could not be observed probably due to the presence of a reactive halo substituent in a silver-catalyzed radical reaction. The protocol worked



Scheme 18: Synthesis of methylcircumdatin (**44**) and circumdatin J (**52**) using ODC via MOC

well on the dimethoxy substituted precursor (–)-**51** and afforded the natural product circumdatin J (**52**) in 30% (63% brsm) yield with 87.3:12.7 *er* (Scheme 18).

After synthesizing the disubstituted circumdatin alkaloids methylcircumdatin (−)-**44** and circumdatin J (**52**), the monomethoxy substituted circumdatin H (**53**, Scheme 19) was taken in to account for its total synthesis using the developed ODC protocol. A new route was designed for the synthesis of quinazolinone **58**. The synthesis began from 2-amino-5-methoxybenzoic acid **54** to deliver benzoxazinone **55**,[11] which was treated with *o*-toluidine **56** without further purification to obtained the quinazolinone **57**.[12] Oxidation of the benzylic methyl of **57** was achieved with catalytic CrO_3 and stoichiometric amount of periodic acid in acetonitrile[13] to deliver quinazolinone benzoic acid **58**. Proline derivative (–)-**60** was synthesized from **58**. The protocol worked well on the monomethoxy substituted proline substrate (–)-**60** and furnished the natural



Scheme 19: Synthesis of circumdatin H (**53**) using ODC via MOC

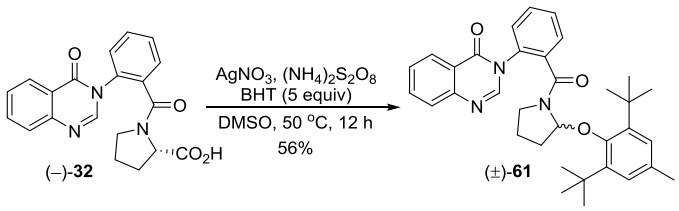
product circumdatin H (**53**) with 36% yield (47% brsm) with 90.6:9.4 *er* using 1.02 equiv $AgNO_3$ (Table 3 & Scheme 19). The quinazolinone substrates (–)-**32**, (–)-**43**, (–)-**51** and (–)-**60** required variable amounts of $AgNO_3$ (Table 2 & 3) probably because of the difference in the extent of silver interaction with the substrates depending on the presence of substituents.[14]

entry[a]	**$AgNO_3$** (equiv)	**44** (% yield)	**52** (% yield)	**53** (% yield)
1	0.02	0	0	0
2	0.2	0	0	0
3	0.5	0	0	11
4	1.02	trace	trace	**36 (47% brsm)**
5	1.52	9	12	32
6	2.02	**28 (62% brsm)**	**30 (63% brsm)**	32
7	3.02	26	28	35

[a]Reactions were performed on 50 mg scale. Starting materials not consumed completely in all the cases.

Table 3: Optimization of equivalents of silver nitrate for circumdatin alkaloids

The monoradical formed in the developed protocol was trapped with butylated hydroxytoluene (BHT, 5 equiv) to obtain the trapped substrate (±)-**61** with 56% crude yield (Scheme 20). The radical trapped product (±)-**61** was characterized with NMR and HRMS.



Scheme 20: Radical trapping experiment with BHT

Based on this observation and literature precedence, a plausible mechanism for the developed oxidative decarboxylative intramolecular asymmetric radical cyclization via MOC is depicted in Figure 2. The proline derivative (–)-**32** on oxidative decarboxylation generates a chiral radical[15] intermediate [**62**], which attacks the internal electrophilic position of the quinazolinone[16] and delivers demethoxycircumdatin H (**27**) via the intermediate [**63**]. We believe that the atropisomerism[17] present in this system plays an important role in MOC.[5e]

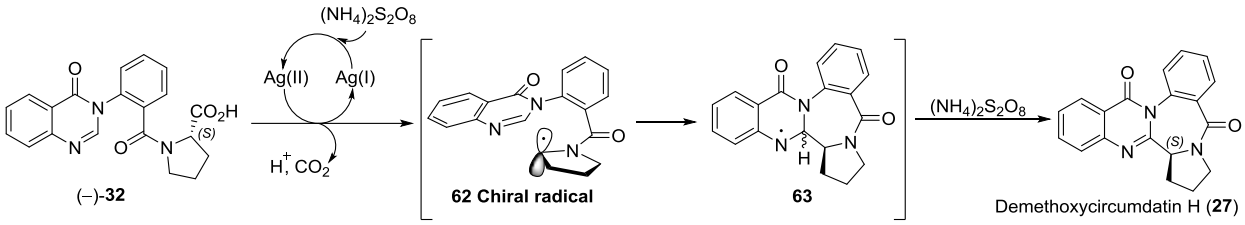


Figure 2: Plausible mechanism for the developed ODC via MOC

3.4 Conclusion

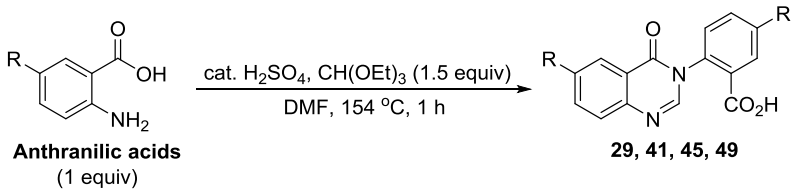
A novel oxidative decarboxylative intramolecular asymmetric radical cyclization via MOC using inexpensive $AgNO_3$, and APS to construct circumdatin natural products and their congeners has been demonstrated. To the best of our knowledge, this is the first report involving a chiral monoradical in an intramolecular ODC of C_{sp^3}–C_{sp^2} via MOC with retention of the configuration. The involvement of a monoradical was confirmed by mechanistic studies. The developed method is operationally simple and has a synthetic potential, which can be explored to construct various chiral heterocyclic scaffolds, biologically active molecules, and natural products. Further improvement of the protocol and finding its new applications is underway in our laboratory.

3.5 Experimental Section

Note 1: For intermediate esters and acids a complex mixture of atropisomers and amide rotamers resulted into multiple peaks and broad signals, hence not all signals are distinguishable /visible.
Note 2: Racemic compounds for HPLC were prepared using general procedures II-IV.

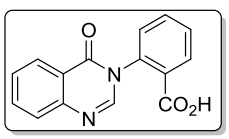
3.5.1. Experimental procedures and data

[A] General procedure-I: Synthesis of 29, 41, 45 and 49.



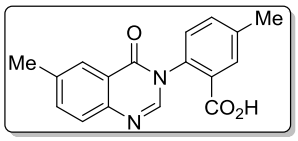
The known compounds **29**, **41** and **45** were prepared using the literature procedure[9] and the same procedure was used for the preparation of the new compound **49**.

To a stirred solution of anthranilic acid (1 equiv), triethylorthoformate (1.5 equiv) and DMF (5 mL for 1 g of anthranilic acid) was added concentrated H_2SO_4 (cat., 2 drops) at room temperature and the reaction mixture was heated gradually. The low-boiling substances formed during the reaction at 80-100 ^oC were removed by distillation. After the temperature rose to 154 ^oC the heating was continued for another 1 h at the same temperature. The reaction mixture was then cooled down to room temperature and poured into ice-water with continuous stirring. The precipitated solid was collected by filtration and recrystallized using DMF:H_2O (1:1) to obtain the corresponding pure acids **29, 41, 45 and 49** after drying.

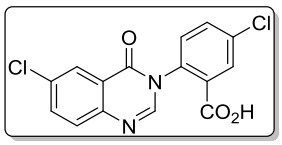


2-(4-Oxoquinazolin-3(4*H*)-yl)benzoic acid (29).[9] Light brown solid; mp: 282-283 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 13.13 (bs, 1H), 8.32 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.89 (t, J = 7.3 Hz, 1H), 7.80 (t, J = 8.3 Hz,

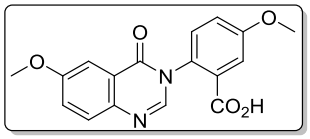
1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.66-7.57 (m, 2H); HRMS-ESI (*m/z*) calcd for $(C_{15}H_{10}O_3N_2 + H)^+$: 267.0764, found: 267.0766.



Methyl 5-methyl-2-(6-methyl-4-oxoquinazolin-3(4*H*)-yl)benzoate (41).[9] Light brown solid; mp: 265-268 ^oC; ^1H NMR (200 MHz, DMSO-d_6): δ 8.20 (s, 1H),7.95 (s, 1H), 7.88 (s, 1H),7.65-7.77 (m, 2H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 2.46 (s, 3H), 2.45 (s, 3H); HRMS-ESI (*m/z*) calcd for $(C_{17}H_{14}O_3N_2+H)^+$: 295.1077, found: 295.1080.



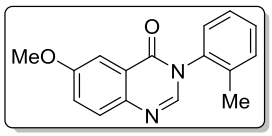
5-Chloro-2-(6-chloro-4-oxoquinazolin-3(4*H*)-yl)benzoic acid (45).[9] Brown solid; mp: 295-297 ^oC; ^1H NMR (200 MHz, DMSO-d_6): δ 8.37 (s, 1H), 8.10 (d, *J* = 1.8 Hz, 1H), 8.05 (d, *J* = 2.1 Hz, 1H), 7.99-7.85 (m, 2H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H); HRMS-ESI (*m/z*) calcd for $(C_{15}H_8Cl_2O_3N_2+H)^+$: 334.9985, found: 334.9986.



5-Methoxy-2-(6-methoxy-4-oxoquinazolin-3(4*H*)-yl)benzoic acid (49). 80%, Light brown solid; mp: 272-275 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 13.11 (bs, 1H), 8.15 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.55-7.45 (m, 4H), 7.33 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.7, 160.3, 159.3, 158.1, 145.4, 142.4, 131.0, 130.4, 129.9, 129.0, 123.9, 122.8, 118.4, 115.9, 106.4, 55.8, 55.7; HRMS-ESI (*m/z*) calcd for $(C_{17}H_{14}O_5N_2 + H)^+$: 327.0975, found: 327.0961.

[B] Synthesis of 2-(6-methoxy-4-oxoquinazolin-3(4*H*)-yl)benzoic acid (**58**)

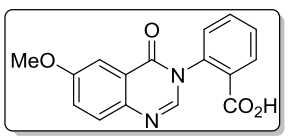
To a two-neck round-bottom flask equipped with magnetic stirring bar and reflux condenser were added 5-methoxy-2-aminobenzoic acid **54** (500 mg, 2.99 mmol, 1 equiv), triethyl orthoformate (7.7 g, 8.6 mL, 44.88 mmol, 15 equiv) and *p*-toluenesulfonic acid (22.1 mg, 0.15 mmol, 0.05 equiv). The resulting reaction mixture was refluxed for 4 h. After completion of the reaction triethyl orthoformate was evaporated under vacuum. The obtained pale yellow residue **55**[11] was dissolved in 5 mL glacial acetic acid. *o*-Toluidine **56** (310 mg, 0.31 mL, 2.89 mmol, 0.96 equiv) was added and the solution was refluxed for 3 hours.[12] Acetic acid was evaporated and the residue was dissolved in ethyl acetate (10 mL). The organic layer was washed with brine (3 X 3 mL), dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash column chromatography using ethyl acetate:petroleum ether (3:7) to afford quinazolinone **57** (484 mg, 60%) as a white solid.



6-Methoxy-3-(o-tolyl)quinazolin-4(3H)-one (57). mp: 135-137 ^{o}C; R_f: 0.6 (3:7, ethyl acetate:petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.78-7.70 (m, 2H), 7.49-7.37 (m, 4H), 7.29 (s, 1H), 3.96 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 159.0, 144.2, 142.6, 136.8, 135.8, 131.3, 129.7, 129.2, 127.8, 127.3, 124.7, 123.3, 106.6, 55.9, 17.7; HRMS-ESI (*m/z*) calcd for $(C_{16}H_{14}O_2N_2+Na)^+$: 289.0947, found: 289.0940.

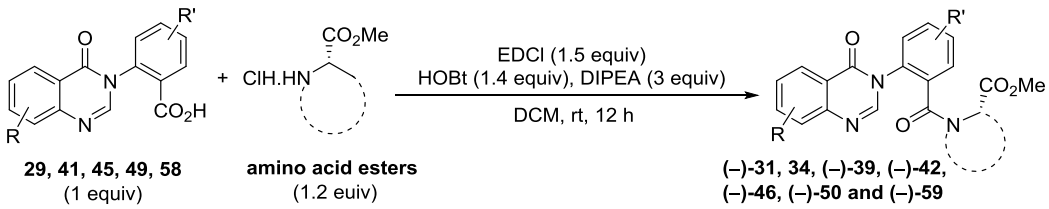
To a round-bottom flask equipped with a magnetic stirring bar was added H_5IO_6 (1.2 g, 5.26 mmol, 3.5 equiv) and acetonitrile (20 mL). To this solution was added CrO_3 (75.1 mg, 0.75 mmol, 0.5 equiv) with vigorous stirring.[13] After the solution becomes clear, quinazolinone **57** (400 mg, 1.5 mmol, 1 equiv) was added and the reaction mixture was stirred at room temperature for 1 h. Formation of white precipitate was observed during the reaction. Acetonitrile was

evaporated in vacuo and the residue was mixed with ethyl acetate (100 mL) and water (50 mL). The ethyl acetate layer was separated and washed with water (3 X 50 mL), aqueous $KHSO_4$ (2 X 50 mL) and brine (2 X 25 mL). The resulting organic layer was dried over sodium sulfate, concentrated under vacuum and the solid residue was recrystallized in ethyl acetate to furnish acid **58** (244 mg, 54%) as a white solid.



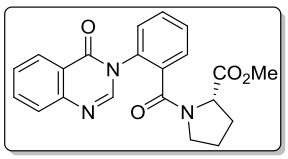
2-(6-Methoxy-4-oxoquinazolin-3(4*H*)-yl)benzoic acid (**58**)**.** mp: 192-194 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.17 (s, 1H), 8.06 (d, J = 6.7 Hz, 1H), 7.79 (t, J = 6.7 Hz, 1H), 7.72-7.63 (m, 2H), 7.56 (d, J = 7.3 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.48 (dd, J = 3.0 & 8.5 Hz, 1H), 7.36-7.45 (m, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.2, 160.5, 158.5, 145.2, 142.6, 137.5, 133.8, 131.4, 130.0 (2 C), 129.4, 129.3, 124.4, 123.0, 106.7, 56.0; HRMS-ESI (*m/z*) calcd for $(C_{16}H_{12}O_4N_2+Na)^+$: 319.0689, found: 319.0699.

[C] General procedure-II: Synthesis of compounds (–)-31, 34, (–)-39, (–)-42, (–)-46, (–)-50 and (–)-59

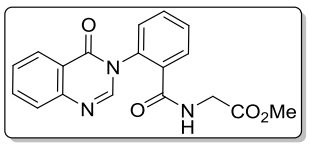


To the solution of acid **29**/**41**/**45**/**49**/**58** (1 equiv), EDCI (1.5 equiv), HOBt (1.4 equiv) and various amino acid esters (1.2 equiv) in dry DCM (20 mL for 1 g of acid) was added diisopropylethylamine (3 equiv) with continuous stirring at room temperature. The stirring was continued for another 12 h. After completion of the reaction, water (10 mL for 1 g of acid) was added and the DCM layer was separated, dried over sodium sulphate and evaporated in vacuo.

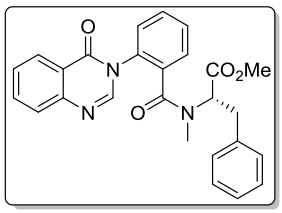
The crude product was purified by column chromatography to obtain corresponding products (–)-**31, 34,** (–)-**39,** (–)-**42,** (–)-**46,** (–)-**50** and (–)-**59** in good yields.



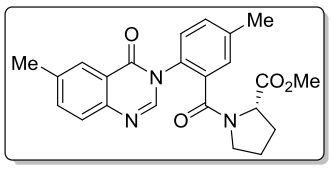
Methyl (2-(4-oxoquinazolin-3(4*H*)-yl)benzoyl)-*L*-prolinate [(–)-31]. 92%, 2.62 g from 2 g of **29**, white solid; mp: 60-62 ^{o}C; R_f: 0.5 (7:3, ethyl acetate:petroleum ether); $[\alpha]^{29}_{D}$ –100 (*c* 2, $CHCl_3$), 99.96:0.04 *er*; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.40-8.21 (m, 1H), 8.10 (s, 1H), 7.81-7.74 (m, 2H), 7.64-7.33 (m, 5H), 4.64-4.37 (m, 1H), 3.77-3.31 (m, 4H), 3.06 (s, 1H), 2.29-2.11 (m, 1H), 2.07-1.80 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 172.5, 171.6, 167.0, 166.9, 166.2, 161.5, 161.2, 161.0, 160.9, 160.7, 148.0, 146.8, 146.43, 146.38, 136.4, 136.0, 135.6, 134.8, 134.6, 134.5, 134.4, 130.8, 130.6, 130.4, 129.6, 129.5, 129.3, 129.2, 128.4, 128.2, 127.8, 127.6, 127.4, 127.3, 127.2, 126.9, 126.8, 126.6, 126.5, 122.5, 122.0, 121.9, 61.4, 58.6, 58.4, 52.25, 52.18, 51.6, 49.7, 49.0, 45.8, 30.9 29.5, 29.4, 29.3, 25.4, 24.6, 22.5; HRMS-ESI (*m/z*) calcd for $(C_{21}H_{19}O_4N_3+H)^+$: 378.1448, found: 378.1450.



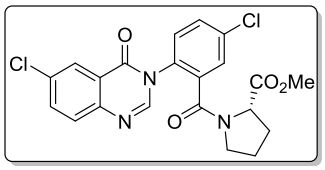
Methyl (2-(4-oxoquinazolin-3(4*H*)-yl)benzoyl)glycinate (**34**). 71%, 452 mg from 500 mg of **29**, white solid; mp: 174-175 ^{o}C; R_f: 0.3 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 7.3 Hz, 1H), 8.21 (s, 1H), 7.79-7.76 (m, 3H), 7.67-7.55 (m, 3H), 7.37 (d, *J* = 4.9 Hz, 1H), 6.96 (s, 1H), 4.03 (s, 2H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 166.5, 161.4, 146.8, 146.6, 135.0, 134.9, 134.4, 132.0, 130.3, 129.1, 128.9, 127.9, 127.1, 127.0, 121.9, 52.3, 41.6; HRMS-ESI (*m/z*) calcd for $(C_{18}H_{15}O_4N_3+H)^+$: 338.1135, found: 338.1138.



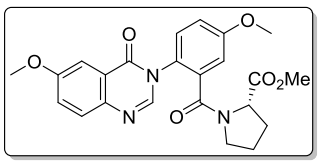
Methyl-*N*-methyl-*N*- (2-(4-oxoquinazolin-3(4*H*)-yl) benzoyl)-*L*-phenylalaninate [(–)-39]. 76%, 631 mg from 500 mg of **29**; thick oil; R_f: 0.5 (8:2, ethyl acetate:petroleum ether); $[\alpha]^{27}_D$ –58 (*c* 2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.40-8.04 (m, 1H), 8.13 (s, 1H), 7.88-7.56 (m, 2H), 7.60-6.95 (m, 10H), 6.74-6.39 (m, 1H), 5.68-5.36 (m, 0.5H), 4.83-4.33 (m, 0.5H), 3.86-2.78 (m, 5H), 2.74 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 168.8, 160.9, 147.8, 146.9, 140.2, 136.6, 136.5, 135.3, 134.7, 130.6, 130.5, 129.7, 129.6, 129.3, 129.2, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 127.7, 127.4, 127.3, 126.9, 126.8, 126.6, 126.4, 122.1, 117.0, 111.2, 63.4, 56.4, 52.4, 52.0, 35.3, 34.1, 33.8, 30.2. HRMS-ESI (*m/z*) calcd for $(C_{26}H_{23}O_4N_3+H)^+$: 442.1761, found: 442.1765.



Methyl (5-methyl-2-(6-methyl-4-oxoquinazolin-3 (4*H*)-yl) benzoyl)-*L*-prolinate [(–)-42]. 94%, 648 mg from 500 mg of **41**; white solid; mp: 63-64^{o}C; R_f: 0.5 (7:3, ethyl acetate:petroleum ether); $[\alpha]^{27}_D$ –92 (*c* 0.5, $CHCl_3$), 99.91:0.09 *er*; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.14-8.03 (m, 1H), 8.04 (s, 1H), 7.66 (d, *J* = 8.5, 1H), 7.59 (d, *J* = 8.0, 1H), 7.45-7.30 (m, 2H), 7.26-7.18 (m, 1H), 4.65-4.37 (m, 1H), 3.79-3.32 (m, 4H), 3.08 (s, 1H), 2.49, 2.46, 2.43, 2.39 (4s, 6H), 2.28-2.03 (m, 1H), 1.98-1.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 173.3, 172.6, 167.2, 167.1, 161.1, 161.0, 146.3, 146.0, 145.9, 139.6, 139.5, 137.6, 137.5, 136.1, 136.0, 135.9, 135.3, 132.3, 132.0, 131.8, 131.3, 131.1, 129.2, 129.1, 128.24, 128.18, 128.0, 127.6, 127.5, 127.4, 126.3, 126.1, 126.0, 121.8, 121.6, 61.3, 58.6, 58.4, 52.2, 51.9, 49.7, 49.0, 45.8, 30.9, 29.6, 29.6, 25.4, 24.7, 22.6, 21.3, 21.1, 20.6; HRMS-ESI (*m/z*) calcd for $(C_{23}H_{23}O_4N_3+H)^+$: 406.1761, found: 406.1768.

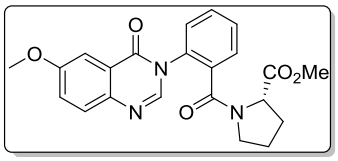


Methyl (5-chloro-2-(6-chloro-4-oxoquinazolin-3(4*H*)-yl)benzoyl)-*L*-prolinate [(–)-46]. 84%, 560 mg from 500 mg of **45**; white solid; mp: 77-80 ^{o}C; R_f: 0.5 (7:3, ethyl acetate:petroleum ether); $[\alpha]^{27}_{D}$ – 63.33 (*c* 0.6, $CHCl_3$), 99.3:0.7*er*; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.29, 8.19 (2s, 1H), 8.05 (s, 1H), 7.77-6.66 (m, 2H), 7.65-7.28 (m, 3H), 4.60-4.31 (m, 1H), 3.88, 3.78, 3.71, 3.59 (4s, 3H), 3.58-3.30 (m, 1H), 3.19 (s, 1H), 2.38-1.08 (m, 1H), 2.07-1.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 172.2, 165.5, 164.8, 160.3, 159.94, 159.87, 146.6, 146.5, 146.24, 146.16, 137.63, 136.9, 135.7, 135.5, 135.2, 135.1, 134.8, 133.5, 133.4, 133.1, 132.7, 131.0, 130.7, 130.6, 129.7, 129.6, 129.5, 129.3, 128.1, 128.0, 127.3, 127.1, 126.3, 126.1, 125.9, 123.0, 122.8, 61.4, 60.4, 58.6, 52.5, 52.3, 51.8, 49.8, 49.1, 46.1, 30.9, 29.5, 29.3, 25.5, 24.6, 22.5; HRMS-ESI (*m/z*) calcd for $(C_{21}H_{17}Cl_2O_4N_3+H)^+$: 446.0669, found: 446.0675.



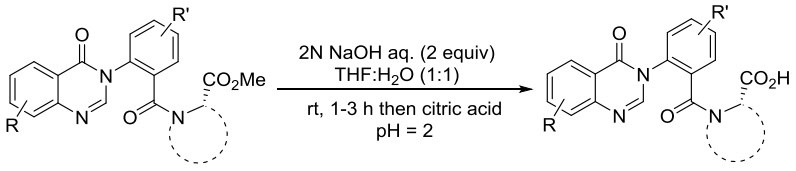
Methyl (5-methoxy-2- (6-methoxy-4-oxoquinazolin -3 (4*H*)-yl)benzoyl)-*L*-prolinate [(–)-50]. 88%, 590 mg from 500 mg of **49**; white solid, mp: 70-72 ^{o}C; R_f: 0.5 (7:3, ethyl acetate:petroleum ether); $[\alpha]^{27}_{D}$ –104 (*c* 0.5, $CHCl_3$), 98.8:1.2 *er*; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 7.99 (s, 1H), 7.71-7.59 (m, 2H), 7.39-7.23 (m, 2H), 7.13-6.94 (m, 2H), 4.50-4.35 (m, 1H), 3.92, 3.91, 3.89, 3.82 (4s, 6H), 3.77-3.69 (m, 3H), 3.66-3.33 (m, 1H), 3.11 (s, 1H), 2.28-1.78 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 172.5, 171.6, 166.8, 166.7, 166.0, 161.2, 161.1, 160.7, 160.0, 159.8, 159.8, 158.8, 158.7, 158.6, 145.2, 144.9, 144.8, 142.7, 137.4, 136.9, 136.7, 130.7, 129.7, 129.6, 129.44, 129.37, 129.2, 127.4, 127.0, 124.3, 116.1, 115.6, 113.3, 112.2, 112.0, 106.6, 106.5 106.4, 61.3, 58.6, 58.4, 56.3, 55.8, 55.7, 52.6, 52.4, 52.2, 51.7,

49.6, 49.0, 46.3, 45.8, 43.9, 38.1, 30.9, 29.6, 29.5, 29.45, 29.37, 25.3, 24.7, 23.9, 22.8, 22.5; HRMS-ESI (*m/z*) calcd for $(C_{23}H_{23}O_6N_3+H)^+$: 438.1660, found: 438.1669.



Methyl (2-(6-methoxy-4-oxoquinazolin-3(4H)-yl)benzoyl)-L-prolinate [(–)-59]. 91%, 627 mg from 500 mg of **58**, white solid; mp: 71-72 ^oC; R_f: 0.5 (7:3, ethyl acetate:petroleum ether); $[\alpha]^{27}_D$ – 126.67 (*c* 3, $CHCl_3$), 99.95:0.05 *er*; ^1H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.01 (s, 1H), 7.75-7.43 (m, 5H), 7.42-7.30 (m, 2H), 4.65-4.35 (m, 1H), 3.91 (s, 3H), 3.80-3.10 (m, 5H), 2.32-1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 172.5, 167.0, 166.9, 160.9, 160.8, 158.9, 158.8, 158.7, 144.7, 144.4, 144.3, 142.6, 136.4, 135.6, 135.0, 134.6, 130.8, 130.6, 129.6, 129.5, 129.4, 129.4, 129.2, 128.5, 128.3, 127.9, 127.0, 126.9, 124.3, 122.9, 122.7, 106.5, 106.4, 61.3, 58.6, 58.4, 55.8, 52.3, 52.2, 49.7, 49.0, 45.8, 41.3, 31.5, 31.0, 29.5, 29.4, 29.0, 25.4, 24.7, 22.6, 22.5; HRMS-ESI (*m/z*) calcd for $(C_{22}H_{21}O_5N_3+Na)^+$: 430.1373, found: 430.1364.

[D] General procedure-III: Synthesis of (–)-32, 35, (–)-40, (–)-43, (–)-47, (–)-51 and (–)-60

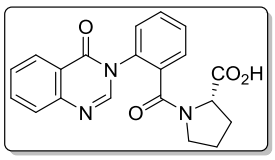


(–)-31, 34, (–)-39, (–)-42, (–)-46, (–)-50 and **(–)-59**

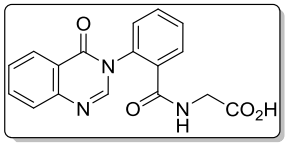
(–)-32, 35, (–)-40, (–)-43, (–)-47, (–)-51 and **(–)-60**

To the solution of ester **(–)-31/34/(–)-39/(–)-42/(–)-46/(–)-50/(–)-59** (1 equiv) in THF:water [(1:1), 10 mL for 1 g of ester] was added aqueous 2N NaOH (2 equiv) dropwise with continuous stirring and the reaction mixture was stirred at ambient temperature until complete consumption of the starting material. Ethyl acetate (10 mL for 1 g) was added and the organic layer was

separated. The aqueous layer was acidified with citric acid up to pH = 2 and extracted with ethyl acetate (15 mL X 3 for 1 g). The ethyl acetate layer was separated, dried over sodium sulfate and concentrated in vacuo to afford the corresponding amino acids (–)-**32, 35,** (–)-**40,** (–)-**43,** (–)-**47,** (–)-**51** and (–)-**60** in good to excellent yields.

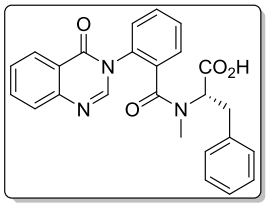


(2-(4-Oxoquinazolin-3(4*H*)-yl)benzoyl)-*L*-proline [(–)-32]. 94%, 907 mg from 1 g of (–)-**31**, white solid; mp: 188-190 ^{o}C; R_f: 0.3 (9:1, ethyl acetate: methanol); $[\alpha]^{29}_{D}$ –93 (*c* 2, $CHCl_3$) with 99.5:0.5 *er*; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.30-8.23 (m, 1H), 8.15 (s, 1H), 7.81-7.70 (m, 1H), 7.70-7.34 (m, 6H), 4.96 (bs, 1 H), 4.61-4.35 (m, 1H), 3.75-3.3.36 (m, 2H), 2.29-2.07 (m, 2H), 2.00-1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 176.0, 175.5, 174.1, 173.3, 168.1, 167.2, 167.0, 161.2, 160.9, 147.6, 147.0, 146.8, 146.6, 135.2, 135.0, 134.7, 134.5, 134.3, 131.1, 130.7, 129.8, 129.7, 129.3, 129.2, 128.4, 128.3, 127.8, 127.6, 127.1, 126.9, 126.8, 126.7, 122.0, 121.9, 121.8, 61.5, 59.2, 50.2, 49.4, 45.9, 44.9, 30.9 29.1, 28.9, 25.2, 24.8, 22.5, 20.7; HRMS-ESI (*m/z*) calcd for $(C_{20}H_{17}O_4N_3 + H)^+$: 364.1292, found: 364.1293.

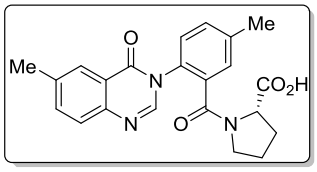


2-(4-Oxoquinazolin-3(4*H*)-yl)benzoyl)glycine (**35**)**.** 79%, 152 mg from 200 mg of **34**, white solid; mp: 231-233 ^{o}C; R_f: 0.3 (1:9 methanol:DCM); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.53 (bs, 1H), 8.84 (t, *J* = 6 Hz, 1H), 8.19 (s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.74-7.64 (m, 3H), 7.60-7.55 (m, 2H), 3.80 (dd, *J* = 6 & 17 Hz, 1H), 3.68 (dd, *J* = 6 & 17 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8, 166.1, 160.1, 147.9, 147.4, 135.8,

134.5, 133.5, 131.5, 129.7, 129.3, 128.6, 127.3, 127.1, 126.4, 122.0, 40.9; HRMS-ESI (*m/z*) calcd for $(C_{17}H_{13}O_4N_3+H)^+$: 324.0979, found: 324.0980.

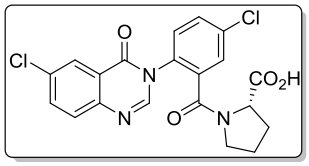


***N*-Methyl-*N*-(2-(4-oxoquinazolin-3(4*H*)-yl)benzoyl)-*L*-phenylalanine [(–)-40].** 86%, 419 mg from 500 mg of (–)-**39**, white solid; mp: 160-164 ^oC; R_f: 0.5 (2:8, methanol:ethyl acetate); $[\alpha]^{27}_D$ –37.33 (*c* 3, MeOH); ^1H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.16-7.99 (m, 1H), 7.90 (s, 0.6H), 7.78-7.70 (m, 0.4H), 7.67-7.43 (m, 2H), 7.41-6.51 (m, 10H), 5.50-4.12 (m, 1H), 3.32-2.91 (m, 1H), 2.89-2.77 (m, 1H), 2.73, 2.69, 2.63, 2.59 (4s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 9:1): δ 174.9, 171.6, 147.4, 146.2, 136.8, 133.9, 129.9, 129.2, 129.0, 128.5, 128.1, 128.0, 127.7, 127.1, 126.8, 126.6, 126.4, 124.4, 121.8, 118.3, 109.6, 72.4, 42.4; HRMS-ESI (*m/z*) calcd for $(C_{25}H_{21}O_4N_3+H)^+$: 428.1605, found: 428.1608.

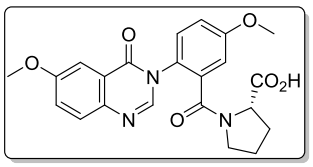


(5-Methyl-2- (6-methyl-4-oxoquinazolin-3 (4*H*)-yl) benzoyl)-*L*-proline [(–)-43]. 93%, 449 mg from 500 mg of (–)-**42**, white solid; mp: 126-128 ^oC; R_f: 0.3 (9:1, ethyl acetate: methanol); $[\alpha]^{27}_D$ –90 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.39 (bs, 1H), 8.12-8.00 (m, 2H), 7.68-7.55 (m, 1H), 7.48-7.37 (m, 2H), 7.35-7.16 (m, 2H), 4.62-4.35 (m, 1H), 3.80-3.29 (m, 2H), 2.54-2.31 (m, 6H), 2.28-2.08 (m, 2H), 2.03-1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 175.7, 174.0, 173.4, 168.4, 167.3, 167.2, 161.2, 161.1, 146.3, 146.1, 146.0, 145.5, 144.7, 140.03, 139.96, 139.6, 137.8, 136.1, 134.9, 134.7, 132.2, 131.9, 131.5, 131.3, 131.2, 128.9, 128.7, 128.2, 128.0, 127.7, 127.5, 127.2, 126.6, 126.3, 126.2, 126.1, 121.6, 121.5,

61.4, 60.4, 59.1, 50.2, 49.3, 45.8, 30.9, 29.7, 29.1, 28.8, 25.1, 24.8, 22.5, 21.3, 21.1, 20.7; HRMS-ESI (*m/z*) calcd for $(C_{22}H_{21}O_4N_3+H)^+$: 392.1605, found: 392.1609.

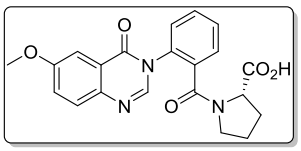


(5-Chloro-2- (6-chloro-4-oxoquinazolin-3(4H)-yl) benzoyl)-*L*-proline [(–)-47]. 91%, 442 mg from 500 mg of (–)-**46**, white solid; mp: 129-131 ^oC; R_f: 0.5 (2:8, methanol:ethyl acetate); $[\alpha]^{27}_D$ –46.66 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.70 (bs, 1H, CO_2H), 8.51-8.10 (m, 2H), 7.79-7.20 (m, 5H), 4.73-4.33 (m, 1H), 3.86-3.31 (s, 2H), 2.45-1.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 175.2, 175.0, 174.7, 171.5, 167.7, 166.7, 166.0, 165.0, 165.9, 160.3, 159.9, 149.5, 147.8, 146.9, 146.5, 145.8, 145.4, 137.0, 136.4, 136.0, 135.6, 135.3, 135.1, 134.8, 134.3, 133.6, 133.5, 133.0, 132.7, 132.5, 131.2, 131.0, 130.8, 130.7, 129.7, 129.5, 129.1, 128.9, 128.8, 128.0, 127.4, 127.3, 127.1, 127.0, 126.5, 126.2, 124.4, 124.3, 123.5, 123.0, 122.8, 122.6, 122.5, 121.9, 121.2, 120.6, 119.3, 118.6, 118.1, 60.4, 60.1, 59.3, 58.8, 58.6, 56.6, 50.4, 50.1, 49.3, 46.1, 29.6, 29.24, 29.16, 26.1, 25.4, 25.2, 24.9, 24.6, 23.4, 21.0, 20.7; HRMS-ESI (*m/z*) calcd for $(C_{20}H_{15}Cl_2O_4N_3+H)^+$: 432.0512, found: 432.0517.



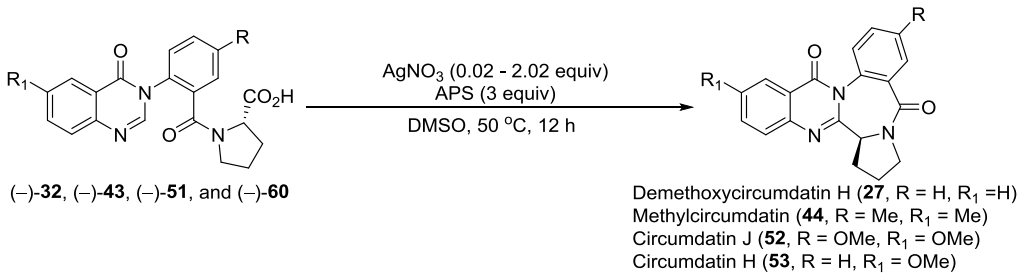
(5-Methoxy-2-(6-methoxy-4-oxoquinazolin-3(4*H*)-yl) benzoyl)-*L*-proline [(–)-51]. 92%, 447 mg from 500 mg of (–)-**50**, white solid; mp: 126-127 ^oC; R_f: 0.3 (9:1, ethyl acetate: methanol); $[\alpha]^{27}_D$ –68 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.04, 7.98 (2s, 1H), 7.76-7.53 (m, 2H), 7.43-7.16 (m, 3H), 7.13-6.97 (m, 2H), 4.60-4.36 (m, 1 H), 3.89, 3.86, 3.71 (3s, 6H), 3.67-3.35 (m, 2H), 2.25-1.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 176.1, 174.0, 173.6, 167.6, 166.9, 166.6, 161.2, 161.1, 161.0, 160.1, 159.9, 159.8, 158.9,

145.24, 145.18, 145.0, 142.1, 142.0, 141.1, 136.2, 136.0, 130.5, 129.6, 129.0, 128.9, 128.2, 127.2, 126.6, 124.5, 124.4, 122.8, 122.7, 122.6, 116.6, 115.7, 113.4, 112.4, 111.7, 106.5, 61.5, 59.0, 55.8, 55.6, 50.1, 49.3, 30.9, 29.2, 28.9, 25.2, 24.8, 22.5; HRMS-ESI (*m/z*) calcd for $(C_{22}H_{21}O_6N_3+H)^+$: 424.1503, found: 424.1504.



(2-(6-Methoxy-4-oxoquinazolin-3(4*H*)-yl)benzoyl)-*L*-proline [(–)-60]. 93%, 449 mg from 500 mg of (–)-**59**, white solid; mp: 113-115 ^oC; R_f: 0.5 (2:8, methanol:ethyl acetate); $[\alpha]^{27}_D$ –100 (*c* 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of atropisomers and rotamers): δ 8.07, 8.06, 8.03 (3s, 1H), 7.72-7.28 (m, 6H), 7.26-7.19 (m, 1H), 7.10 (bs, 1H), 4.71-4.39 (m, 1H), 3.92, 3.90, 3.88, 3.79, 3.77 (5s, 3H), 3.75-3.32 (m, 2H), 2.32-2.08 (m, 2H), 2.02-1.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.0, 175.8, 174.4, 173.8, 167.9, 167.0, 161.0, 160.8, 160.7, 159.4, 159.0, 144.8, 144.7, 144.6, 142.0, 135.3, 135.0, 134.9, 134.6, 134.4, 131.0, 130.7, 129.7, 129.6, 129.3, 129.0, 128.5, 128.4, 127.9, 127.1, 124.6, 123.8, 122.9, 122.8, 106.6, 61.4, 59.0, 55.8, 50.5, 50.1, 49.3, 29.7, 29.1, 29.0, 25.2, 24.8, 22.6, 22.4, 20.6; HRMS-ESI (*m/z*) calcd for $(C_{21}H_{19}O_5N_3+Na)^+$: 416.1217, found: 416.1216.

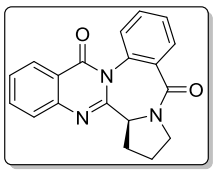
[E] General procedure-IV: Synthesis of demethoxycircumdatin H (27), methylcircumdatin (44), circumdatin J (52), and circumdatin H (53)



(–)-**32**, (–)-**43**, (–)-**51**, and (–)-**60**

Demethoxycircumdatin H (**27**, R = H, R_1 =H)
Methylcircumdatin (**44**, R = Me, R_1 = Me)
Circumdatin J (**52**, R = OMe, R_1 = OMe)
Circumdatin H (**53**, R = H, R_1 = OMe)

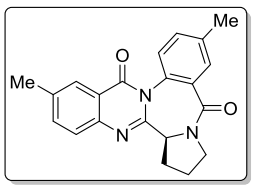
A round-bottom flask containing a magnetic stirring bar, acid (–)-**32**/(–)-**43**/(–)-**51**/(–)-**60** (1 equiv), silver nitrate (0.02 equiv – 2.02 equiv) and APS (3 equiv) was evacuated well and flushed with argon. DMSO (4 mL for 100 mg) was added and the resulting reaction mixture was heated at 50 ^{o}C for 12 h with continuous stirring. It was then cooled to room temperature and diluted with ethyl acetate (20 mL for 4 mL DMSO). The organic layer was washed with brine (5 X 2 mL for 10 mL ethyl acetate), water (5 X 2 mL for 10 mL ethyl acetate) and aqueous $NaHCO_3$ followed by drying over sodium sulphate. Evaporation of the organic layer under vacuum and flash column chromatography of the crude product using ethyl acetate:petroleum ether as eluents furnished circumdatin alkaloids demethoxycircumdatin H (**27**), methylcircumdatin (**44**), circumdatin J (**52**), and circumdatin H (**53**). The aqueous $NaHCO_3$ layer was acidified with citric acid up to pH = 2 and the unreacted starting material were recovered by ethyl acetate extraction.



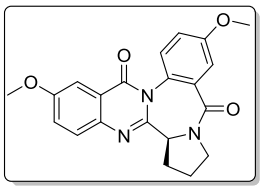
Demethoxycircimdatin H (**27**)**. For 50 mg scale** [**27** (41%, 18 mg from 50 mg of (–)-**32**) 18.5 mg of (–)-**32** recovered, hence 65% brsm]

For 1 mmol scale [**27** (45%, 145 mg from 364 mg of (–)-**32**) 94 mg of (–)-**32** recovered, hence 61% brsm], white solid; mp: 214-216 ^{o}C; R_f: 0.5 (7:3, ethyl acetate:petroleum ether); $[\alpha]^{29}_{D}$ –76.9 (*c* 1.3, $CHCl_3$) with 91:9 *er*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 7.3 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.72 (d, 7.9 Hz, 1H), 7.62-7.50 (m, 4H), 4.56 (d, *J* = 7.3 Hz, 1H), 3.84-3.77 (m, 1H), 3.67-3.56 (m, 1H), 3.22-3.16 (m, 1H), 2.39-2.27 (m, 1H), 2.21-2.13 (m, 1H), 2.11-2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 161.7, 153.6, 146.1, 134.8, 133.2, 132.4, 130.8, 129.9, 128.7, 128.3, 127.60, 127.57, 127.5,

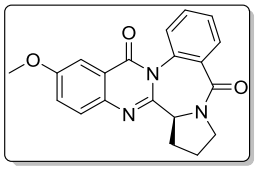
121.5, 58.9, 46.5, 27.0, 23.7; HRMS-ESI (*m/z*) calcd for $(C_{19}H_{15}O_2N_3+H)^+$: 318.1237, found: 318.1238.



Methylcircumdatin (**44**)**.** 28% (25 mg from 100 mg of (–)-**43**) 55 mg of (–)-**43** was recovered, hence 62% brsm; white solid; mp: 206-208 ^oC; R_f: 0.3 (6:4, ethyl acetate:petroleum ether); $[\alpha]^{27}_D$ –88 (*c* 0.5, $CHCl_3$); 88.2:11.8 *er*; ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.80 (s, 1H), 7.61 (s, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 1.5 & 8.4 Hz, 1H), 4.55 (d, *J* = 6.9 Hz, 1H), 3.82-3.74 (m, 1H), 3.65-3.56 (m, 1H), 3.20-3.16 (m, 1H), 2.51 (s, 3H), 2.46 (s, 3H), 2.36-2.27 (m, 1H), 2.19-2.11 (m, 1H), 2.10-2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 161.8, 152.9, 144.1, 138.9, 137.8, 136.1, 132.1, 131.6, 130.9, 130.1, 128.1, 127.4, 126.9, 121.3, 58.9, 46.5, 27.0, 23.7, 21.4, 21.0; HRMS-ESI (*m/z*) calcd for $(C_{21}H_{19}O_2N_3+Na)^+$: 368.1369, found: 368.1358.



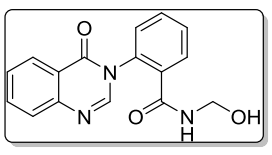
Circumdatin J (**52**)**.** 30% (27 mg from 100 mg of (–)-**51**) 52 mg of (–)-**51** was recovered, hence 63% brsm; white solid; mp: 179-182 ^oC; R_f: 0.5 (7:3, ethyl acetate:petroleum ether); $[\alpha]^{27}_D$ –60 (*c* 0.5, MeOH-DCM [1:1]) with 87.3:12.7 *er*; ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 2.7 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.50-7.46 (m, 2H), 7.38 (dd, *J* = 3.05 & 9.0 Hz, 1H), 7.11 (dd, *J* = 3.05 & 9.0 Hz, 1H), 4.57 (d, *J* = 6.9 Hz, 1H), 3.93 (s, 3H), 3.92 (3H), 3.81-3.76 (m, 1H), 3.65-3.58 (m, 1H), 3.20-3.14 (m, 1H), 2.36-2.27 (m, 1H), 2.19-2.13 (m, 1H), 2.11-2.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.4, 161.8, 159.2, 159.0, 151.7, 140.7, 133.5, 129.7, 129.1, 126.3, 124.8, 122.3, 118.0, 112.9, 106.9, 58.8, 55.9, 55.8, 46.6, 27.0, 23.7; HRMS-ESI (*m/z*) calcd for $(C_{21}H_{19}O_4N_3+H)^+$: 378.1448, found: 378.1452.



Circumdatin H (**53**)**.** 36% (32 mg from 100 mg of (–)-**60**) 24 mg of (–)-**60** was recovered, hence 47% brsm; white solid; mp: 196-200 ^{o}C; R_f: 0.3 (6:4, ethyl acetate:petroleum ether); $[\alpha]^{27}_{D}$ –40 (*c* 1, $CHCl_3$) with 90.6:9.4 *er*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.3 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.61-7.48 (m, 3H), 7.39 (dd, *J* = 3.5 & 9.1 Hz, 1H), 4.55 (d, *J* = 7.3 Hz, 1H), 3.93 (s, 3H), 3.83-3.74 (m, 1H), 3.63-3.56 (m, 1H), 3.22-3.13 (m, 1H), 2.37-2.25 (m, 1H), 2.21-2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 161.7, 159.0, 151.5, 140.6, 133.4, 132.5, 130.7, 129.9, 129.2, 128.6, 128.4, 124.9, 122.3, 106.9, 58.8, 55.9, 46.5, 27.0, 23.7; HRMS-ESI (*m/z*) calcd for $(C_{20}H_{17}O_3N_3+Na)^+$: 370.1162, found: 370.1154.

[F] *N*-(Hydroxymethyl)-2-(4-oxoquinazolin-3(4*H*)-yl)benzamide (**36**)

A round-bottom flask containing a magnetic stirring bar, acid **35** (100 mg, 0.3 mmol, 1 equiv), silver nitrate (10.5 mg, 0.06 mmol, 0.2 equiv) and APS (211.7 mg, 0.92 mmol, 3 equiv) was evacuated well and flushed with argon. DMSO (4 mL) was added and the resulting reaction mixture was heated at 50 ^{o}C for 12 h with continuous stirring. It was then cooled to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with brine (5 X 2 mL) and water (5 X 2 mL) followed by drying over sodium sulphate. Evaporation of the organic layer under vacuum and flash column chromatography of the crude product using ethyl acetate as an eluent afforded the alcohol **36** (58 mg, 63%) as thick oil.

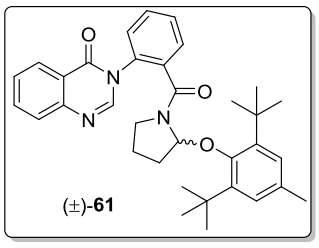


R_f: 0.3 (ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (t, *J* = 6.1 Hz, 1H), 8.21 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 8.2 Hz, 2H), 7.69-7.62 (m, 2H), 7.57 (t, *J* = 7.6 Hz, 2H), 5.82 (t, *J* = 7.3 Hz, 0.3H), 5.65 (t, *J* = 6.7 Hz, 0.7H), 4.72-4.35 (m, 2H); ^{13}C NMR (100 MHz, DMSO-

d_6): δ 165.8, 160.1, 148.0, 147.5, 135.9, 134.6, 133.8, 131.4, 129.7, 129.4, 128.6, 127.3, 127.2, 126.4, 122.0, 62.7; HRMS-ESI (*m/z*) calcd for $(C_{16}H_{13}O_3N_3+H)^+$: 296.1030, found: 296.1026.

3-(2-(2-(2,6-di-*tert*-Butyl-4-methylphenoxy) pyrrolidine-1-carbonyl)phenyl) quinazolin-4(3*H*)-one (**61**)

A round-bottom flask containing a magnetic stirring bar, (–)-**32** (50 mg, 0.137 mmol, 1 equiv), silver nitrate (4.6 mg, 0.027 mmol, 0.2 equiv), APS (94.2 mg, 0.413 mmol, 3 equiv) and BHT (151.6 mg, 0.688 mmol, 5 equiv) was evacuated well and flushed with argon. DMSO (3 mL) was added and the resulting reaction mixture was heated at 50 ^oC for 12 h with continuous stirring. It was then cooled to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with brine (5 X 2 mL) and water (5 X 10 mL) followed by drying over sodium sulphate. Evaporation of the organic layer under vacuum and flash column chromatography of the residue using ethyl acetate:petroleum ether (8:2) as eluents provided the racemic product **61** (42 mg, crude yield 56%) as a thick oil.



R_f: 0.4 (7:3, ethyl acetate:petroleum ether).

HRMS-ESI (*m/z*) calcd for $(C_{34}H_{39}O_3N_3+H)^+$: 538.3064, found: 538.3069.

^1H, ^{13}C NMR spectra and HPLC chromatogram of the crude sample is provided. The crude sample did not show any optical rotation. HPLC analysis also indicated racemic nature of the compound.

3.6 References

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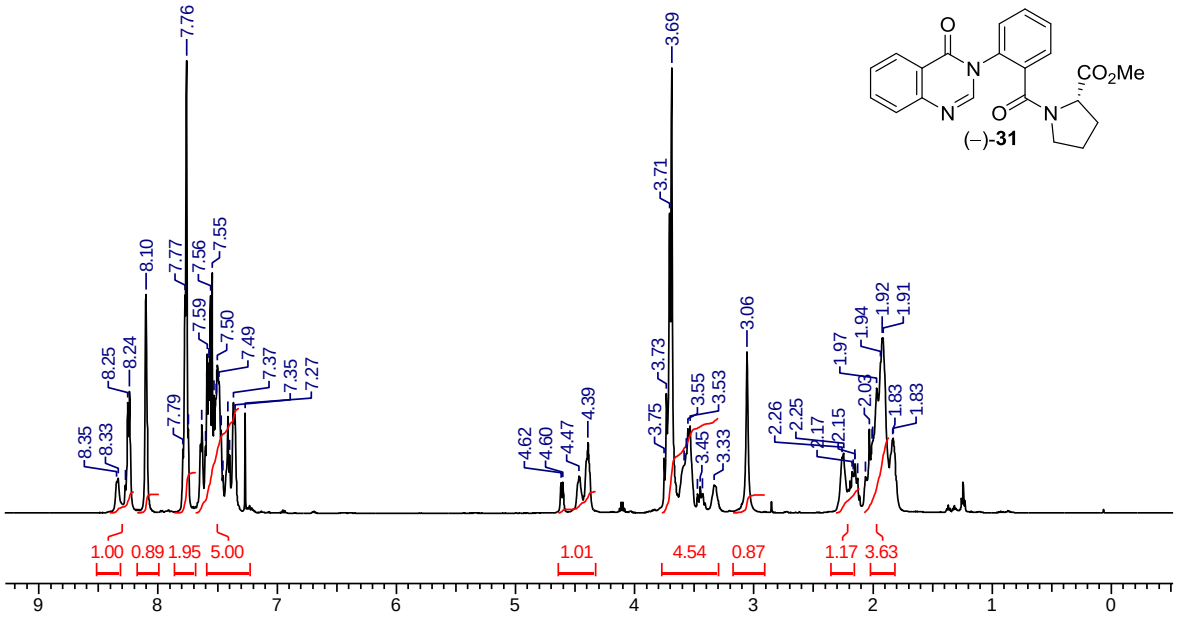
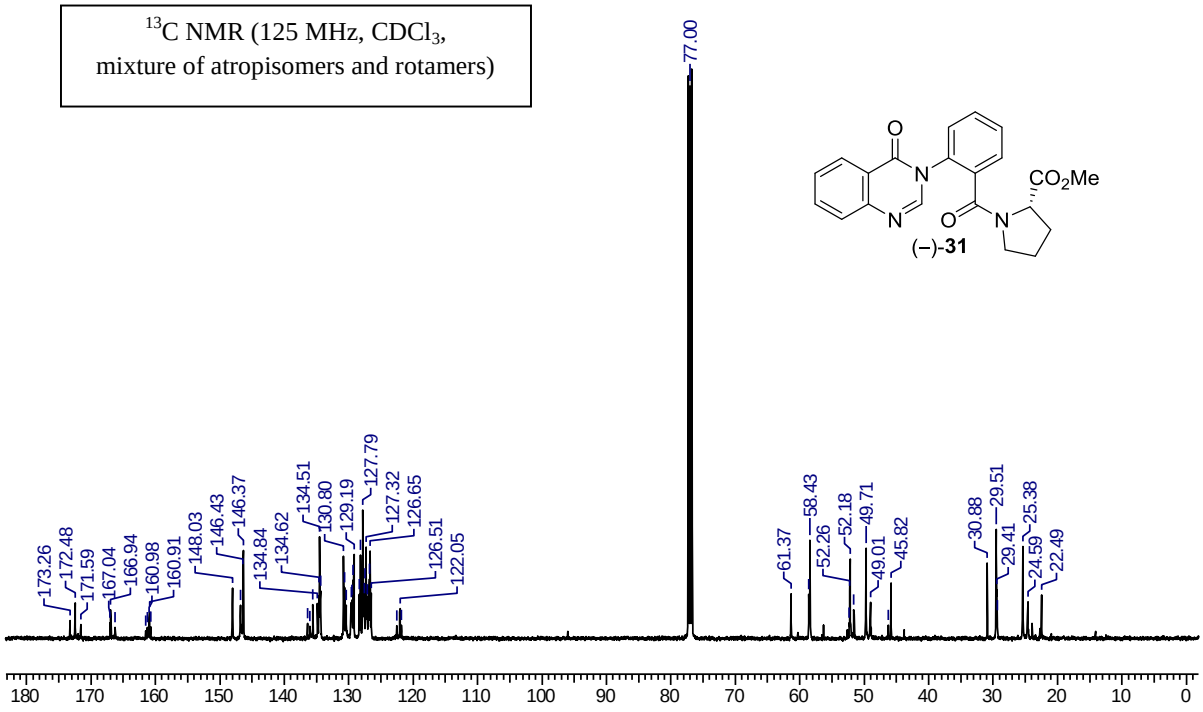
3.7 Selected copies of ^{1}H, ^{13}C NMR

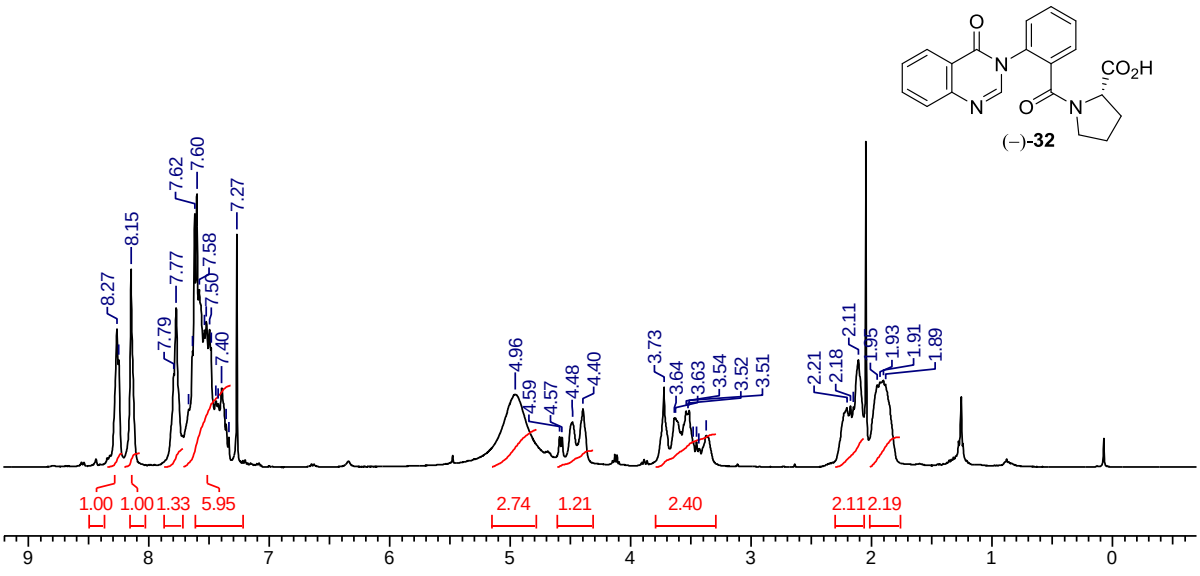
^{1}H NMR (500 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



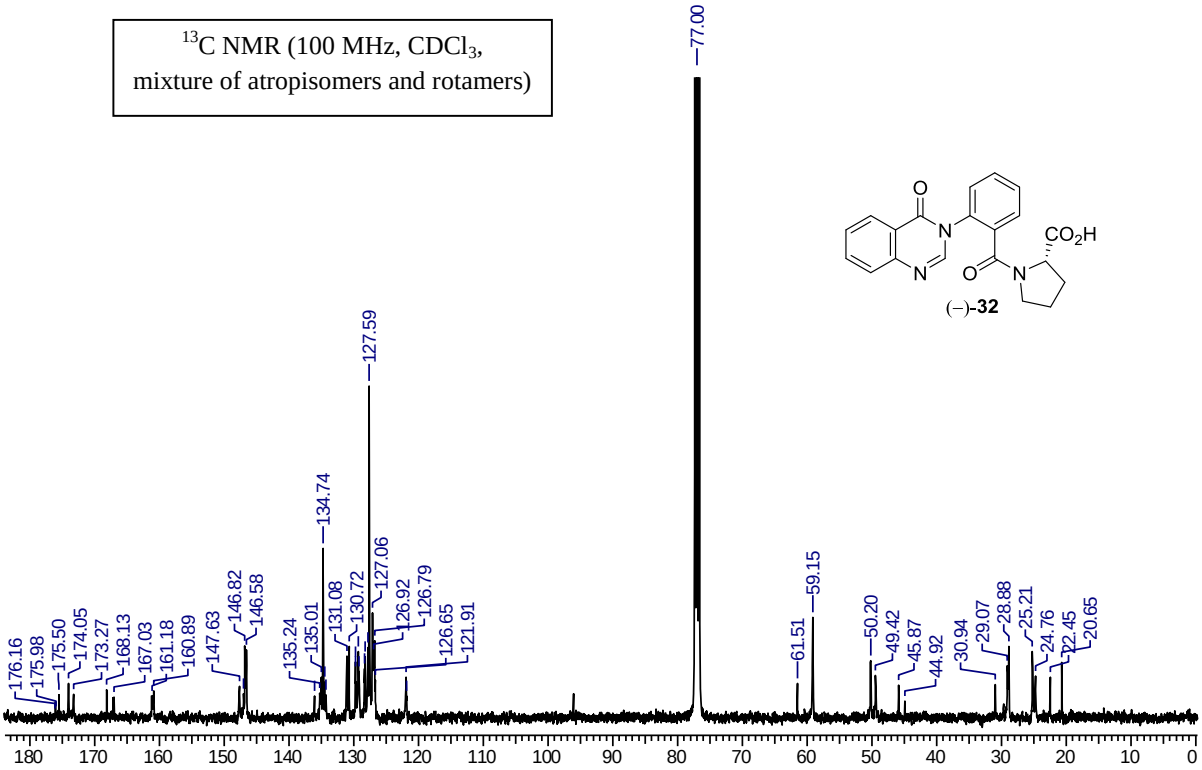
^{13}C NMR (125 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



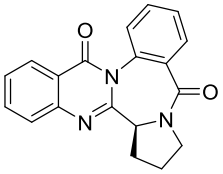
^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



^{13}C NMR (100 MHz, $CDCl_3$, mixture of atropisomers and rotamers)

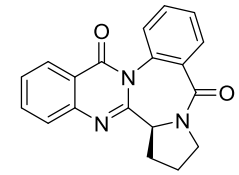


^{1}H NMR (400 MHz, $CDCl_3$)



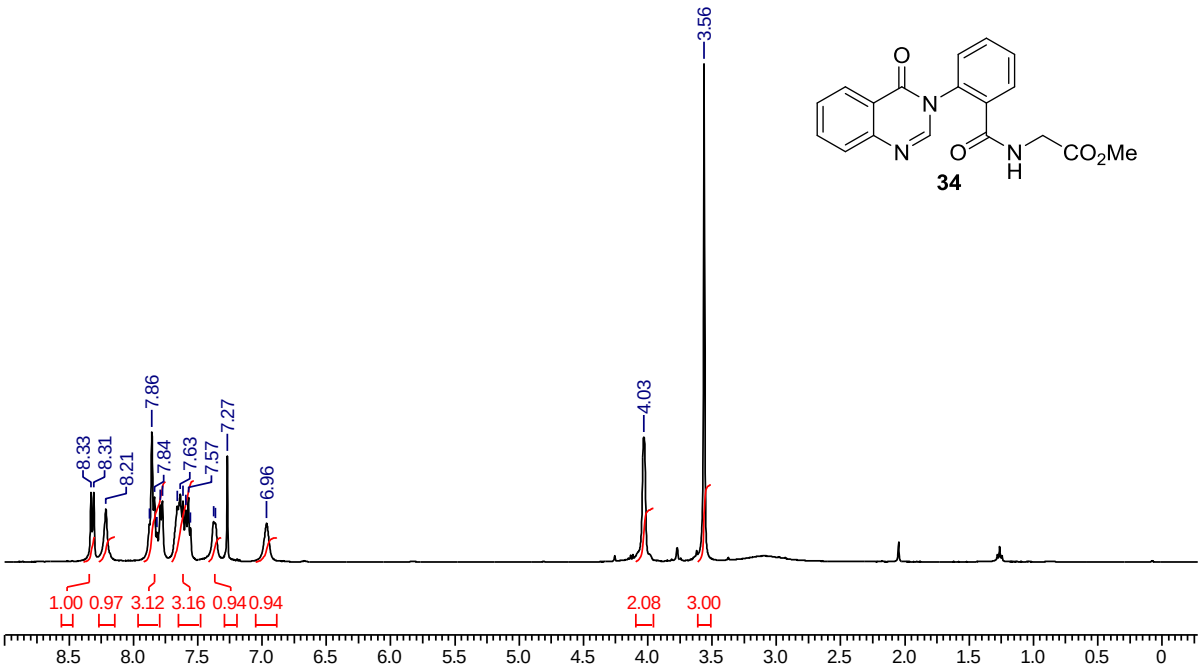
Demethoxycircumdatin H (**27**)

^{13}C NMR (100 MHz, $CDCl_3$)

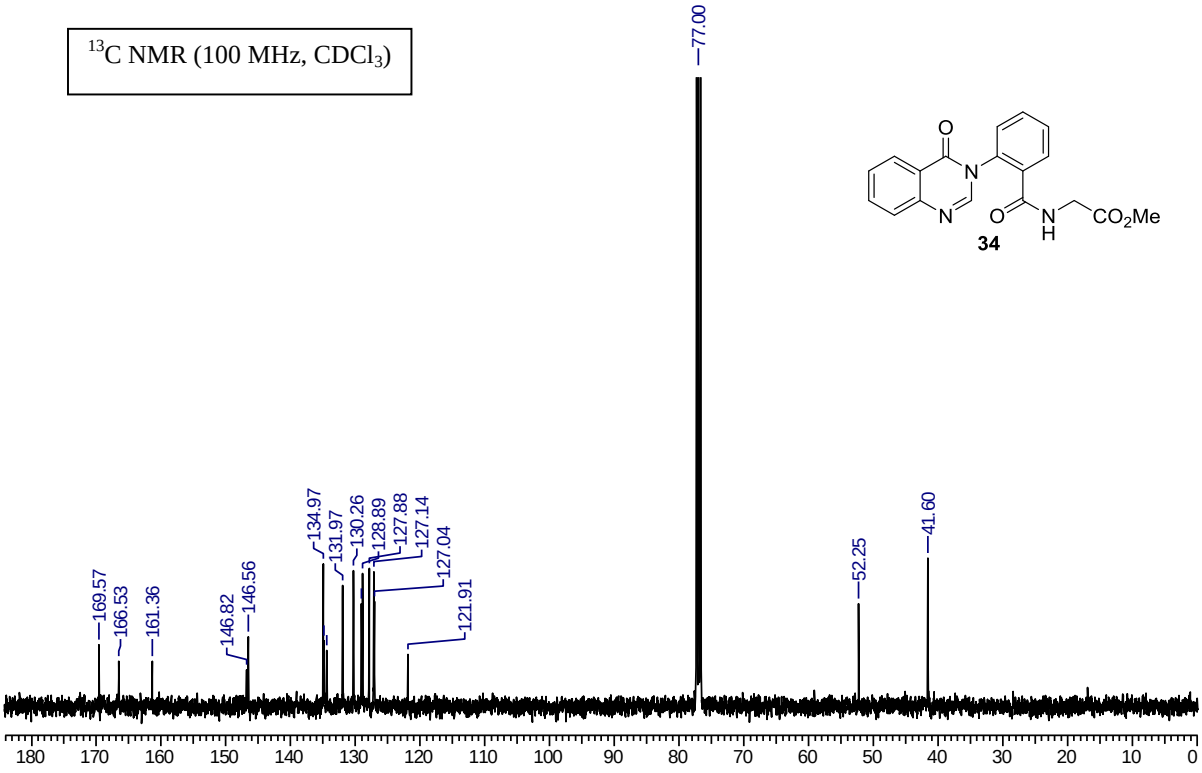


Demethoxycircumdatin H (**27**)

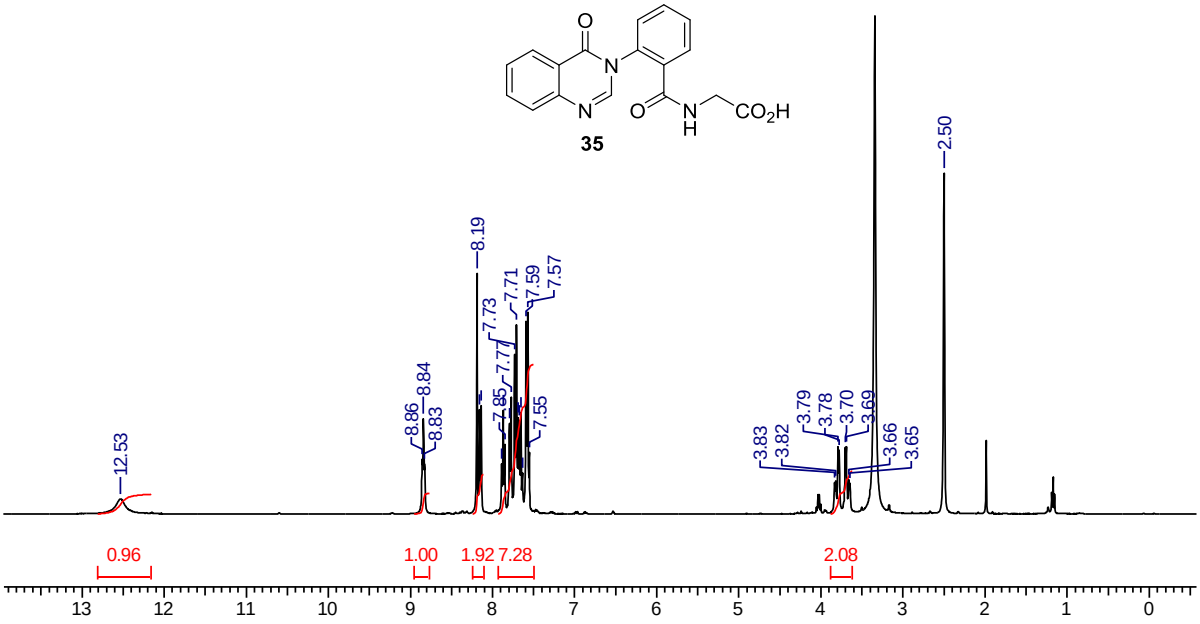
^{1}H NMR (400 MHz, $CDCl_3$)



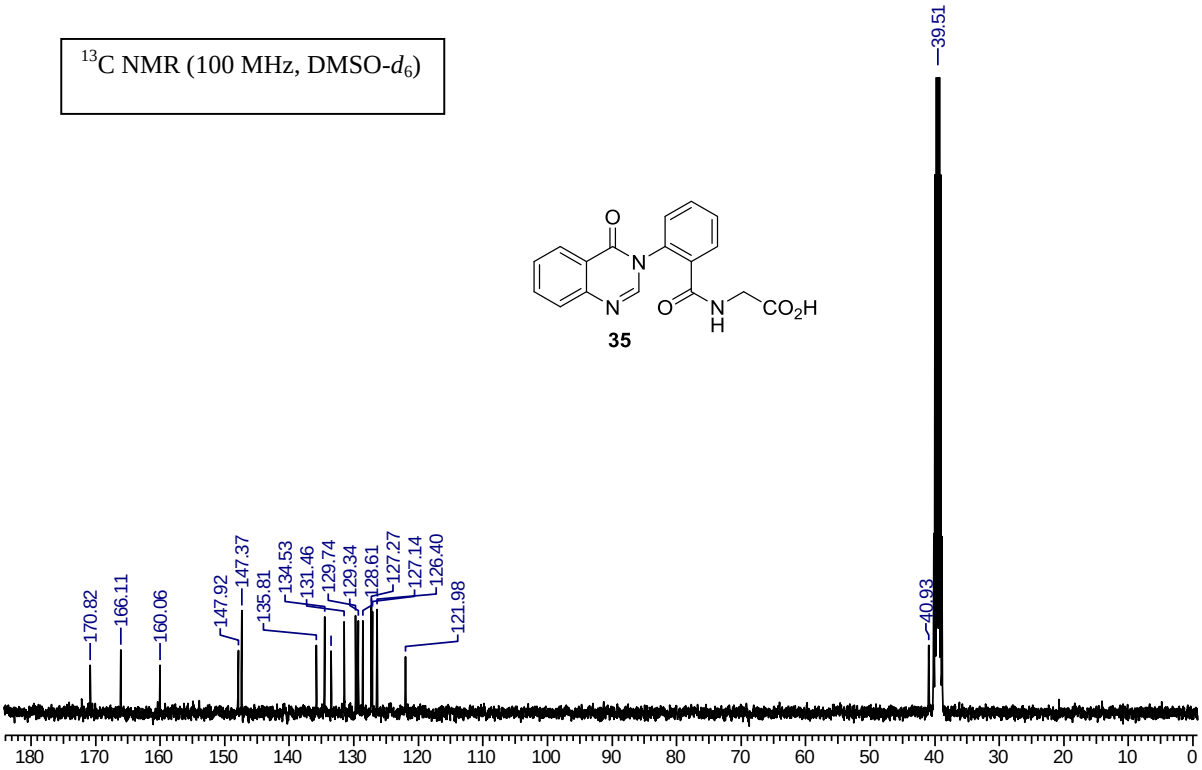
^{13}C NMR (100 MHz, $CDCl_3$)



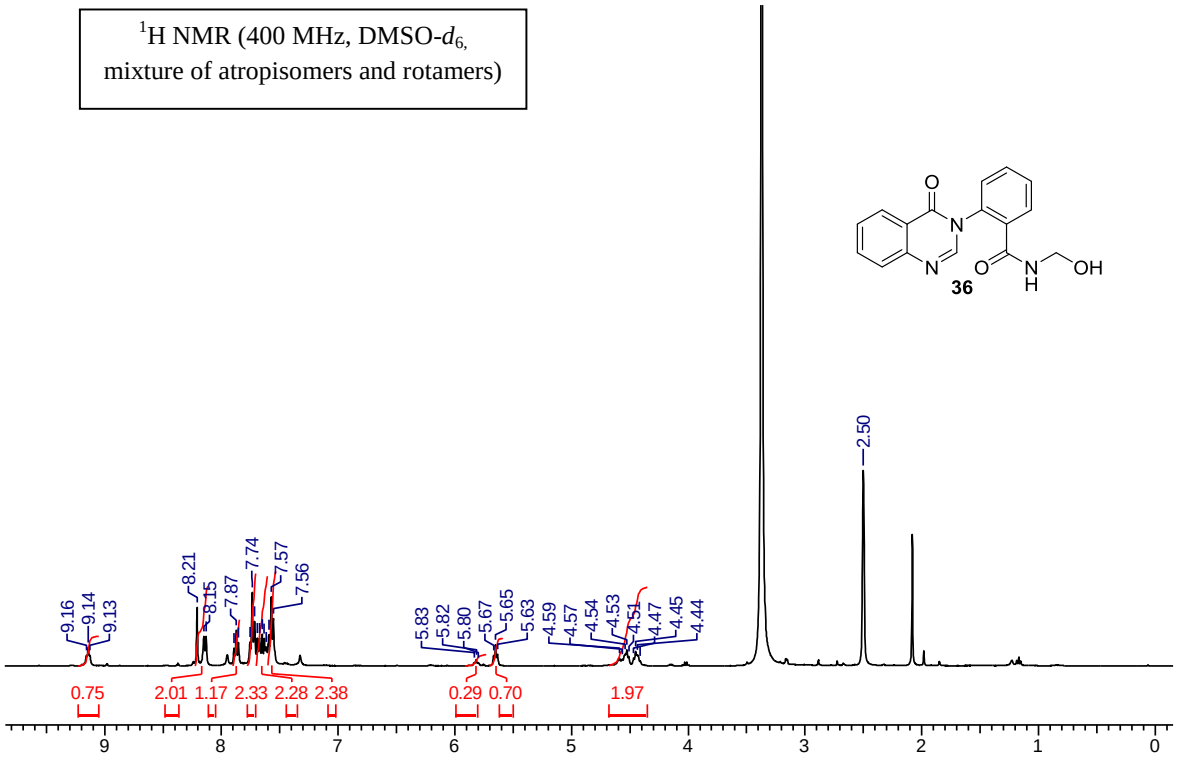
^{1}H NMR (400 MHz, DMSO-d_6)



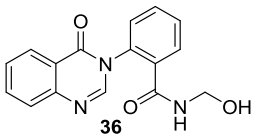
^{13}C NMR (100 MHz, DMSO-d_6)



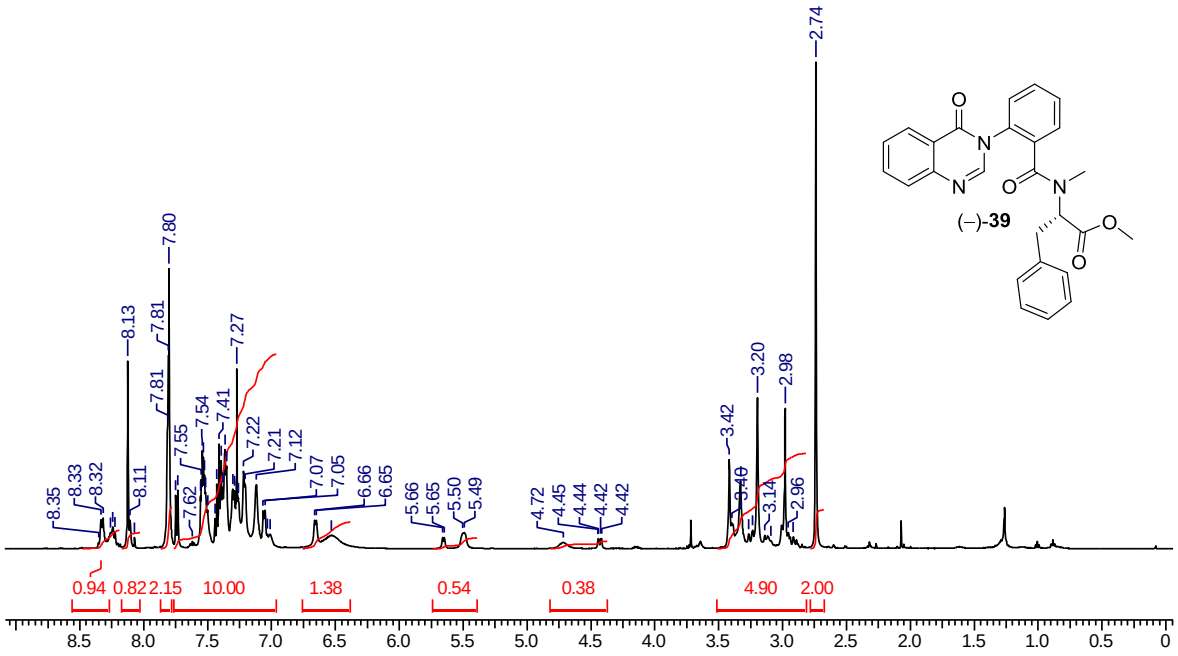
^{1}H NMR (400 MHz, DMSO-d_6, mixture of atropisomers and rotamers)



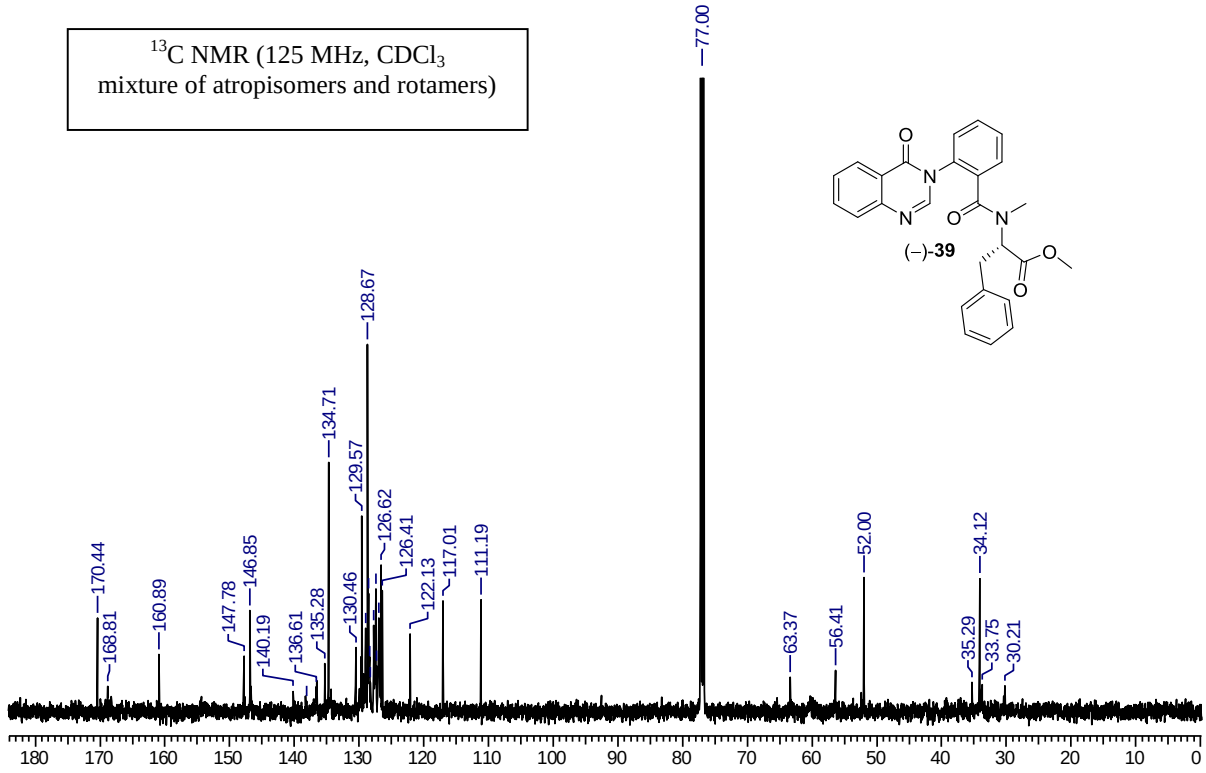
^{13}C NMR (100 MHz, DMSO-d_6, mixture of atropisomers and rotamers)



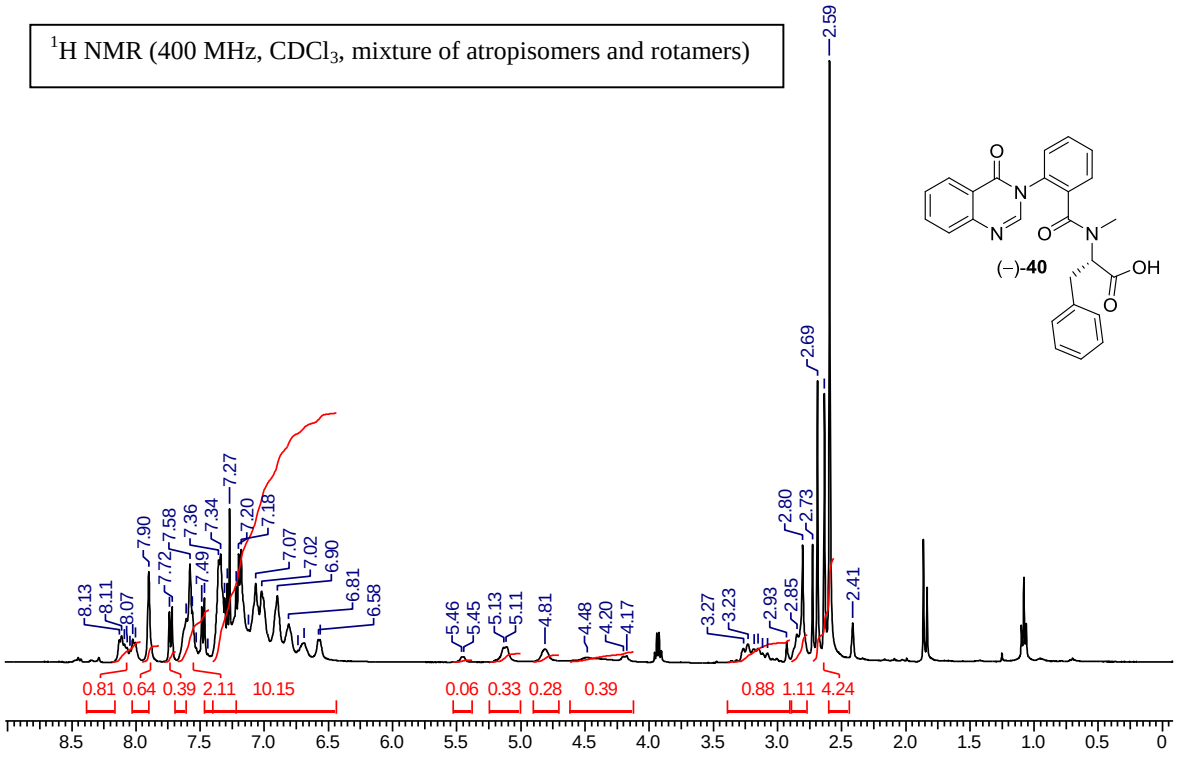
^{1}H NMR (500 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



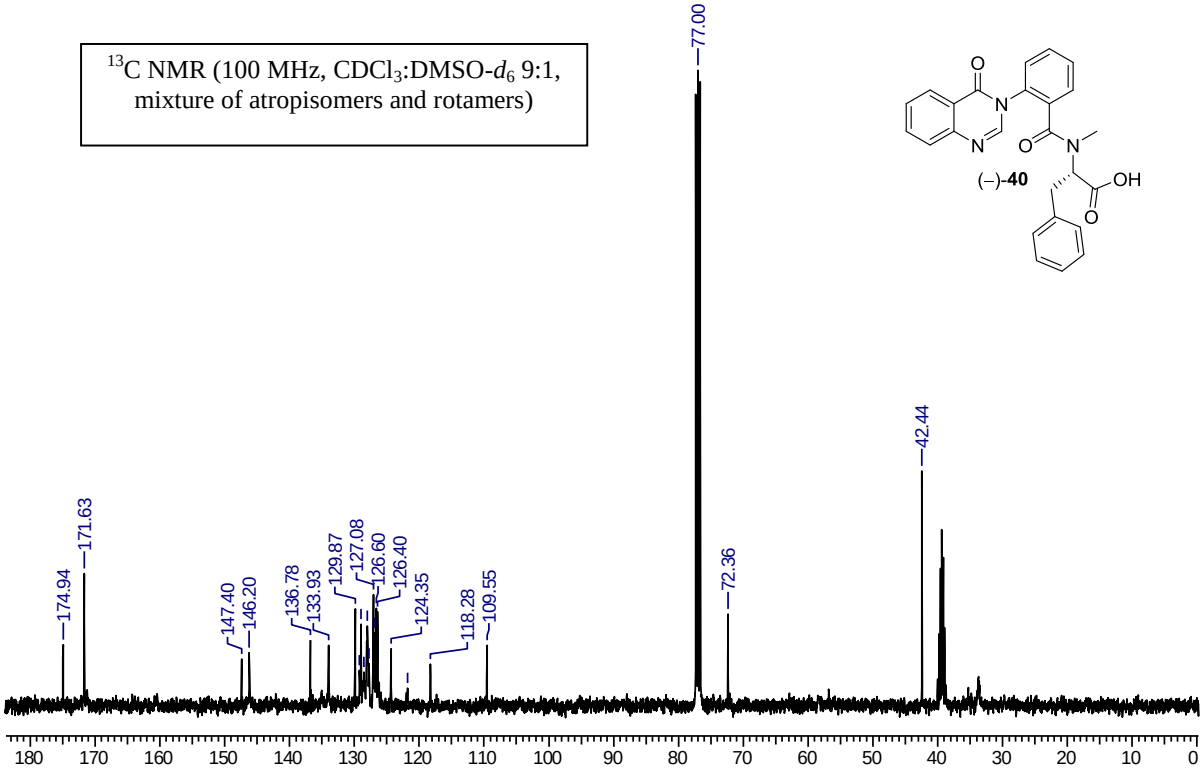
^{13}C NMR (125 MHz, $CDCl_3$
mixture of atropisomers and rotamers)



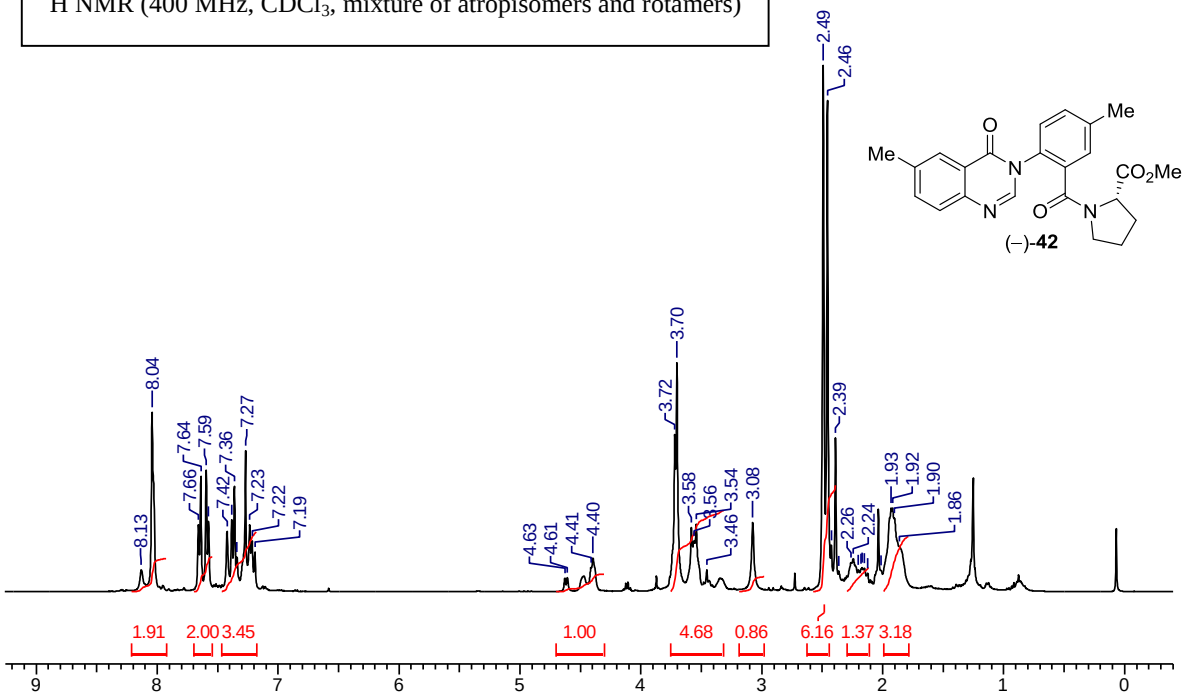
^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



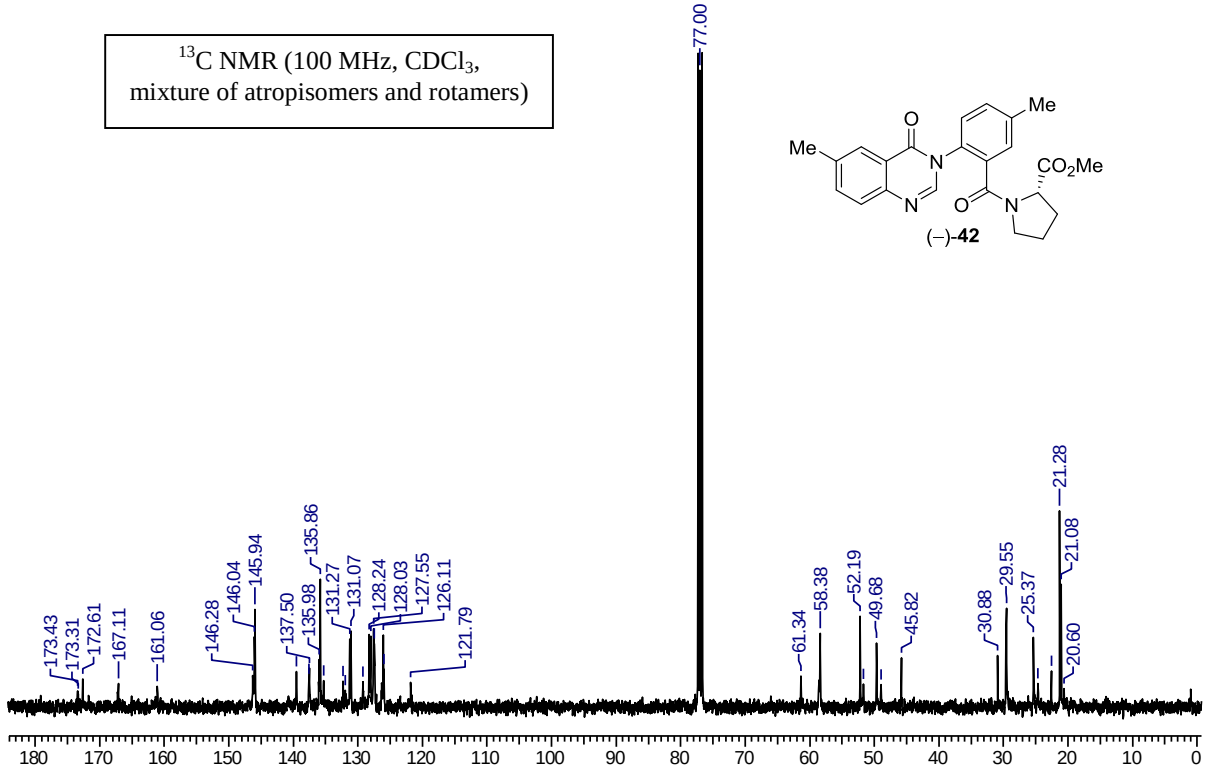
^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 9:1, mixture of atropisomers and rotamers)



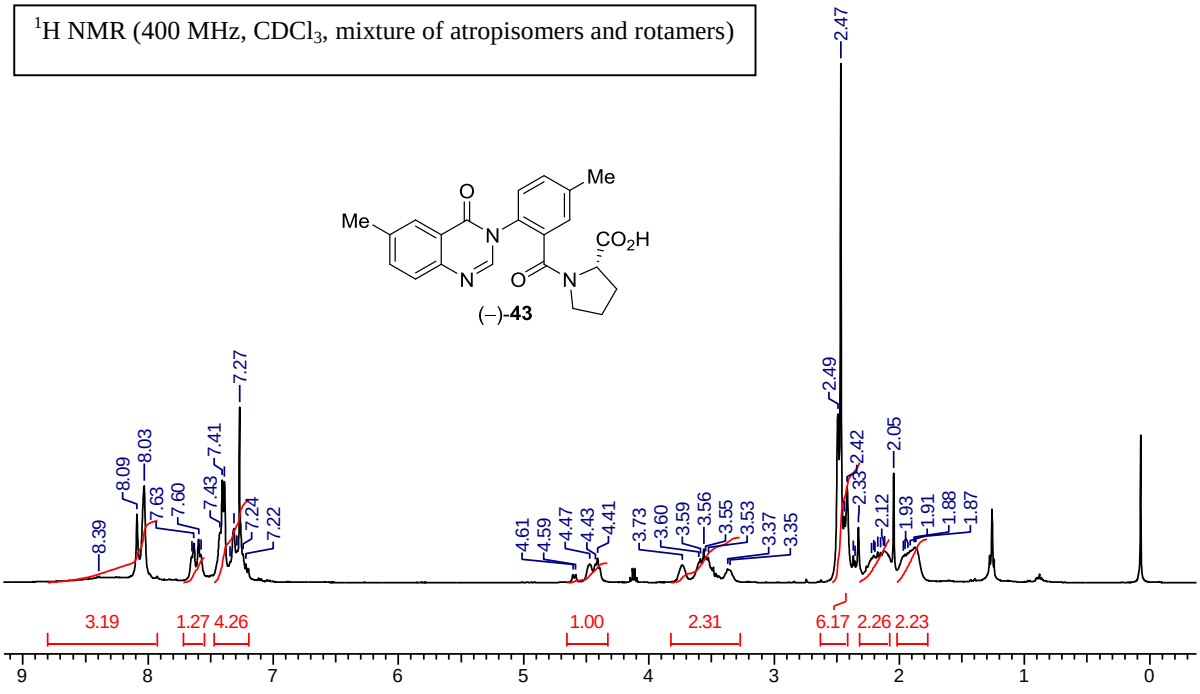
^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



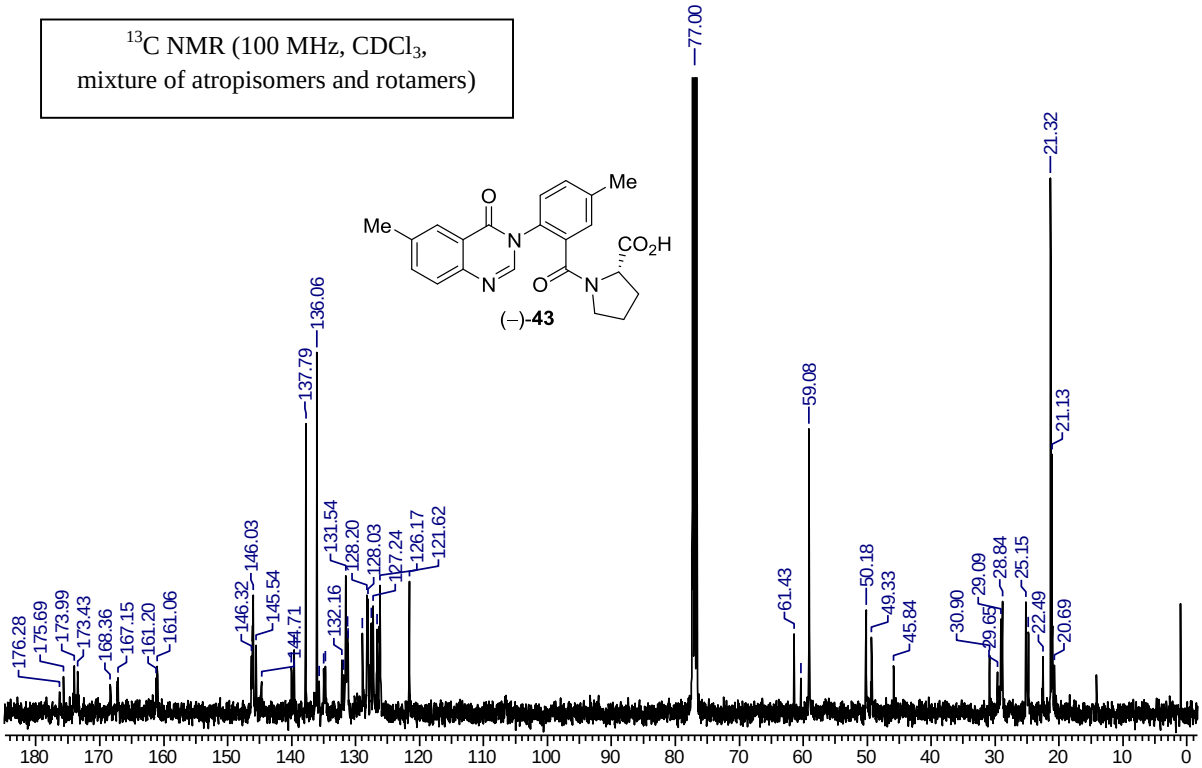
^{13}C NMR (100 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



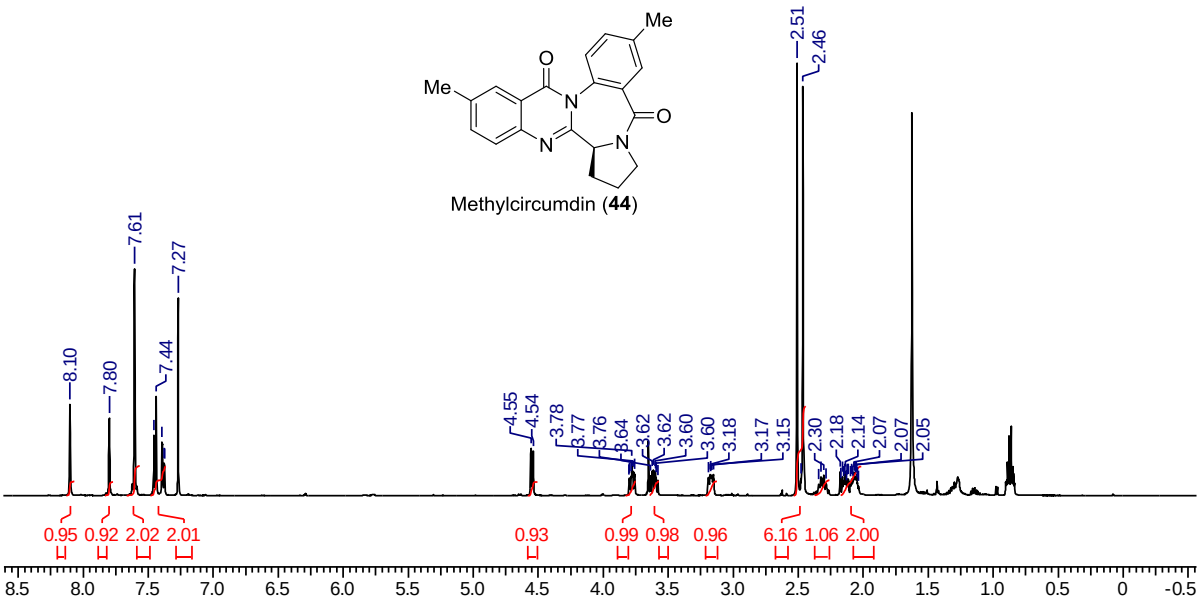
^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



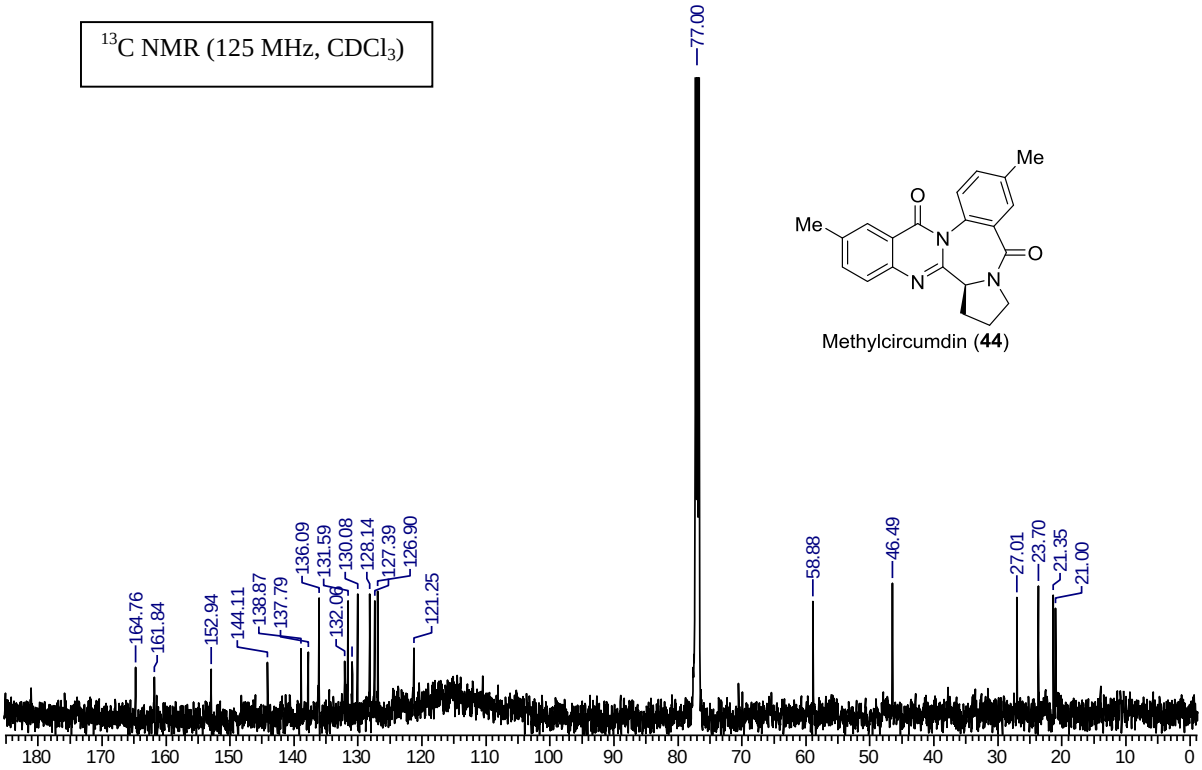
^{13}C NMR (100 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



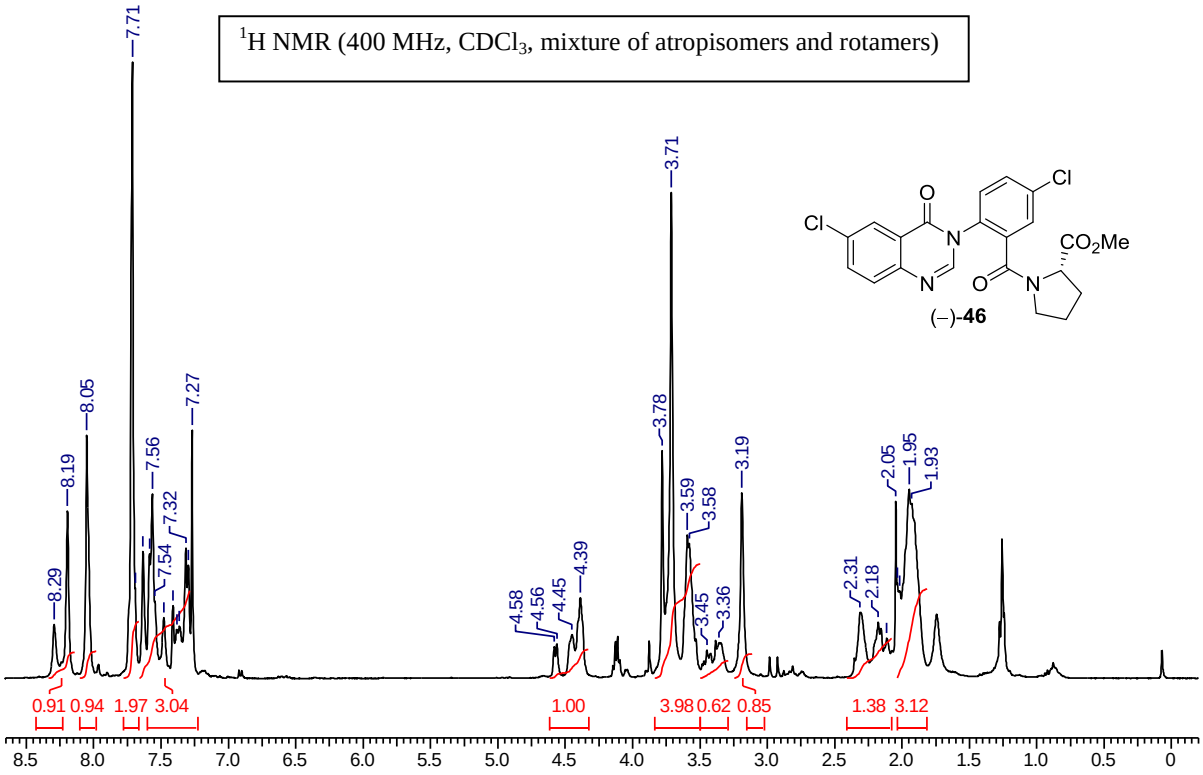
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

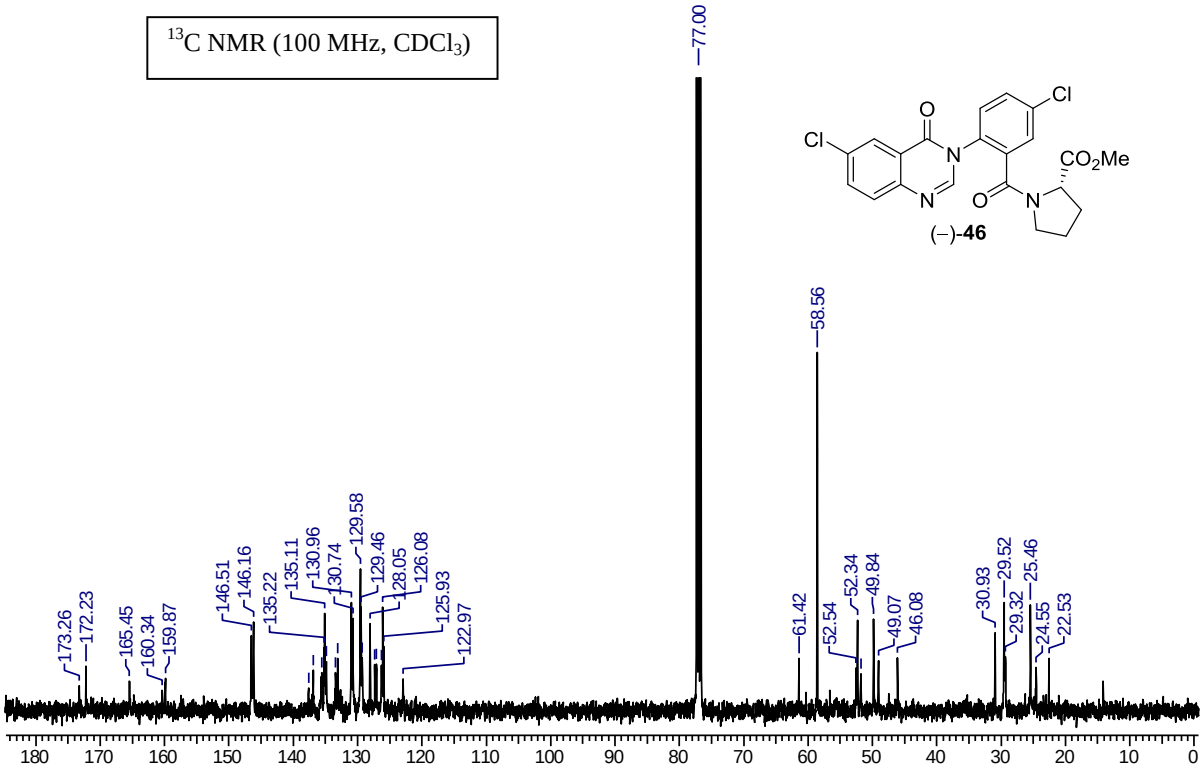


^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



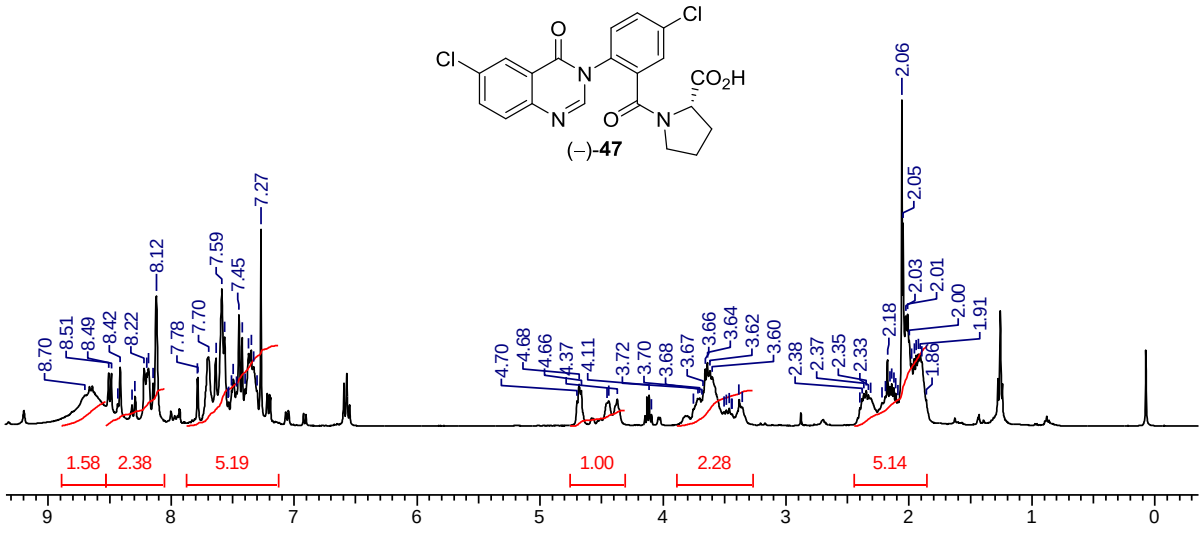
(−)-**46**

^{13}C NMR (100 MHz, $CDCl_3$)

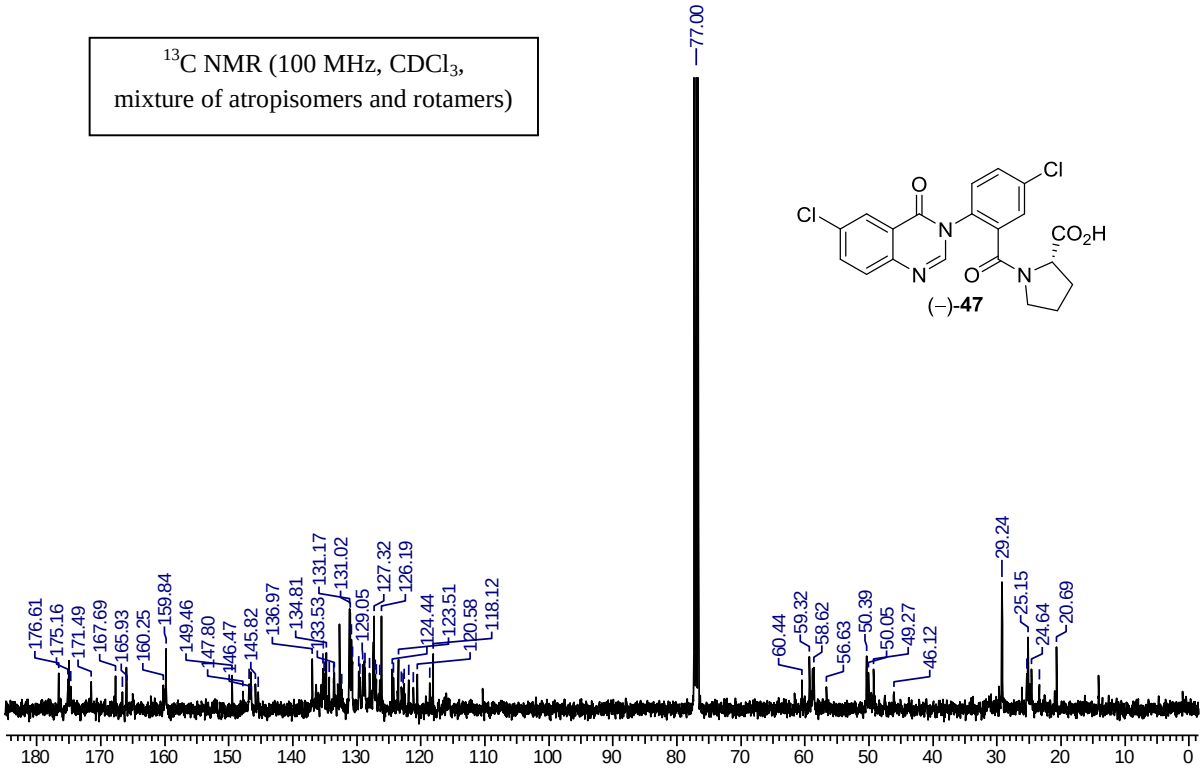


(−)-**46**

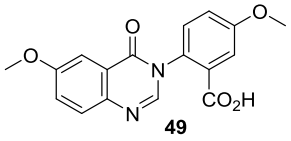
^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



^{13}C NMR (100 MHz, $CDCl_3$, mixture of atropisomers and rotamers)

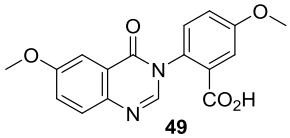


^{1}H NMR (400 MHz, DMSO-d_6)



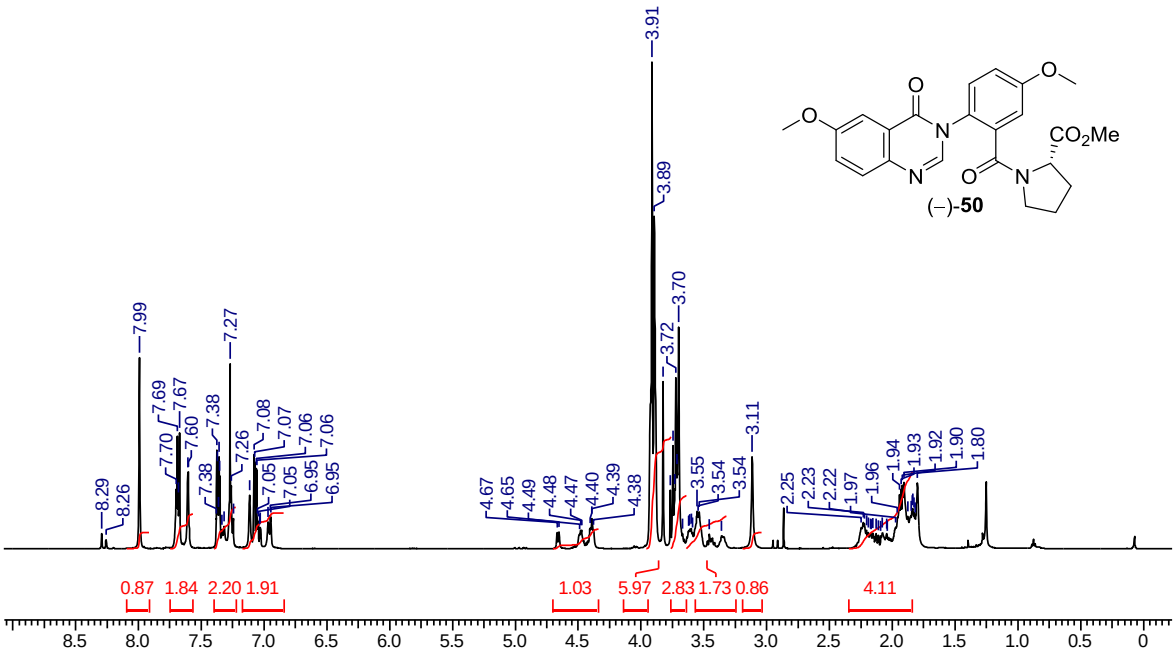
49

^{13}C NMR (100 MHz, DMSO-d_6)

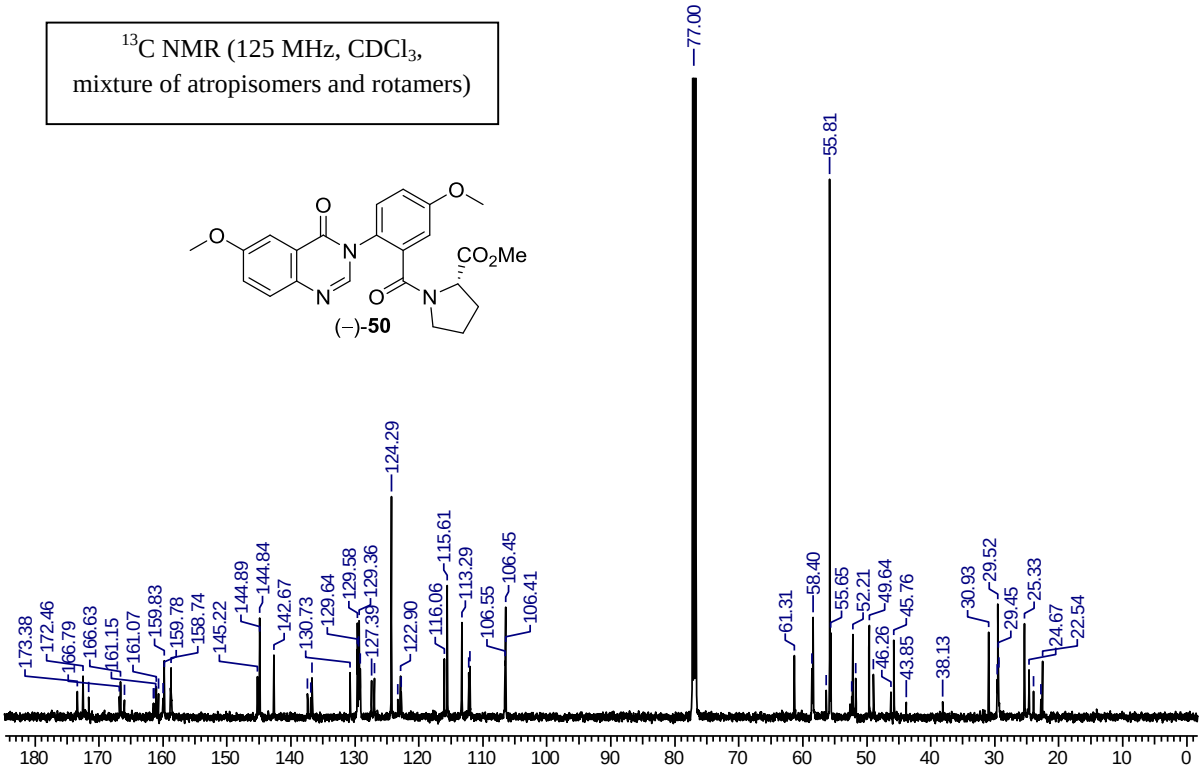


49

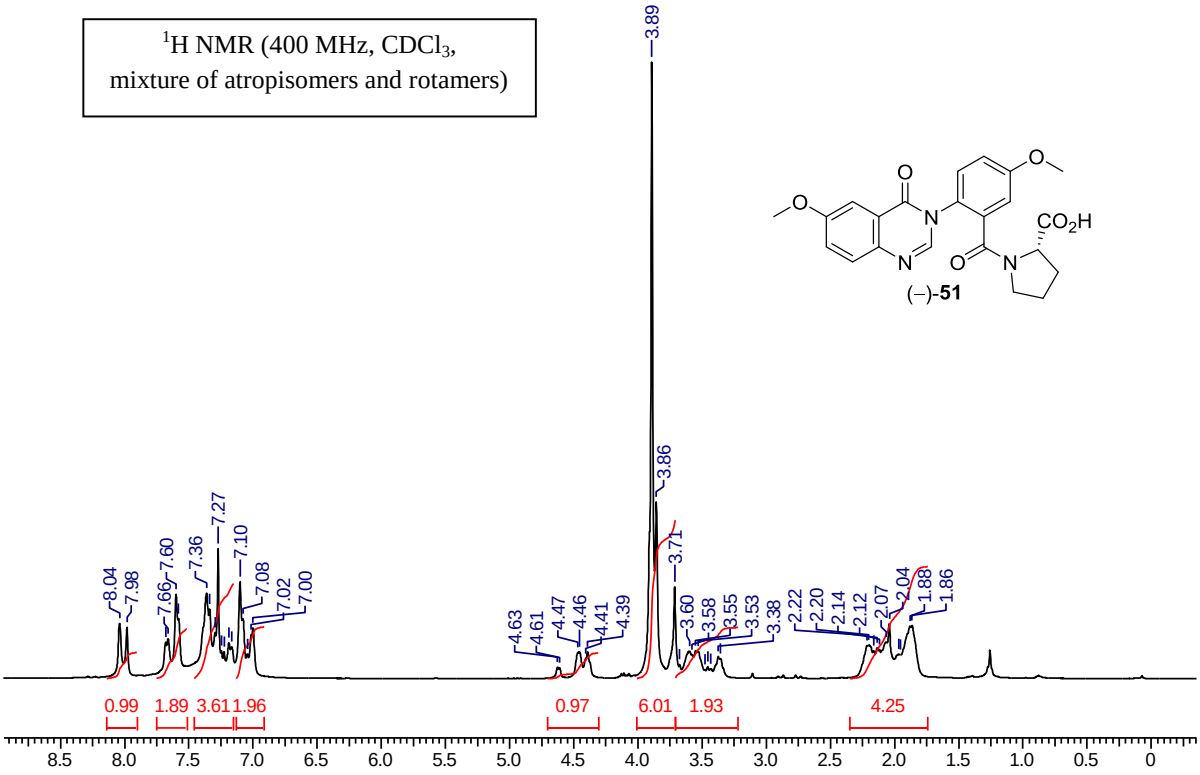
^{1}H NMR (500 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



^{13}C NMR (125 MHz, $CDCl_3$, mixture of atropisomers and rotamers)

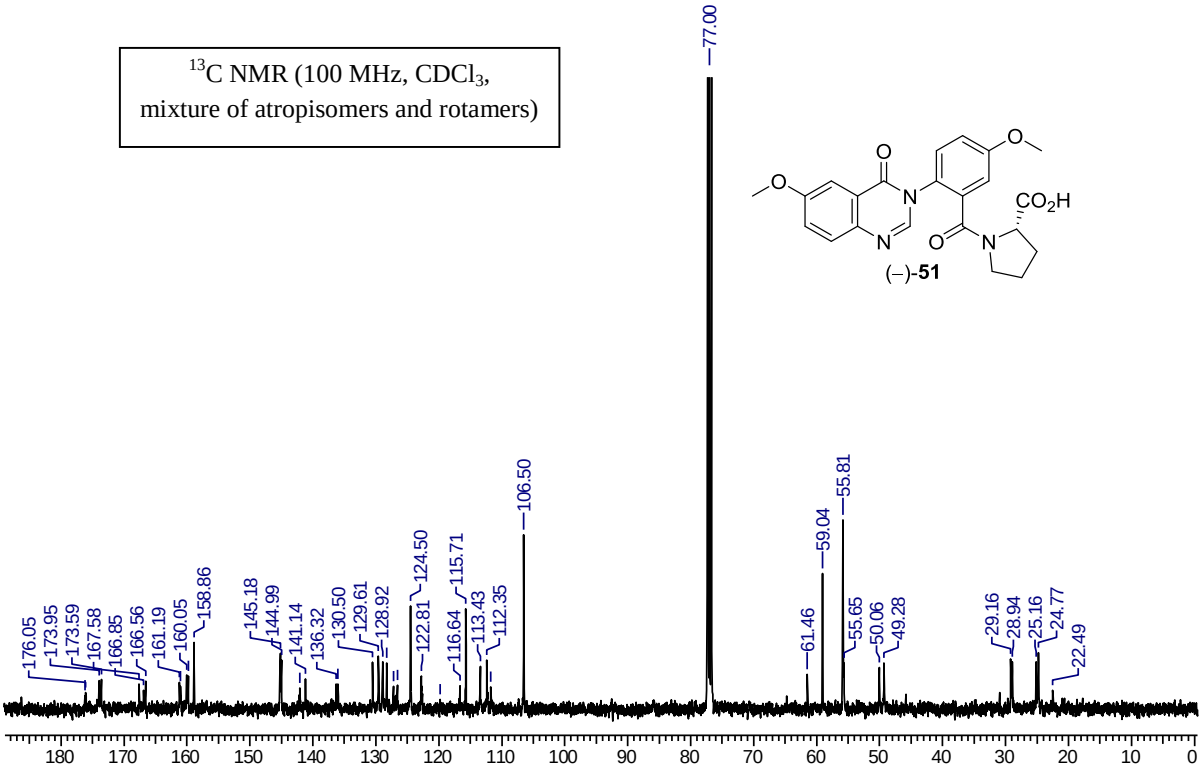


^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



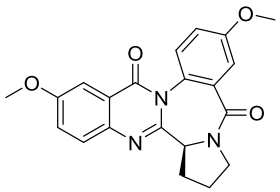
(−)-**51**

^{13}C NMR (100 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



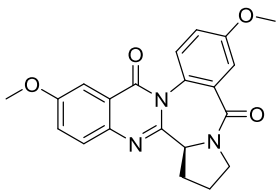
(−)-**51**

^{1}H NMR (500 MHz, $CDCl_3$)



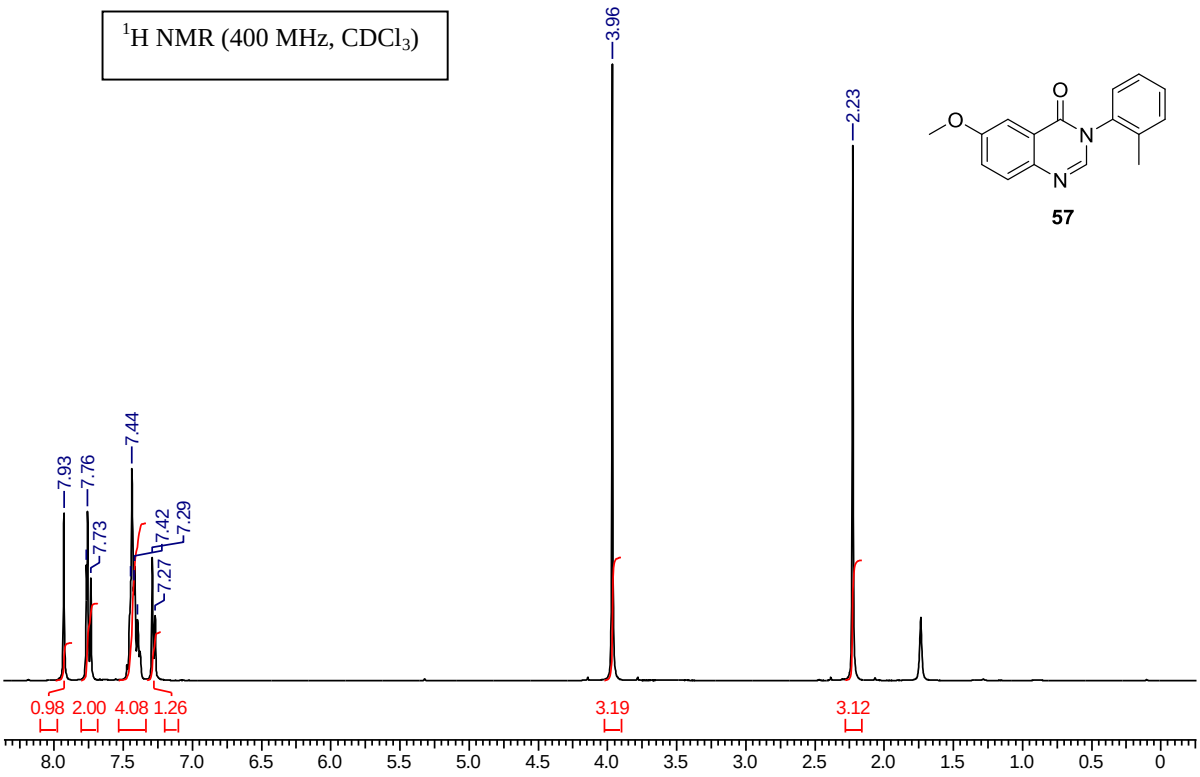
Circumdatin J (**52**)

^{13}C NMR (125 MHz, $CDCl_3$)



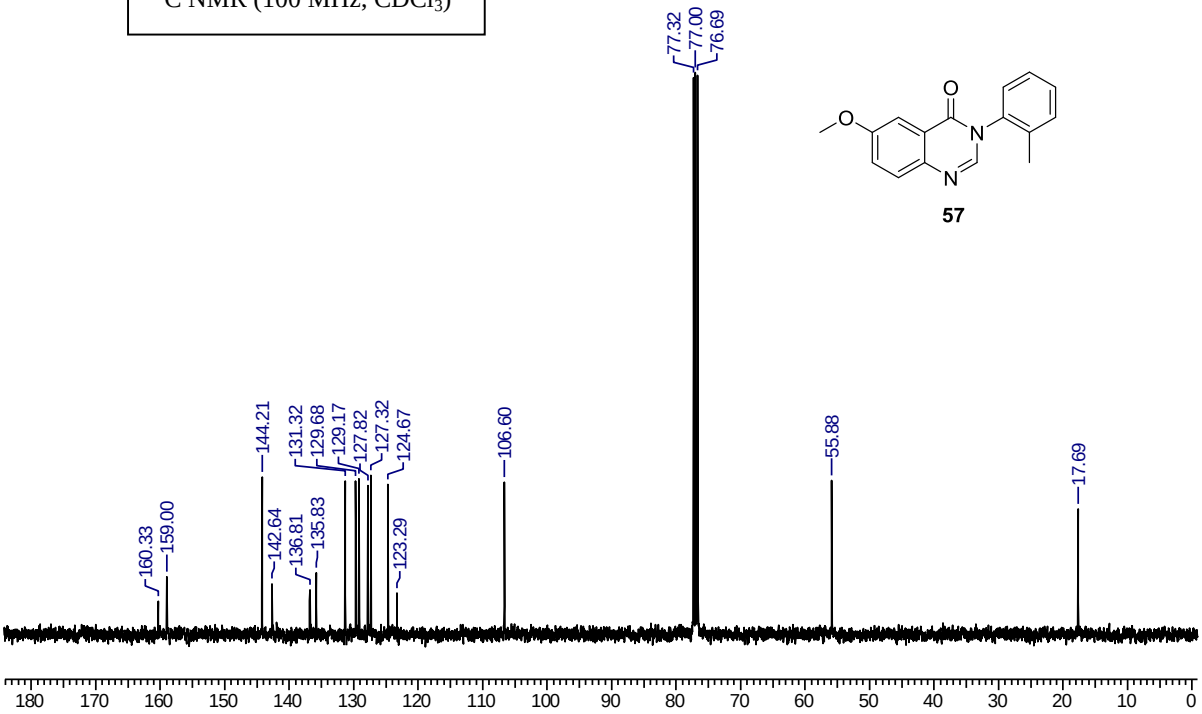
Circumdatin J (**52**)

^{1}H NMR (400 MHz, $CDCl_3$)



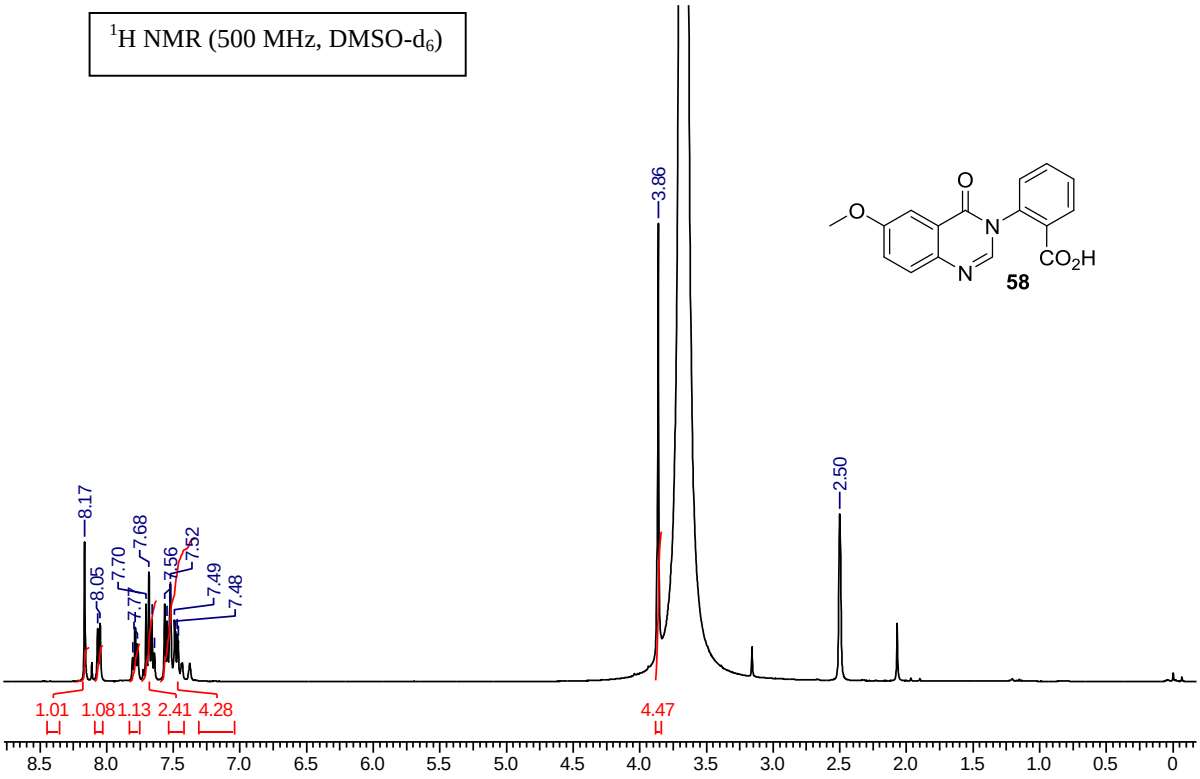
57

^{13}C NMR (100 MHz, $CDCl_3$)



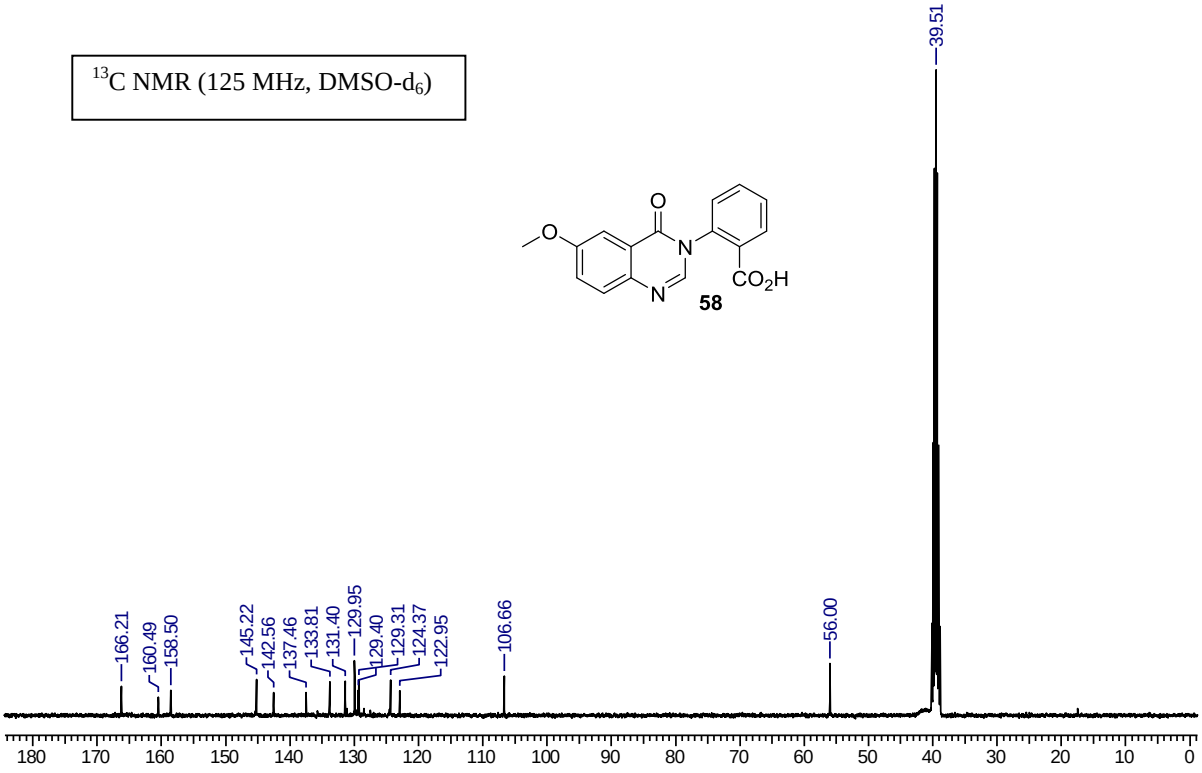
57

^{1}H NMR (500 MHz, DMSO-d_6)



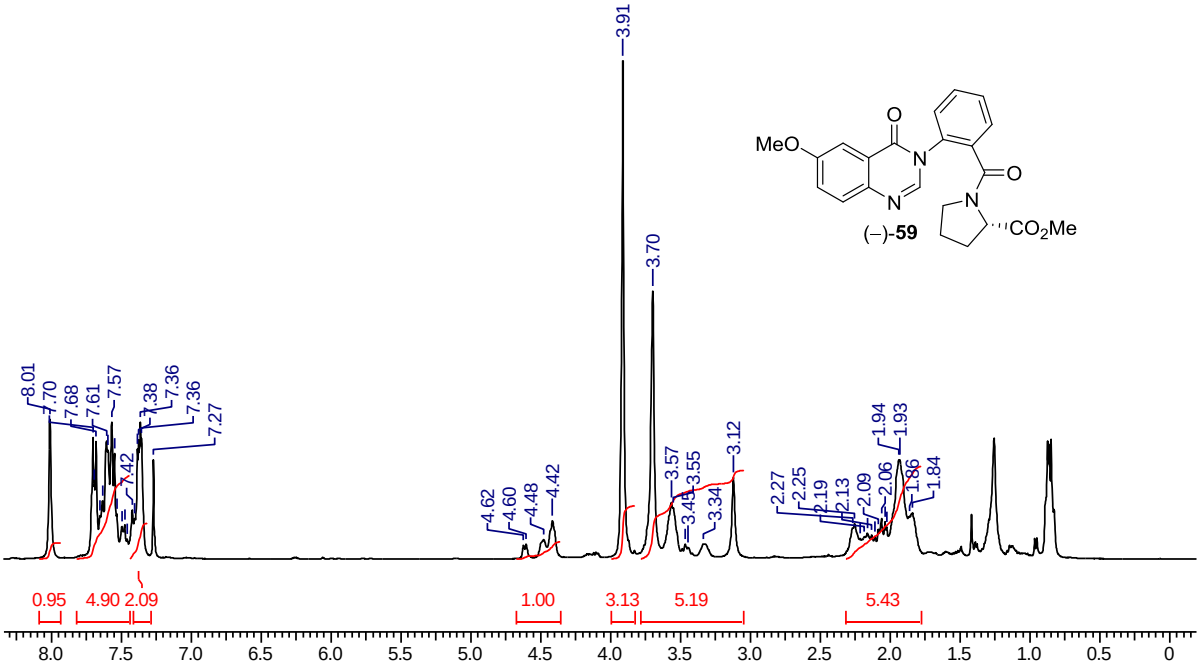
58

^{13}C NMR (125 MHz, DMSO-d_6)

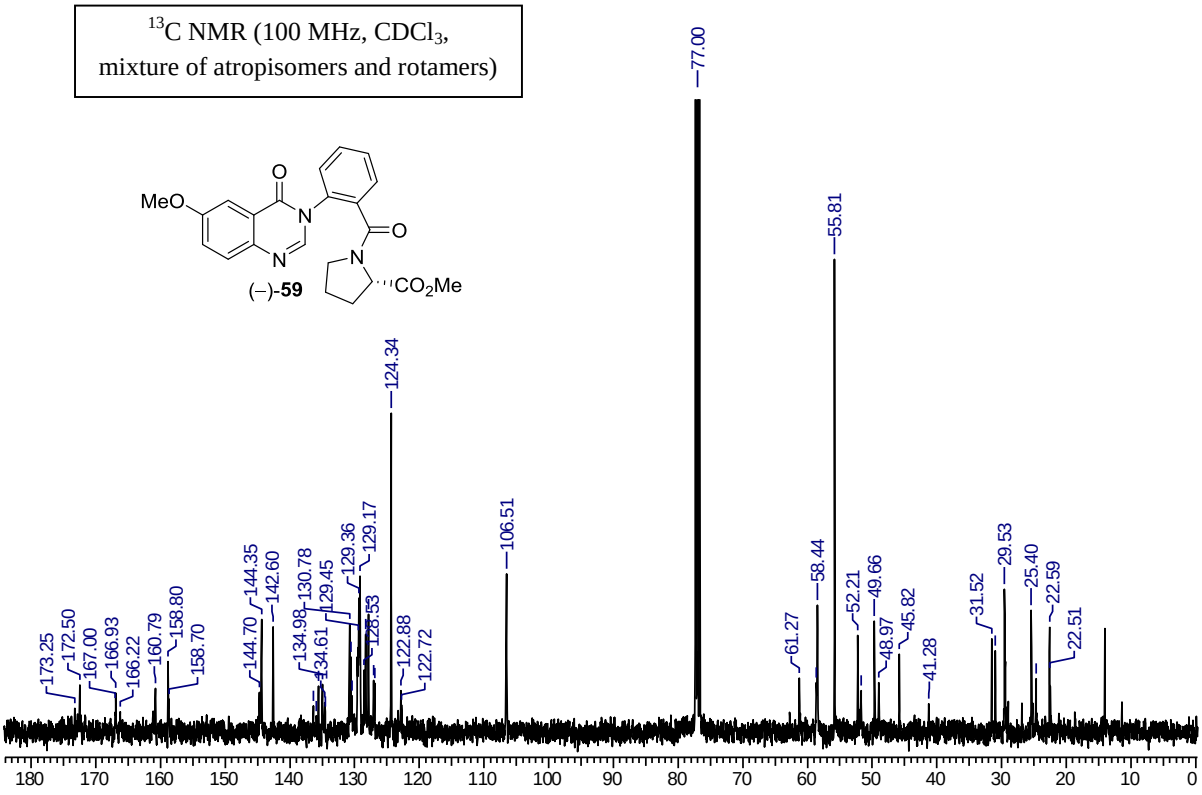


58

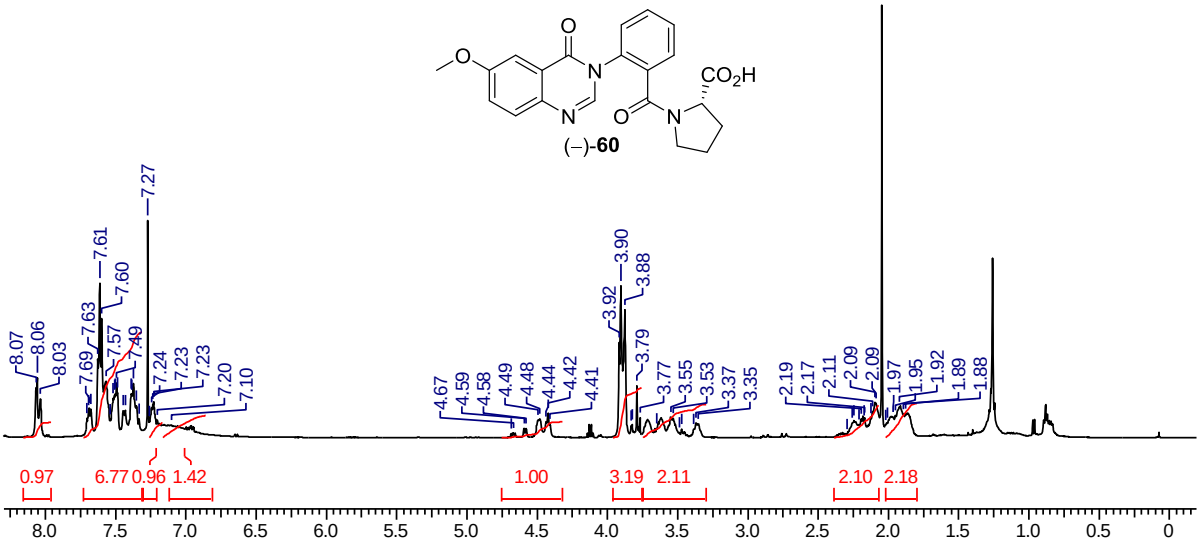
^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



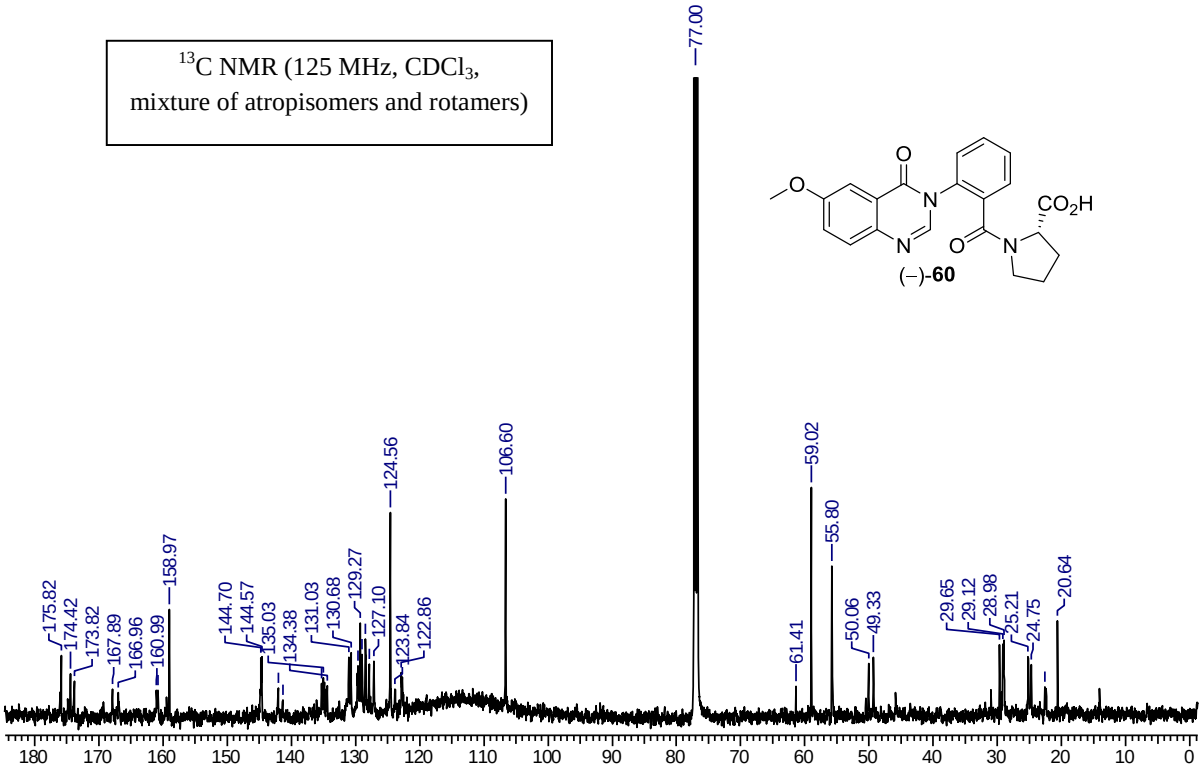
^{13}C NMR (100 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



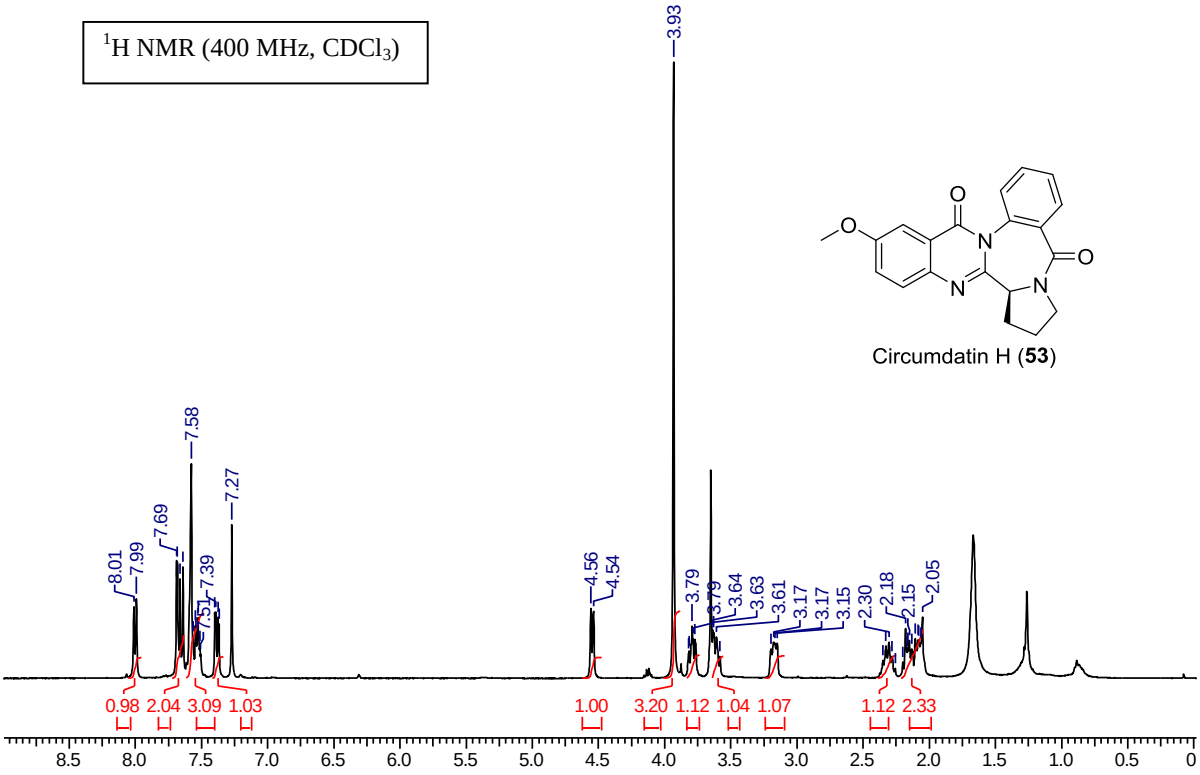
^{1}H NMR (500 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



^{13}C NMR (125 MHz, $CDCl_3$, mixture of atropisomers and rotamers)

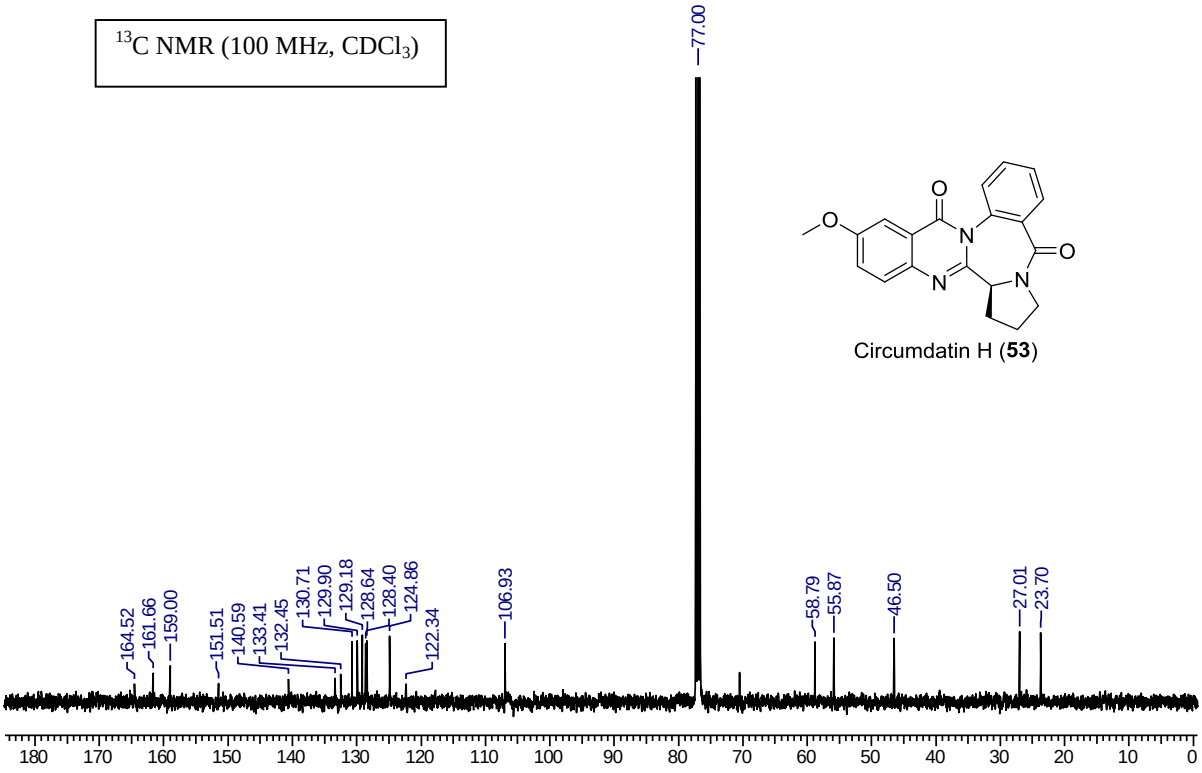


^{1}H NMR (400 MHz, $CDCl_3$)



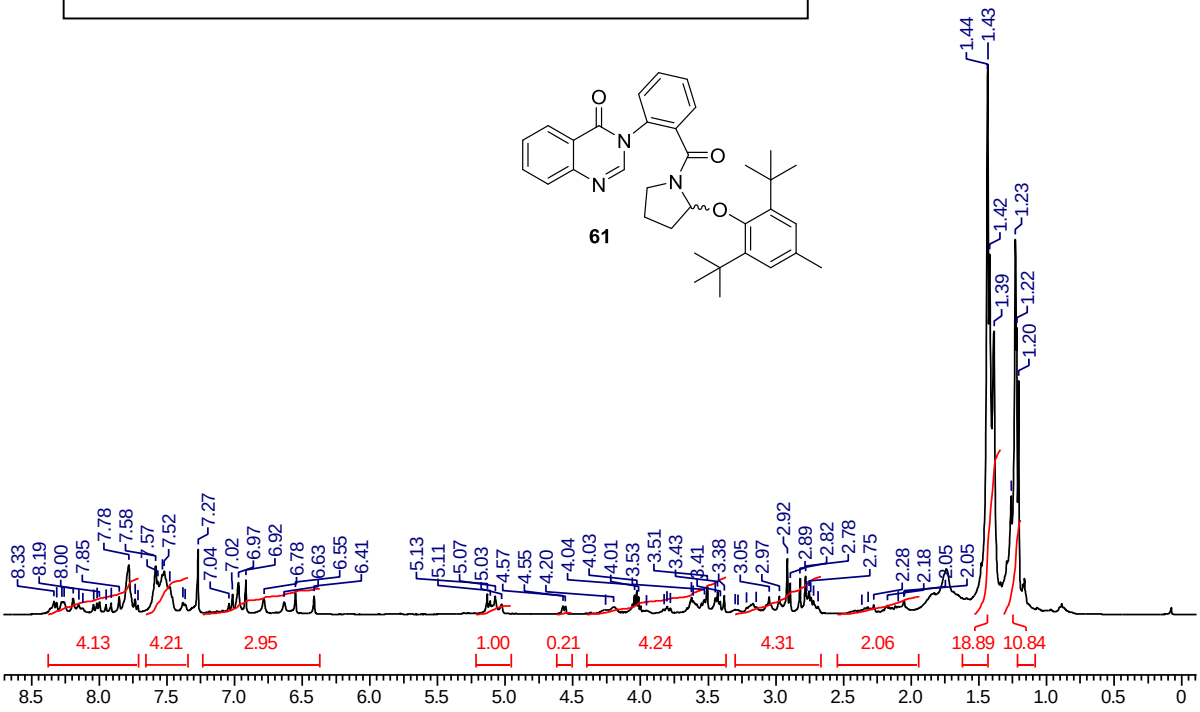
Circumdatin H (**53**)

^{13}C NMR (100 MHz, $CDCl_3$)

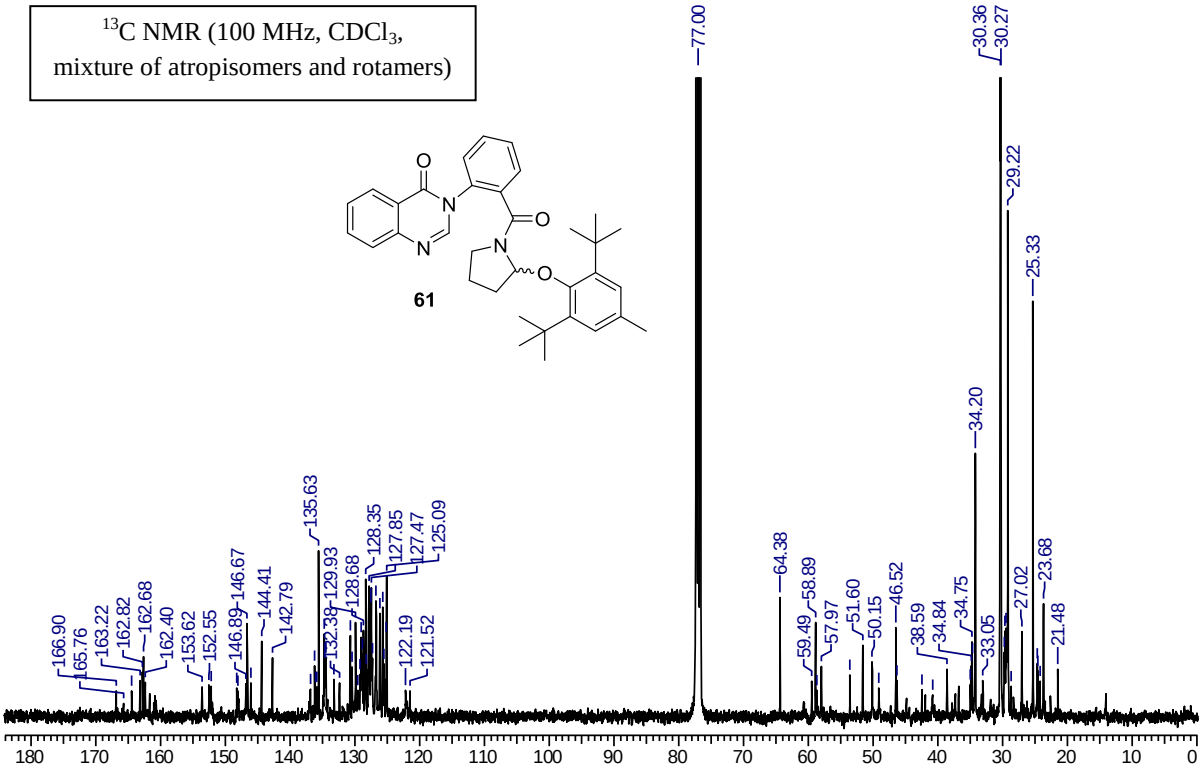


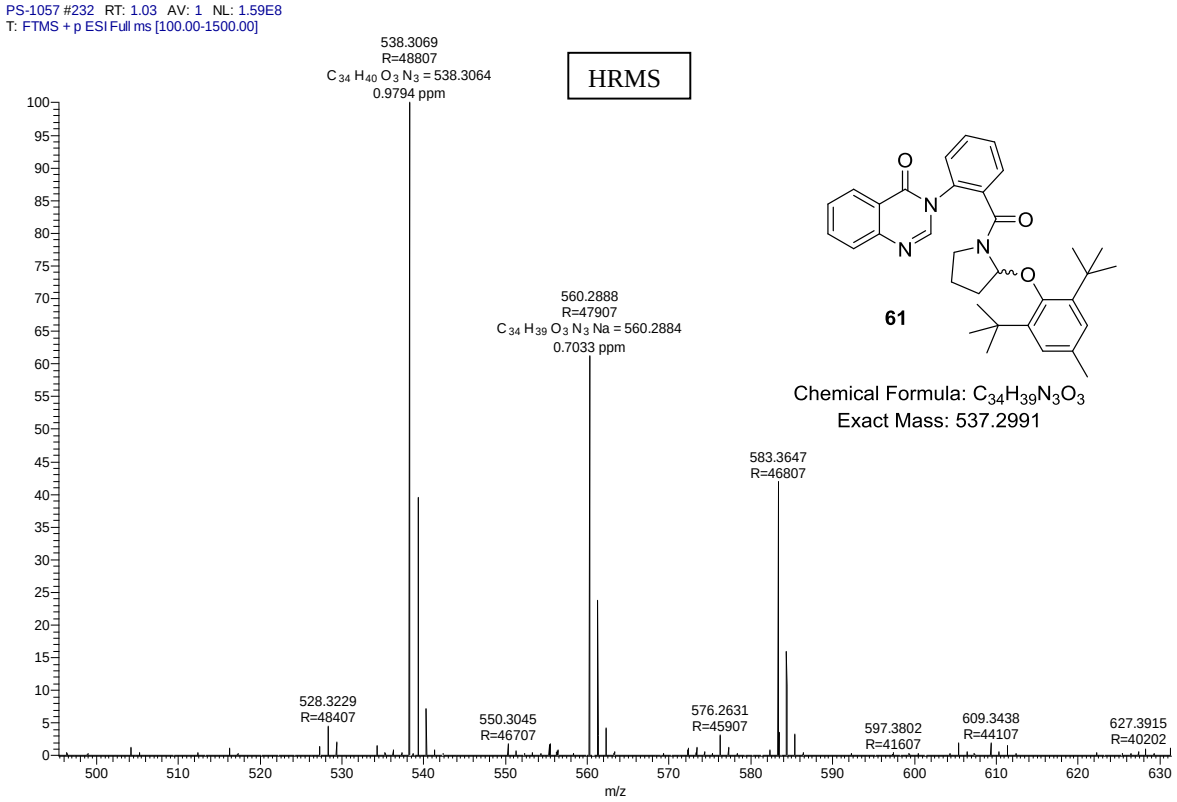
Circumdatin H (**53**)

^{1}H NMR (400 MHz, $CDCl_3$, mixture of atropisomers and rotamers)



^{13}C NMR (100 MHz, $CDCl_3$, mixture of atropisomers and rotamers)

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583.3647
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627.3915
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m/z
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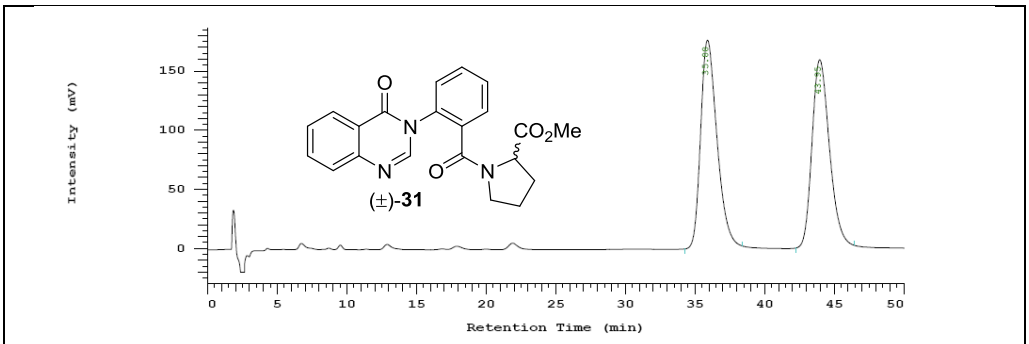
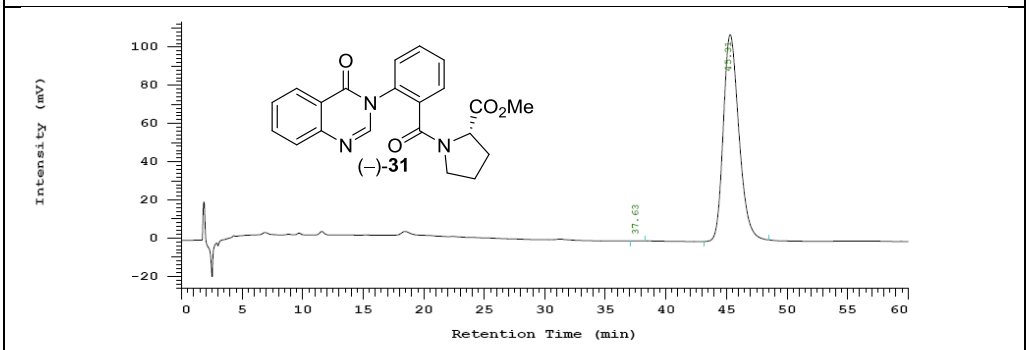
Exact Mass: 537.2991

3.8 Copies of HPLC chromatograms

Column: Chiralpak IA (150 mm x 4.6 mm); **Mobile Ph**: IPA:PE:DEA (10:90:0.25); **Wavelength**: 254 nm; **Flow**: 1.0 ml/min.; Inject vol: 5µl

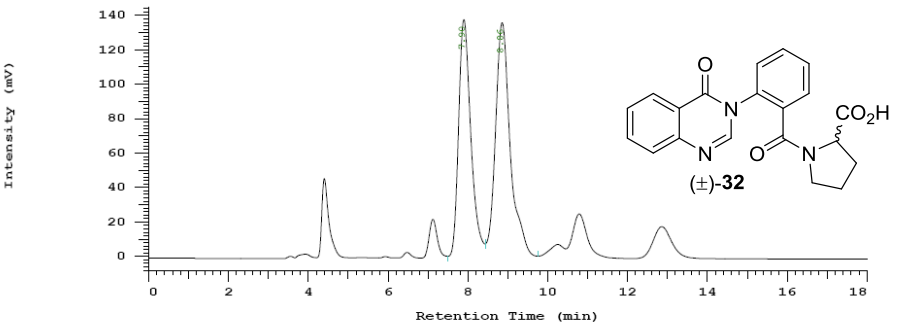


No.	RT	Area	Conc 1	BC
1	35.88	14274494	51.071	BB
2	43.95	13675692	48.929	BB
		27950186	100.000	

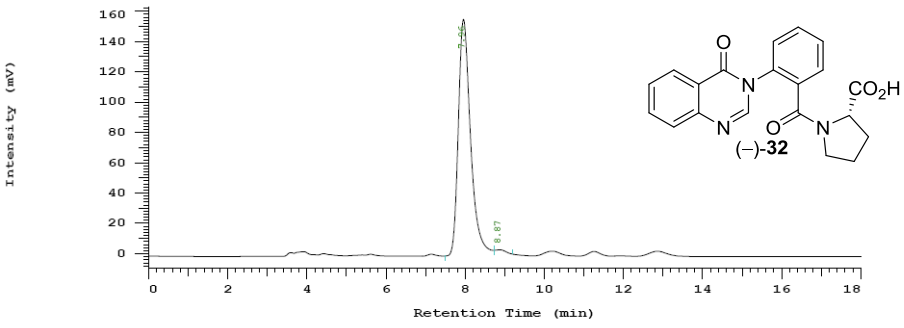


No.	RT	Area	Conc 1	BC
1	37.63	3531	0.037	BB
2	45.31	9613290	99.963	BB
		9616821	100.000	

Column: Chiralcel OD-RH (150 mm x 4.6 mm); **Mobile Ph**: ACN:H_2O:TFA (30:70:0.1); **Wavelength** : 254 nm; **Flow** : 1.0 ml/min.; Inject vol: 2µl



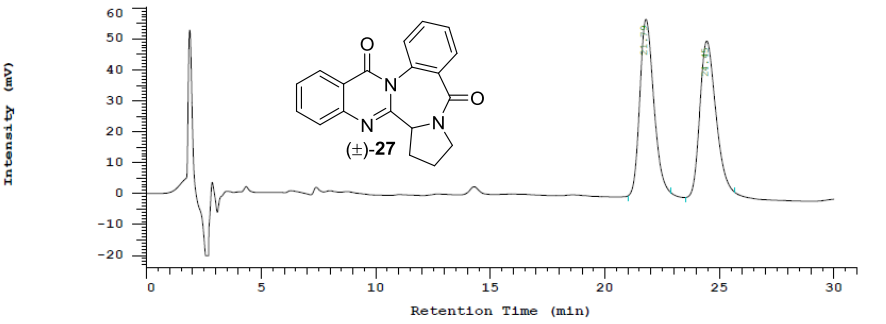
No.	RT	Area	Conc 1	BC
1	7.90	2917961	45.695	BV
2	8.86	3467804	54.305	VB
		6385765	100.000	



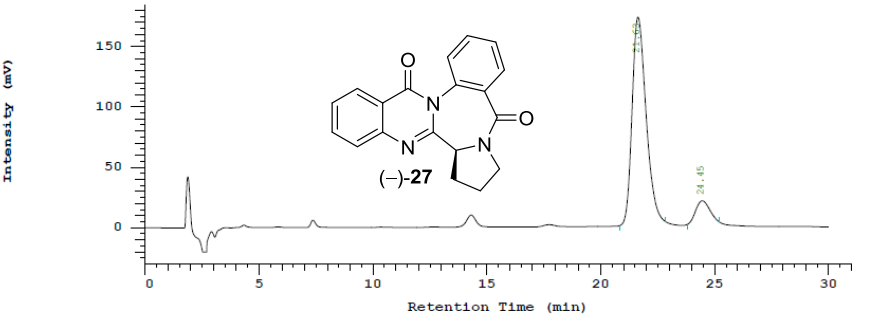
No.	RT	Area	Conc 1	BC
1	7.96	3404778	99.475	BV
2	8.87	17958	0.525	TBB
		3422736	100.000	

Column: Chiralpak IA (150 mm x 4.6 mm); **Mobile Ph**: IPA:PE:DEA (10:90:0.25); **Wavelength**: 254 nm; **Flow**: 1.0 ml/min.; Inject vol: 10µl

(**Table 1, entry 1**)



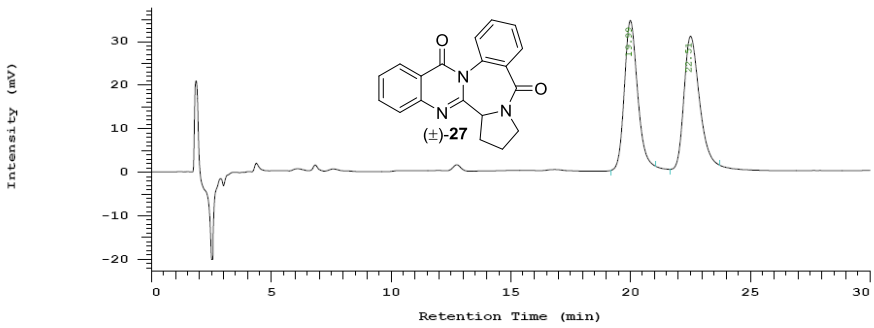
No.	RT	Area	Conc 1	BC
1	21.79	2377289	49.928	BB
2	24.45	2384152	50.072	BB
		4761441	100.000	



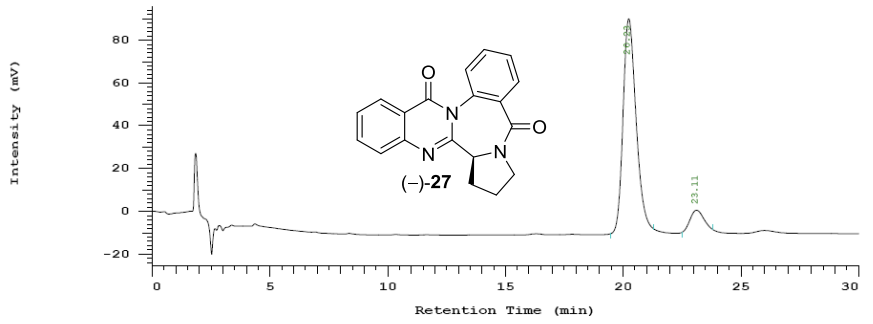
No.	RT	Area	Conc 1	BC
1	21.63	7215189	90.381	BB
2	24.45	767900	9.619	BB
		7983089	100.000	

Column: Chiralpak IA (150 mm x 4.6 mm); **Mobile Ph**: IPA:PE:DEA (10:90:0.25); **Wavelength**: 254 nm; **Flow**: 1.0 ml/min.; Inject vol: 10µl

(HPLC for **1 mmol scale**)

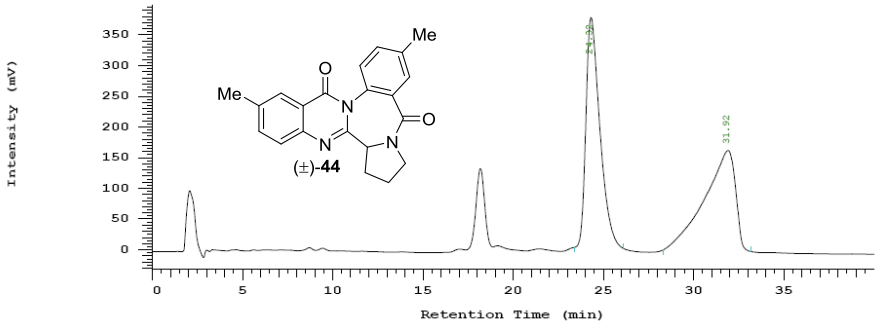


No.	RT	Area	Conc 1	BC
1	19.99	1280071	49.206	BB
2	22.51	1321380	50.794	BB
		2601451	100.000	

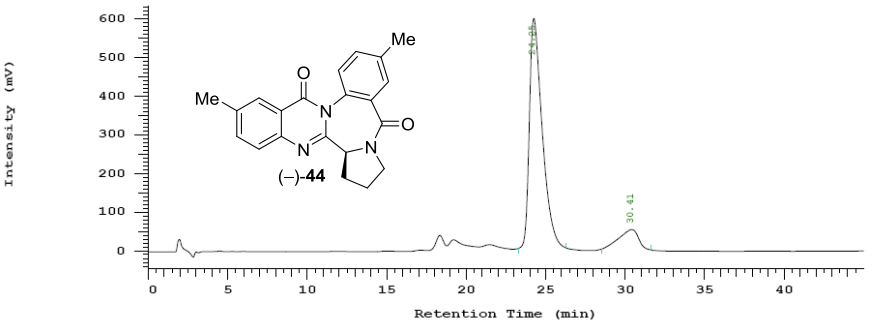


No.	RT	Area	Conc 1	BC
1	20.23	3778742	91.046	BB
2	23.11	371617	8.954	BB
		4150359	100.000	

Column: Chiralpak IA (150 mm x 4.6 mm); **Mobile Ph**: IPA:PE:DEA (10:90:0.25); **Wavelength**: 254 nm; **Flow**: 1.0 ml/min.; Inject vol: 10µl

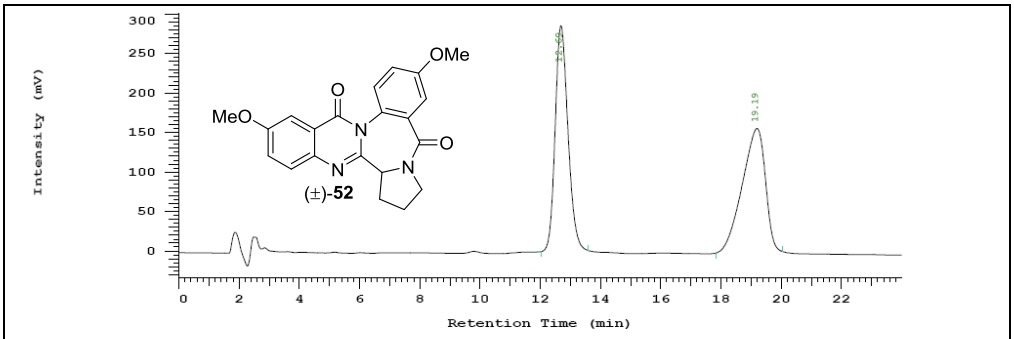


No.	RT	Area	Conc 1	BC
1	24.32	20095587	50.831	BB
2	31.92	19438758	49.169	BB
		39534345	100.000	

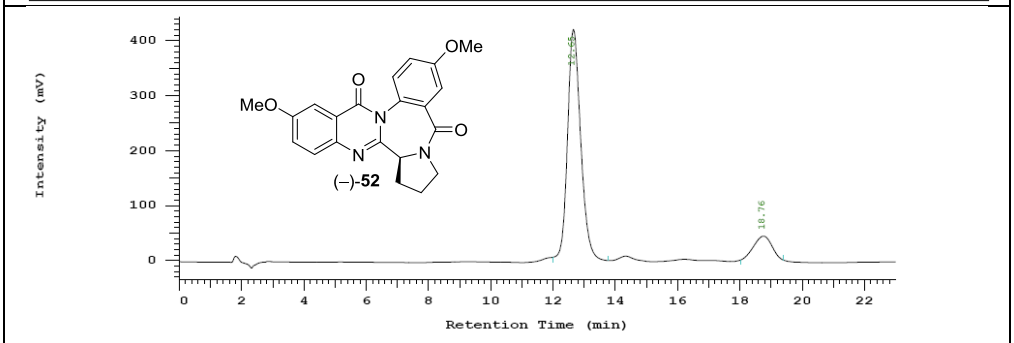


No.	RT	Area	Conc 1	BC
1	24.25	32894704	88.191	BB
2	30.41	4404542	11.809	BB
		37299246	100.000	

Column: Chiralpak IA (150 mm x 4.6 mm); **Mobile Ph**: IPA:PE:DEA (20:80:0.25); **Wavelength**: 254 nm; **Flow** : 1.0 ml/min.; Inject vol: 5µl

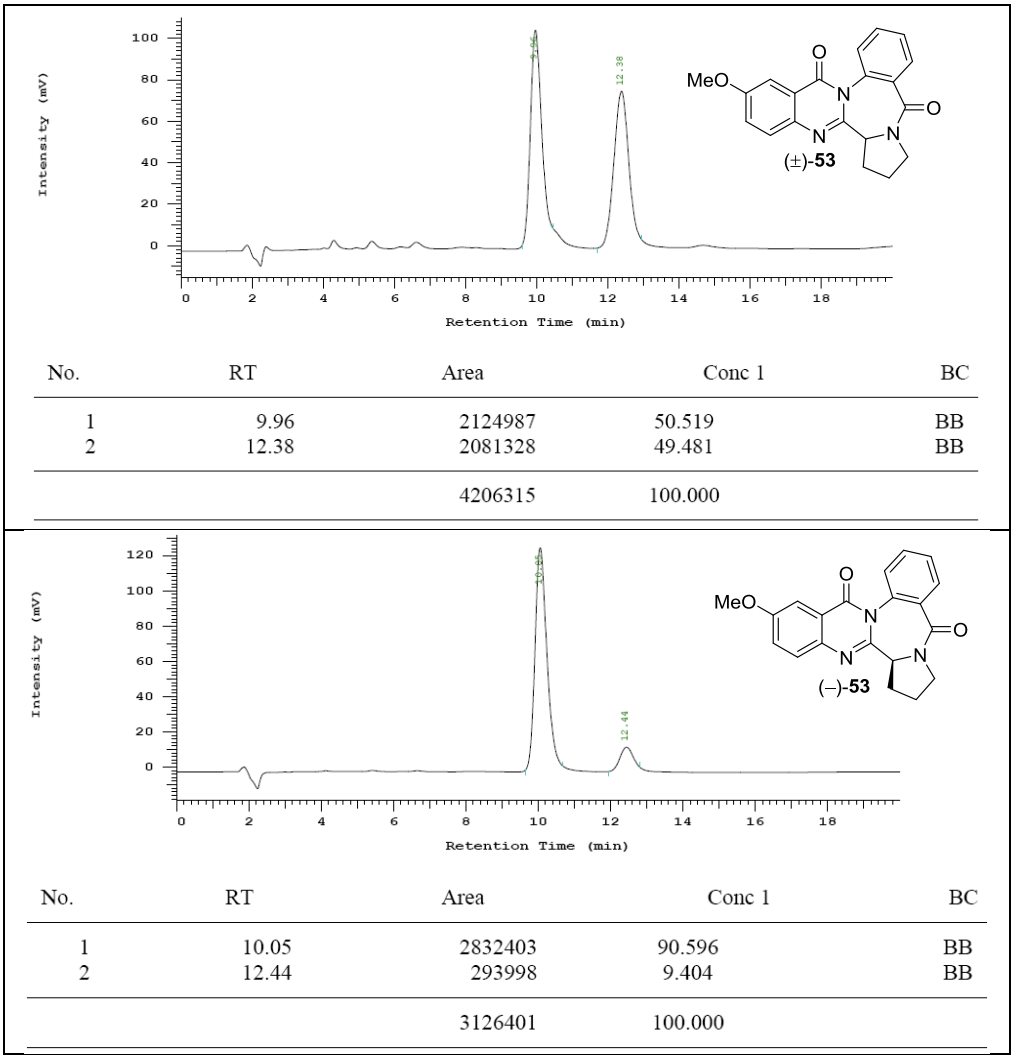


No.	RT	Area	Conc 1	BC
1	12.69	8384665	50.177	BB
2	19.19	8325366	49.823	BB
		16710031	100.000	



No.	RT	Area	Conc 1	BC
1	12.65	12075171	87.328	BB
2	18.76	1752282	12.672	BB
		13827453	100.000	

Column: Chiralpak IA (150 mm x 4.6 mm); **Mobile Ph**: IPA:PE:DEA (30:70:0.25); **Wavelength**: 254 nm; **Flow** : 1.0 ml/min.; Inject vol: 5µl

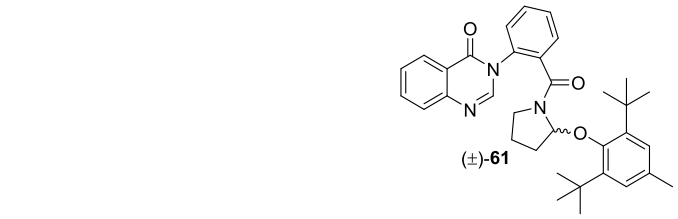


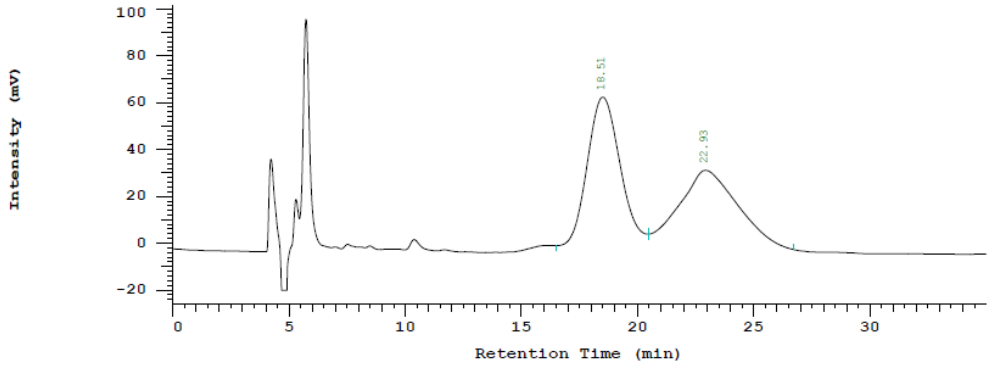
No.	RT	Area	Conc 1	BC
1	9.96	2124987	50.519	BB
2	12.38	2081328	49.481	BB
		4206315	100.000	

No.	RT	Area	Conc 1	BC
1	10.05	2832403	90.596	BB
2	12.44	293998	9.404	BB
		3126401	100.000	

Column: Kromasil 5-AmyCoat (250 mm x 4.6 mm); **Mobile Ph**: IPA:n-hexane:TFA(20:80:0.1);

Wavelength: 220 nm; **Flow**: 0.7 ml/min; Inject vol: 5µl





No.	RT	Area	Conc 1	BC
1	18.51	6240196	51.445	BV
2	22.93	5889691	48.555	VB
		12129887	100.000	

List of publications

1. Achmatowicz Reaction: A Versatile Tool in Bioactive Natural Products Synthesis (comprehensive review)
   Mahajan, **P. S.**; Humne, V. T.; Mhaske, S. B. *Curr. Org. Chem.* **2017**, *21*, 503.

2. Protecting-Group-Free Diastereoselective Total Synthesis of (±)-6-*epi*-Cleistenolide and Chemoenzymatic Synthesis of (–)-6-*epi*-Cleistenolide
   Mahajan, **P. S.**; Gonnade, R. G.; Mhaske, S. B. *Eur. J. Org. Chem.* **2014**, 8049.

3. Ammonium persulfate activated DMSO as a one-carbon synthon for the synthesis of methylenebisamides and other applications
   Mahajan, **P. S.**; Tanpure, S. D.; More, N. A.; Gajbhiye, J. M.; Mhaske, S. B. *RSC Adv.* **2015**, *5*, 101641.

4. Radical Beckmann Rearrangement and Its Application in the Formal Total Synthesis of Antimalarial Natural Product Isocryptolepine via C–H Activation
   Mahajan, **P. S.**; Humne, V. T.; Tanpure, S. D.; Mhaske, S. B. *Org. Lett.* **2016**, *18*, 3450.

5. Silver-Mediated Oxidative Decarboxylative Intramolecular Asymmetric Radical Cyclization (Csp^3–Csp^2) via Memory of Chirality: Access to Circumdatin Alkaloids
   Mahajan, **P. S.**; Mhaske, S. B. *Org. Lett.* **2018**, *20*, 2092.

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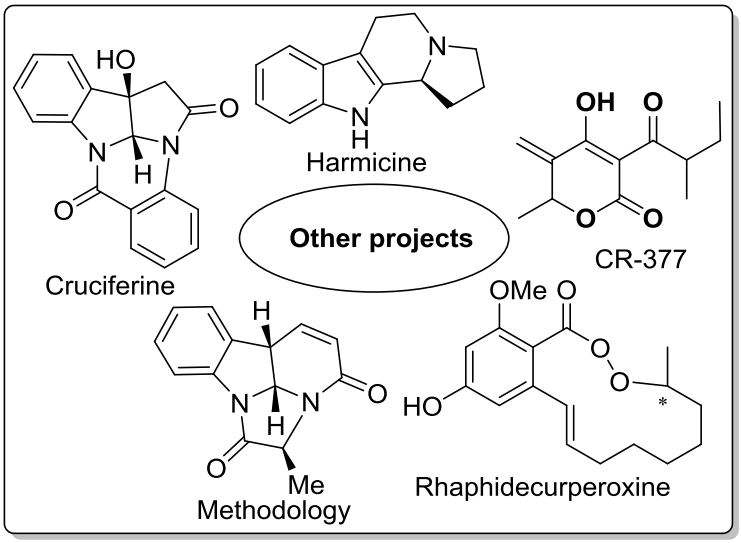
6. A Switch-On NIR Probe for Specific Detection of Hg^{2+} Ion in Aqueous Medium and in Mitochondria.
   Agarwalla, H.; **Mahajan**, **P. S.**; Sahu, D.; Taye, N.; Ganguly, B.; Mhaske, S. B.; Chattopadhyay, S.; Das, A. *ACS Inorg. Chem.* **2016**, *55*, 12052.

7. Malonic Ester Amide Synthesis: An Efficient Methodology for Synthesis of Amides
   Mahajan, **P. S.**; Mahajan, J. P.; Mhaske, S. B. *Synth. Commun.* **2013**, *43*, 2508.

8. Novel hybrids of Fluconazole and Furanones: Design, synthesis and antifungal activity
   Borate, H. B.; Sawargave, S. P.; Chavan, S. P.; Chandavarkar, M. A.; Iyer, R.; Tawte, A.; Rao, D.; Deore, J. V.; Kudale, A. S.; **Mahajan**, **P. S.**; Kangire, G. S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4873.

Miscellaneous



Natural products synthesis is at certain stages, will be credited upon completion.