A Thesis Entitled

SYNTHETIC STUDIES IN SELECTED HETEROCYCLIC COMPOUNDS

Submitted to Goa University for the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMISTRY

By

Ms. DURGA PANDHARINATH KAMAT

M. Sc.

Under the Guidance of

PROF. VIJAYENDRA P. KAMAT

Department of Chemistry

and

PROF. SANTOSH G. TILVE

Department of Chemistry

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DEPARTMENT OF CHEMISTRY

CERTIFICATE

This is to certify that the thesis entitled, "**Synthetic Studies in Selected Heterocyclic Compounds**" submitted by Ms. **DURGA PANDHARINATH KAMAT**, is a record of research work carried out by the candidate during the period of study under our supervision and that it has not previously formed the basis for the award of any degree or diploma or other similar titles.

Goa University
October 2017

Prof. Vijayendra P. Kamat
Research Guide
Department of Chemistry
Goa University

Prof. Santosh G. Tilve
Research Guide
Department of Chemistry
Goa University

DECLARATION

I hereby declare that the work embodied in the thesis entitled "**Synthetic Studies in Selected Heterocyclic Compounds**" is the result of investigations carried out by me under the guidance of **PROF. VIJAYENDRA P. KAMAT** and **PROF. SANTOSH G. TILVE** at Department of Chemistry, Goa University and that it has not previously formed the basis for the award of any degree or diploma or other similar titles.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Goa University
October 2017

Ms. Durga P. Kamat
Ph.D. Student
Department of Chemistry
Goa University

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Finally with silent words I thank all mighty for granting me good health and strength needed at every stage of my life.


..... Ms. Durga P. Kamat


Dedicated to
my
beloved parents

TABLE OF CONTENT

GENERAL REMARKS

1) The compound numbers, figure numbers, scheme numbers and reference numbers given in each chapter refer to that particular chapter only.

2) All melting points and boiling points were recorded using Thiele's tube and are uncorrected.

3) Commercial reagents were used without further purification.

4) All solvents were distilled prior to use and then dried using standard procedure.

5) All reagents were prepared using literature methods.

6) Chromatographic purification was conducted by column chromatography using silica gel (60 – 120 mesh size) or by flash chromatography using silica gel (200-400 mesh size).

7) Thin layer chromatography (TLC) was carried out on silica gel 60 F254 aluminium plates purchased from Merck.

8) The IR spectra were recorded on Shimadzu FT-IR spectrophotometer.

9) ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Brucker AVANCE 400 instrument and the multiplicities of carbon signals were obtained from DEPT experiment (^{1}H NMR (300 MHz) spectrum was also recorded on a Brucker AVANCE 300 instrument). Chemical shifts are expressed in δ relative to tetramethylsilane (TMS) which is expressed in ppm.

10) The high resolution mass spectra (HRMS) were recorded on MicroMass ES- QTOF mass spectrometer.

11) The absorbance values were obtained from UV-Vis spectrophotometer (Shimadzu-1800) at 517 nm.

DEFINITION OF ABBREVIATIONS

General Abbreviations

g	Gram/s	*dr*	Diastereomeric ratio
mg	Milligram/s	conc.	Concentrated
µg	Microgram/s	aq.	Aqueous
mol	Mole/s	*o*	Ortho
mmol	Millimole/s	*m*	Meta
mL	Milliliter/s	*p*	Para
mm	Millimeter/s	*MS*	Molecular sieves
nm	Nanometre/s	*psi*	Pounds per square inch
m.p.	Melting point	*cat.*	Catalytic
b.p.	Boiling point	*atm.*	Atmospheric
ev	Electron volt	*et al.*	Et alia (and others)
lit.	Literature	TLC / tlc	Thin layer chromatography
d	Day/s	sat.	Saturated
h	Hour/s	MW	Microwave
min	Minute/s	anhyd.	Anhydrous
µM	Micromolar	°C	Degree Celcius
nM	Nanomolar	rt	Room temperature
ppm	Parts per million	*Z*	Zussamen (together)
hv	Irradiation	*E*	Eentegegen (opposite)
%	Percentage	equiv.	Equivalent
R	Rectus	W/W	Weight per unit weight
S	Sinister	Å	Ångström
ee	Enantiomeric excess	RCM	Ring Closing Metathesis

Compound Abbreviations

Ac	Acetyl	binap	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
AcOH	Acetic acid	BMIM	1-Butyl-3-methyimidazolium
Ac_2O	Acetic anhydride	Bn	Benzyl
acac	Acetylacetone	BnBr	Benzyl bromide
AIBN	2,2′-azobisisobutyronitrile	Boc	*t*-butyloxycarbonyl
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)	Boc_2O	Di-*t*-butyl dicarbonate
$BF_3.OEt_2$	Boron trifluoride diethyl etherate	bpy	2,2″-bipyridyl

Bu, *n*-Bu	normal (primary) Butyl	DME	Dimethoxyethane
t-Bu	*t*-Butyl	DMF	*N*,*N*-Dimethylformamide
n-BuLi	*n*-Butyl lithium	DMP	Dess–Martin periodinane
t-BuLi	*t*-Butyl lithium	DMS	Dimethyl sulfide
t-BuOH	*t*-Butyl alcohol	DMSO	Dimethyl sulfoxide
CF_3SO_3H	Triflic acid	DPPH	2,2-diphenyl-1-picrylhydrazyl
CH_3SO_3H	Methane sulfonic acid	dppf	1,1'-bis(diphenylphosphanyl)ferrocene
COD	Cycloocta-1,5-diene	EDCl	1-Ethyl-3-(3dimethylamino-propyl)-carbodiimide
m-CPBA	*m*-Chloroperbenzoic acid	EtOAc	Ethyl acetate
$Cu(OTf)_2$	Copper(II) trifluoromethanesulfonate	EtOH	Ethanol
CuTc	Copper(I)thiophene-2-carboxylate	Et_2O	Diethyl ether
Cy	Cyclohexyl	Et_3N	Triethylamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	Et_2Zn	Diethyl zinc
o-DCB	*o*-Dichlorobenzene	HMPA	Hexamethylphosphoramide
DCC	Dicyclohexylcabodiimide	HOBt	Hydroxybenzotriazole
DCM	Dichloromethane	KO*t*-Bu	Potassium *t*-butoxide
DCE	1,2-Dichloroethane	LAH	Lithium aluminium hydride
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone	LDA	Lithium diisopropylamide
N,*N*-DEA	*N*,*N*-Diethylaniline	LiHMDS	Lithium hexamethyldisilazide
DEMS	Diethoxymethylsilane	LTB	Lithium *t*-butoxide
DIAD	Diisopropyl azodicarboxylate	$MeNO_2$	Nitromethane
DIBALH	Diisobutylaluminum hydride	MEPY	Methylpyridine
DIPEA	*N*,*N*-Diisopropylethylamine	MOM	Methoxymethyl ether
DMAP	4-Dimethylaminopyridine	MTBE	Methyl *t*-butyl ether

NaHMDS	Sodium bis(trimethylsilyl)amide	TBSCl	*t*-Butyldimethylsilyl chloride
NBS	*N*-Bromosuccinimide	THF	Tetrahydrofuran
NCS	*N*-Chlorosuccinimide	TFA	Trifluoro acetic acid
n-Non	*n*-Nonyl	Tf_2NPh	*N*-Phenyl-bis(trifluoromethanesulfonimide)
n-Pr	*n*-Propyl	TTFA	Thenoyl trifluoro acetone
PCC	Pyridinium chlorochromate	TFAA	Trifluoro acetic anhydride
PCy_3	Tricyclohexylphosphine	TMEDA	Tetramethylethylenediamine
Pd/C	Palladium on activated charcoal	TMS	Tetramethylsilane
Ph_2O	Diphenyl ether	TsCl	Tosyl chloride
$P(OEt)_3$	Triethylphosphite	*p*-TsOH	*p*-Toluene sulfonic acid
$P(o\text{-tol})_3$	Tri(*o*-tolyl)phosphine	TBDMS	*t*-Butyldimethylsilyl
PPA	Polyphosphoric acid	TBSOTf	*t*-Butyldimethylsilyl trifluoromethanesulfonate
PPh_3	Triphenylphosphine	TMSCl	Trimethylsilyl chloride
PinBH	Pinacolborane	TMSOTf	Trimethylsilyl trifluoromethanesulfonate
PBu_3	Tributylphosphine	$Yb(OTf)_3$	Ytterbium(III) trifluoromethanesulfonate
TBAF	Tetra-*n*-butylammonium fluoride	$Sm(OTf)_3$	Samarium(III) trifluoromethanesulfonate

Spectroscopic Abbreviations

IR	Infrared	ppm	Parts per million
υ_{max}	Frequency maximum	δ	Delta (Chemical shift in ppm)
cm^{-1}	Frequency in wavenumber	MHz	Megahertz
UV	Ultra violet	Hz	Hertz
NMR	Nuclear magnetic resonance	s	Singlet
$CDCl_3$	Deuterated chloroform	d	Doublet
DMSO-d_6	Deuterated dimethyl sulfoxide	t	Triplet
acetone-d6	Deuterated acetone	q	Quartet

m	Multiplet	*J*	Coupling constant
dd	Doublet of doublet	DEPT	Distortionless Enhancement by Polarization Transfer
td	Triplet of a doublet	NOESY	Nuclear Overhauser effect spectroscopy
dt	Doublet of a triplet	HRMS	High Resolution Mass Spectrometry
br s	Broad singlet	HSQC	Heteronuclear single quantum correlation
M^+	Molecular ion	HMBC	Heteronuclear multiple bond correlation
m/z	Mass to charge ratio	HPLC	High performance liquid chromatography

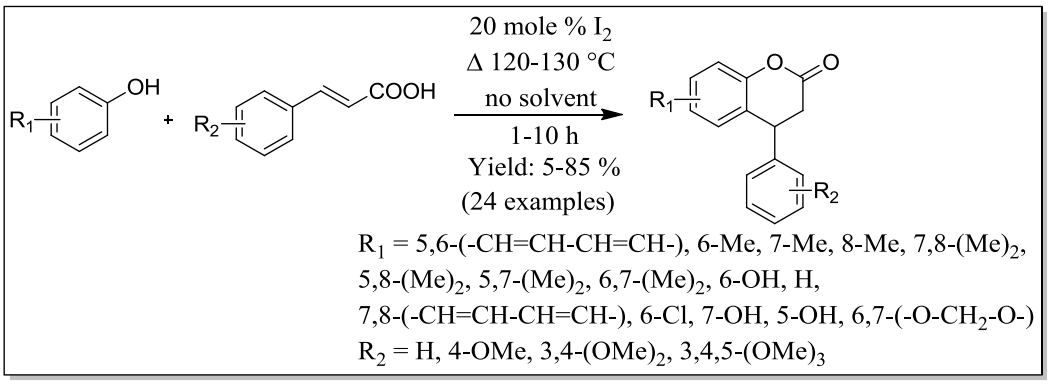
ABSTRACT OF THESIS

TITLE: **SYNTHETIC STUDIES IN SELECTED HETEROCYCLIC COMPOUNDS**

Heterocyclic chemistry is one of the most rewarding, applied branches of organic chemistry, as a result of which, a great endeavour of scientific research is devoted to this field. The present thesis is devoted to the development of a mild method for the synthesis of 4-phenyl-chroman-2-ones and synthesis of naturally occurring carbazole alkaloids which are of significant biological importance.

The first chapter provides a comprehensive review on the various synthetic methodologies employed for the synthesis of chroman-2-ones. Literature pertaining to the natural occurrence and the biological activities is also briefly described. The further synthetic applications of chroman-2-ones leading to generation of important building blocks, essentially naturally occurring and/or biologically active moieties are mostly included within this classification wherever possible.

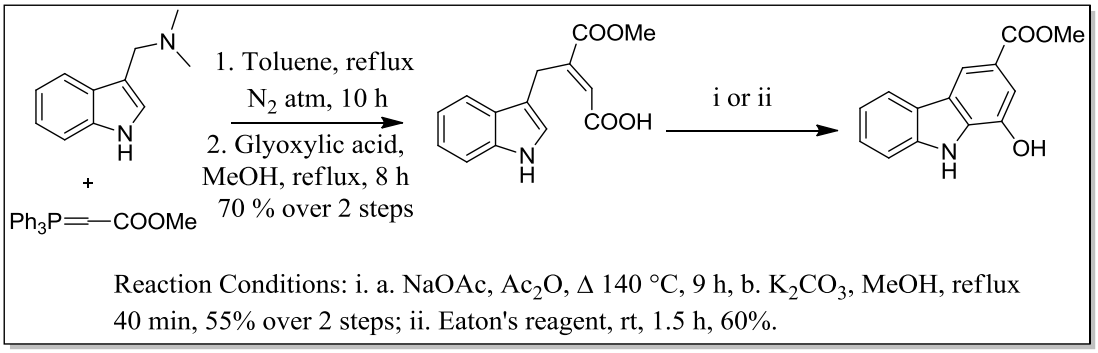
The second chapter describes a green protocol for the synthesis of 4-phenyl-chroman-2-ones *via* the [3+3] cyclocoupling of phenols with cinnamic acids using molecular iodine as a catalyst at 120-130 °C under solvent free conditions *(Scheme I)*. The reaction occurred *via* a tandem esterification-hydroarylation process in presence 20 mol % iodine. Furthermore, attempts to extend the iodine catalysed protocol towards the synthesis of naturally occurring 4-phenyl-chroman-2-one, Vittarin F are also included.



Scheme I

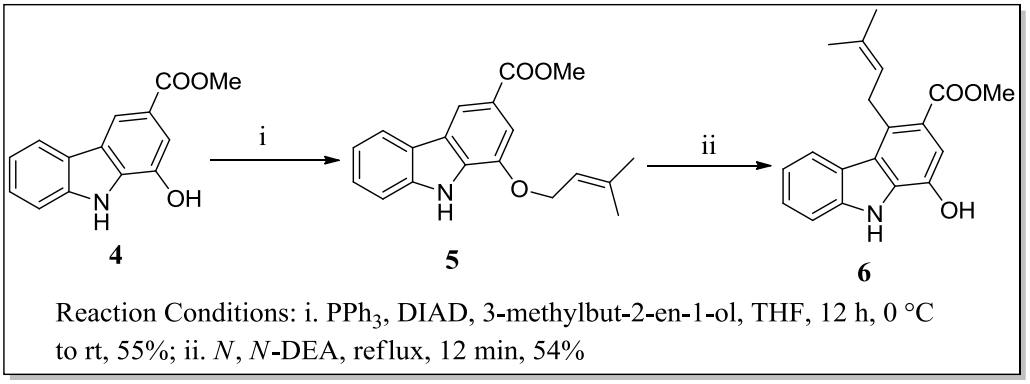
The third chapter deals with the total synthesis of various naturally occurring tricyclic 1-oxygenated carbazole alkaloids and a formal synthesis of naturally occurring furocarbazole alkaloid. This chapter presents a concise three step method for the

synthesis of clausine E, starting from gramine, employing Wittig reaction and annulation as the key steps *(Scheme II)*. Initially, the annulation step was carried out using sodium acetate in refluxing acetic anhydride followed by treatment with potassium carbonate in methanol. Further optimization of the annulation step is presented which showed that the use of Eaton's reagent helped in decreasing the reaction time and improving the product yield.



Scheme II

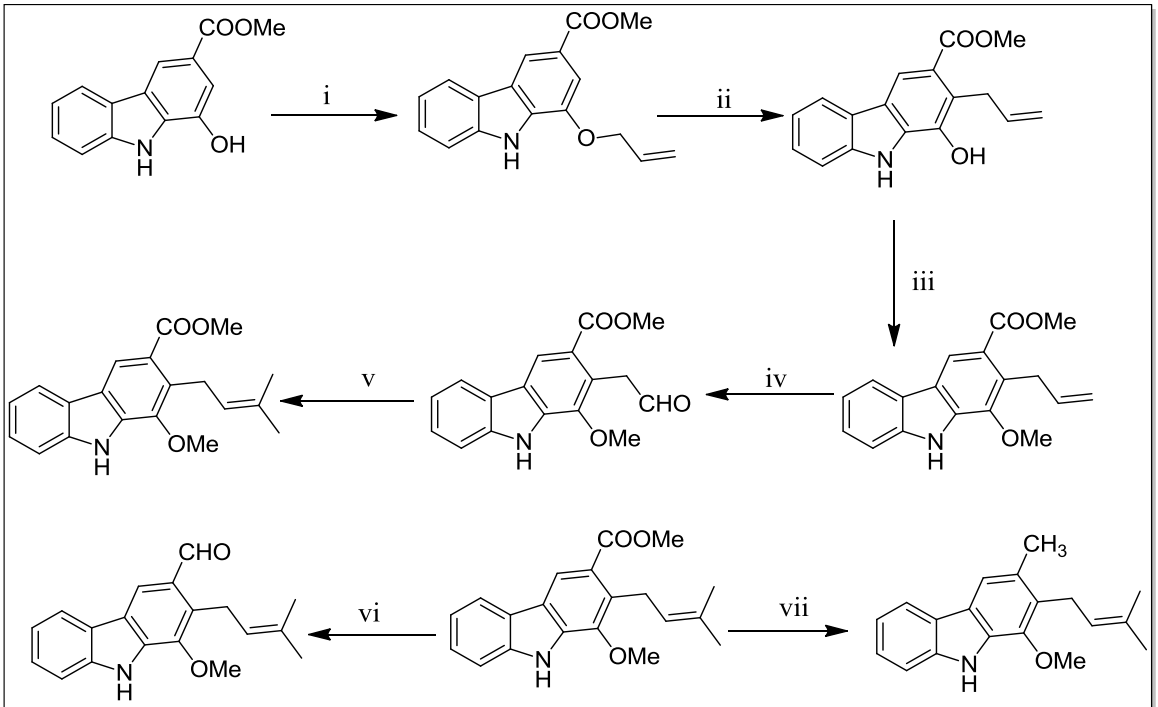
This chapter also describes the synthesis of clausine F, clausenaline D, indizoline and clausenapin starting from clausine E. Clausine F was synthesized from clausine E using Mitsunobu reaction and *p*-Claisen rearrangement as the crucial steps *(Scheme III)*.



Scheme III

A formal synthesis of clausenaline D was accomplished through methyl 1-acetoxy-9-acetyl-2-allyl-9*H*-carbazole-3-carboxylate. This carbazole intermediate was synthesized starting from clausine E *via* *O*-allylation followed by *o*-Claisen rearrangement in refluxing *o*-dichlorobenzene and acetylation with sodium acetate in acetic anhydride. The desired carbazole intermediate was also synthesized directly from *O*-allylation product of clausine E by refluxing with sodium acetate in acetic anhydride, involving a one pot *o*-Claisen rearrangement and acetylation sequence.

A rapid entry into indizoline and clausenapin was established through the elaboration of a common intermediate, methyl 1-methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carboxylate involving transformation of the ester function. This intermediate was synthesized from clausine E using allylation, *o*-Claisen rearrangement, methylation, oxidative cleavage of the terminal double bond and Wittig olefination as the key steps *(Scheme IV)*.



Reaction conditions: i. K_2CO_3, acetone, allyl bromide, reflux, 2 h, 71%; ii. *o*-DCB, reflux, 45 min, 75%; iii. K_2CO_3, acetone, MeI, rt, 2 h, 89%; iv. OsO_4, $NaIO_4$,THF:H_2O (3:1), 0 °C-rt, 10 h, 70%; v. triphenylphosphonium isopropyl iodide, NaHMDS, THF -10 °C-rt, 1 h, 70%; vi. a. LAH, THF, rt, 2 h, b. DMP, DCM, 0 °C, 0.5 h, 78%; vii. LAH, DCM:Et_2O (1:1), rt, 5 h, 75%.

Scheme IV

This chapter also deals with the evaluation of selected carbazoles having phenolic hydroxyl group, for their possible potential to antioxidant action by DPPH radical scavenging method. Clausine E, 1-hydroxy-9*H*-carbazole-3-carboxylic acid, methyl 2-allyl-1-hydroxy-9*H*-carbazole-3-carboxylate and clausine F were used as the test compounds. Of these, 1-hydroxy-9*H*-carbazole-3-carboxylic acid demonstrated the highest antioxidant activity.

LIST OF PUBLICATIONS

Journal articles:

1. D. P. Kamat, S. G. Tilve and V. P. Kamat, Solvent-free synthesis of 4-aryl-3,4-dihydrobenzopyran-2-ones *via* [3+3] cyclocoupling of phenols with cinnamic acid catalyzed by molecular iodine; *Tetrahedron Lett.* **2012**, 53, 4469-4472.
https://doi.org/10.1016/j.tetlet.2012.06.069

2. M. M. Naik, D. P. Kamat, S. G. Tilve and V. P. Kamat, Molecular iodine catalyst promoted synthesis of chromans and 4-aryl-3,4-dihydrobenzopyran-2-ones *via* [3+3] cyclocoupling; *Tetrahedron* **2014**, 70, 5221-5233.
https://doi.org/10.1016/j.tet.2014.05.093

3. D. P. Kamat, S. B. Parsekar, V. P. Kamat and S. G. Tilve, A Concise Synthesis of 1-Oxygenated Carbazole Alkaloids, Clausine E and Clausine F; *Synthesis* **2014**, 46, 2789-2793.
https://doi.org/10.1055/s-0034-1378521

4. D. P. Kamat, S. G. Tilve, V. P. Kamat and J. K. Kirtany, Syntheses and Biological Activities of Chroman-2-ones. A Review; *Org. Prep. Proc. Int.* **2015**, 47, 1-79.
http://dx.doi.org/10.1080/00304948.2015.983805

5. S. G. Tilve, P. S. Torney, R. E. Patre, D. P. Kamat, B. R. Srinivasan and F. I. Zubkov, Domino Wittig - Diels Alder reaction: synthesis of carbazole lignans; *Tetrahedron Lett.* **2016**, 57, 2266-2268.
https://doi.org/10.1016/j.tetlet.2016.04.038

6. D. P. Kamat and S. G. Tilve, Total synthesis of naturally occurring 1-oxygenated carbazole alkaloids - clausine E, clausenapin, indizoline and formal synthesis of clausenaline D; *Arkivoc*, **2016**, 2016, 11-22.
http://dx.doi.org/10.3998/ark.5550190.p009.836

Papers presented at National/ International conferences:

1. D. P. Kamat, S. G. Tilve and V. P. Kamat "Synthesis of 1-oxygenated carbazole alkaloids, Clausine E and Clausine F,'' 16th Chemical Research Society of India National Symposium, 16th CRSI National Symposium **2014**, Department of chemistry, IIT-Bombay, Maharashtra (7-9th February **2014**).

2. D. P. Kamat, M. M. Naik, P. T. Parvatkar, V. P. Kamat and S. G. Tilve "Iodine catalyzed synthesis of structurally diverse fused heterocyclic compounds," the International Conference on Green Chemistry, ICGC **2015**, Department of chemistry, Goa University, Goa (22-24th January **2015**).

3. D. P. Kamat, V. P. Kamat and S. G. Tilve "Synthesis of naturally occurring 1-oxygenated carbazole alkaloids," National Conference on New Frontiers in Chemistry from Fundamentals to Applications, NFCFA **2015**, Department of Chemistry, BITS Pilani, K.K. Birla campus, Goa (18-19th December **2015**) (selected for Energy and Environmental Science Poster Prize and awarded with a Silver medal of the International Royal Society of chemistry).

Conferences attended:

1.Participated in J-NOST Conference for Research Scholars in IISER-Bhopal, Madhya Pradesh (4th – 6th December **2013**).

2. Participated in National Symposium on Transcending Frontiers in Organic Chemistry at CSIR-NIIST-Trivandrum, Kerala (9-11 October **2014**).

3. Participated in Conference on Chemical Industrial Disaster Management (CIDM): Emergency Planning and Disaster Management in Chemical, Petroleum, Petrochemical and Pharmaceutical Industry at Cidade De Goa, Goa (29th September – 1st October **2014**).

Chapter 1

Syntheses and Biological Activities of Chroman-2-ones. A Review

1.1: Introduction

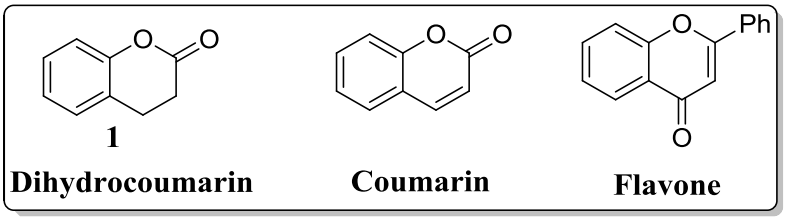


Figure 1

Chroman-2-one (**1**), also referred to as dihydrocoumarin, and its derivatives have attracted the attention of chemists due to their broad range of properties. Dihydrocoumarin contains a pyran ring attached to a benzene ring and more systematically it can be described as 3,4-dihydro-1*H*-benzo[*e*]pyran-2-one. The 4-aryl substituted dihydrocoumarins are also referred to as neoflavonoids as they are structural isomers of flavonoids. Though considerable data are available on its dehydrogenated structure, *i. e.* coumarin, on its natural occurrence and synthesis, not much effort has been devoted to chroman-2-ones. This review attempts to substantially cover the literature pertaining to dihydrocoumarins with special emphasis on recent advances (2000-2013) in the syntheses. Literature pertaining to the natural occurrence and the biological activities is also briefly described. The various methods reported for the syntheses of dihydrocoumarins are classified based on the bond forming reactions as shown in the retrosynthetic analysis *(Scheme 1).* The further synthetic applications of dihydrocoumarins leading to generation of important building blocks, essentially naturally occurring and/or biologically active moieties, are mostly included within this classification wherever possible.

1.1.1: Natural Occurrence

Compared to coumarins, the corresponding dihydrocoumarins are scarce in nature. The parent dihydrocoumarin **1** (DHC), is found in *Melilotus officinalis* (sweet clover),[1,2] *Prunus mahaleb* seeds,[3] deertongue leaf[4] and *Dipteryx odorata* wild[5,6] (tonca beans). Dihydrocoumarin was also found in *Mikania laevigata* Shultz Bip. ex Baker.[7] Herbertenolide **2** was isolated from the liverwort *Herbertus sakuraii,*[8] and from the liverwort *Herberta adunca*.[9] (-)-6-Hydroxy-3,4-dihydro-4,7-dimethylcoumarin **3** was isolated and characterized by Cambie and co-workers from *Heritiera ornithocephala*.[10] Neoflavonoids 3,4-dihydro-4-aryl-coumarins, *e. g.* [(**4a**, $R_1 = R_2 = H$) (**4b**, $R_1 = R_2 = Me$) (**4c**, $R_1 = Me$, $R_2 = H$) and (**4d,** $R_1 = H$, $R_2 = Me$)] were isolated from the whole plant of *Polygonum perfoliatum*.[11] The 4-aryl-3,4-dihydrocoumarin skeleton is also found in

tannins and related compounds.[12] Vittarin F [**5,** 4-(3′,4′-dihydroxyphenyl)-6-(3′′,4′′-dimethoxyphenylethyl)-7-hydroxydihydrocoumarin] was isolated from the methanol extract of the whole plant of *Vittaria anguste-elongata*.[13] The benzo[*f*]chroman-3-one **6** was isolated from *Cape aloe*[14] and dihydrocoumarin **7** was extracted from *Aloe vera*.[15] Mammea dihydrocoumarin **8** was obtained from the seeds of the West African tree *Mammea africana* Sabine (Guttiferae).[16,17]

6-Methoxy-5,7-dihydroxy-3,4-dihydrocoumarin-8-*C*-glucopyranoside **9** and 5-vinyl-6,7-dimethoxy-3,4-dihydrocoumarin-8-*C*-glucopyranoside **10**, were isolated from the aerial parts of *Diceratella elliptica* (DC).[18] Recedensolide **11** was isolated from *Calophyllum recedens* bark[19] and isorecedensolide **12** from the seeds of *Calophyllum blancoi*.[20] Dichloromethane extracts of wood and dark heartwood of *Thespesia populnea*[21] gave populene E **13**. Calomelanols [(**14a**, R_1 = OMe, R_2 = H) (**14b**, R_1 = OH, R_2 = H) (**14c**, R_1 = H, R_2 = OH) (**14d**, R_1 = R_2 = H) (**15a**, R_1 = R_2 = OH) (**15b**, R_1 = OMe, R_2 = OH) (**15c**, R_1 = OH, R_2 = H) (**15d**, R_1 = H, R_2 = OH) (**15e**, R_1 = R_2 = H) and (**16a**, R_1 = R_2 = OH) (**16b**, R_1 = H, R_2 = OH)] and a complex flavonoid (**16c**, R_1 = R_2 = H)] were obtained from farinose exudate of *Pityrogramma calomelanos.*[22-25] 5,7-Dihydroxy-8-cinnamoyl-4-phenyldihydrocoumarins **17a** (R_1 = R_2 = R_3 = R_4 = H); **17b** (R_1 = R_2 = R_4 = H, R_3 = OH); **17c** (R_1 = R_2 = H, R_3 = R_4 = OH) were isolated from *Pityrogramma trifoliata* and these were synthesized for the confirmation of their structure by Iinuma *et al*.[26]

1.1.2: Biological Activity

Natural dihydrocoumarin (DHC) **1** is of great interest in the flavor industry. Synthetic DHC is manufactured for use as a common fragrance in perfumes,[27] cosmetics, lotions, soaps, and as a flavoring agent in beverages and chewing gum.[28- 30] DHC is present at concentrations above 100 ppm (670 µM) in gelatins, puddings, soft candy, frozen dairy products, and baked goods.[31] Dihydrocoumarin was found to disrupt epigenetic processes in the yeast *Saccharomyces cerevisiae*. Dihydrocoumarin also inhibited several human Sir2 family deacetylases (SIRT1 and SIRT2) and increased p53 tumor suppressor protein acetylation with elevated levels of apoptosis when added to cells in culture.[32] 3-Substituted-3,4-dihydrobenzo[*f*]chromen-2-ones showed high pro-apoptotic and or cytodifferentiating properties in human leukemia cell line (U937).[33] Several 3-methylidene chroman-2-ones (**19**, R_1 = H, OMe; R_1, R_2 = -CHCHCHCH, -CHC(OH)CHCH; R_2 = H; R_2, R_3 = -CH_2OCH_2-; R_3 = OMe, H; R_4 = Me, *n*-Bu, *i*-Pr, vinyl) showed potent cytotoxic activity on screening against several cancer cell lines with

IC_{50} values below 1 μM and exhibited interesting structure-activity relationships.[34] Neoflavonoids, including some of the 3,4-dihydro-4-aryl-coumarin derivatives **4-7**, display pharmacological properties, such as bactericidal,[35] molluscicidal[36] and insecticidal.[37] Cortez and co-workers demonstrated that 5,7-dihydroxy-8-(2-methylbutanoyl)-6-(3-methylbutyl)-4-phenyl-chroman-2-one **20** prepared by

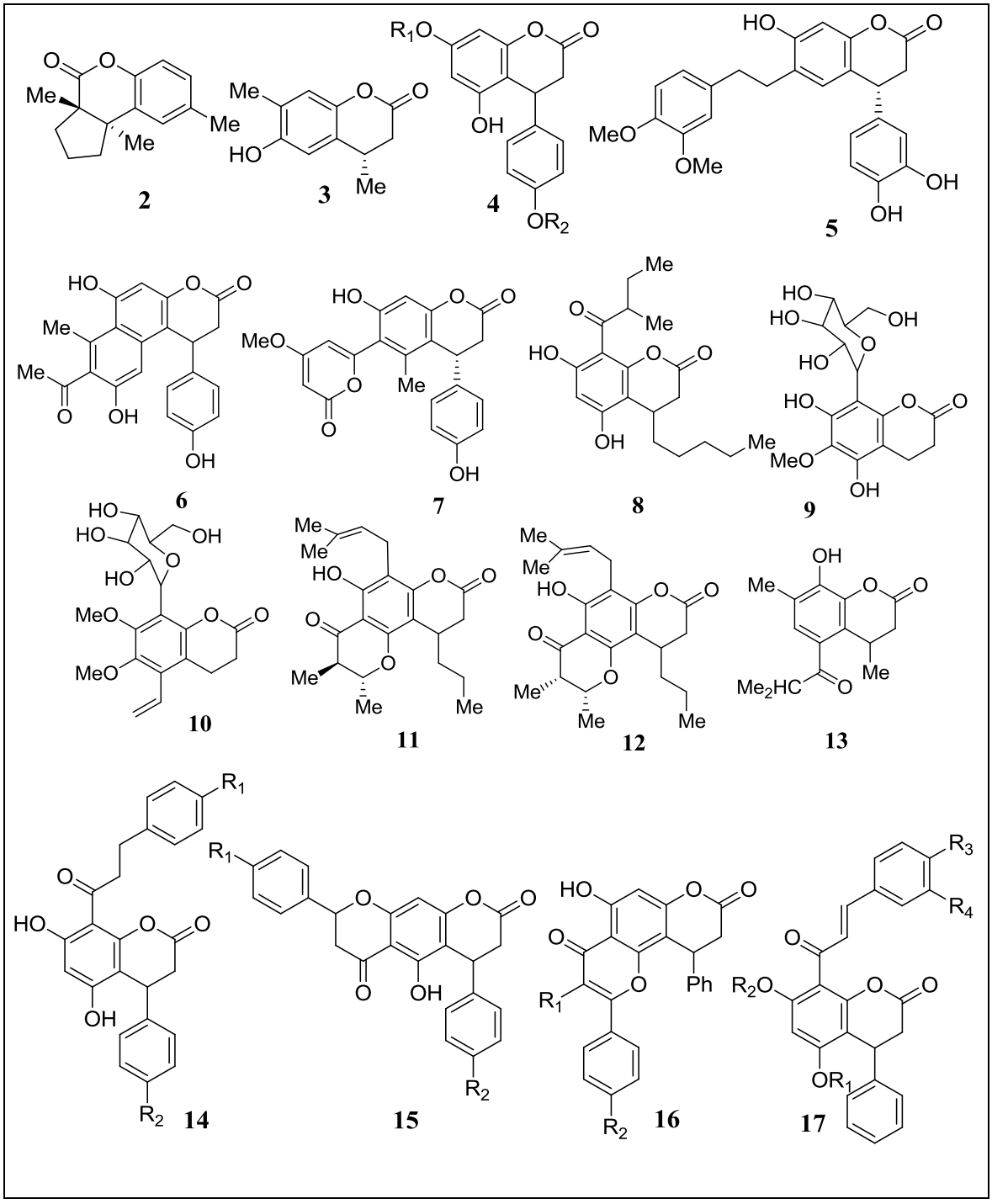


Figure 2

hydrogenation of mammea A/BB coumarin exhibited greater anti-leishmanial activity than mammea A/BB coumarin. Compound **20** was found to be most effective in killing intracellular amastigote forms of *Leishmania amazonensis.*[38] Nishiyama *et al.* showed that 6,7-dihydroxy-4,4-dimethyldihydrocoumarin **21** can serve as an effective antioxidant for preventing the oxidation of oils and fats. Also, substituted dihydrocoumarins having the basic structural motif of **21**, behaved as better chain-breaking antioxidants for the autooxidation of tetralin and linoleic acid than structurally comparable α-tocopherol.[39] Aloe dihydrocoumarin **7** is an antioxidant, a candidate immunomodulatory drug on the immune system and can balance physiological reactive oxygen species (ROS) levels, which may be useful to maintain homeostasis. Tang and co-workers have investigated the binding action of Aloe dihydrocoumarin with human serum albumin (HSA) using various techniques such as fluorescence, ultraviolet, circular dichroism and Fourier transform infrared spectroscopy, fluorescence dynamics and molecular dynamic docking.[40] Studies suggest that Aloe dihydrocoumarin is a strong quencher of fluorescence of HSA and has high binding affinity for protein (binding parameters calculated using the Stern-Volmer equation). It binds to residues located in subdomain IIA of HSA. This binding causes a conformational change of the protein, with loss of α-helix stability and increase of β-sheet and β-turn content. Compounds **9** and **10** exhibited relatively high cytotoxic activity against three human carcinoma cell lines namely liver (HEPG2), cervix (HELA) and colon (HCT116).[18] Rapid and complete inactivation of α-chymotrypsin was effected by a series of halomethylated derivatives of dihydrocoumarins at pH 7 and a temperature 25 ^{o}C.[41] 3,4-Dihydrocoumarins also display biological activities like aldose reductase inhibition,[42] protein kinases,[43] anti-herpetic,[44] and moderate estrogenic activity.[45] Nishimura *et al.* have observed that 4-aryl-3,4-dihydrocoumarin derivatives (**18a**, R = H and **18b**, R = Ac) have an estrogenic activity comparable to that of the isoflavone, genistein.[46] Several 4-arylcoumarins and 4-aryldihydrocoumarins have been shown to possess anti-inflammatory,[47] anti-fungal,[48] cytotoxic and anti-microbial activities.[49] Tavori *et al.* have used a modeling technique to predict the PON1 (Paraoxonase 1, a calcium dependent high density lipoprotein-bound enzyme) active site and analyze the engagement of its amino acids with binding ligands such as dihydrocoumarin.[50] Splitomicin (3,4-dihydrobenzocoumarin) and its analogues have been studied as Sirtuin inhibitors.[51,52] Chroman **22** at 30 nM displayed 80% inhibition of ornithine decarboxylase.[53] Compounds **23** and **24** act as β-lactamase substrates.[54] A class of β-amino acids derived from 4-aminodihydrocoumarin **25**, mimic the aspartic acid moiety in

the RGDF sequence of fibrinogen. The RGDF peptidomimetics are potent platelet aggregation inhibitors.[55]

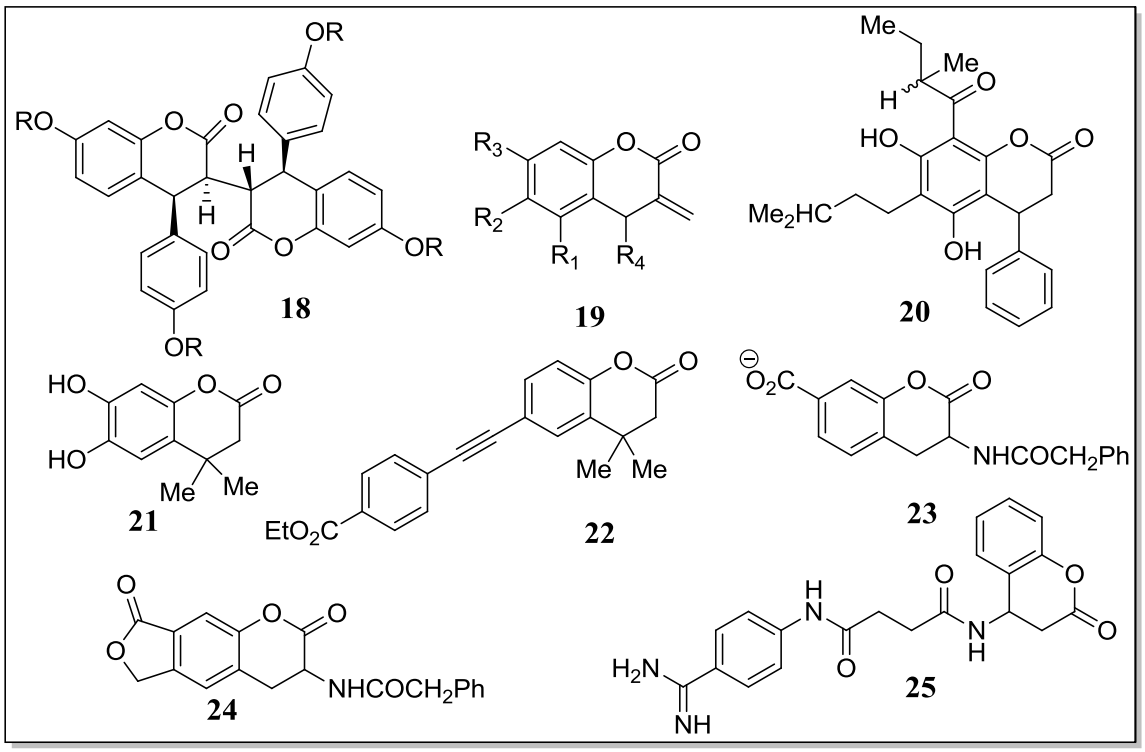
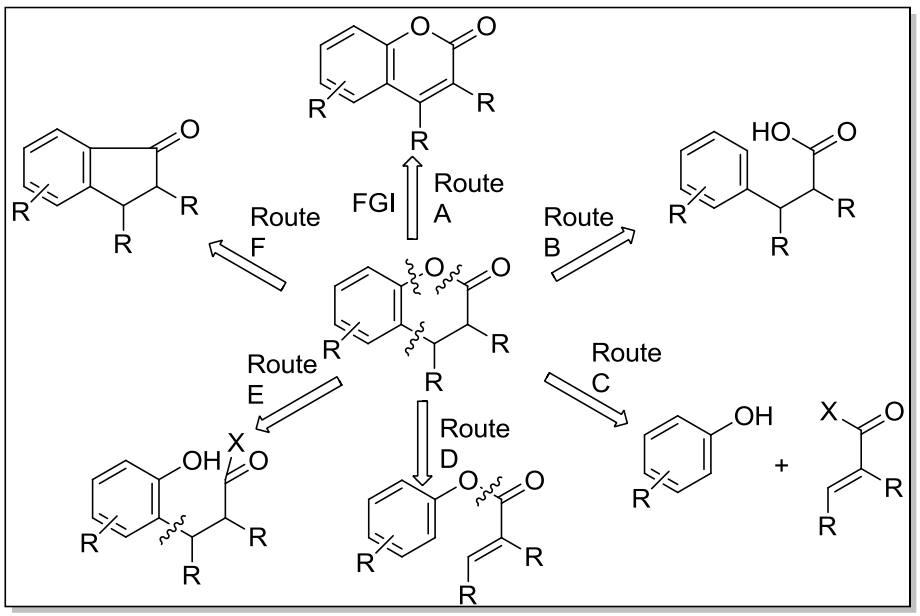


Figure 3

1.2: Syntheses

There are a wide variety of methods reported for the synthesis of dihydrocoumarins.

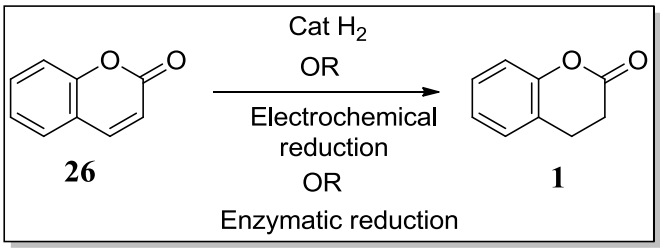


Scheme 1

To comprehend these methods better, a retrosynthetic scheme depicting six different routes [routes A-F] to dihydrocoumarins is shown in *Scheme 1* based on different bond forming procedures.

1.2.1: From Pre-formed Coumarins (Route A)

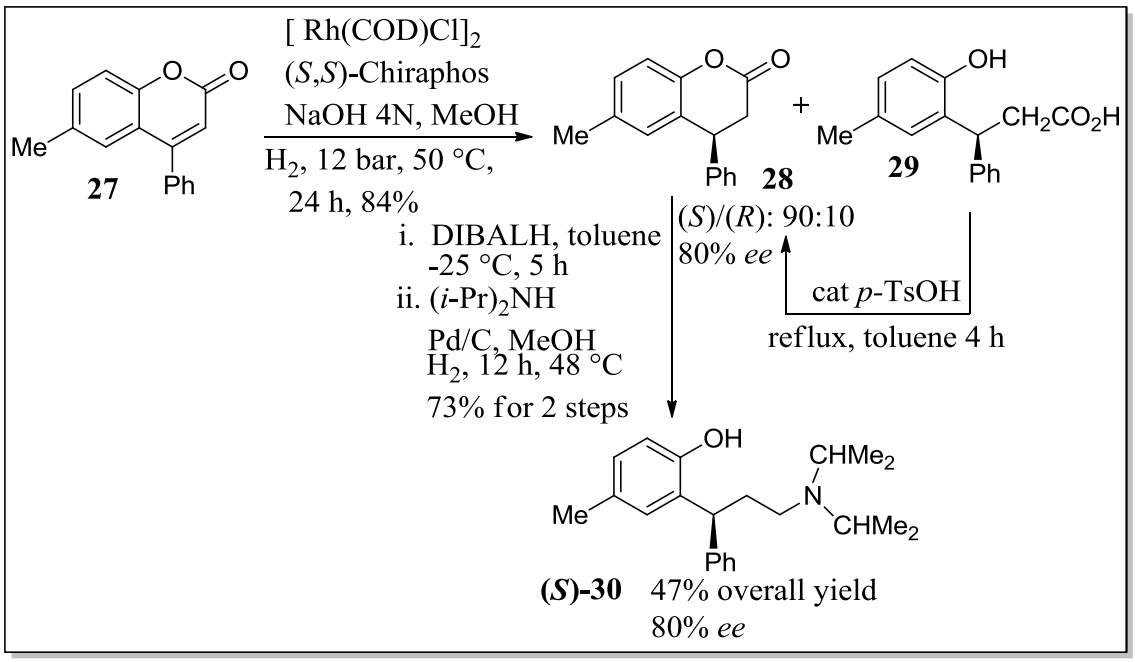
Various synthetic methods such as hydrogenation and conjugate addition using pre-formed coumarins as starting materials are included here for the preparation of dihydrocoumarins. There are several examples for the preparation of dihydrocoumarins involving [3+2], [4+2], [2+2] and 1,3-dipolar cycloadditions to coumarins. However, the vast literature pertaining to cycloadditions is beyond the scope of this review. The literature detailing the synthesis of chroman-2-ones by the reduction of corresponding coumarins has been extensively reviewed by Semeniuchenko *et al*. and is not described here (*Scheme 2*).[56]



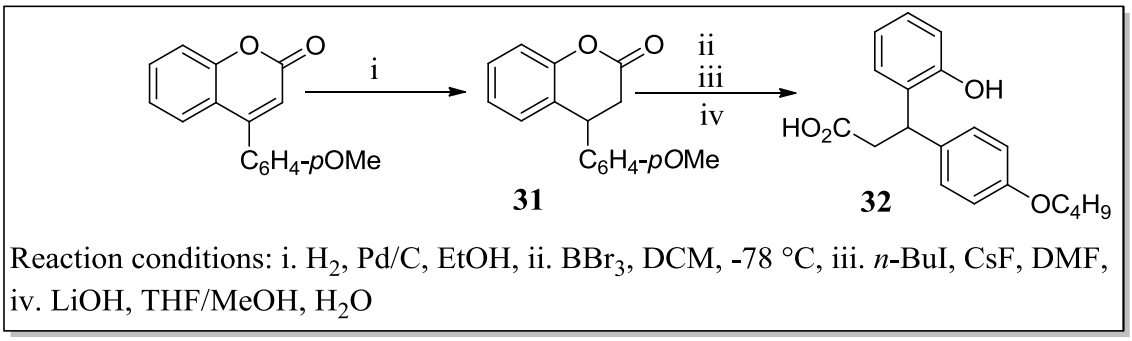
Scheme 2

Ulgheri *et al.* have reported a short four-step enantioselective synthesis of (*S*)- and (*R*)-tolterodine.[57] Coumarin **27**, obtained by a Heck reaction between 2-bromo-4-methylphenol and a *trans*-cinnamate derivative, was subjected to asymmetric hydrogenation using $[Rh(COD)Cl]_2$ and (*S, S*)-Chiraphos as the chiral ligand, which gave a mixture of dihydrocoumarin **28** and acid **29**. The dihydrocoumarin **28** was then reduced with DIBALH to the lactol and then subjected to reductive amination with $(i\text{-Pr})_2NH$, Pd/C in methanol to give (*S*)-tolterodine **30** in an overall 47% yield and 80% *ee (Scheme 3)*. The same procedure led to (*R*)-tolterodine in 45% overall yield and 81% *ee* using (*R, R*)-Chiraphos as the chiral ligand.

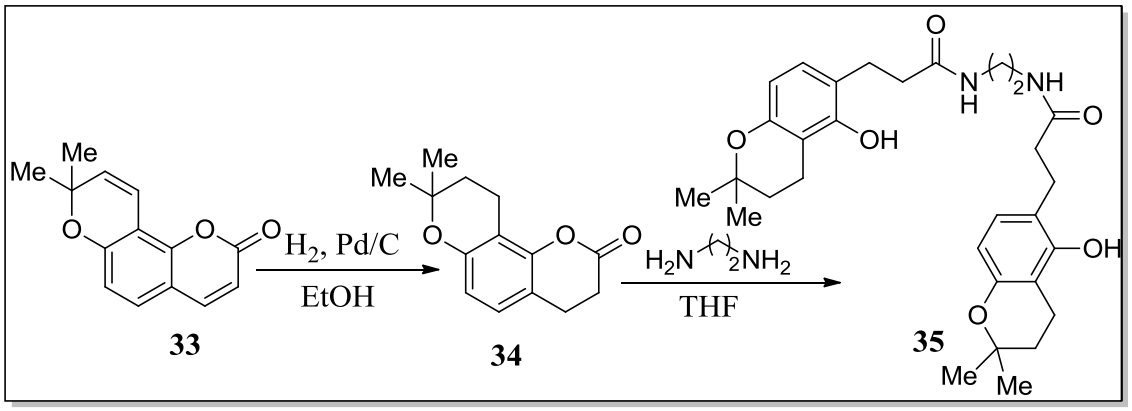
Song *et al.* synthesized dihydrocoumarin **31** by Suzuki coupling reaction of 4-tosyloxy coumarin with 4-methoxyphenylboronic acid followed by hydrogenation. This was followed by demethylation, alkylation and hydrolysis to give **32** which is an analogue of GPR40 agonist *(Scheme 4)*. GPR40 agonist is able to induce glucose-mediated insulin secretion in the mouse MIN6 pancreatic β-cell line.[58] Potent anti-thrombotic agent **35** was synthesized from dihydrocoumarin **34**, obtained by hydrogenation of **33** *(Scheme 5)*.[59]



Scheme 3



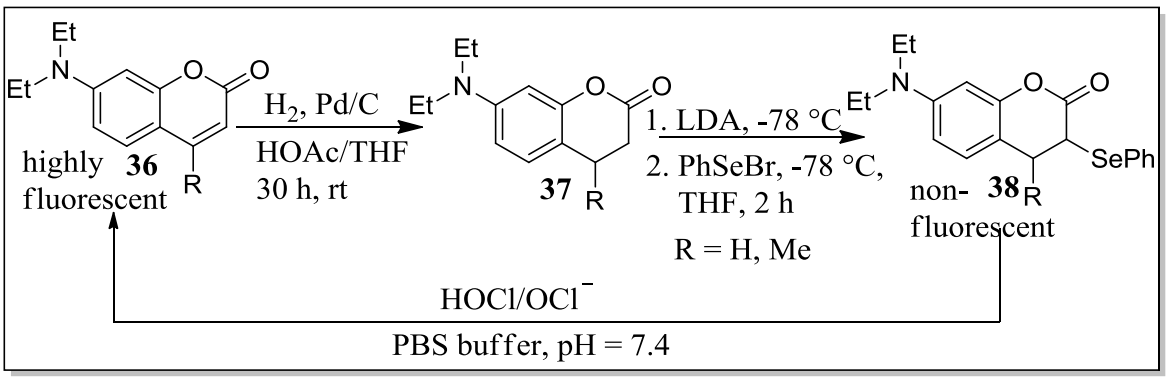
Scheme 4



Scheme 5

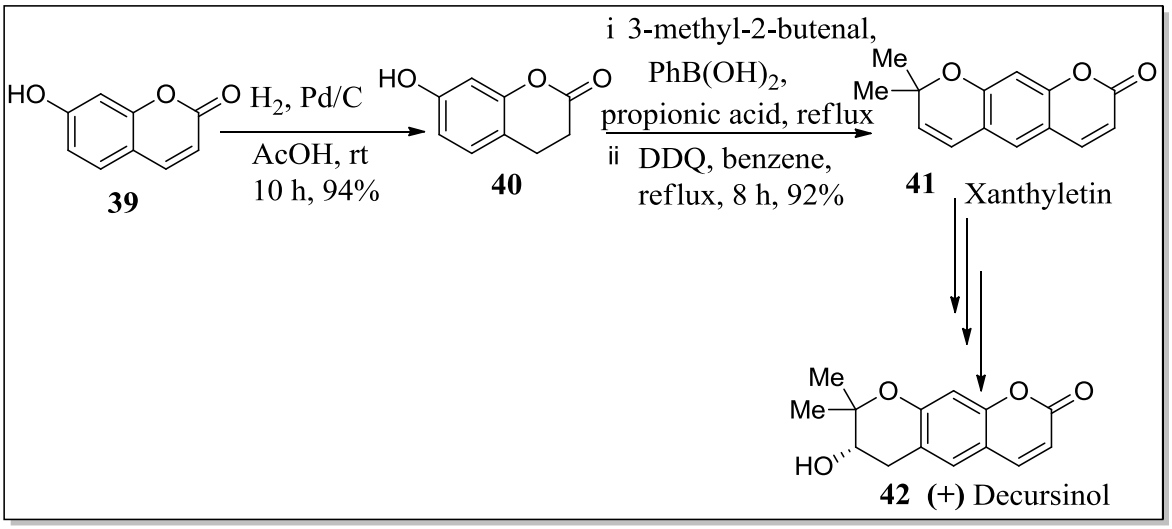
Jiang and co-workers synthesized the probes **38** by reduction of coumarin dyes **36** to dihydrocoumarins **37** and subsequent selenylation.[60] The non-fluorescent dihydrocoumarins **38** were then treated with hypochlorite solution which resulted in selenoxide elimination to give the conjugated system of the highly fluorescent coumarins **36** *(Scheme 6)*. The authors have demonstrated the use of fluorescent probes for the

selective detection of hypochlorite on the basis of the intramolecular selenoxide elimination reaction.



Scheme 6

Jun and co-workers reported the enantioselective total synthesis of (+)-decursinol **42**.[61] Reduction of umbelliferone **39** to dihydrocoumarin **40** followed by condensation with 3-methyl-2-butenal and DDQ oxidation gave xanthyletin **41** which is an efficient growth inhibitor of *Phytophthora citrophthora*. Xanthyletin **41** was further transformed into (+)-decursinol **42**, which displays diverse biological properties such as anti-cancer, anti-nociceptive, *etc. (Scheme 7).*

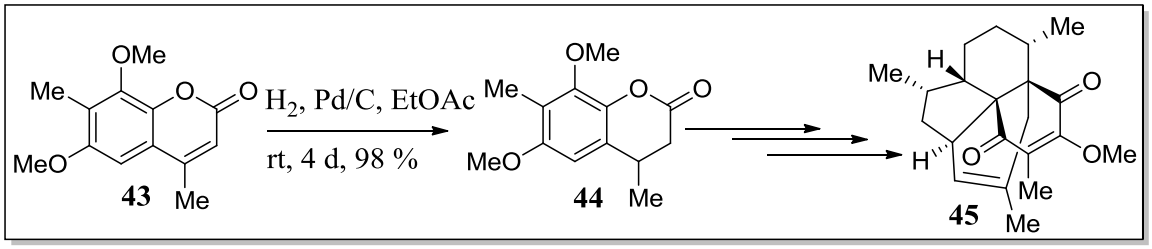


Scheme 7

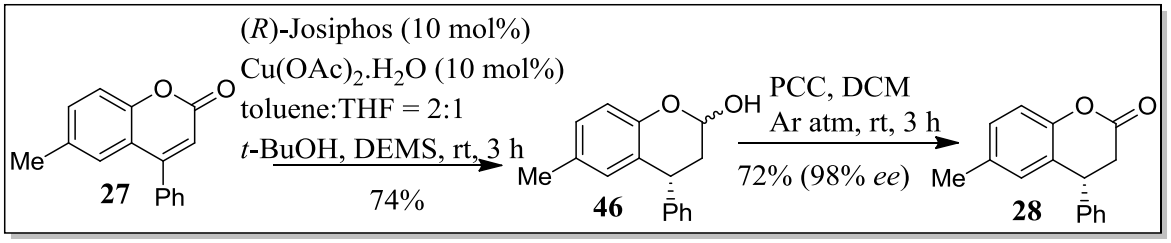
Harrowven *et al.* synthesized an unnatural diastereoisomer of colombiasin A **45** *via* dihydrocoumarin intermediate **44**. Triflic acid mediated Pechmann reaction of 2,4-dimethoxy-3-methylphenol with ethyl acetoacetate gave coumarin **43** which was reduced to the required dihydrocoumarin **44** *(Scheme 8).*[62]

Correia and co-workers have prepared several coumarin derivatives using a tandem Heck-Matsuda cyclization reaction. The synthesis of (*R*)-tolterodine in high yield and enantiomeric excess was also accomplished.[63] Heck-Matsuda cyclization between ethyl

2-hydroxy-5-methyl cinnamate and the 4-bromobenzenediazonium tetrafluoroborate gave coumarin **27** which was reduced to chiral lactol **46** *(Scheme 9)*. Lactol **46** was oxidized into dihydrocoumarin **28** using PCC.

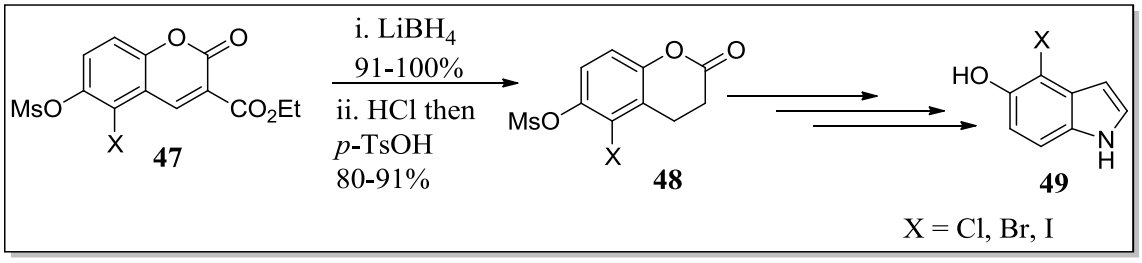


Scheme 8



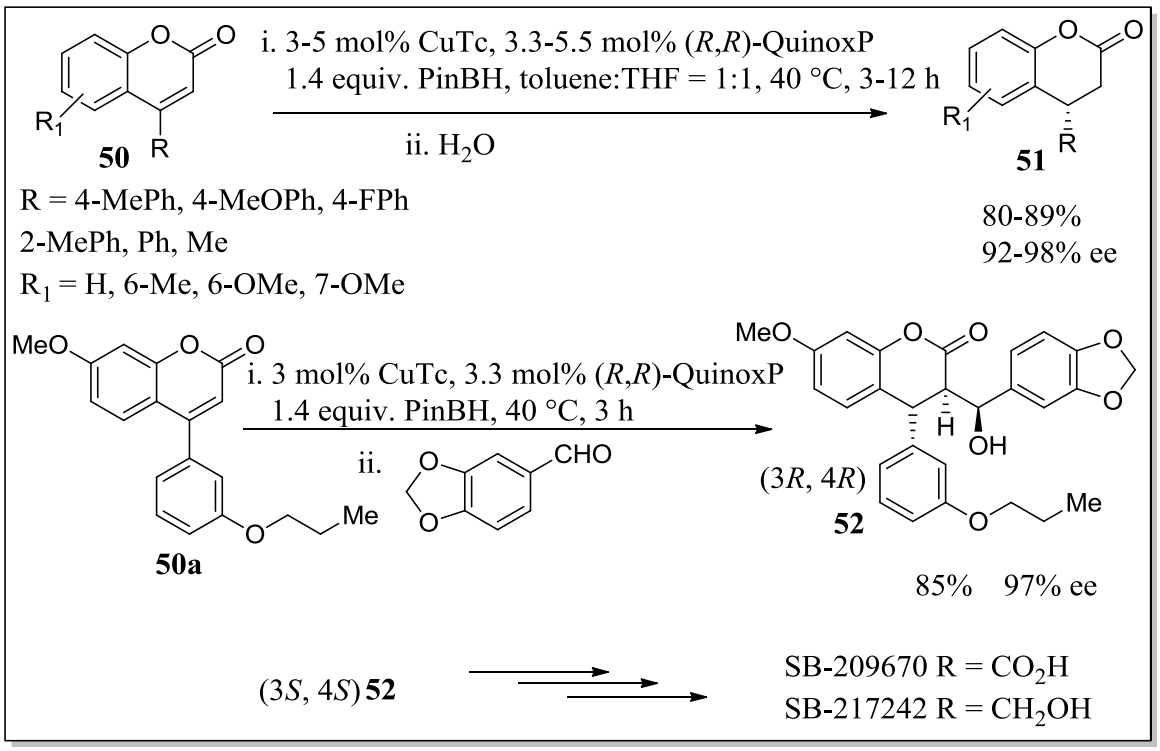
Scheme 9

3-Alkoxycarbonyl-6-hydroxy-5-halocoumarins were converted into 4-halo-5-hydroxyindoles *via* the corresponding dihydrocoumarins.[64] Conjugate reduction of coumarins **47** followed by decarboxylation gave dihydrocoumarins **48**. Lactone ring-opening with ammonia gave amide intermediates which were then transformed into 4-halo-5-hydroxyindoles **49** *(Scheme 10)*. The same authors applied this methodology to the preparation of a number of 4-haloserotonin derivatives and to the synthesis of the toad alkaloid dehydrobufotenine.[65]



Scheme 10

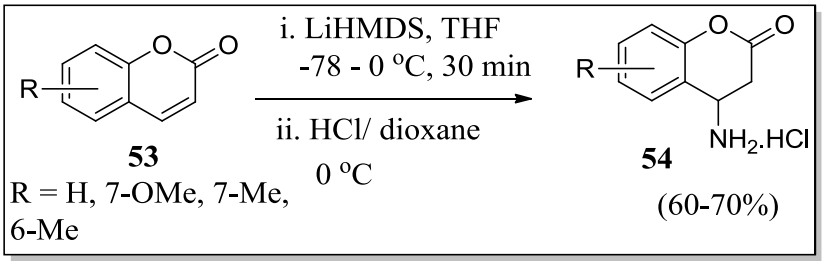
Kim and Yun obtained enantiomerically enriched dihydrocoumarins **51** through stereoselective 1,4-hydroboration of coumarins **50** by employing pinacolborane in the presence of a copper catalyst and subsequent reaction with electrophiles (water or piperonal). Furthermore they demonstrated the utility of this protocol for the synthesis of SB-209670 and SB-217242 *via* benzopyranone intermediate **52** *(Scheme 11)*.[66]



Scheme 11

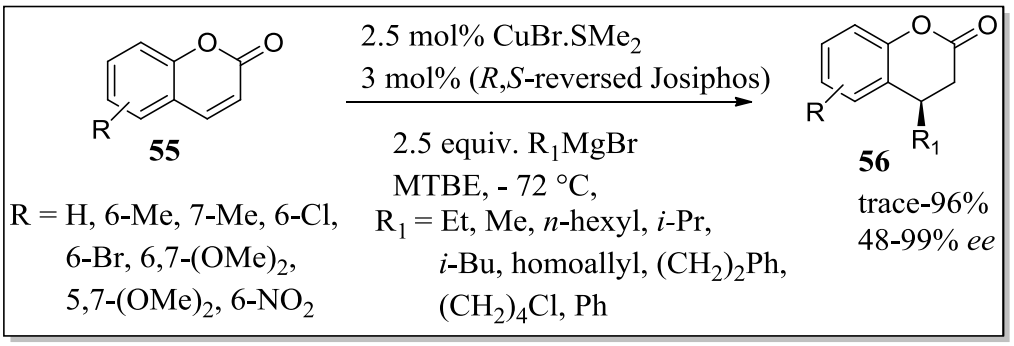
A straightforward approach for conjugate addition to coumarins leading to synthesis of dihydrocoumarins has been known for the last few decades.[67] As early as 1928, Seshadri *et al.* synthesized 3,4-dihydrocoumarin-4-cyanoacetamide by 1,4-addition of cyanoacetamide to coumarin in the presence of piperidine.[68]

Rico has prepared several new 4-aminodihydrocoumarins, from which biologically important *β*-amino acids are derived.[55] The synthesis was achieved *via* Michael addition of LiHMDS to commercially available coumarins **53** at low temperature; the trimethyl silyl group was removed using dry HCl/dioxane to give the 4-aminodihydrocoumarins **54** as their hydrochloride salts *(Scheme 12).*



Scheme 12

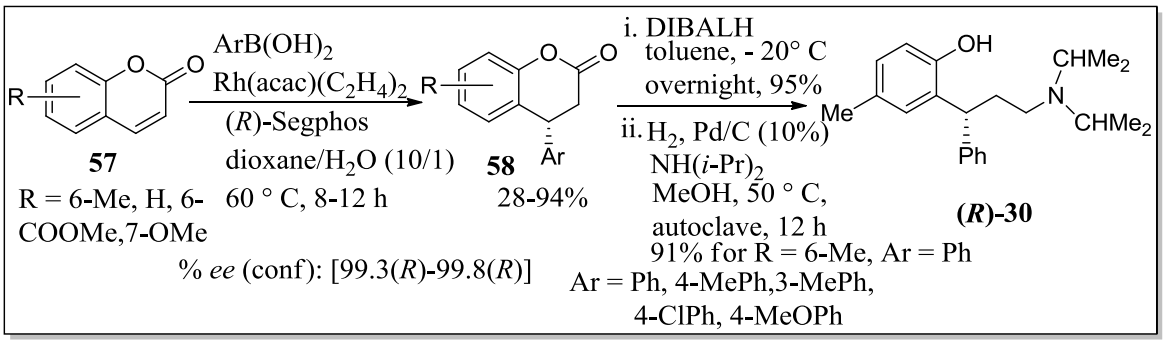
Copper-catalyzed asymmetric conjugate addition of Grignard reagents to coumarins **55** was developed by Feringa and co-workers *(Scheme 13).*[69]



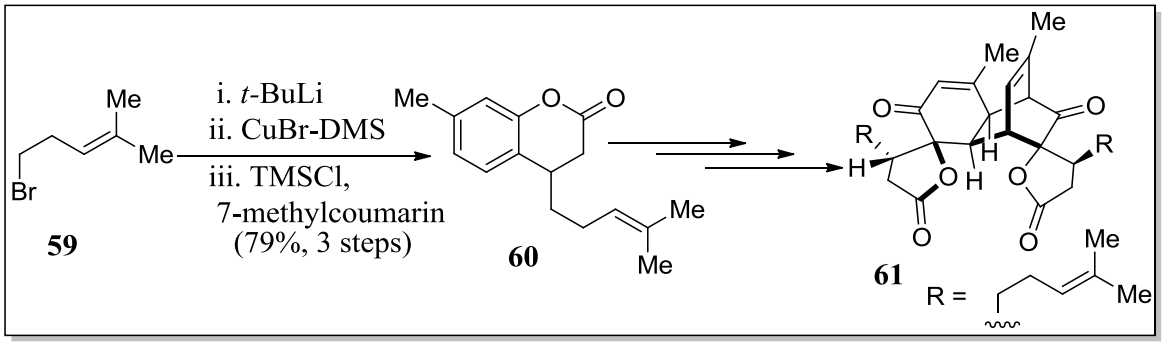
Scheme 13

Chen *et al.* have reported rhodium catalyzed asymmetric 1,4-addition of arylboronic acids to coumarin derivatives **57** in the presence of axially chiral biarylbiphosphine ligands (*R*)-Binap, (*R*)-P-Phos, (*R*)-Segphos resulting in the formation of dihydrocoumarins **58** in high yields and enantioselectivities.[70] (*R*)-Segphos led to the greatest enantioselectivity in this reaction. Further, (*R*)-6-methyl-4-phenylchroman-2-one **58** was converted into (*R*)-tolterodine **30** by subjecting it to DIBALH reduction and palladium-catalyzed hydrogenation in the presence of diisopropylamine *(Scheme 14).*

Conjugate addition of bromo compound **59** to 7-methylcoumarin provided the alkylated dihydrocoumarin **60** which was transformed into bacchopetiolone carbocyclic core **61** using a tandem phenolic oxidation, Diels-Alder reaction *(Scheme 15).*[71]

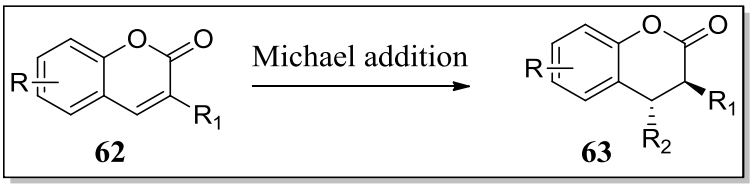


Scheme 14



Scheme 15

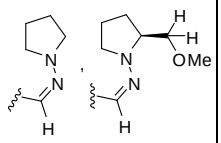
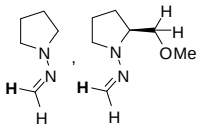
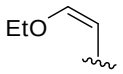
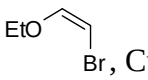
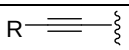
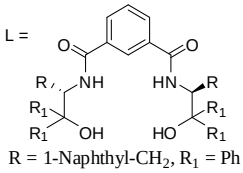
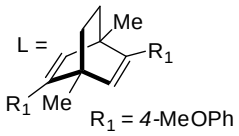
Fernández and co-workers have synthesized 3,4-disubstituted dihydrocoumarins **63** as Michael adducts by nucleophilic conjugate addition of chiral formaldehyde *N*,*N*-dialkylhydrazones to 3-substituted coumarins **62** *(Scheme 16).*[72] *Table 1* provides information about the enantioselective and/or diastereoselective conjugate addition to coumarins **62** resulting in the formation of dihydrocoumarin derivatives **63**.

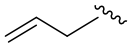
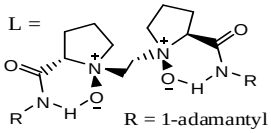
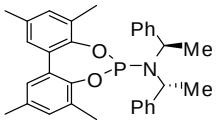


Scheme 16

Conjugate addition of (*Z*)-2-ethoxy vinyl anion to 3-carbethoxycoumarin *via* Noyori type organocopper reagents was reported by Bennabi *et al*.[73] Enantioselective synthesis of 4-substituted dihydrocoumarins *via* the alkynylation of 3-carboalkoxycoumarins was achieved by Blay *et al.*[74] The synthesis was extended to afford the product having a tetrahydrofuro[2,3-*b*]benzofuran skeleton characteristic of the fungal metabolite, aflatoxin, and other natural products. Conjugate addition of dialkyl zinc to 3-nitrocoumarins **62** (R = H, OMe, Br, Me, R_1 = NO_2) resulted in the formation of the corresponding dihydrocoumarins **63 (**R = H, OMe, Br, Me, R_2 = Me, Et, Bu, R_1 = NO_2).[75] One-pot, tandem Michael addition of indole derivatives to 3-nitrocoumarins, followed by methyl vinyl ketone (MVK), was developed by Ye and co-workers as a route to multi-functionalized 3,4-dihydrocoumarins.[76] Asymmetric conjugate addition of phenyl boronic acid $PhB(OH)_2$ to coumarins giving 4-substituted dihydrocoumarins was also reported.[77,78] Feng and co-workers synthesized several potential pharmacologically active 4-allyl-2-oxochromans **63** (R = H, OMe, Me, *t*-Bu, Br, Cl, NO_2, 5,6-(-CH=CH-CH=CH-), R_2 = allyl, R_1 = CO_2*t*-Bu) *via* asymmetric conjugate allylation of coumarins **62** (R = H, OMe, Me, *t*-Bu, Br, Cl, NO_2, 5,6-(-CH=CH-CH=CH-), R_1 = CO_2*t*-Bu).[79] Coumarins **62** were activated toward Michael reaction by using chiral *N*,*N*′-dioxide-$Yb(OTf)_3$ as a Lewis acid and $(CuOTf)_2.C_7H_8$ for tetraallyltin *via* transmetalation. Subsequent decarboxylation of **63** (R = H, R_2 = allyl, R_1 = CO_2*t*-Bu) was achieved by using *p*-toluenesulfonic acid in toluene to obtain enantiomerically pure 4-allyl-2-oxochroman. Woodward and co-workers have synthesized dihydrocoumarins in good yields and enantioselectivity using alanes for the reduction of various 3-substituted coumarins.[80]

Table 1: Enantioselective and/or Diastereoselective Conjugate Addition to Coumarins **62** resulting in the Formation of Dihydrocoumarin derivatives **63**.

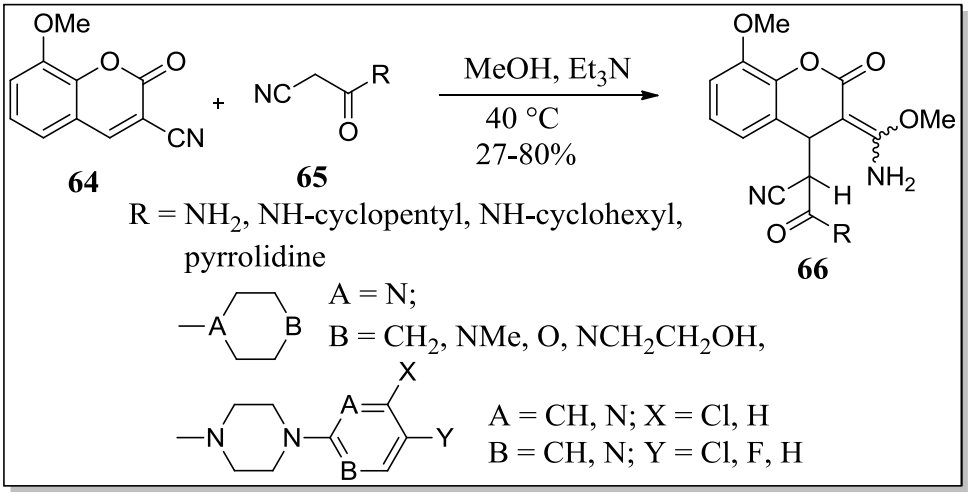
62-63			Reaction conditions	Yield (%)	Ref
R	R_1	R_2			
H	COMe, CO_2Et		DCM, rt, Ar atm, MgI_2 	75-85	*72*
H	CO_2Et		*t*-BuLi, -78 °C,  , CuI, PBu_3	89	*73*
H, OMe, Me, *t*-Bu, Br, Cl	CO_2*t*-Bu	 R = Ph, $Ph(CH_2)_2$, 3FPh, 4MeOPh, 4FPh, CO_2Me, Me_3Si	Et_2Zn   R = 1-Naphthyl-CH_2, R_1 = Ph toluene, rt *N*-methyl piperidine	36-99 (60-95% *ee*)	*74*
H, OMe, Br, Me	NO_2	Me, Et, Bu	1. R_2Zn, $Cu(OTf)_2$ (1.2 mol%), toluene, -70 °C, 16 h 2. 1 N HCl	90-99	*75*
Me	H	Ph	$PhB(OH)_2$ $[\{RhCl(C_2H_4)_2\}_2]$/L =(1:1)  R_1 = *4*-MeOPh (dioxane/H_2O) KOH, 30 °C, 3 h	95 (98% *ee*)	*77*
Me, OMe, H	H	Ph	$PhB(OH)_2$ $[\{RhCl(C_2H_4)_2\}_2]$/L =(1:1) L = (R)-MeO-F_{12}-BIPHEP toluene/aq. $NaHCO_3$	85-94, (>99% *ee*)	*78*

			20-30 °C, 1 h		
H, OMe, Me, *t*-Bu, Br, Cl, NO_2, 5,6-(-CH=CH-CH=CH-)	CO_2*t*-Bu		 Yb(OTf)$_3$/L (1:1 10 mol%) Cu(OTf)$_2$·C_7H_8 (10 mol%) 40 °C, THF, 48 h L =  R = 1-adamantyl	35-99 (88-93% *ee*)	*79*
H, Br, OMe, Me, -$(CH)_4$-	COPh, CO_2Et	Me, Et, *i*-Bu	Al(R_2)$_3$ Cu(OAc)$_2$·H_2O (2 mol%), L (4 mol%) -40 °C, Et_2O, L =  20 h	40-94 (37-98% *ee*)	*80*

The reaction of 3-acylsubstituted-2*H*-1-benzopyran-2-ones with acid anhydrides in the presence of potassium fluoride/molecular sieves gave 4-(2-oxoalkyl)-2-oxochromans as the major products. Also the 3-carboxylic acid derivatives of 2*H*-1-benzopyran-2-ones reacted with isobutyric acid anhydride to give the corresponding 2-oxochroman-4-acetic acid derivatives.[81] Beley and co-workers reported that nucleophilic addition of the anion from 2-acetylpyridine with 3-aroylcoumarin in a Michael type reaction resulted in the formation of 3,4-disubstituted dihydrocoumarins.[82] Conjugate addition of *tris*-(dimethylamino)phosphine or trialkyl phosphites to 3-acetyl coumarins to furnish various 4-substituted benzopyranones was demonstrated by Abdou and Sediek.[83] The addition of nitromethane to 3-substituted 2*H*-1-benzopyran-2-ones to give chroman-2-ones catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene, in the presence of allyl bromide, was reported by Bojilova *et al*.[84]

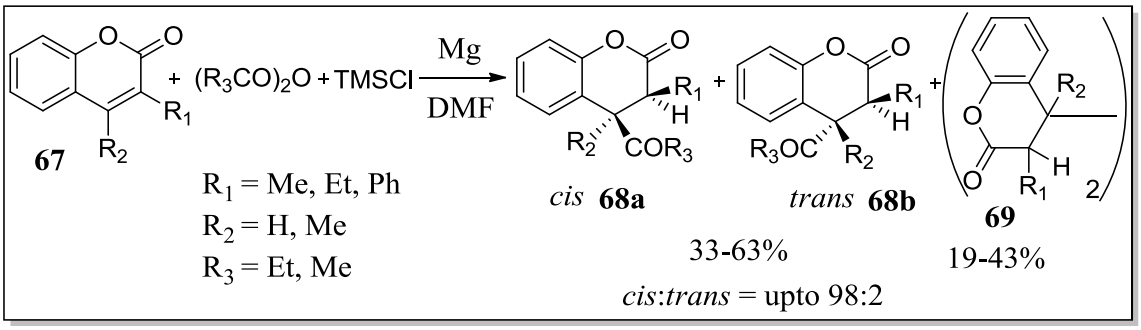
A one-pot synthesis of 3-[amino(methoxy)methylene]-2-oxo-3,4-dihydro-2*H*-chromen-4-yl)-4-cyanoacetamides **66** was developed by Costa *et al.* from cyanoacetamides **65** and 2-oxo-2*H*-chromene-3-carbonitriles **64** in methanol and triethylamine at 40 °C *(Scheme*

17).[85] Under reflux conditions the formation of a tricyclic product occurred. These products proved to be active at adenosine receptors.



Scheme 17

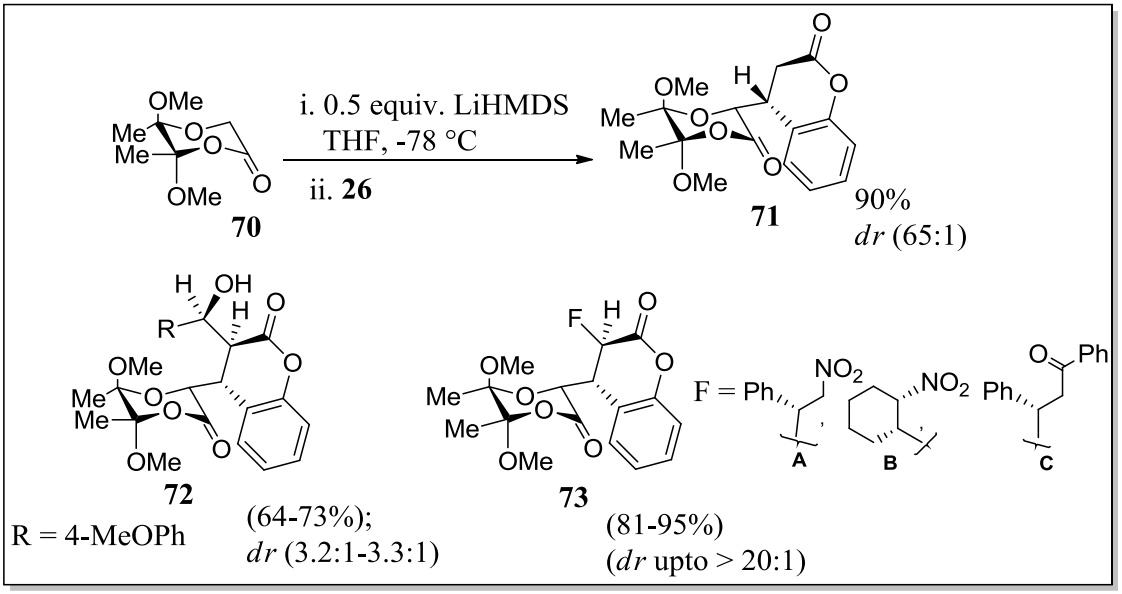
Magnesium-promoted cross-coupling of coumarins **67** with acid anhydrides/TMSCl resulted in regio- and stereoselective *C*-acylation to give dihydrocoumarins **68**.[86] Dimerized product **69** was also formed in certain cases *(Scheme 18)*.



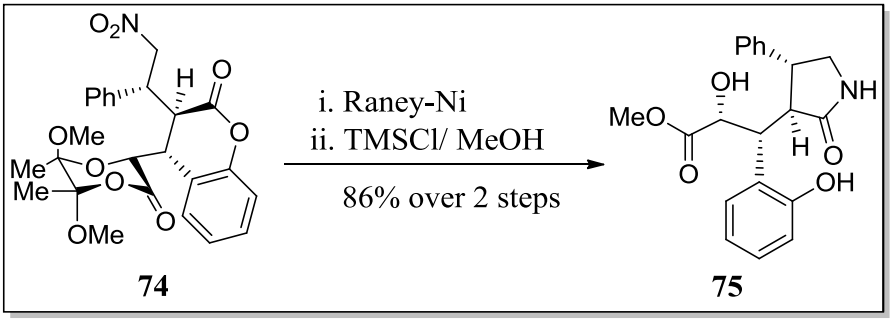
Scheme 18

Ley and co-workers carried out highly diastereoselective lithium enolate Michael addition of butane-2,3-diacetal (BDA)-desymmetrized glycolic acid **70** to coumarin forming benzopyranone **71** *(Scheme 19)*.[87] In addition, the same authors further described a three-component, one- pot Michael-aldol reaction of lactone **70** with the coumarin and an electrophilic coupling partner, an aldehyde, to give **72** *(Scheme 19)*.[88] Similarly dihydrocoumarins **73** were obtained by one-pot, Michael-Michael three-component coupling reactions with coumarin followed by reaction with several second Michael acceptors. Deprotection of the butane diacetal (BDA) was achieved by treatment with TMSCl and methanol. Ley and co-authors also explored the Michael-aldol and Michael-Michael reactions to give multi-functional benzopyranones with high diastereoselectivity.[89] They also examined the further applicability of the benzopyranone

74 by reducing it with Raney-Ni; the lactone underwent spontaneous ring-opening, forming *γ*-lactam **75** after the usual methanolysis. This demonstrated the potential of this methodology to deliver highly functionalized single enantiomers from simple starting materials *(Scheme 20)*.



Scheme 19

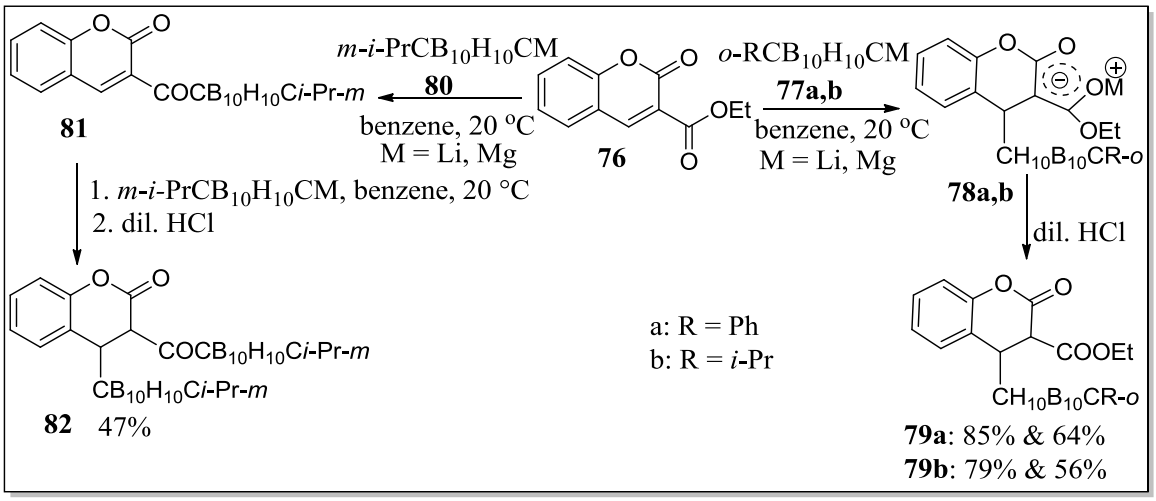


Scheme 20

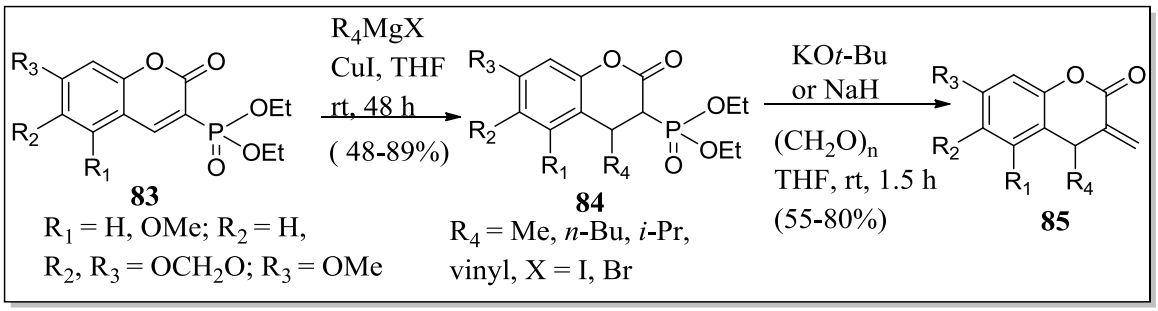
Adekenov and co-workers have described reactions of lithium and magnesium derivatives of *o*- and *m*-carboranes with 3-ethoxycarbonyl coumarin and coumarin for the synthesis of 3,4-dihydrocoumarin derivatives.[90] Lithium and magnesium derivatives of substituted *o*-carboranes **77a** and **77b** reacted with 3-ethoxycarbonylcoumarin **76** to give **78** which on acidification gave 3-ethoxy carbonyl-4-(*R*-*o*-carboranyl)-3,4-dihydrocoumarins (**79a** and **79b**). The *m*-carboranes, *m*-*i*-Pr$CB_{10}H_{10}$CM (**80**) were also used to give **82** *(Scheme 21)*.

Janecki and co-worker synthesized 3-methylidenechroman-2-ones, or their rearrangement products 3-methylchromen-2-ones, by nucleophilic Michael addition to 3-diethoxyphosphorylcoumarins followed by Horner-Wadsworth-Emmons (HWE)

reaction of the adducts with formaldehyde.[91] The same authors also employed a Michael addition/HWE olefination reaction sequence for the synthesis of biologically important 3-methylidenechroman-2-ones **85** from 3-diethoxyphosphorylchromen-2-ones **83**.[92] These chromenones **83** were in turn prepared by the reaction of 3-methoxy-2-diethoxyphosphoryl acrylate with phenols in the presence of methanesulfonic or trifluoromethanesulfonic acids *(Scheme 22)*. Similarly, several 3-diethoxyphosphorylbenzochromen-2-ones were subjected to a Michael addition/HWE olefination reaction sequence for the synthesis of biologically important 2-methylidenedihydrobenzochromen-3-ones.

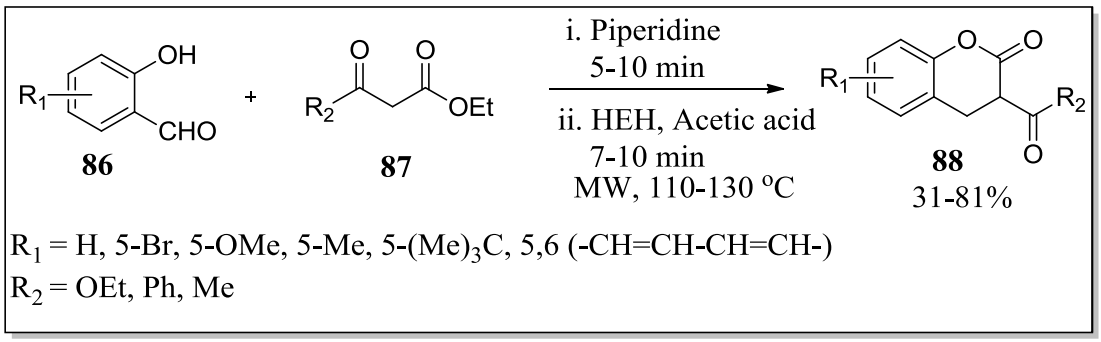


Scheme 21



Scheme 22

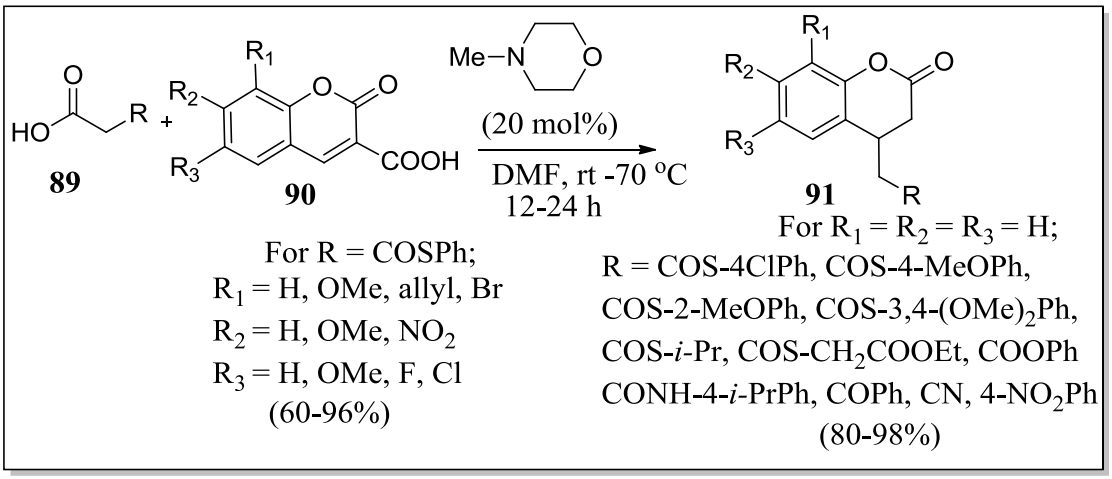
Zhou and co-workers have described a facile route to 3-substituted 3,4-dihydrocoumarins **88** from salicylaldehyde derivatives **86** and 1,3-dicarbonyl compounds **87** *via* tandem Knoevenagel and Hantzsch reactions under solvent-free microwave irradiation conditions *(Scheme 23)*.[93] Piperidine and acetic acid were used as catalysts and Hantzsch 1,4-



Scheme 23

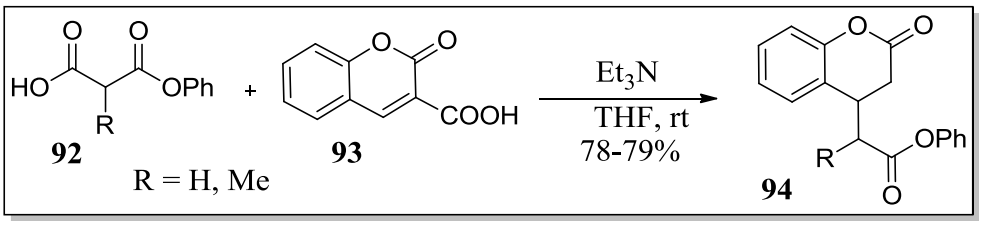
dihydropyridine (HEH) was used as a reducing agent. It was observed that the reducing action of HEH was inhibited by piperidine and hence, a two-step reaction was carried out in one-pot which involved addition of piperidine followed by HEH and acetic acid to the reaction mixture, without isolation of the coumarin intermediate.

Wang and co-workers have reported a facile double decarboxylation process for the synthesis of 4-substituted dihydrocoumarins **91** *(Scheme 24)* in moderate to excellent yields starting from acids **89** and coumarin 3-carboxylic acids **90** under base catalysis.[94]



Scheme 24

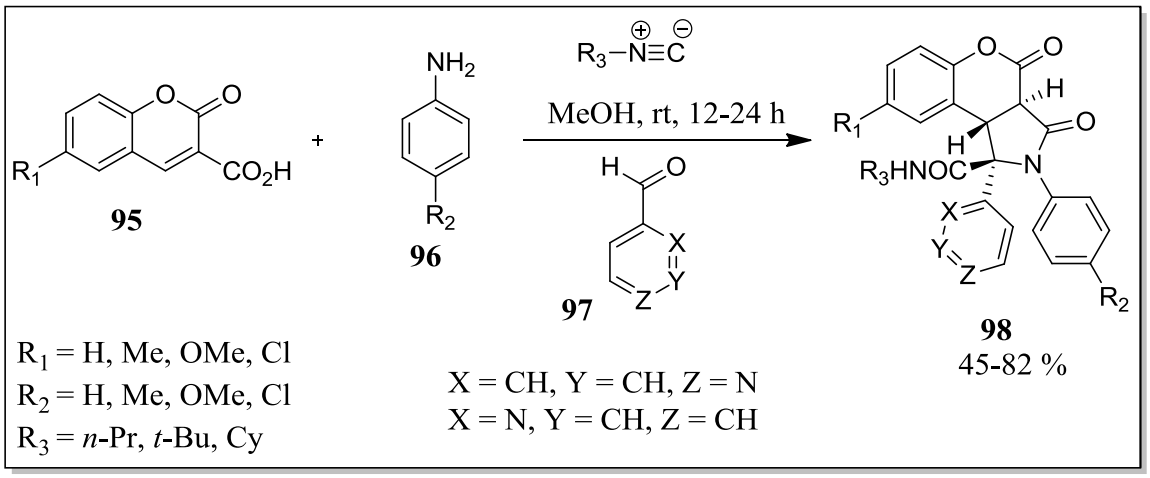
Malonic acid half oxyesters (MAHOs) **92** were shown by Fagnou and co-workers[95] to undergo decarboxylative nucleophilic addition reactions with coumarin **93** in the presence of triethylamine *(Scheme 25)*.



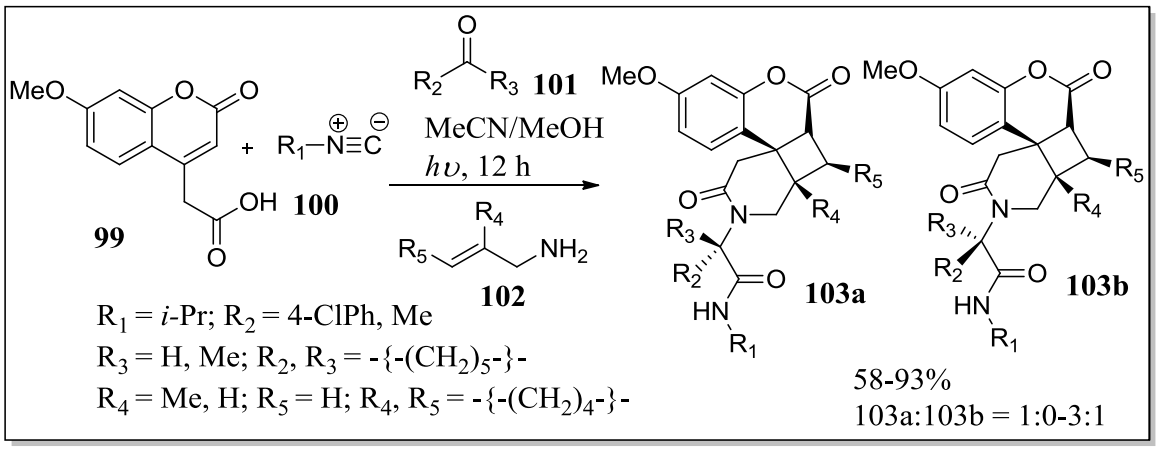
Scheme 25

Che and co-workers have synthesized chromeno[3,4-*c*]pyrrole-3,4-diones **98** starting from coumarin-3-carboxylic acids **95** by employing sequential Ugi and intramolecular Michael reactions *(Scheme 26)*.[96]

Zanze *et al*. have synthesized novel chromanones **103** starting from chromenone acetic acid **99** by carrying out sequential Ugi multicomponent reaction and [2+2] enone-olefin photochemical cycloaddition. In most cases only two diastereomers were formed *(Scheme 27)*.[97]



Scheme 26



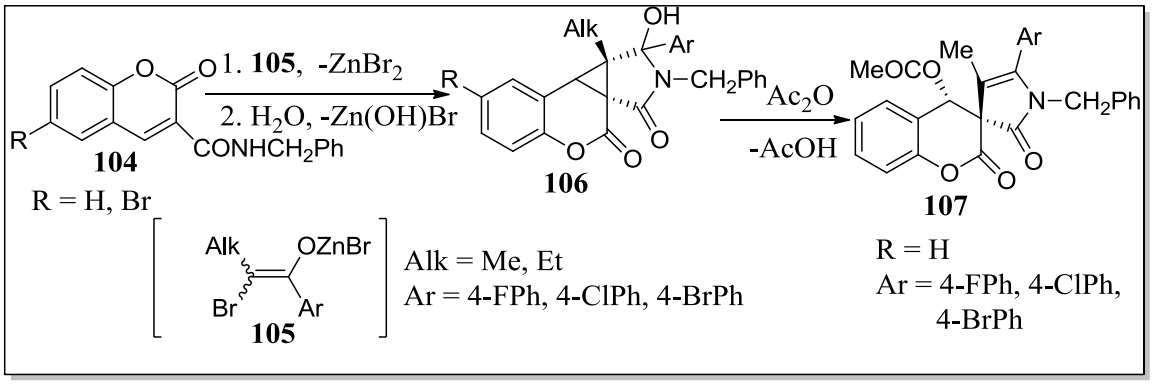
Scheme 27

Shchepin *et al.*[98] described the reaction of zinc enolates[99] **105** with 6-substituted 2-oxochromene-3-carboxylic acid *N*-benzylamine **104** to give 8-substituted 9*c*-alkyl-1-aryl-2-benzyl-1-hydroxy-1,2,9*b*,9*c*-tetrahydro-5-oxa-2-aza-cyclopenta[2,3]cyclopropa[1,2-*a*]naphthalene-3,4-diones **106**; the acylation of these compounds occurred *via* an unexpected rearrangement to give 4′-alkyl-5′-aryl-1′-benzyl-3,4,2′,3′-tetrahydro-2,2′-dioxospiro[chroman-3,3′-pyrrol]-4-yl acetates **107** *(Scheme 28)*.

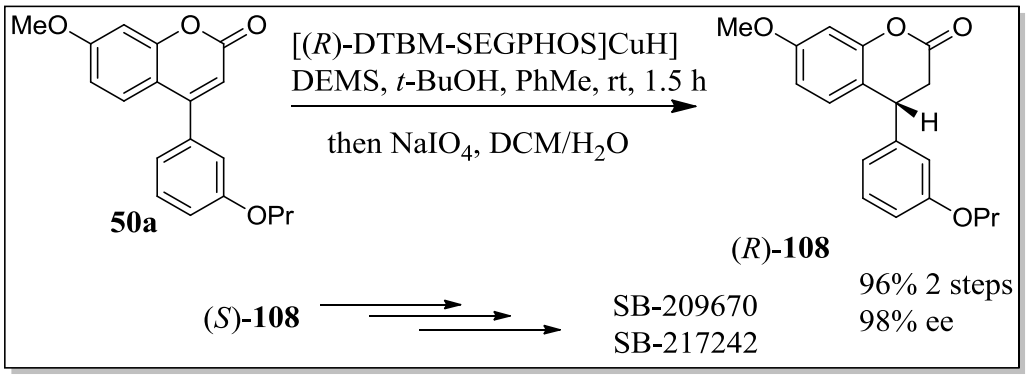
Gallagher *et al.* synthesized the *R*-enantiomer of dihydrocoumarin **108** from **50a** by metal-catalyzed hydrosilylation, followed by oxidation of the crude material by $NaIO_4$.

The *S*-isomer of **108** serves as a starting point for preparation of potent endothelin antagonists, SB-209670 and SB-217242 *(Scheme 29).*[100]

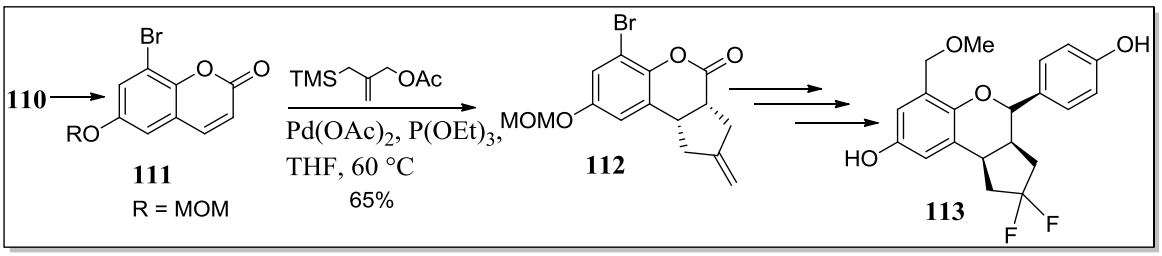
Richardson *et al.*[101,102] have successfully prepared a benzopyran derivative, a late stage intermediate **113** *(Scheme 30)*[101] and combined A-ring and C-ring modifications of benzopyran scaffolds to carry out simultaneous structure-activity relationship (SAR) studies. Modifications improved the estrogen receptor (ER) *β*-selectivity up to 83-fold. MOM Ether of 8-bromo-6-hydroxycoumarin **110** was subjected to Trost transition metal-catalyzed [3+2] trimethylenemethane (TMM) cycloaddition to give a cyclopentane ring containing an *exo*-methylene group onto lactone **112**, which was transformed into the desired compound **113**.



Scheme 28

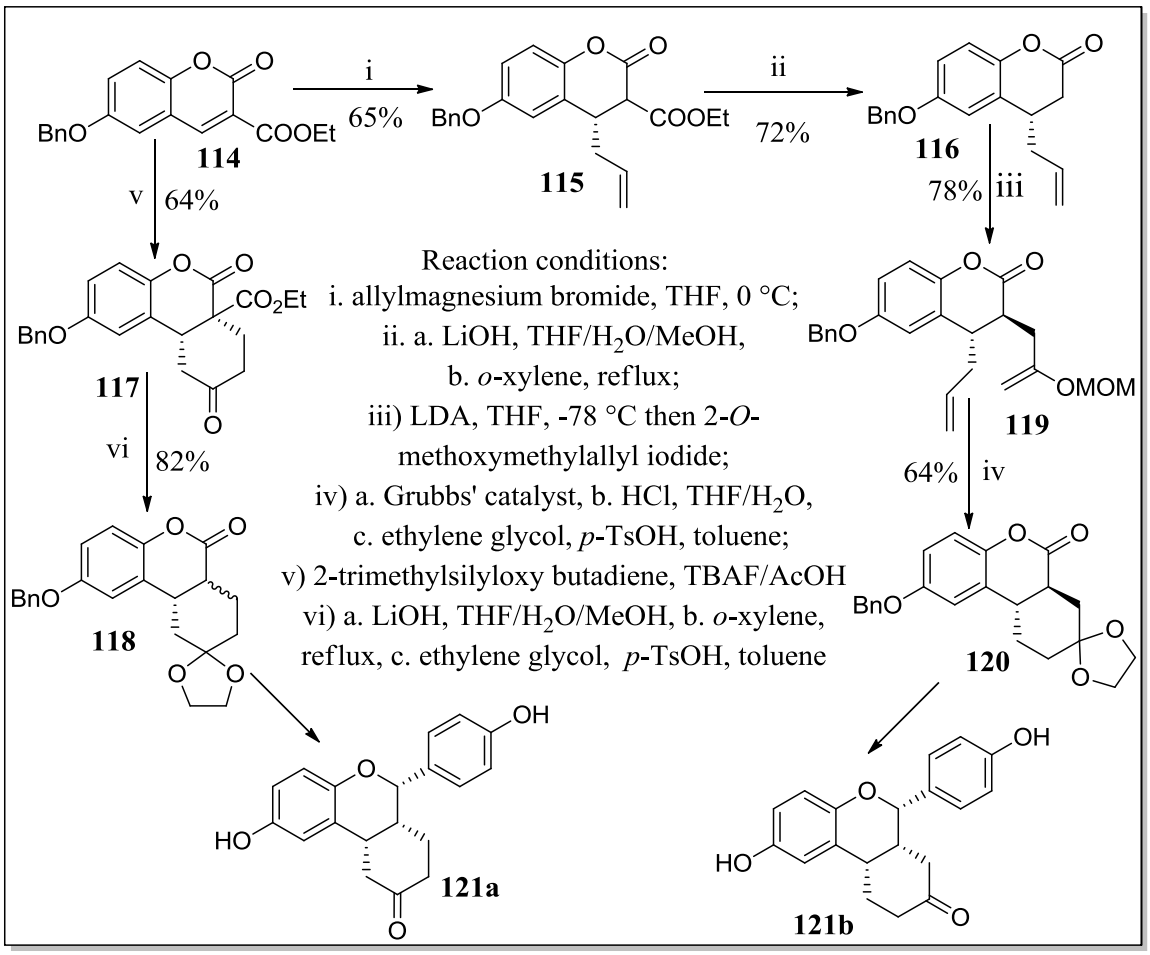


Scheme 29



Scheme 30

Richardson *et al.*[102] also described the synthesis of cyclohexanones **121a** and **121b** intermediates for SAR studies of the C-ring on the benzopyran scaffold. Coumarin **114** underwent a Diels-Alder reaction with 2-trimethylsilyloxybutadiene under thermal conditions to give tricycle **117** *(Scheme 31)*. It was decarboxylated *via* a two-step protocol, and the ketone moiety of the resultant intermediate was protected as a ketal to afford **118**. Michael addition of allylmagnesium bromide to **114** gave the *β*-ketolactone **115** which, on saponification and decarboxylation, afforded *β*-allyl lactone **116**. Alkylation of **116** with 2-*O*-methoxymethylallyl iodide gave the Ring Closing Metathesis (RCM) substrate **119**, which was subjected to the RCM protocol using the second generation Grubbs' catalyst to afford compound **120**. Compounds **118** and **120** were further elaborated to the cyclohexanones **121a** and **121b**.

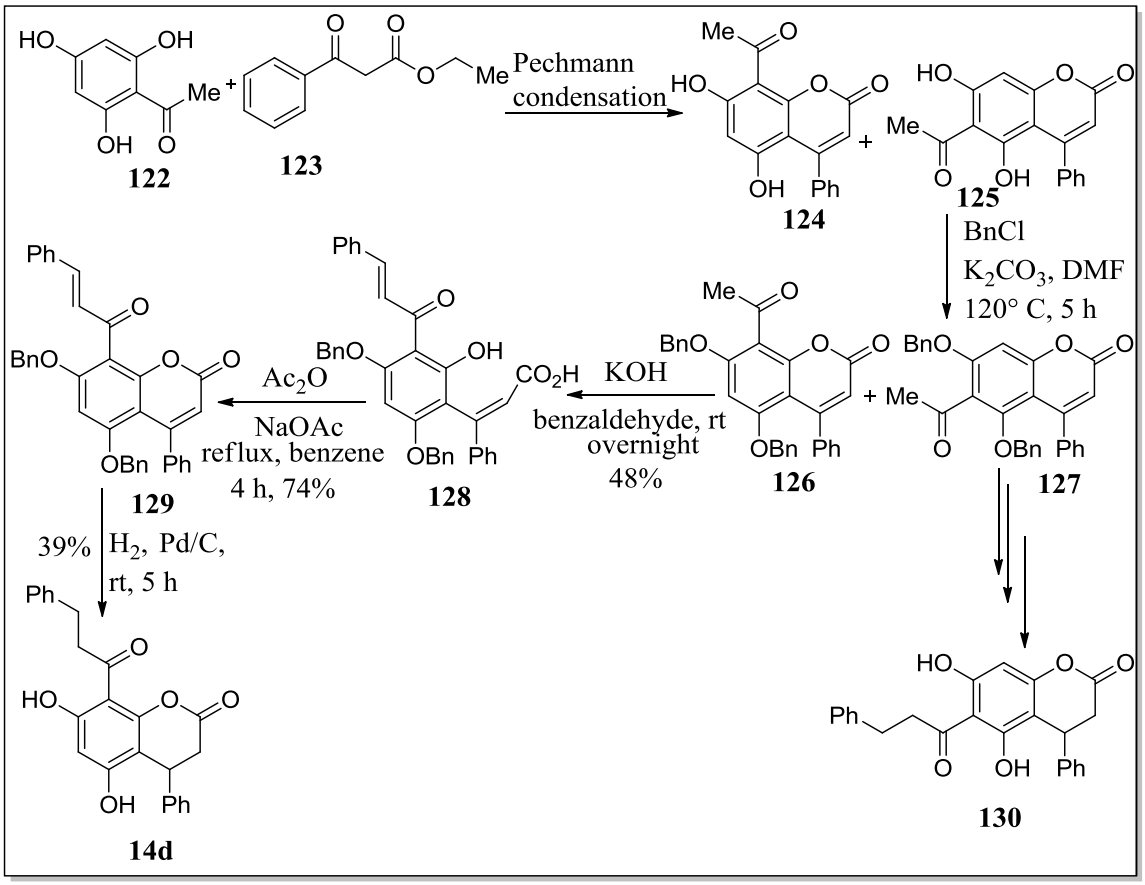


Scheme 31

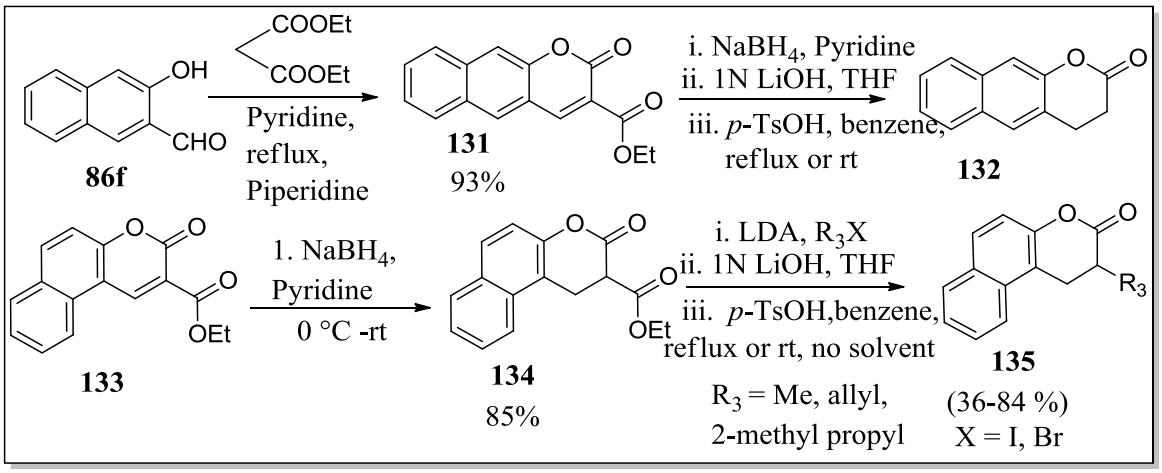
Asai *et al.* have confirmed the structures of naturally occurring compounds **14d** and **16c**, by authentic synthesis, **14d** and **16c** are important constituents of exudates of *Pityrogramma calomelanos*.[103] Pechmann condensation of phloroacetophenone with ethyl benzoylacetate afforded a mixture of compounds **124** and **125**, which on

benzylation gave a mixture of dibenzyl ethers **126** and **127**, respectively *(Scheme 32)*. Condensation of **126** with benzaldehyde in the presence of KOH gave the chalcone **128** *via* lactone cleavage. Further cyclization of **128** into **129** was accomplished by treatment with acetic anhydride and fused sodium acetate. Hydrogenation of **129** over Pd-C gave **14d**. Similarly, the synthesis of compound **130** was achieved from **127**.

Bedalov and co-workers prepared analogues of splitomicin (and evaluated their relative sir2 growth stimulating activity) through several reactions such as the Knoevenagel condensation, $NaBH_4$ reduction, alkylation, ester hydrolysis, decarboxylation/ring closure *etc. (Scheme 33)*.[51]

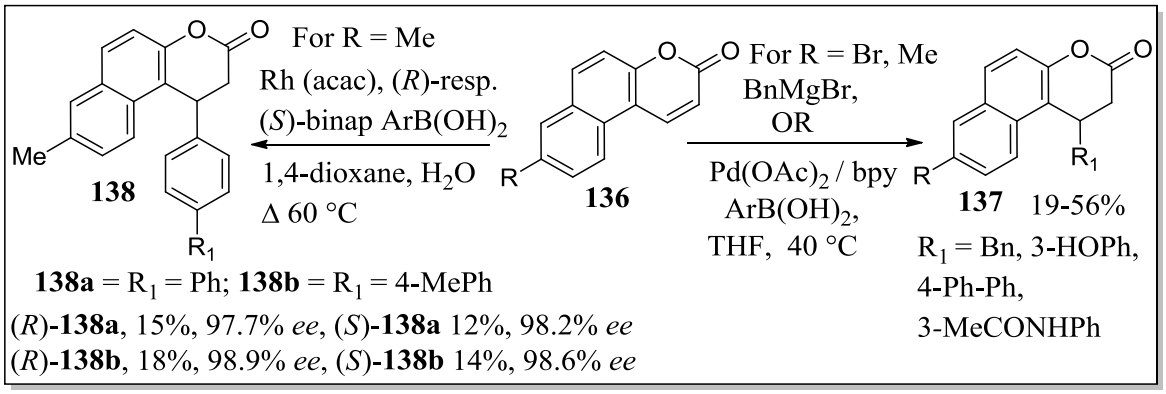


Scheme 32



Scheme 33

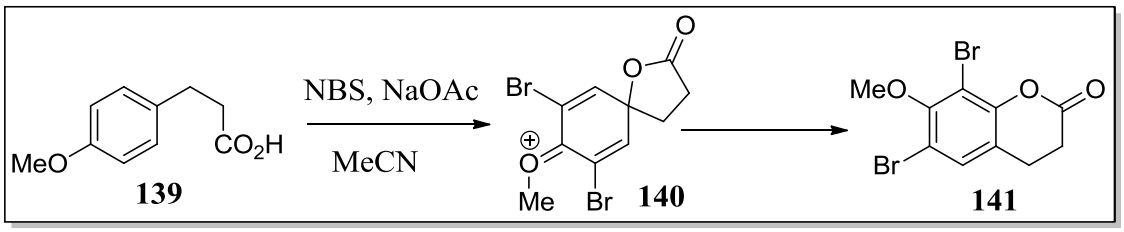
Jung and co-workers have demonstrated detailed SAR on splitomicin derivatives and their inhibition of recombinant sirt2. They synthesized a series of *β*-aryl-splitomicins **136** by acid-catalyzed cyclization of *β*-naphthols and propiolic acid. Further, palladium-catalyzed conjugate addition of arylboronic acids or Grignard reagent was used to make derivatives **137**. Two *β*-phenyl-8-methylsplitomicins **138** were synthesized *via* asymmetric conjugate addition to angular naphthocoumarins using a chiral rhodium catalyst *(Scheme 34).*[52]



Scheme 34

1.2.2: From 3-Phenylpropanoic acids (Route B)

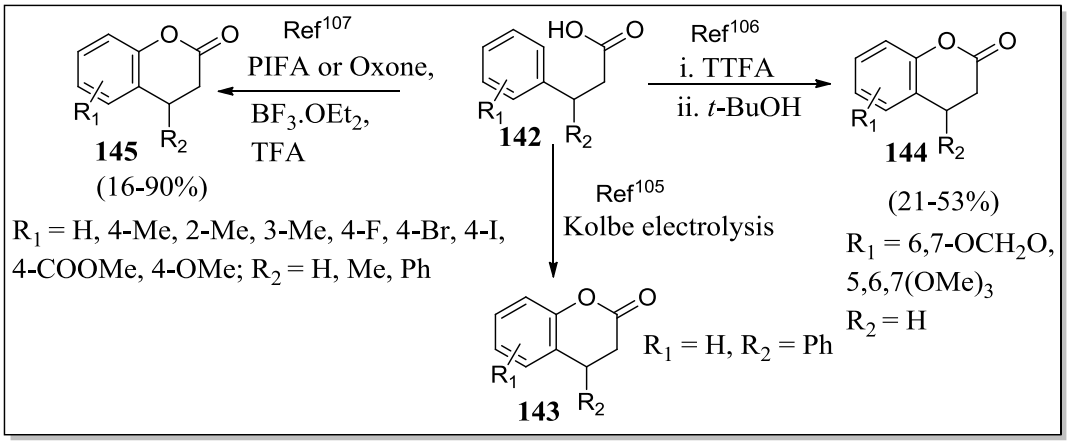
Reaction of 4-methoxyphenylpropanoic acid with NBS in buffered (NaOAc-MeCN) solution gave dihydrocoumarin **141** by way of intermediate **140** *(Scheme 35).*[104]



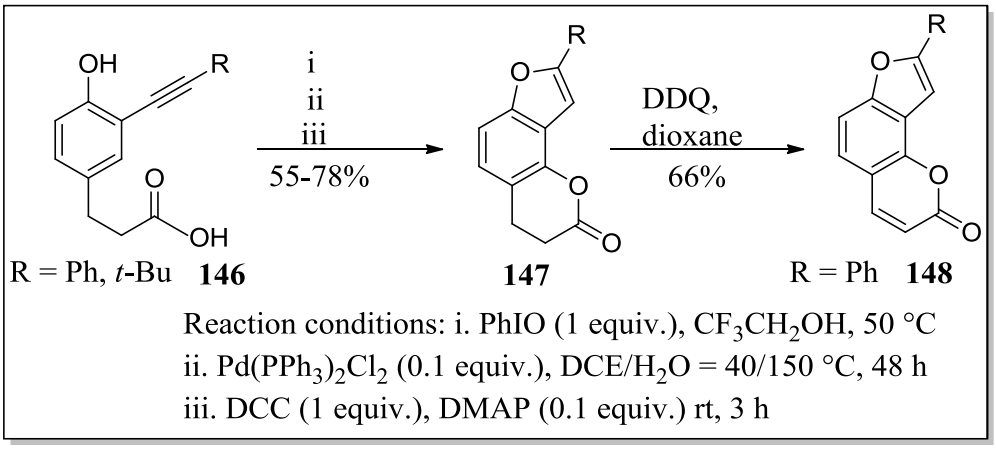
Scheme 35

In 1964, Bonner and Mango found 4-phenyl-3,4-dihydrocoumarin **143** as a product of Kolbe electrolysis of 3,3-diphenylpropanoic acid in acetic acid containing acetate ion *(Scheme 36).*[105] Dihydrocoumarins **144** have also been synthesized *via* intramolecular capture of radical cation intermediates from 3-(alkoxyaryl)propanoic acids **142** *(Scheme 36)* by oxidation with thallium (III) trifluoroacetate, followed by quenching with *t*-butyl alcohol.[106] Gu and Xue developed a novel method for the synthesis of 3,4-dihydrocoumarins **145** through direct oxidative cyclization of 3-arylpropanoic acids **142** using phenyliodine(III) *bis*(trifluoroacetate) (PIFA) or oxone as an oxidant.[107] PIFA (or oxone) as an oxidant and $BF_3 \cdot OEt_2$ as an additive in TFA was chosen as the most desirable condition *(Scheme 36).*

Ye *et al.*[108] synthesized 3,4-dihydrofuro[2,3-*h*]chromen-2-ones **147** by oxidative de-aromatization of 3-(3-alkynyl-4-hydroxyphenyl)propanoic acids **146** along with a cascade transition metal catalyzed cyclization/addition/aromatization/lactonization sequence. Further oxidation of **147** with DDQ afforded angelicin derivative **148** *(Scheme 37).*

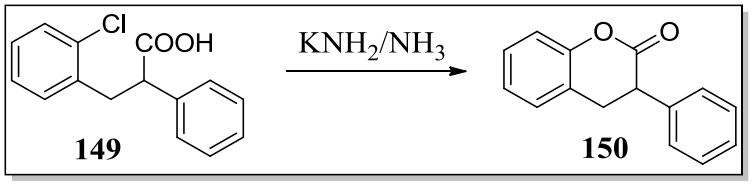


Scheme 36



Scheme 37

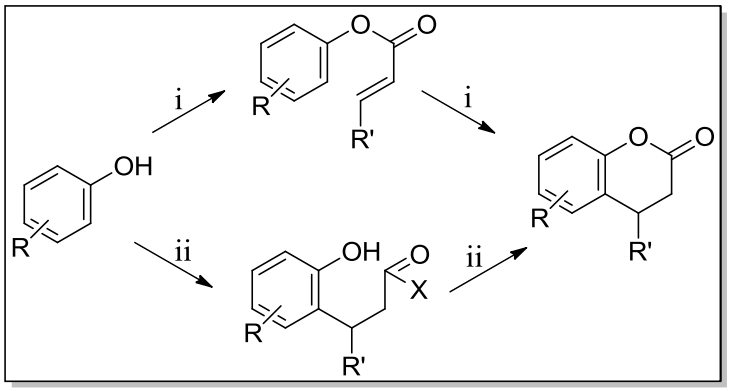
Kessar *et al.* obtained 3-phenyl-3,4-dihydrocoumarin **150** from *α*-(*o*-chlorobenzyl)phenylacetic acid **149** on treatment with potassium amide in liquid ammonia *(Scheme 38).*[109]



Scheme 38

1.2.3: From Phenols (Route C)

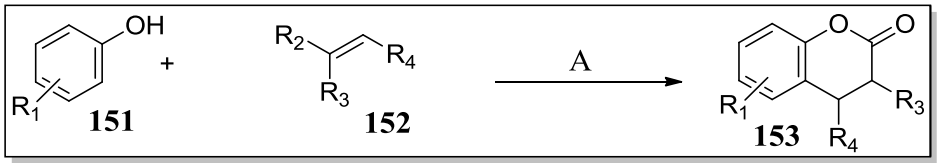
The synthesis of chroman-2-ones starting from phenols can proceed through two paths, either *via* esterification followed by intramolecular Michael reaction (i) or *via* intermolecular Michael reaction followed by an intramolecular lactonization reaction (ii) *(Scheme 39).* Most examples follow the first reaction pathway of esterification followed by Michael reaction while in the case of activated Michael acceptors the second pathway is followed.



Scheme 39

Several synthetic approaches towards the construction of 4-arylcoumarins have been reviewed by Garazd and co-workers.[110] The synthesis of dihydrocoumarins has also been mentioned briefly using the Pondorf reaction of phenols with maleic or fumaric acids in the presence of sulfuric acid. Several 3,4-dihydro-4-phenylcoumarins have been prepared by reactions of phenols with cinnamic acids or cinnamates or the corresponding nitriles. Various condensation agents such as $AlCl_3$, HCl, $ZnCl_2$, PPA, *etc.* have been employed.[111-118] Synthetic methods for the preparation of dihydrocoumarins from phenols and various Michael acceptors *via* route C are summarized in *Table 2*. The condensation of phenols with cinnamic acid to give 4-aryl-3,4-dihydrocoumarins using

sulfuric acid in acetic acid was first demonstrated by Liebermann and Hartmann.[119] It was subsequently applied by von Auwers to *β*-naphthol for the preparation of 3,4-dihydro-4-phenyl-5,6-benzocoumarin.[120]



Scheme 40

Later Buu-Hoï *et al.* extended this protocol to a series of phenols and substituted cinnamic acids. They found that the reaction was best performed in toluene or tetralin.[121] PPA has been used extensively as a condensing agent in the reaction of phenols and cinnamic acids.[122,123] In the course of these reactions it was observed that the nature of

Table 2: Synthetic methods for the Preparation of Dihydrocoumarins from Phenols.

151	**152**					
R_1	R_2	R_3	R_4	A	Yield (%)	Ref
H, Me, Cl, *i*-Pr, OMe, 2,3-(-CH=CH-CH=CH-), 3,4-(-$CH_2CH_2CH_2$-)	COOH	H	Ph, 4-MeOPh, 4-ClPh, 3,4 (MeO)(HO)Ph	**H_2SO_4** tetralin/ toluene, Δ 2 h	29-60	*121*
H, Me, OMe, Cl	CN	H	H, Me	1. **$AlCl_3$** 2. **HCl**	4-80	*132*
H, OH, Me, Cl	COOH	H	H, Me	**$AlCl_3$/ PPE**	20-58	*133*
H, Me, OH, 3,4-(-CH=CH-CH=CH-)	COOEt	H	3,4(OMe)(OH)Ph, 3,4-$(OMe)_2$Ph, Ph	**$FeCl_3$** rt or Δ 2 h $CHCl_3$	6-92	*134*
OMe, *t*-Bu, Me, Cl	COOH	H	4-MeOPh, 3,4,5-$(MeO)_3$Ph, 4-MePh, 3MePh, 3,4-(OCH_2O)-Ph, 2-MeOPh	**TFA**-DCM, rt, 16-40 h	72-99	*137*

OMe, H, Me, Br, 3,4-(-CH=CH-CH=CH-), 3,4-(-OCH_2O-)	COOH, COOEt	H	3,4-Me_2Ph, 4-MeOPh, 3,4-$(MeO)_2$Ph, 3,4-(Me) (HO)Ph, 3,4(MeO) (HO)Ph, 4-MePh, 3,4,5-$(MeO)_3$Ph, 2,3,4-$(MeO)_3$Ph	**TFA**, rt 24 h	8-100	*138*
$NHCO_2Me$	COOH, COOEt	H	4-MeOPh, 3,4-$(MeO)_2$ Ph, 3,4-(-OCH_2O-)Ph	**TFA**-DCM, rt, 24 h	35-85	*140*
OMe	COOMe	H	Me_2	**$MeSO_3H$**, 70 °C , 3 h	40	*141*
OH	COOH	H	H	**Mont. KSF**, MW, 95-110 °C 10 min	72-84	*143*
H, OMe, Cl, Me, 3,4-(-CH=CH-CH=CH-)	COCl	H	Ph	**Mont. K-10** MW**,** PhCl, 160 °C 5 min	19-92	*146*
H, OH,	COOH	H, Ph	H, Ph	**1% WD/SiO_2** MW 5-15 min	40-82	*148*
H, Me, OMe	COOH	H	Ph, 4-MeOPh, 3,4-$(MeO)_2$Ph, 3,4,5-$(MeO)_3$Ph	**HY Zeolite** reflux, toluene, 4h	65-82	*149*
OH, Me	COOH	H	Ph	1. Conc. **HCl**, HCl gas	81-91	*150*

				reflux, 4-6 h 2. **Ac_2O**, pyridine, 12 h		
OH, Me	COOH	H	4-MeOPh, 2,5-$(MeO)_2$Ph, 3,4,5-$(MeO)_3$Ph	1. **$BF_3.OEt_2$**, **$POCl_3$** 4-12 h 2. **Ac_2O**, pyridine, 12 h	54-96	*150*
H, OMe, Me	COOH	H	Ph, 4-MeOPh, 3,4-$(MeO)_2$Ph, 3,4,5-$(MeO)_3$Ph	**TFA** Δ toluene 30 min	65-82	*151*
H, Me, Cl, *t*-Bu, 2,3-(-CH=CH-CH=CH-)	COOH	H	Ph, 4-ClPh, 4-MeOPh	***p*-TsOH** 125 °C , 3 h	87-99	*154*
OH	COOH	H	4-MeOPh, 3-MeOPh, 2-MeOPh, 4-HOPh, 3,4-(HO)(MeO)Ph, 3,4-(MeO)(HO)Ph, 2,3-$(HO)_2$-4-MeOPh	**$(CF_3SO_3)_3$ Y** MW neat 7-20 min	65-80	*156*
H, OH, Me, OMe	COOH	H, Me	H	**Zeolite H-Beta** Δ toluene, 4 h	2-73	*157*
Me, OH, H, Cl , 2,3-(-CH=CH-CH=CH-),	COOH	H	Ph, 4-MeOPh	20 mol% **Iodine** Δ	60-85	*158*

3,4-(-CH=CH-CH=CH-)				120-130 °C 1-5 h		
OMe, OH, 3,4-(-OCH_2O-)	COOMe	CO-OMe	Ph, 2-CF_3Ph,4-BrPh, 4-CO_2MePh, 2-MeO Ph, 3-MeOPh,4-MeO Ph, 2-BrPh, 2,4-$(MeO)_2$ Ph, 4-MePh, 4-FPh, 2,4-$(NO_2)_2$Ph, 4-NO_2Ph	2.5-10 mol% **$TiCl_4$** DCM 0 °C - rt 30-72 h	63-95 dr 7:1 - >20:1	*159*
H, Me, F, Cl, 3,4-(-CH=CH-CH=CH-)	COOH	CF_3	H	**CF_3SO_3H** rt- 50 °C 4-24 h	17-95	*160*
OH, Me, OMe, 3,4-(-CH=CH-CH=CH-), 4,5-(-CH=CH-CH=CH-), 3,4-[-CH=C(OH)-CH=CH-]	COOMe	H	4-MeOPh, 4-OHPh, 4-Me_2NPh, 4-MePh, Ph, 4-FPh, 4-ClPh, 4-BrPh, 4-CF_3Ph	*o*-xylene Δ 142 °C , N_2 1-17 h	21-90	*161*
3,5-$(OH)_2$, 3-OH-4,5-(-CH=CH-CH=CH-)	COY Y= *N*-imidazolyl, 1,2,4-triazol-1-yl	H	4-MeOPh, 4-MePh, Ph, 4-FPh, 4-ClPh, 4-BrPh, 4- NO_2Ph	**DBU**, DCM/THF reflux, N_2 1-2.5 h	31-80	*162*
OH, 3,4-(-CH=CH-CH=CH-)	COOH	H	ferrocenyl	Conc. **H_2SO_4** Δ 90 °C 0.5-3 h	45-50	*163*
OH, Cl, Me, Br, OMe	COOH	H	4-HOPh, 3,4-(MeO)(HO)Ph	**TFA**, NaOAc THF:	< 1-99	*164*

				benzene Δ 7-48 h		
H, Me, Et, *i*-Pr, *t*-Bu, OMe, Cl	CO_2Et, CO_2-2 MeOPh, CO_2 *o*-cresyl	H	H	20 mol% **LiH**, Δ 180-230 °C, 1-91 h	trace -73	*165*

products obtained was determined by various factors such as the nature of the phenol, the position and the type of substituent on the phenyl ring of the cinnamic acid, the stoichiometry of the reactants, the composition of PPA, the temperature, the reaction period, the solvent, *etc.* In addition, the reactions of cinnamic acid with phenol, catechol, hydroquinone, pyrogallol, 2-naphthol and resorcinol in the presence of PPA were studied by Majumder *et al.*[124] Interestingly, resorcinol yielded 7-hydroxy-3,4-dihydro-4-phenylcoumarin as the sole product instead of 7-hydroxyflavanone, contrary to earlier observations made by Talapatra *et al.*[123] Amsberry and Borchardt synthesized dihydrocoumarins from phenols and acrylate in the presence of sulfuric acid,[125] which were then converted into model hydroxy amides (prodrugs).

Carpino *et al*. utilized methanesulfonic acid both as solvent and as catalyst for the synthesis of benzopyranones by condensation of phenols and 3,3-dimethylacrylate. Furthermore, these workers extended the synthesis for the preparation of biologically important quinone propionic acid esters or amides.[126] The carbon-carbon cyanoethylation of activated phenols, such as resorcinol, is known to give *β*-substituted propionitriles in the presence of anhyd. zinc chloride and dry hydrogen chloride;[127] phenol itself does not react under these conditions. The addition of vinylidene cyanide to phenol in the presence of anhyd. aluminium chloride gives *β*-(*p*-hydroxyphenyl)-*α*-cyanopropionitrile and traces of dihydrocoumarin.[128] The cyanoethylation of phenol by acrylonitrile gives *β*-(*p*-hydroxyphenyl)cyanopropionitrile and a small amount of dihydrocoumarin.[129] Kost and co-authors have reported the cyanoethylation of *p*-cresol to give *β*-(2-hydroxy-5-methylphenyl)propionitrile and a trace of 6-methyldihydrocoumarin.[130,131] Sato *et al.* showed that the reaction of vinylidene cyanide with phenol or *para*-substituted phenols in the presence of anhydrous aluminium chloride and dry hydrogen chloride gives dihydrocoumarin or 6-substituted dihyrocoumarins in one step.[132] However this method

failed for phenols which are sufficiently deactivated by electron-withdrawing groups. Similarly, reaction of crotononitrile with *para*-substituted phenols gave the corresponding 4-methyldihydrocoumarin derivatives. This methodology was also extended to α,β-unsaturated acids and their esters. Dihydrocoumarins were also obtained using the ethyl ester of polyphosphoric acid (PPE).[133] Das *et al.* have reported the synthesis of dihydrocoumarins from phenols and cinnamates using $FeCl_3$ as catalyst.[134]

Activation of aromatic C-H bonds for addition to C-C multiple bonds is an important synthetic tool for synthesizing dihydrocoumarins.[135] Fujiwara and co-workers demonstrated the formation of 3,4-dihydrocoumarins by addition of electron-rich phenols to 4-methoxycinnamic acids in excellent yields using TFA-DCM at room temperature in the presence of 1 mol% $Pd(OAc)_2$.[136] Tunge and co-workers found that 4-aryl-3,4-dihydrocoumarins can be prepared from phenols and cinnamic acids in TFA-DCM at room temperature in the absence of $Pd(OAc)_2$ without affecting the yield.[137] In the same year, Kitamura and co-workers also described a facile procedure for the synthesis of 4-aryl substituted dihydrocoumarins from phenols and cinnamic acid and esters using trifluoroacetic acid at room temperature.[138] The combination of electron-rich cinnamic acids/esters and electron-rich phenols gave nearly quantitative yields. With electron poor constituents it was observed that the reaction became sluggish. Some dihydrocoumarin derivatives were also formed as side products of the Pt-catalyzed reaction between phenols and propiolic acids in the presence of TFA.[139]

Imasheva *et al.* have used the same TFA mediated procedure for the synthesis of dihydrocoumarins with a carbamate function attached to C-6 or C-7 from *meta*- and *para*- hydroxy substituted methylphenylcarbamates with cinnamic acids or esters containing electron donating substituents.[140] Condensation of dimethoxyphenol with 3,3-dimethylacrylate in methanesulfonic acid was carried out to give a dihydrocoumarin which was reduced to a diol using LAH and the primary alcohol was then protected as a TBDMS ether.[141] This product was used as a coupling linker for the synthesis of cyclic pro-drugs; a new pro-drug with a modified phenylpropionic acid promoiety was also synthesized.[142] Condensation of phenols with propenoic acid using solid acid catalysts and microwave irradiation was employed by Hoz *et al.* to prepare dihydrocoumarins in good yields.[143]

Negi and co-workers obtained a series of dihydrocoumarin derivatives as novel podophyllotoxin (PDT) analogues and evaluated their cytotoxic activity against various human cancer cell lines.[144] Dihydrocoumarins were prepared using the reported method

from phenols and cinnamates in the presence of TFA. Estrone, when treated with methyl-3,4,5-trimethoxy phenylcinnamate, gave 3′,4′-dihydro-4′-(3,4,5-trimethoxyphenyl)estra-1(10),2,4-trieno[3,2-*b*]pyran-2′,17-dione in 58% yield. 3,4-Dihydro-5,7-dimethoxy-4-(3,4,5-trimethoxy phenyl)coumarin exhibited good cytotoxicity against colon cancer cell lines.

A simple, one-pot synthesis of 3,4-dihydro-4-phenylcoumarins from phenols and cinnamic acids using Montmorillonite K-10 clay in conjuction with microwave irradiation was described by Singh *et al*.[145] Microwave assisted one-pot synthesis of dihydrocoumarins from phenols and cinnamoyl chloride has been reported by Ma and co-workers[146] using Montmorillonite K-10 catalyst. Lee *et al.* reported the preparation of 3,4-dihydrocoumarins using Montmorillonite K-10 catalyzed condensation of cinnamoyl chlorides and variously substituted phenols in nitrobenzene.[147] Romanelli and co-workers have reported a simple, clean preparation of dihydrocoumarins from phenols and cinnamic acids or propenoic acid under microwave heating using a silica supported Wells-Dawson heteropolyacid as catalyst.[148] Synthesis of substituted (±)-3,4-dihydrocoumarins involving esterification followed by ring closure was reported by Salunkhe and co-workers *via* reaction between phenols and substituted cinnamic acids catalysed by the ecofriendly catalyst H-Y Zeolite.[149]

Parmar and co-workers have carried out the condensation of various phenols with substituted cinnamic acids using conc. HCl-HCl gas or $BF_3{\cdot}OEt_2$ along with $POCl_3$ followed by acetylation of the free hydroxy group of the dihydrocoumarins.[150] They have also carried out biocatalytic resolution studies on these dihydrocoumarins. Thus, *Candida antarctica* lipase-catalyzed deacetylation of the racemic acetoxydihydrocoumarins was found to occur with moderate enantioselectivity. Zou and co-workers also made use of $BF_3{\cdot}OEt_2$ and $POCl_3$ to carry out condensation of phenols and cinnamic acids to give twelve 4-aryl-3,4-dihydrocoumarins.[49]

Salunkhe and co-workers reported the synthesis of 4-aryl-dihydrocoumarins by the condensation of phenols with cinnamic acids in refluxing trifluoroacetic acid. The structure of the products were confirmed by 2D-NOESY spectrum.[151] This was reported earlier by Kirtany[152] based on the IR absorption data for the compounds synthesized by Chaturvedi and Mulchandani.[153] Hydroarylation of cinnamic acids with electron-rich phenols mediated by *p*-TsOH to give dihydrocoumarins under metal-free and solvent-free conditions has been described by Jagdale and Sudalai.[154] In the case of phenolic substrates with *ortho* substituents such as Cl, Br, OMe and COOMe, the

dihydrocoumarins formed were labile and underwent hydrolysis on treatment with water and ethyl acetate to give the corresponding acids. If the reaction mixture was quenched with ethyl acetate followed by addition of water the corresponding phenolic esters were obtained. The authors also showed that esterification occurs first, followed by intramolecular hydroarylation and also synthesized (*R*)-tolterodine from 6-methyl-4-phenyl-3,4-dihydrocoumarin prepared by using the above mentioned methodology.[155]

Echevarria and co-worker have reported an efficient and rapid synthesis of 4-aryl-3,4-dihydrocoumarins by $(CF_3SO_3)_3Y$ catalysis under microwave irradiation, using substituted resorcinols and substituted cinnamic acids.[156] The direct synthesis of dihydrocoumarin derivatives from *m*-substituted phenols and *α, β*-unsaturated carboxylic acids catalyzed by zeolite H-Beta or Amberlyst-15 using toluene as solvent was studied by van Bekkum and co-workers.[157] The reaction mechanism was found to involve esterification followed by ring closure.

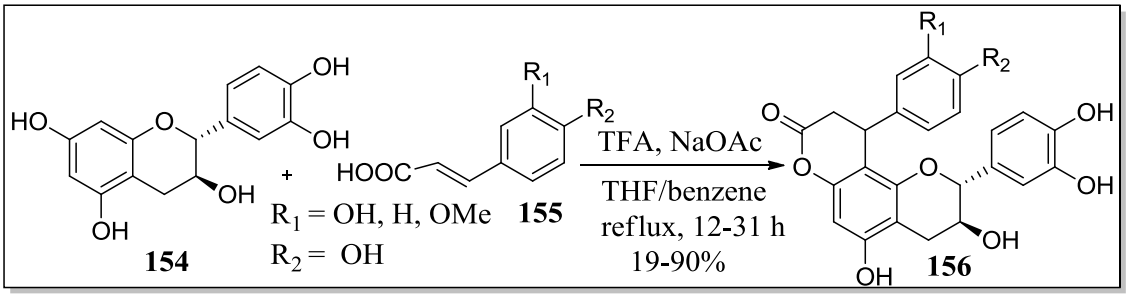
Recently, we reported the synthesis of 4-aryl-3,4-dihydrocoumarins by the reaction of phenols with cinnamic acids using molecular iodine as catalyst.[158] The reaction occurred *via* a tandem esterification-hydroarylation process.

Tunge and co-workers described the $TiCl_4$ catalyzed diastereoselective hydroarylation of benzylidene malonates by phenols to produce *trans*-substituted dihydrocoumarins.[159] They have also proved mechanistically the most probable sequence of the reaction to be hydroarylation followed by transesterification. Reaction of phenol and its derivatives with 2-(trifluoromethyl)acrylic acid in the presence of excess of triflic acid to give 3,4-dihydro-3-trifluoromethyl-*2H*-1-benzopyran-2-ones has been described by Surya Prakash *et al.*[160] Activated phenols reacted more rapidly compared to unactivated phenols, which gave mainly uncyclized vinyl aryl esters.

Speranza *et al.* have reported the uncatalyzed synthesis of dihydrocoumarins in moderate to good yields by reaction of phenols or naphthols with *p*-substituted cinnamates in *o*-xylene under reflux.[161] Further, this methodology was applied for the synthesis of calomelanol C by reacting 3-phenyl-1-(2,4,6-trihydroxyphenyl)-propan-1-one, (obtained by the reaction of phloroglucinol with 3-phenylpropionitrile and $ZnCl_2$) with methyl *p*-hydroxycinnamate in *o*-xylene. However, in the case of cinnamates bearing electron-withdrawing groups such as a nitro group, the reaction failed to give the desired product. However, they could overcome this problem by using *N*-(*E*)-cinnamoylazoles instead of cinnamates in the presence of DBU.[162]

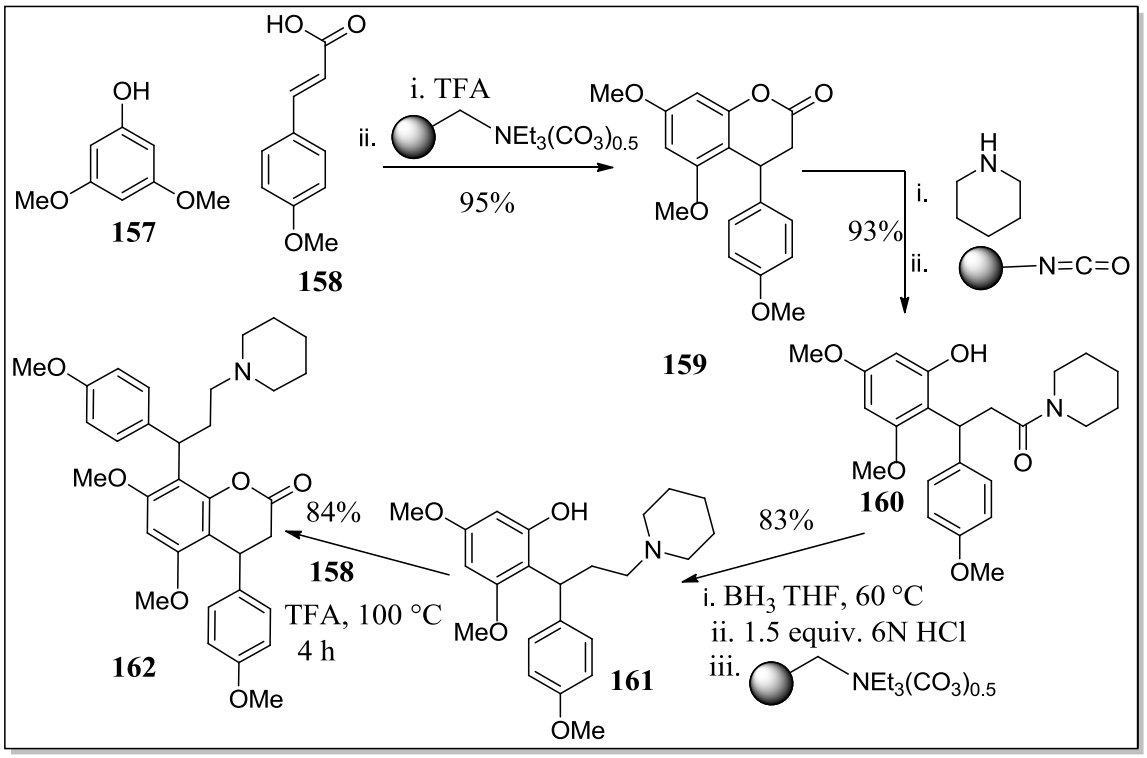
Wang *et al.* treated ferrocenylacrylic acid with a series of phenols; only resorcinol and 2-naphthol gave ring closure products namely ferrocenyl dihydrocoumarins. Other phenols gave esterified products.[163] A one-step synthesis of 4′,7-dihydroxy-4-phenyl-chroman-2-ones is described by Suthunuru and Biehl by treatment of phenols with cinnamic acids using TFA and NaOAc. The mechanism involves a dienone-phenol rearrangement followed by a Michael-type reaction.[164] Pickett and van Dort have reported the synthesis of DHC by heating an acrylic ester with an excess of a phenol in the presence of a base catalyst. Besides acrylic esters, methyl methacrylate, ethyl crotonate, ethyl 3,3-dimethylacrylate were also used.[165]

A one-pot regioselective synthesis of a series of phenylpropanoid-substituted flavan-3-ols **156** by treatment of catechin **154** and substituted cinnamic acids **155** with TFA and sodium acetate was developed by Kadota and co-workers *(Scheme 41)*. This reaction was also carried out using *epi*catechin in place of catechin. Mechanistically, the reaction was postulated to involve a dienone-phenol rearrangement followed by Michael-type reaction.[166]



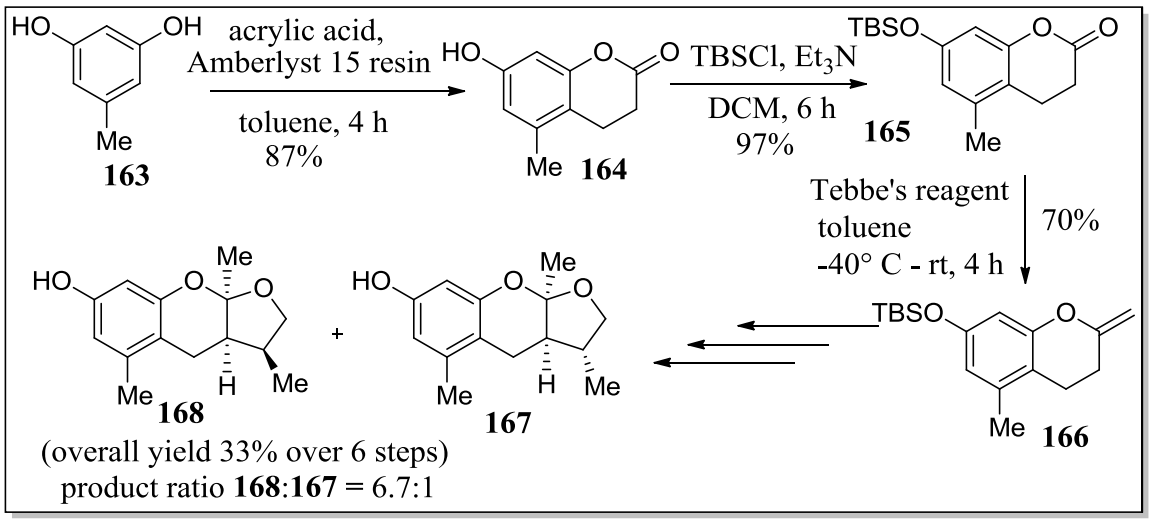
Scheme 41

Li and Tunge have extended their TFA catalyzed hydroarylation protocol to the synthesis of various 4-substituted dihydrocoumarins *(Scheme 42)*.[167] Thus, hydroarylation of cinnamic acid **158** with 3,5-dimethoxyphenol **157** in the presence of an acid scavenger (polystyrene supported MP-carbonate) to remove any unreacted starting materials provided the dihydrocoumarin **159** in 95% yield. Ring opening of dihydrocoumarin with piperidine in the presence of a polystyrene supported isocyanate (MP-NCO) scavenger of piperidine gave phenolic propanamide **160** which was reduced with borane. TFA-catalyzed hydroarylation of cinnamic acid with this product provided dihydrocoumarin **162** in 84% yield as a 1:1 mixture of diastereomers **162** *(Scheme 42)*.



Scheme 42

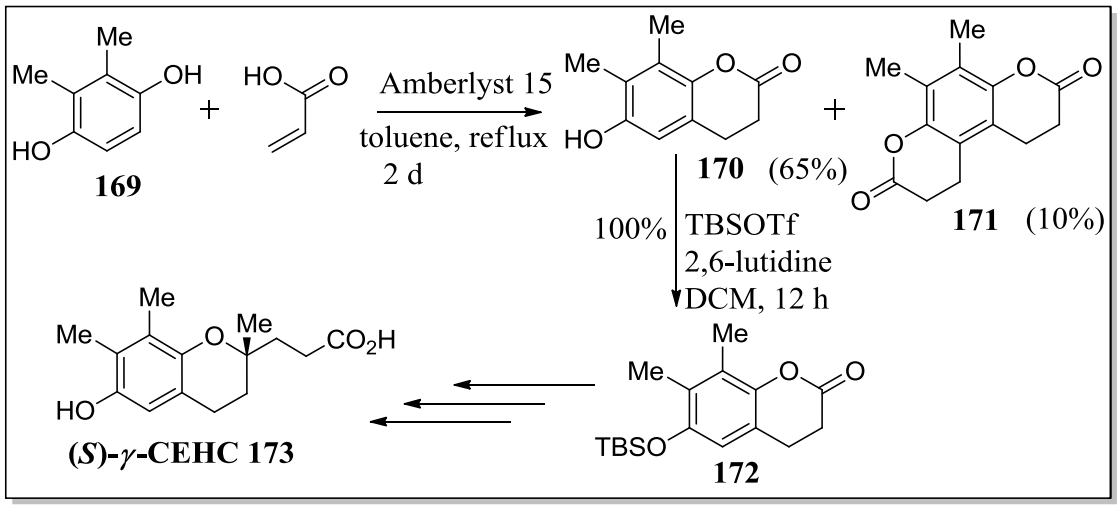
Murphy and co-workers have synthesized phytotoxic metabolite alboatrin **168** and its epimer **167** from 5-methyl-7-hydroxy-3,4 dihydrocoumarin **164** prepared from acid catalyzed condensation of orcinol with acrylic acid.[168] The free hydroxy group in **164** was protected, followed by formation of the exocyclic enol ether **166** using the Tebbe's reagent, which was transformed into a mixture of two diastereomers (6.7:1 ratio), with naturally occurring diastereomer **167** being the minor isomer *(Scheme 43)*. Similarly, splitomicin and derivatives were prepared by reaction of naphthols with excess acrylic acid in the presence of Amberlyst-15 ion exchange resin.[51] Jung and co-workers synthesized a series of *β*-arylsplitomicins by sulfuric acid-catalyzed cyclization of *β*-naphthols with cinnamic acids or acrylic acids.[52]



Scheme 43

The asymmetric synthesis of *γ*-tocopherol metabolite (*S*)-*γ*-CEHC was accomplished in 18.4% overall yield *via* the dihydrocoumarin intermediate **170** *(Scheme 44).*[169] (*S*)-*γ*-CEHC

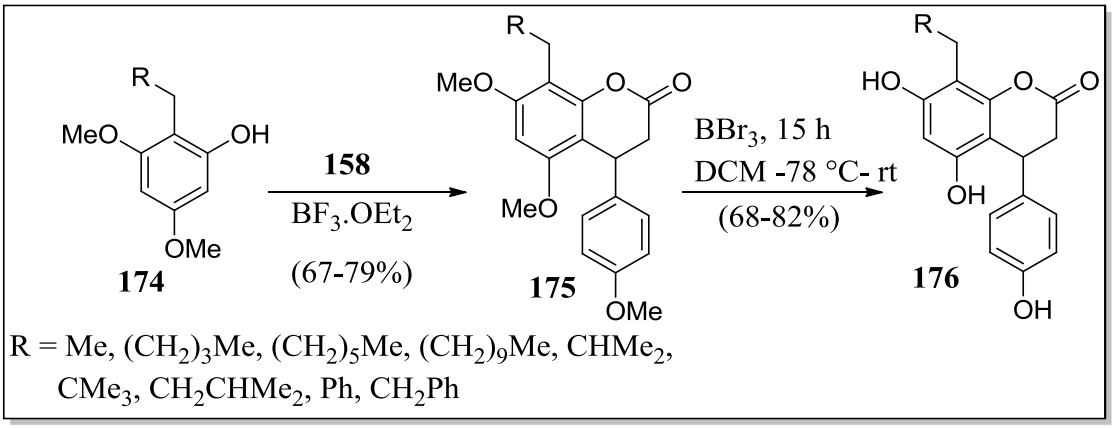
shows anti-oxidant, natriuretic, anti-inflammatory properties and inhibits the generation of prostaglandin E_2 synthesized during inflammation. Dihydrocoumarin **170** was obtained by condensation of 2,3-dimethyl-1,4-hydroquinone **169** with acrylic acid in the presence of an amberlyst in refluxing toluene. A small amount of dicoumarin **171** was also isolated and (*S*)-*γ*-CEHC **173** was obtained from compound **170**.



Scheme 44

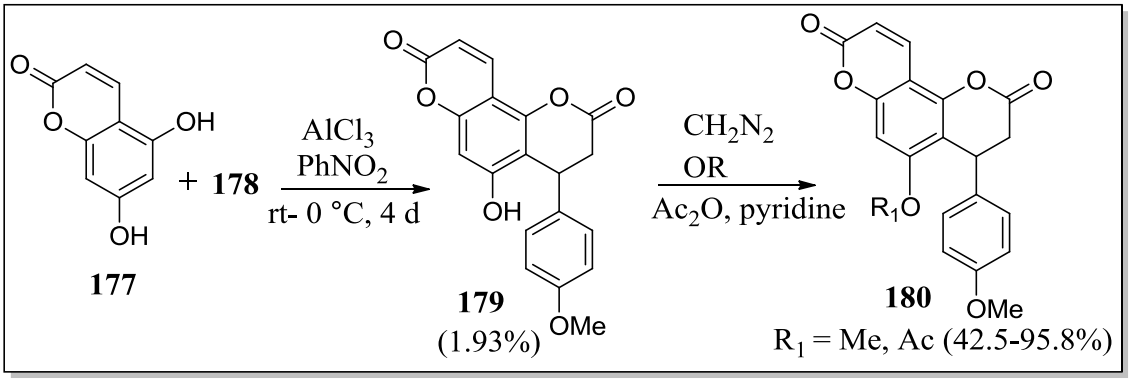
A short synthetic route to a series of (+/-)-8-alkyl-5,7-dihydroxy-4-(4-hydroxyphenyl)-3,4-dihydrocoumarins has been described by Roelens *et al.* Selective deprotection of 2,4,6-trimethoxybenzaldehyde was carried out followed by alkylation using organometallic reagents leading to unstable secondary benzylic alcohols.[45] Deoxygenation by treatment with triethysilane and TFA gave compounds **174**. Further

condensation with *p*-methoxycinnamic acid in the presence of $BF_3 \cdot OEt_2$, followed by a deprotection step using BBr_3, gave the desired compounds **176** *(Scheme 45)*.



Scheme 45

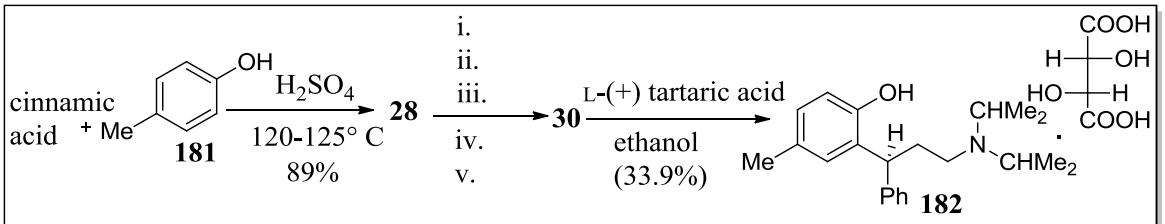
Some 4-(4-methoxyphenyl)-3,4-dihydrocoumarins were prepared by Bezerra *et al.* from variously substituted phenols and 4-methoxycinnamoyl chloride in the presence of aluminum chloride in carbon disulfide.[170] 5,7-Dihydroxycoumarin **177** was also subjected to $AlCl_3$ mediated condensation with cinnamoyl chloride **178** in nitrobenzene. The dihydrocoumarins **179** were further derivatized into compounds **180** *(Scheme 46)*.



Scheme 46

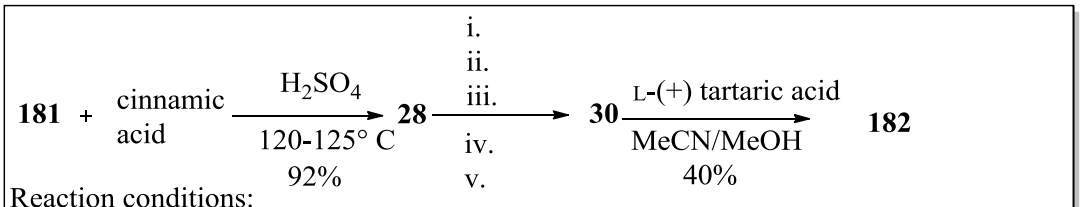
The first reported synthetic route for tolterodine tartrate (muscarine receptor antagonist used in the treatment of urinary bladder disorders) involved the acid-catalyzed reaction of cinnamic acid and 4-methylphenol **181** in sulfuric acid to give dihydrocoumarin derivative **28**; this was followed by ring opening of the lactone to give a methyl ester, which was reduced to an alcohol using LAH. Tosylation of the resultant alcohol, followed by condensation of the tosyl derivative with diisopropylamine, yielded a tertiary amine, which on treatment with BBr_3 gave phenol **30** *(Scheme 47a)*.[171] The latter, upon resolution with L-(+) tartaric acid gave tolterodine tartrate **182** with a 5.5% overall yield. Mathad and co-workers have developed an improved, industrially feasible process for the preparation of tolterodine tartrate *(Scheme 47b)*.[172] Initially, they started with the same

starting materials, cinnamic acid and *p*-cresol, to obtain intermediate **28** but lactone ring opening was followed by benzyl protection of the phenolic hydroxy group, which could circumvent the problem of using hazardous BBr_3 for deprotection of the methoxy group. The ester was then reduced to the alcohol using vitride in good yields. Further tosylation followed by treatment with diisopropylamine in an autoclave and debenzylation gave compound **30**. Resolution with L-(+) tartaric acid yielded the final product **182** with an overall yield of around 30%.



Reaction conditions: i. MeI/K_2CO_3, acetone/MeOH, reflux, 92%; ii. LAH/dry ether, 25-35 ° C, 93%;
iii. *p*-TsCl, pyridine, $CHCl_3$ -10 to -15 ° C, 99%; iv. HN(*i*-Pr)$_2$, MeCN, 80-85 ° C, 4-6 d, 69%; v. BBr_3
20-25 ° C, 2-3 d, 31.5%.

Scheme 47a

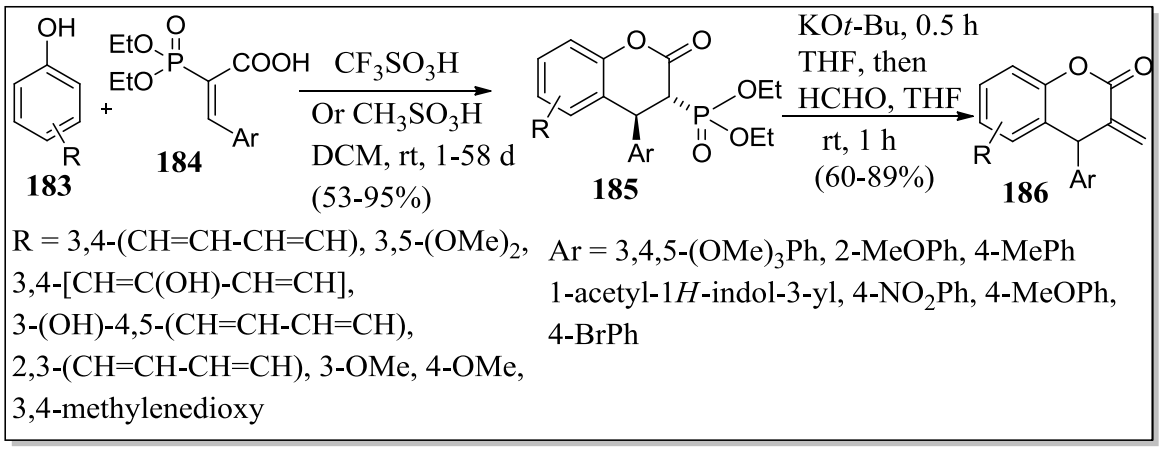


Reaction conditions:
i. BnBr/K_2CO_3/acetone, MeOH reflux, 96%; ii. vitride/THF 25-35° C, 97%;
iii. EtN(*i*-Pr)$_2$, *p*-TSCl, 25-35° C, 99%; iv. HN(*i*-Pr)$_2$, MeCN, 110-115° C, 12-14 h, 95%;
v. H_2 / Raney Ni, MeOH, 25-35° C, 5 h, 94%.

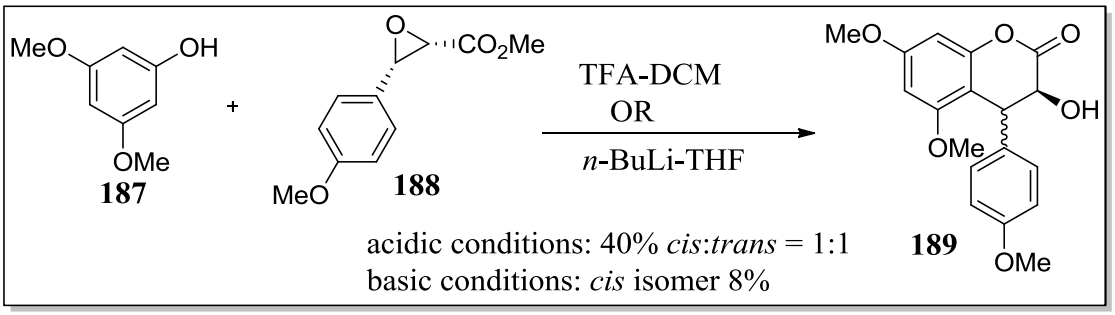
Scheme 47b

Synthesis of *trans*-3-diethoxyphosphoryl-4-aryl-3,4-dihydrocoumarins **185** has been described by Krawczyk *et al.* by the reaction of electron rich phenols **183** and (*E*)-3-aryl-2-(diethoxyphosphoryl)acrylic acids **184** using CF_3SO_3H or CH_3SO_3H as catalyst *(Scheme 48)*. The products **185** were then transformed to corresponding *α*-methylene-*δ*-valerolactones **186** by the HWE reaction.[173]

Roux and co-workers synthesized dihydrocoumarins by the reaction of phloroglucinol with epoxide **188** followed by lactonization in ethereal sulfuric acid.[174] Brown *et al.* carried out a similar reaction under both acidic as well as basic conditions. The formation of lactone **189** was rationalized by alkylation of the phenol **187** at the electron-rich *ortho* position followed by lactonization *(Scheme 49)*.[175]

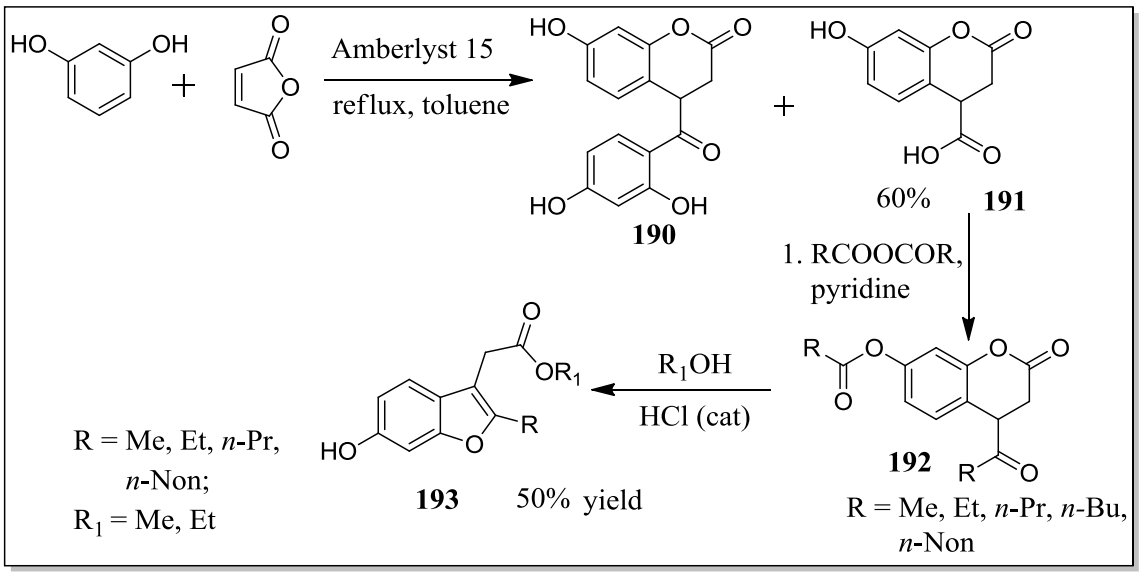


Scheme 48



Scheme 49

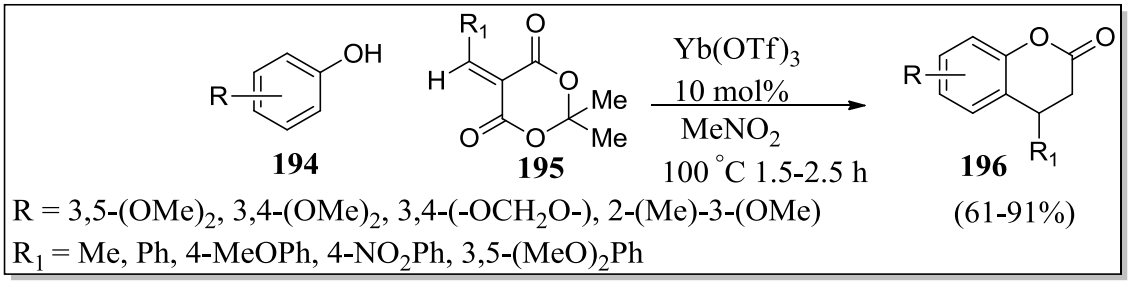
Shachan-Tov and Frimer obtained dihydrocoumarin **191** by condensation of resorcinol with maleic anhydride, which also resulted in the formation of side-product **190** *(Scheme 50)*.



Scheme 50

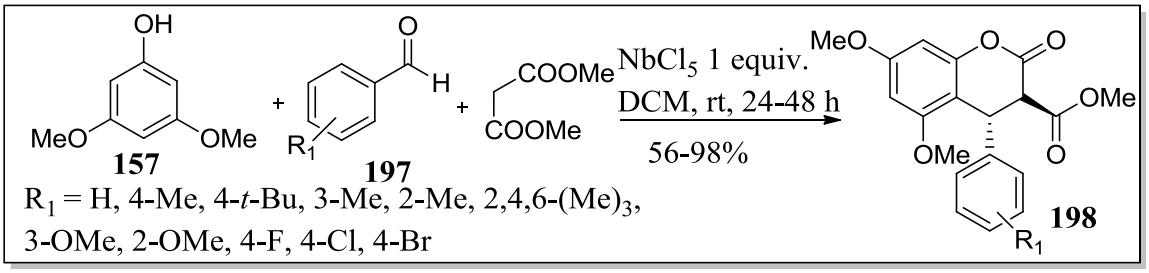
Further acylation of dihydrocoumarin-4-carboxylic acid **191** with anhydrides gave benzopyranones **192**.[176] Acid alcoholysis of **192** led to a convenient synthesis of a broad family of 6-hydroxybenzofurans **193**.

Fillion *et al.* have reported $Yb(OTf)_3$ catalyzed assembly to 4-substituted 3,4-dihydrocoumarins **196** from phenols **194** and 5-alkylidene Meldrum's acid **195** *(Scheme 51).*[177] The same products could also be obtained using an excess of TFA instead of $Yb(OTf)_3$.



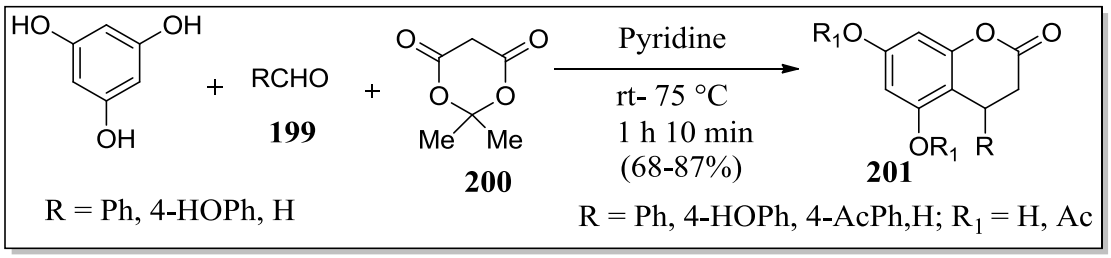
Scheme 51

Cinnamates and acrylates generated *in situ* from aromatic aldehydes and dimethyl malonate react with phenols in a three-component reaction to lead to dihydrocoumarins. Thus, a $NbCl_5$ catalyzed, three-component reaction was described by Santos and Silva-Filho for the synthesis of several 4-aryl-3,4-dihydrocoumarins **198** *(Scheme 52).*[178]



Scheme 52

Nair has obtained some dihydrocoumarins **201** by reaction of methylidene derivatives, resulting from the reaction of aldehydes **199** and Meldrum's acid **200**, with phloroglucinol in the presence of pyridine *(Scheme 53);*[179] acetylation of the dihydrocoumarins products was also carried out.

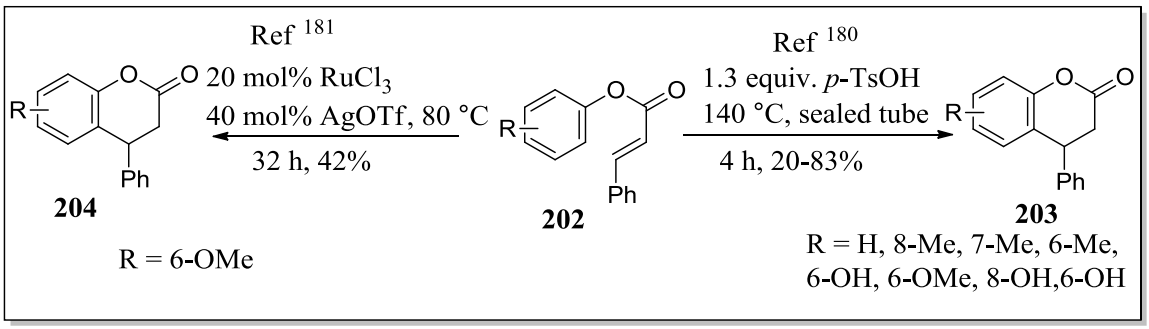


Scheme 53

1.2.4: From Phenyl Acrylates (Route D)

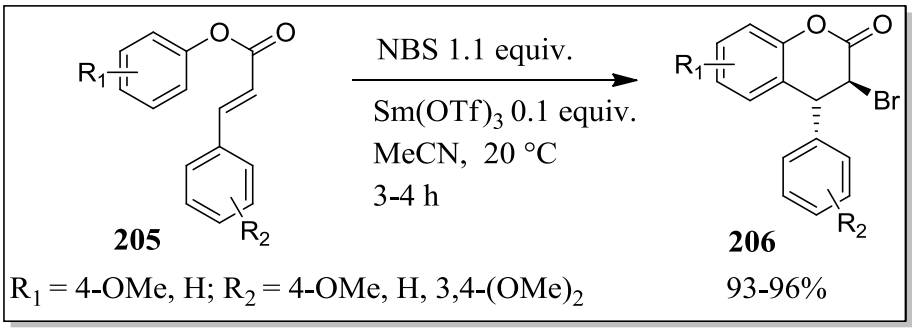
Dihydrocoumarins were prepared by Jun and co-workers *via* intramolecular cyclization of phenyl cinnamates using *p*-toluenesulfonic acid under solvent free conditions.[180]

Furthermore, Youn *et al.* used a $RuCl_3$/AgOTf catalyst to give 4-phenyl-6-methoxy-3,4-dihydrocoumarins *(Scheme 54).*[181]



Scheme 54

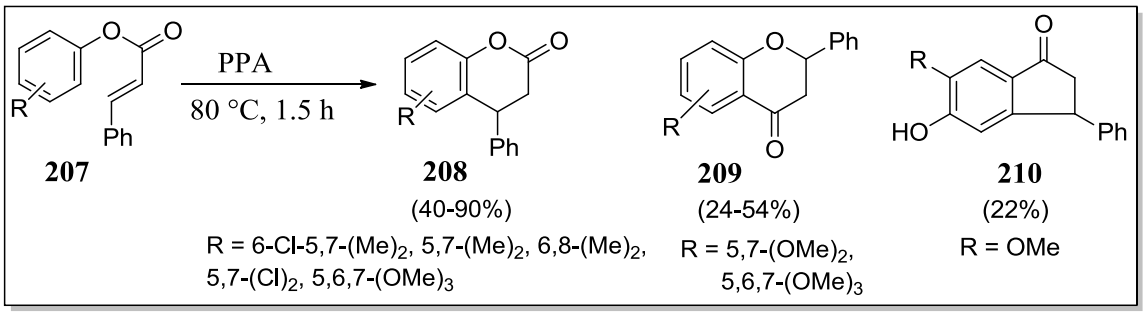
Hajra *et al.* synthesized dihydrocoumarins **206** *via* $Sm(OTf)_3$ catalyzed intramolecular haloarylation of tethered alkenes **205** using *N*- bromosuccinimide *(Scheme 55).*[182]



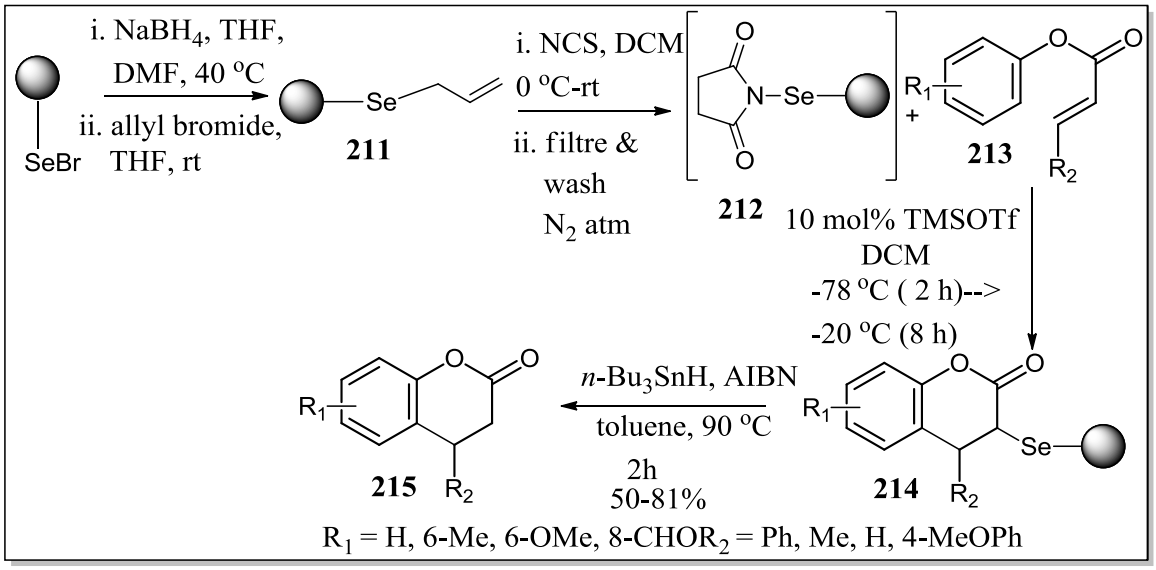
Scheme 55

Dupin and Chenault have shown that various phenyl-substituted cinnamates **207** react in polyphosphoric acid (PPA) to give 4-phenyl-3,4-dihydrocoumarins **208**, flavanones **209** or phenylindanone **210** depending upon the nature of the substituent on the phenyl ring *(Scheme 56).*[183] The presence of weakly donating and withdrawing-substituents resulted in the formation of phenyl dihydrocoumarins **208**. However, the presence of strong electron-donating substituents gave flavanones **209**. In the case of 2-methoxyphenyl cinnamate **207** (R = OMe) as starting material, the phenyl-3-indanone **210** was formed.

Tang *et al.* have developed a solid-phase synthesis of dihydrocoumarins **215** *(Scheme 57).* TMSOTf- catalyzed intramolecular seleno-arylation of substituted phenyl acrylates **213** was performed using supported succinimidyl selenide **212** as the selenium source, which was prepared from polystyrene-supported allyl selenide **211**. The final cleavage of DHCs **214** from the resin was achieved by *n*-Bu_3SnH mediated reduction.[184] The same authors synthesized additional dihydrocoumarin derivatives employing the same strategy and Suzuki cross-coupling reaction of the resin-bound bromo dihydrocoumarin was also carried out.[185]

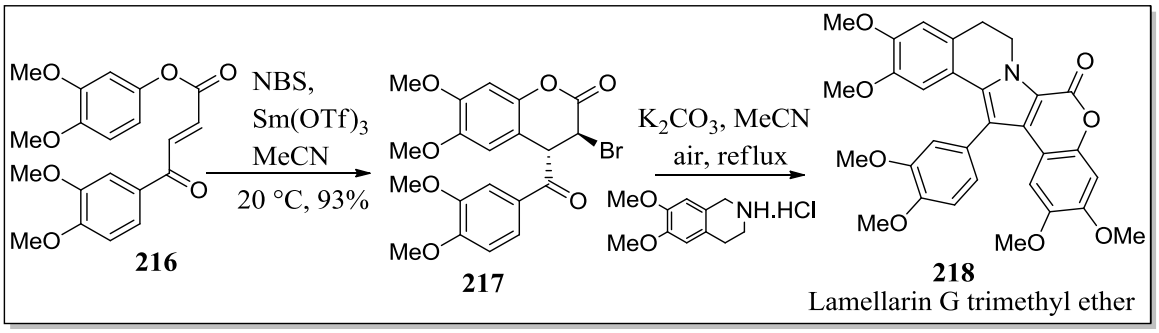


Scheme 56



Scheme 57

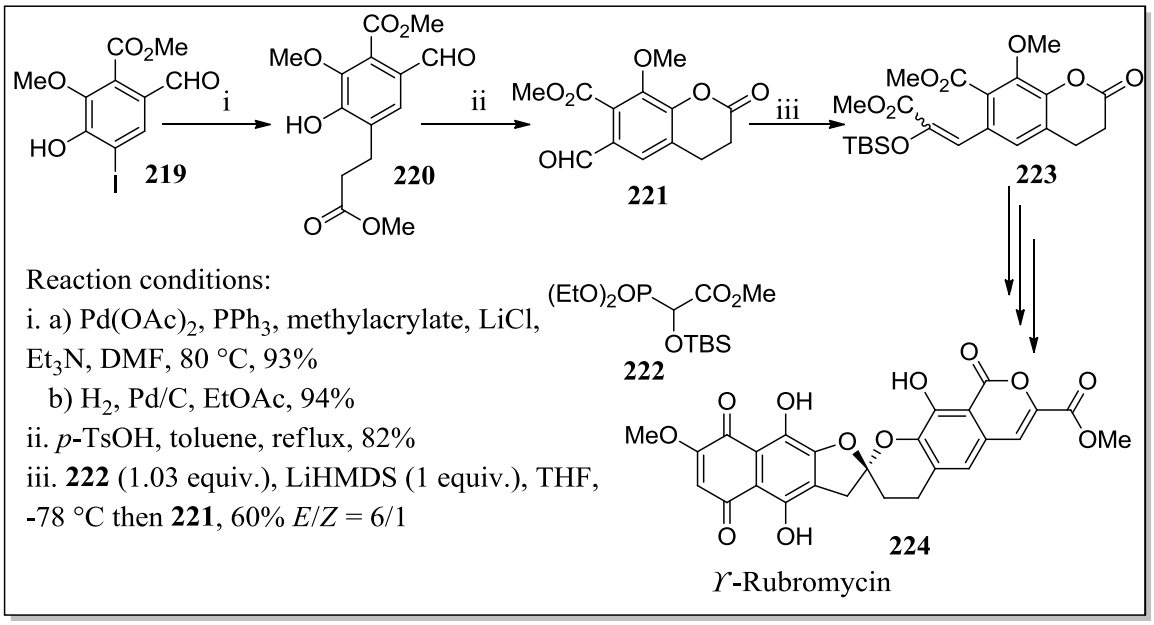
Yadav *et al.* prepared the benzopyranone **217** by employing sequential Friedel-Crafts acylation, esterification and bromoarylation steps. The benzopyranone **217** was used to accomplish modular synthesis of lamellarin G trimethyl ether **218** by coupling **217** with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride *(Scheme 58).*[186]



Scheme 58

1.2.5: By Cyclization of 3-(o-Hydroxyphenyl)propanoic Acids and Precursors (Route E)

Pettus and co-workers have synthesized dihydrocoumarin **221** from the Reissig's aldehyde **219**. Heck reaction of **219** with methyl acrylate followed by catalytic hydrogenation gave ester **220**, which was subjected to subsequent *p*-TsOH promoted lactonization to give dihydrocoumarin **221**. Further HWE reaction of **221** with Thompson's phosphonate **222** afforded dihydrocoumarin **223** as a 6:1 mixture of *E*/*Z* isomers. Further steps led to a total synthesis of racemic *γ*-rubromycin **224** from **223** *(Scheme 59)*.[187]

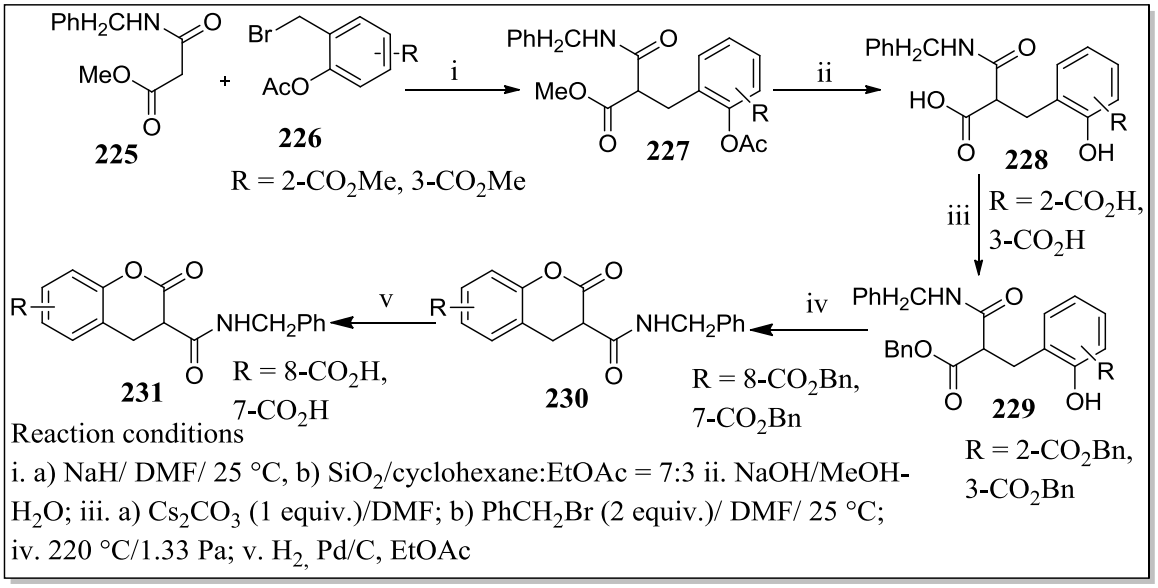


Scheme 59

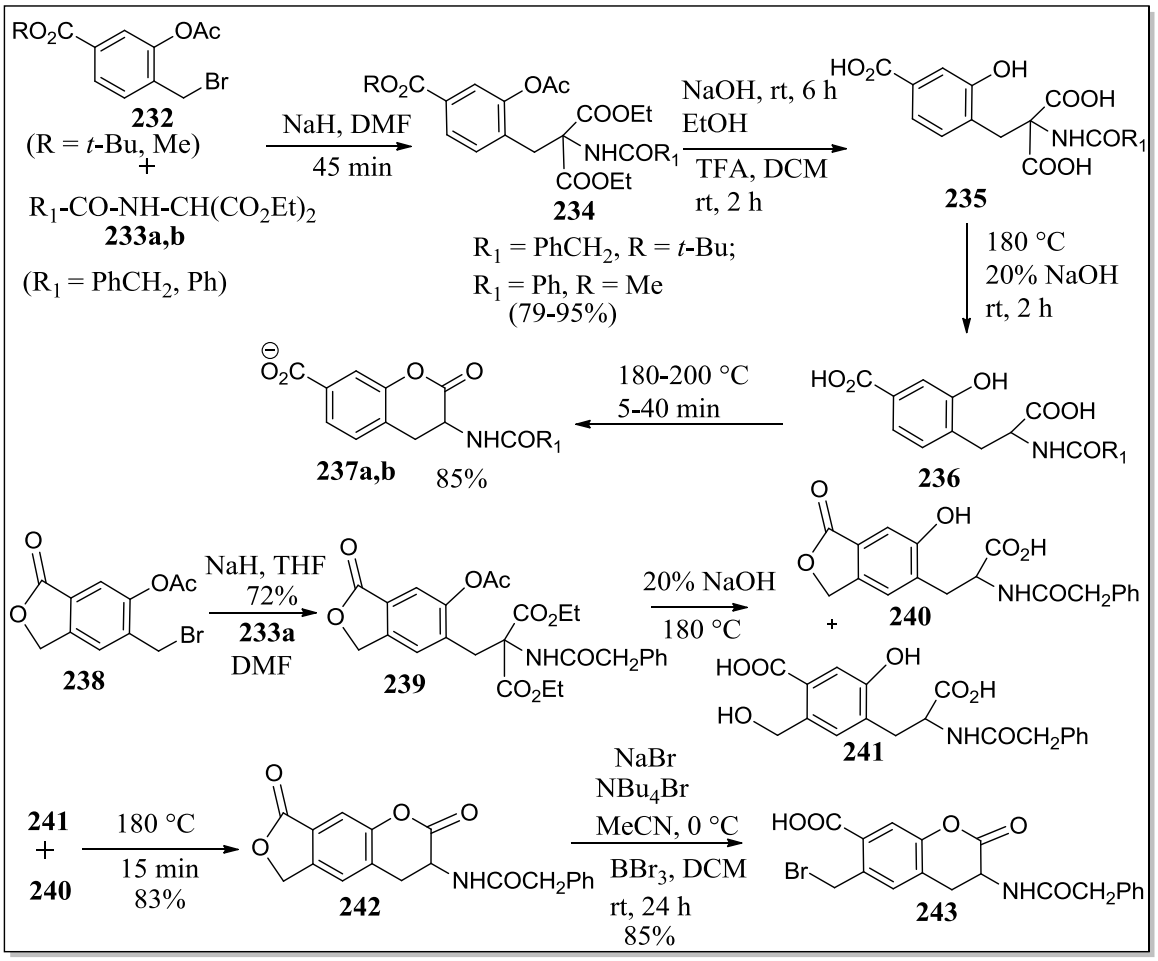
In 2004, Adediran *et al*. designed and evaluated several benzopyranones as potential (inhibitory) substrates of *β*-lactam recognizing enzymes.[188] The monoalkylated product **227**, obtained by alkylation of **225** with substituted benzyl bromides **226**, was subjected to alkaline hydrolysis followed by benzylation of the carboxyl groups to give **229** *(Scheme 60)*. Subsequent thermal lactonization gave benzopyranones **230**, which furnished the target benzopyranones **231** upon hydrogenolysis.

Wakselman and co-workers synthesized several 7-carboxy-3-amido-3,4-dihydro-2*H*-1-benzopyran-2-ones as potential *β*-lactamase mechanism-based inhibitors *(Scheme 61)*.[54] Compound **234** was obtained by alkylation of diethyl phenylacetamido- or benzamidomalonates with benzyl bromide **232**. Conversion of **234** into **235** was accomplished by alkaline hydrolysis followed by acidification. Further decarboxylation to give compound **236** was followed by thermal cyclization at 180-200 ^{o}C to give compounds **237a** and **237b**. Treatment of compound **238** with diethyl phenylacetamidomalonate **233a** in the presence of NaH gave compound **239**, which on

treatment with NaOH and heating at 180 ^{o}C gave a mixture of diacid **241** and phthalide **240**. Heating this mixture at 180 ^{o}C led to dilactone **242**, which was then converted to **243**.

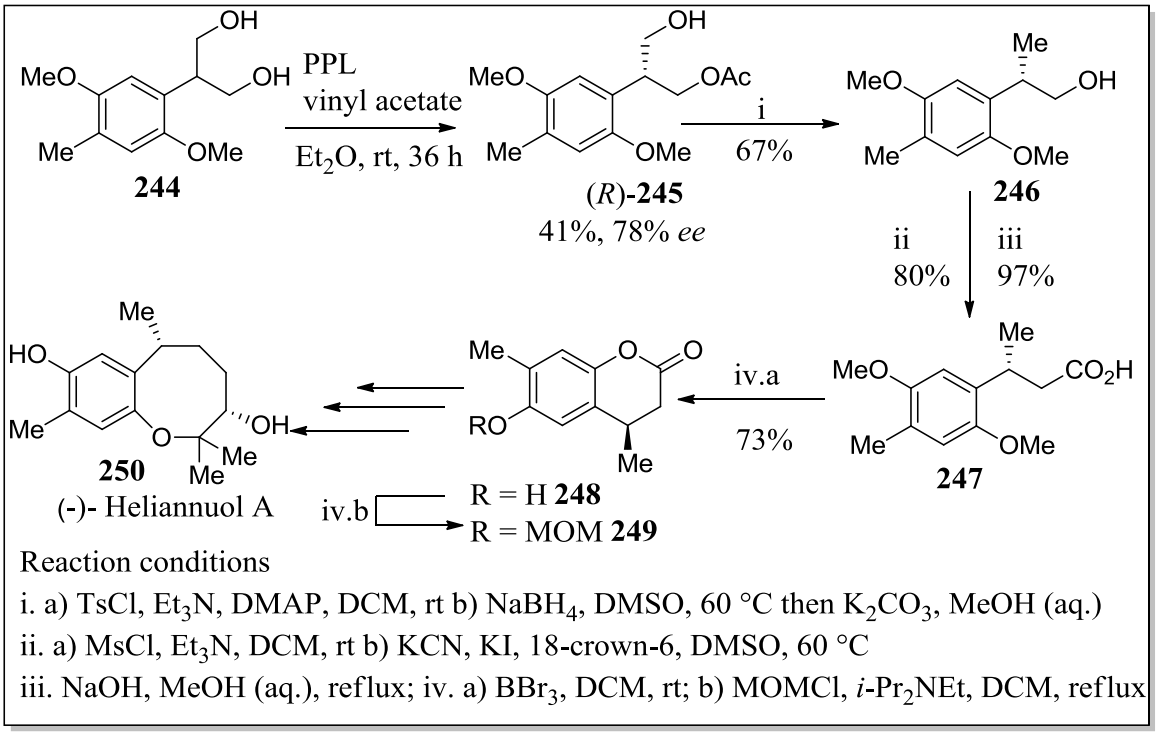


Scheme 60



Scheme 61

Shishido and co-workers accomplished the first enantioselective synthesis of (-) heliannuol A **250** involving dihydrocoumarin intermediate **249**.[189] The monohydrate of (*R*)-**245** was obtained from prochiral diol **244** using porcin pancreatic lipase (PPL) mediated transesterification. Removal of the hydroxy group in **245**, by tosylation and subsequent reduction followed by hydrolysis, gave alcohol **246**. Mesylation followed by cyanation and hydrolysis furnished acid **247**. Removal of the methoxy group and lactonization gave benzopyranone **248**, whose phenolic hydroxy group was protected as the methoxymethylether, giving benzopyranone **249** *(Scheme 62).*

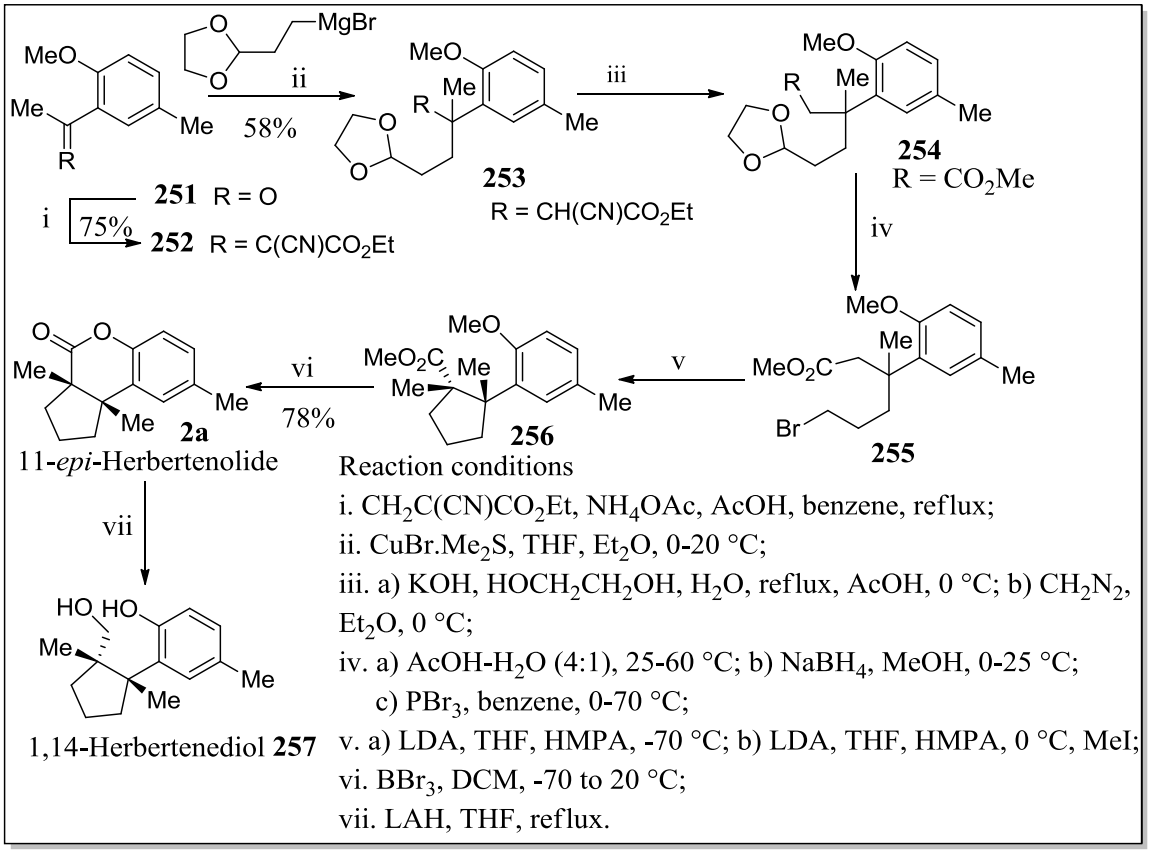


Scheme 62

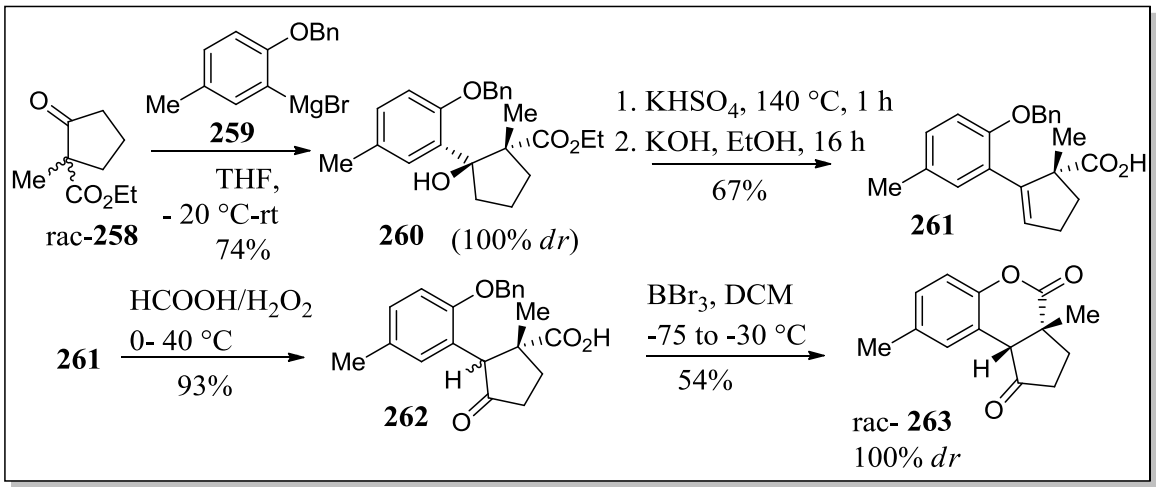
Mukherjee and co-workers synthesized 11-*epi*-herbertenolide **2a**. Acetophenone **251** was condensed with ethyl cyanoacetate to give the cyanoester **252** *(Scheme 63).*[190] Conjugate addition of 3,3-ethylenedioxypropylmagnesium bromide to **252** furnished **253**, which on hydrolysis, decarboxylation and esterification gave methyl ester **254**. This was followed by deacetalization, reduction and bromination steps, resulting in the formation of bromoester **255**. One pot transformation of **255** into cyclopentacarboxylate **256** was followed by lactonization into *β*- herbertenolide **2a** by treatment with BBr_3, thus accomplishing a total synthesis of racemic 1,14-herbertenediol **257** from **2a**.

Speicher and co-workers described the preparation of oxolactone **263** by 1,2-addition of the Grignard reagent **259** to the racemic lactone **258**, followed by dehydration and saponification of the resulting tertiary alcohol **260**, giving **261**.[191] Next, the carbonyl

group was introduced *via* epoxidation and oxirane ring opening to afford **262**. Deprotection of the *O*-benzyl group of **262** and concomitant lactonization was achieved using BBr_3, giving lactone **263** *(Scheme 64)*. Further the synthesis of herbertenolide **2** was accomplished from **263**. The overall yield of racemic herbertenolide from **259** was 13%. Initially the synthesis was reported using methyl ether of **259** instead of benzyl wherein the overall yield was only 6%.

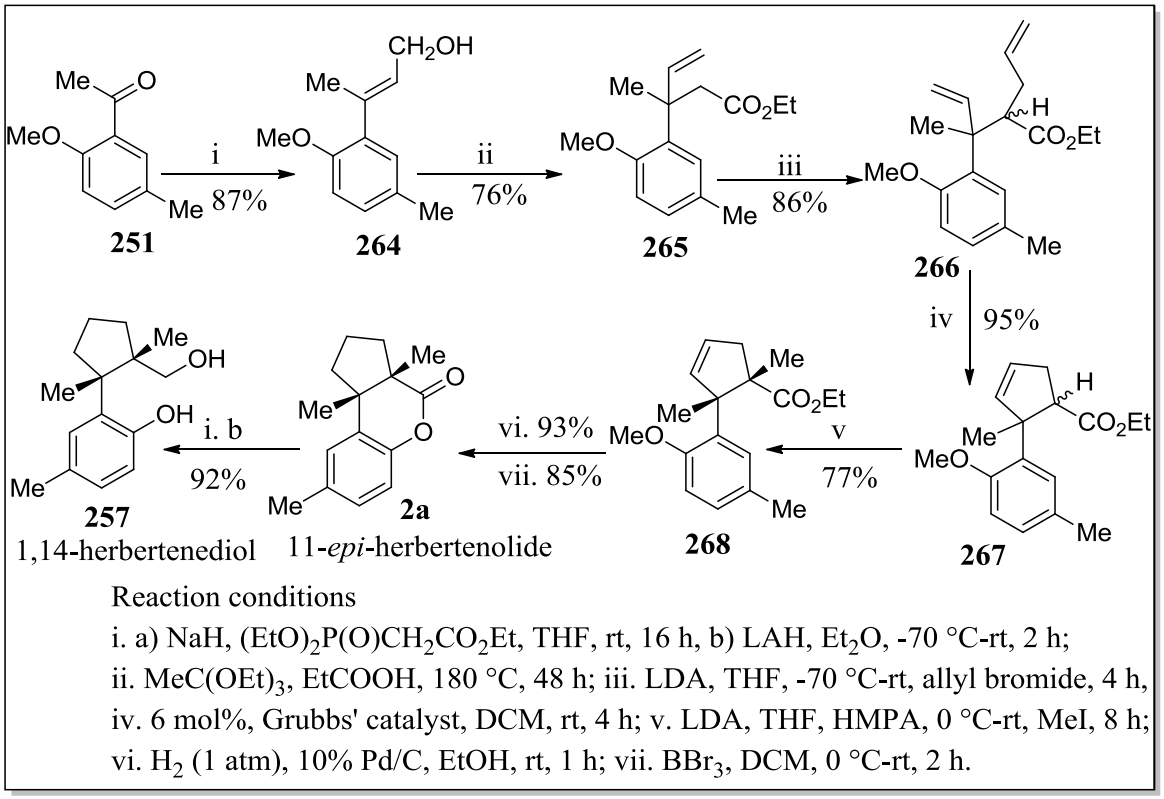


Scheme 63



Scheme 64

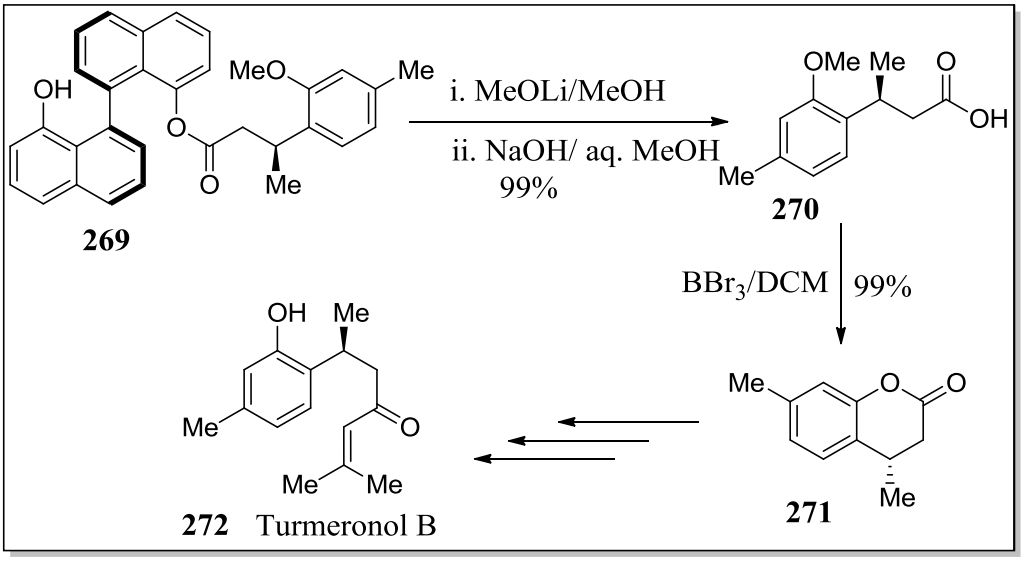
Later, Srikrishna and Rao reported the total synthesis of 1,14-herbertenediol **257** *via* 11-*epi*-herbertenolide **2a** involving a ring closing metathesis (RCM) based approach *(Scheme 65)*.[192] Cinnamyl alcohol **264**, obtained from **251** by HWE reaction and LAH reduction, was subjected to *ortho* ester Claisen rearrangement to give **265**. Alkylation of ester **265** followed by RCM transformed the diene **266** into cyclopentenecarboxylate **267**. Alkylation with methyl iodide led to stereoselective synthesis of **268**. Hydrogenation, followed by treatment with BBr_3, gave 11-*epi*-herbertenolide **2a**. Finally, reduction of **2a** with LAH resulted in the formation of 1,14-herbertenediol **257**.



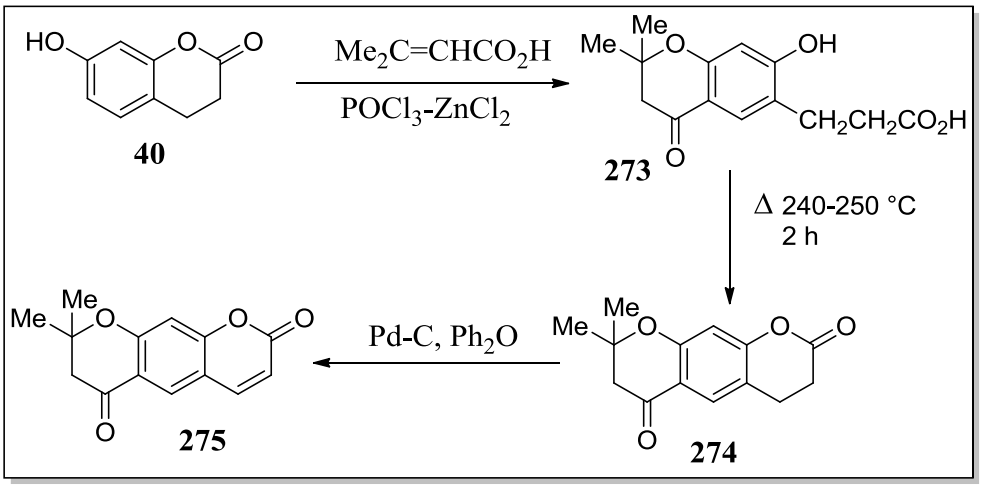
Scheme 65

Fuji and co-workers synthesized turmeronol B *via* dihydrocoumarin intermediate **271**, which was synthesized *via* demethylation and concomitant lactonization of **270** using boron tribromide *(Scheme 66)*.[193]

The coumarin **275**, isolated from Dill (*Anethum graveolens*), was obtained from 3,4-dihydro-7-hydroxycoumarin **40** in a three-step sequence involving condensation of **40** with *β,β*-dimethylacrylic acid, with simultaneous cleavage of the lactone ring to give chromanone **273**.[194] On heating the chromanone **273** cyclized readily into **274**, which was dehydrogenated to furnish **275**. The same reaction sequence was applied to 3,4-dihydro-5,7-dihydroxycoumarin, which yielded the angular isomer of the naturally occurring coumarin, clausenin *(Scheme 67)*.



Scheme 66

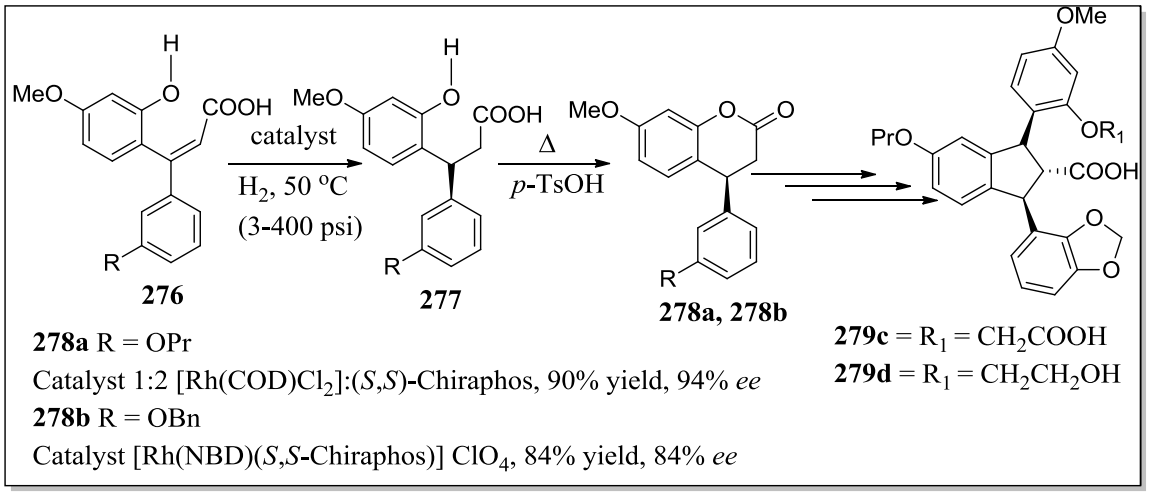


Scheme 67

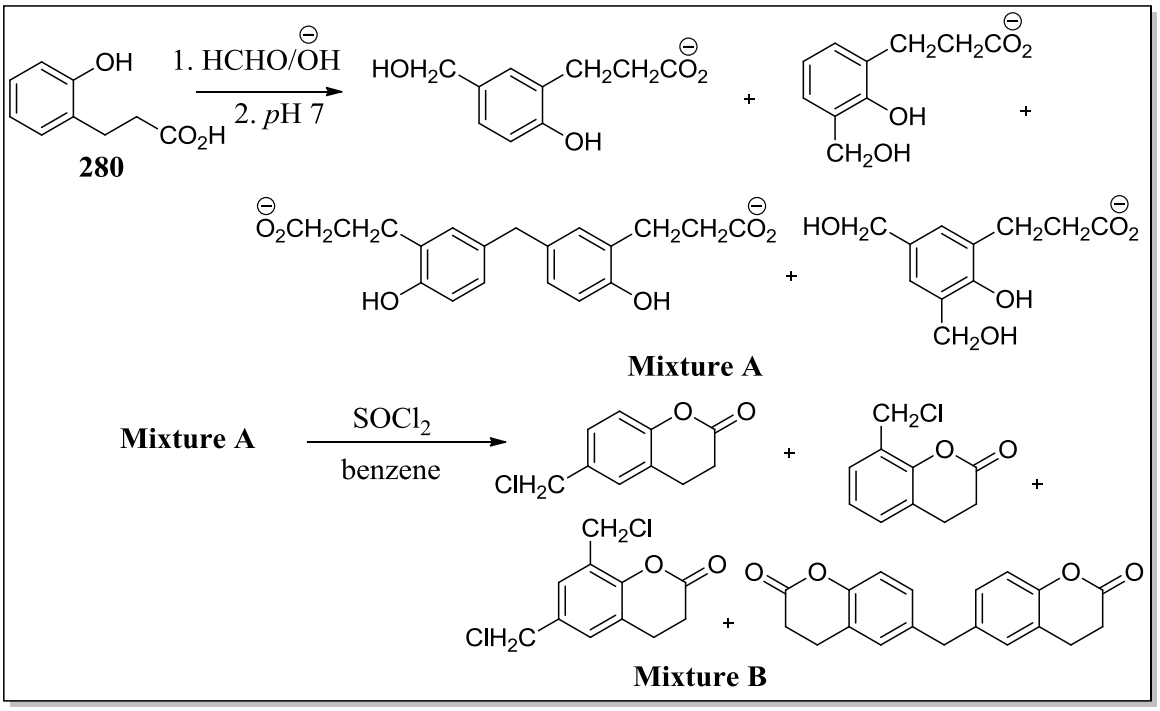
McGuire *et al.* have described an enantioselective synthesis of **278**. Cinnamic acid **276,** obtained from the base-catalyzed ring opening of the corresponding coumarin, was hydrogenated in the presence of a chiral catalyst at 50 ^{O}C and pressures of 3-400 psi. Out of the many catalysts used, an *in-situ* catalyst system comprising of a 1:2 molar mixture of $[Rh(COD)Cl]_2$ and *S,S*-Chiraphos gave products with better yields and enantioselectivities *(Scheme 68a).*[195] Compounds **277** gradually lactonized upon standing, but heating in the presence of *p*-TsOH speeded-up the transformation to **278**. Compound **278a** is a key intermediate for the synthesis of endothelin antagonists **279c** and **279d**.

Cyclization of *β*-(2-methoxy-5-bromophenyl)propionic acid under Friedel-Crafts conditions has been reported.[196] Also, cyclization of *o*-hydroxyphenylsuccinic acid with

phosphoric oxide gives 4-substituted-3,4-dihydrocoumarins.[197] The *o*-hydroxyphenylpropionic acid **280** on hydroxymethylation gave a mixture of four products (**mixture A**) which on treatment with thionyl chloride provided a mixture of 3,4-dihydrocoumarins (**mixture B**) *(Scheme 68b)*.[198]



Scheme 68a

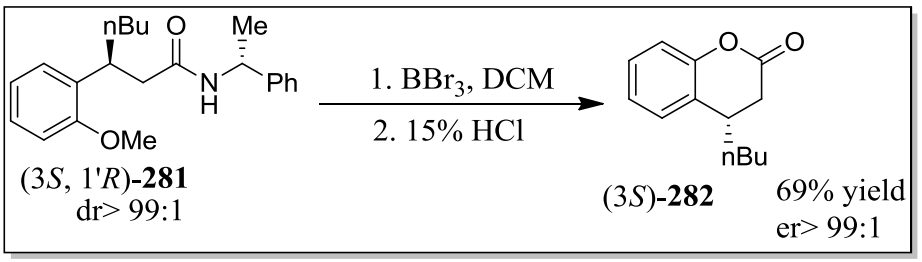


Scheme 68b

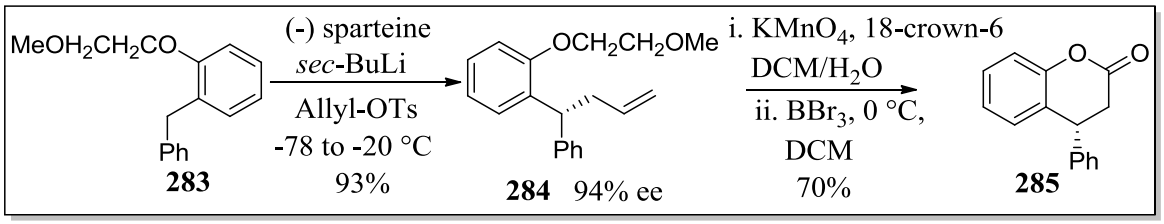
Enantiomerically pure 4-substituted dihydrocoumarin **282** was prepared from amide **281** by demethylation and subsequent acid-catalyzed ring closure *(Scheme 69)*.[199,200]

Wilkinson *et al.* reported the synthesis of dihydrocoumarin **285** from compound **284** by oxidative cleavage of the double bond with potassium permanganate in the presence of crown ether and treatment with boron tribromide to remove the methoxyethyl group with

concomitant cyclization *(Scheme 70)*.[201] Compound **284** was obtained by asymmetric alkylation of **283** using *s*-BuLi and (-)-sparteine.[202]

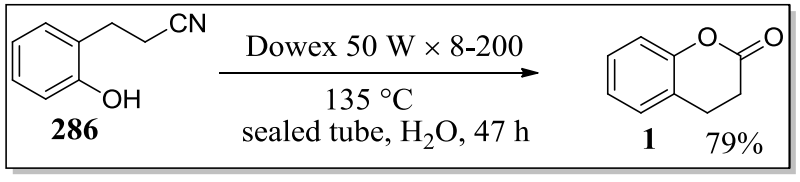


Scheme 69

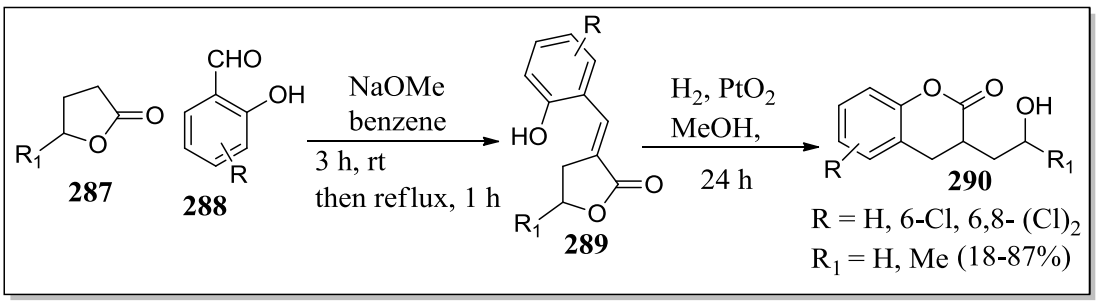


Scheme 70

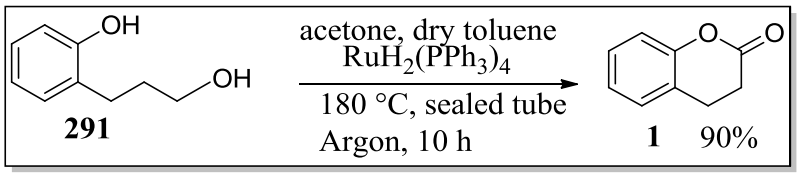
Cyclization of hydroxynitrile **286** in water using a recyclable cation exchange resin was reported by Lindström and co-workers to give dihydrocoumarin *(Scheme 71)*.[203] 3,4-Dihydrocoumarins **290** were obtained by hydrogenating condensation products **289** of *o*-hydroxybenzaldehyde **288** and *γ*-butyrolactones[204] **287** *(Scheme 72)*. Murahashi *et al.* have described the ruthenium catalyzed lactonization of a 1,5-diol, *viz.* 2-(3-hydroxy)propylphenol **291**, into dihydrocoumarin **1** in the presence of acetone acting as a hydrogen acceptor *(Scheme 73)*.[205]



Scheme 71

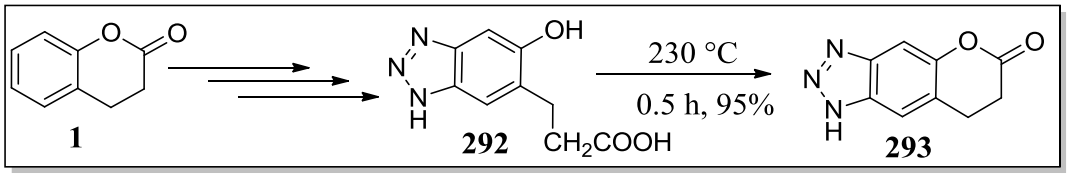


Scheme 72



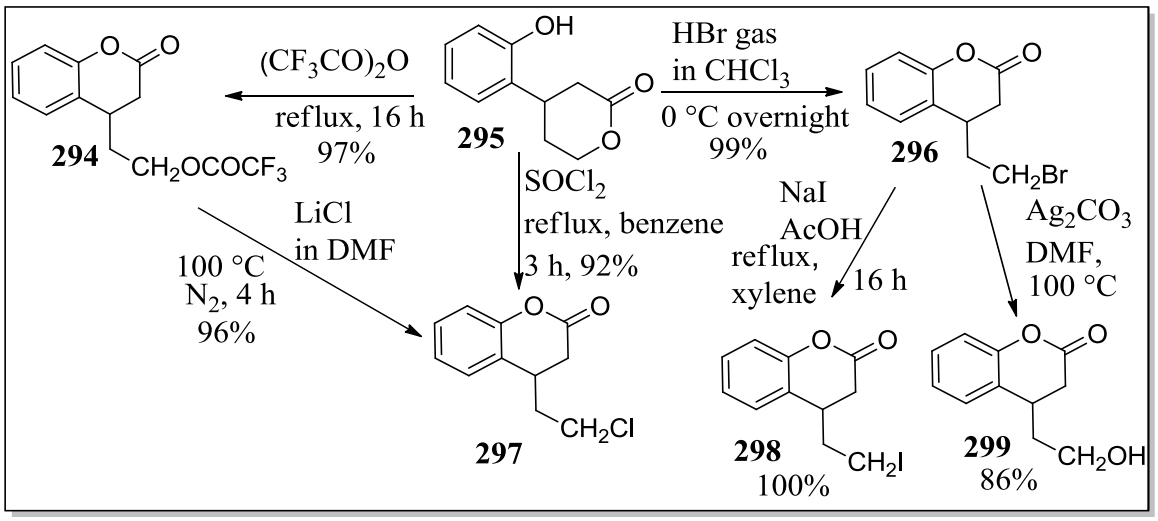
Scheme 73

Triazolo [6,7-*d*] dihydrocoumarin **293** has been prepared in nine steps from dihydrocoumarin **1** in 20% overall yield. The final step in the synthesis involved lactonization of 3-(1*H*-5-hydroxybenzotriazol-6-yl)propionic acid **292**, obtained in eight steps from dihydrocoumarin by simply heating at 230 ^{O}C, to give 7,8-dihydro-1*H*-pyrano[2,3-*f*]benzotriazol-6-one **293** *(Scheme 74)*.[206]



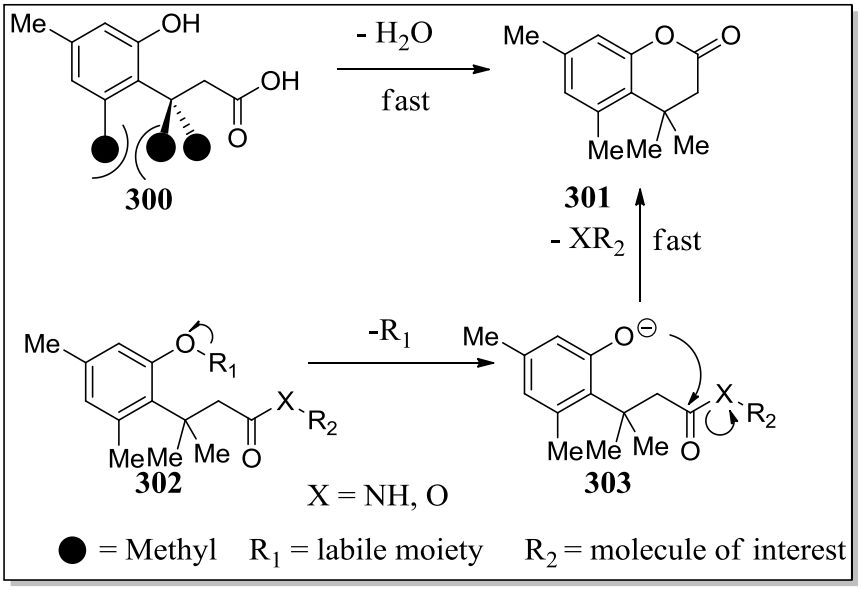
Scheme 74

Vida and Gut have described the conversion of 2-(*o*-hydroxyphenyl)-4-hydroxybutane-1-carboxylic acid lactone **295** *(Scheme 75)* into 4-substituted 3,4-dihydrocoumarins using various electrophilic reagents, *e. g.* trifluoroacetic anhydride gave 3,4-dihydro-4-(*β*-trifluoroacetoxy- ethyl)coumarin **294**, thionyl chloride in benzene resulted in the formation of 3,4-dihydro-4-(*β*-chloroethyl)coumarin **297** and gaseous hydrobromic acid in chloroform led to 3,4-dihydro-4-(*β*-bromoethyl)coumarin **296**. Compound **297** could also be obtained from **294** by treatment with lithium chloride in DMF.[207] Both **298** and **299** were obtained from **296** using NaI in AcOH and silver carbonate in DMF, respectively.



Scheme 75

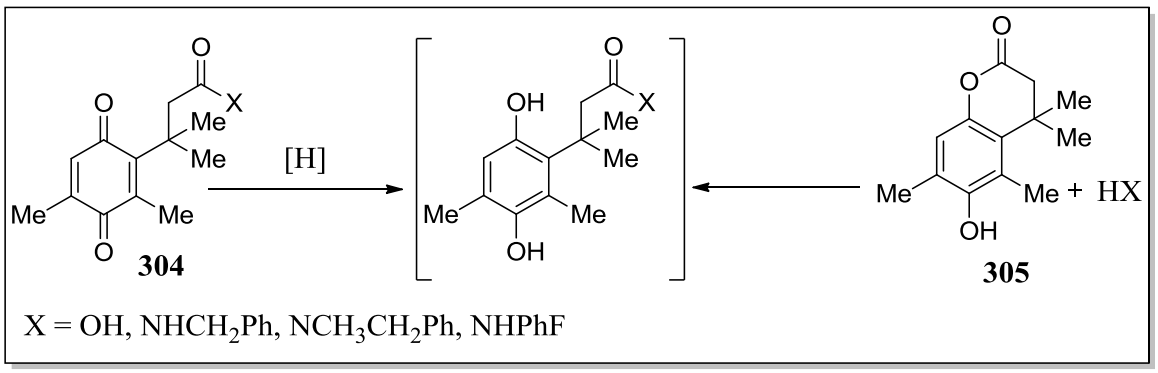
The "trimethyl lock" term is used to describe the promotion of lactonization of *o*-hydroxydihydrocinnamic acid **300** into dihydrocoumarin **301** by the steric interaction of three pendant methyl groups *(Scheme 76a)*.[208-211] Reports of "trimethyl lock" facilitated lactonization reactions created considerable interest as its effect was said to approach that of an enzyme in promoting these reactions.



Scheme 76a

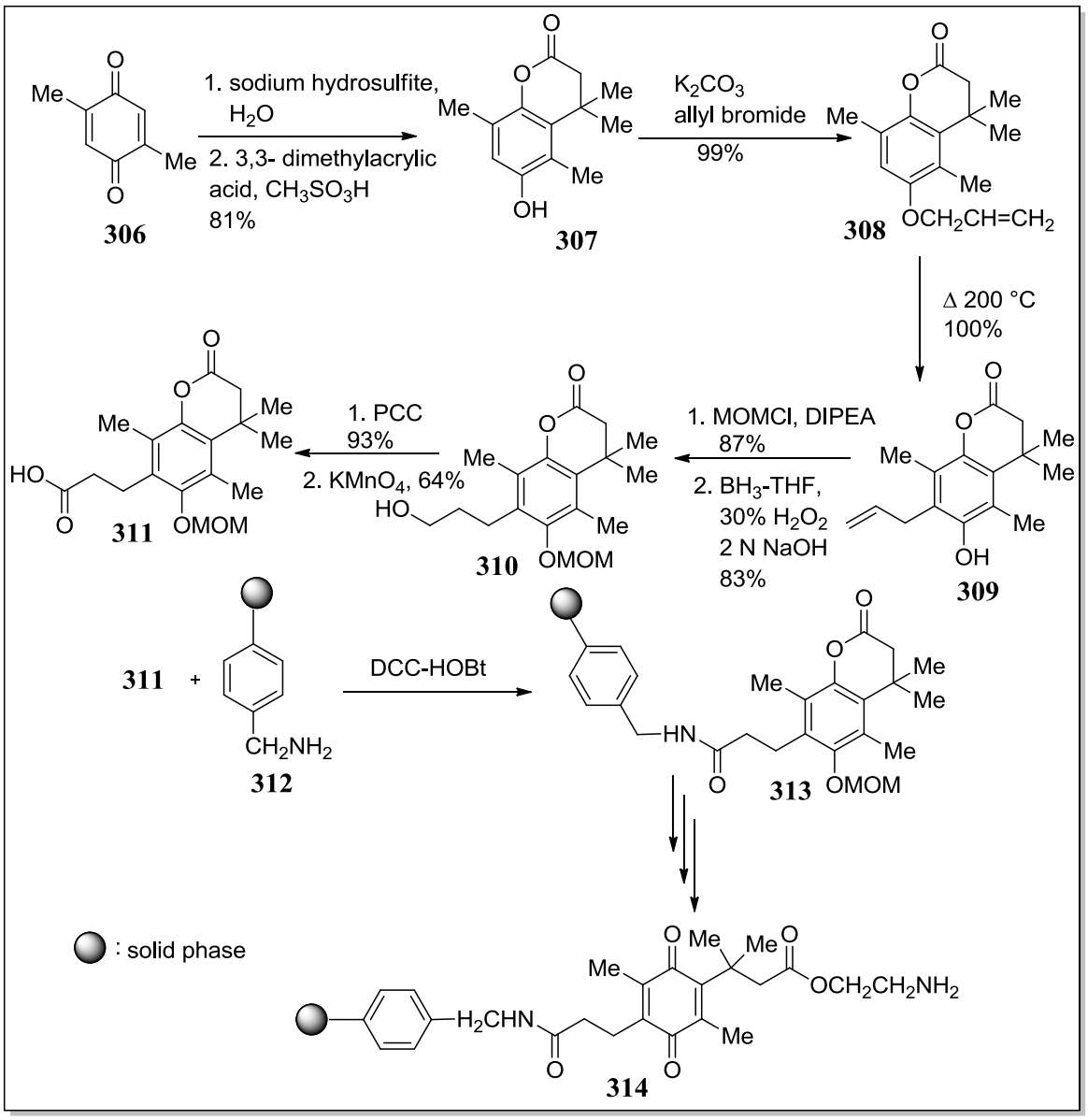
This high reactivity is applied to release an amine or alcohol after enzymatic, chemical, or photolytic deprotection of a trimethyl lock amide/ester **302** *(Scheme 76a)*.[208] Milstien and Cohen observed that enhancement of reaction rate of lactonization in *o*-hydroxydihydrocinnamic acid was achieved by substitution of methyl groups both on the ring and the side chain.[210] Wang *et al.* found that substitution on the side-chain had a minimal effect on the overall conformation of the system *(Scheme 76b)*. "Trimethyl lock"

facilitated the lactonization entropically through a ground state steric strain relief upon cyclization, which proved to be consistent with earlier reports.[212]



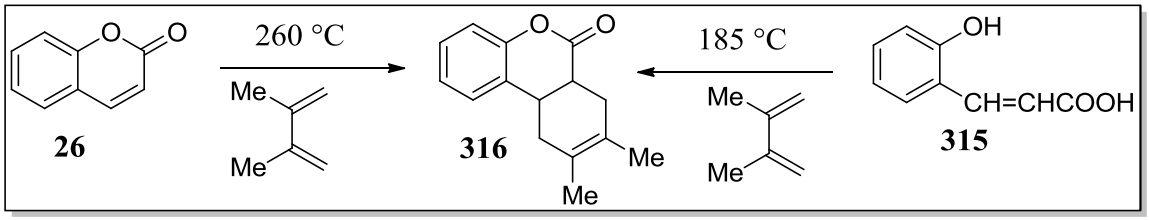
Scheme 76b

Wang and co-workers[213] synthesized three peptides Boc-D-Ala-Gly-Phe-$NHCH_2CH_2OH$, Boc-Leu-D-Ala-Gly-Phe-$NHCH_2CH_2OH$ and Boc-Trp(For)-Leu-D-Ala-Gly-Phe-$NHCH_2CH_2OH$, using a new linker **314** obtained from 2,5-dimethylbenzoquinone **306**. The quinone **306** was reduced and converted into benzopyranone **307** by reaction with 3,3-dimethylacrylic acid under acidic conditions followed by allylation of phenolic hydroxy group and subsequent Claisen rearrangement giving **309**. The free phenolic hydroxy group was protected using MOMCl and then the allyl side chain was converted into alcohol **310** by hydroboration-oxidation. The alcohol **310** was oxidized to acid **311** and then attached to resin **312** by DCC-HOBt mediated coupling to give **313**, which was further transformed into the linker **314** *(Scheme 76c)*.



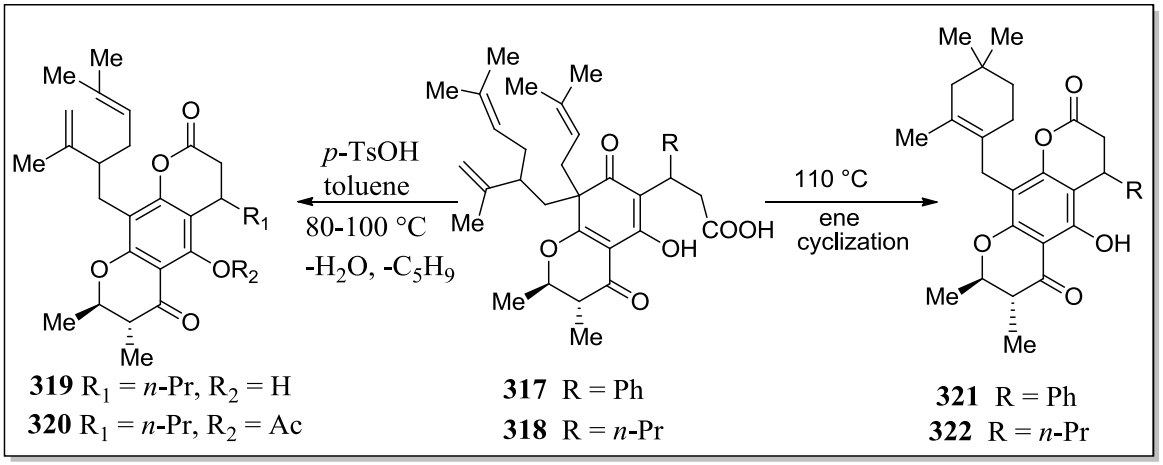
Scheme 76c

As early as 1943, Adams *et al.* demonstrated that [4+2] cycloaddition of 2,3-dimethyl-1,3-butadiene and coumarin **26** gave dihydrocoumarin **316**,[214] albeit in low yield. However, the coupling of 2,3-dimethyl-1,3-butadiene with *trans-o*-hydroxycinnamic acid **315** occurred readily at 185 ^{O}C to directly give **316** probably *via* [4+2] cycloaddition followed by cyclization *(Scheme 77)*.



Scheme 77

Shen *et al.* synthesized four novel pyranocoumarin designated inocalocyclides A-D (**319-322**), involving elimination of an isoprene unit and an *ene* cyclization.[215] When inocalophyllin B **318** was treated with *p*-TsOH at 80 ^{O}C for 5 h, inocalocyclide A **319** was formed in 30%. However, at 110 ^{O}C, inocalocyclide C **321** and inocalocyclide B **322** were generated, respectively, from inocalophyllin A **317** and inocalophyllin B **318**. Upon acetylation, compound **319** gave inocalocyclide D **320** *(Scheme 78).*

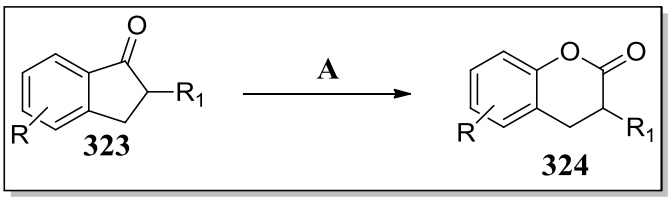


Scheme 78

1.2.6: From Indanones (Route F)

Stephan found that CF_3CO_3H (trifluoroperacetic acid) was more effective than *m*-CPBA for the Baeyer-Villiger reaction of indanones.[216] The same author and his group, synthesized optically active 4-substituted dihydrocoumarins from chiral 3-alkylindanones in the presence of CF_3CO_3H and/ or *m*-CPBA.[217] *Table 3* presents the information regarding the synthesis of dihydrocoumarins **324** from 1-indanones **323**. Hydrotalcites promoted Baeyer-Villiger reaction of 1-indanone using *m*-CPBA gave dihydrocoumarin in good yield.[218] Gotor and co-workers have described the conversion of 1-indanones into 3,4-dihydrocoumarins by utilizing 4-hydroxyacetophenone monooxygenase (HAPMO), one of the Baeyer-Villiger monooxygenase (BVMO) enzymes (summarized in *Table 3*).[219] They achieved an enantioselective synthesis of 3-methyl-3,4-dihydrocoumarin in low yield and low *ee* from 2-methyl indanone using HAPMO (BVMO) enzyme.[220] Gutiérrez *et al.* have obtained 3,4-dihydrocoumarins from 1-indanone derivatives *via* the Baeyer-Villiger oxidation using whole cells of the wild type bacteria Pseudomonas sp. NCIMB 9872 in excellent yield.[221] Although the reaction could also be performed on a preparative scale, it failed with several other substituted indanones. Sonnet and Oliver

showed that aryl group migration is favored over secondary alkyl group migration in peracid oxidation of 7-and 5-acetoxyindan-1-ones.[222]

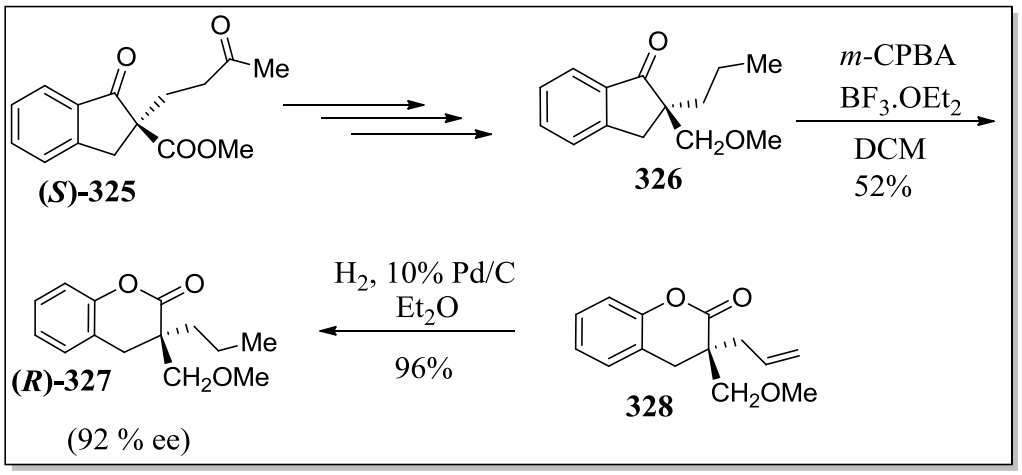


Scheme 79

Table 3: Synthesis of dihydrocoumarins from 1-indanones.

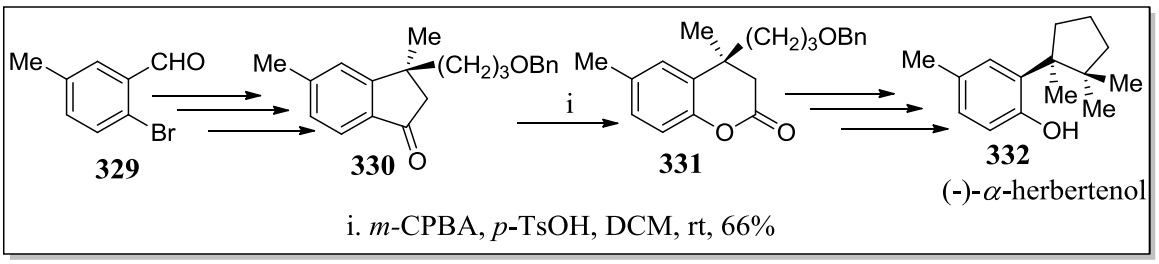
323				
R	R_1	A	Yield (%)	Ref.
H	H	**CF_3CO_3H**, 30% H_2O_2 rt, 2-3 h; or ***m*-CPBA** reflux, DCM, 5 h	>90 or 75	*216*
H, Cl, Br, OMe	H	**HAPMO**, buffer, G6P/G6PDH/NADPH 20 °C/250 rpm, 72 h	3-87	*219*
H	Me	**HAPMO**, 20 °C, 72 h	13; (6% *ee*)	*220*
H, F, Cl, OMe	H	**Pseudomonas sp. NCIMB 9872**	91-94	*221*
OAc	Me	**Disodium hydrogen phosphate, CF_3CO_3H**, DCM, reflux, overnight	80-88	*222*

Murakata *et al.* synthesized (*R*)-(-)3-methoxymethyl-3-propyl-3,4-dihydrocoumarin **327** from a chiral Michael adduct **325**.[223] The final step of the synthesis involved Baeyer-Villiger oxidation of indanone **326**, which gave (*R*)-**327** in 52% yield, with 92% *ee (Scheme 80).* Hydrogenation of **328** (obtained by enantioselective radical- mediated allylation[224,225] of 3-(methoxymethyl)-3-iododihydrocoumarin catalyzed by a chiral Lewis acid) also afforded **327** with a specific rotation identical to that of (*R*)- **327** prepared from the chiral Michael adduct (*S*)-**325**.



Scheme 80

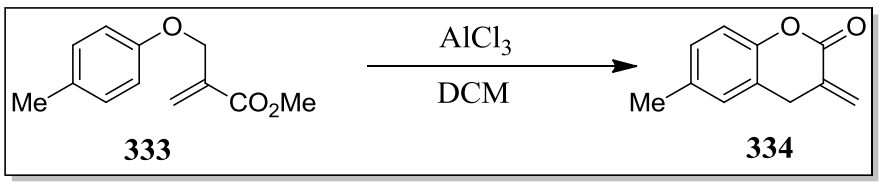
Matsuda *et al.* developed an enantioselective synthesis of benzopyranone **331** by Baeyer-Villiger oxidation of chiral indanone **330**, prepared from aldehyde **329**, by a rhodium catalyzed asymmetric addition/ring opening reaction of a cyclobutanone intermediate,[226] thus demonstrating the utility of this approach for the synthesis of (-)-α-herbertenol **332** *(Scheme 81)*.



Scheme 81

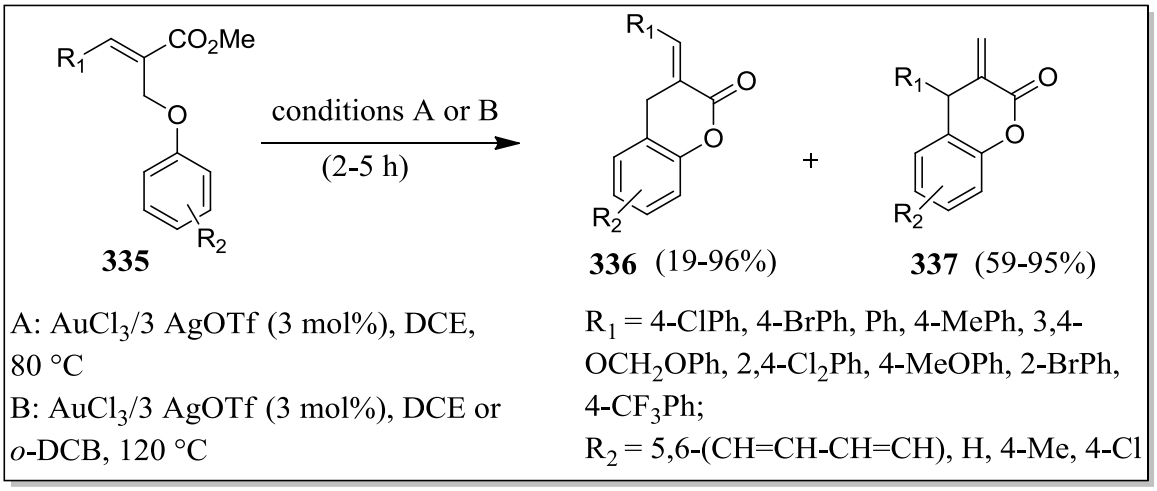
1.2.7: Miscellaneous Routes

Drewes and Roos described the preparation of 6-methyl-3-methylene-3,4-dihydrocoumarin **334** *via* $AlCl_3$ catalyzed Claisen rearrangement of methyl α-aryloxymethyl acrylates **333** *(Scheme 82)*;[227] 4-methyl-3-methylene-3,4-dihydrocoumarin from 3-ethoxy carbonyl-4-phenyloxy-but-2-ene was obtained *via* the Claisen rearrangement in the presence of TFA.[228] The requisite allyl ether systems were derived from Baylis-Hillman adducts.



Scheme 82

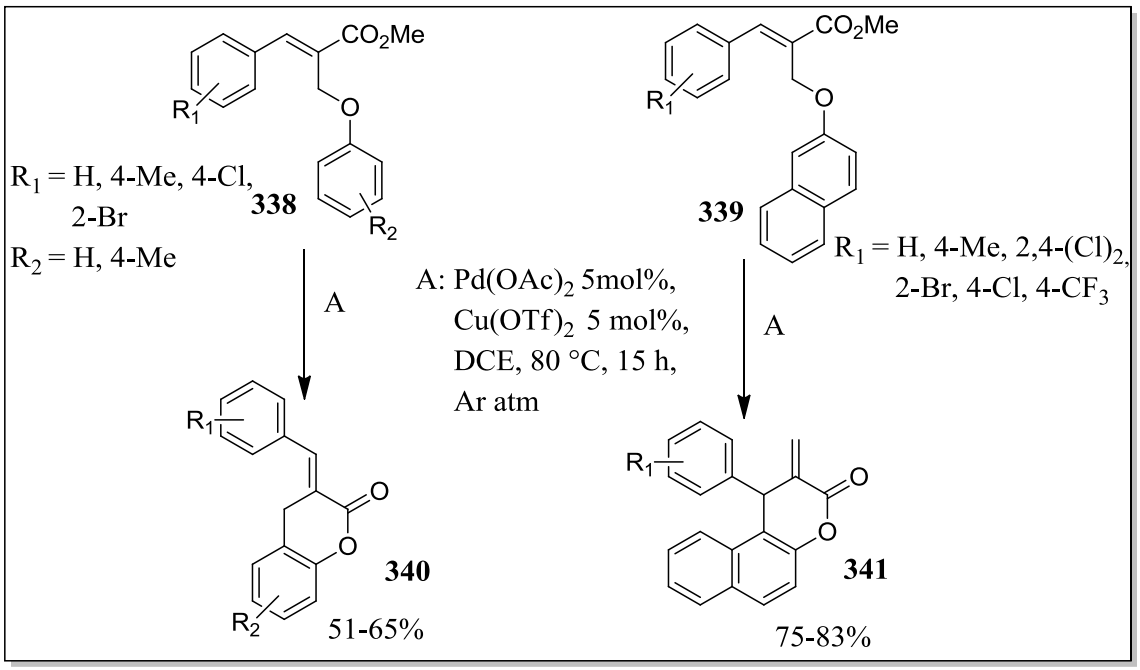
Gold-catalyzed synthesis of variously substituted benzopyranone derivatives **336** and **337** was achieved *via* temperature controlled, tandem *sigmatropic* rearrangement/cyclization of *E*- 2- (aryloxymethyl)alk-2-enoates **335**. Under conditions A, compound **336** was found to form exclusively, *via* [1,3]-sigmatropic rearrangement followed by cyclization. However, under conditions B a thermally concerted [3,3]-sigmatropic rearrangement was postulated to occur predominantly followed by cyclization to give **337** as major product *(Scheme 83).*[229]



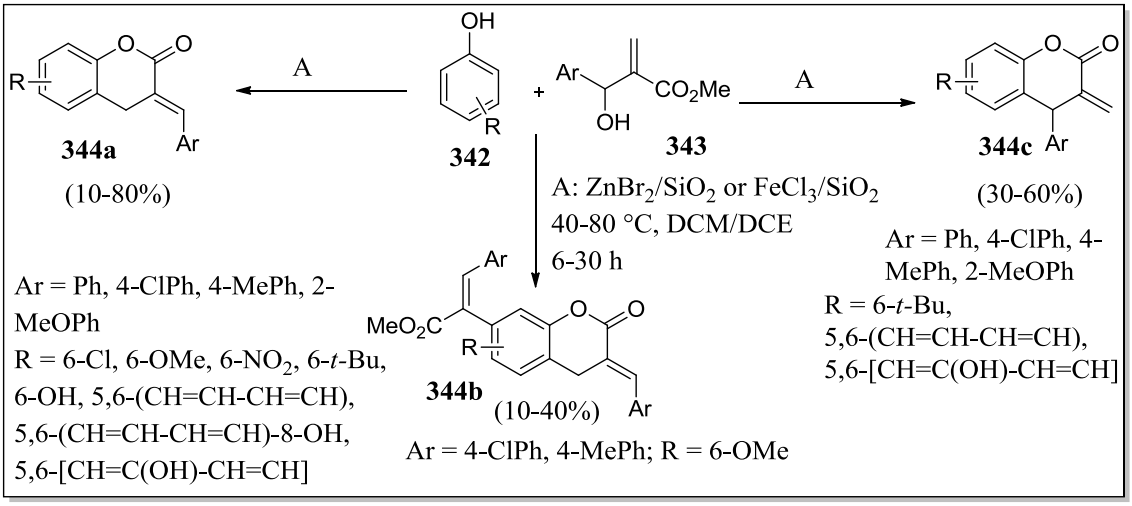
Scheme 83

Xu *et al.* have reported Pd/Cu catalyzed regiospecific synthesis of benzopyranone derivatives **340** and **341** *via* substrate controlled, not temperature controlled, [1,3] or [3,3] sigmatropic rearrangements of *E*-2-(aryloxymethyl)alk-2-enoates **338** and **339** *(Scheme 84).*[230] It was observed that in the case of phenyloxyallyl derivatives **338**, the reaction mechanism proceeded *via* [1,3]-sigmatropic rearrangement whereas, in the case of naphthoxyallyl derivatives **339**, [3,3]-sigmatropic rearrangement was predominant.

Foucaud and Brine reported the synthesis of 3-arylidene-3,4-dihydrocoumarins **344a,b** from phenols and methyl 3-aryl-3-hydroxy-2-methylenepropionates **343** in the presence of silica-gel supported $ZnBr_2$ or $FeCl_3$. Alkylation of the phenol in the *ortho* position to the OH group and intramolecular transesterification gave dihydrocoumarin **344a**.[231] In the case of phenols bearing two reactive hydroxy groups, such as 4-4′-biphenol, 2,3-dihydroxynaphthalene, 2,7-dihydroxynaphthalene, both the hydroxy groups reacted to form *bis*-dihydrocoumarins of type **344a**. When 4-methoxyphenol was used, additional alkylation on the 7-position of the initially formed dihydrocoumarin occurred, giving compound **344b**. The dihydrocoumarin **344c** was formed from *O*-alkylation of the phenol, followed by Claisen rearrangement and intramolecular transesterification *(Scheme 85).*

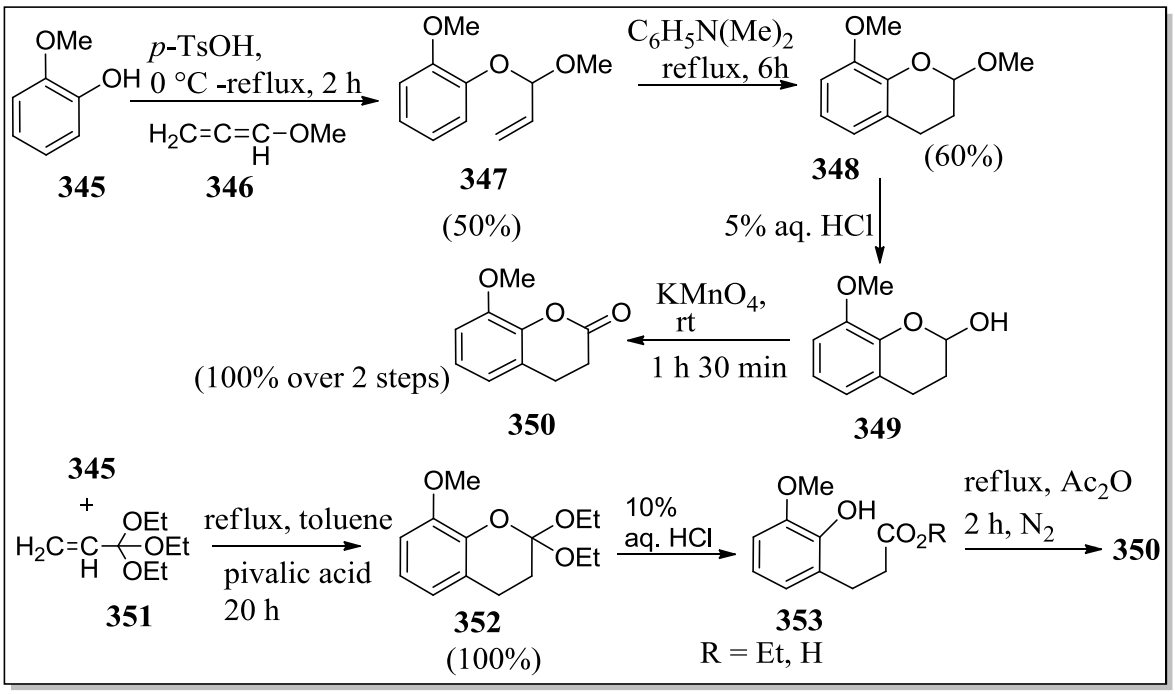


Scheme 84



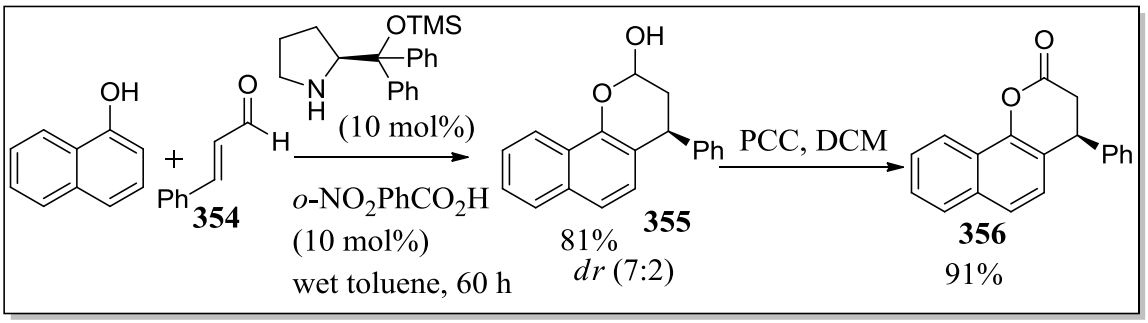
Scheme 85

Panetta and Rapoport have described a high yielding approach to dihydrocoumarins from phenols and triethyl orthoacrylate *via* the Claisen rearrangement.[232] Acid-catalyzed addition of guaiacol **345** to methoxyallene **346** gave *α*-methoxyallyl ether **347**. Next, reflux in dimethylaniline resulted in formation of chroman **348** *via* a Claisen rearrangement, followed by intramolecular cyclization. Further, treatment with dil. HCl gave lactol **349**, which was oxidized to dihydrocoumarin **350** with permanganate. Similarly, triethyl orthoacrylate **351** and guaiacol **345** were mixed in refluxing toluene containing a *cat.* amount of pivalic acid, resulting in formation of 2,2-diethoxychroman **352**. Hydrolysis, followed by ring closure, resulted in dihydrocoumarin **350** formation *via* intermediate **353** *(Scheme 86).*



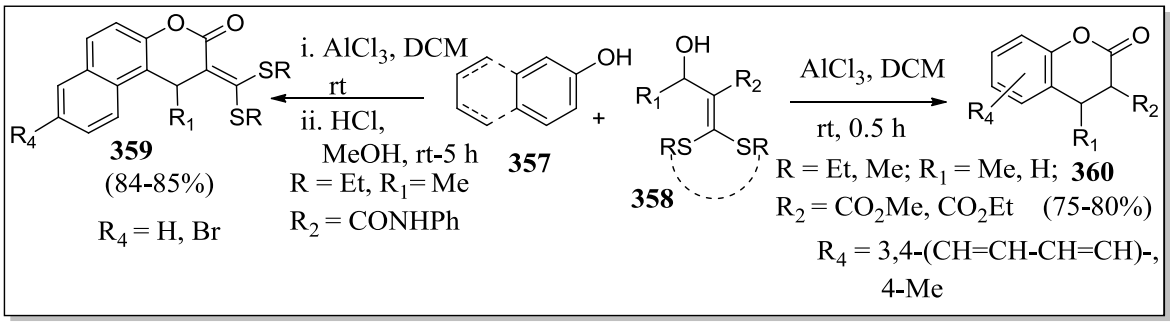
Scheme 86

Wang and co-workers employed an organocatalytic asymmetric Friedel-Crafts alkylation/cyclization cascade reaction for the synthesis of several chromanes **355** starting from 1-naphthols and *α,β*-unsaturated aldehyde **354** *(Scheme 87).* Further oxidation with PCC gave dihydrocoumarin **356.**[233]



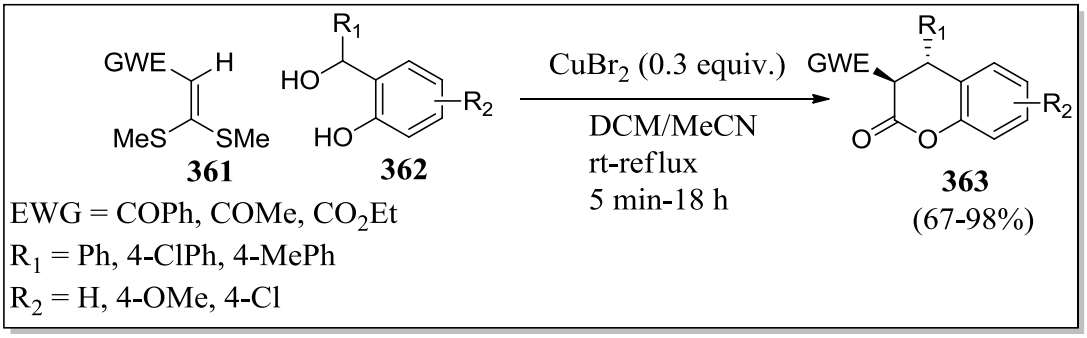
Scheme 87

Piao *et al.* have reported the synthesis of a series of biologically and pharmacologically important 3,4-disubstituted dihydrocoumarins **359**, **360** by an efficient $AlCl_3$ mediated sequential alkylation and intramolecular annulation reaction of *α*-hydroxyketene acyclic –*S,S*- acetals **358** with phenols **357** *(Scheme 88).*[234]



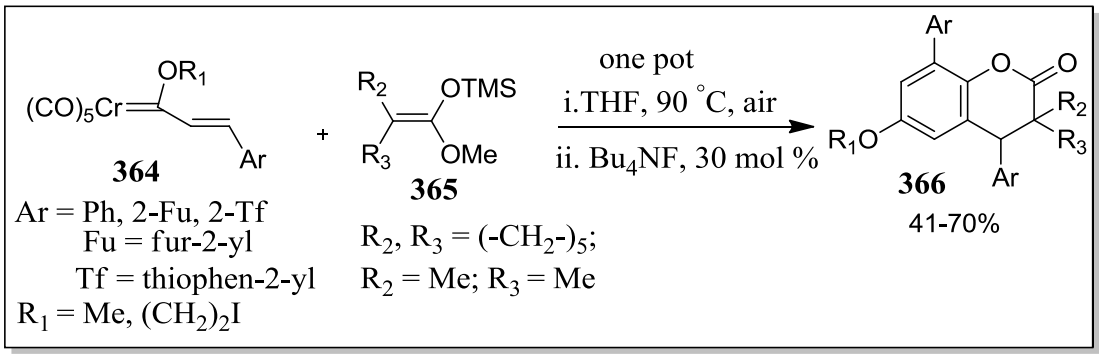
Scheme 88

Liu and co-workers developed a $CuBr_2$ catalyzed synthesis of several 3,4-disubstituted dihydrocoumarin derivatives **363** from ketene dithioacetals **361** and 2-(hydroxymethyl)phenols **362** *(Scheme 89).*[235]



Scheme 89

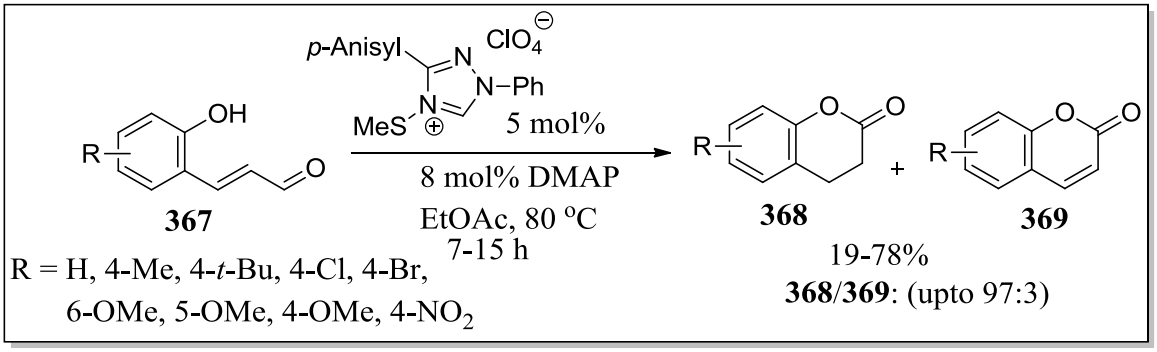
Barluenga *et al.* have described a unique reactivity pattern of alkenyl carbene chromium (0) complexes **364** with ketene acetals **365**, resulting in the formation of 4-aryl-3,4-dihydrocoumarins **366** *(Scheme 90)*. This approach has been optimized to a multigram scale process.[236]



Scheme 90

A mild, *N*-heterocyclic carbene-catalyzed, atom-economical access to DHCs **368** has been demonstrated by Zeitler and Rose *via* a "domino" oxidation-lactonization of *o*-hydroxycinnamaldehydes **367** *(Scheme 91).*[237] Small amounts of coumarin side-products

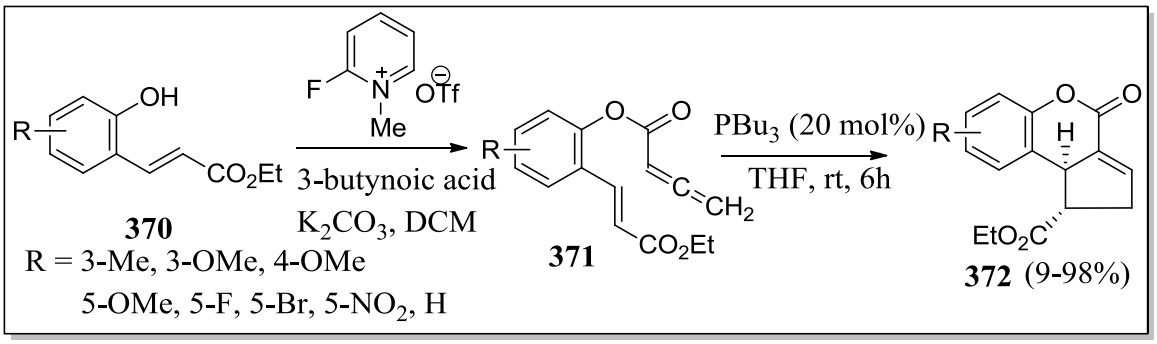
369 were also observed and electron rich substrates were more prone to such side-reactions.



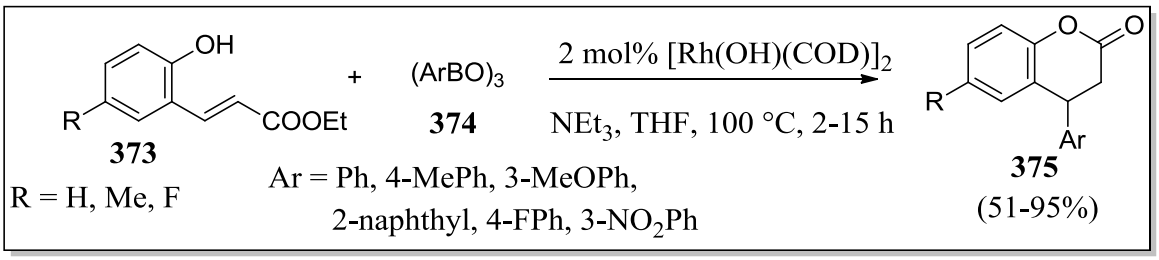
Scheme 91

Henry and Kwon described conversion of 2-styrenylallenoates **371** into cyclopenten-fused dihydrocoumarins **372** through phosphine-catalyzed regio- and diastereoselective [3 + 2] cycloadditions.[238] Compounds **371** were prepared from substituted ethyl cinnamates **370** by a coupling reaction with 3-butynoic acid in the presence of Mukaiyama's reagent *(Scheme 92).*

Park and Youn have reported a rhodium (I) catalyzed "domino" conjugate addition-cyclization reaction of **373** with various arylboroxines **374** to form 3,4-dihydrocoumarins **375**, *(Scheme 93).*[239]

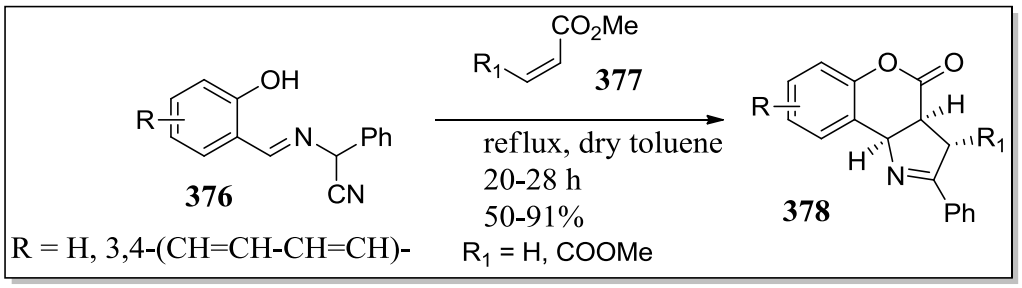


Scheme 92



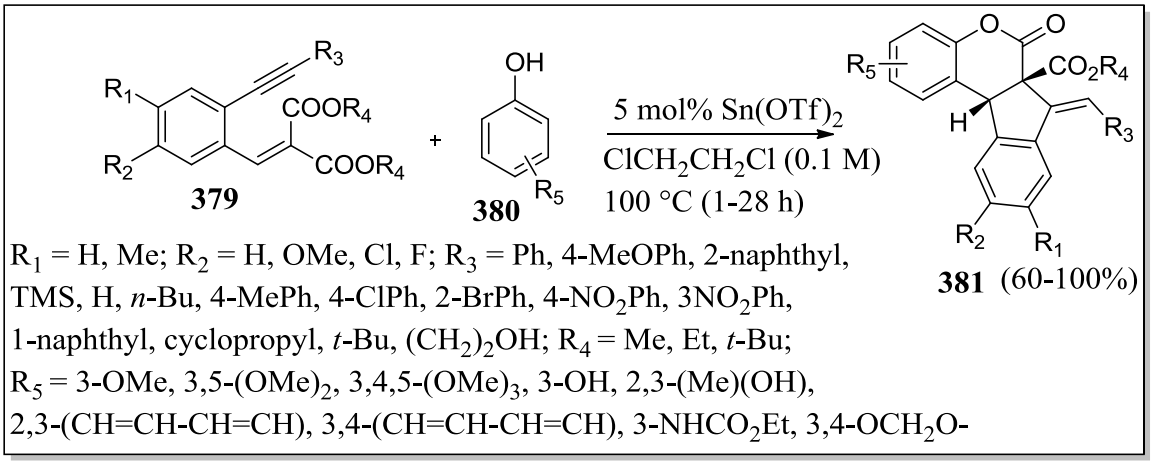
Scheme 93

Cycloaddition of 2-(2-hydroxybenzylidenamino)-2-phenylacetonitrile/2-[(2-hydroxy-1-naphthyl)methylenamino]-2-phenylacetonitrile **376** with dimethyl maleate/methyl acrylate **377** in refluxing toluene gave benzopyranones **378** *(Scheme 94).*[240]



Scheme 94

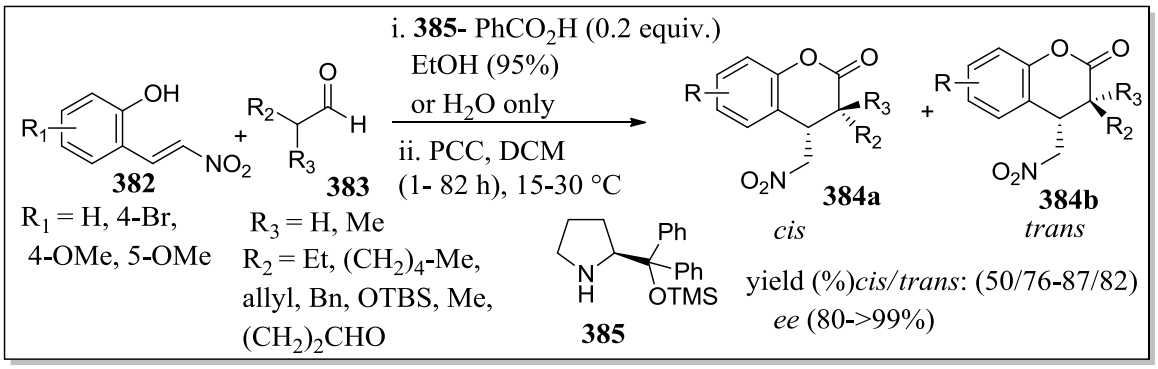
Joo and Youn have developed a $Sn(OTf)_2$ catalyzed "domino" hydroarylation-cyclization methodology to synthesize a wide variety of methyleneindane-fused dihydrocoumarins **381** *(Scheme 95)*.[241]



Scheme 95

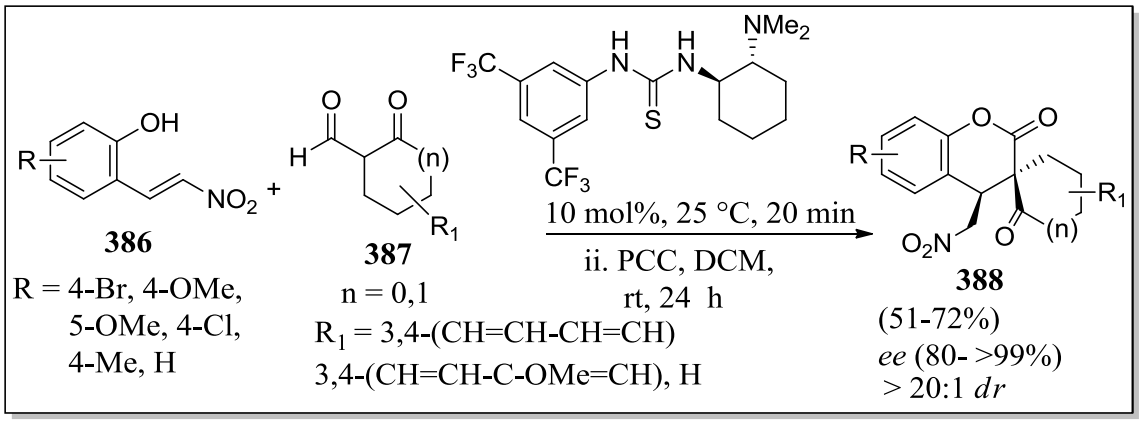
In 2010, Gong and co-workers developed a tandem Michael addition hemi-acetalization reaction between aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols mediated by secondary amine catalysts (*e. g.* L,L-prolylprolinol) for the synthesis of chiral chroman-2-ols. The latter were oxidized subsequently to chiral 3,4-dihydrocoumarins.[242] An organocatalytic, Michael addition, hemi-acetalization reaction[244] resulting in the synthesis of chromans, followed by subsequent oxidation into 3,4-dihydrocoumarins, was also reported by Enders *et al.*[243] Enders *et al.* identified (*E*)-2-(2-nitrovinyl)phenols and *α,β*-unsaturated aldehydes as potential substrates for Michael addition-hemi-acetalization reactions.[245]

Hong *et al.* also carried out a domino Michael-acetalization reaction with 2-hydroxynitrostyrenes **382** and aldehydes **383** on water, followed by oxidation using Jørgensen-Hayashi catalyst **385** *(Scheme 96)*.[246]



Scheme 96

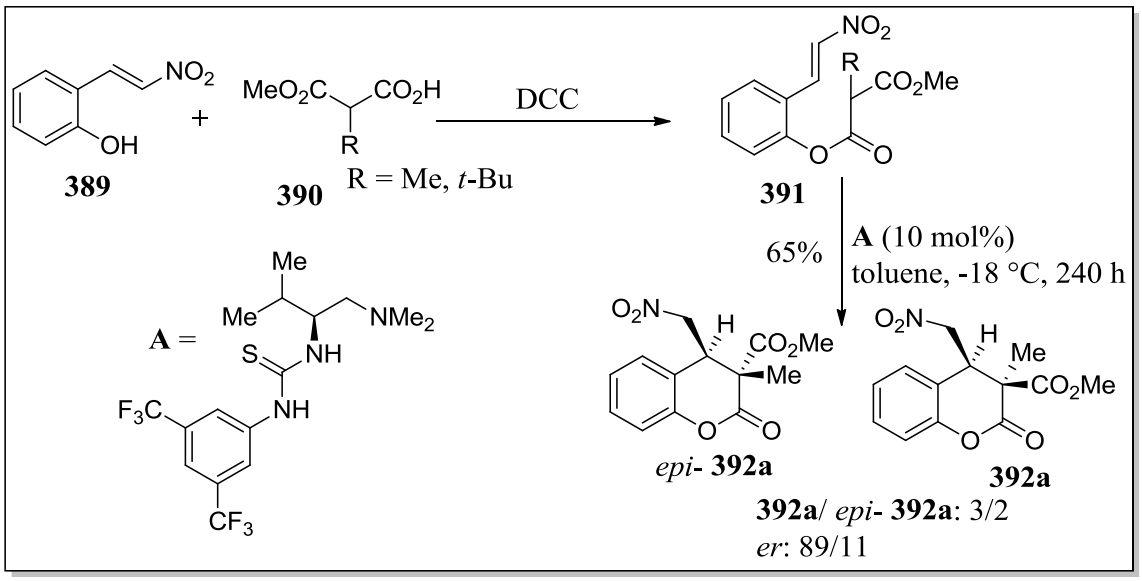
The same group reported that asymmetric "domino" Michael acetalization reactions of 2-hydroxynitrostyrenes **386** and 2-oxocyclohexenecarbaldehydes **387** with a bifunctional thiourea-tertiaryamine organocatalyst, followed by oxidation, yielded the 1′,3-spiro-2′-oxocyclohexane-3,4-dihydrocoumarins **388** with excellent diastereo- and enantioselectivities *(Scheme 97)*.[247]



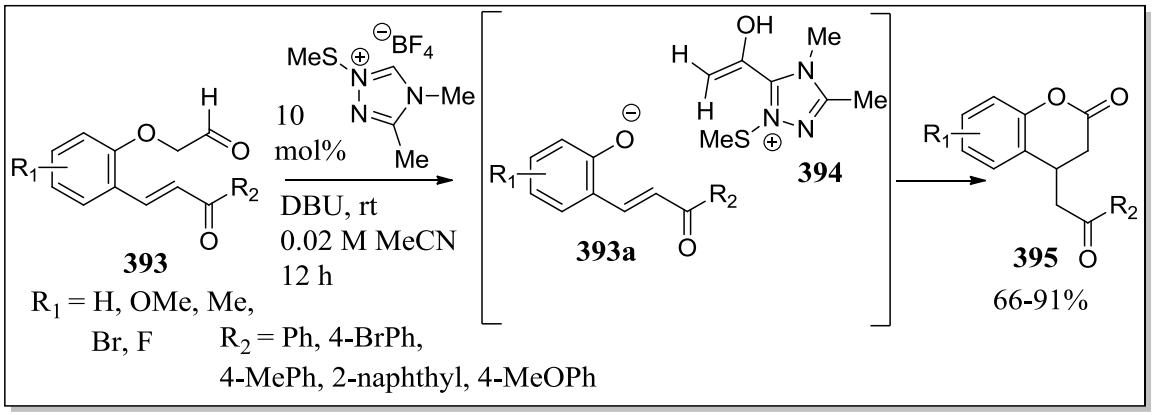
Scheme 97

The intramolecular Michael addition of nitroolefins **391** (obtained by reaction of *trans*-(*o*-hydroxy)- *β*-nitrostyrene **389** with the hemiesters of 2-methyl-and 2-*t*-butylmalonic acid **390** in the presence of DCC), *(Scheme 98)* was catalyzed by a thiourea **A** (derived from L-valine) to give (3*S*, 4*R*)-methyl 3-methyl-4-(nitromethyl)-2-oxochroman-3-carboxylate **392a** and its epimer.[248]

Scheidt and co-workers have described an *N*-heterocyclic carbene (NHC)-catalyzed "domino" Michael addition/acylation reaction to form 3,4-dihydrocoumarins **395** *(Scheme 99)*. The reaction proceeds through addition of the NHC to the aryloxyaldehyde **393** followed by elimination of a phenoxide group **393a**, generating an enol intermediate **394**.[249] Michael addition of **394** to **393a** followed by regeneration of catalyst upon acylation of the phenoxide anion accounts for the formation of 3,4-dihydrocoumarins **395**.



Scheme 98



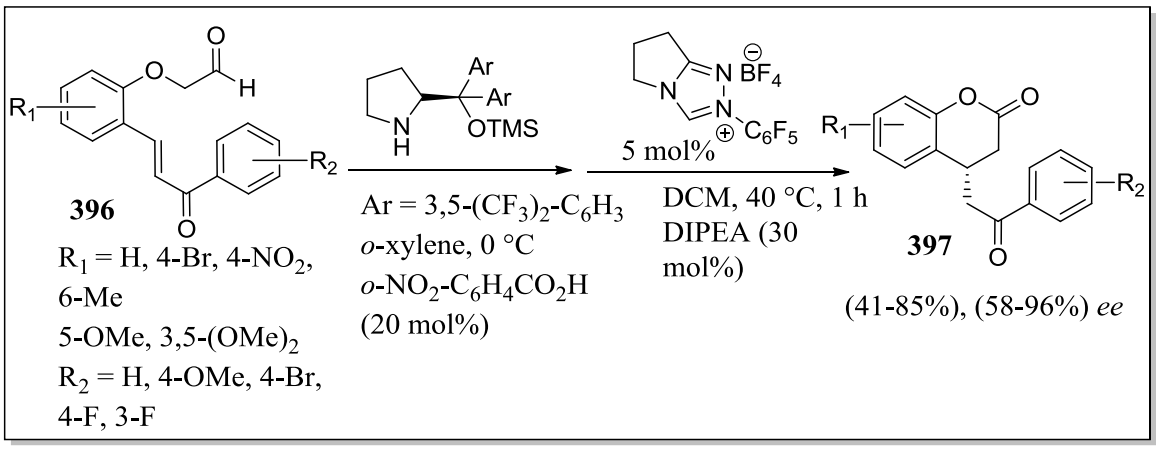
Scheme 99

Jørgensen and co-workers have synthesized several optically active 3,4-dihydrocoumarins **397** by a multicatalytic one-pot reaction sequence using a diarylprolinol silyl ether catalyst and an achiral NHC-catalyst *(Scheme 100)*.[250] The reaction proceeded through a *N*-heterocyclic carbene-catalyzed internal redox reaction of the aryloxyacetaldehyde **396**.

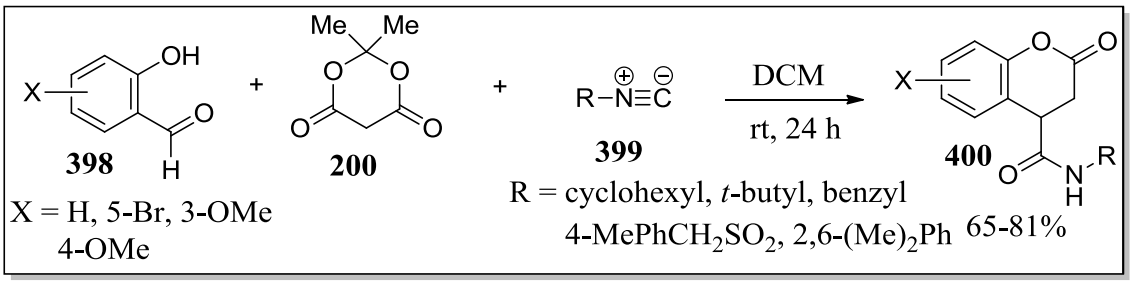
A three-component reaction between 2-hydroxybenzaldehydes **398**, Meldrum's acid **200** and isocyanides **399** to give DHC derivatives **400** has been described by Shaabani *et al. (Scheme 101)*.[251]

In the same laboratory, an isocyanide-based four-component reaction leading to the facile synthesis of fully substituted dihydrocoumarins was reported;[252] the condensation reaction of a 2-hydroxybenzaldehyde **401**, Meldrum's acid **200**, an alkyl or aryl isocyanide **402** and an aromatic or aliphatic alcohol **403** at room temperature gave several dihydrocoumarin derivatives in good yields (70-96%). Interestingly, it was

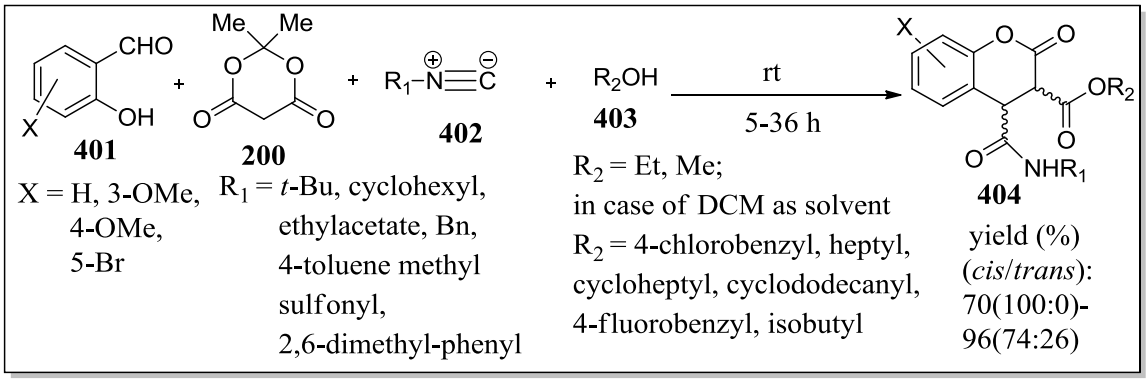
possible to synthesize dihydrocoumarin derivatives bearing both electron-releasing as well as electron-withdrawing groups on the aromatic ring *(Scheme 102).*



Scheme 100



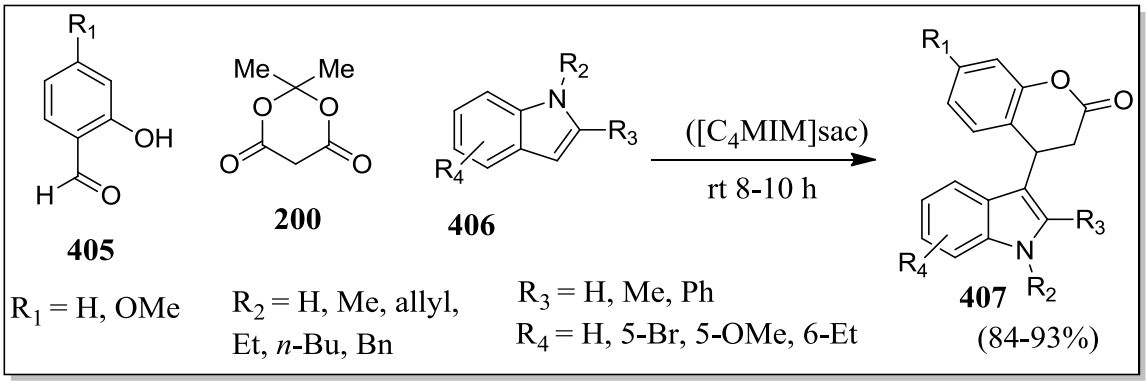
Scheme 101



Scheme 102

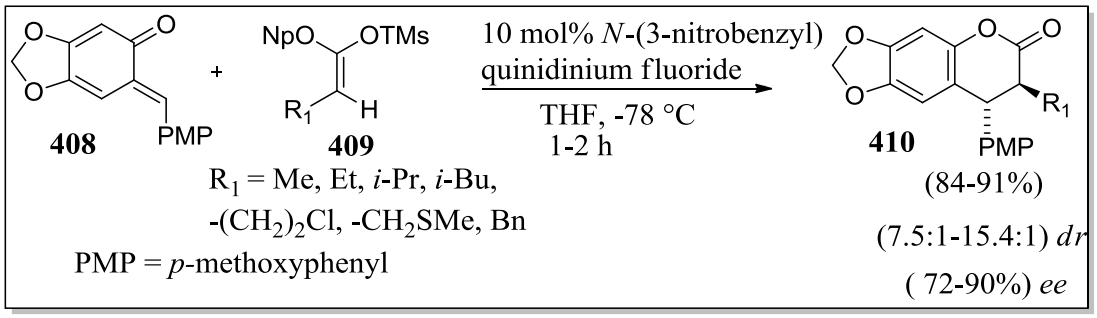
Recently, Rezayan carried out the synthesis of 3,4-dihydro-7-nitrocoumarins, again *via* a four-component condensation of 2-hydroxy-4-nitrobenzaldehyde, Meldrum's acid, a substituted isocyanide and aromatic or aliphatic alcohols without using any activator or catalyst.[253] Similarly, the multi-component coupling of a sugar hydroxyaldehyde, Meldrum's acid, isocyanide and a secondary alcohol in dichloromethane was developed by Subba Reddy *et al.* to accomplish the stereoselective synthesis of 5-oxo-perhydrofuro[3,2-*b*]pyrans with *trans*- selectivity.[254]

Kumar *et al.* demonstrated a multi-component reaction for the synthesis of indole-3-substituted dihydrocoumarin derivatives **407** using an artificial sweetener (saccharin)-based functional ionic liquid ([C_4MIM]sac)-mediated synthesis. Mechanistically, Knoevenagel coupling of aldehyde **405** and Meldrum's acid **200**, followed by a Michael type reaction with the indole **406**, and concomitant lactonization *via* decarboxylative elimination to give the desired dihydrocoumarin **407** was postulated *(Scheme 103)*.[255]



Scheme 103

Lectka and co-workers described the enantioselective [4+2] cycloadditions of *o*-quinonemethides **408** with silyl keteneacetals **409** catalyzed by a chiral cinchona alkaloid-derived ammonium fluoride pre-catalyst complex to give various alkyl and aryl substituted 3,4-dihydrocoumarins **410** in excellent yields *(Scheme 104)*.[256]

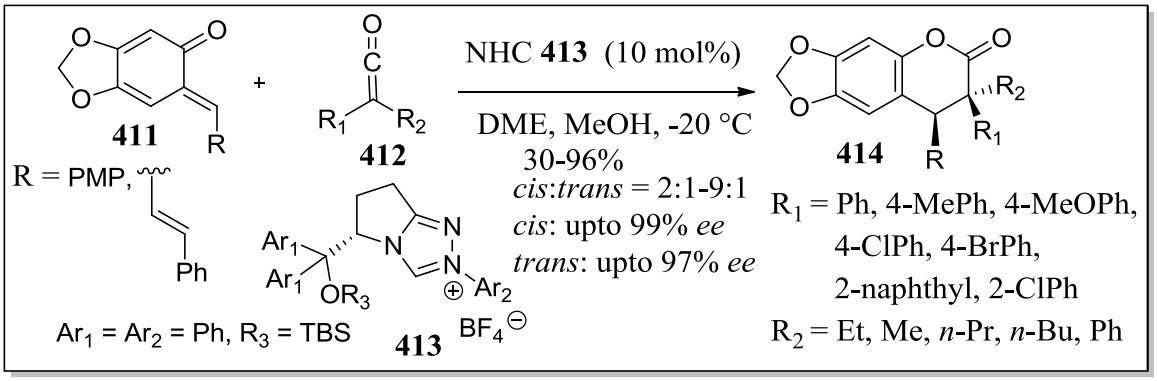


Scheme 104

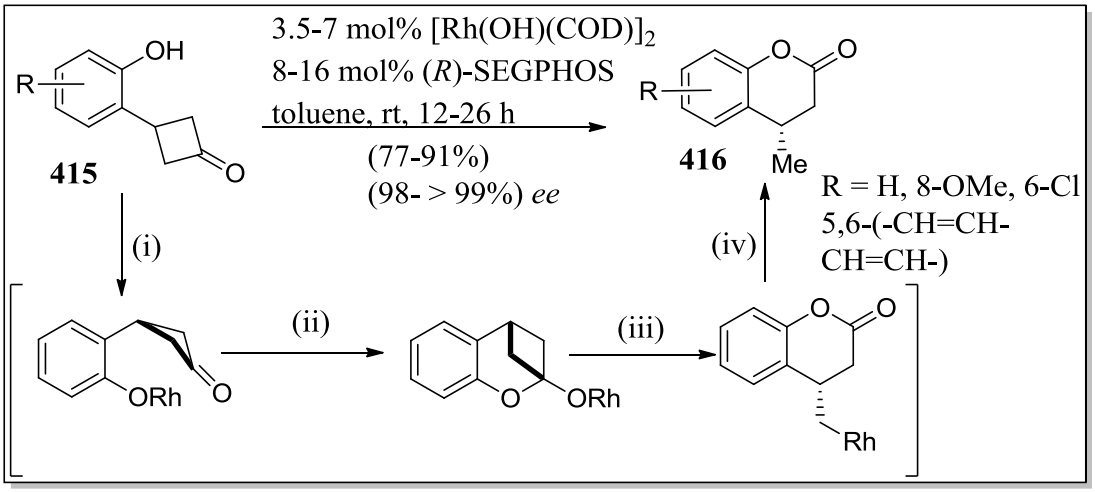
Similarly, the reaction of *o*-quinonemethides **411** and alky(aryl)ketenes **412**, catalyzed by NHC **413**, gave 3,3,4-tri-substituted-3,4-dihydrocoumarins **414** *(Scheme 105)*.[257]

Murakami and co-workers[258] developed an efficient, rhodium-catalyzed[259,260] enantioselective route to 4-substituted 3,4-dihydrocoumarins **416** *(Scheme 106a)* from various 3-(2-hydroxyphenyl)cyclobutanone derivatives **415**. They proposed a possible mechanism involving *i)* generation of a rhodium aryloxide, *ii)* addition to the carbonyl group forming a rhodium cyclobutanolate, *iii)* ring opening by *β*-carbon elimination, *iv)* protonolysis. Deuterium labeling experiments helped in determining the mechanistic

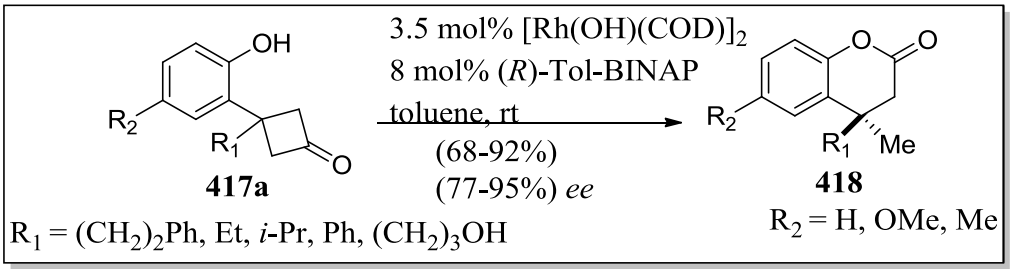
pathway. The reaction of 3,3-disubstituted cyclobutanone **417** was also examined *(Scheme 106b)*. The same workers also carried out this reaction in the presence of electron-deficient alkenes **419** *(Scheme 106c)*.



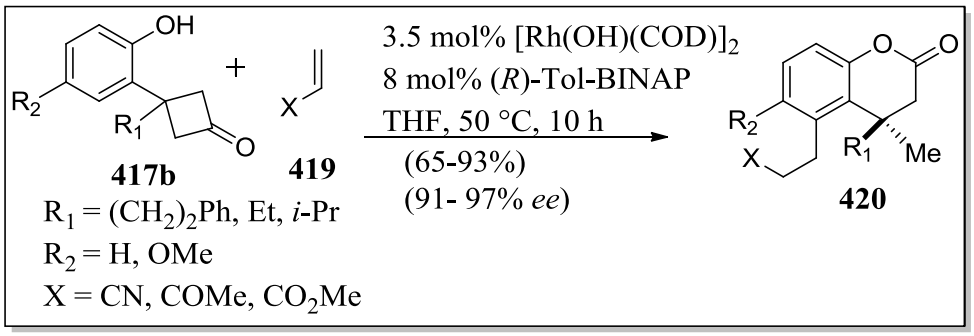
Scheme 105



Scheme 106a

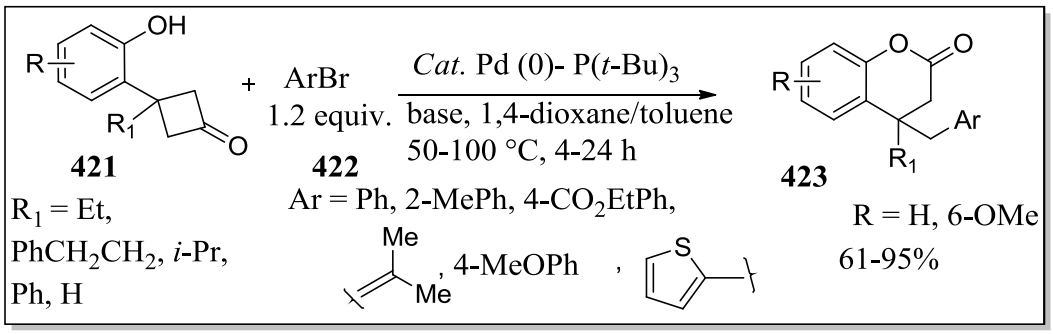


Scheme 106b



Scheme 106c

Palladium-catalyzed synthesis of 4-arylmethyl-3,4-dihydrocoumarins **423** from 3-(2-hydroxyphenyl) cyclobutanones **421** and aryl bromides **422** was reported by Matsuda *et al.* through a sequence involving carbon-carbon bond cleavage and formation *(Scheme 107).*[261]

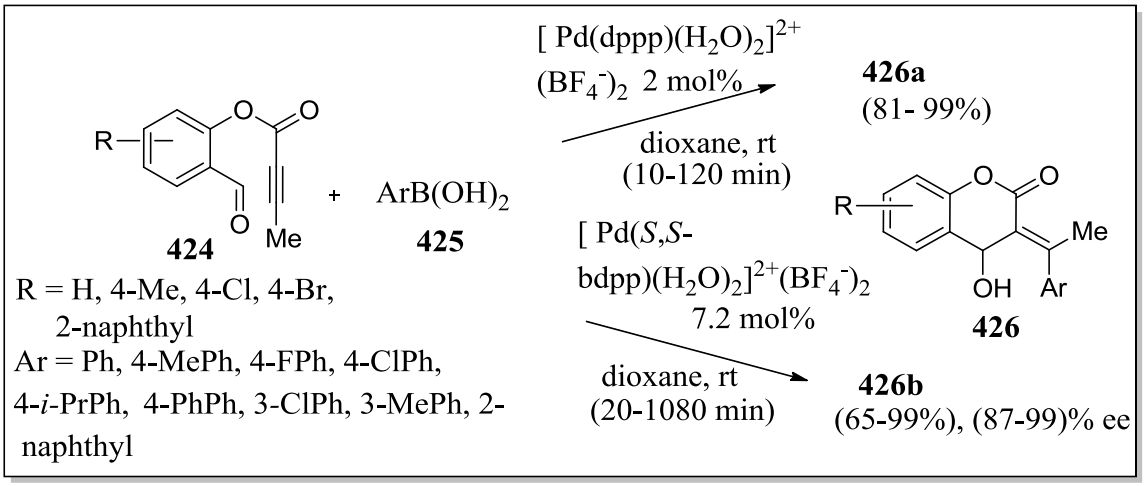


Scheme 107

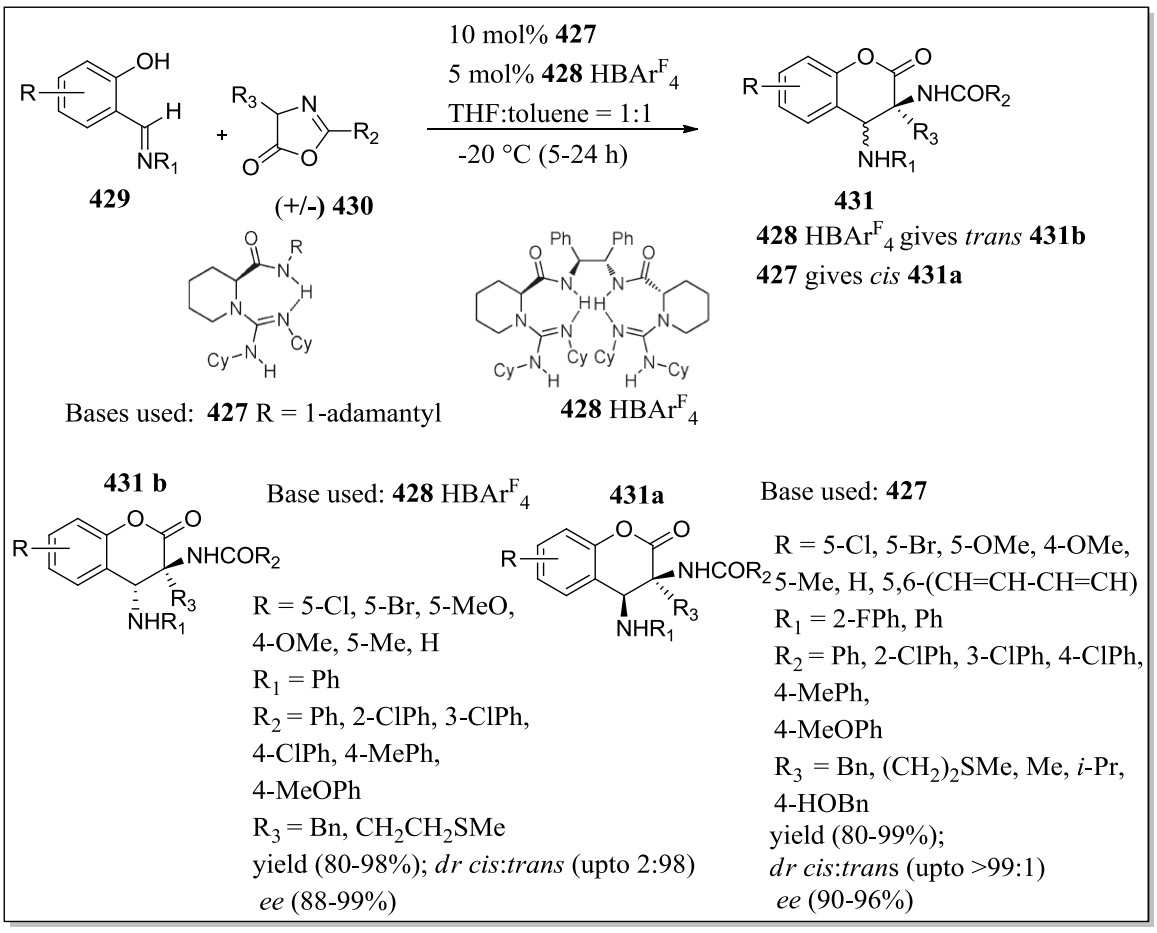
Han and Lu obtained 3,4-disubstituted dihydrocoumarins **426a** in excellent yields using substituted alkynals **424** in combination with $ArB(OH)_2$ **425** in the presence of catalytic amounts of cationic palladium complexes.[262] They have also synthesized asymmetric dihydrocoumarins **426b** using chiral *bis*phosphines as ligands, in good yields and high enantioselectivities *(Scheme 108).* A plausible mechanism involves trans-metalation of the arylboronic acid with the palladium catalyst, carbopalladation of the alkynoates and addition of the vinylpalladium species to the aldehyde.

Asymmetric "domino" reaction of *o*-hydroxy aromatic aldimines **429** and azalactones **430** was carried out for the preparation of *cis*- or *trans*-3,4-diaminochroman-2-ones,[263] depending on the catalyst used. Use of guanidine **427** delivered the *cis*-diastereomer **431a** as the major product and *bis*guanidium salt **428** ($HBAr^F_4$) gave the *trans*-diastereomer **431b** as the major product. The reaction conditions were investigated by using aldimines with different protecting groups, which included the *o*-fluorophenyl protected aldimines *(Scheme 109).* The position of the substituent on the phenyl ring of the aldimine had some effect on the product formation; *N*-phenylaldimines with a 5-chloro- or 5-bromo-

substituent gave the desired adducts in a slightly lower *dr* than those with a methyl or methoxy group.



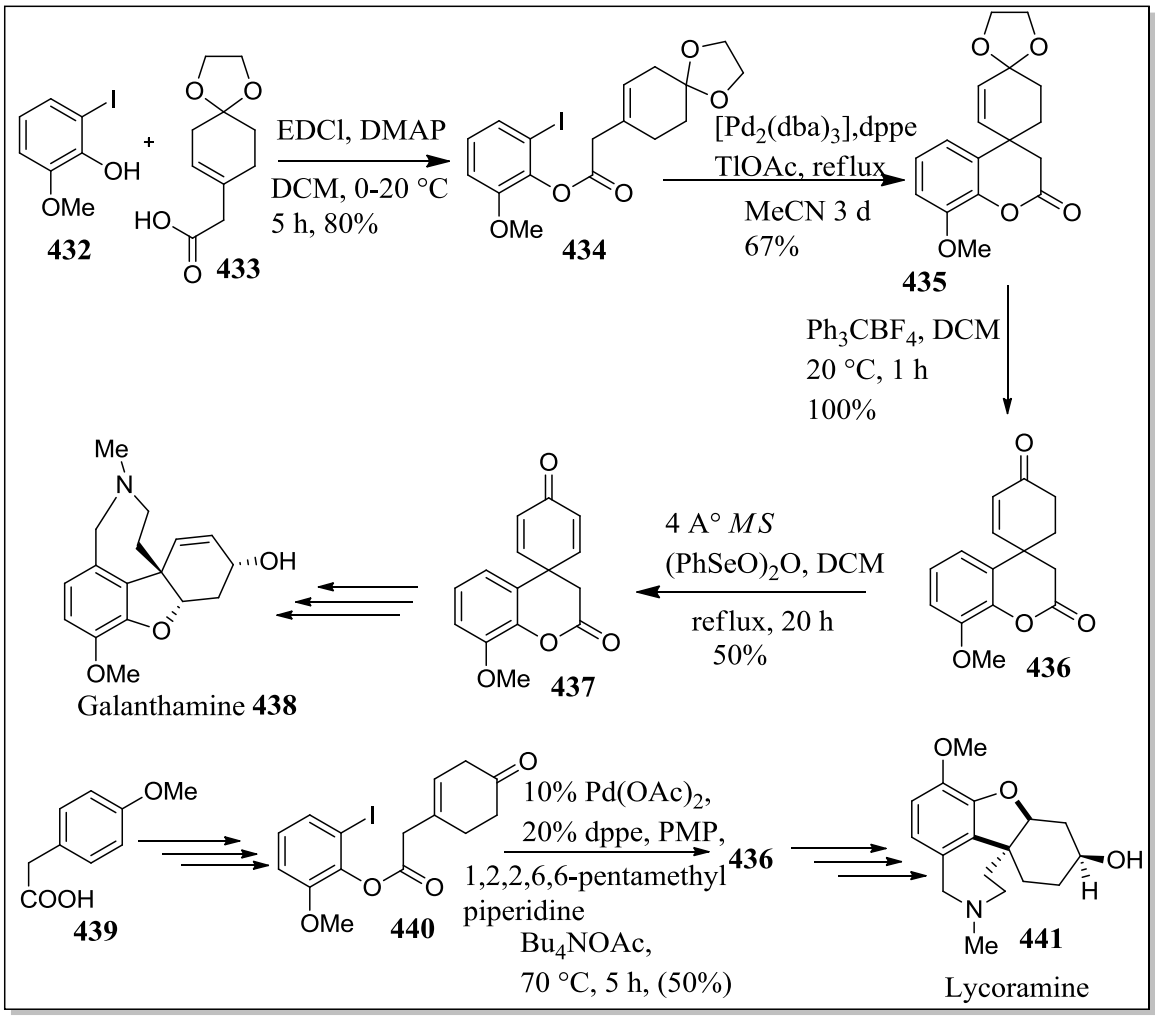
Scheme 108



Scheme 109

Guillou *et al.* synthesized benzopyranone **437**, which served as a key intermediate for the total synthesis of racemic galanthamine **438**.[264] Ester **434**, obtained by condensation of acid **433** with 2-iodo-6-methoxyphenol **432**, was subjected to Heck cyclization to give intermediate **435**. Deprotection of the dioxolane group of **435**, followed by oxidation of

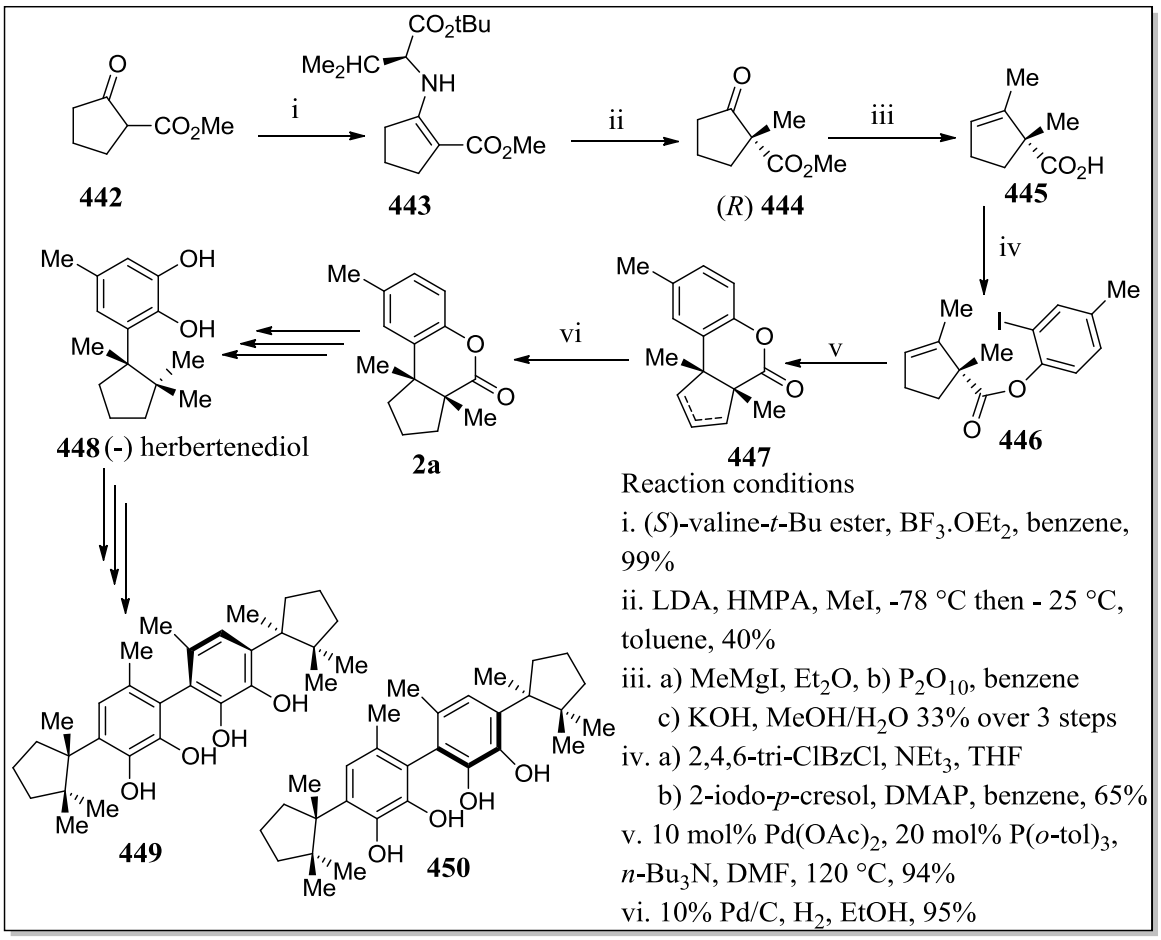
α,β-unsaturated ketone **436**, gave the required spirocyclohexadienone **437** *(Scheme 110)*. Furthermore, Guillou and co-workers carried out a formal synthesis of racemic lycoramine **441** *via* the same dihydrocoumarin intermediate **436** obtained from 4-methoxyphenylacetic acid **439**.[265]



Scheme 110

In 1996, Fukuyama *et al.* reported the first total synthesis of racemic herbertenediol **448** using an intramolecular Heck reaction as the key step for the synthesis of the benzopyranone intermediate **447**.[266] In a second article, the same author and his group obtained (-) herbertenediol **448**, mastigophorene A **449** and mastigophorene B **450**, which exhibit neurotrophic properties *(Scheme 111)*.[267] Chiral enamine **443** was alkylated and hydrolysed to give **444**. Then, (*R*)-**444** was converted into an optically active carboxylic acid **445**, which underwent Yamaguchi coupling with 2-iodo-*p*-cresol to furnish ester **446**. Intramolecular Heck reaction of **446** gave benzopyranone **447**, which was reduced by hydrogenation to **2a**. Stereoselective total synthesis of sesquiterpene

herbertenediol **448** and of its naturally occurring dimers, mastigophorenes A **449** and B **450**, was also accomplished by Bringmann *et al.*[268]



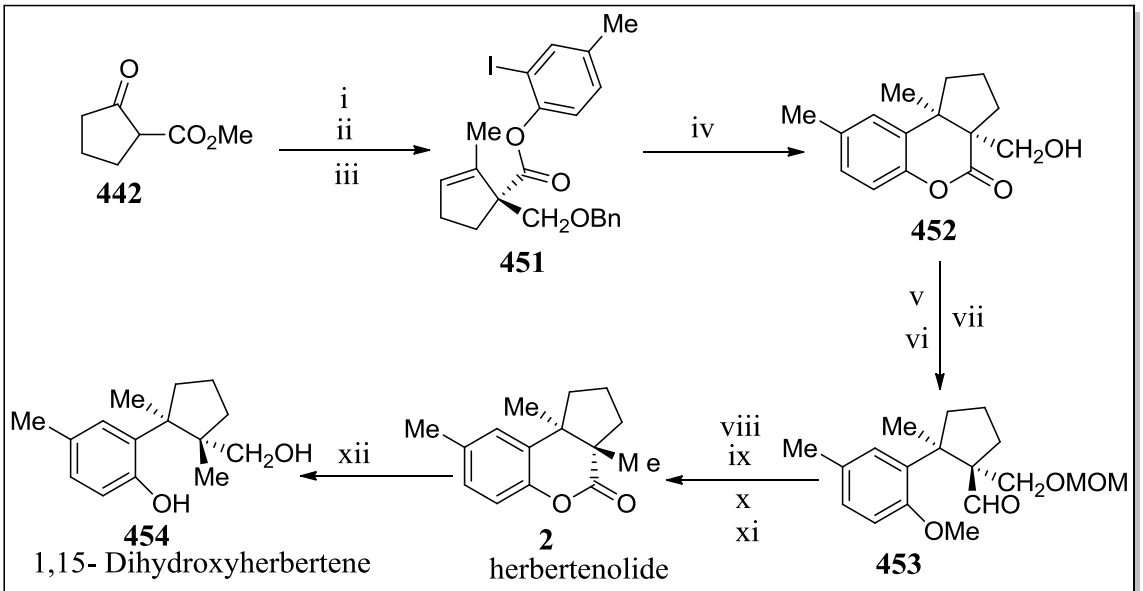
Scheme 111

By a similar route, Fukuyama *et al.* accomplished the synthesis of herbertenolide **2** and 1,15-dihydroxyherbertene **454** by utilizing an intramolecular Heck reaction for the construction of adjacent quaternary centers *(Scheme 112)*.[269]

Hoshino and co-workers described the total synthesis of lycoramine **441** *via* a dihydrocoumarin intermediate **461**. Reaction of **455** with 1,4-cyclohexanedione monoketal **456** gave alcohol **457**.[270] The product of the dehydration of **457** was subjected to radical reaction with AIBN and Bu_3SnH to give the spiro compound **459**, which was converted to spiro [2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexane]-2,4′-dione **460** which was subsequently converted to enone **461** with benzeneselenic anhydride, which was transformed into lycoramine *(Scheme 113)*.

Groutas *et al*. synthesized 5-acetoxy-3-methylene-3,4-dihydrocoumarin **466** starting from diketone **462**. Michael addition of phenylselenide to compound **462** was accompanied by concomitant ester cleavage to furnish acid **463**, which, upon reflux in trifluoroacetic

anhydride, gave lactone **464**.[271] Further, refluxing this product in a mixture of acetic anhydride/acetic acid/sulfuric acid gave dihydrocoumarin **465**. The desired compound **466** was obtained by oxidation of **465** with 30% aq. hydrogen peroxide and treatment of the resulting selenoxide with dilute sodium bicarbonate *(Scheme 114)*.



Reaction conditions:
i. 60% NaH, $PhCH_2OCH_2Cl$, toluene, 49%; ii. a) MeMgI, ether, b) P_2O_5, then NaOH, MeOH-H_2O 66% over 3 steps; iii. 2-iodo-*p*-cresol, DCC, DMAP, DCM, 87%; iv. 10 mol% $Pd(OAc)_2$, 20 mol% dppf, *n*-Bu_3N, DMF, 120 °C, then H_2, 10 mol% Pd/C, EtOH, 71%; v. CH_3OCH_2Cl, NEt_3, 97%; vi. a) LAH, THF, 0 °C; b) MeI, K_2CO_3, acetone, 89% over 2 steps; vii. DMSO, $(COCl)_2$, NEt_3, DCM, -78 °C then 0 °C, 74%; viii. $NH_2.NH_2.H_2O$, NaOH, diethylene glycol, 150 °C, 76%; ix. 40% HBr, MeOH, 87%; x. Jones reagent, acetone, 64%; xi. BBr_3, DCM, rt, 46%; xii. LAH, THF, 0 °C, 83%

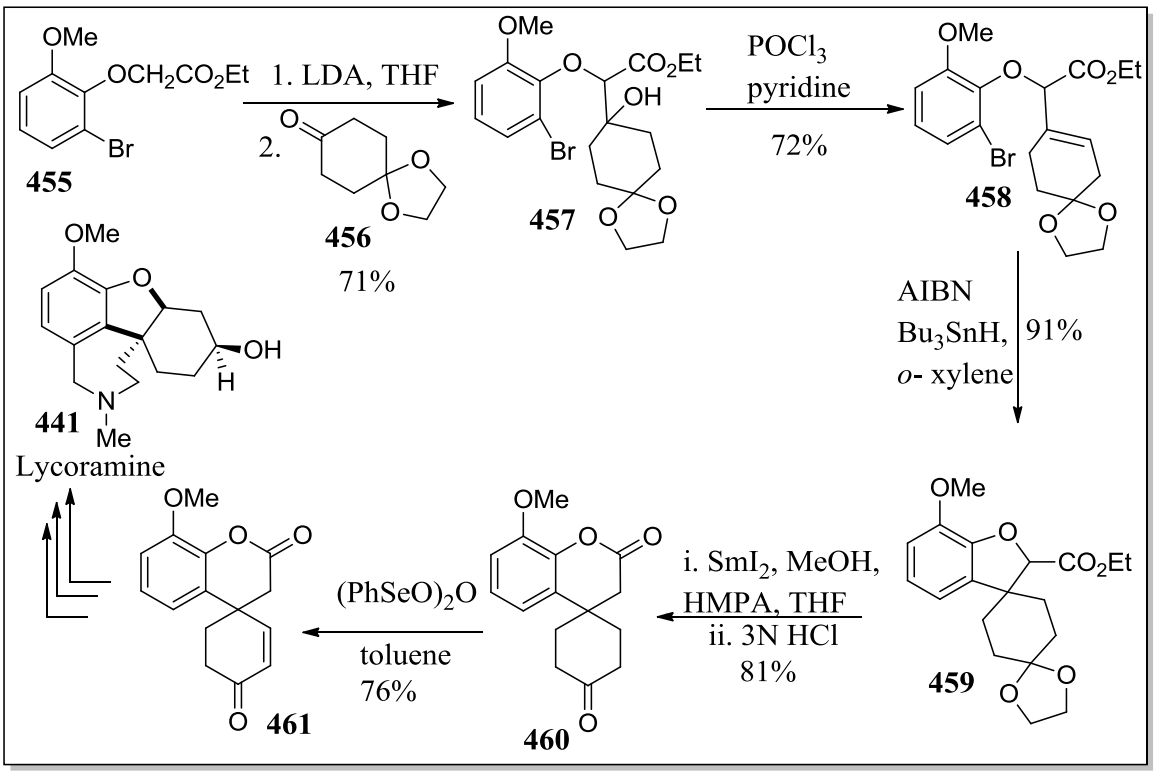
Scheme 112

Ramani *et al.* reported the synthesis of 3,4-dihydrocoumarin **469** by treatment of 2-methyl-1,3-cyclohexanedione **467** with 1,1-*bis*-diethylaminoethyl acetone **468** in the presence of pyridine *(Scheme 115)*.[272]

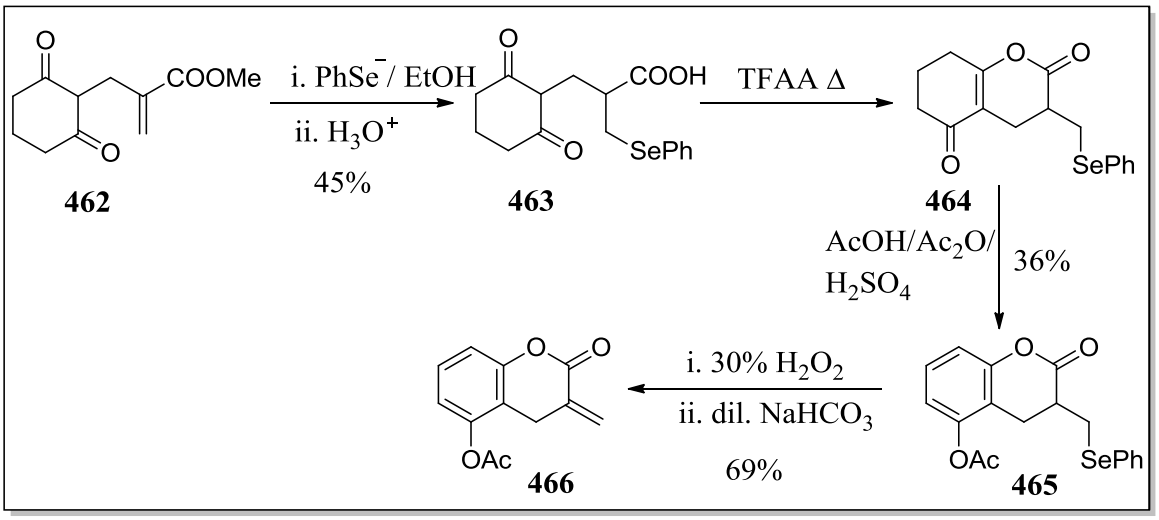
Alper and co-workers developed a palladium-catalyzed cyclocarbonylation of 2-vinylphenols **470** in the presence of ionic liquids as an avenue to dihydrocoumarins **471**. Benzofuran-2-ones were also obtained as side-products of this reaction *(Scheme 116)*.[273]

Reaction of resorcinols **472** and dimethyl acetonedicarboxylate **473** through electrophilic alkylation and lactonization with the formation of a 4,7-dihydroxychroman-2-one intermediate **474** was reported by Dubovik *et al.*[274] Condensation of this intermediate with another molecule of resorcinol resulted in the formation of 4,4′-spirodichroman-2-

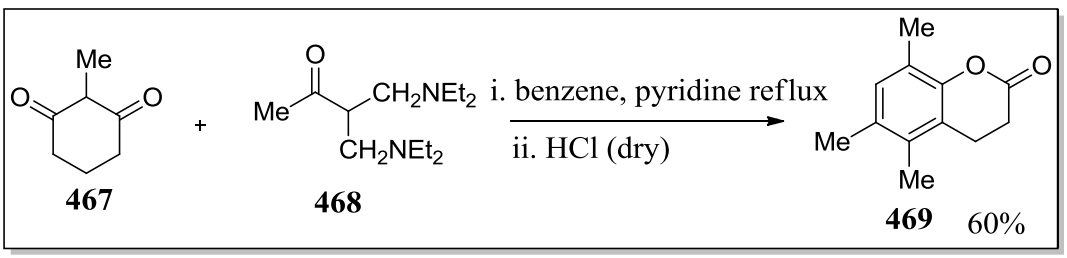
one **475**. Further alkylation of phenolic hydroxy groups of **475** furnished the corresponding methyl ethers **476** *(Scheme 117)*.



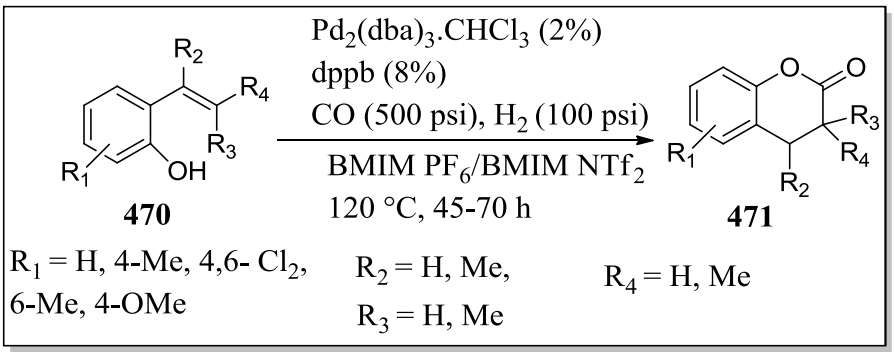
Scheme 113



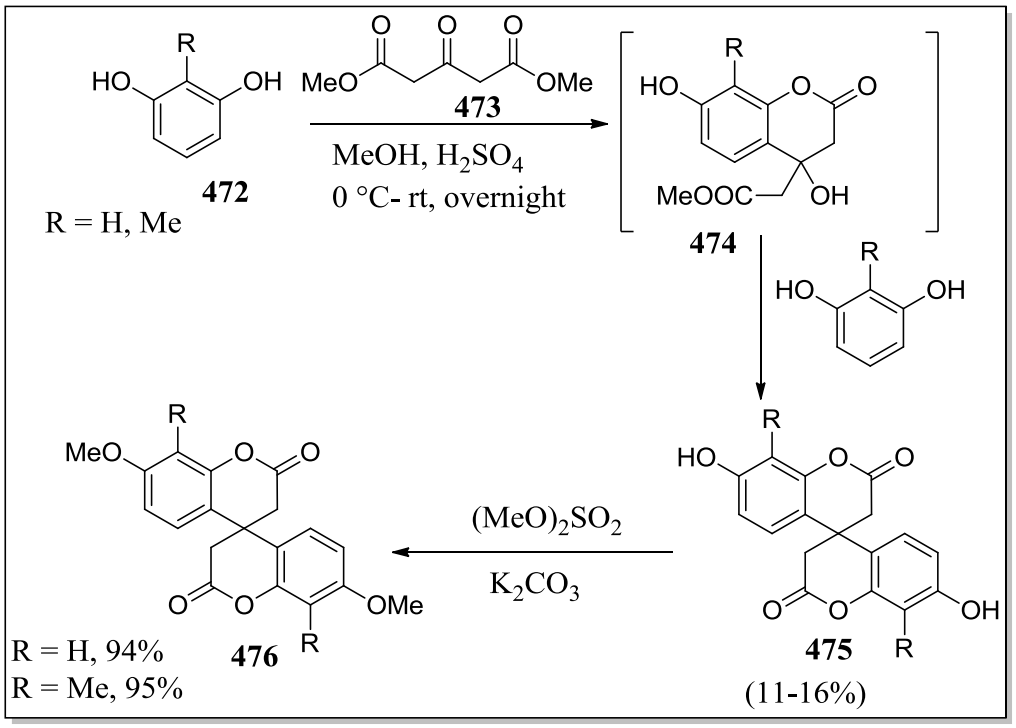
Scheme 114



Scheme 115

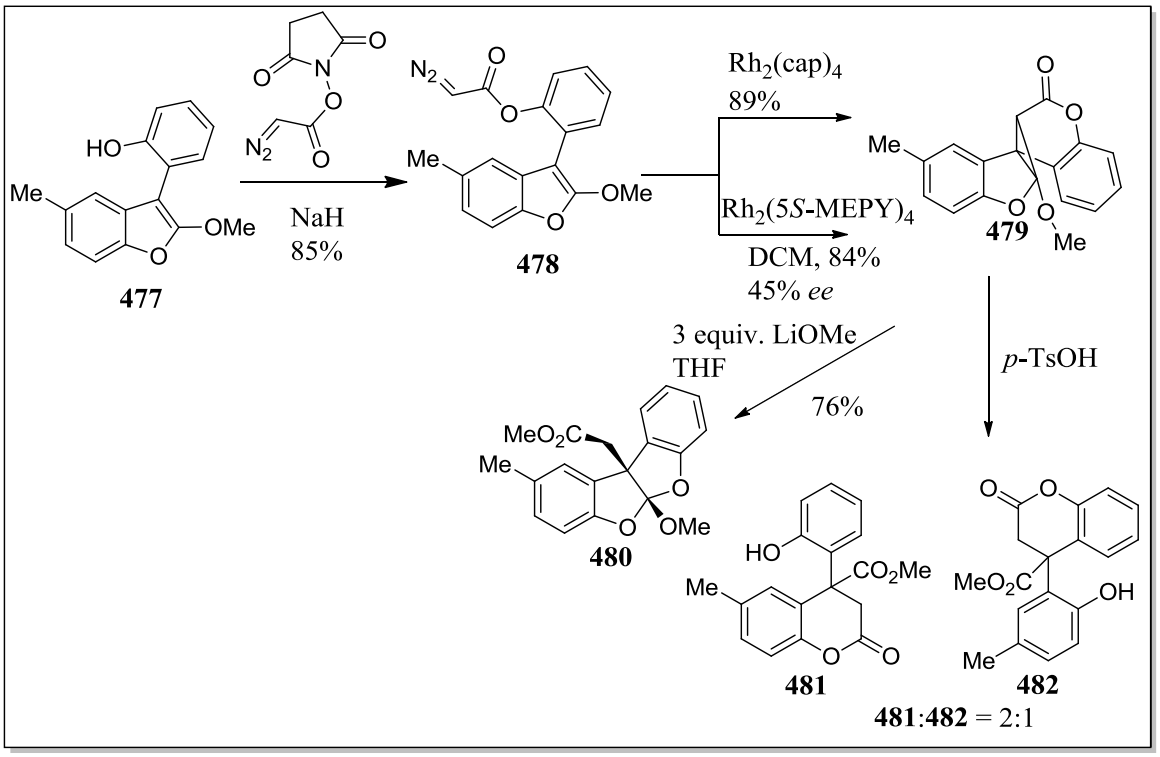


Scheme 116



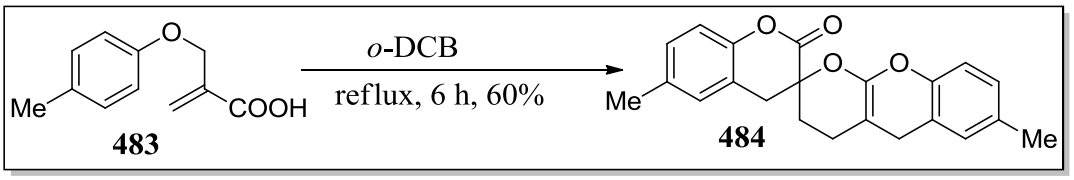
Scheme 117

Wood and co-workers described the synthesis of **480**, representing the diazonamide A *bis*aryl quaternary center, *via* a benzopyranone intermediate.[275] Compound **477** was obtained from 3-(*o*-benzyl)phenyl-5-methylbenzofuran by various chemical transformations such as oxidation at the C-2 position using peracetic acid, *O*-methylation and deprotection. Further, **477** was further acylated to yield *α*-diazo ester **478**, which decomposed with $Rh_2(Cap)_4$ to give cyclopropane **479**. Additionally, treatment of **478** with Doyle's catalyst gave rise to an optically active cyclopropane product in 45% *ee*. Treatment of **479** with LiOMe gave *ortho* ester **480**. Cyclopropane **479** could also be opened under acidic conditions to give benzopyranones **481** and **482** *(Scheme 118)*.



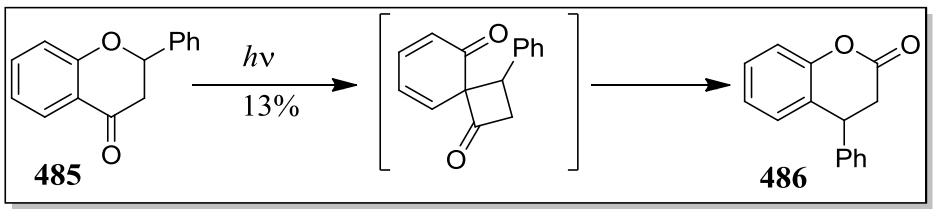
Scheme 118

Formation of the spiro dimer **484** was encountered by Swaminathan and co-workers when a solution of *α*-(*p*-cresoxymethyl)acrylic acid **483** was refluxed in *o*-dichlorobenzene *(Scheme 119).*[276]



Scheme 119

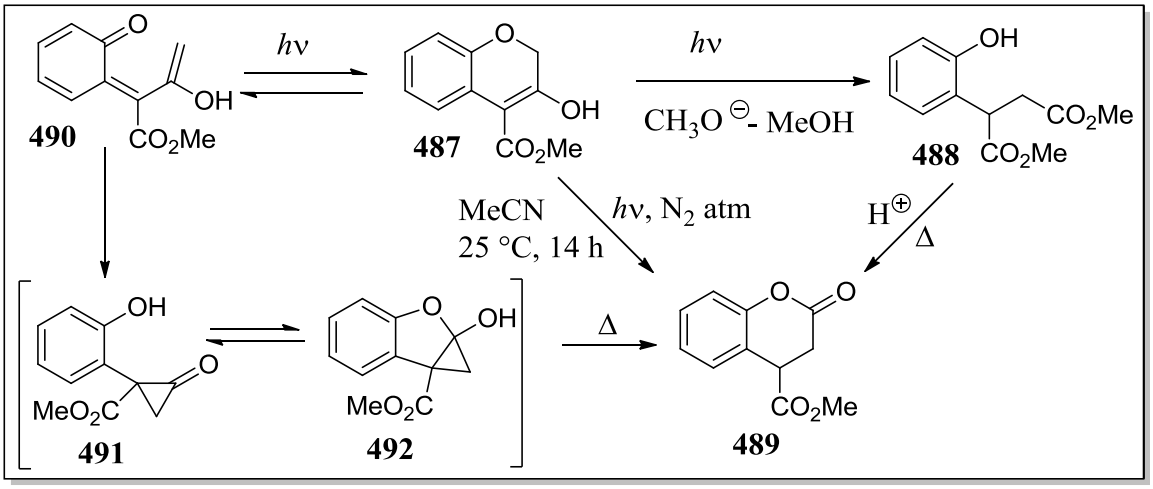
Light-induced rearrangement of flavanone **485** to 4-phenyldihydrocoumarin **486** was reported by Mack and Pinhey *(Scheme 120).*[277]



Scheme 120

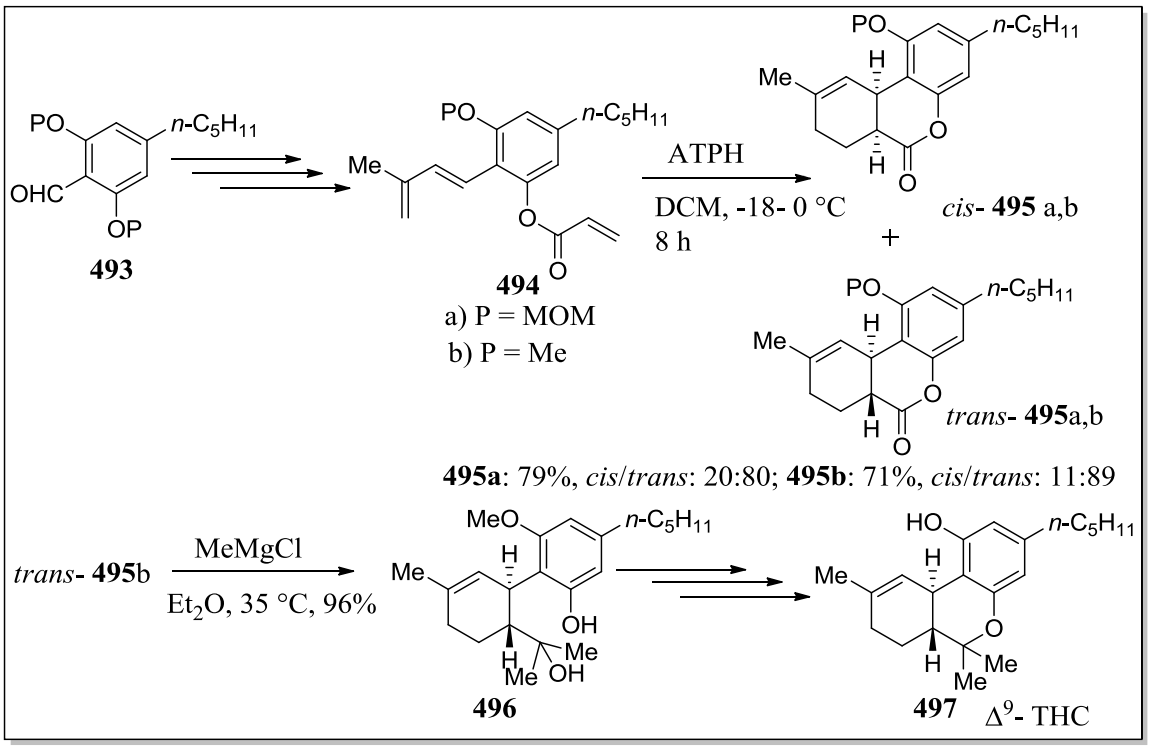
In 1975, Padwa and Au reported conversion of a methanolic solution of **487** into methyl 3(*o*-hydroxyphenyl)-3-carbomethoxypropanoate **488** by treatment with sodium methoxide, followed by irradiation with light λ = >300 nm.[278] Next, facile conversion of **488** to 4-carbomethoxydihydrocoumarin **489** was carried out by heating in the presence

of a trace amount of acid. Irradiation of **487** in acetonitrile also gave **489**. The mechanism was postulated as photoinduced ring-opening of chromanone **487** to an intermediate **490** followed by ring closure to give 2-carbomethxy-2-(*o*-hydroxyphenyl)cyclopropanone **491** as a transient intermediate, existing in equilibrium with **492**. In polar solvents, rapid opening of **492** presumably gave dihydrocoumarin **489** *(Scheme 121)*.



Scheme 121

Diastereoselective synthesis of Δ^9-THC **497** was developed by Sherburn and co-workers *via* a *trans*-selective intramolecular Diels-Alder (IMDA) reaction of benzo- tethered, ester linked 1,3,9-decatriene **494** as the key step. IMDA reaction of trienes **494** catalyzed by aluminum *tris*(2,6-diphenylphenoxide) (ATPH) gave *cis/trans* isomers **495**.[279] The *trans*-isomer **495b** was utilized further for a formal synthesis of Δ^9-tetrahydrocannabinol (Δ^9-THC) **497**, the key psychoactive constituent of marijuana. However, thermally promoted IMDA reactions of trienes **494** in the presence of butylated hydroxytoluene (BHT), gave cycloadduct mixtures rich in *cis* diastereomers *(Scheme 122)*.



Scheme 122

1.3: Conclusion

This review covers the literature pertaining to isolation, biological activities, syntheses and applications of dihydrocoumarins. A plethora of reports are available on the syntheses of this system. Most of the routes employ phenols as the starting substrates. A few reports on asymmetric synthesis are also available. We hope this review will provide the requisite background to allow the devising of new, greener and multi-component routes for the system.

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Chapter 2

Molecular iodine catalyzed synthesis of 4-phenylchroman-2-ones

2.1: Introduction

Iodine is non-metallic and has the following physical properties.

m.p.- 112.5 °C; b.p.- 184.4 °C; Specific gravity- 4.933; Electron affinity - 3.06 eV; Vapour pressure- 0.3 mm of Hg at 20 °C.

Iodine is a bluish black solid with an irritating pungent odour. Its name originates from the Greek word *iodes* (meaning violet). It readily sublimes to a deep-violet-coloured vapor. Iodine is the heaviest essential element needed by all living organisms.

Commercially, it is available as a brown solid. The two major sources of iodine are

1. The caliche (nitrate-bearing earth), found in Chile
2. The iodine containing brines of gas and oil fields, especially in Japan and the United States.

Molecular iodine has received a considerable attention for last few years as an inexpensive, non-toxic, readily available catalyst for various organic transformations.[1] Iodine has high tolerance to air as well as moisture making it an ideal catalyst. It can be easily removed from the reaction mixture by washing with reducing agents. Moreover, the mild Lewis acidity associated with iodine has enhanced its usage in several organic transformations.

In the year 2011, use of iodine as a reagent and catalyst for transformation of molecules containing oxygen functional groups was reviewed.[1c] In the following year, a review on synthesis of five- and six-membered heterocycles using molecular iodine was published by our research group.[1d]

One of the most important challenges in green chemistry includes the development of safe, atom efficient acid-catalyzed organic process. Commonly used acid catalysts continue to present serious problems through health and safety hazards. The large-scale workup procedure for these transformations becomes tedious, involving destructive aqueous quenches.

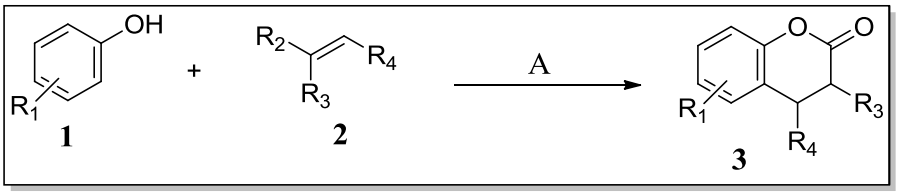
Several important heterocycles, such as furans, benzofurans, thiophenes, benzothiophenes, benzopyrans, indoles, quinolines, isoquinolines, isocoumarins, isoxazoles, spiro[4.5]trienones, chromones, lactams, 2,3-dihydropyrroles, pyrroles, furopyridines, furanones, isochromenes etc. have been prepared *via* iodine-mediated domino or one-pot multicomponent reactions. However, to the best of our knowledge, dihydrocoumarins have not been synthesized using iodine-mediated/catalyzed method.

2.2: Literature synthetic methods

In the previous chapter we have already described the syntheses of dihydrocoumarin scaffold through various routes. In this chapter, the review restricts only to the recent (2013 onwards) literature references pertaining to the synthesis of 4-substituted or 3,4-disubstituted dihydrocoumarins starting from phenols.

2.2.1: From Phenols

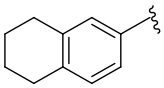
Chen *et al.* synthesized 7-hydroxy-4-phenyl-3,4-dihydrocoumarins[2a] by the condensation of resorcinol with cinnamic acid in presence of HCl gas. Further this compound was treated with 1,4-dibromobutane in acetone and the product obtained was reacted with



Scheme 1

Table 1: Synthetic methods for the Preparation of Dihydrocoumarins from Phenols.

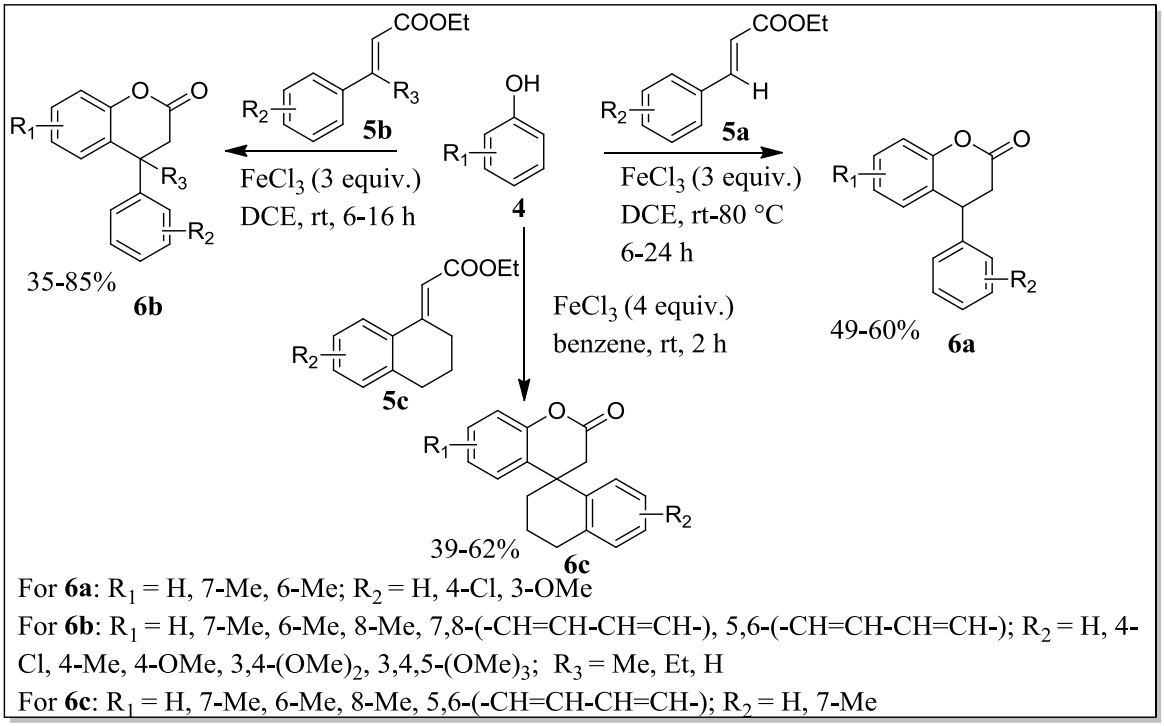
1	**2**					
R_1	**R_2**	**R_3**	**R_4**	**A**	**Yield (%)**	**Ref**
3-OH	COOH	H	Ph	**37% HCl gas**, reflux, 6 h	83	*2a*
2,3-$(OH)_2$, 3-OH, 4-OH	COOH	H	3,4(OH)(MeO)Ph , 3,4,5-$(MeO)_3$Ph, 3,4-$(MeO)_2$ Ph	**$POCl_3$ & $BF_3.OEt_2$** 0 °C-rt, 4-18 h	52-73	*2b*
4-(MeO-CO-O-CH_2-CH_2-)	COOMe	H	4-MeOPh, 3,4-$(MeO)_2$Ph, 3,4,5-$(MeO)_3$Ph, 4-AcOPh, 3,4(MeO)(AcO)Ph,	**TFA**- rt or reflux 5-24 h	42-78	*2c*

			3,4-$(AcO)_2$Ph , 3,5-$(MeO)_2$-4(AcO)Ph,			
3-OMe	COOEt	H	2,4,6-$(MeO)_3$Ph	**$Pd(TFA)_2$** (10 mol%), $Cu(OAc)_2$ (2 equiv.), AcOH, O_2, 100 °C, 12 h	68	*2d*
H, 4-Me, 3-Me, 2-Me	COOH	H	Ph, 4-MePh	**$H_{14}P_5NaW_{30}O_{110}$** (0.5%) 130 °C, solvent free, 2 h	61-77	*2e*
H, 2-Me, 3-Me, 4-Me, 4-Cl, 4-*t*Bu, 5,6-(CH=CH-CH=CH)	COOH	H	Ph, 4-ClPh, 4-OMePh	[H-NMP]HSO_4 120 °C, 2-5 h	82-95	*2f*
H, 4,5-(CH=CH-CH=CH), 5,6-(CH=CH-CH=CH)	COOH	H	-COAr Ar = 	Glacial AcOH, EtOH, reflux, 4h	30-42	*2g*
4-Me	COOH	H	3-CF_3Ph	*Cat.* Conc. H_2SO_4, 110 °C, 12 h	85	*2h*

arylpiperazine to give 7-(4-(4-(6-fluorobenzo[d]isooxazol-3-yl)piperidin-1-yl)butoxy)-4-phenylchroman-2-one and its affinity for dopamine and serotonin receptors was investigated *(Scheme 1, Table 1)*. Sun *et al.* synthesized several 4-aryl-3,4-dihydrocoumarins using $POCl_3/BF_3.OEt_2$ and their ^1H and ^{13}C NMR spectral data were fully assigned based on a combination of 1D and 2D NMR experiments including HSQC and HMBC.[2b] TFA-mediated condensation of tyrosol methyl carbonate with cinnamate derivatives to give 4-aryl-3,4-dihydrocoumarins was reported by Barontini *et al.* [2c] These dihydrocoumarins were subjected to basic hydrolysis to give the corresponding ring opening products which were evaluated for the DPPH radical scavenging activity. Pawar *et al.* synthesized 7-methoxy-4-(2,4,6-trimethoxyphenyl)chroman-2-one as an intermediate for the synthesis of the racemic form of core structure of Myristinin B, *via* annulation reaction and an oxidative-Heck using 3-methoxy phenol and (*E*)-ethyl-3-(2,4,6-trimethoxyphenyl)acrylate as starting materials.[2d] Escobar *et al.* synthesized several dihydrocoumarins under solvent free conditions starting from phenols and cinnamic acids using a compound with Preyssler structure ($H_{14}P_5NaW_{30}O_{110}$) as heterogeneous catalyst.[2e]

Zadsirjan *et al.* used *N*-methyl-2-pyrrolidonum hydrosulfate, an acidic ionic liquid for the synthesis of dihydrocoumarins.[2f] Salem *et al.* synthesized three 4-phenyl chroman-2-one derivatives in presence of catalytic amount of glacial acetic acid.[2g] Yatcherla *et al.* synthesized 4-(3-(trifluoromethyl)phenyl)-3,4-dihydro-6-methyl-chromen-2-one using catalytic amount of conc. sulfuric acid.[2h] Similarly Siva Prasad *et al.* used conc. sulfuric acid for the synthesis of 3,4-dihydro-6-methyl-4-phenyl-2*H*-benzopyran-2-one.[2i]

Niharika *et al.* have reported Lewis acid promoted synthesis of dihydrocoumarins **6a**, **6b** and spiro-tetracyclic dihydrocoumarins **6c**.[3] The reaction condition standardized for the synthesis was, heating the required cinnamates **5** and phenol **4** (1.5 equiv.) in dichloroethane at 80 °C in presence of $FeCl_3$ (3 equiv.). The standard conditions however failed in case of electron-rich cinnamate esters. Good yields of the desired products in these cases were obtained at room temperature. Also, in the case of *β*-alkyl ethyl cinnamates reaction was found to be temperature and system dependent. Again these reactions were successful only at room temperature. Spiro-tetracyclic dihydrocoumarins **6c** were synthesized with either 5 or 10 equivalents of phenol **4** in benzene *(Scheme 2)*.



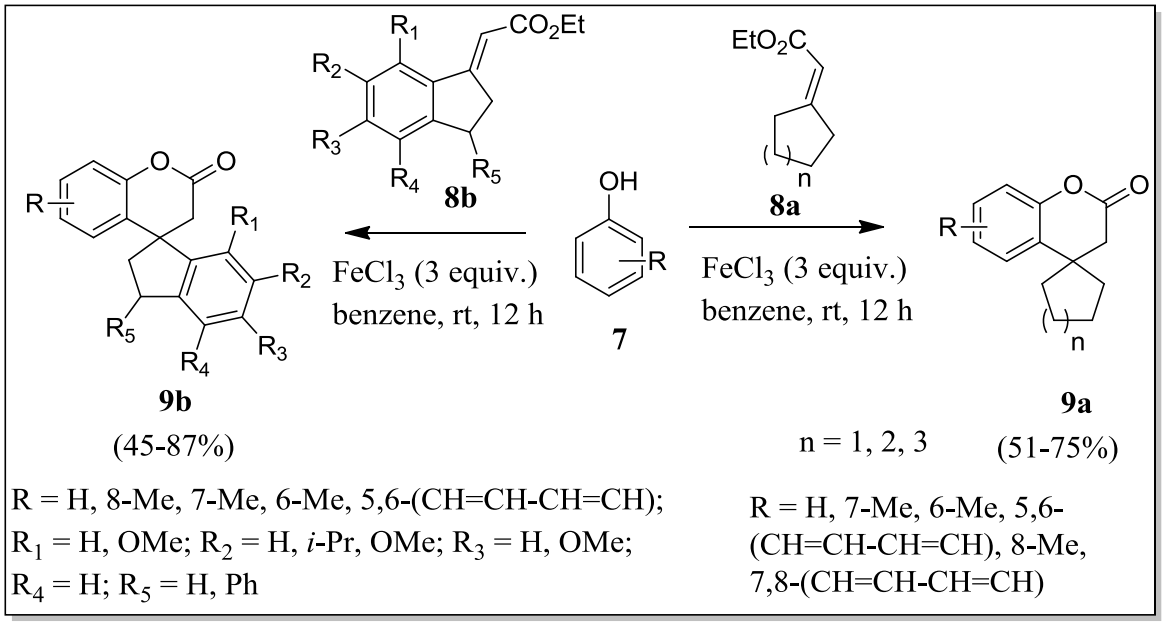
For **6a**: R_1 = H, 7-Me, 6-Me; R_2 = H, 4-Cl, 3-OMe

For **6b**: R_1 = H, 7-Me, 6-Me, 8-Me, 7,8-(-CH=CH-CH=CH-), 5,6-(-CH=CH-CH=CH-); R_2 = H, 4-Cl, 4-Me, 4-OMe, 3,4-$(OMe)_2$, 3,4,5-$(OMe)_3$; R_3 = Me, Et, H

For **6c**: R_1 = H, 7-Me, 6-Me, 8-Me, 5,6-(-CH=CH-CH=CH-); R_2 = H, 7-Me

Scheme 2

Furthermore Niharika and Satyanarayana reported $FeCl_3$ mediated synthesis of several spirocyclic chromanones **9a** & **9b** starting from phenols **7** and the exocyclic α, β-unsaturated esters **8a** or exocyclic indanone based esters **8b** *(Scheme 3)*.[4]

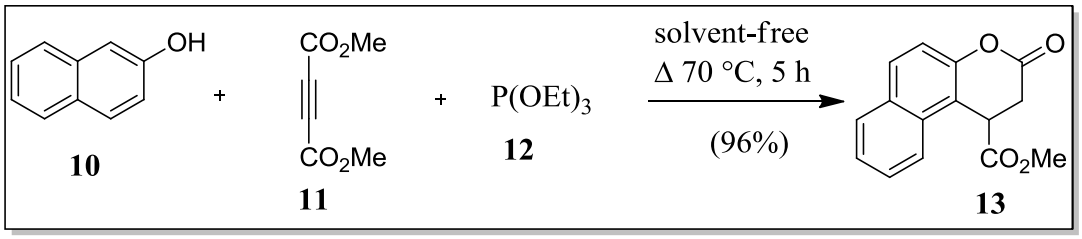


R = H, 8-Me, 7-Me, 6-Me, 5,6-(CH=CH-CH=CH);
R_1 = H, OMe; R_2 = H, *i*-Pr, OMe; R_3 = H, OMe;
R_4 = H; R_5 = H, Ph

R = H, 7-Me, 6-Me, 5,6-(CH=CH-CH=CH), 8-Me, 7,8-(CH=CH-CH=CH)

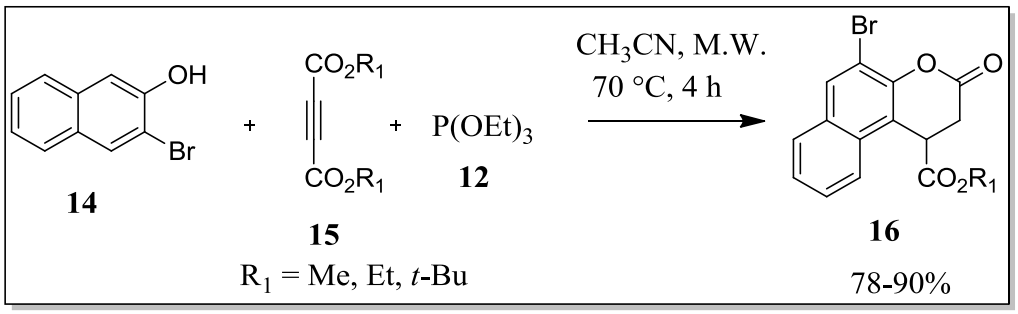
Scheme 3

The reaction of *β*-naphthol (**10**) with dimethylacetylenedicarboxylate (**11**) in presence of triethyl phosphite (**12)** under neat heating at 70 °C produced the 4-substituted dihydrocoumarins **13** in excellent yield *(Scheme 4)*.[5]



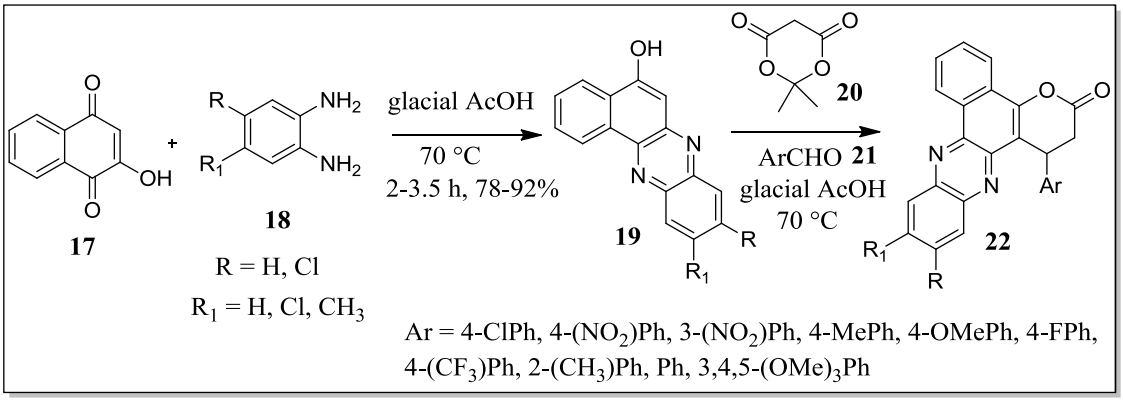
Scheme 4

Hossaini *et al.* reported the microwave-assisted synthesis of chroman-2-ones **16** by the reaction of 3-bromo-2-naphthol **14** with dialkyl acetylenedicarboxylate **15** in presence of triethyl phosphite (**12**) *(Scheme 5)*.[6]



Scheme 5

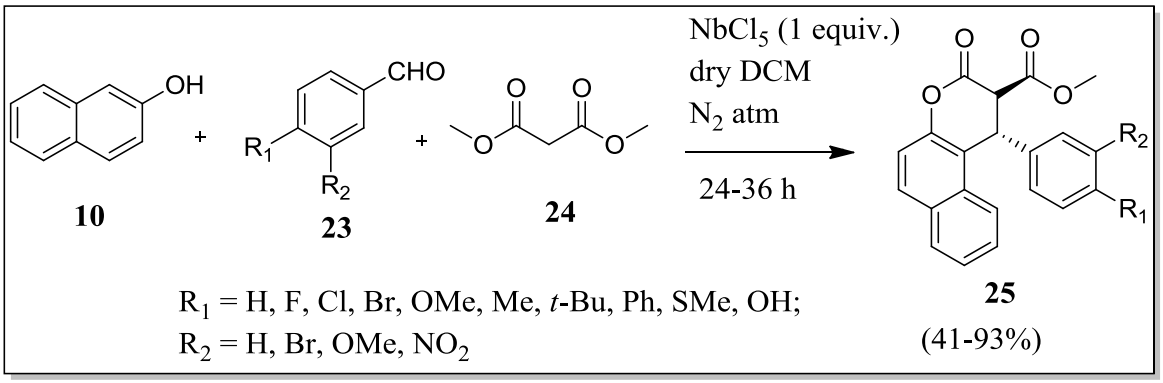
Khurana and co-workers have developed an efficient one-pot route to novel fluorescent benzo[*a*]pyrano[2,3-*c*]phenazines **22** *via* four component reaction between 2-hydroxynaphthalene-1,4-dione (**17**), 1,2-phenylenediamines **18**, Meldrum's acid (**20**) and aromatic aldehydes **21** in presence of catalytic amount of glacial acetic acid at 70 °C *(Scheme 6)*.[7]



Scheme 6

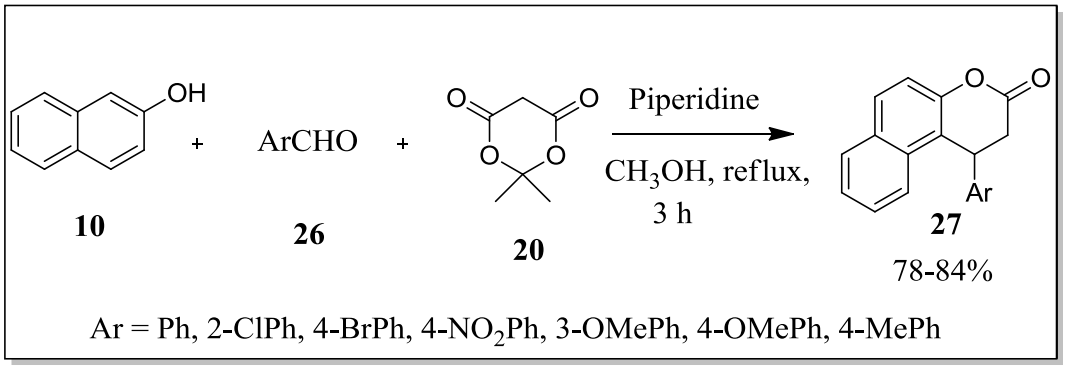
Silva-Filho and co-workers extended the $NbCl_5$ promoted multicomponent reaction protocol towards the synthesis of several 4-aryl-3,4-dihydrobenzo[*f*]coumarins **25** using

β-naphthol (**10**), substituted aromatic aldehydes **23** and dimethyl malonate (**24**) *(Scheme 7)*.[8]



Scheme 7

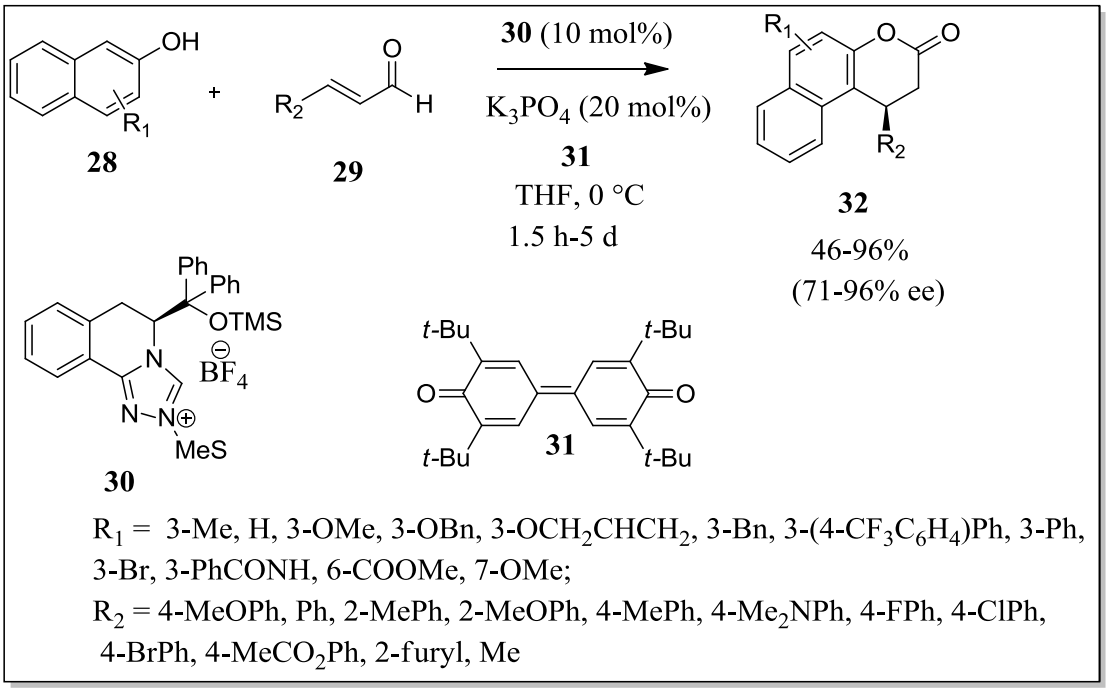
A multicomponent reaction between *β*-naphthol (**10**), substituted aryl aldehydes **26** and Meldrum's acid (**20**) in presence of catalytic amount of piperidine for the synthesis of 4-aryl-chroman-2-ones (**27**) has also been reported *(Scheme 8)*.[9]



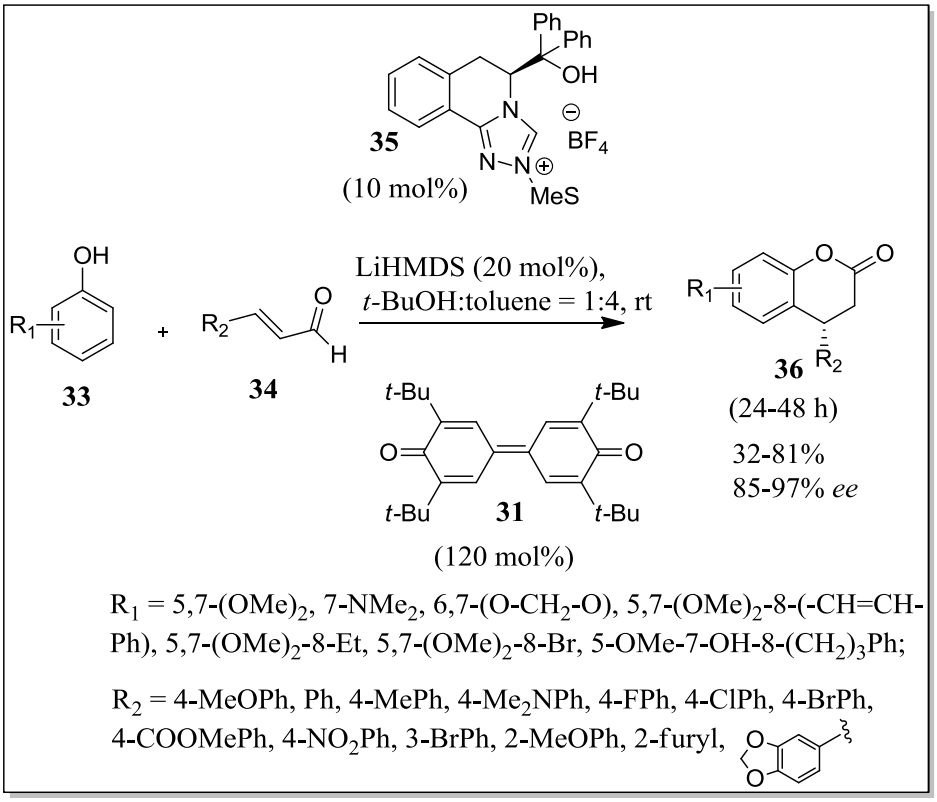
Scheme 8

Li *et al.* synthesized several 4-arylchroman-2-ones **32** in good yields and upto 96% *ee* starting from *α*, *β*-unsaturated aldehydes **29** and 2-naphthols **28** catalyzed by *N*-heterocyclic carbene **30**.[10] The reaction was also successful when enals **29** were replaced either by 2-bromo-3-phenyl enal or 3-phenyl ynal *(Scheme 9)*.

Recently these authors have reported enantioselective synthesis of 4-aryl-3,4-dihydrocoumarins **36** using phenols **33** and *α*,*β*-unsaturated aldehydes **34** in presence of catalytic amount of dihydroisoquinoline-type *N*-heterocyclic carbene **35** *(Scheme 10)*.[11]



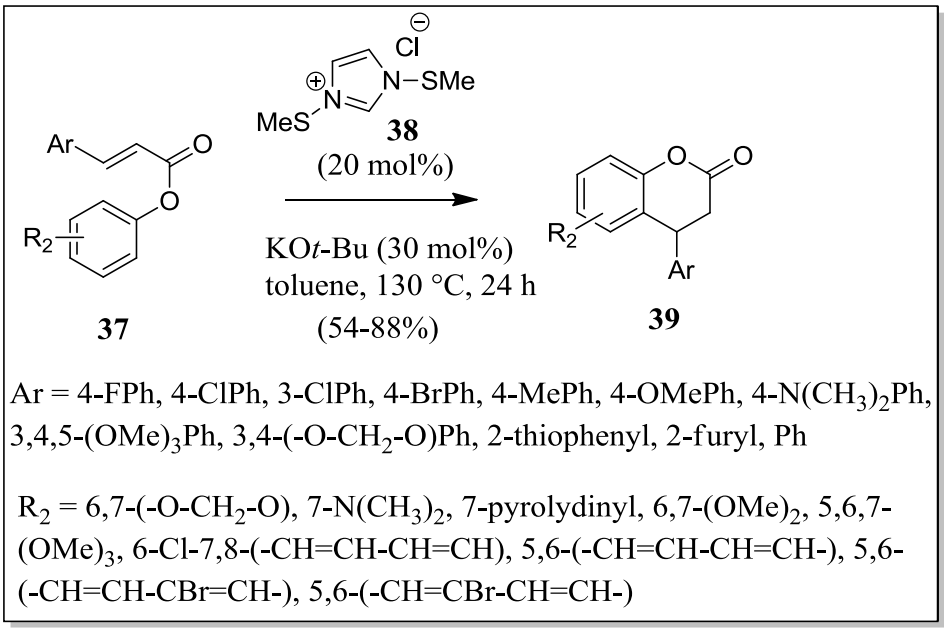
Scheme 9



Scheme 10

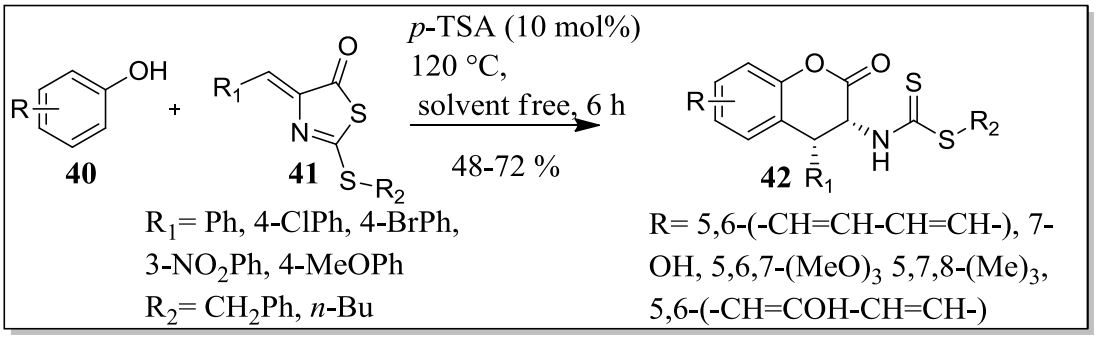
Cheng and coworkers have reported the synthesis of 4-phenyl chroman-2-ones **39** *via* an *insitu* generation of *α, β*- unsaturated acylazoliums and phenolates from *α, β*- unsaturated phenolic esters **37**, co-operatively catalyzed by *N*-heterocyclic carbene **38** and potassium

ion. The [3+3] annulation involved a dearomatization-rearomatization process *(Scheme 11)*.[12]



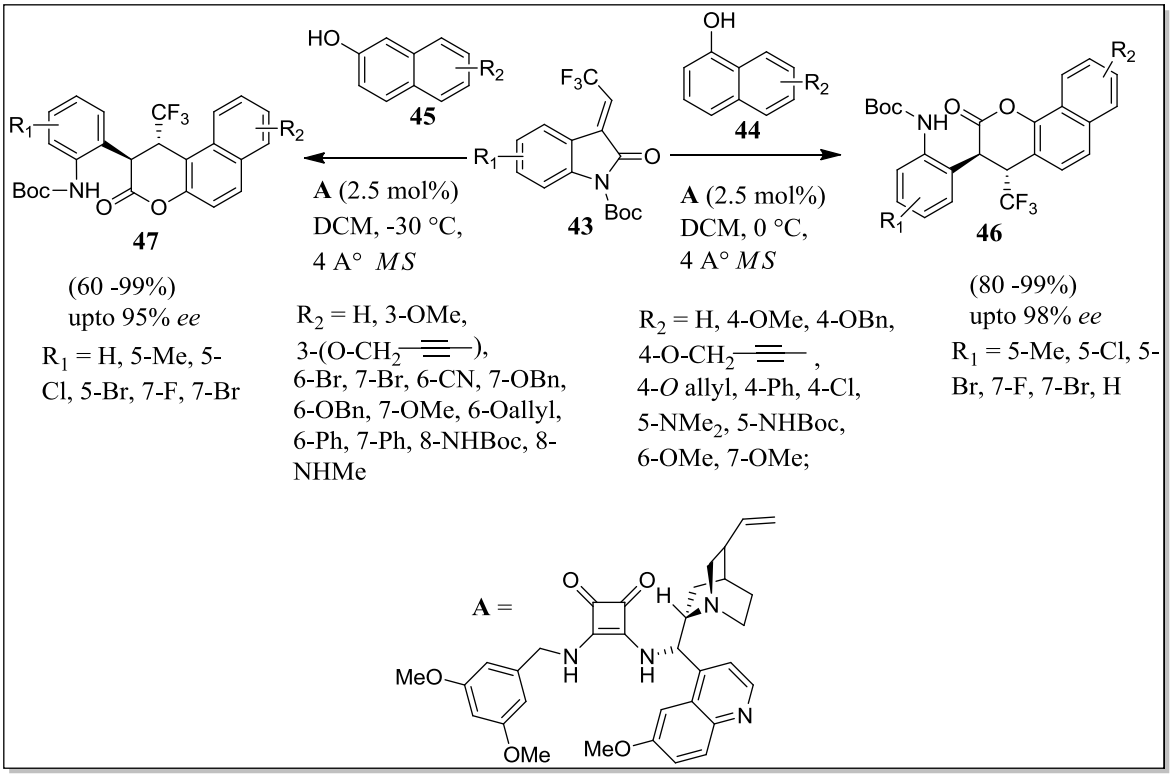
Scheme 11

Halimehjani and Khoshdoun have developed *p*-TSA catalyzed access to a variety of functionalized dihydrocoumarins **42** by reacting phenols **40** with olefinic thioazalactones **41** in good diastereoselectivity and yield. The reaction proceeded through a domino esterification/intramolecular 1,4-addition type Friedel-Crafts alkylation *(Scheme 12)*.[13]



Scheme 12

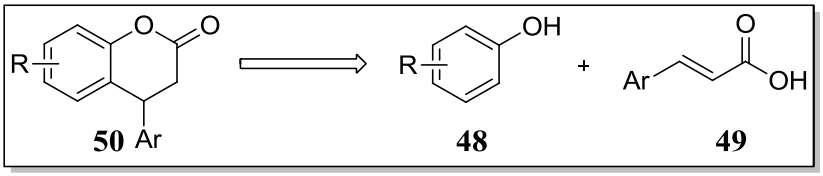
Zhao and co-workers have reported the synthesis of several *α*-aryl-*β*-trifluoromethyl dihydrocoumarins **46** and **47** starting from 3-trifluoroethylidene oxindoles **43** and naphthols **44** or **45** using catalytic amount of a quinine-derived squaramide catalyst A *(Scheme 13)*.[14] The reaction proceeded *via* an asymmetric Friedel-Crafts alkylation/lactonization sequence. The products were obtained in high yields and excellent enantio- and diastereoselectivities (upto 98% *ee*, > 20:1 *dr*)



Scheme 13

2.3: Results and Discussion

As evident from the literature review, 4-phenyl dihydrocoumarins have been synthesized using various catalysts. However use of iodine for the preparation of this important scaffold has not been reported till date. Earlier in our group, iodine was found to be an effective catalyst for the synthesis of important heterocycles.[15] As a continuation of our interest in exploring the use of this mild Lewis acid for synthesis of myriad heterocycles, we aimed at building the dihydrocoumarin skeleton **50** *via* a [3+3] cyclocoupling of phenol **48** with cinnamic acid **49** using molecular iodine as catalyst *(Scheme 14).*



Scheme 14

The initial studies were carried out using *β*-naphthol and cinnamic acid as substrates. These substrates were taken in stoichiometric amount (1:1) and mixed in different solvents such as ethyl alcohol, methyl alcohol, chloroform, dichloromethane, acetonitrile,

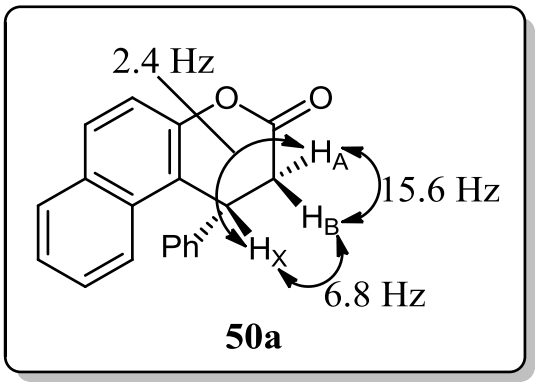
dioxane and water at room temperature using 10-20 mol% of iodine. However, no product formation was observed upto 48 hours (monitored by TLC). So, these reaction masses were subjected to reflux conditions.

Table 2. Screening of solvents under refluxing conditions using *β*-naphthol and cinnamic acid.

Entry	Solvent	Time (h)	Yield (%)
1	Methanol	24	30
2	Chloroform	24	0
3	Acetonitrile	24	25
4	1,2-Dichloroethane	24	30
5	Ethanol	24	10
6	1,4-Dioxane	24	10
7	Water	24	10
8	Toluene	24	20
9	Acetic acid	24	30
10	Xylene	5	70
11	1,2-Dichlorobenzene	5	30

On monitoring progress of the reaction using TLC it was found that, in case of refluxing xylene *(entry 10, Table 2)* the spot corresponding to starting phenol disappeared completely and a new spot was clearly visible after a couple of hours. This spot was also observed in case of other solvents along with starting phenol. The product corresponding to this new spot was isolated by column chromatography. In its IR spectrum, a strong band at 1762 cm^{-1} was seen which could be attributed to the C=O group of dihydrocoumarins.[16]

In its ^{1}HNMR spectrum two sharp doublet of doublets were observed at δ 3.18 (J = 15.6, 2.4 Hz, 1H) and δ 3.25 (J = 15.6, 6.8 Hz, 1H) which could be assigned to methylene protons of the C-3 carbon atom. A broad doublet of doublet was observed at δ 4.98 (J = 6.8, 2.0 Hz, 1H) which could be attributed to the proton attached to the C-4 position. The remaining peaks between δ 7.15-7.90 could be attributed to the aromatic protons.

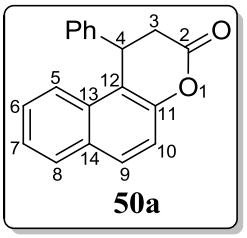


50a

The product formation was further confirmed from ^{13}C NMR experiment. In ^{13}C NMR spectrum, the peak at δ 37.5 was assigned to the C-3 carbon while peak at δ 37.7 was assigned to the C-4 carbon. The peaks between δ 117.6-149.8 were attributed to the aromatic carbons. The peak at δ 167.2 was assigned to the carbonyl carbon. The multiplicities of these signals were assigned on basis of the DEPT experiment. The complete spectroscopic data is provided below.

Spectroscopic data

5,6-Benzo-4-phenyl-3,4-dihydrobenzopyran-2-one (50a)



50a

IR (KBr): υ_{max} = 1178, 1377, 1490, 1762, 2910, 3055 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.18 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.25 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.98 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.15 (d, *J* = 6.8 Hz, 2H), 7.23-7.31 (m, 3H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.44-7.54 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.88-7.90 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 37.50 (CH_2), 37.65 (CH), 117.59 (CH), 117.66 (Cq), 123.12 (CH), 125.33 (CH), 126.99 (2 × CH), 127.53 (CH), 127.63 (CH), 128.81 (CH), 129.28 (2×CH), 129.99 (CH), 131.03 (Cq), 131.13 (Cq), 140.60 (Cq), 149.83 (Cq), 167.22 (Cq) ppm.

m.p.: 115-117 ^{O}C; lit.[17] 115-116 ^{O}C.

Hence, based on the above spectral analysis and closeness of melting point with the literature melting point, structure **50a** was assigned to it.

Maximum product formation was observed in case of refluxing xylene. After trying various solvents, we thought of carrying out the reaction under solvent-free conditions.

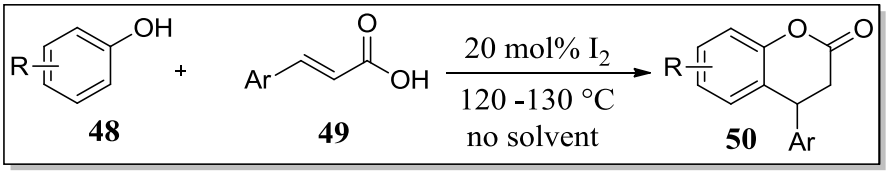
The reaction was studied at varying ranges of temperature. The product formation was observed in the range of 80-130 °C. To our delight, the reaction was complete within one hour without solvent at 120-130 °C. This reaction condition was chosen for further studies. Carrying out the reaction at lower temperatures (80-100 °C) prolonged the reaction time.

Next, for optimizing the catalyst concentration we used different catalyst loadings *(Table 3)*. It was evident that, higher catalyst loading neither enhanced the reaction rate nor increased the yield of the product. When less than 20 mol% of iodine was used, prolonged reaction time was required. No product formation was observed in the absence of iodine.

Table 3. Optimization of iodine concentration

Entry	Iodine (mol%)	Time (h)	Yield (%)
1	0	24	0
2	1	24	0
3	5	8	30
4	10	8	50
5	15	3	70
6	20	1	80
7	25	1	78
8	30	1	70

Considering the various factors explored above, the following reaction condition was optimized *(Scheme 15)*.



Scheme 15

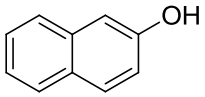
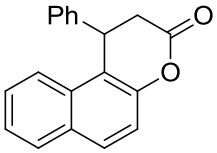
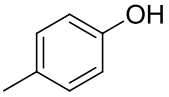
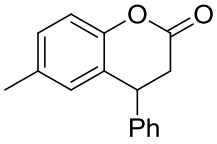
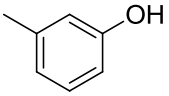
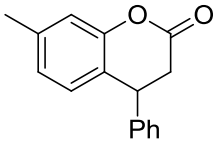
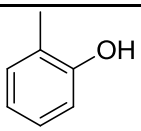
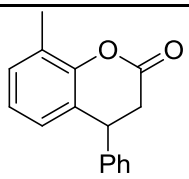
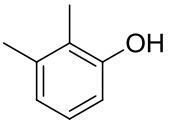
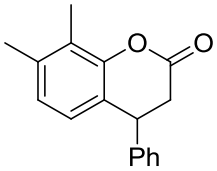
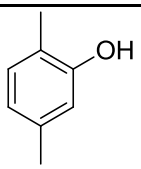
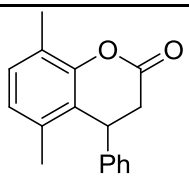
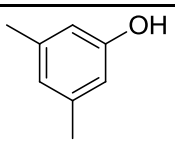
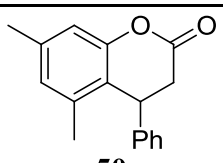
To study the generality of optimized reaction condition, the reaction was explored for substrate scope *(Table 4)*. Phenols with electron donating groups were rapidly converted into dihydrocoumarins in good yields. Several phenols with substituted methyl groups

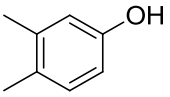
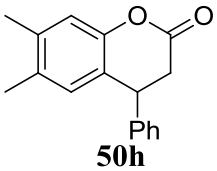
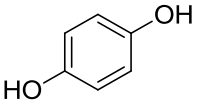
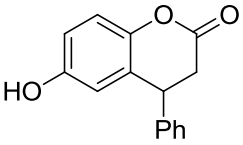
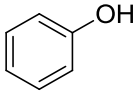
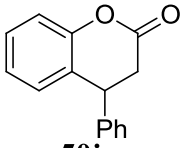
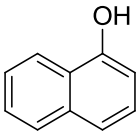
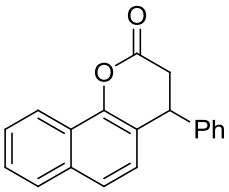
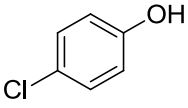
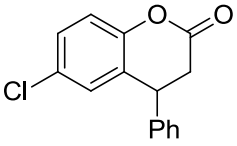
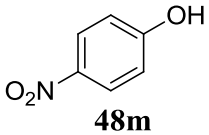
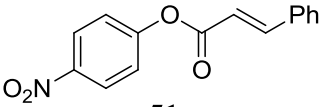
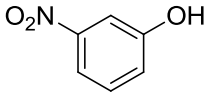
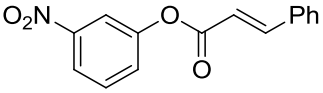
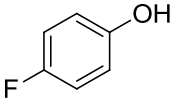
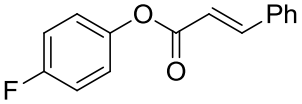
gave desired products **50b-h** in good yields. The ^{1}HNMR spectrum of chroman-2-one **50c** (obtained from *m*-cresol) showed a singlet at δ 2.38 (3H) corresponding to the methyl group attached to the aromatic ring. It also showed two sharp well-resolved doublet of doublets corresponding to the methylene protons of C-3 carbon atom at δ 3.02 (J = 16.0, 7.6 Hz, 1H) and δ 3.09 (J = 15.6, 6.0 Hz, 1H). A triplet at δ 4.33 (J = 7.2 Hz, 1H) was observed (instead of a doublet of doublet as in case of **50a**) for the methine proton at C-4. The remaining peaks between δ 6.86-7.39 could be attributed to the aromatic protons. Parent phenol gave 60% yield of the product **50j** in 4 hours. α-Naphthol was converted into the dihydrocoumarin **50k** in 65% yield. Also, electron deficient *p*-chlorophenol gave the product **50l** in good yield. Phenols with strong electron withdrawing nitro groups at *para* and *meta* positions were not converted into the expected dihydrocoumarins even after continuing the reaction for 24 hours. Instead, formation of the corresponding nitro phenyl cinnamates **51a** and **51b** in low yield was observed. Similarly, reaction with *p*-fluorophenol resulted in the formation of ester **51c** in 50% yield.

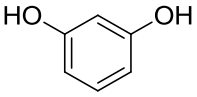
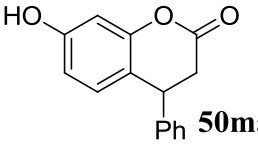
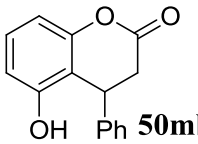
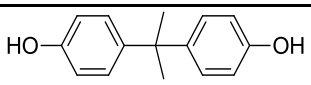
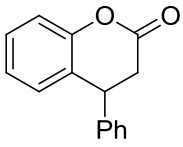
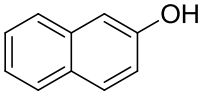
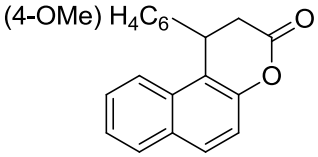
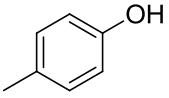
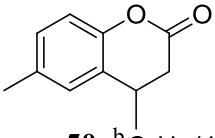
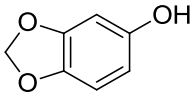
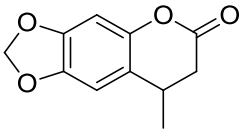
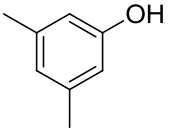
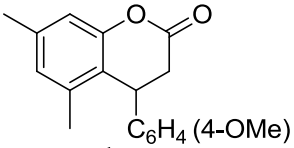
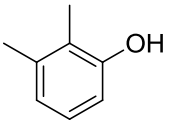
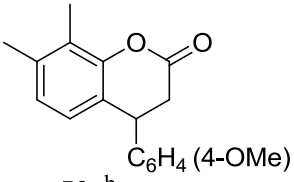
In case of resorcinol a mixture of two regioisomeric dihydrocoumarins **50m** was obtained in 5:1 ratio. When bisphenol A was reacted with cinnamic acid, a complex mixture was obtained, from which only 5% of the product dihydrocoumarin **50j** was isolated. This product formation could be explained by concomitant dearylation.

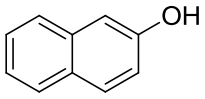
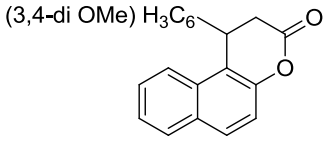
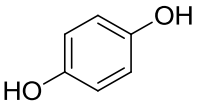
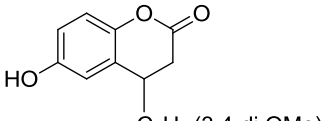
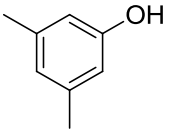
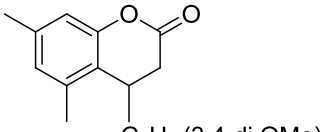
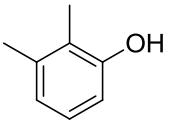
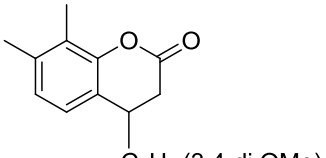
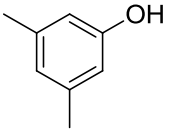
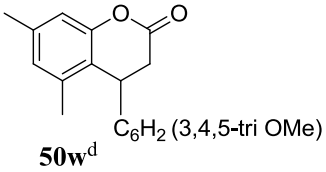
We then planned of synthesizing more derivatives of these dihydrocoumarins by using substituted cinnamic acids. 4-Methoxy cinnamic acid reacted smoothly with various phenols to give the expected products **50n-50r** in good yields. Also, 3,4-dimethoxy cinnamic acid underwent cyclization to form dihydrocoumarins **50s-50v** in good yields. 3,4,5-Trimethoxy cinnamic acid on reaction with 3,5-dimethyl phenol delivered the desired product **50w** in 63% yield. We also attempted the reaction of acrylic acid with *m*-cresol. However the reaction failed to deliver the corresponding dihydrocoumarin product.

Table 4: Various 4-aryl-3,4-dihydrobenzopyran-2-one derivatives **50a-w** and substituted phenyl cinnamates **51a-c** produced under optimized reaction conditions.

Entry	Substituted phenol	Product	Time (h)	Yield (%)
1	 **48a**	 **50a**	1	80
2	 **48b**	 **50b**	1	83
3	 **48c**	 **50c**	1.5	78
4	 **48d**	 **50d**	3	60
5	 **48e**	 **50e**	4	83
6	 **48f**	 **50f**	5	65
7	 **48g**	 **50g**	2	85

8	 **48h**	 **50h**	2	85
9	 **48i**	 **50i**	2	77
10	 **48j**	 **50j**	4	60
11	 **48k**	 **50k**	4	65
12	 **48l**	 **50l**	3	70
13	 **48m**	 **51a**	24	20
14	 **48n**	 **51b**	24	30
15	 **48o**	 **51c**	24	50

16	 **48p**	 **50ma**  **50mb** **50ma:50mb (**5:1)	5	70
17	 **48q**	 **50j*** *obtained from bisphenol A	10	5
18	 **48a**	 **50n**[b]	4	85
19	 **48b**	 **50o**[b] C_6H_4 (4-OMe)	1.5	78
20	 **48r**	 **50p**[b] C_6H_4 (4-OMe)	4	68
21	 **48g**	 **50q**[b]	3	82
22	 **48e**	 **50r**[b]	1	83

23	 **48a**	 **50s**[c]	1.45	80
24	 **48i**	 **50t**[c]	4	72
25	 **48g**	 **50u**[c]	2	77
26	 **48e**	 **50v**[c]	2	60
27	 **48g**	 **50w**[d]	2.3	63

[a] Isolated % yield after column chromatography.

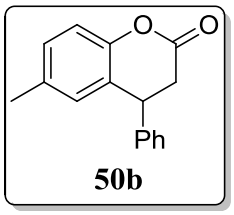
[b] In this case 4-methoxy cinnamic acid was used.

[c] In this case 3,4-dimethoxy cinnamic acid was used.

[d] In this case 3,4,5-trimethoxy cinnamic acid was used.

Spectroscopic data of all compounds

6-Methyl-4-phenyl-3,4-dihydrobenzopyran-2-one (50b)



50b

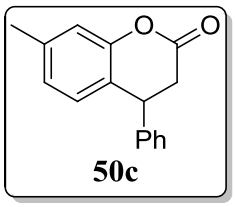
IR (KBr): υ_{max} = 1126, 1201, 1494, 1764, 1890, 2900, 3028 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3 H), 3.02 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.25 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.32 (t, *J* = 6.4 Hz, 1H), 6.81 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.29-7.40 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.80 (CH_3), 37.16 (CH_2), 40.74 (CH), 116.87 (CH), 125.34 (Cq), 127.56 (2× CH), 127.63 (CH), 128.70 (CH), 129.15 (2× CH), 129.33 (CH), 134.36 (Cq), 140.54 (Cq), 149.67 (Cq), 167.90 (Cq) ppm.

m.p.: 80-83 ^{O}C; lit.[18] 83 ^{O}C.

7-Methyl-4-phenyl-3,4-dihydrobenzopyran-2-one (50c)



50c

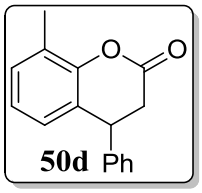
IR (KBr): υ_{max} = 1211, 1512, 1764, 2850, 3066 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3 H), 3.02 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.09 (dd, *J* = 15.6, 6.0 Hz, 1H),4.33 (t, *J* = 7.2 Hz, 1H), 6.86-6.93 (m, 2H), 6.97 (s, 1H), 7.17-7.19 (m, 2H), 7.30-7.32 (m, 1H), 7.35-7.39 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.13 (CH_3), 37.23 (CH_2), 40.39 (CH), 117.52 (CH), 122.65 (Cq), 125.45 (CH), 127.57 (2× CH), 127.61 (CH), 128.08 (CH), 129.12 (2× CH), 139.15 (Cq), 140.60 (Cq), 151.59 (Cq), 167.94 (Cq) ppm.

m.p.: 123-124 ^{O}C; lit.[19] 124 ^{O}C.

8-Methyl-4-phenyl-3,4-dihydrobenzopyran-2-one (50d)



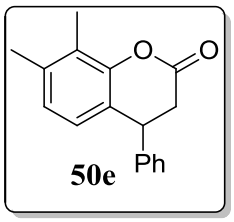
IR (KBr): υ_{max} = 1190, 1263, 1452, 1589, 1764, 2922, 3005 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3 H), 3.02 (dd, *J* = 15.6, 7.2 Hz, 1H), 3.08 (dd, *J* = 15.6, 6.0 Hz, 1H), 4.33 (t, *J* = 6.8 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 3H), 7.28-7.37 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.90 (CH_3), 36.99 (CH_2), 40.80 (CH), 124.17 (CH), 125.59 (Cq), 125.89 (CH), 126.48 (Cq), 127.58 (2× CH), 127.61 (CH), 129.11 (2× CH), 130.33 (CH), 140.45 (Cq), 150.00 (Cq), 167.91 (Cq) ppm.

m.p.: 106-108 ^{O}C; lit.[20] 108 ^{O}C.

7,8-Dimethyl-4-phenyl-3,4-dihydrobenzopyran-2-one (50e)



50e

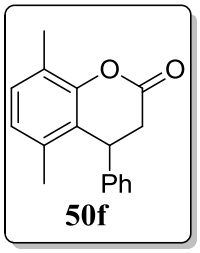
IR (KBr): υ_{max} = 1197, 1454, 1768, 2877, 3034 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3 H), 2.29 (s, 3H), 2.99 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.04 (dd, *J* = 15.6, 6.0 Hz, 1H), 4.30 (t, *J* = 6.8 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.25-7.36 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.89 (CH_3), 19.95 (CH_3), 37.02 (CH_2), 40.74 (CH), 123.09 (Cq), 124.96 (CH), 125.58 (CH), 127.52 (2× CH), 127.57 (CH), 129.06 (2× CH), 137.79 (Cq), 140.68 (Cq), 149.80 (Cq), 168.17 (Cq), 168.19 (Cq) ppm.

Melting Point: 119-120 ^{O}C.

5,8-Dimethyl-4-phenyl-3,4-dihydrobenzopyran-2-one (50f)



50f

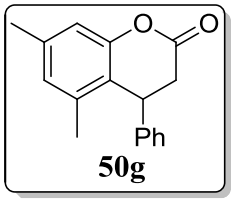
IR (KBr): υ_{max} = 1138, 1178, 1492, 1764, 2922, 3026 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3 H), 2.37 (s, 3H), 3.07 (t, *J* = 3.6 Hz, 2H), 4.42 (dd, *J* = 5.2, 3.2 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.24-7.31 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.80 (CH_3), 18.56 (CH_3), 37.56 (CH_2), 38.34 (CH), 123.01 (Cq), 124.10 (Cq), 125.91 (CH), 127.03 (2× CH), 127.44 (CH), 129.11 (2× CH), 130.06 (CH), 134.14 (Cq), 140.08 (Cq), 150.42 (Cq), 167.52 (Cq) ppm.

m.p.: 78-80 ^{O}C; lit.[20] 78 ^{O}C.

5,7-Dimethyl-4-phenyl-3,4-dihydrobenzopyran-2-one (50g)



50g

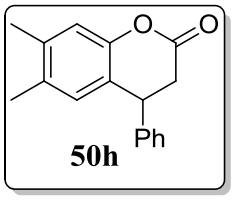
IR (KBr): υ_{max} = 1134, 1452, 1753, 2916 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3 H), 2.37 (s, 3H), 3.01-3.11 (m, 2H), 4.40 (d, *J* = 6.0 Hz, 1H), 6.86 (d, *J* = 5.6 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 7.22-7.31 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.71 (CH_3), 21.12 (CH_3), 37.79 (CH_2), 38.00 (CH), 115.45 (CH), 120.11 (Cq), 126.98 (2× CH), 127.35 (CH), 127.42 (CH), 129.11 (2× CH), 136.64 (Cq), 138.83 (Cq), 140.36 (Cq), 152.11 (Cq), 167.58 (Cq) ppm.

m.p.: 130-132 ^{O}C; lit.[18] 134 ^{O}C.

6,7-Dimethyl-4-phenyl-3,4-dihydrobenzopyran-2-one (50h)



50h

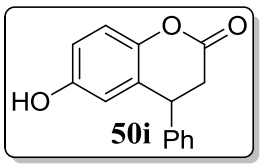
IR (KBr): υ_{max} = 1130, 1178, 1454, 1492, 1759, 2950, 3000, 3050 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3 H), 2.28 (s, 3H), 2.99 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.07 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.30 (t, *J* = 6.4 Hz, 1H), 6.76 (s, 1H), 6.94 (s, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 6.8 Hz, 1H), 7.35 (d, *J* = 6.8 Hz, 1H), 7.38 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.12 (CH_3), 19.63 (CH_3), 37.40 (CH_2), 40.45 (CH), 117.90 (CH), 122.53 (Cq), 127.51 (2× CH), 127.54 (CH), 129.03 (CH), 129.10 (2× CH), 133.00 (Cq), 137.49 (Cq), 140.85 (Cq), 149.69 (Cq), 168.11 (Cq) ppm.

m.p.: 110-113 ^{O}C; lit.[20] 111 ^{O}C.

6-Hydroxy-4-phenyl-3,4-dihydrobenzopyran-2-one (50i)



50i

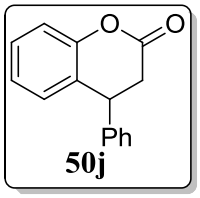
IR (KBr): υ_{max} = 1141, 1195, 1492, 1741, 2950, 3331 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.06 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.28 (t, *J* = 7.2 Hz, 1H), 5.55 (br s, 1H), 6.44 (s, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.29-7.38 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 36.87 (CH_2), 40.69 (CH), 114.70 (CH), 115.47 (CH), 118.03 (CH), 126.96 (Cq), 127.47 (2× CH), 127.76 (CH), 129.17 (2× CH), 139.95 (Cq), 145.41 (Cq), 152.62 (Cq), 168.48 (Cq) ppm.

m.p.: 125-130 ^{O}C; lit.[21] 133 ^{O}C.

4-Phenyl-3,4-dihydrobenzopyran-2-one (50j)



50j

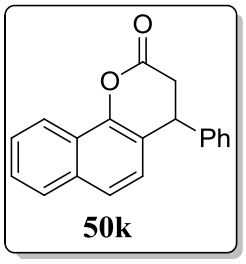
IR (KBr): υ_{max} = 1125, 1200, 1350, 1500, 1759, 2900, 3030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.12 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.38 (t, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.15 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.31-7.40 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 37.03 (CH_2), 40.68 (CH), 117.15 (CH), 124.70 (CH), 125.79 (Cq), 127.60 (2× CH), 127.70 (CH), 128.36 (CH), 128.84 (CH), 129.17 (2× CH), 140.27 (Cq), 151.71 (Cq), 167.73 (Cq) ppm.

m.p.: 78-80 ^{O}C; lit.[19] 78 ^{O}C.

7,8-Benzo-4-phenyl-3,4-dihydrobenzopyran-2-one (50k)



50k

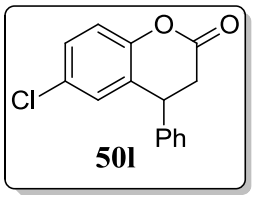
IR (KBr): υ_{max} = 1126, 1215, 1377, 1762, 2910, 3055 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (d, *J* = 13.2 Hz, 1H), 3.24 (d, *J* = 14.8 Hz, 1H), 4.52 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 6.4 Hz, 2H), 7.32-7.36 (m, 3H), 7.57 (s, 1H), 7.60 (d, *J* = 9.2 Hz, 2H), 7.85 (d, *J* = 7.2 Hz, 1H), 8.34 (d, *J* = 7.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 37.33 (CH_2), 41.10 (CH), 119.89 (Cq), 121.36 (CH), 123.73 (Cq), 124.31 (CH), 125.34 (CH), 126.78 (CH), 126.88 (CH), 127.54 (2× CH), 127.61 (CH), 127.69 (CH), 129.20 (2× CH), 133.72 (Cq), 140.65 (Cq), 146.76 (Cq), 167.46 (Cq) ppm.

m.p.: 111-112 ^{O}C; lit.[20] 112 ^{O}C.

6-Chloro-4-phenyl-3,4-dihydrobenzopyran-2-one (50l)



50l

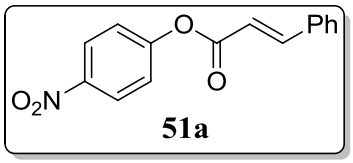
IR (KBr): υ_{max} = 879, 1122, 1213, 1483, 1770, 3032 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (dd, *J* = 16, 8.4 Hz, 1H), 3.10 (dd, *J* = 16, 6.0 Hz, 1H), 4.34 (t, *J* = 6.8 Hz, 1H), 6.97 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.30 (s, 1H), 7.35-7.42 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 36.61 (CH_2), 40.64 (CH), 118.52 (CH), 127.53 (2× CH), 127.56 (Cq), 128.03 (CH), 128.18 (CH), 128.88 (CH), 129.36 (2× CH), 129.83 (Cq), 139.39 (Cq), 150.24 (Cq), 166.95 (Cq) ppm.

m.p.: 108-110 ^{O}C; lit.[22] 103-104 ^{O}C.

4-Nitro-phenyl cinnamate (51a)



51a

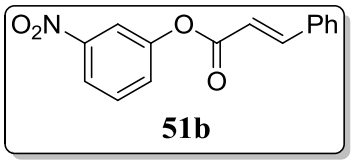
IR (KBr): υ_{max} = 761, 977, 1147, 1219, 1348, 1519, 1631, 1735, 3030, 3115 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (d, *J* = 16.0 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.38-7.39 (m, 3H), 7.53-7.55 (m, 2H) 7.85 (d, *J* = 16.0 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 115.11 (CH), 121.46 (2× CH), 124.21 (2× CH), 127.45 (2× CH), 128.08 (2× CH), 130.17 (CH), 132.73 (Cq), 144.22 (Cq), 147.03 (CH), 154.58 (Cq), 163.34 (Cq) ppm.

m.p.: 142-144 ^{O}C; lit.[23] 142-46 ^{O}C.

3-Nitro-phenyl cinnamate (51b)



51b

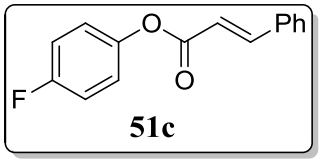
IR (KBr): υ_{max} = 761, 975, 1147, 1211, 1352, 1531, 1633, 1732, 3115 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (d, *J* = 16.0 Hz, 1H), 7.45-7.47 (m, 3H), 7.56-7.63 (m, 4H) 7.93 (d, *J* = 16.0 Hz, 1H), 8.09 (t, *J* = 2.2 Hz, 1H), 8.13-8.16 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 115.11 (CH), 116.44 (CH), 119.70 (CH), 126.71 (CH), 127.44 (2× CH), 128.07 (2× CH), 129.00 (CH), 130.12 (CH), 132.77 (Cq), 146.91 (CH), 147.76 (Cq), 150.06 (Cq), 163.68 (Cq) ppm.

m.p.: 106-108 ^{O}C; lit.[23] 108-110 ^{O}C.

4-Fluoro-phenyl cinnamate (51c)



51c

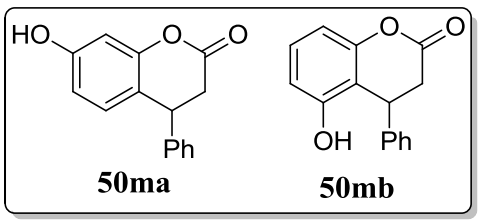
IR (KBr): υ_{max} = 972, 1139, 1307, 1502, 1735, 2927, 3064 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64 (d, *J* = 15.6 Hz, 1H), 7.12-7.15 (m, 4H), 7.46 (s, 3H) 7.61 (s, 2H), 7.90 (d, *J* = 16.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 115.99 (CH), 116.22 (CH), 116.98 (CH), 123.01 (CH), 123.09 (CH), 128.35 (2× CH), 129.04 (2× CH), 130.84 (CH), 134.09 (Cq), 146.89 (CH), 159.02 (Cq), 161.45 (Cq), 165.44 (Cq).

m.p.: 70-75 ^{O}C; lit.[24] 73-74.5 ^{O}C.

7-Hydroxy-4-phenyl-3,4-dihydro-2*H*-chromen-2-one and 5-hydroxy-4-phenyl-3,4-dihydro-2*H*-chromen-2-one (50ma+50mb)[25]



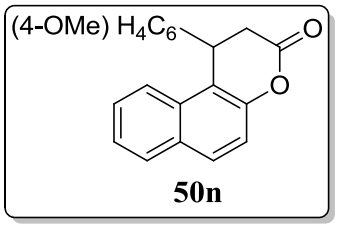
50ma **50mb**

IR (KBr): υ_{max} = 1109, 1149, 1230, 1279, 1454, 1600, 1622, 1766, 1778, 3028, 3381 cm^{-1}.

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

Chemical Shift (δ ppm)	Multiplicity	Position
2.99-3.12	m	-C**H**$_2$- (H-3)
4.30 (4.65)	t	-C**H**Ph- (H-4)
6.60	d	Ar-**H**
6.71	s	Ar-**H**
6.84	d	Ar-**H**
7.17	d	Ar-**H**
7.29-7.38	m	Ar-**H**

5,6-Benzo-4-(4-methoxyphenyl)-3,4-dihydrobenzopyran-2-one (50n)



50n

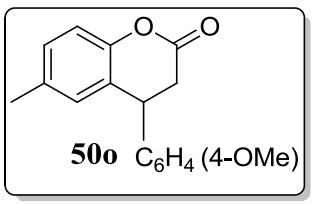
IR (KBr): υ_{max} = 1176, 1247, 1508, 1762, 2835, 2954 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (dd, J = 15.6, 2.4 Hz, 1H), 3.13 (dd, J = 15.6, 6.8 Hz, 1H), 3.66 (s, 3H), 4.85 (dd, J = 6.4, 2.0 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 9.2 Hz, 1H), 7.37-7.43 (m, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 9.2 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 36.81 (CH), 37.67 (CH_2), 55.24 (OCH_3), 114.59 (2× CH), 117.57 (CH), 118.06 (Cq), 123.14 (CH), 125.31 (CH), 127.50 (CH), 128.06 (2× CH), 128.79 (CH), 129.86 (CH), 131.00 (Cq), 131.11 (Cq), 132.57 (Cq), 149.68 (Cq), 158.90 (Cq), 167.43 (Cq) ppm.

m.p.: 128-130 ^{O}C; lit.[26] 130-131 ^{O}C.

6-Methyl-4-(4-methoxyphenyl)-3,4-dihydrobenzopyran-2-one (50o)



50o

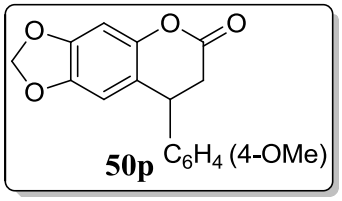
IR (KBr): υ_{max} = 1180, 1247, 1492, 1757, 2837, 2962, 3012 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.98 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.05 (dd, *J* = 15.6, 5.6 Hz, 1H), 3.82 (s, 3H), 4.27 (t, *J* = 6.4 Hz, 1H), 6.79 (s, 1H), 6.90 (d, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.80 (CH_3), 37.34 (CH_2), 39.94 (CH), 55.31 (CH_3), 114.47 (2× CH), 116.82 (CH), 125.79 (Cq), 128.61 (2× CH), 128.63 (CH), 129.22 (CH), 132.45 (Cq), 134.31(Cq), 149.55 (Cq), 158.94 (Cq), 168.07 (Cq) ppm.

m.p.: 115-117 ^{O}C; lit.[20] 120 ^{O}C.

6,7-Methylenedioxy-4-(4-methoxyphenyl)-3,4-dihydrobenzopyran-2-one (50p)



50p

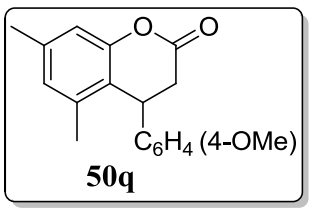
IR (KBr): υ_{max} = 1145, 1182, 1249, 1255, 1483, 1504, 1579, 1753, 2835, 2908 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (dd, *J* = 16, 8.0 Hz, 1H), 2.94 (dd, *J* = 16, 6.0 Hz, 1H), 3.73 (s, 3H), 4.11 (dd, *J* = 8.0, 6.0 Hz, 1H), 5.88 (s, 2H) 6.32 (s, 1H), 6.58 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 2H) 6.99 (d, *J* = 8.8 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 37.21 (CH_2), 39.85 (CH), 55.33 (OCH_3), 99.13 (CH), 101.71 (CH_2), 107.21 (CH), 114.50 (2× CH), 118.41 (Cq), 128.55 (2× CH), 132.36 (Cq), 144.41(Cq), 146.12(Cq), 147.45 (Cq), 159.01 (Cq), 167.84 (Cq) ppm.

m.p.: 136-138 ^{O}C; lit.[26] 136.5-137.5 ^{O}C.

5,7-Dimethyl-4-(4-methoxyphenyl)-3,4-dihydrobenzopyran-2-one (50q)



50q

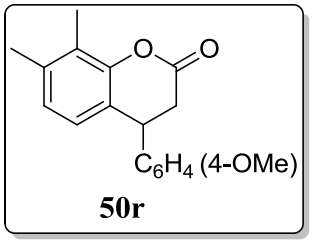
IR (KBr): υ_{max} = 1134, 1253, 1510, 1766, 2837, 2970 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.27 (s, 3H), 2.90 (dd, *J* = 15.6, 2.4 Hz, 1H), 2.96 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.68 (s, 3H), 4.25 (dd, *J* = 6.0, 2.4 Hz, 1H), 6.72 (dd, *J* = 6.8, 2.0 Hz, 2H), 6.76 (d, *J* = 3.2 Hz, 2H), 6.88 (dd, *J* = 6.8, 2.0 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.65 (CH_3), 21.10 (CH_3), 37.17 (CH), 37.99 (CH_2), 55.26 (OCH_3), 114.44 (2× CH), 115.41 (CH), 120.47 (Cq), 127.31 (CH), 128.04 (2× CH), 132.31 (Cq), 136.56 (Cq), 138.69 (Cq), 152.01 (Cq), 158.78 (Cq) 167.75 (Cq) ppm.

m.p.: 166-168 ^{O}C; lit.[27] 166-168 ^{O}C.

7,8-Dimethyl-4-(4-methoxyphenyl)-3,4-dihydrobenzopyran-2-one (50r)



50r

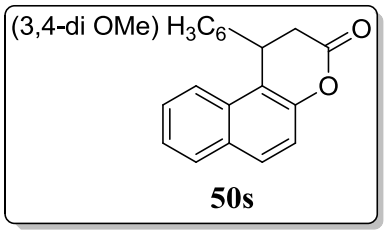
IR (KBr): υ_{max} = 1138, 1249, 1510, 1749, 1890, 2914, 2981 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.22 (s, 3H), 2.89 (dd, J = 16.0, 8.0 Hz, 1H), 2.94 (dd, J = 16.0, 6.0 Hz, 1H), 3.72 (s, 3H), 4.18 (t, J = 6.8 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 6.78-6.82 (m, 3H), 7.00 (d, J = 8.8 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.88 (CH_3), 19.94 (CH_3), 37.20 (CH_2), 39.94 (CH), 55.31 (OCH_3), 114.39 (2× CH), 123.51 (Cq), 124.89 (CH), 124.93 (Cq), 125.55 (CH), 128.61 (2× CH), 132.60 (Cq), 137.69 (Cq), 149.73 (Cq), 158.86 (Cq), 168.39 (Cq) ppm.

m.p.: 112-114 ^{O}C; lit.[28] 114 ^{O}C.

5,6-Benzo-4-(3,4-dimethoxyphenyl)-3,4-dihydrobenzopyran-2-one (50s)



50s

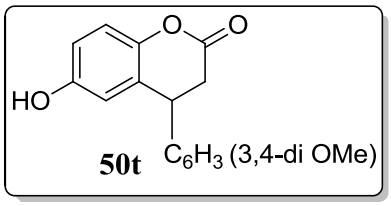
IR (KBr): υ_{max} = 1163, 1236, 1253, 1514, 1600, 1757, 2596, 2953, 3068 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (dd, J = 15.6, 2.4 Hz, 1H), 3.13 (dd, J = 15.6, 6.4 Hz, 1H), 3.72 (s, 3H), 3.73 (s, 3H), 4.84 (dd, J = 6.4, 2.4 Hz, 1H), 6.52 (dd, J = 8.4, 2.0 Hz, 1H), 6.63 (t, J = 2.0 Hz, 1H), 6.66 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.36-7.44 (m, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.8 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 37.30 (CH), 37.69 (CH_2), 55.85 (CH_3), 55.87 (CH_3), 110.02 (CH), 111.56 (CH), 117.51 (CH), 117.86 (Cq), 119.06 (CH), 123.08 (CH), 125.30 (CH), 127.49 (CH), 128.77 (CH), 129.92 (CH), 131.00 (Cq), 131.09 (Cq), 133.03 (Cq), 148.42 (Cq), 149.47 (Cq), 149.69 (Cq), 167.35 (Cq) ppm.

m.p.: 152-154 ^{O}C; lit.[26] 156-159 ^{O}C.

6-Hydroxy-4-(3,4-dimethoxyphenyl)-3,4-dihydrobenzopyran-2-one (50t)



50t

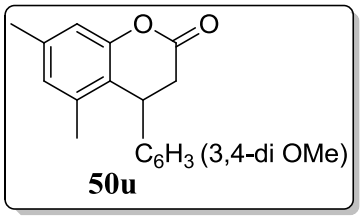
IR (KBr): υ_{max} = 1184, 1269, 1278, 1483, 1710, 3076, 3267 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.97 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.15 (dd, *J* = 8.8 Hz, 6.0 Hz, 1H), 4.86 (br s, 1H), 6.35 (dd, *J* = 3.2, 0.4 Hz, 1H), 6.60 (d, *J* = 2.0 Hz, 1H), 6.64 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 6.68 (dd, *J* = 8.8 Hz, 2.8 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 37.00 (CH_2), 40.37 (CH), 55.92 (2× OCH_3), 110.58 (CH), 111.53 (CH), 114.58 (CH), 115.39 (CH), 117.97 (CH), 119.88 (CH), 127.30 (Cq), 132.40 (Cq), 145.29 (Cq), 148.43 (Cq), 149.31 (Cq), 152.72 (Cq), 168.44 (Cq) ppm.

m.p.: 164-166 ^{O}C; lit.[29] 168-170 ^{O}C.

5,7-Dimethyl-4-(3,4-dimethoxyphenyl)-3,4-dihydrobenzopyran-2-one (50u)



50u

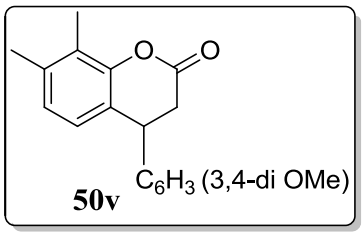
IR (KBr): υ_{max} = 1165, 1240, 1512, 1764, 2914, 2937, 3510 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.26 (s, 3H), 2.92-2.94 (m, 2H), 3.72 (s, *3*H), 3.73 (s, *3*H), 4.23-4.25 (m, 1H), 6.44 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.67 (CH_3), 21.10 (CH_3), 37.61 (CH), 37.97 (CH_2), 55.85 (2× OCH_3), 110.15 (CH), 111.49 (CH), 115.36 (CH), 119.01 (CH), 120.33 (Cq), 127.34 (CH), 132.89 (Cq), 136.62 (Cq), 138.73 (Cq), 148.27 (Cq), 149.33 (Cq), 152.0 (Cq), 167.74 (Cq).

m.p.: 137-139 ^{O}C; lit.[30] 135 ^{O}C.

7,8-Dimethyl-4-(3,4-dimethoxyphenyl)-3,4-dihydrobenzopyran-2-one (50v)



50v

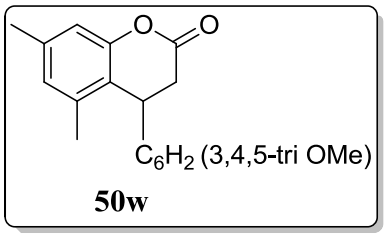
IR (KBr): υ_{max} = 1195, 1253, 1244, 1516, 1766, 2937, 2978 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.31 (s, 3H), 2.99-3.02 (m, 2H), 3.84 (s, 3H), 3.87 (s, *3*H), 4.23-4.25 (m, 1H), 6.69-6.70 (m, 1H), 6.74 (s, 1H), 6.82-6.89 (m, 1H), 6.90 (d, *J* = 7.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.84 (CH_3), 19.90 (CH_3), 37.09 (CH_2), 40.34 (CH), 55.90 (2× OCH_3), 110.64 (CH), 111.47 (CH), 119.75 (CH), 123.44 (Cq), 124.86 (CH), 124.97 (Cq), 125.54 (CH), 133.07 (Cq), 137.67 (Cq), 148.35 (Cq), 149.31 (Cq), 149.69 (Cq), 168.26 (Cq) ppm.

m.p.: 98-100 ^{O}C; lit.[30] 98-99 ^{O}C.

5,7-Dimethyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzopyran-2-one (50w)



50w

IR (KBr): υ_{max} = 1126, 1246, 1454, 1508, 1593, 1774, 2939, 2968 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 3H), 2.28 (s, 3H), 2.94-2.96 (m, 2H), 3.68 (s, 6H), 3.72 (s, *3*H), 4.22-4.24 (m, 1H), 6.17 (s, 2H), 6.77 (s, 2H) ppm.

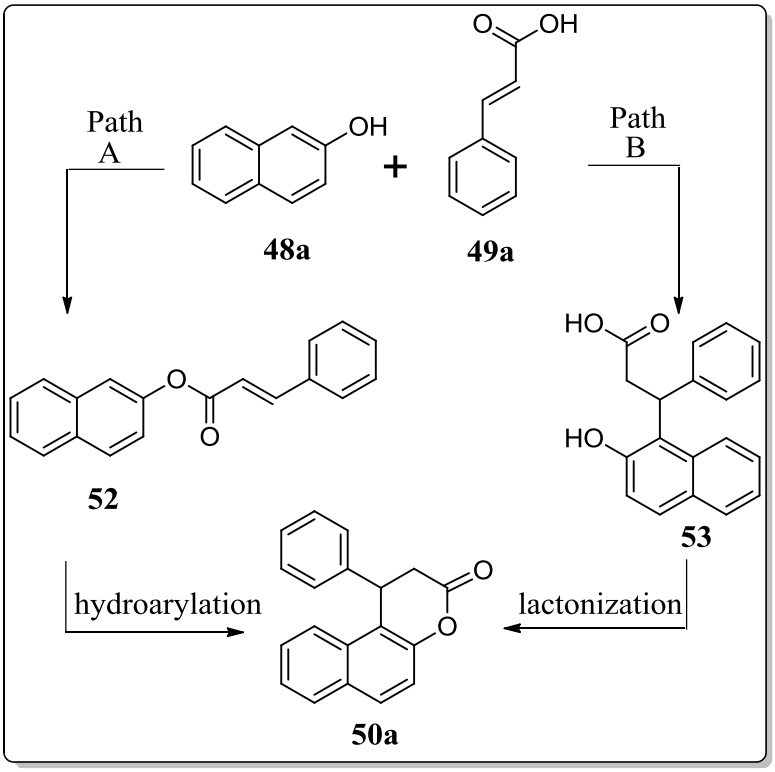
^{13}C NMR (100 MHz, $CDCl_3$): δ 18.75 (CH_3), 21.12 (CH_3), 37.87 (CH_2), 38.31 (CH), 56.08 (2× OCH_3), 60.79 (CH_3), 103.96 (2× CH), 115.39 (CH), 119.97 (Cq), 127.41 (CH), 136.21 (Cq), 136.69 (Cq), 137.21 (Cq), 138.92 (Cq), 152.00 (Cq), 153.60 (2× Cq), 167.66 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{20}H_{22}O_5Na$: 365.1365, found: 365.1362.

Melting Point: 110-112 ^{O}C.

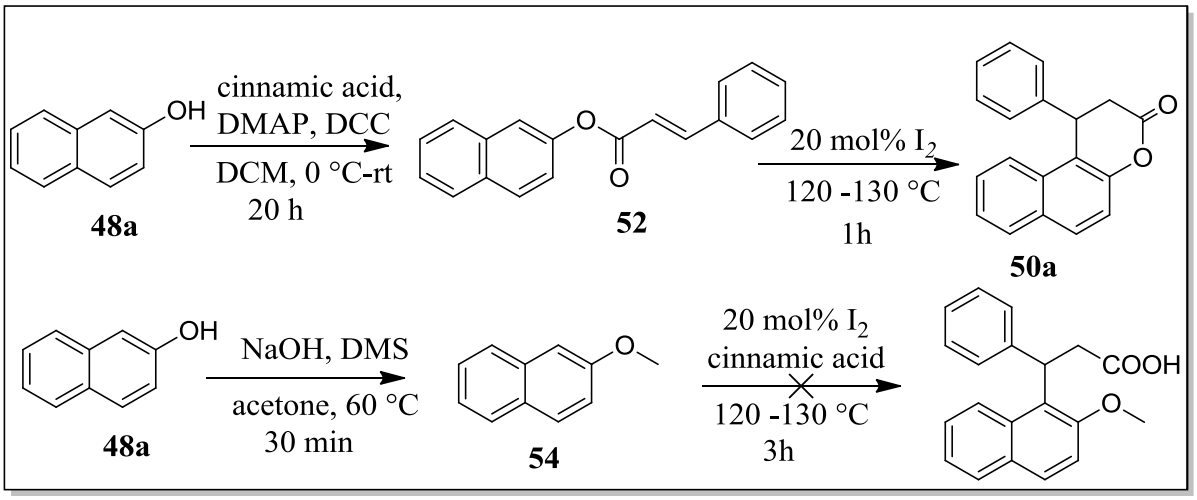
The formation of dihydrocoumarins can be accounted by two different pathways *(Scheme 16)*. Either *via* esterification followed by hydroarylation *(path A, Scheme 16)* or *via* hydroarylation followed by lactonization *(path B, Scheme 16)*.

As reported by Jagdale *et al*., in case of reaction of phenols with cinnamic acid mediated by *p*-toluene sulfonic acid, dihydrocoumarin formation occurs *via* esterification followed by intramolecular Friedel Crafts type cyclization *(path A, Scheme 16)*.[31] However, in case of reaction of phenols with benzylidene malonates in presence of a catalytic amount of $TiCl_4$, product formation occurs *via* hydroarylation followed by lactonization *(path B, Scheme 16)*.[32]



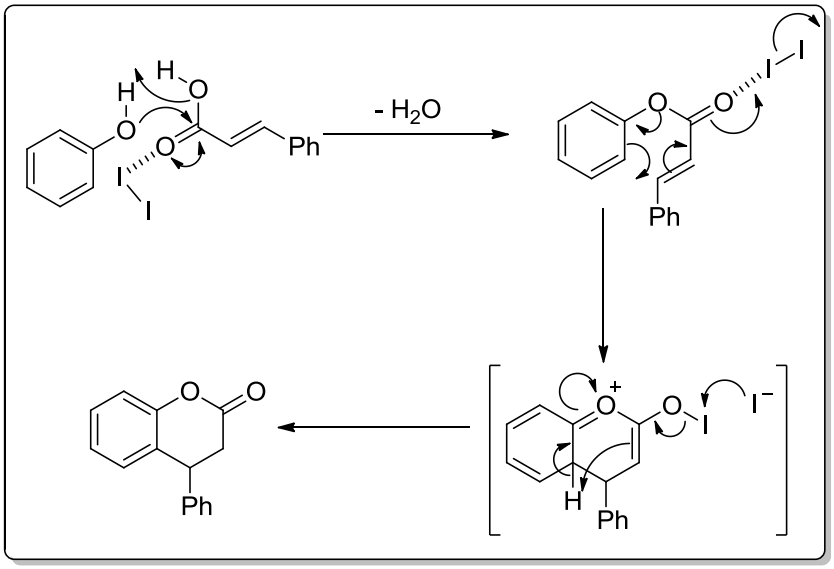
Scheme 16

In order to study the reaction mechanism, (*E*)-2-naphthyl cinnamate (**52**), was subjected to the standardized reaction condition *(Scheme 17)*. Formation of dihydrocoumarin **50a** was observed along with the trace amounts of *β*-naphthol and cinnamic acid. Next, we carried out neat heating of methyl ether of *β*-naphthol **54** with cinnamic acid in the presence of 20 mol% of iodine at 120-130 °C for upto 3 hours to evaluate the possibility of direct hydroarylation. However no change in the reaction mass was observed.



Scheme 17

Thus, based on the above observations, most likely, the reaction occurs *via* path A *i.e.* esterification takes place first followed by hydroarylation. The probable mechanism for the product formation *via* iodine catalyzed cyclocoupling is depicted in *Scheme 18.*



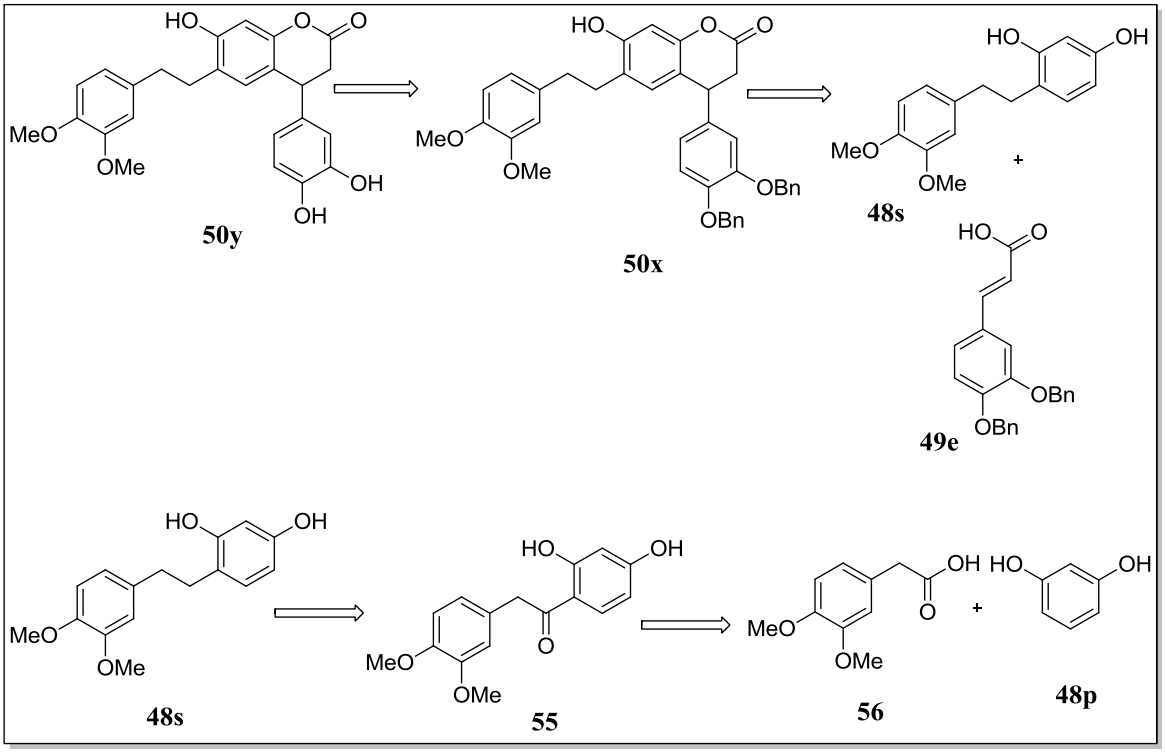
Scheme 18

Next, in order to extend our iodine catalyzed protocol towards the synthesis of a naturally occurring 4-phenyl chroman-2-one, we attempted the synthesis of Vittarin F (**50y**, 4-(3′,4′-dihydroxyphenyl)-6-(3′′,4′′-dimethoxyphenylethyl)-7-hydroxydihydrocoumarin), isolated from the methanol extract of the whole plant of *Vittaria anguste elongata*.[33] Till date there are no reports for the synthesis of this molecule.

Accordingly, a synthetic strategy for the same was planned. Our retrosynthetic analysis of this molecule **50y** identified corresponding phenol **48s** and the cinnamic acid **49e** as the key intermediates *(Scheme 19).*

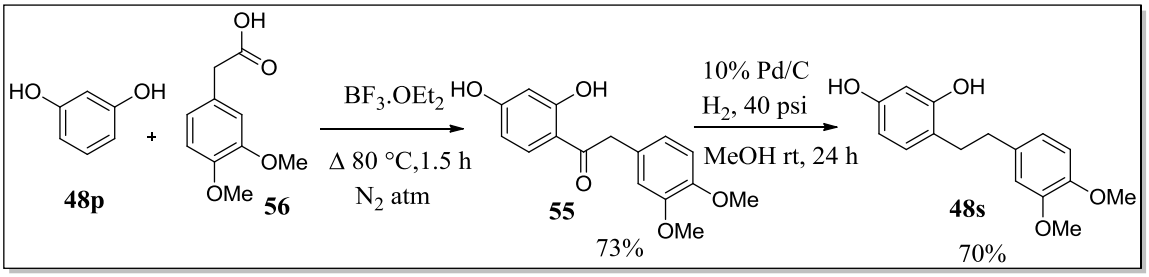
Intermediate **48s** could be obtained by the reduction of intermediate **55**, which in turn could be derived by Friedel Crafts acylation of resorcinol (**48p**) with homoveratric acid (**56**).

The iodine catalyzed [3+3] cyclocoupling of phenol **48s** wih cinnamic acid **49e** was then planned to get the intermediate **50x**. Furthermore, the deprotection of the *O*-benzyl groups in **50x** would give Vittarin F.



Scheme 19

Initially the Friedel Crafts acylation of resorcinol with homoveratric acid was carried out using $BF_3.OEt_2$ as Lewis acid and also as solvent to give the product **55**, as light pink solid, melting at 170-172 °C by referring to the literature method *(Scheme 20)*.[34]

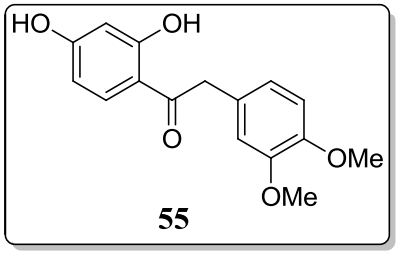


Scheme 20

Its IR spectrum showed a sharp band at 1712 cm^{-1} indicating the presence of a carbonyl group. Peak due to phenolic hydroxy group was observed at 3348 cm^{-1}. In its ^1H NMR spectrum the singlet at δ 3.88 for six protons was assigned to the protons of the two methoxy groups. The peaks between δ 6.40-7.78 were attributed to the aromatic protons. Compound **55** was obtained in 73% yield.

Spectroscopic data

1-(2,4-Dihydroxyphenyl)-2-(3,4-dimethoxyphenyl)ethanone (55)



55

IR (neat): υ_{max} 1024, 1155, 1325, 1444, 1512, 1712, 2974, 3348 cm^{-1}.

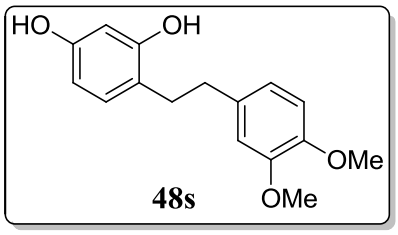
^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 6H), 4.18 (s, 2H), 6.41 (d, J = 9.6 Hz, 2H), 6.80-6.85 (m, 3H), 7.78 (d, J = 8.8 Hz, 1H) ppm.

The product **55** was then subjected to catalytic hydrogenation in presence of 10% Pd/C at room temperature. After 24 hours, the TLC of the reaction mixture showed complete disappearance of the starting material and appearance of a new spot. Column chromatographic purification of the crude product yielded a pale yellow solid, melting at 70-72 °C.

Disappearance of carbonyl stretching at 1712 cm^{-1} in its IR spectrum indicated the complete reduction of the carbonyl group of ketone in **55**. Its ^1H NMR spectrum showed a singlet at δ 2.73 integrating for four protons which was assigned to the methylene protons of the two adjacent methylene groups. Two singlets at δ 3.72 and δ 3.76 integrating for three protons each were assigned to the two methoxy groups attatched to the aromatic ring. The remaining peaks between δ 6.17-6.82 were attributed to the aromatic protons. Complete spectral analysis of the compound is provided below.

Spectroscopic data

4-(3,4-Dimethoxyphenethyl)benzene-1,3-diol (48s)



48s

IR (neat): υ_{max} 1101, 1257, 1452, 1608, 2941, 2953, 3325, 3396 cm^{-1}.

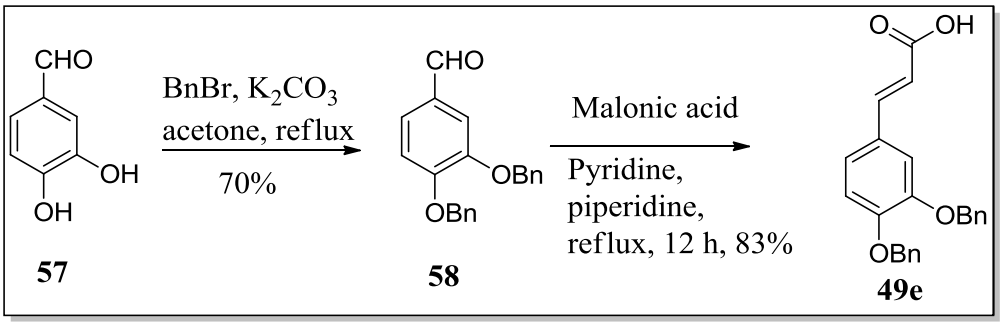
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (s, 4H), 3.72 (s, 3H), 3.77 (s, 3H), 6.17 (d, *J* = 2.4 Hz, 1H), 6.27 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 31.81 (CH_2), 36.11 (CH_2), 55.76 (CH_3), 55.90 (CH_3), 102.92 (CH), 107.64 (CH), 111.33 (CH), 112.10 (CH), 120.12 (Cq), 120.46 (CH), 131.08 (CH), 134.82 (Cq), 147.04 (Cq), 148.48 (Cq), 154.56 (Cq), 154.91 (Cq) ppm.

m.p.: 70-72 °C

The compound **48s** was formed in 70% yield.

In order to prepare the desired cinnamic acid derivative **49e**, 3, 4-benzyloxybenzaldehyde (**58**) was prepared by treatment of 3,4-dihydroxy benzaldehyde (**57**) with benzyl bromide *(Scheme 21).*



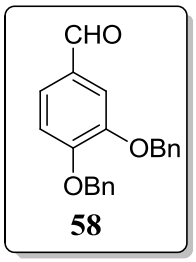
57 **58** **49e**

Scheme 21

Compound **58** was obtained as a pale yellow solid (m.p. 89-90 °C; lit.[35] 90-91 °C). The structure was further confirmed by agreeable spectral data.

Spectroscopic data

Synthesis of 3,4-Bis(benzyloxy)benzaldehyde (58)



58

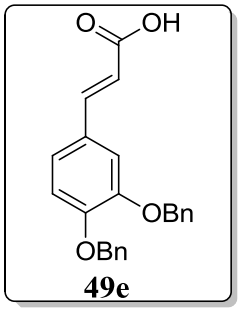
IR (neat): υ_{max} 1678, 2819, 3026, 3078 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (s, 2H), 5.18 (s, 2H), 6.94 (d, J = 8.4 Hz, 1H), 7.24-7.42 (m, 12H), 9.73 (s, 1H) ppm.

This product was obtained in 70% yield. Further, Knoevenagel condensation of 3, 4-benzyloxy benzaldehyde (**58**) with malonic acid in presence of pyridine and piperidine gave a pale yellow solid (m.p. 200-202 °C; lit.[35] m.p. 201-202 °) which was confirmed by agreeable spectral data.

Spectroscopic data

Synthesis of (*E*)-3-(3,4-Bis(benzyloxy)phenyl)acrylic acid (49e)



49e

IR (neat): υ_{max} 1545, 1622, 1664, 2949, 3059 cm^{-1}.

^{1}H NMR (400 MHz, CDCl3): δ 5.19 (d, J = 8.8 Hz, 4H), 6.24 (d, J = 16.0 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.08-7.10 (m, 1H), 7.14 (d, J = 1.6 Hz, 1H), 7.30-7.47 (m, 10H), 7.65 (d, J = 15.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl3): δ 70.96 (CH_2), 71.36 (CH_2), 113.88 (CH), 114.19 (CH), 114.76 (CH), 123.27 (Cq), 123.32 (CH), 125.43 (CH), 127.16 (2×CH), 127.3 (2×CH), 128.01 (2×CH), 128.60 (3×CH), 136.66 (Cq), 136.82 (Cq), 146.72 (CH), 148.97 (Cq), 151.41 (Cq), 170.71 (Cq) ppm.

Once both starting materials were in hand, the next task was to subject them to our iodine catalyzed [3+3] cyclocoupling protocol.

Hence the phenol **48s** was treated with cinnamic acid **49e** using several reaction conditions *(Scheme 22, Table 5)*. Initially we carried out the reaction in absence of catalyst at room temperature (entry 1). However reaction did not occur (monitored by TLC) even after 24 hours and both starting reactants remained intact. Similar result was obtained when the starting materials were neat heated at 120 °C (entry 2).

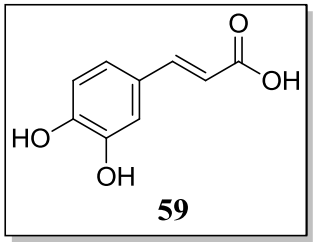
Neat heating at higher temperatures resulted in decomposition of starting phenol **48s**, whereas the starting acid **49e** remained intact (entry 3).

In presence of catalytic amount of iodine, decomposition of phenol **48s** was observed while the starting cinnamic acid **49e** remained intact (entry 4).

When the reaction mass was neat heated at 120 – 130 °C, again decomposition of phenol **48s** occurred within an hour and 30 % of cinnamic acid **49e** could be recovered (entry 5). When an excess of iodine was used (entry 6), TLC showed appearance of a new spot along with the spot corresponding to starting cinnamic acid. Column chromatographic separation of the crude mass accounted for two products. The starting **49e** corresponding to less polar spot was obtained in 15 % yield. The compound corresponding to more polar spot was obtained as a pale yellow solid melting in the range 180-182 ^{O}C. Its IR spectrum showed a strong band at 1643 cm^{-1} indicating the presence of an α, β-unsaturated acid carbonyl group. The broad band at 3433 cm^{-1} corresponding to the phenolic hydroxyl group was also observed. In its ^{1}H NMR spectrum the doublet corresponding to δ 6.19 (J = 15.6 Hz, 1H) and a doublet corresponding to δ 7.44 (J = 16 Hz, 1H) were attributed to the olefinic protons. The peaks between δ 6.77-7.03 ppm corresponding to the aromatic protons were also observed. The broad singlet at δ 12.13 (1 H) accounted for the carboxylic acid proton. The structure of this compound was further confirmed by recording its ^{13}C NMR and DEPT spectra. The detailed spectroscopic data is given below.

Spectroscopic data

(*E*)-3-(3,4-dihydroxyphenyl)acrylic acid



59

IR (KBr): υ_{max} 3433, 2989, 1643, 1620, 1598 cm^{-1}.

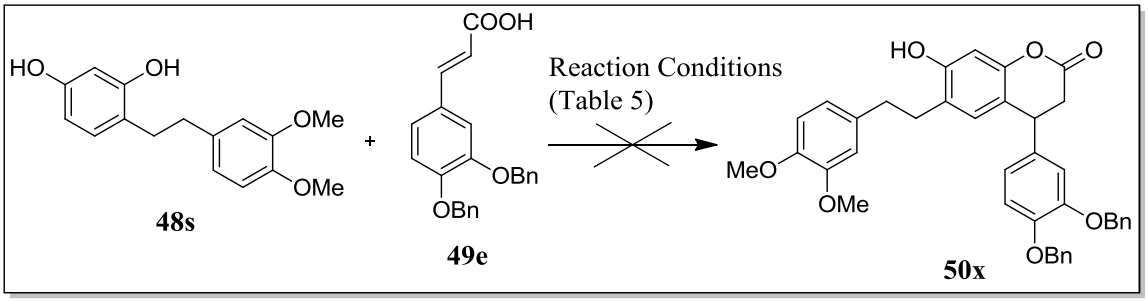
^{1}H NMR (400 MHz, DMSO): δ 6.19 (d, J = 15.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 2.0, 8.0 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 16.0 Hz, 1H), 9.17 (br s, 1H), 9.56 (br s, 1H), 12.13 (br s, 1H).

^{13}C NMR (100 MHz, DMSO): δ 114.57 (CH), 115.01 (CH), 115.71 (CH), 121.16 (CH), 125.6 (Cq), 144.59 (CH), 145.48 (Cq), 148.06 (Cq), 167.92 (Cq).

m.p.: 180-182 °C; lit.[38] 181-183 °C.

Thus based on the mode of formation and spectral data mentioned above, structure **59** was assigned to this compound. This compound **59** was obtained in very low yield, resulting from the debenzylation of starting cinnamic acid **49e**.

Hence no expected product was observed in any case.



Scheme 22

Table 5

Entry	Reaction condition	Observation
1	No catalyst, N_2 atm, DCM, rt, 24 h	No reaction (starting reactants **48s** & **49e** intact)
2	No catalyst, N_2 atm, Δ 120 °C, neat, 24 h	No reaction (starting reactants **48s** & **49e** intact)
3	No catalyst, N_2 atm, Δ 150 °C, neat, 24 h	starting reactant **49e** intact (Decomposition of **48s** observed)
4	5 -80 mol% Iodine, N_2 atm, DCM, rt, upto 2 h	starting reactant **49e** intact (Decomposition of **48s** observed)
5	5 -80 mol% Iodine, N_2 atm, Δ 120 - 130 °C, neat, upto 1 h	30% of starting **49e** obtained (Decomposition of **48s** observed)
6	2-3 equiv. Iodine, N_2 atm, Δ 120 - 130 °C, neat, upto 1 h	15% of starting **49e** and 3 % of **59** obtained (decomposition of **48s** observed)

2.4: Conclusion

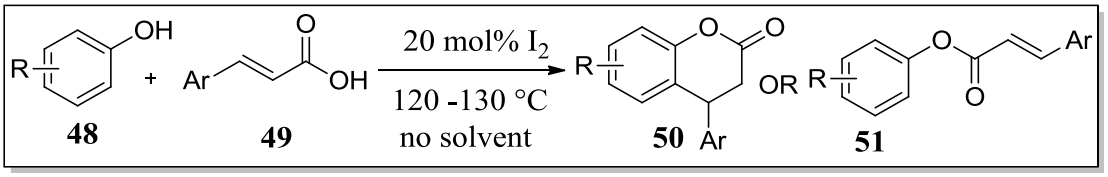
We have developed a molecular iodine catalyzed one-pot protocol for the synthesis of 4-aryl-3,4-dihydrocoumarins using inexpensive and readily available starting materials in good to moderate yields.

The main feature of this metal and solvent-free process is that it provides an efficient, cost-effective, easy to handle and environmentally benign route, with the use of iodine as a mild and safer catalyst.

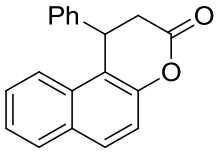
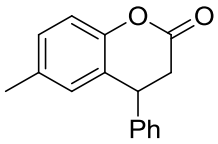
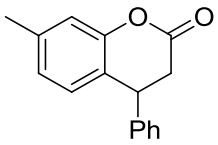
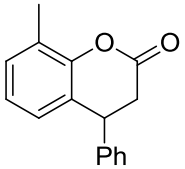
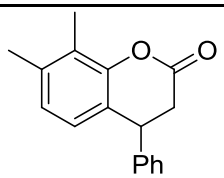
This methodology is important from green chemistry point of view also because hydroarylation exhibits perfect atom economy.

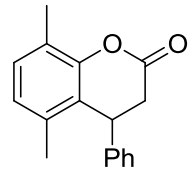
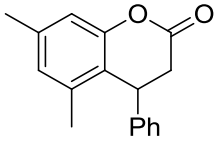
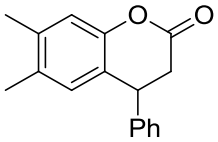
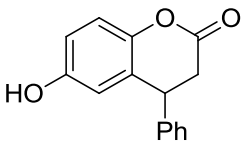
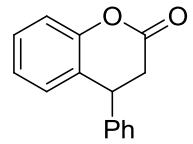
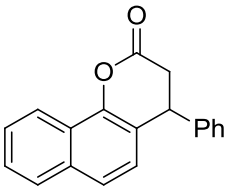
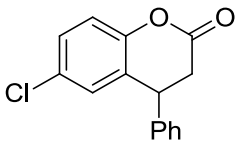
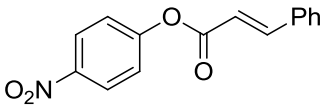
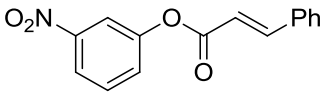
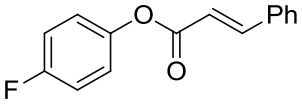
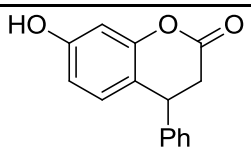
However, we could not successfully extend this methodology towards the synthesis of naturally occurring 4-phenyl-chroman-2-one, Vittarin F.

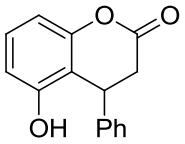
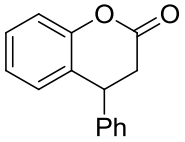
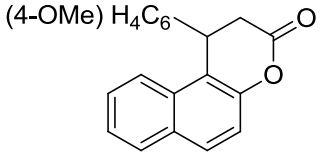
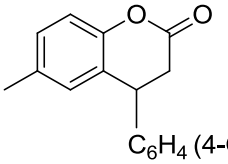
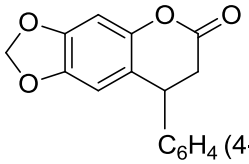
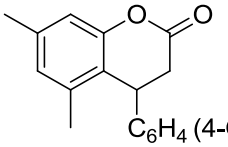
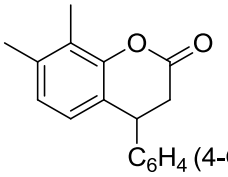
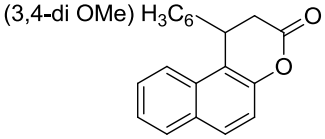
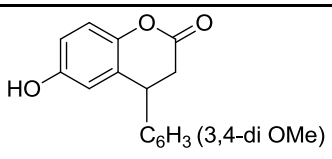
2.5: Experimental

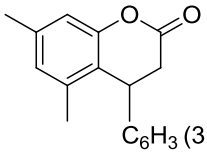
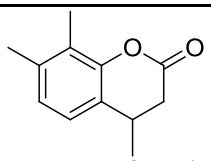
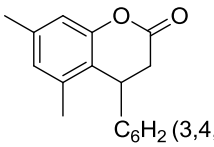


2.5.1: General Procedure: A mixture of iodine (0.13 mmol), phenol (0.69 mmol) and cinnamic acid (0.69 mmol) was neat heated under an air atmosphere at 120-130 °C for a period of time (1-24 h). Following completion of the reaction as monitored by TLC, the reaction mixture was cooled, diluted with ethyl acetate (20 mL), washed with aqueous sodium thiosulfate solution and dried over anhyd. sodium sulfate. The solvent was removed under vacuum to give the crude product. Further purification was carried out using column chromatography on silica gel with hexanes- EtOAc (8:2) as an eluent for all the compounds except for **50w** for which hexanes- EtOAc (7:3) was used as an eluent.

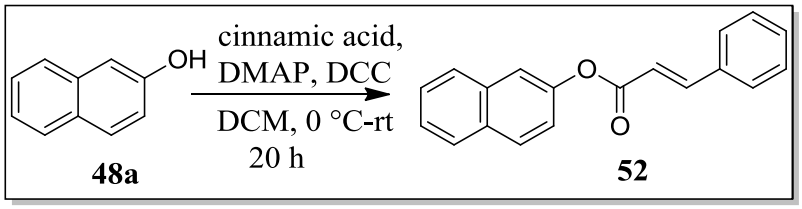
Product		Time (h)	Yield (%)	Nature	m.p. (°C)
50a		1	80	colorless solid	115-117
50b		1	83	colorless solid	80-83
50c		1.5	78	colorless solid	124
50d		3	60	colorless solid	106-108
50e		4	83	colorless solid	119-120

50f		5	65	colorless solid	78-80
50g		2	85	colorless solid	130-132
50h		2	85	pale yellow solid	110-113
50i		2	77	colorless solid	125-130
50j		4	60	colorless solid	78-80
50k		4	65	pale yellow solid	112
50l		3	70	colorless solid	110
51a		24	20	colorless solid	142-144
51b		24	30	colorless solid	106-108
51c		24	50	colorless solid	70-75
50ma & 50mb		5	70	colorless solid	-

	 **50ma:50mb (**5:1)				
50j	 *obtained from bisphenol A	10	5	colorless solid	78-80
50n		4	85	colorless solid	128-130
50o		1.5	78	colorless solid	115
50p		4	68	colorless solid	136-138
50q		3	82	colorless solid	166-168
50r		1	83	colorless solid	112-114
50s		1.45	80	colorless solid	152-154
50t		4	72	colorless solid	164-166

50u		2	77	colorless solid	137-139
50v		2	60	colorless solid	98-100
50w		2.3	63	colorless solid	110-112

2. 5. 2: Preparation of (E)-2-naphthyl cinnamate (52):



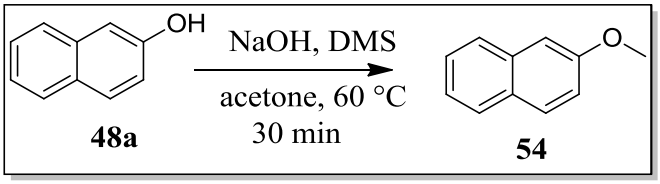
Procedure: *β*- Naphthol (**48a**, 1.0 g, 6.94 mmol), cinnamic acid (**49a**, 1.03 g, 6.94 mmol) and DMAP (0.085 g, 0.694 mmol) were dissolved in DCM (mL) and cooled to 0 °C. To this solution, DCC (2.15 g, 10.4 mmol) was added and stirred at 0 °C – room temperature for 20 h. This suspension was cooled to 0 °C and filtered. This was repeated thrice and organic layer was washed with water, brine and dried over Na_2SO_4. Solvent was removed under vacuum and crude product was purified by flash chromatography on silica gel using hexanes- EtOAc (9:1) as an eluent to give **52** as a white solid in 59 % (1.12 g) yield.

Colorless solid, **m.p.:** 107-109 °C; lit.[37] 109-110 ^{O}C.

IR (KBr): υ_{max} = 1159, 1211, 1309, 1448, 1510, 1597, 1634, 1738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (d, J = 16.0 Hz, 1H), 7.32 (dd, J = 8.8, 2.4 Hz, 1H), 7.43-7.51 (m, 5H), 7.60-7.65 (m, 3H), 7.82-7.95 (m, 4H) ppm.

2.5.3: Preparation of 2-methoxy naphthalene (54):



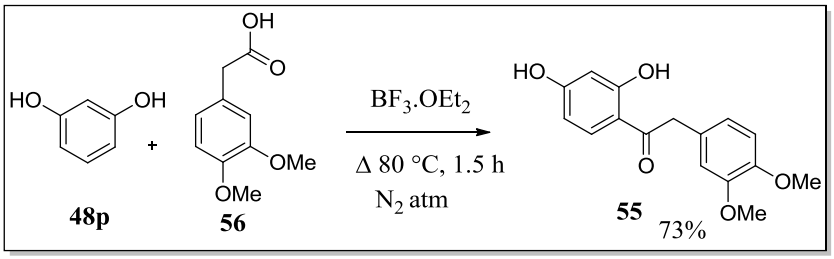
Procedure: To a mixture of *β*-naphthol (0.5 g. 0.0034 mol) and sodium hydroxide (0.277 g, 0.006 mol) in acetone (10 mL), dimethyl sulfate (1.3 mL, 0.0138 mol) was added and the resultant mixture was heated at 60 °C for thirty minutes. The reaction mixture was poured into ice water. It was neutralized by using 10% HCl and extracted with Et_2O (3 × 30 mL). The organic layer was washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL). respectively and dried over anhyd. sodium sulfate. The solvent was concentrated under reduced pressure to give the desired product in 80% yield.

Colorless solid, **m.p.:** 71-73 °C; lit.[36] 70-71 ^{O}C.

IR (KBr): υ_{max} = 935, 1228, 1448, 1631, 1678, 2617, 2833 cm^{-1}.

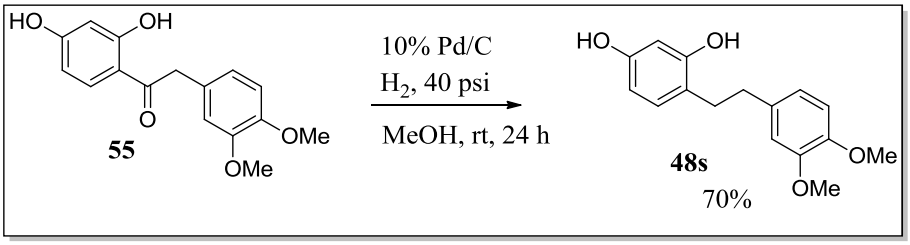
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.13-7.16 (m, 2H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.72-7.77 (m, 3H) ppm.

2.5.4: Synthesis of 1-(2,4-dihydroxyphenyl)-2-(3,4-dimethoxyphenyl)ethanone (55)



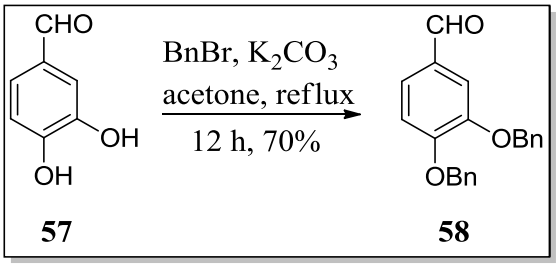
To a mixture of resorcinol (**48p**, 0.5 g, 4.54 mmol) and homoveratric acid (**56**, 0.89 g, 4.54 mmol) $BF_3.OEt_2$ (7 mL) was added and the mixture was heated at 80 °C under nitrogen atmosphere for 1.5 hours. The resulting mixture was cooled followed by addition of water (40 mL) to it. This aqueous layer was extracted with Et_2O (3 × 30 mL). The combined ether layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude residue obtained was subjected to column chromatographic purification on silica gel using hexanes- EtOAc (7:3) as an eluent to give **55** as a light pink solid in 73% (0.953 g) yield. (**m.p.:** 170-172 °C; lit.[34] 171-172 °C).

2.5.5: Synthesis of 4-(3,4-dimethoxyphenethyl)benzene-1,3-diol (48s)



To a solution of **55** (0.8 g, 2.77 mmol) in methanol (10 mL) was added 10% w/w Pd/C (0.08 g) and the mixture was subjected to hydrogenation on a par hydrogenator for 24 hours. The suspension was then filtered and the filtrate was subjected to evaporation under reduced pressure. The crude residue was subjected to column chromatographic purification on silica gel using hexanes- EtOAc (6:4) as an eluent to give **48s** as a pale yellow solid in 70% (0.532 g) yield (**m.p.:** 70-72 °C).

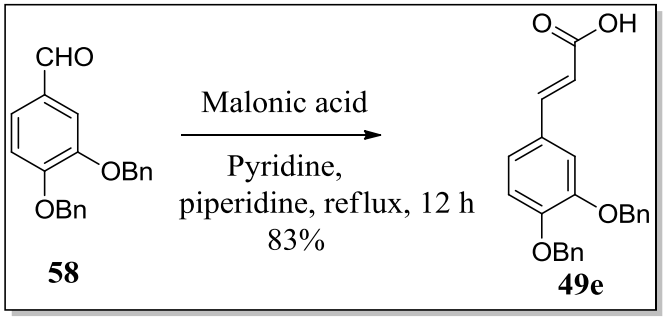
2.5.6: Synthesis of 3,4-Bis(benzyloxy)benzaldehyde (58)



57 **58**

To a mixture of 3,4-dihydroxybenzaldehyde **57** (0.5g, 3.6 mmol) and K_2CO_3 (1.5 g, 10.86 mmol) in acetone, was added benzyl bromide (1.3 mL, 10.86 mmol) dropwise. The reaction mixture was refluxed for 12 h. The reaction mixture was then cooled and poured into water (30 mL) followed by extraction with EtOAc (3 × 15 mL). The organic layer was washed with water (2 × 10 mL). The combined organic layers were dried over anhyd. Na_2SO_4. The solvent was removed under vacuum to give crude compound, which was purified by column chromatography on silica gel (60-120 mesh) using hexanes-EtOAc (8:2) as an eluent to afford compound **58** in 70% (0.803 g) yield as pale yellow solid (**m.p.:** 89-90 °C; lit.[35] 90-91 °C).

2.5.7: Synthesis of (*E*)-3-(3,4-bis(benzyloxy)phenyl)acrylic acid (49e)

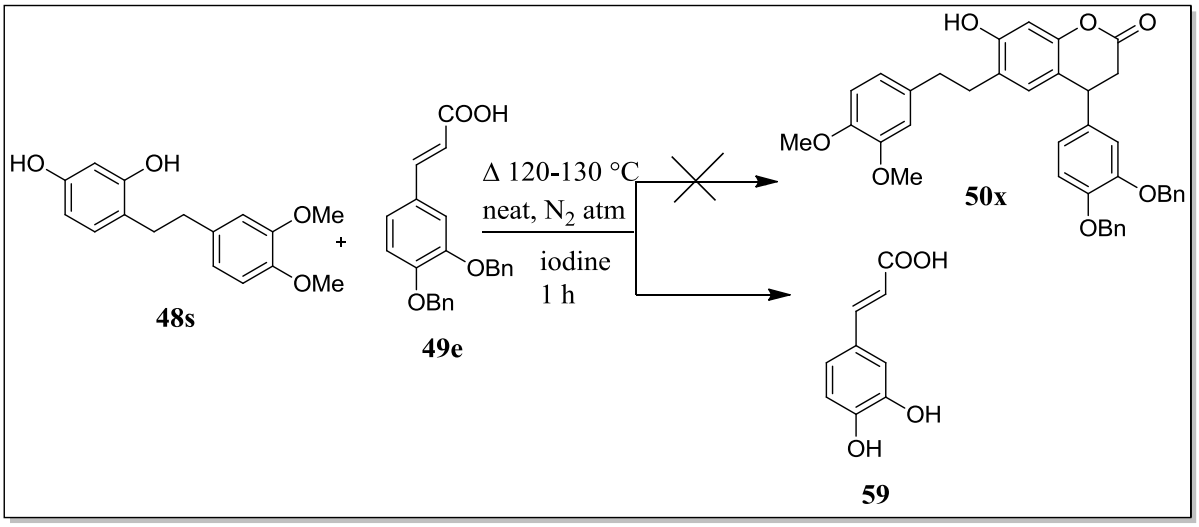


58 **49e**

To a mixture of compound **58** (0.5 g, 1.57 mmol), pyridine (0.5 mL), piperidine (0.0133 g, 0.157 mmol) and malonic acid (0.359 g, 3.455 mmol) were added and the reaction mixture was refluxed for 12 h. The reaction mixture was then cooled and poured into excess water containing HCl (pH was maintained at 3). The solid obtained was filtered

and washed with water (2 × 10 mL). The solid was dried under vacuum to give 83% (0.472 g) of compound **49e** as a pale yellow solid (**m.p.:** 200-202 °C; lit.[35] 201-202 °C).

2.5.8: Attempted synthesis of 4-(3,4-bis(benzyloxy)phenyl)-6-(3,4-dimethoxyphenethyl)-7-hydroxychroman-2-one (50x)



To a mixture of compound **48s** (0.1 g, 0.365 mmol) and compound **49e** (0.13 g, 0.365 mmol), iodine (0.28 g, 1.09 mmol) was added and the reaction mixture was neat heated at 120-130 °C for 1 hour under nitrogen atmosphere. The reaction mixture was then cooled and EtOAc (30 mL) was added to it. The organic layer was washed with aq. sodium thiosulfate solution (10 × 3 mL). The organic layer was dried over anhyd. Na_2SO_4. The solvent was removed under vacuum to give a mixture which was separated by column chromatography on silica gel (60-120 mesh) using hexanes- EtOAc (8:2) as an eluent to afford starting compound **49e** in 15 % (0.02 g) yield and EtOAc as an eluent to give compound **59** as a pale yellow solid (**m.p.:** 180-182 °C; lit.[38] 181-183 °C) in 3 % (0.0019 g) yield.

2.6: References

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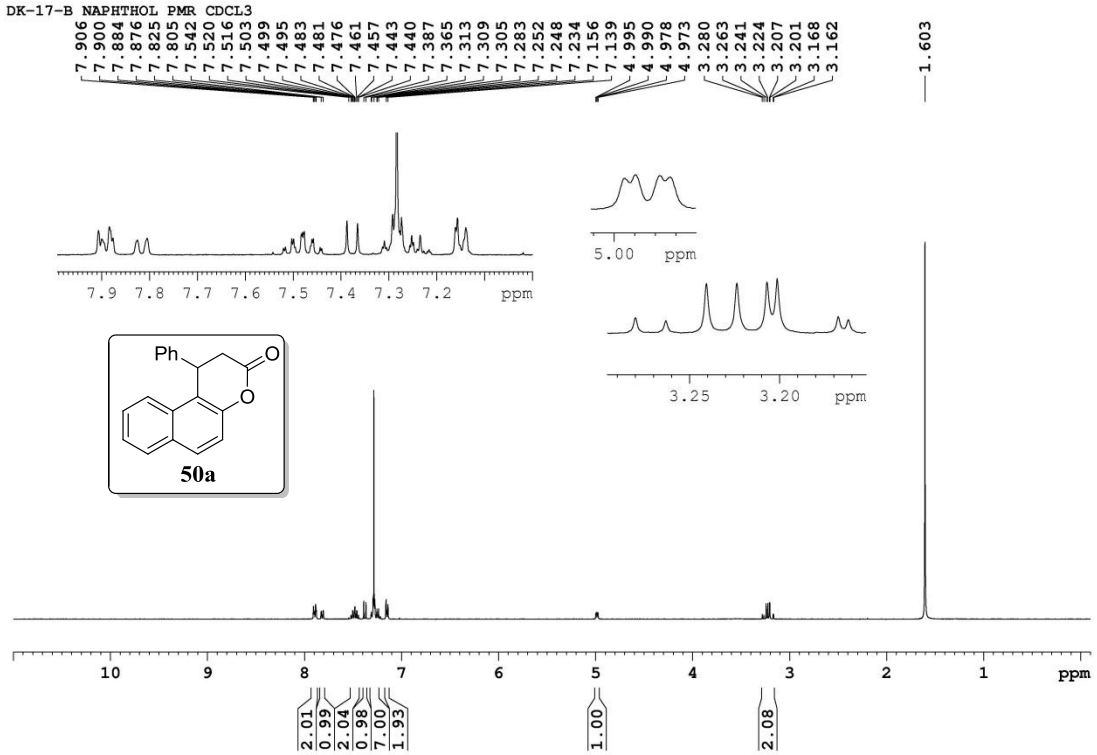
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3.224
3.207
3.201
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5.00 ppm
3.25 3.20 ppm
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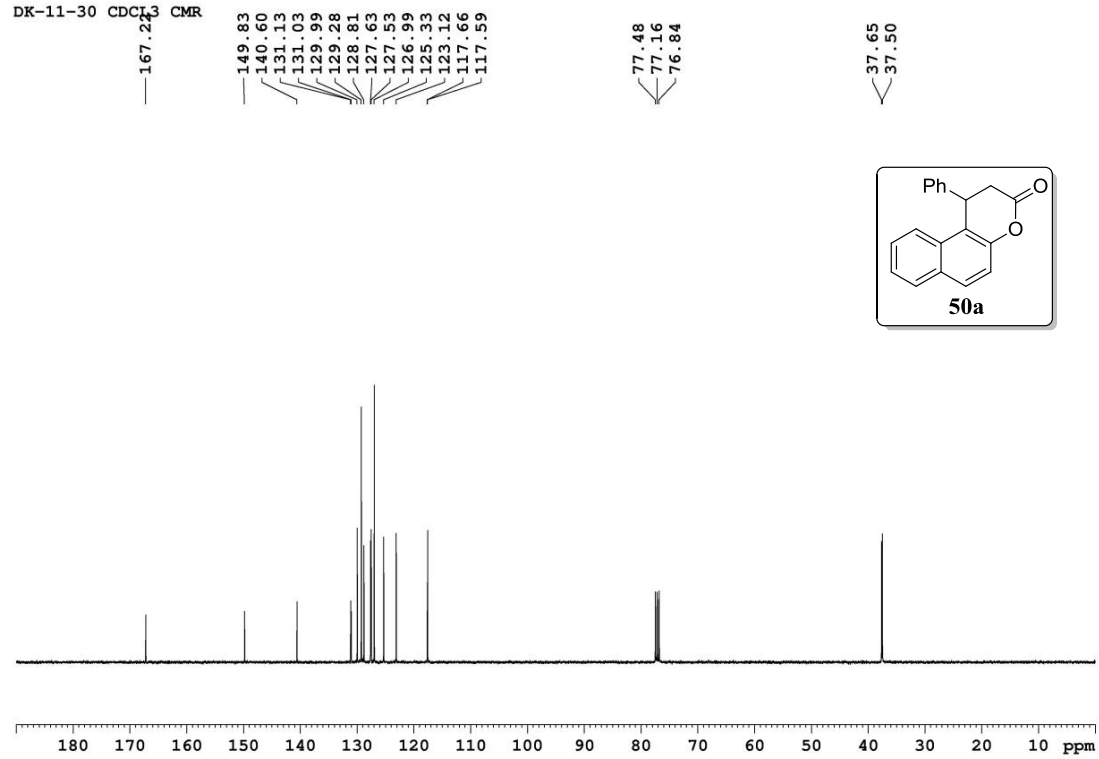
1.93
1.00
2.08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117.66
117.59
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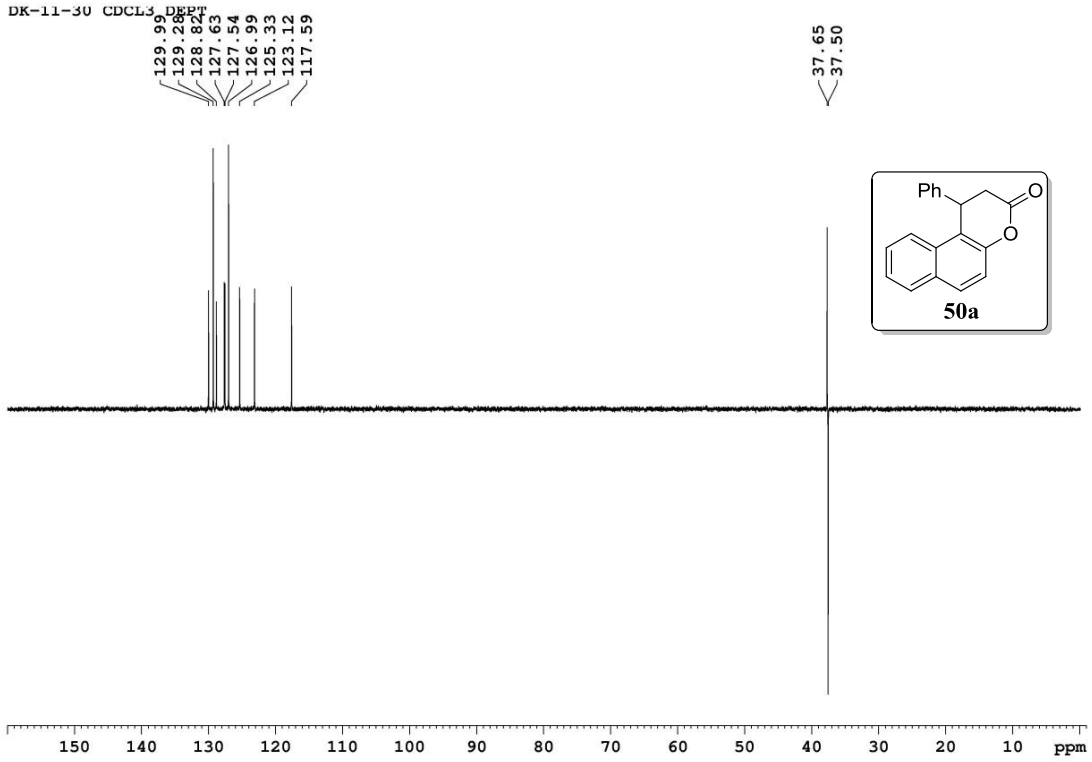
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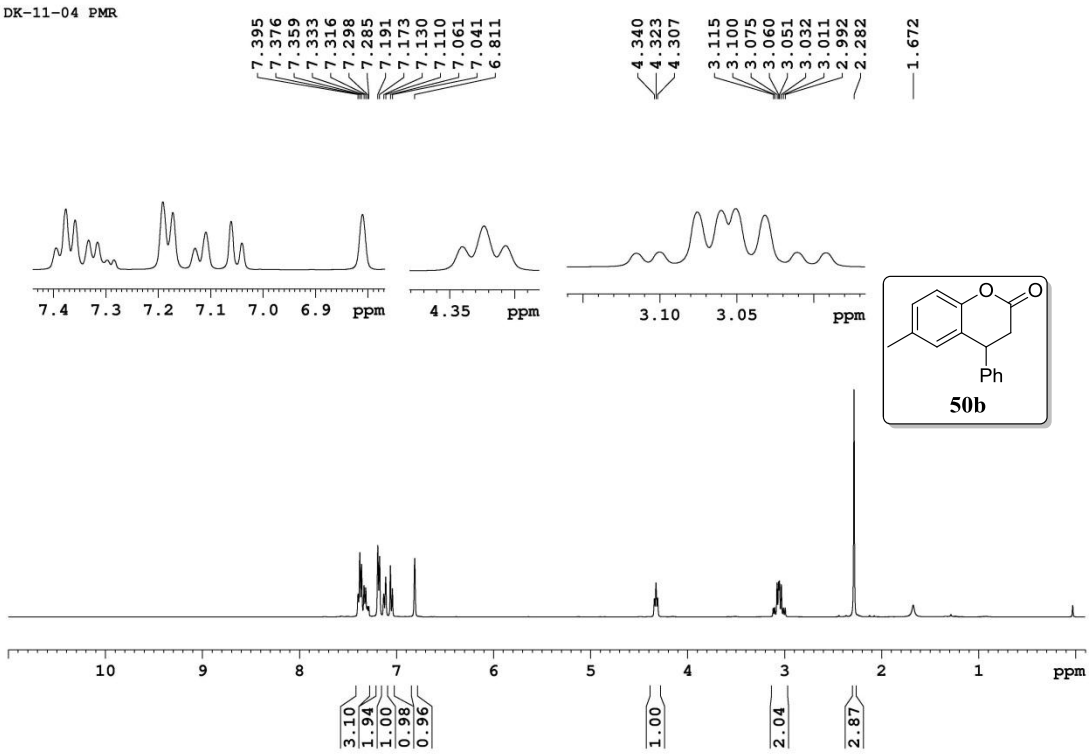
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7.041
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4.323
4.307
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3.075
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3.032
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4.35 ppm
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O
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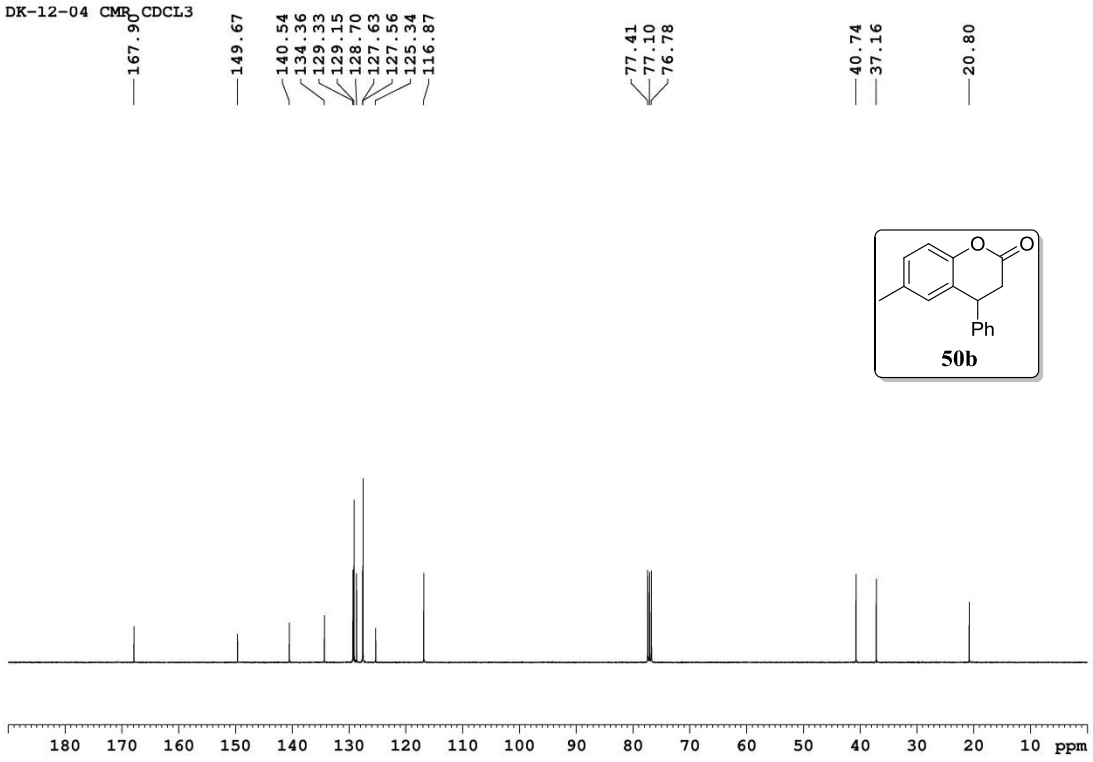
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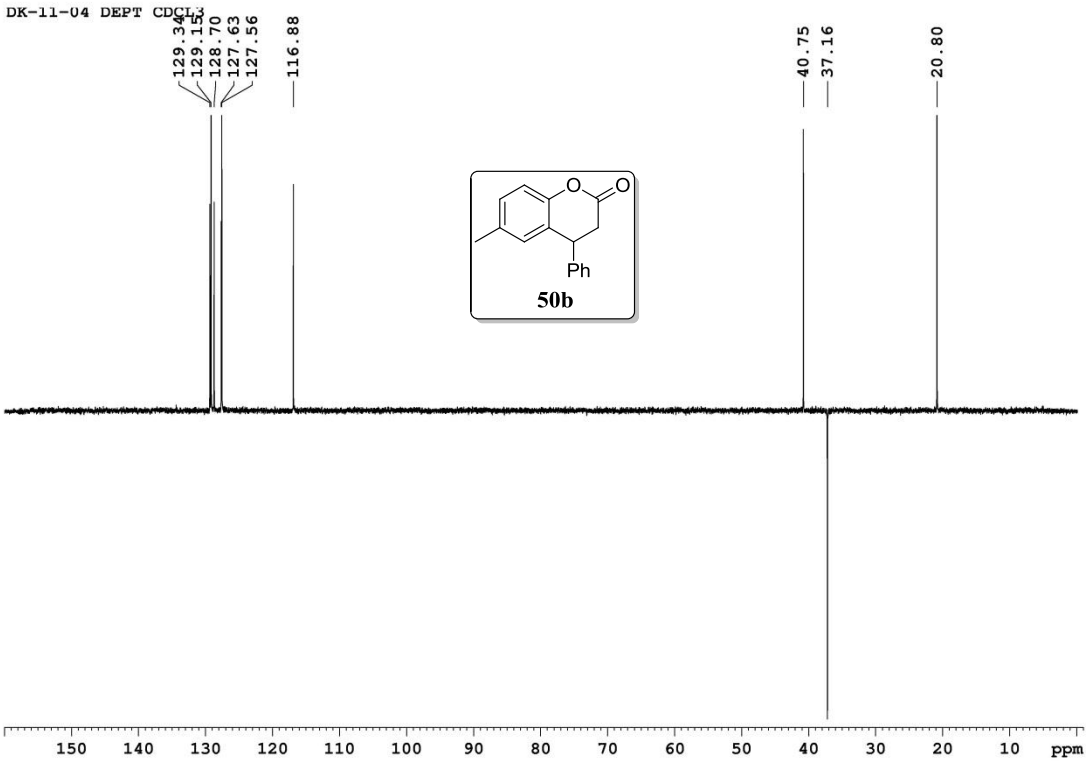
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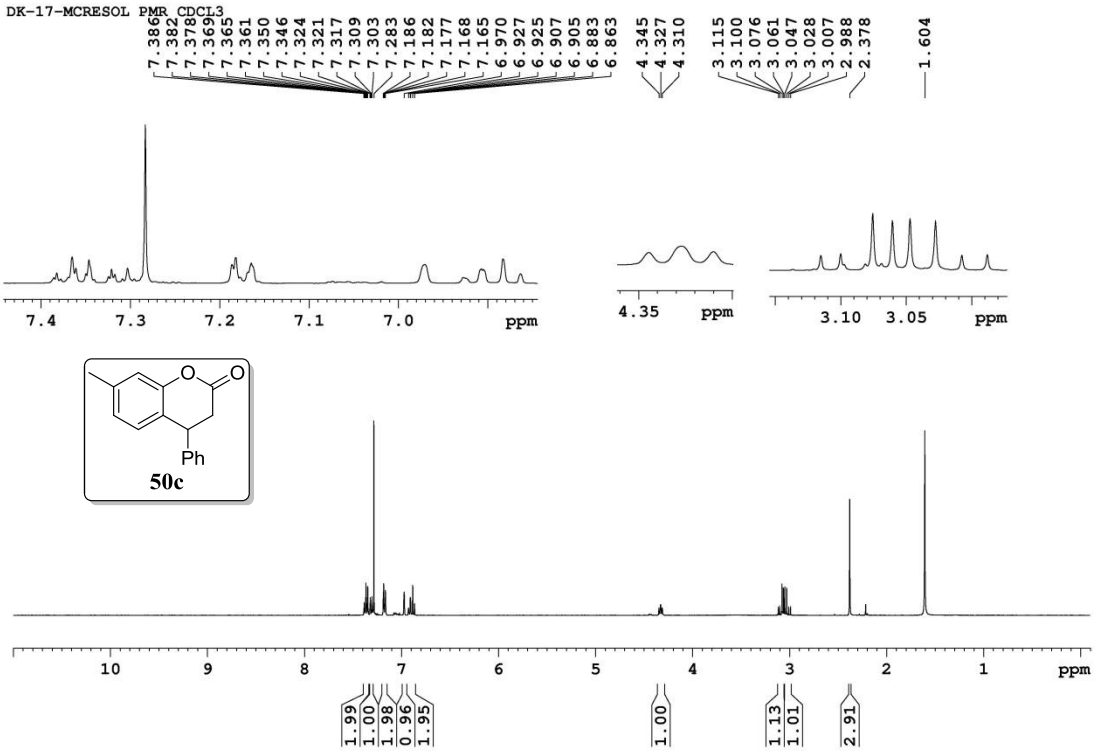
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7.2
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ppm
4.35
ppm
3.10
3.05
ppm
O
O
Ph
50c
10
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8
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6
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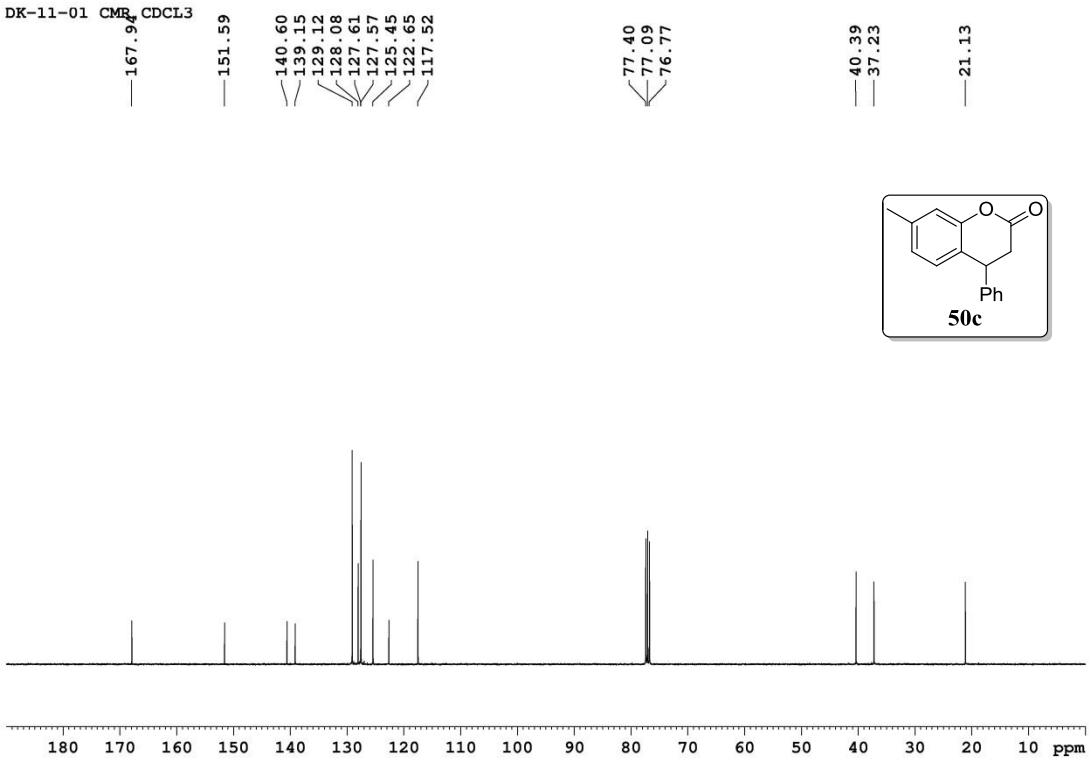
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O
O
Ph
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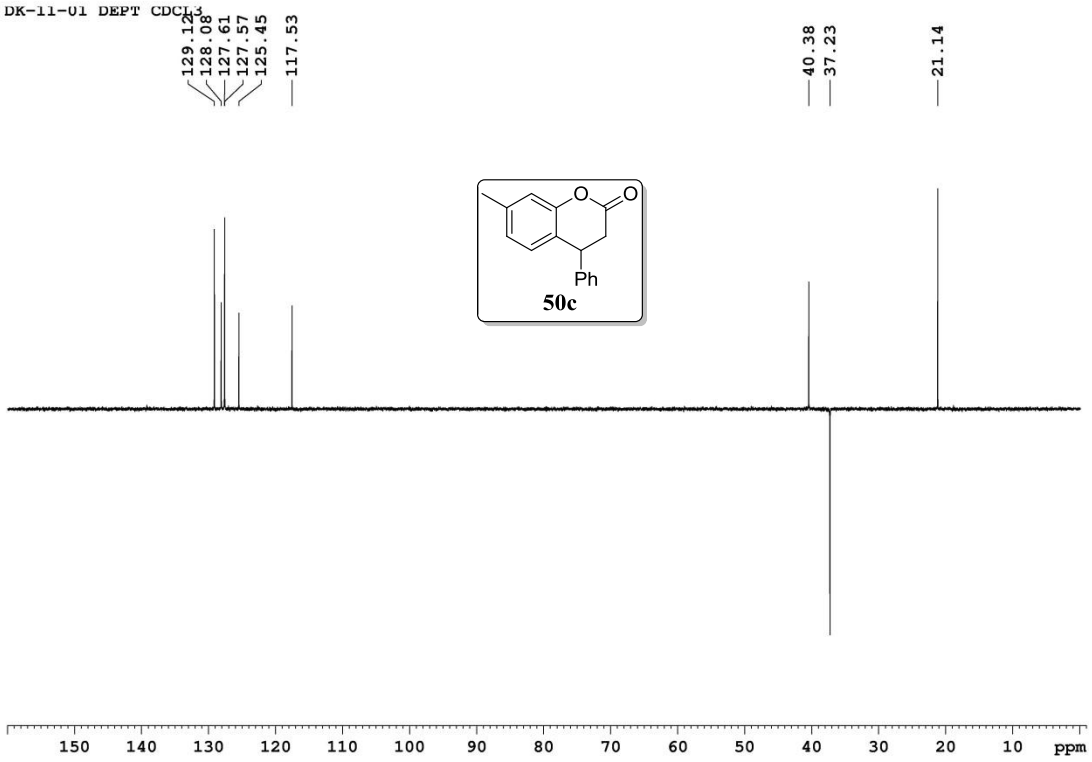
10
ppm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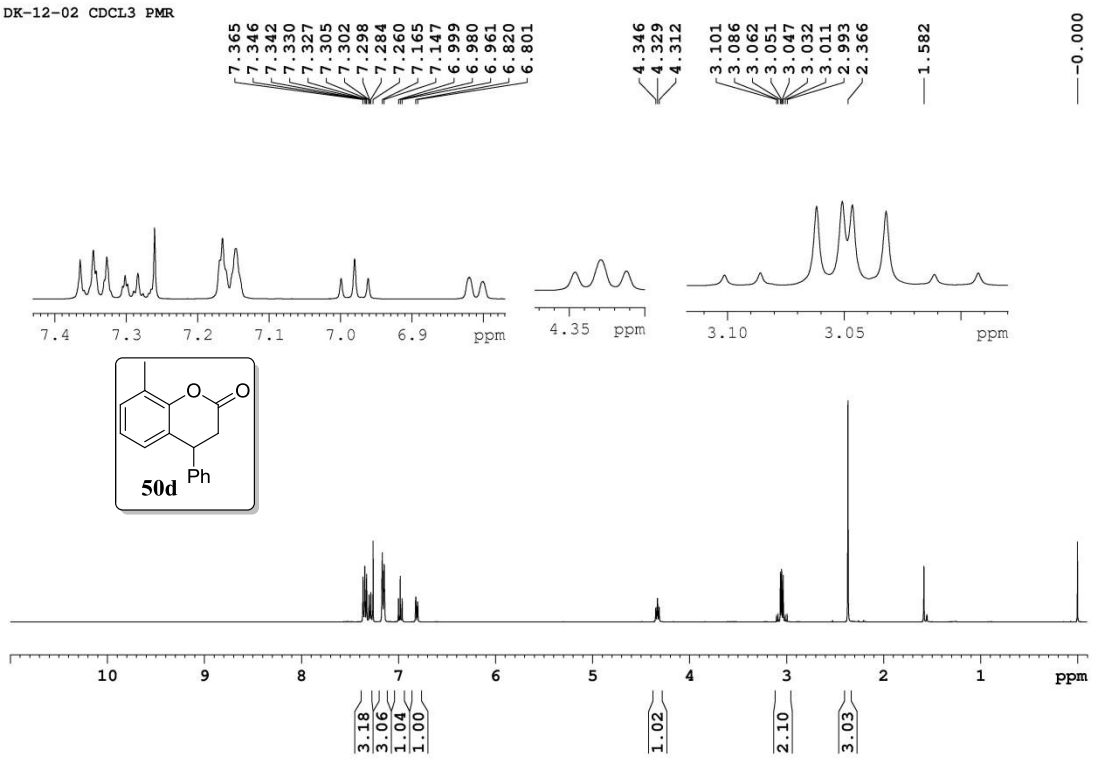
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6.820
6.801
4.346
4.329
4.312
3.101
3.086
3.062
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3.047
3.032
3.011
2.993
2.366
1.582
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7.4 7.3 7.2 7.1 7.0 6.9 ppm
4.35 ppm
3.10 3.05 ppm
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3.06
1.04
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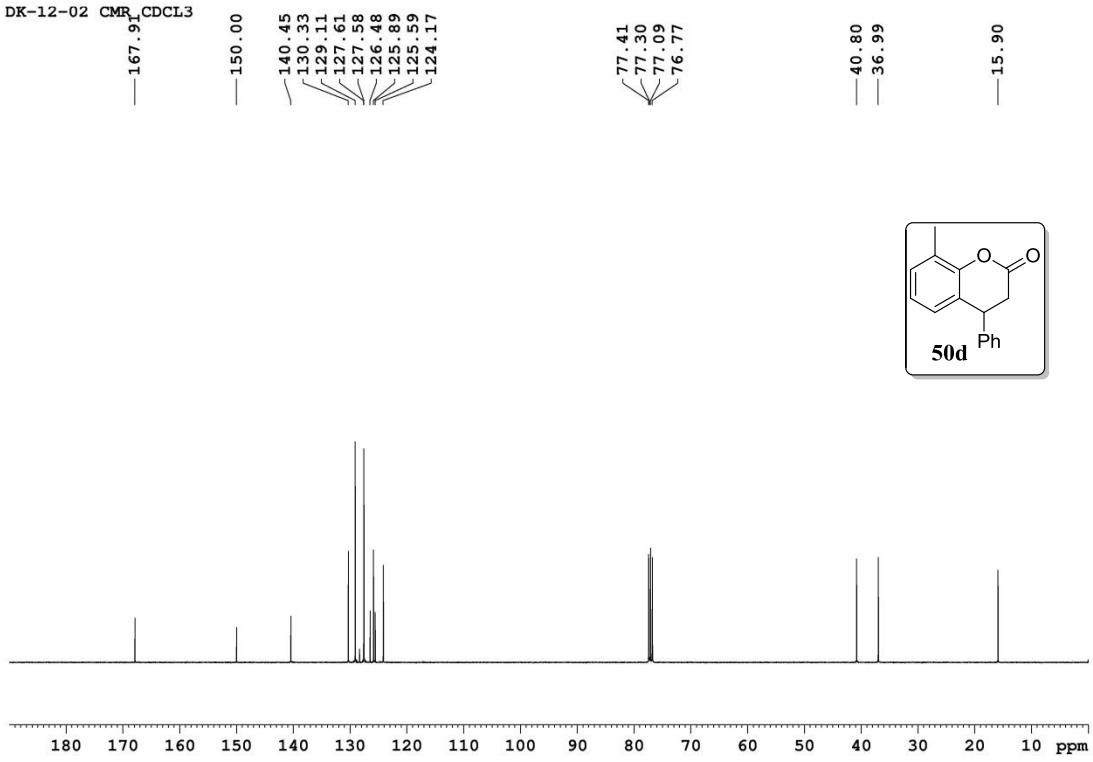
1.02
2.10
3.03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50d
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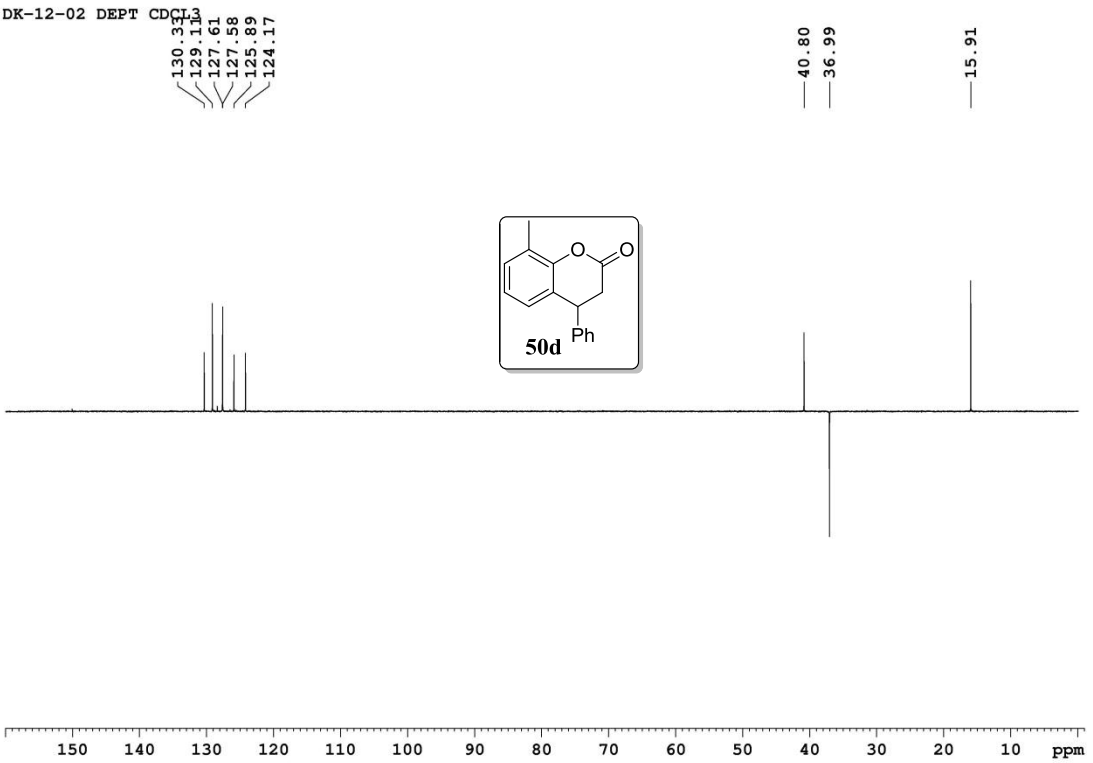
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50d
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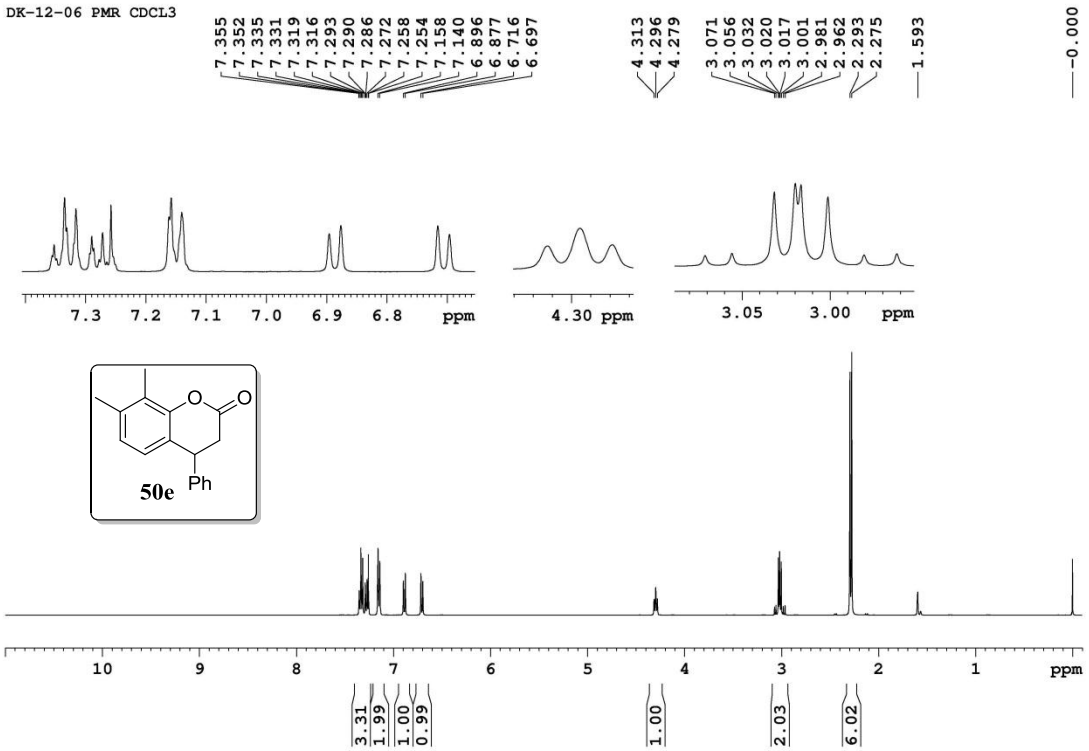
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4.279
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3.056
3.032
3.020
3.017
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2.981
2.962
2.293
2.275
1.593
0.000
7.3 7.2 7.1 7.0 6.9 6.8 ppm
4.30 ppm
3.05 3.00 ppm
O
O
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10 9 8 7 6 5 4 3 2 1 ppm
3.31
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1.00
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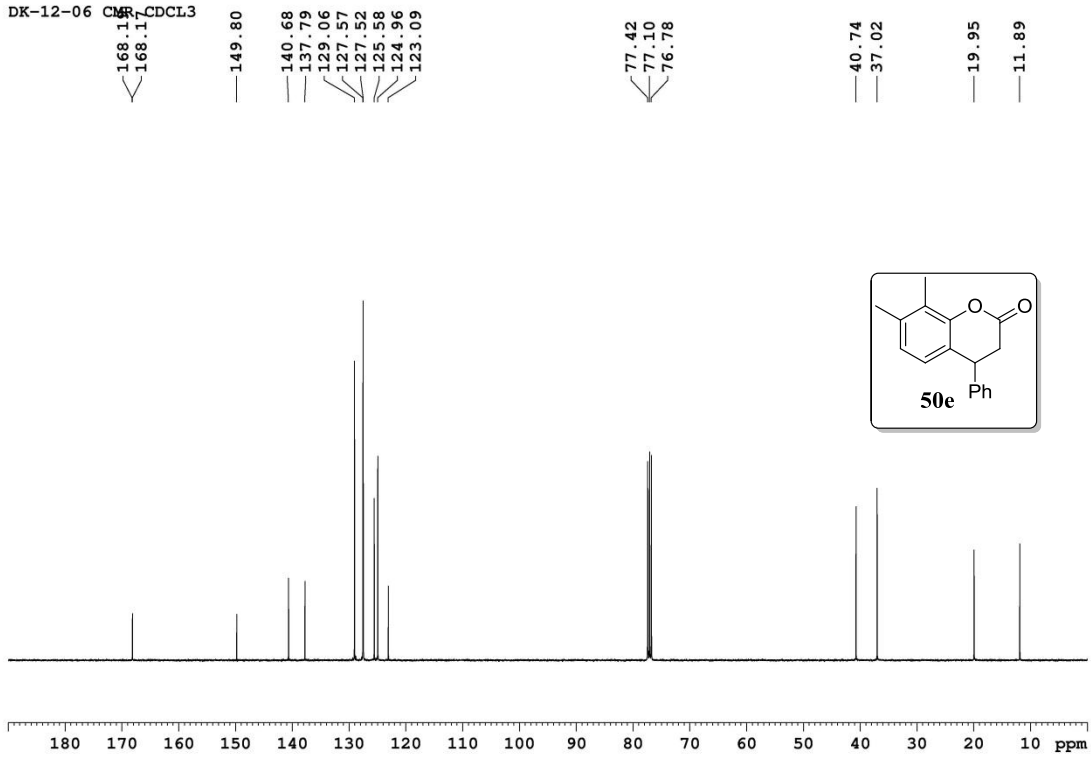
2.03
6.02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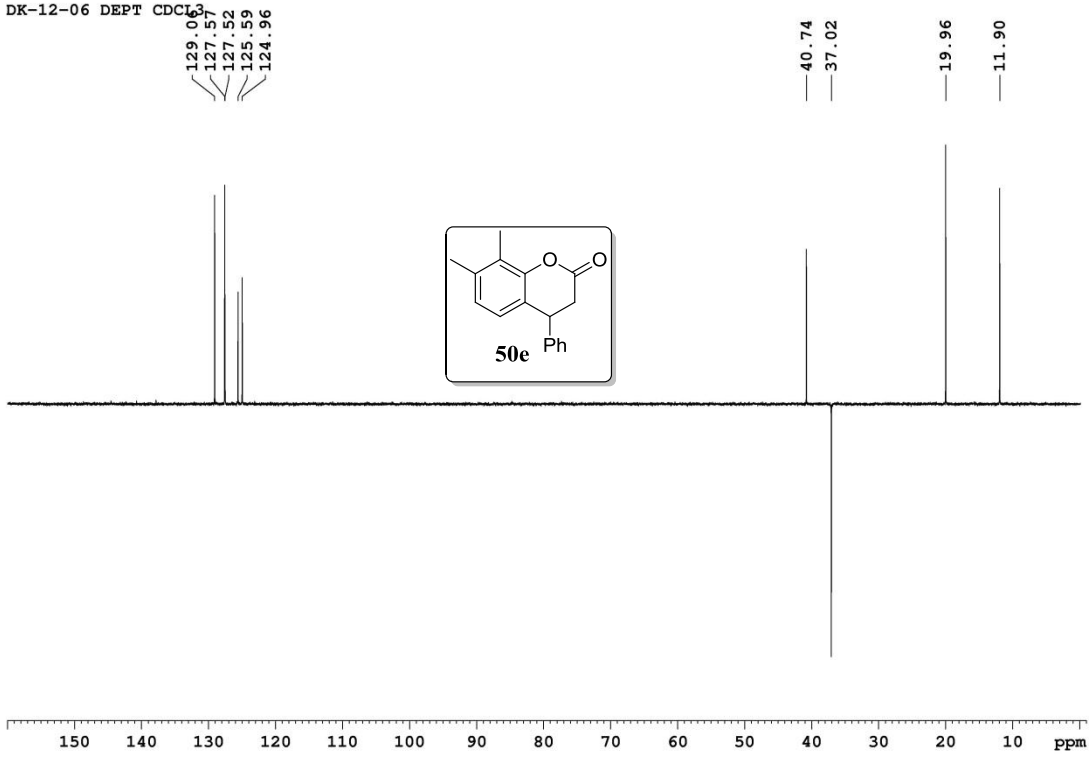
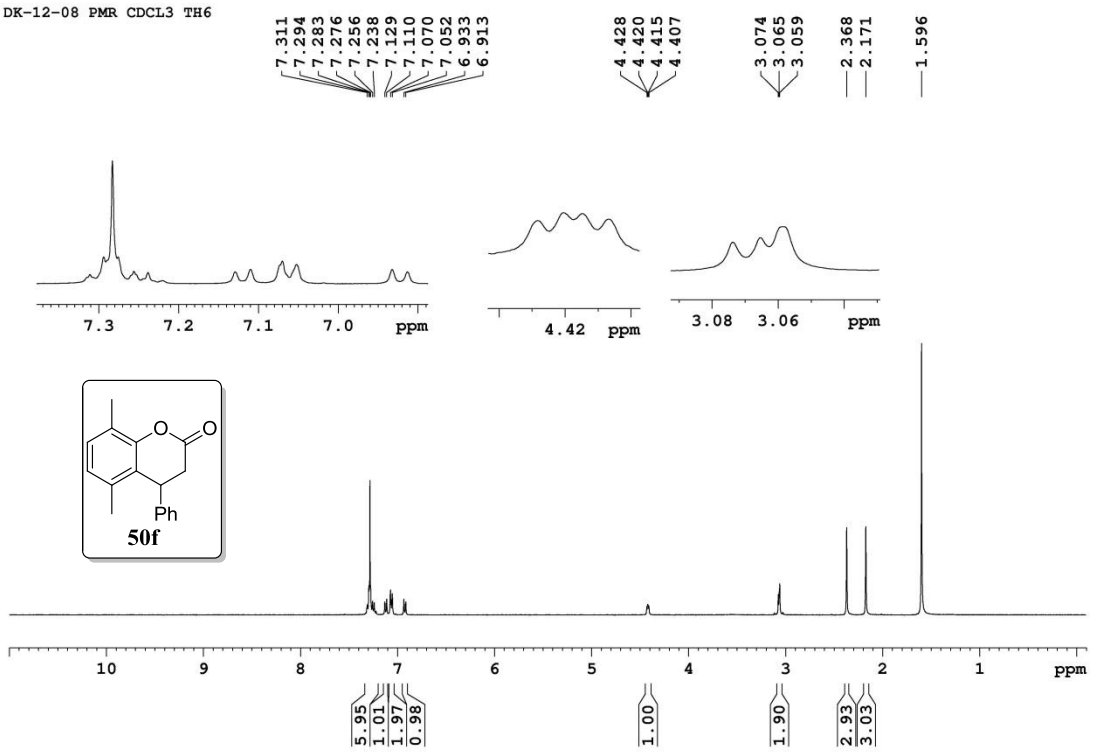
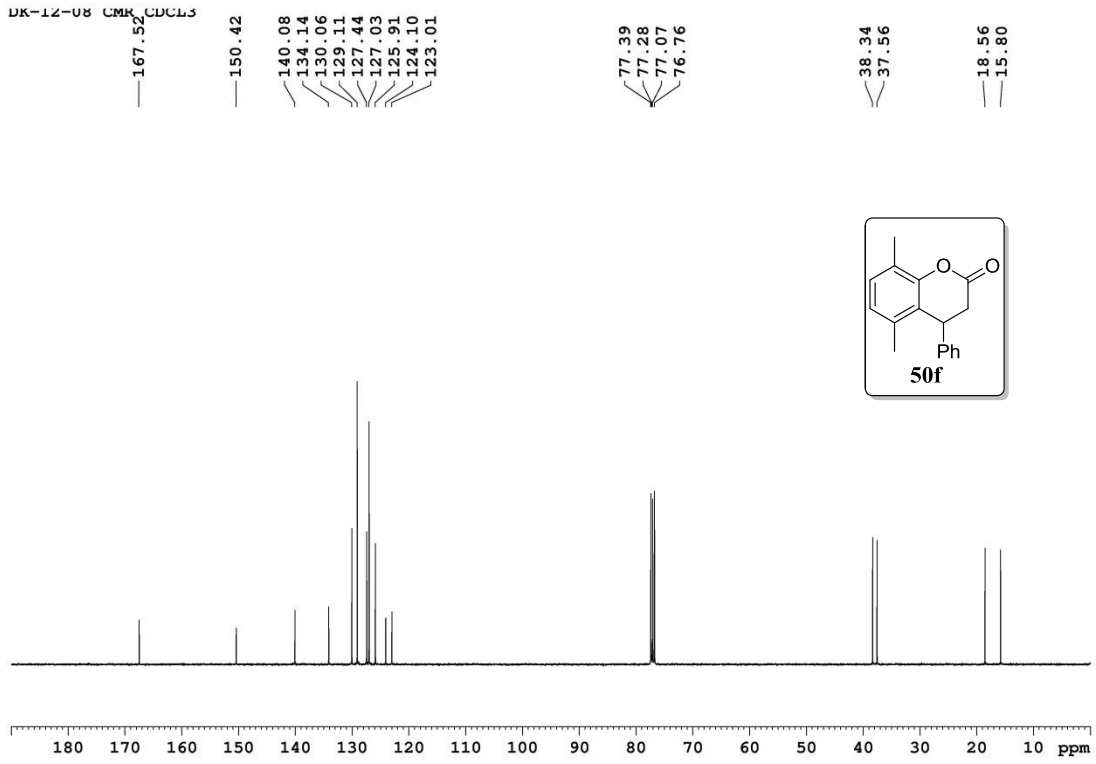
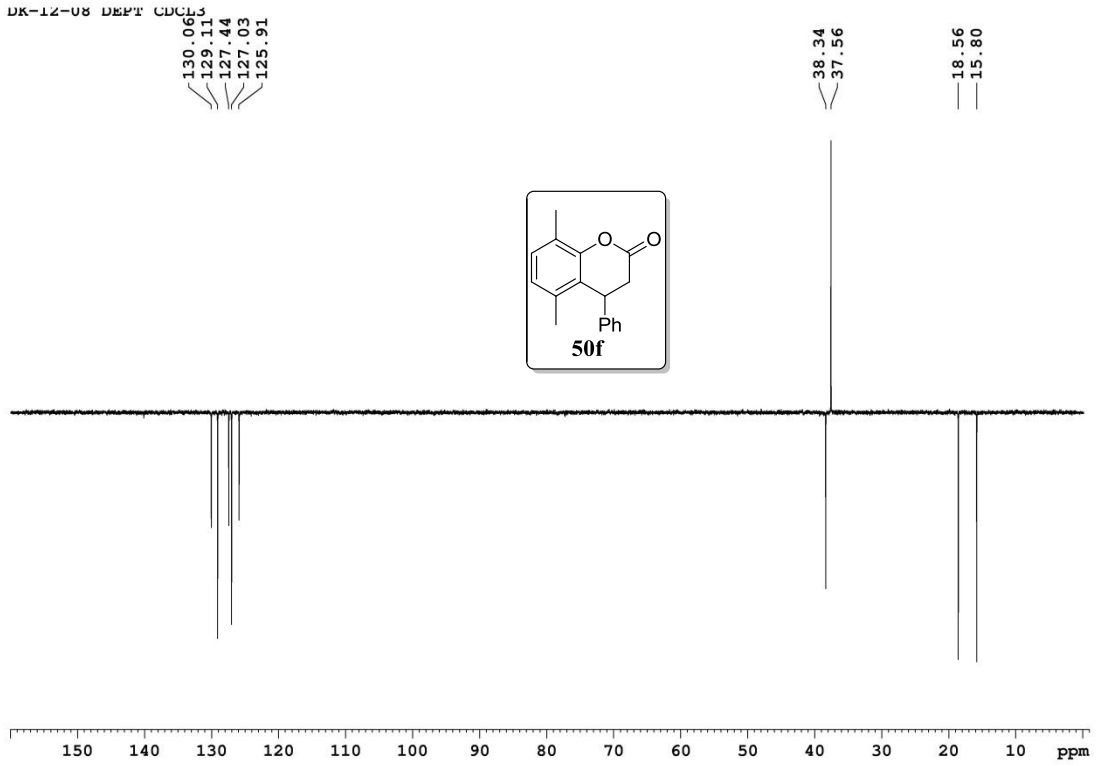
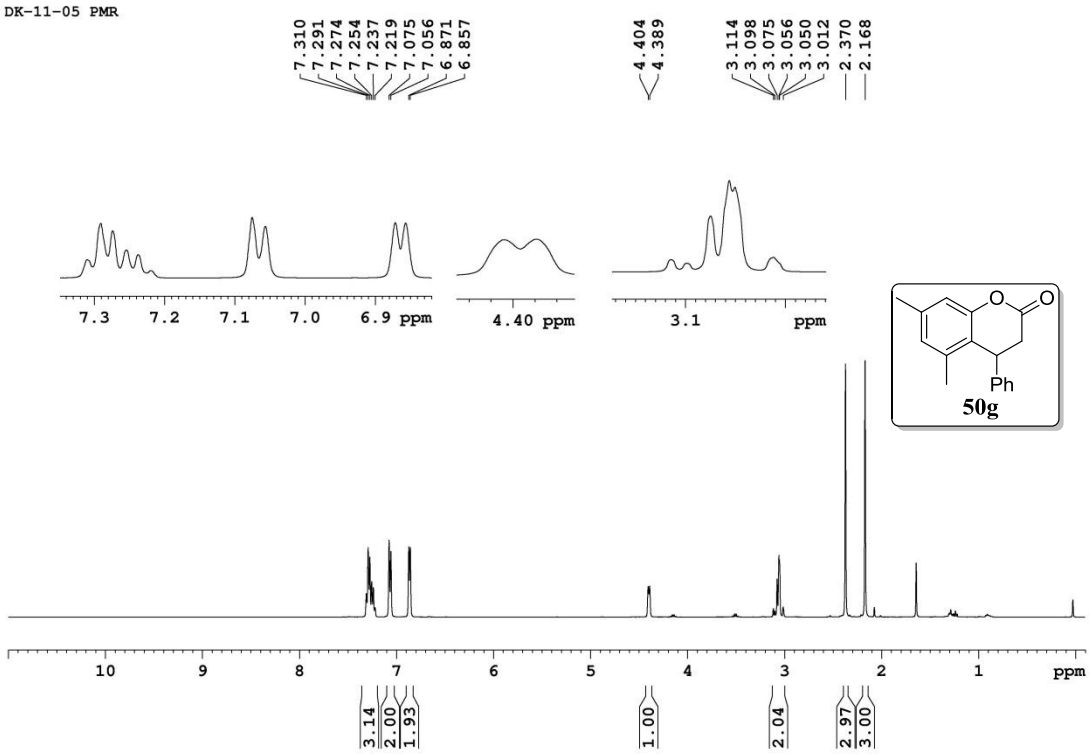
40.74
37.02
19.95
11.89
O
O
Ph
50e
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

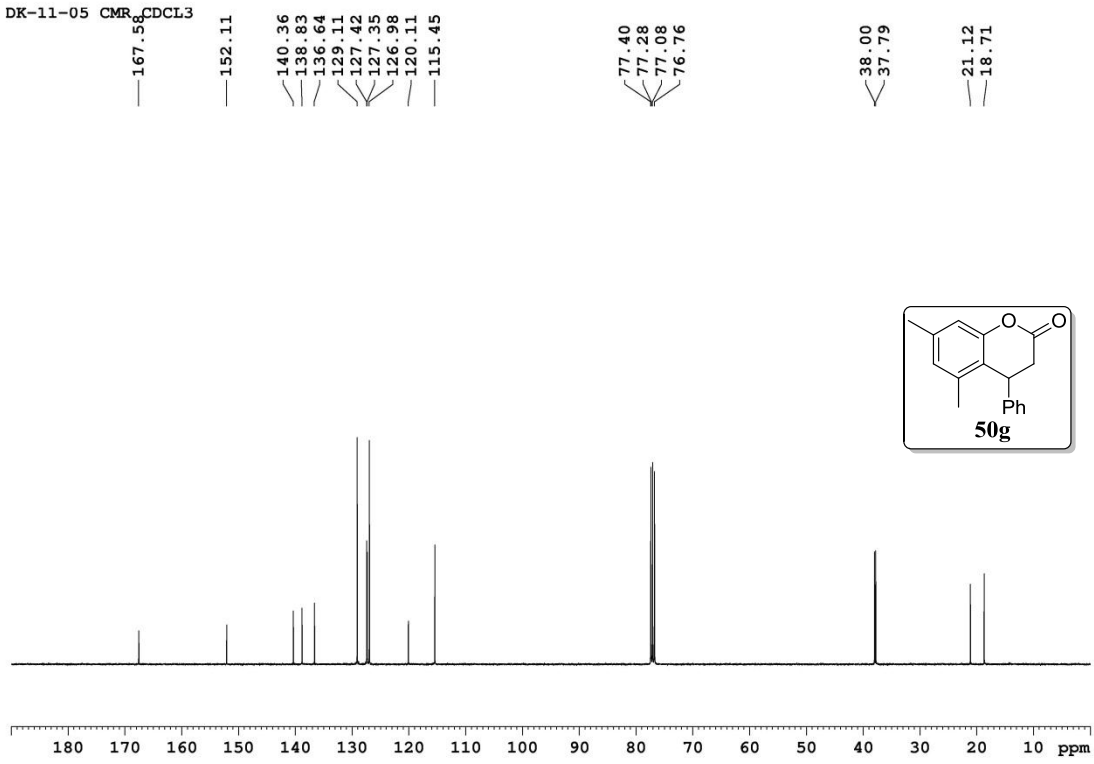

DK-12-06 DEPT CDCL3
129.05
127.57
127.52
125.59
124.96
40.74
37.02
19.96
11.90
50e
Ph
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

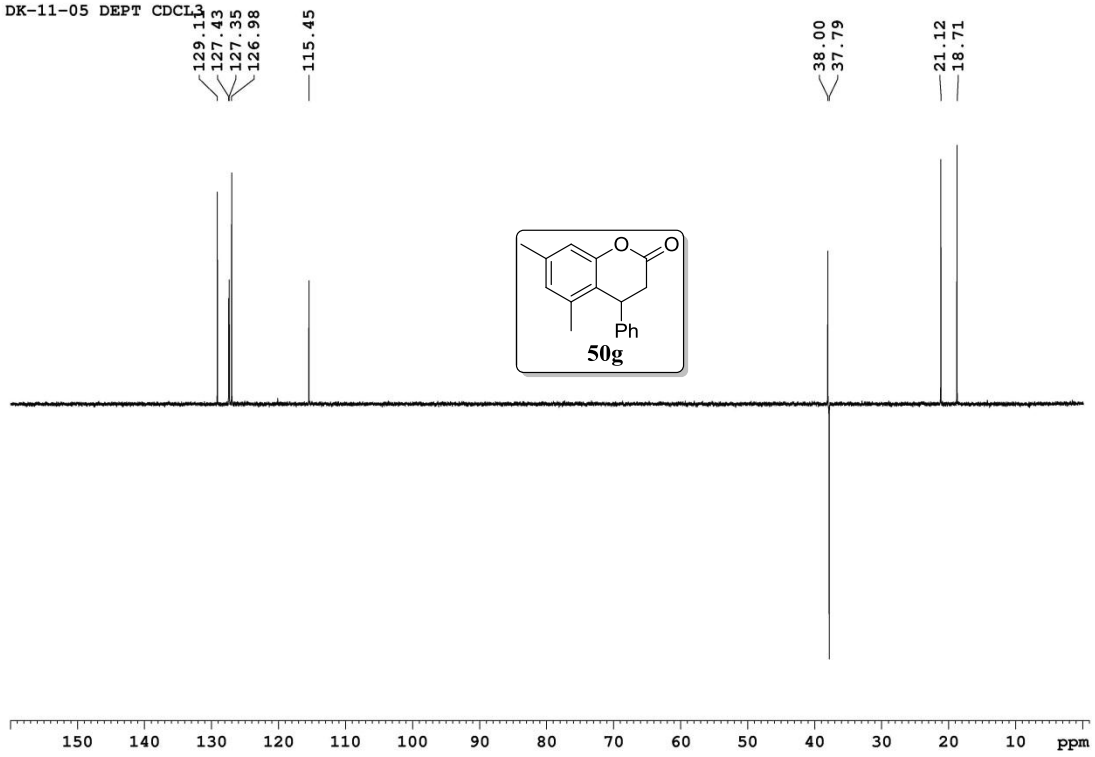

DK-12-08 PMR CDCL3 TH6
7.311
7.294
7.283
7.276
7.256
7.238
7.129
7.110
7.070
7.052
6.933
6.913
4.428
4.420
4.415
4.407
3.074
3.065
3.059
2.368
2.171
1.596
7.3 7.2 7.1 7.0 ppm
4.42 ppm
3.08 3.06 ppm
50f
Ph
10 9 8 7 6 5 4 3 2 1 ppm
5.95
1.01
1.97
0.98
1.00
1.90
2.93
3.03

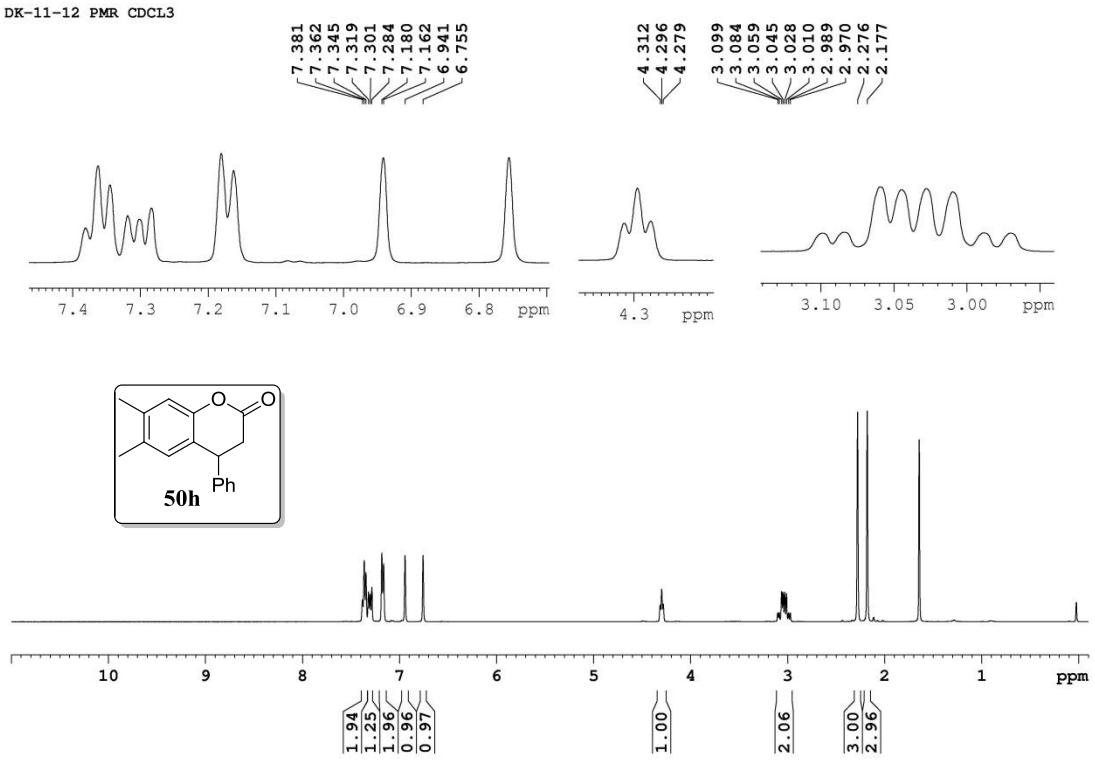

DK-12-08 CMR CDCL3
167.52
150.42
140.08
134.14
130.06
129.11
127.44
127.03
125.91
124.10
123.01
77.39
77.28
77.07
76.76
38.34
37.56
18.56
15.80
O
O
Ph
50f
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

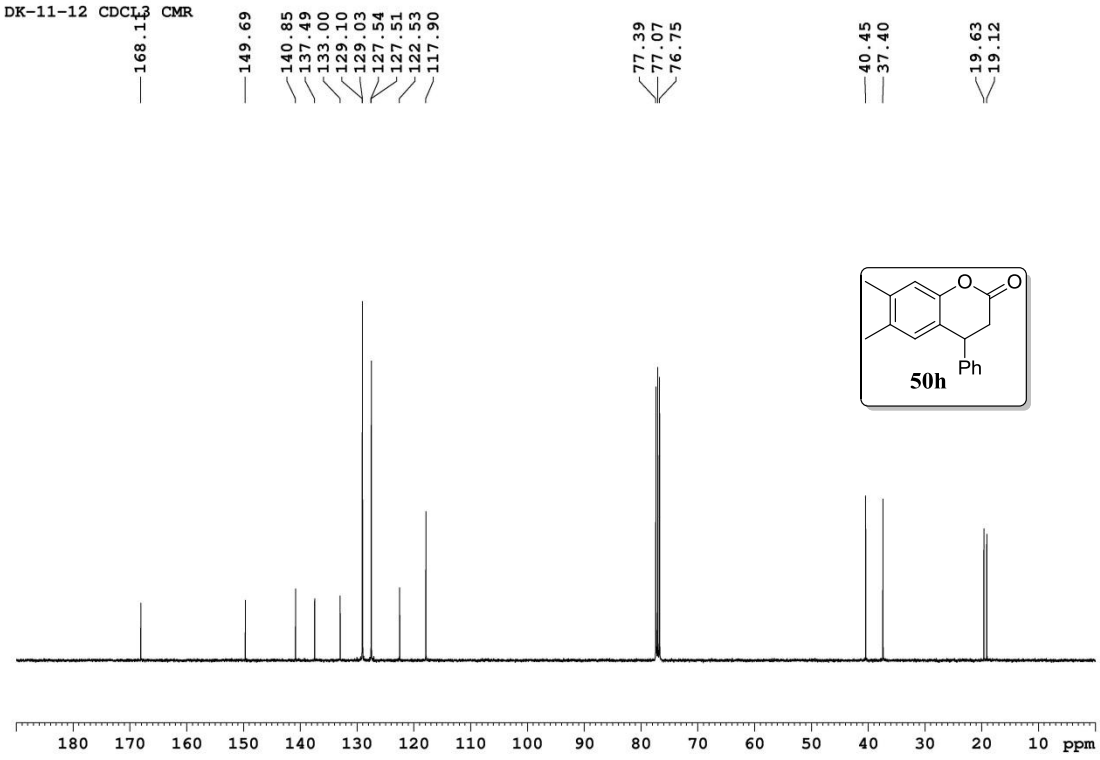

DK-12-08 DEPT CDCL3
130.06
129.11
127.44
127.03
125.91
38.34
37.56
18.56
15.80
O
O
Ph
50f
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

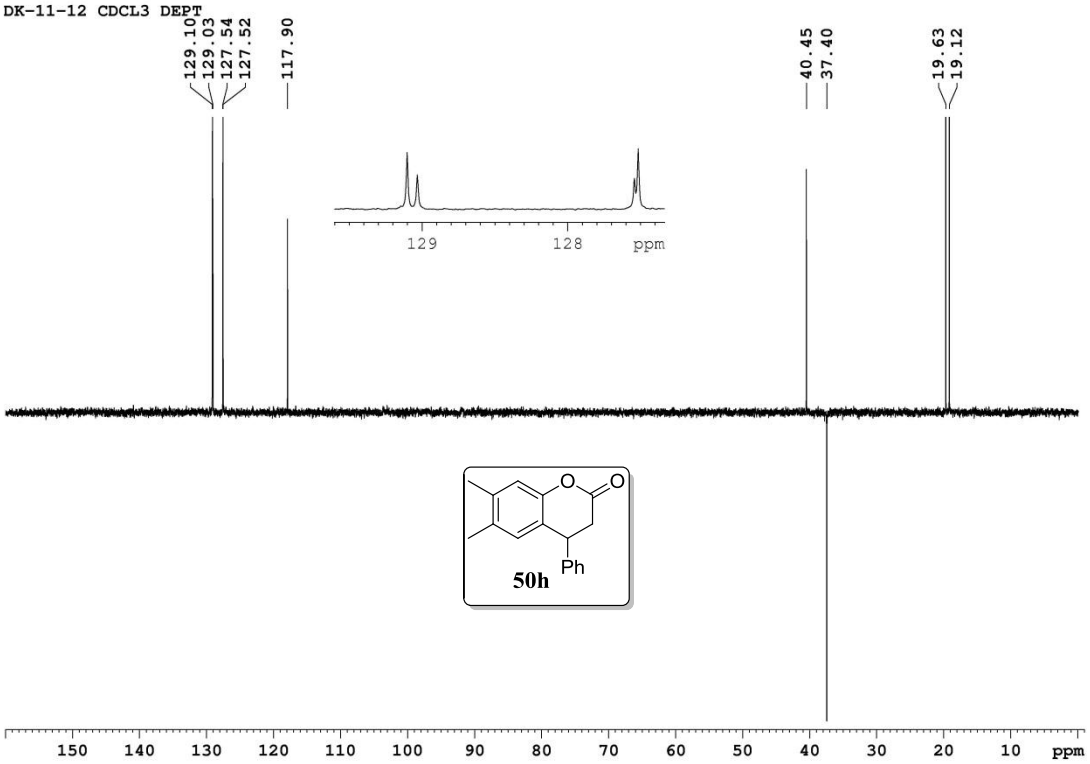

DK-11-05 PMR
7.310
7.291
7.274
7.254
7.237
7.219
7.075
7.056
6.871
6.857
4.404
4.389
3.114
3.098
3.075
3.056
3.050
3.012
2.370
2.168
7.3
7.2
7.1
7.0
6.9 ppm
4.40 ppm
3.1
ppm
O
O
Ph
50g
10
9
8
7
6
5
4
3
2
1
ppm
3.14
2.00
1.93
1.00
2.04
2.97
3.00

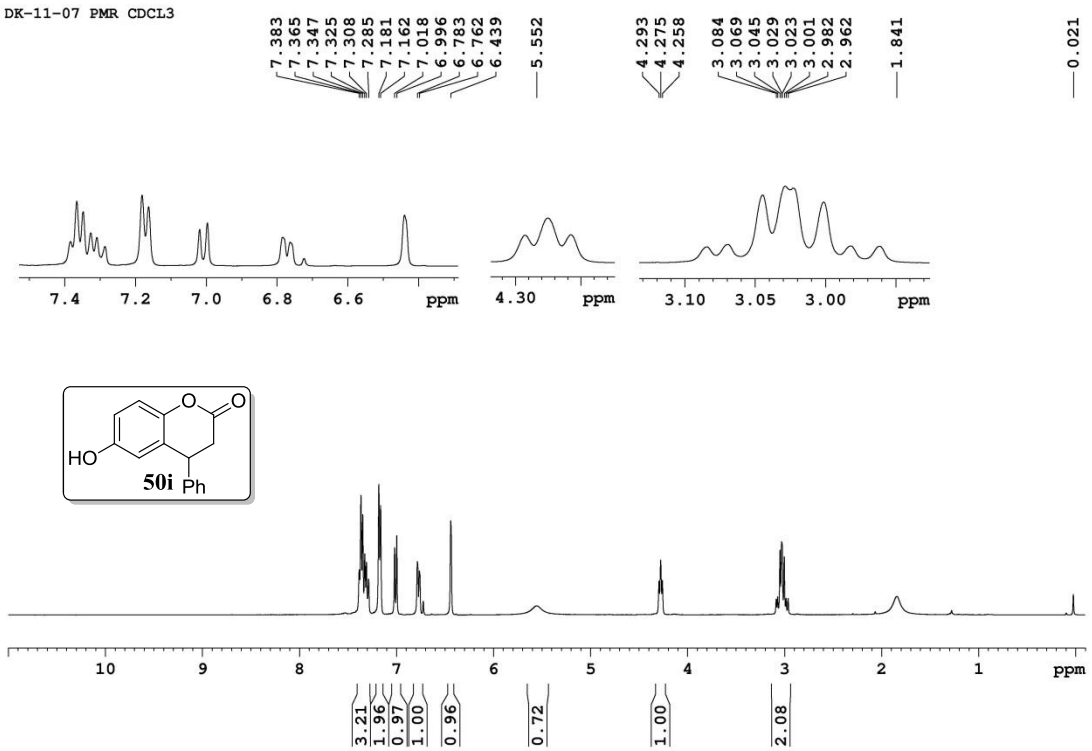

DK-11-05 CMR_CDCL3
167.58
152.11
140.36
138.83
136.64
129.11
127.42
127.35
126.98
120.11
115.45
77.40
77.28
77.08
76.76
38.00
37.79
21.12
18.71
O
O
Ph
50g
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

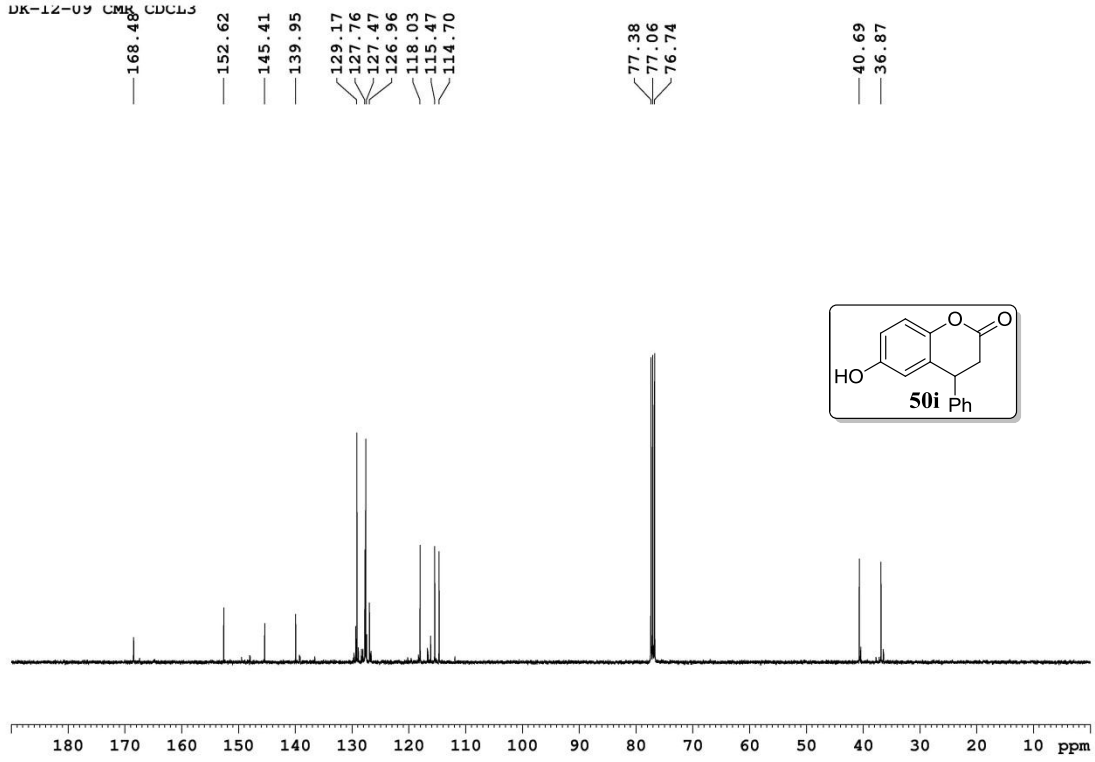

DK-11-05 DEPT CDCL3
129.11
127.43
127.35
126.98
115.45
38.00
37.79
21.12
18.71
O
O
Ph
50g
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

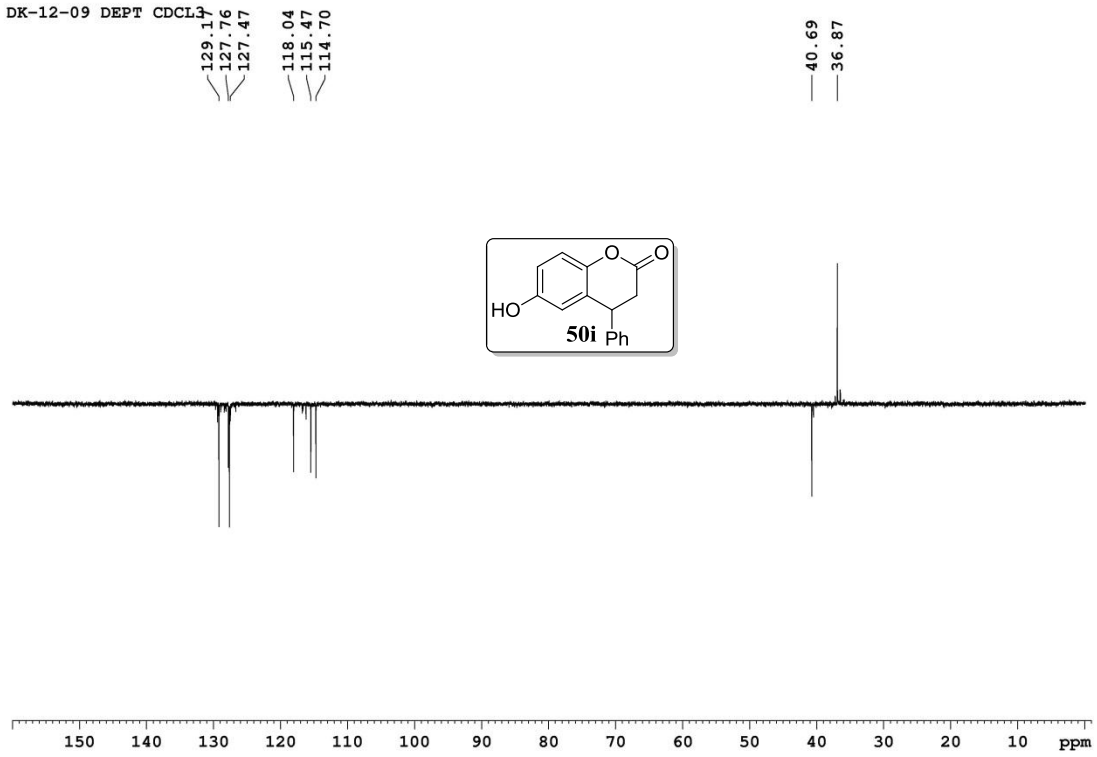

DK-11-12 PMR CDCL3
7.381
7.362
7.345
7.319
7.301
7.284
7.180
7.162
6.941
6.755
4.312
4.296
4.279
3.099
3.084
3.059
3.045
3.028
3.010
2.989
2.970
2.276
2.177
7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm
4.3 ppm
3.10 3.05 3.00 ppm
O
O
Ph
50h
10 9 8 7 6 5 4 3 2 1 ppm
1.94
1.25
1.96
0.96
0.97
1.00
2.06
3.00
2.96

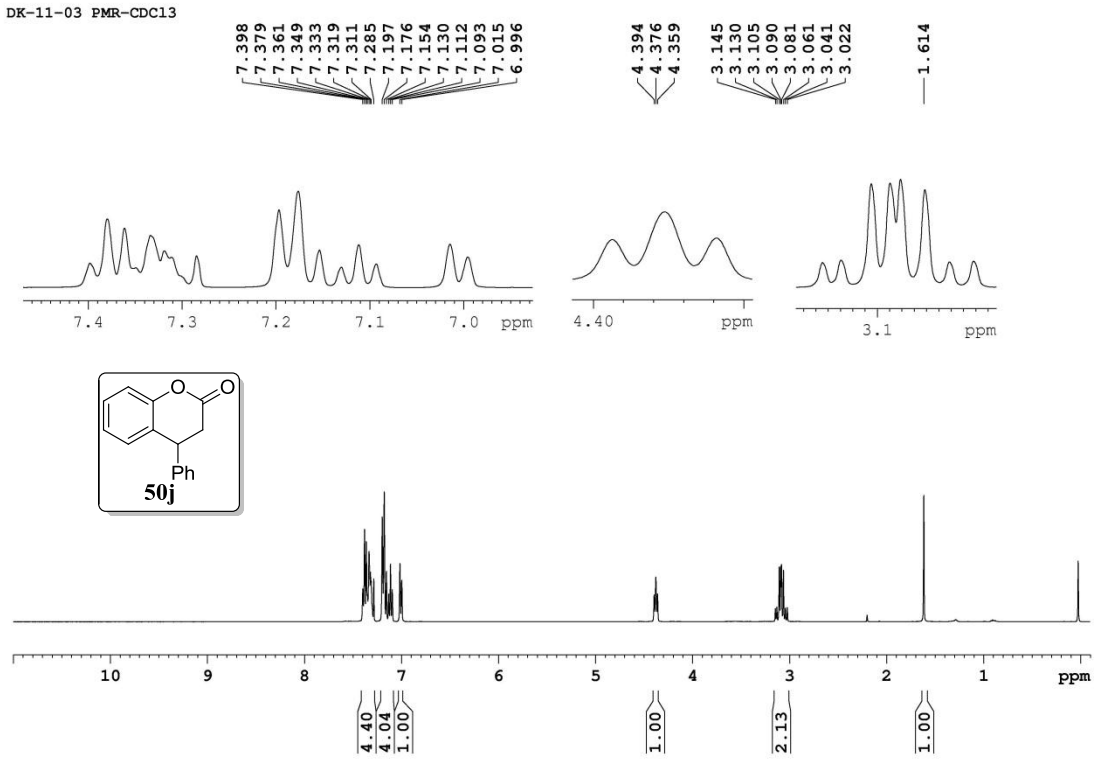

DK-11-12 CDCL3 CMR
168.11
149.69
140.85
137.49
133.00
129.10
129.03
127.54
127.51
122.53
117.90
77.39
77.07
76.75
40.45
37.40
19.63
19.12
O
O
Ph
50h
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

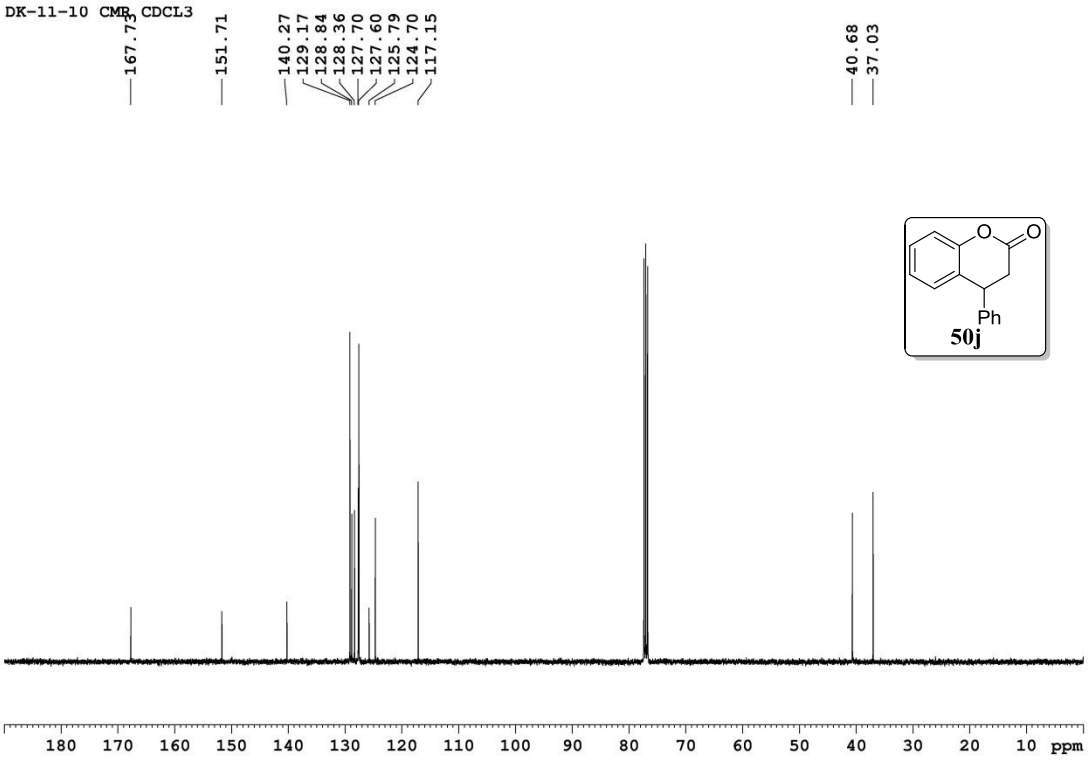

DK-11-12 CDCL3 DEPT
129.10
129.03
127.54
127.52
117.90
40.45
37.40
19.63
19.12
129
128
ppm
O
O
Ph
50h
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

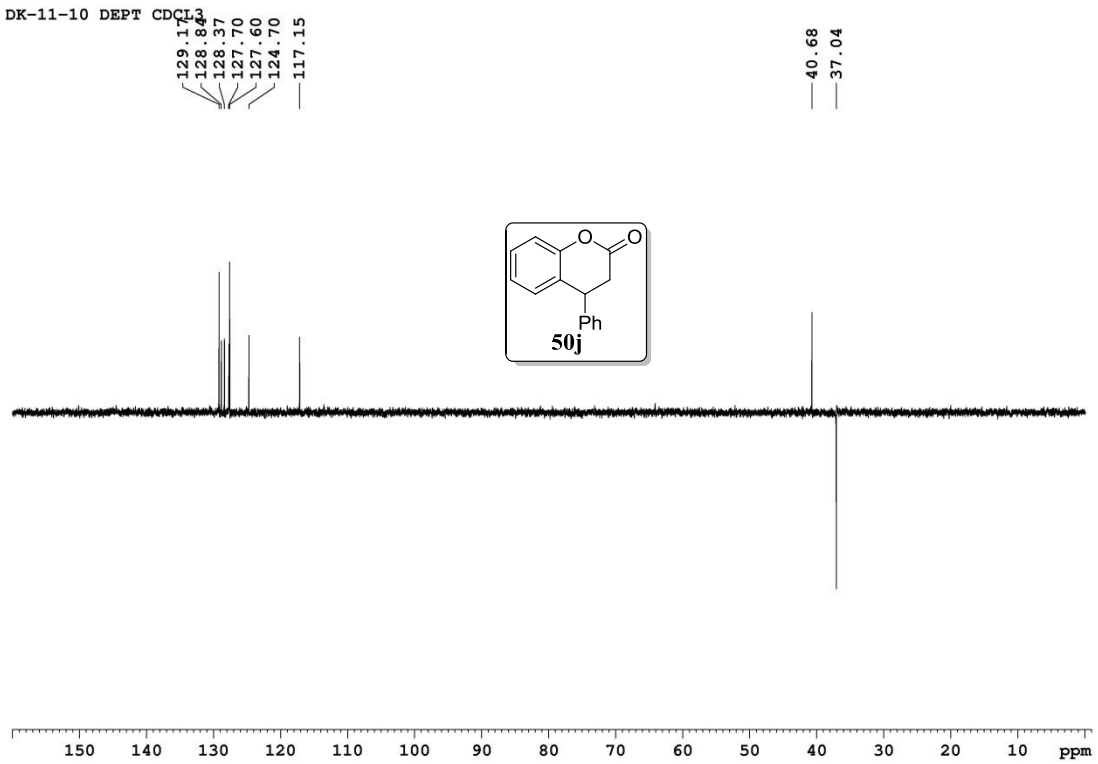

DK-11-07 PMR CDCL3
7.383
7.365
7.347
7.325
7.308
7.285
7.181
7.162
7.018
6.996
6.783
6.762
6.439
5.552
4.293
4.275
4.258
3.084
3.069
3.045
3.029
3.023
3.001
2.982
2.962
1.841
0.021
7.4
7.2
7.0
6.8
6.6
ppm
4.30
ppm
3.10
3.05
3.00
ppm
HO
O
O
50i Ph
10
9
8
7
6
5
4
3
2
1
ppm
3.21
1.96
0.97
1.00
0.96
0.72
1.00
2.08

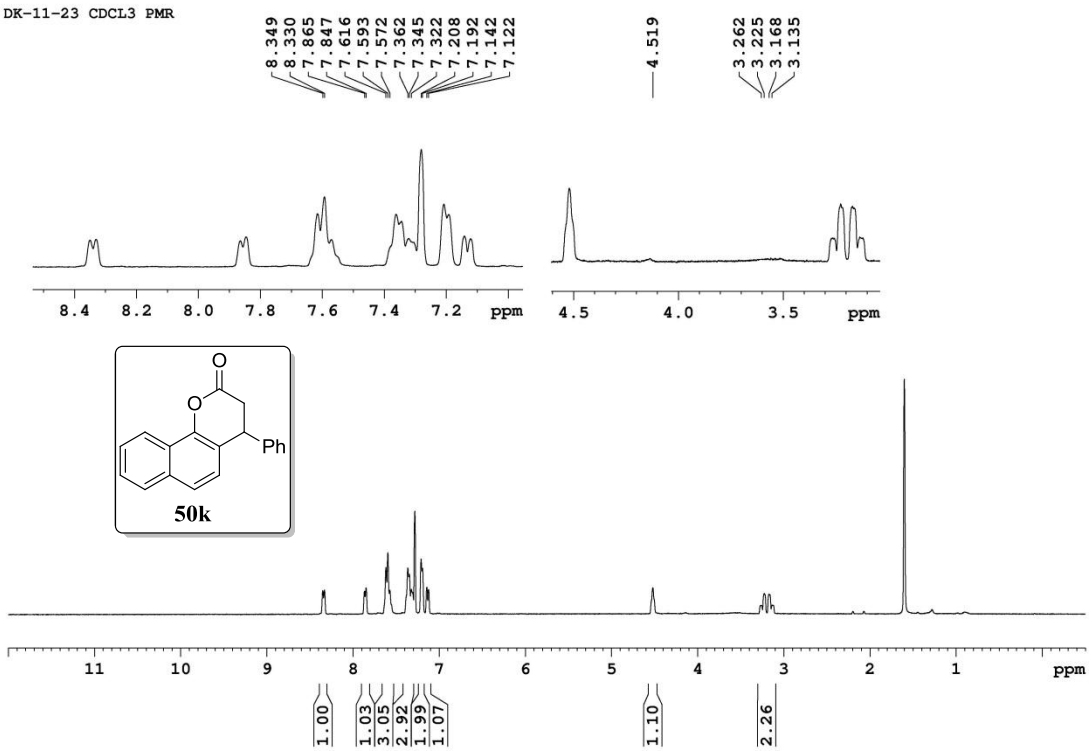

DK-12-09 CMR CDCL3
168.48
152.62
145.41
139.95
129.17
127.76
127.47
126.96
118.03
115.47
114.70
77.38
77.06
76.74
40.69
36.87
HO
O
O
50i Ph
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

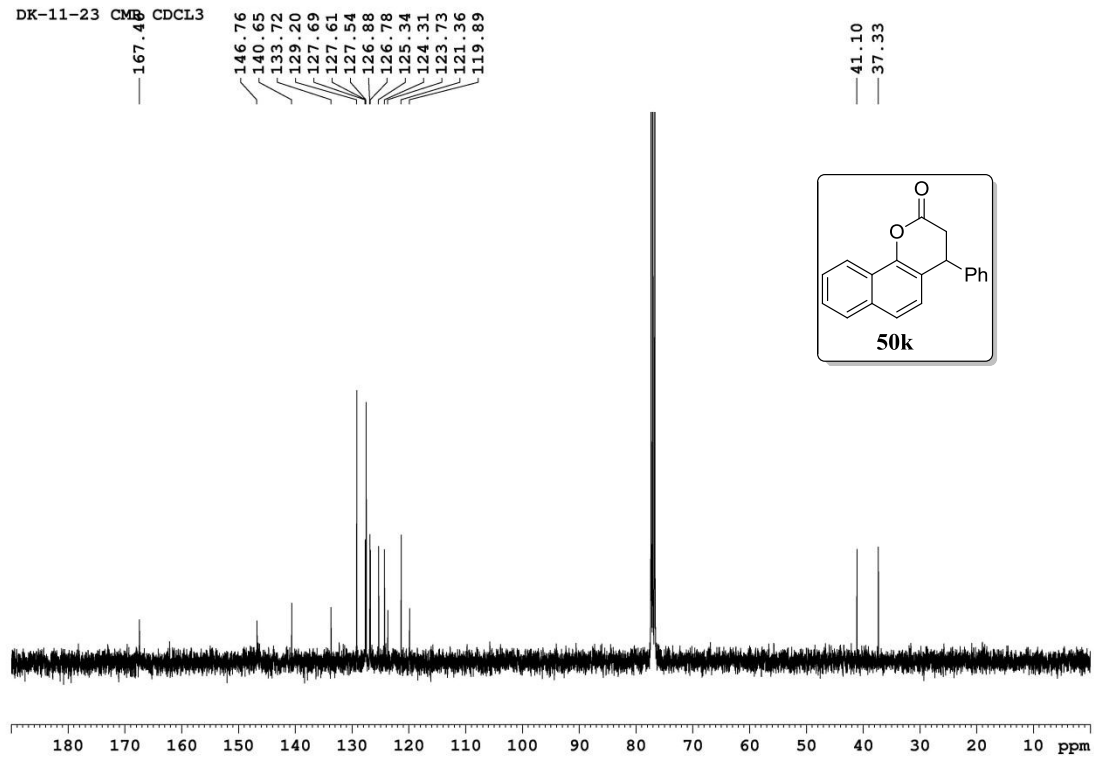

DK-12-09 DEPT CDCL3
129.17
127.76
127.47
118.04
115.47
114.70
40.69
36.87
HO
O
O
50i Ph
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

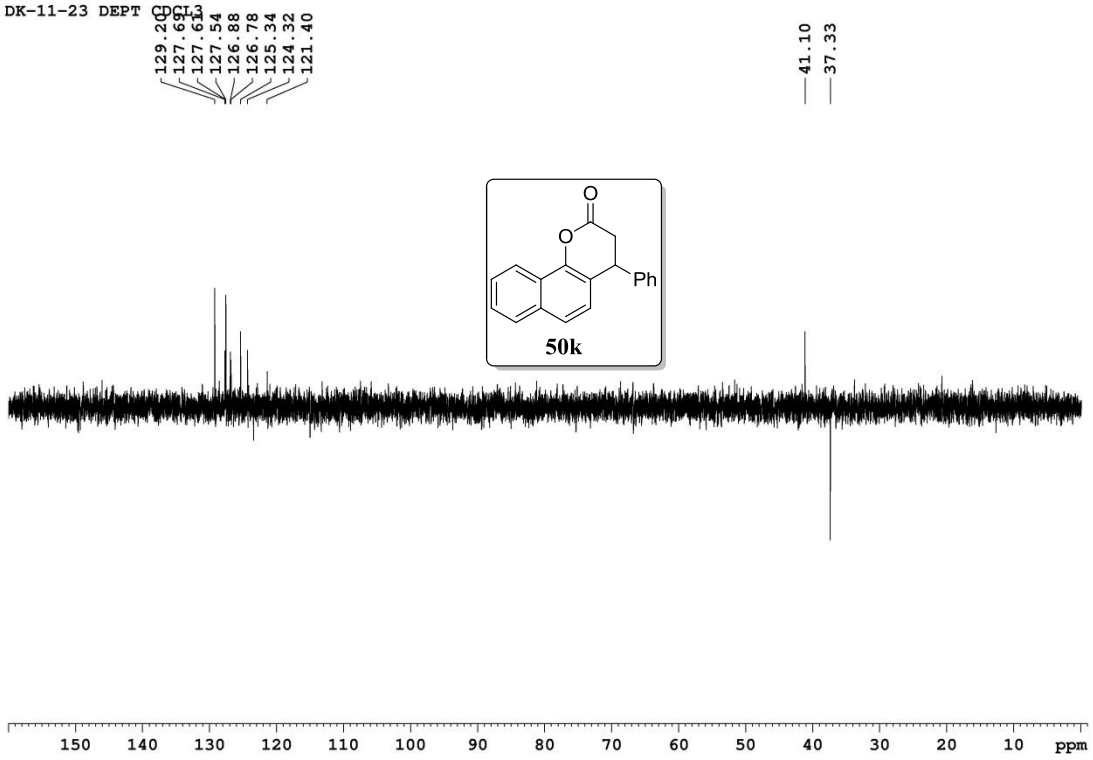

DK-11-03 PMR-CDCl3
7.398
7.379
7.361
7.349
7.333
7.319
7.311
7.285
7.197
7.176
7.154
7.130
7.112
7.093
7.015
6.996
4.394
4.376
4.359
3.145
3.130
3.105
3.090
3.081
3.061
3.041
3.022
1.614
7.4 7.3 7.2 7.1 7.0 ppm
4.40 ppm
3.1 ppm
O
O
Ph
50j
10 9 8 7 6 5 4 3 2 1 ppm
4.40
4.04
1.00
1.00
2.13
1.00

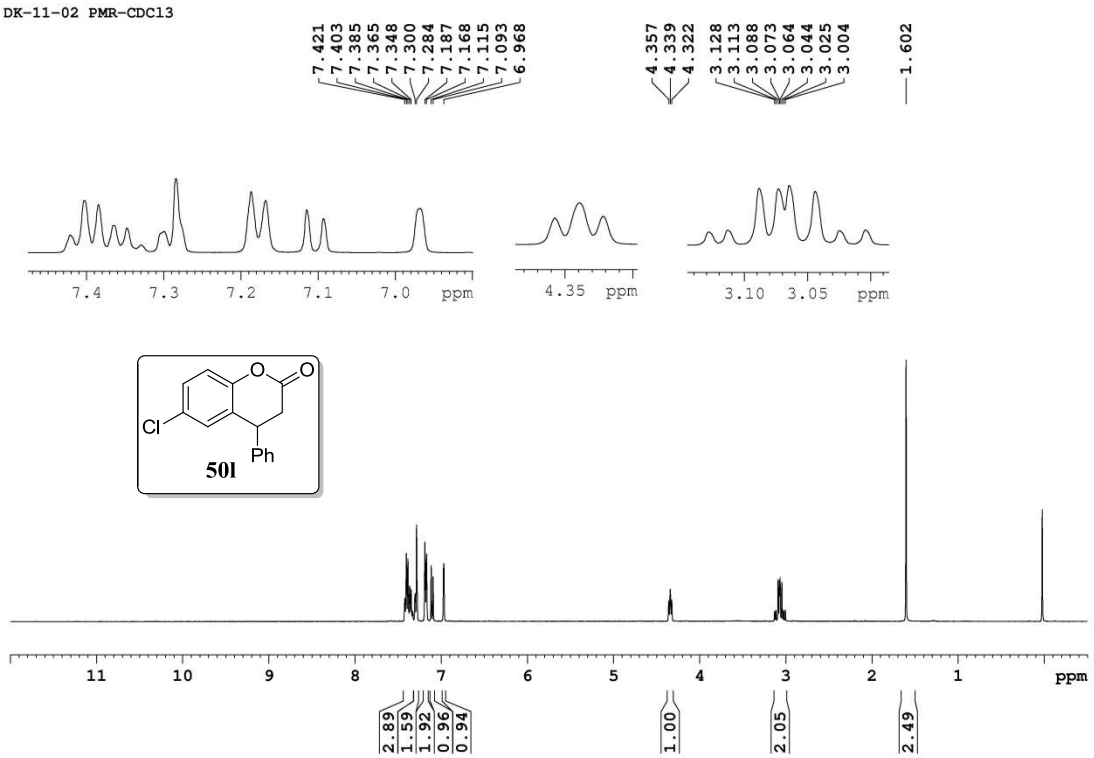

DK-11-10 CMR CDCL3
167.73
151.71
140.27
129.17
128.84
128.36
127.70
127.60
125.79
124.70
117.15
40.68
37.03
O
O
Ph
50j
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

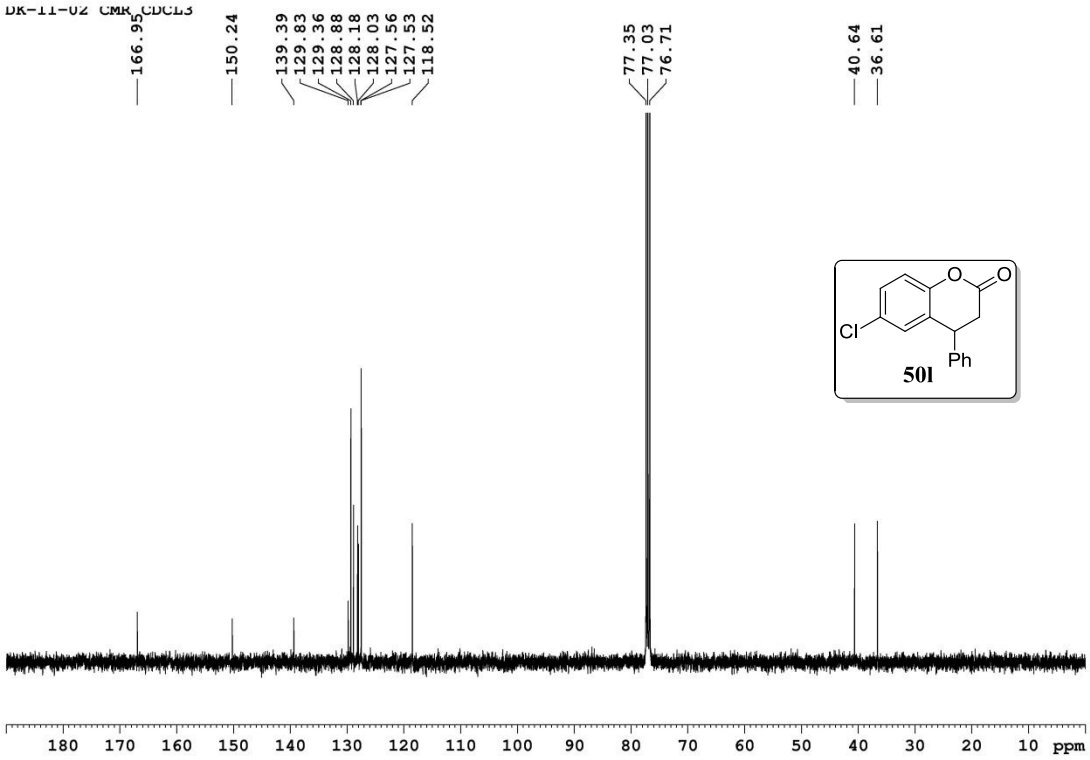

DK-11-10 DEPT CDCL3
129.17
128.84
128.37
127.70
127.60
124.70
117.15
40.68
37.04
O
O
Ph
50j
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

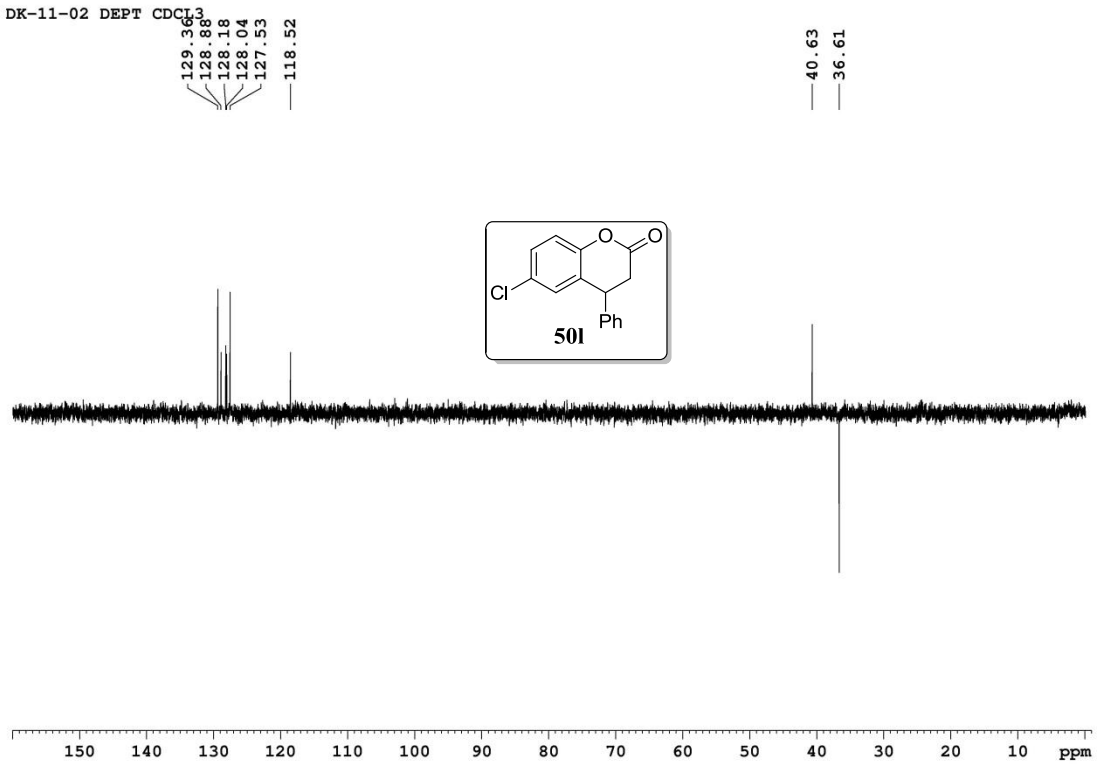

DK-11-23 CDCL3 PMR
8.349
8.330
7.865
7.847
7.616
7.593
7.572
7.362
7.345
7.322
7.208
7.192
7.142
7.122
4.519
3.262
3.225
3.168
3.135
8.4
8.2
8.0
7.8
7.6
7.4
7.2
ppm
4.5
4.0
3.5
ppm
O
O
Ph
50k
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
3.05
2.92
1.99
1.07
1.10
2.26

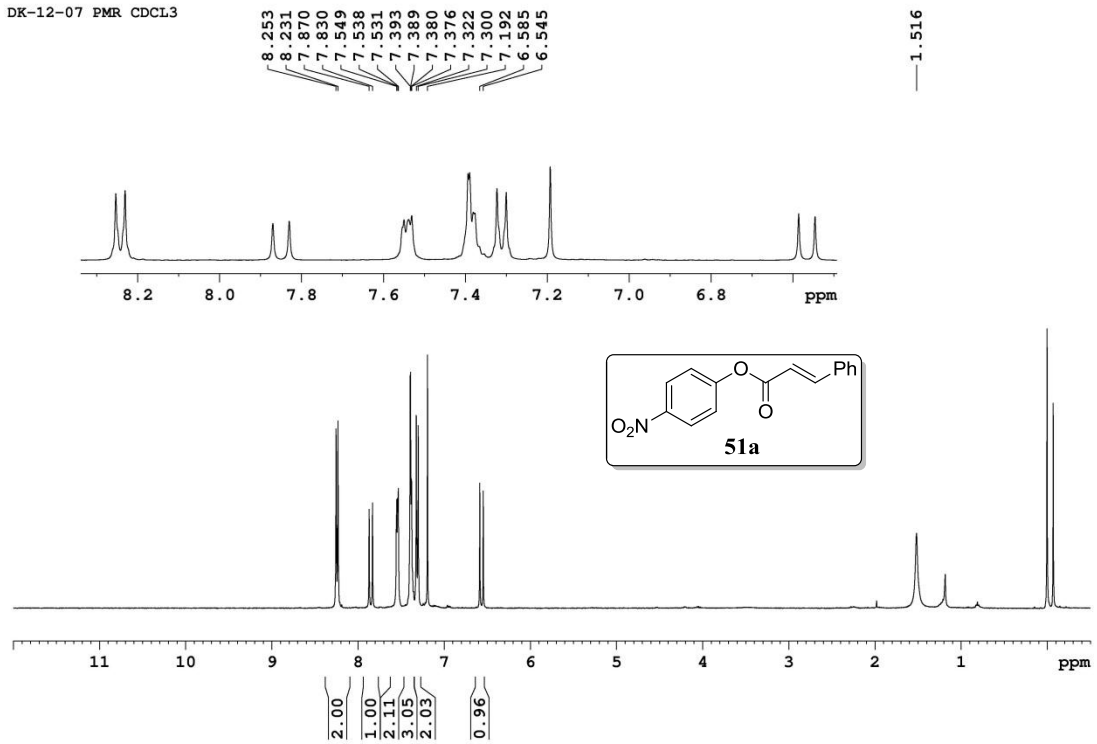

DK-11-23 CMR CDCL3
167.48
146.76
140.65
133.72
129.20
127.69
127.61
127.54
126.88
126.78
125.34
124.31
123.73
121.36
119.89
41.10
37.33
O
O
Ph
50k
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

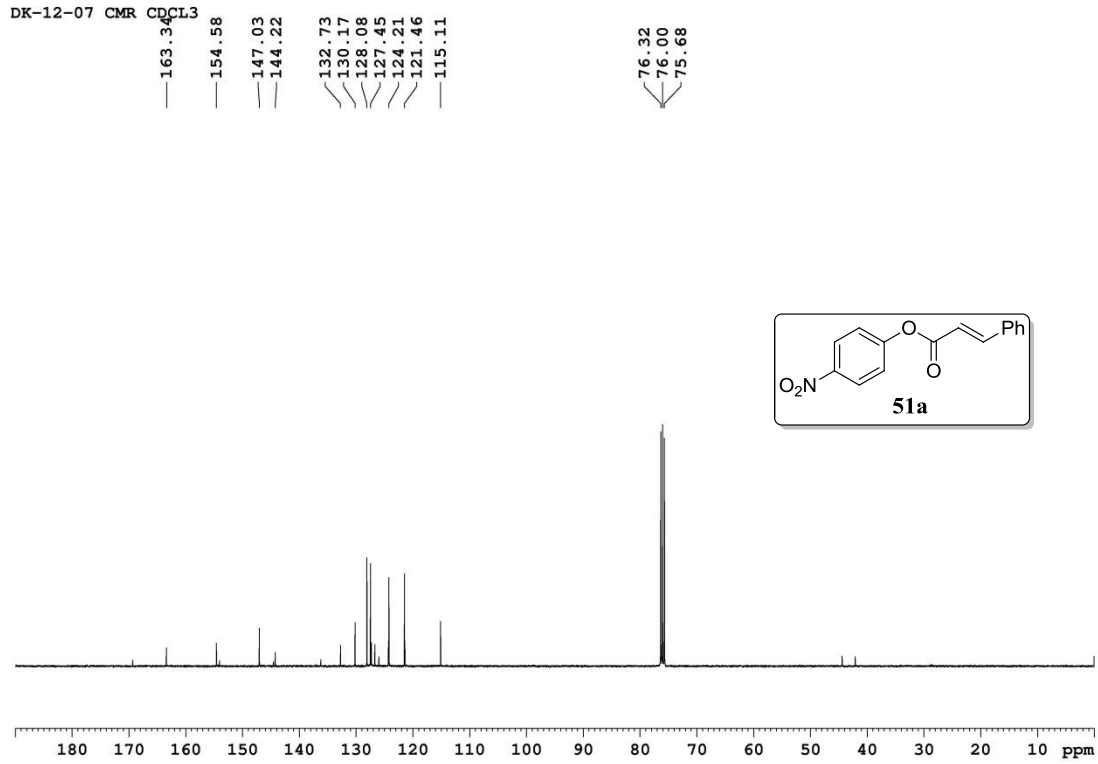

DK-11-23 DEPT CDCL3
129.20
127.61
127.54
126.88
126.78
125.34
124.32
121.40
41.10
37.33
O
O
Ph
50k
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

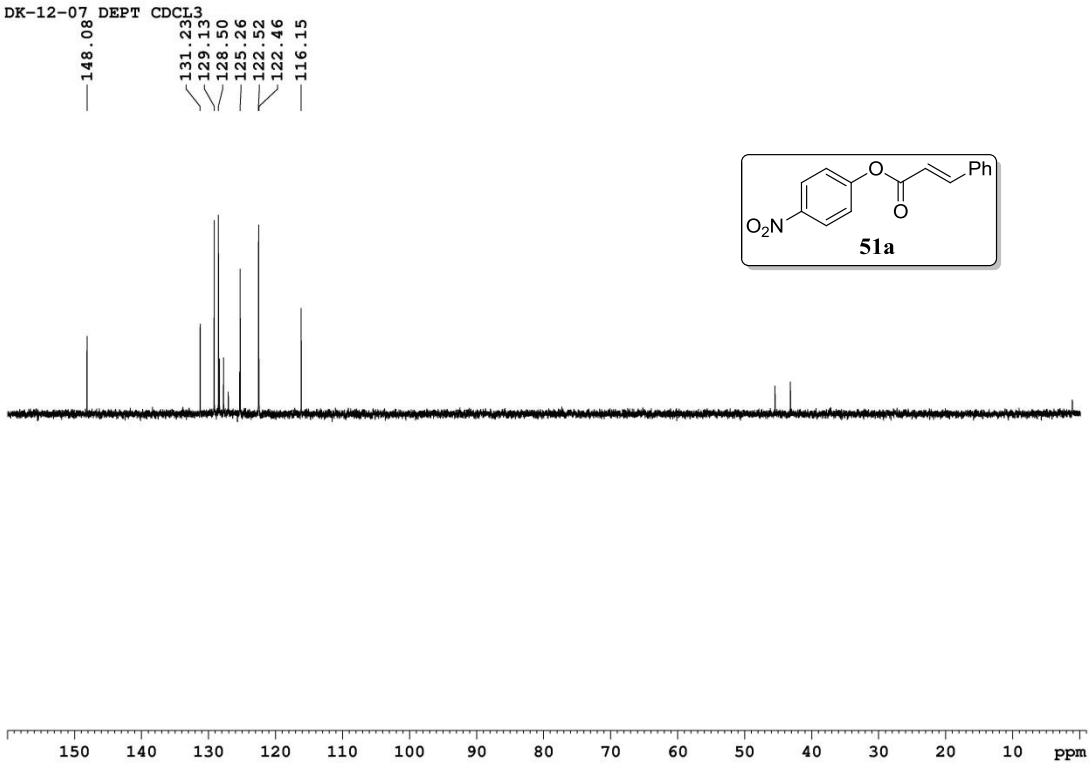

DK-11-02 PMR-CDCl3
7.421
7.403
7.385
7.365
7.348
7.300
7.284
7.187
7.168
7.115
7.093
6.968
4.357
4.339
4.322
3.128
3.113
3.088
3.073
3.064
3.044
3.025
3.004
1.602
7.4 7.3 7.2 7.1 7.0 ppm
4.35 ppm
3.10 3.05 ppm
O
O
Cl
Ph
50l
11 10 9 8 7 6 5 4 3 2 1 ppm
2.89
1.59
1.92
0.96
0.94
1.00
2.05
2.49

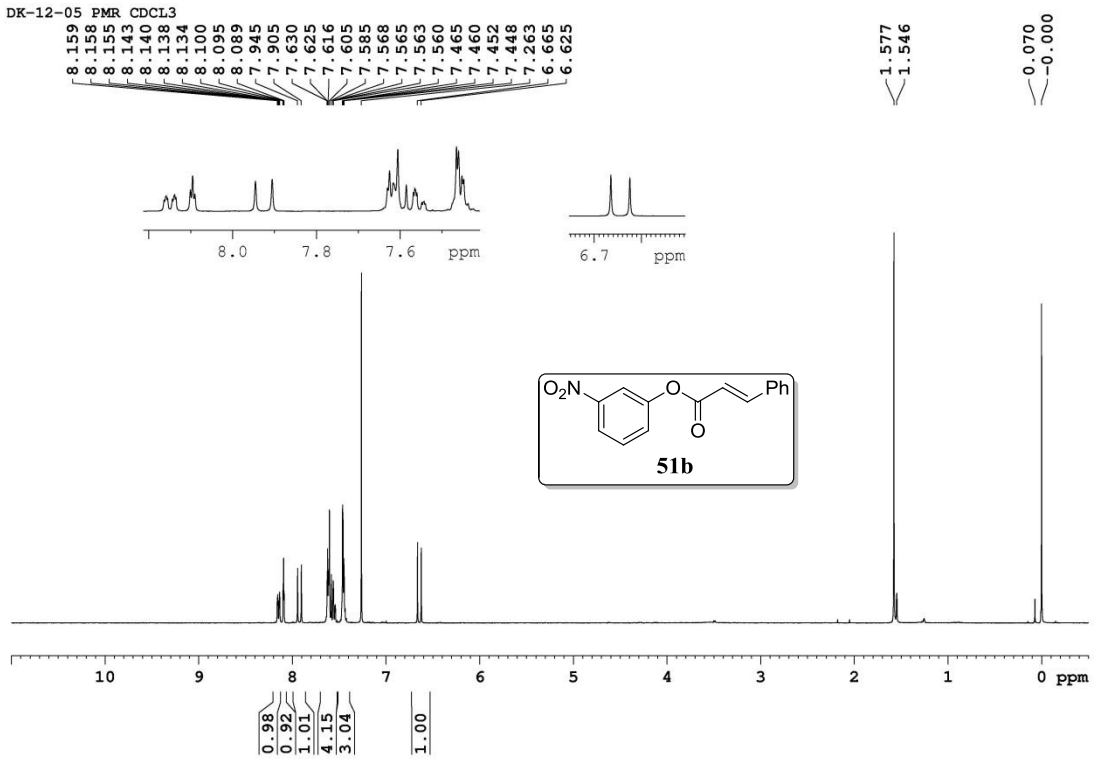

DK-11-02 CMR CDCL3
166.95
150.24
139.39
129.83
129.36
128.88
128.18
128.03
127.56
127.53
118.52
77.35
77.03
76.71
40.64
36.61
Cl
O
O
Ph
501
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

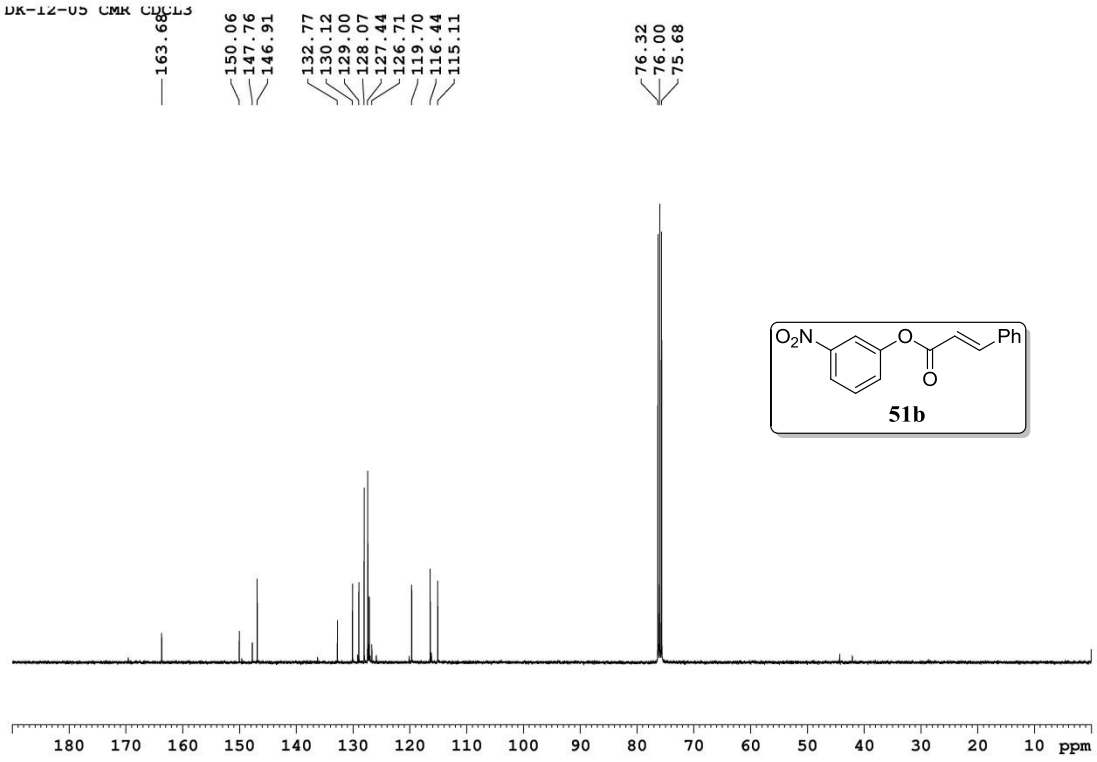

DK-11-02 DEPT CDCL3
129.36
128.88
128.18
128.04
127.53
118.52
40.63
36.61
Cl
O
O
Ph
501
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

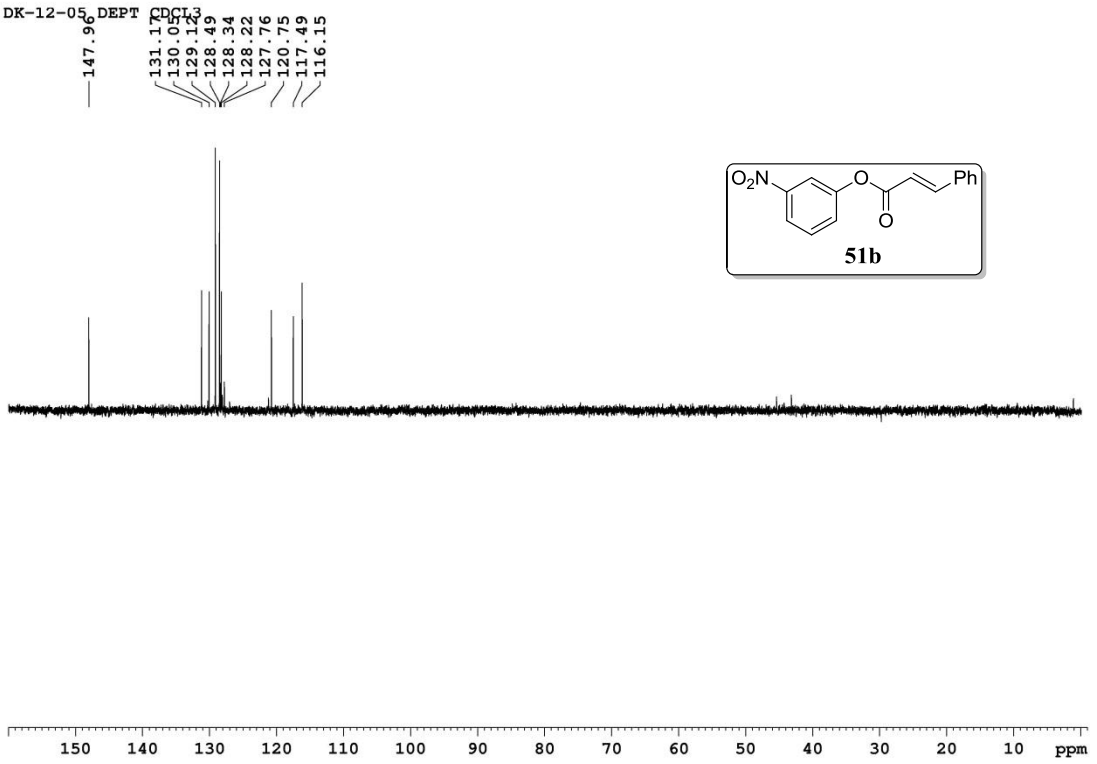

DK-12-07 PMR CDCL3
8.253
8.231
7.870
7.830
7.549
7.538
7.531
7.393
7.389
7.380
7.376
7.322
7.300
7.192
6.585
6.545
1.516
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
ppm
O
Ph
O
O2N
51a
11
10
9
8
7
6
5
4
3
2
1
ppm
2.00
1.00
2.11
3.05
2.03
0.96

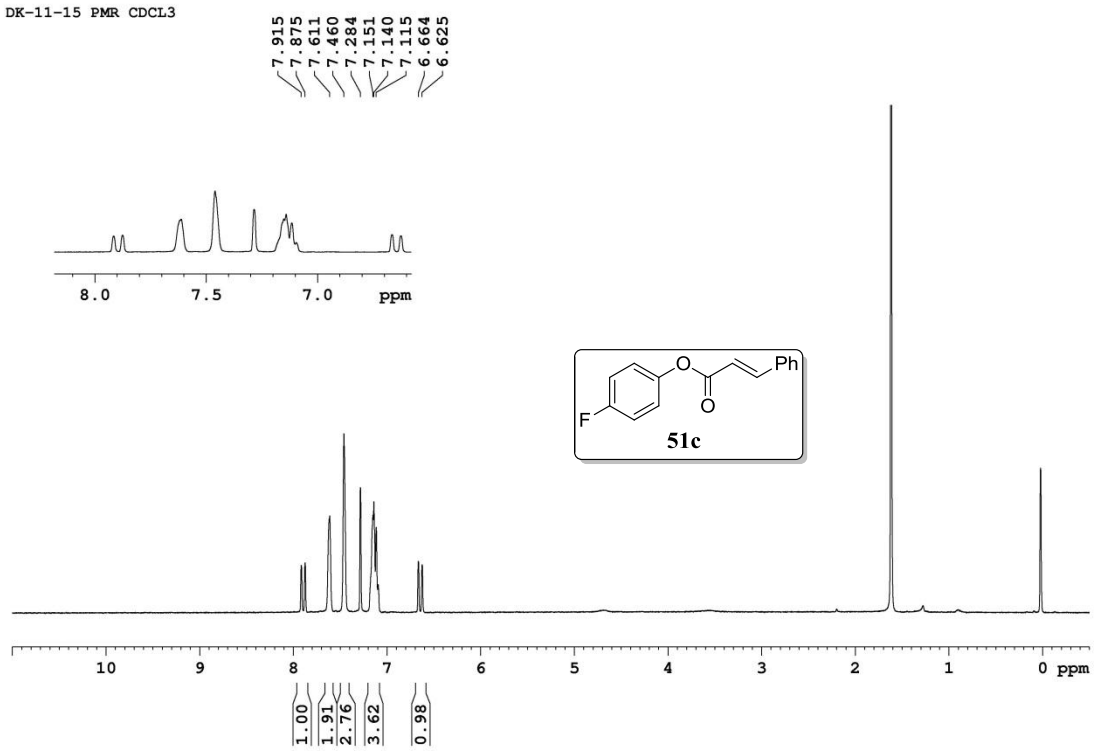

DK-12-07 CMR CDCL3
163.34
154.58
147.03
144.22
132.73
130.17
128.08
127.45
124.21
121.46
115.11
76.32
76.00
75.68
O
Ph
O
O2N
51a
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

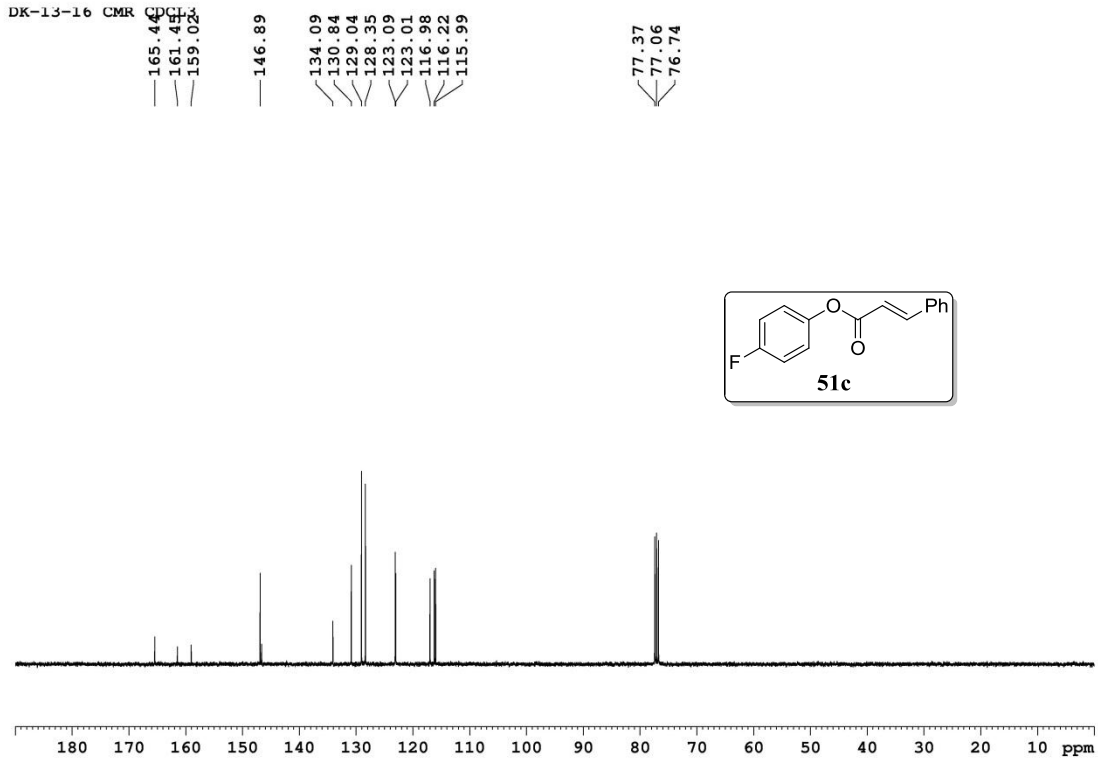

DK-12-07 DEPT CDCL3
148.08
131.23
129.13
128.50
125.26
122.52
122.46
116.15
O
Ph
O
O2N
51a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

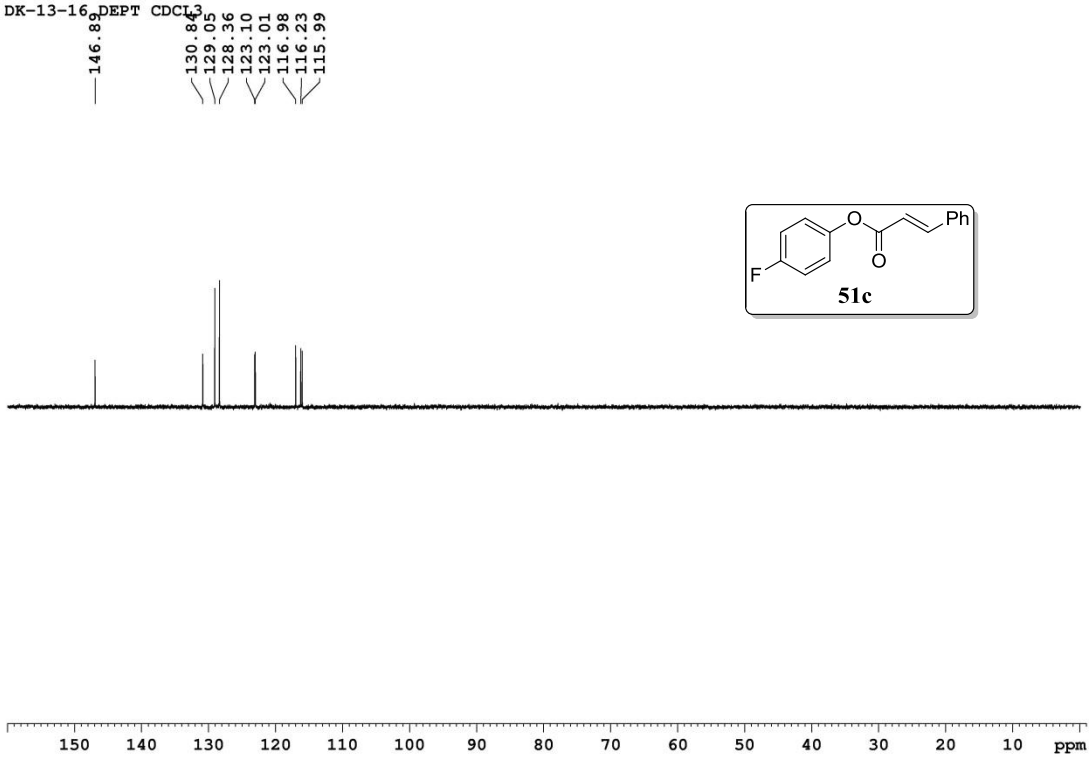

DK-12-05 PMR CDCL3
8.159
8.158
8.155
8.143
8.140
8.138
8.134
8.100
8.095
8.089
7.945
7.905
7.630
7.625
7.616
7.605
7.585
7.568
7.565
7.563
7.560
7.465
7.460
7.452
7.448
7.263
6.665
6.625
1.577
1.546
0.070
-0.000
8.0 7.8 7.6 ppm
6.7 ppm
O2N
O
Ph
O
51b
10 9 8 7 6 5 4 3 2 1 0 ppm
0.98
0.92
1.01
4.15
3.04
1.00

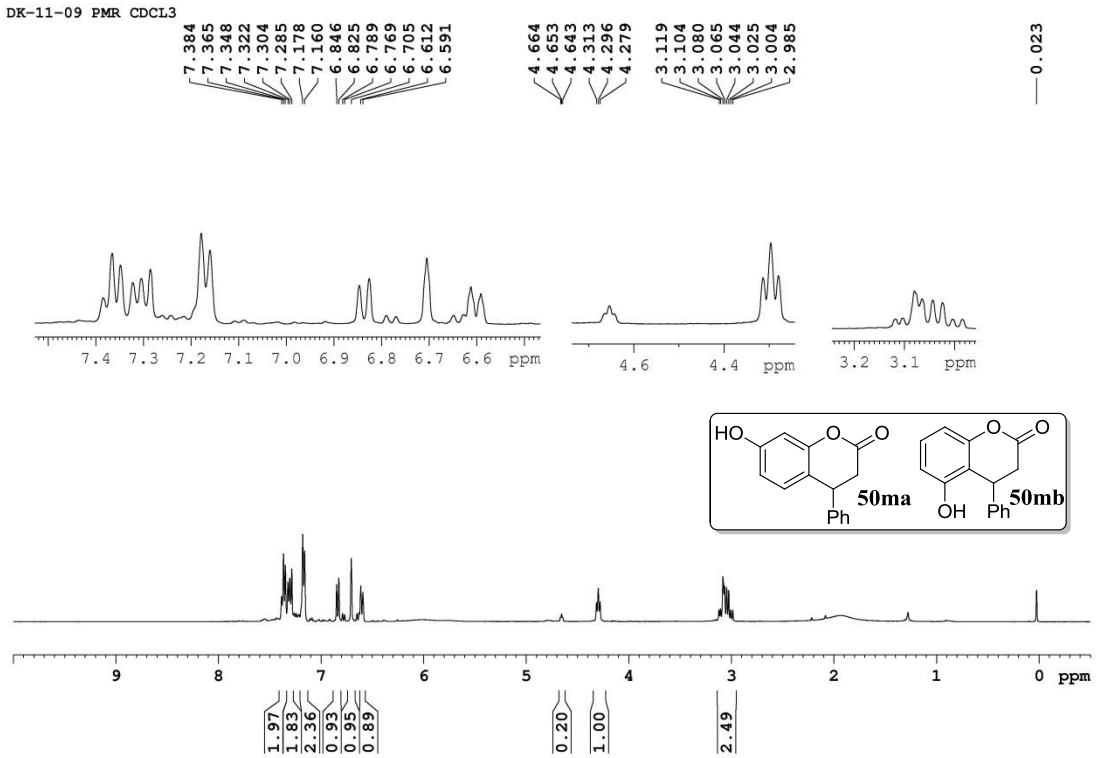

DK-12-05 CMR CDCL3
163.68
150.06
147.76
146.91
132.77
130.12
129.00
128.07
127.44
126.71
119.70
116.44
115.11
76.32
76.00
75.68
O2N
O
Ph
O
51b
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

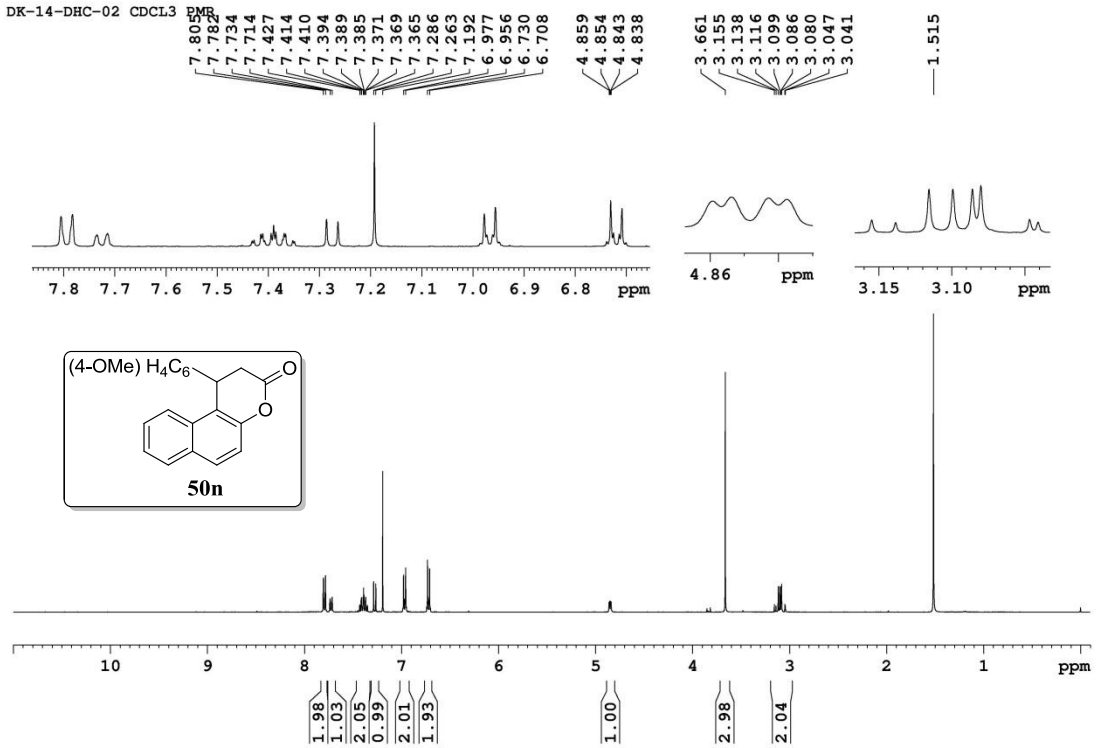

DK-12-05 DEPT CDCL3
147.96
131.17
130.05
129.14
128.49
128.34
128.22
127.76
120.75
117.49
116.15
O2N
O
Ph
O
51b
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

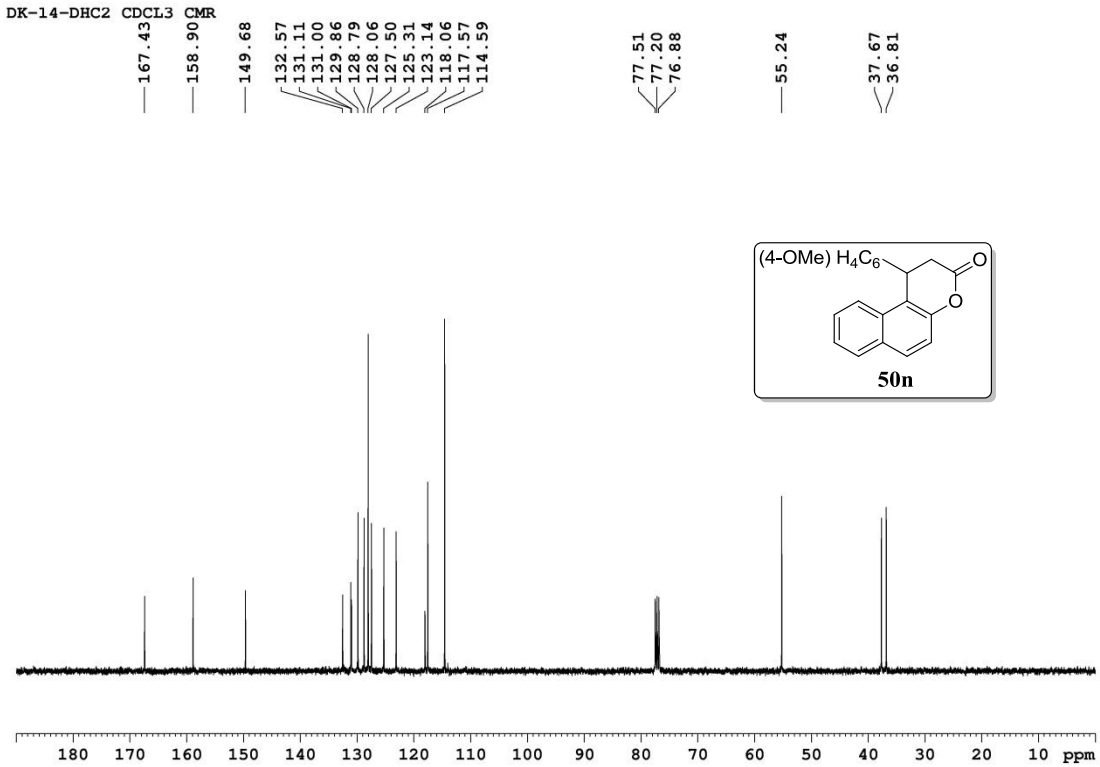

DK-11-15 PMR CDCL3
7.915
7.875
7.611
7.460
7.284
7.151
7.140
7.115
6.664
6.625
8.0
7.5
7.0
ppm
O
Ph
O
F
51c
10
9
8
7
6
5
4
3
2
1
0 ppm
1.00
1.91
2.76
3.62
0.98

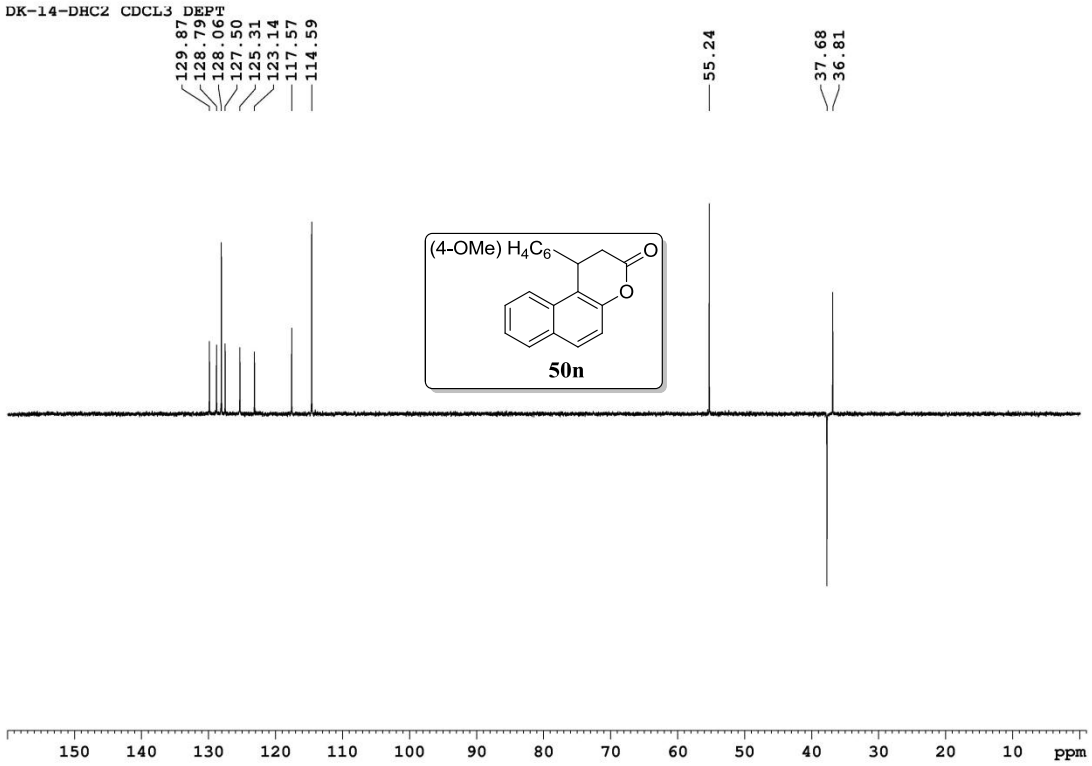

DK-13-16 CMR CDCL3
165.44
161.45
159.02
146.89
134.09
130.84
129.04
128.35
123.09
123.01
116.98
116.22
115.99
77.37
77.06
76.74
O
Ph
O
F
51c
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

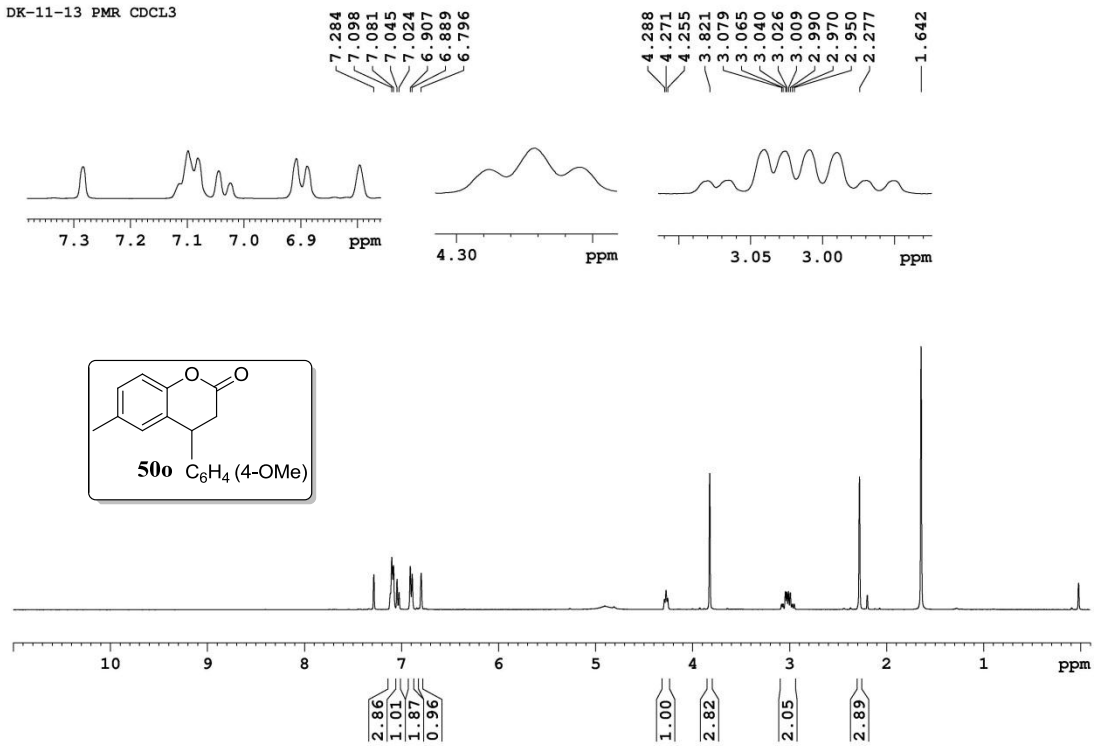

DK-13-16_DEPT CDCL3
146.89
130.84
129.05
128.36
123.10
123.01
116.98
116.23
115.99
O
Ph
O
F
51c
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

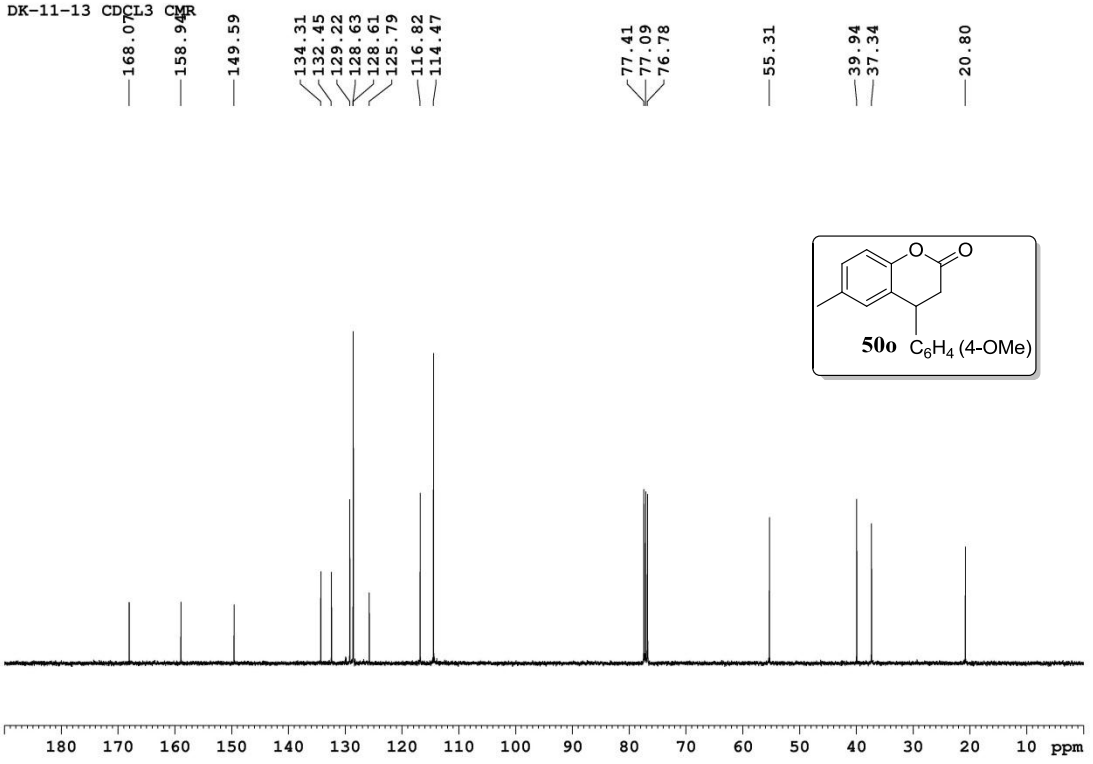

DK-11-09 PMR CDCL3
7.384
7.365
7.348
7.322
7.304
7.285
7.178
7.160
6.846
6.825
6.789
6.769
6.705
6.612
6.591
4.664
4.653
4.643
4.313
4.296
4.279
3.119
3.104
3.080
3.065
3.044
3.025
3.004
2.985
0.023
7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 ppm
4.6 4.4 ppm
3.2 3.1 ppm
HO
O
O
Ph
50ma
O
O
OH
Ph
50mb
9 8 7 6 5 4 3 2 1 0 ppm
1.97
1.83
2.36
0.93
0.95
0.89
0.20
1.00
2.49

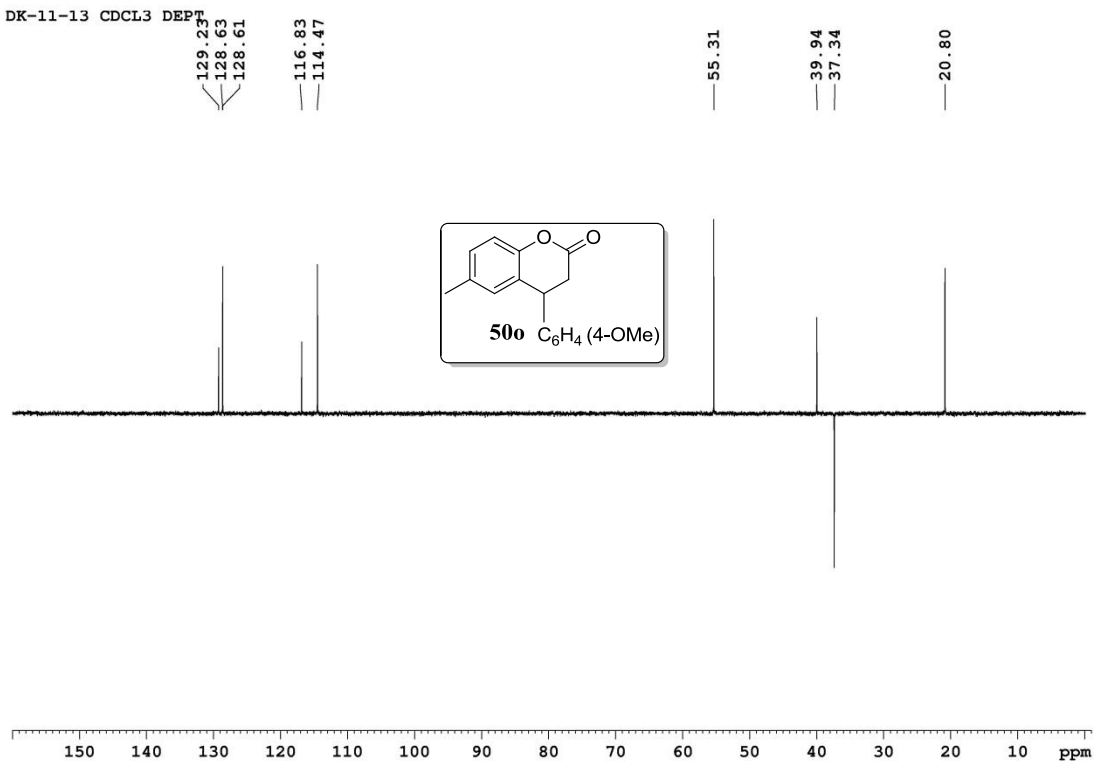

DK-14-DHC-02 CDCL3 PMR
7.805
7.782
7.734
7.714
7.427
7.414
7.410
7.394
7.389
7.385
7.371
7.369
7.365
7.286
7.263
7.192
6.977
6.956
6.730
6.708
4.859
4.854
4.843
4.838
3.661
3.155
3.138
3.116
3.099
3.086
3.080
3.047
3.041
1.515
7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm
4.86 ppm
3.15 3.10 ppm
(4-OMe) H4C6
50n
10 9 8 7 6 5 4 3 2 1 ppm
1.98
1.03
2.05
0.99
2.01
1.93
1.00
2.98
2.04

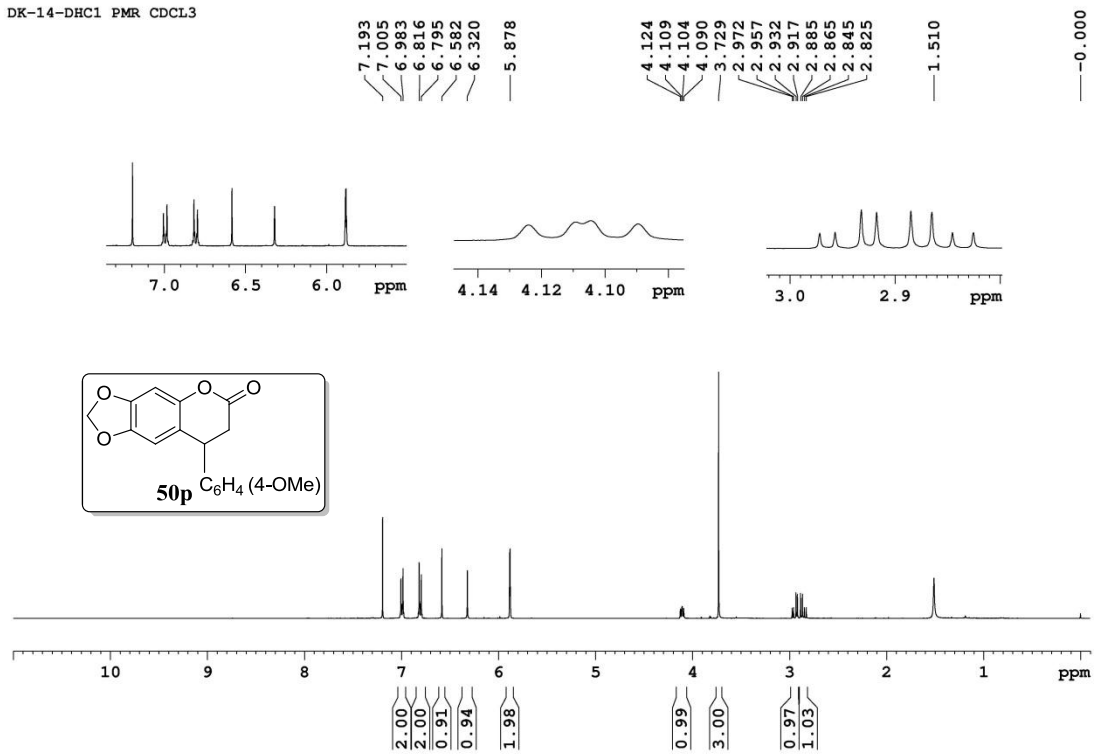

DK-14-DHC2 CDCL3 CMR
167.43
158.90
149.68
132.57
131.11
131.00
129.86
128.79
128.06
127.50
125.31
123.14
118.06
117.57
114.59
77.51
77.20
76.88
55.24
37.67
36.81
(4-OMe) H4C6
50n
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

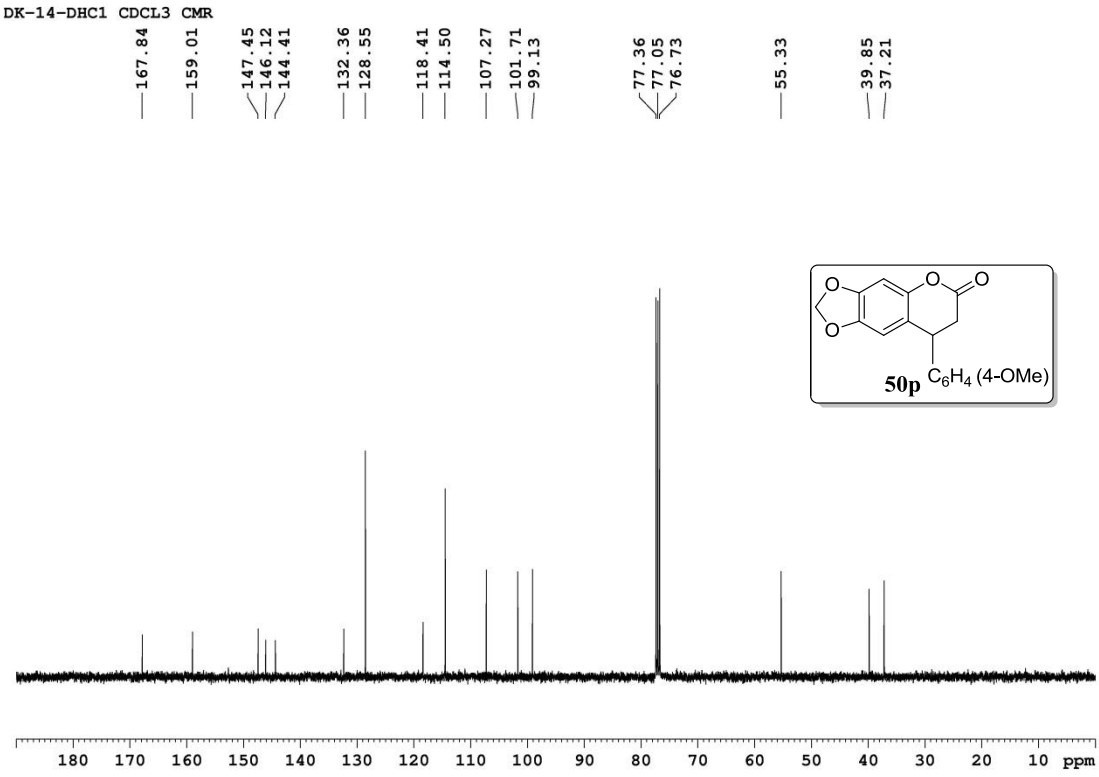

DK-14-DHC2 CDCL3 DEPT
129.87
128.79
128.06
127.50
125.31
123.14
117.57
114.59
55.24
37.68
36.81
(4-OMe) H4C6
O
O
50n
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

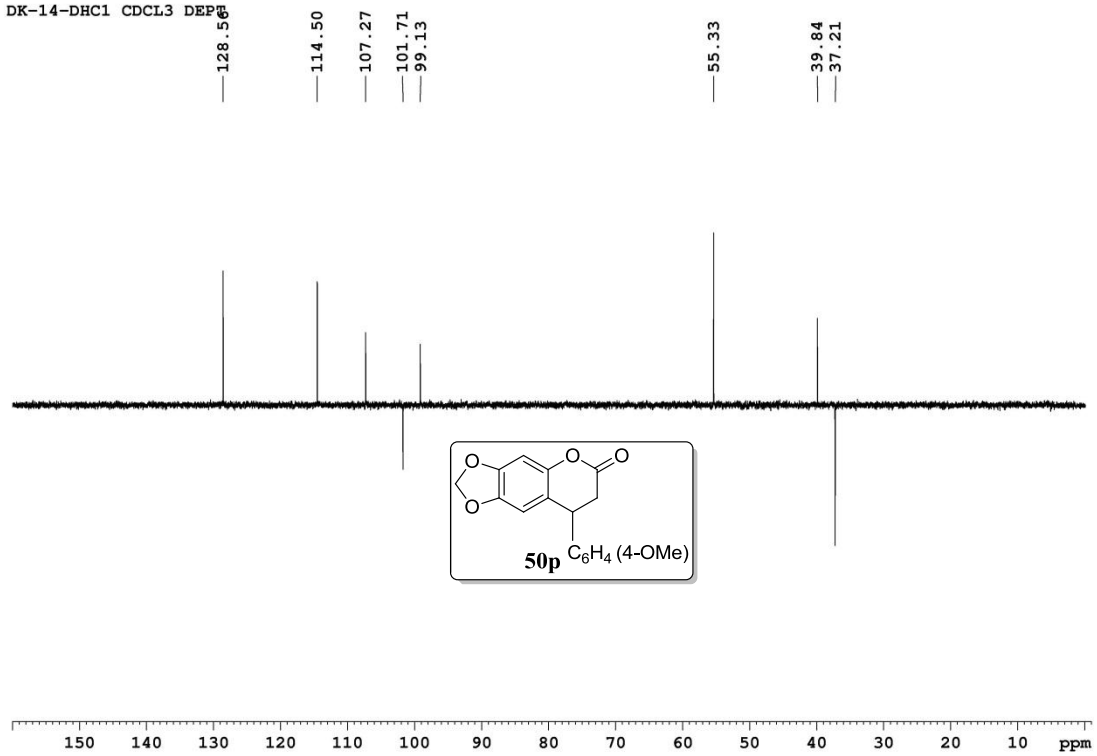

DK-11-13 PMR CDCL3
7.284
7.098
7.081
7.045
7.024
6.907
6.889
6.796
4.288
4.271
4.255
3.821
3.079
3.065
3.040
3.026
3.009
2.990
2.970
2.950
2.277
1.642
7.3 7.2 7.1 7.0 6.9 ppm
4.30 ppm
3.05 3.00 ppm
O
O
50o C6H4 (4-OMe)
10 9 8 7 6 5 4 3 2 1 ppm
2.86
1.01
1.87
0.96
1.00
2.82
2.05
2.89

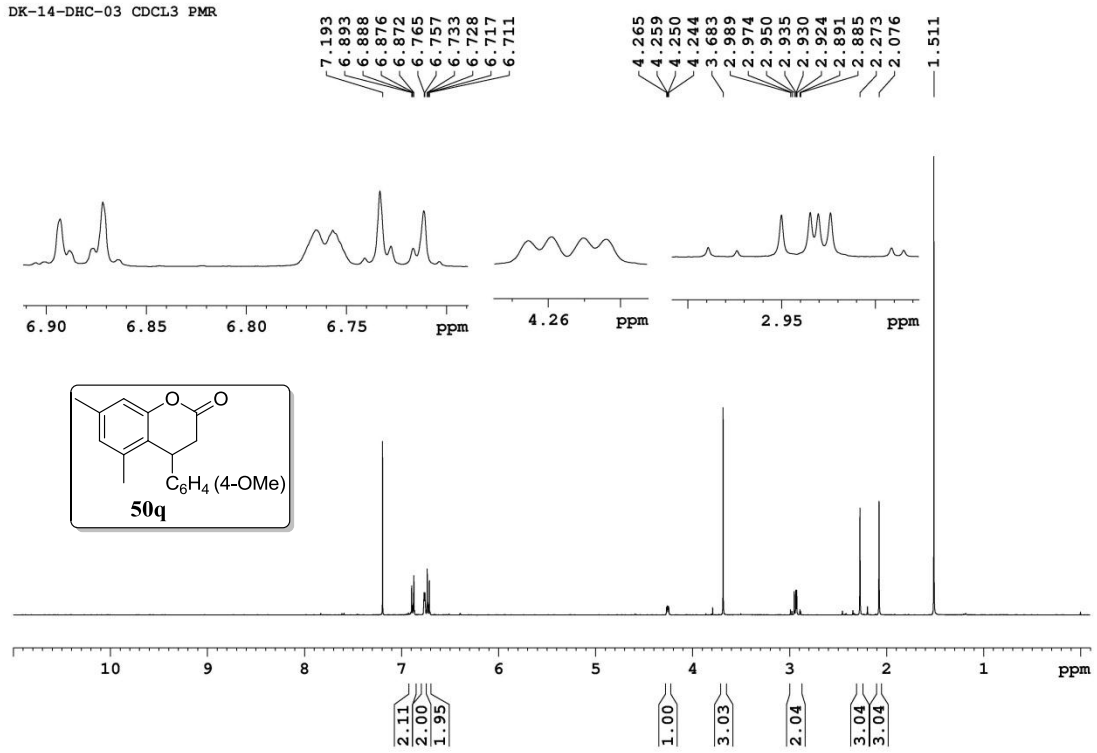

DK-11-13 CDCL3 CMR
168.07
158.94
149.59
134.31
132.45
129.22
128.63
128.61
125.79
116.82
114.47
77.41
77.09
76.78
55.31
39.94
37.34
20.80
50o C6H4 (4-OMe)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

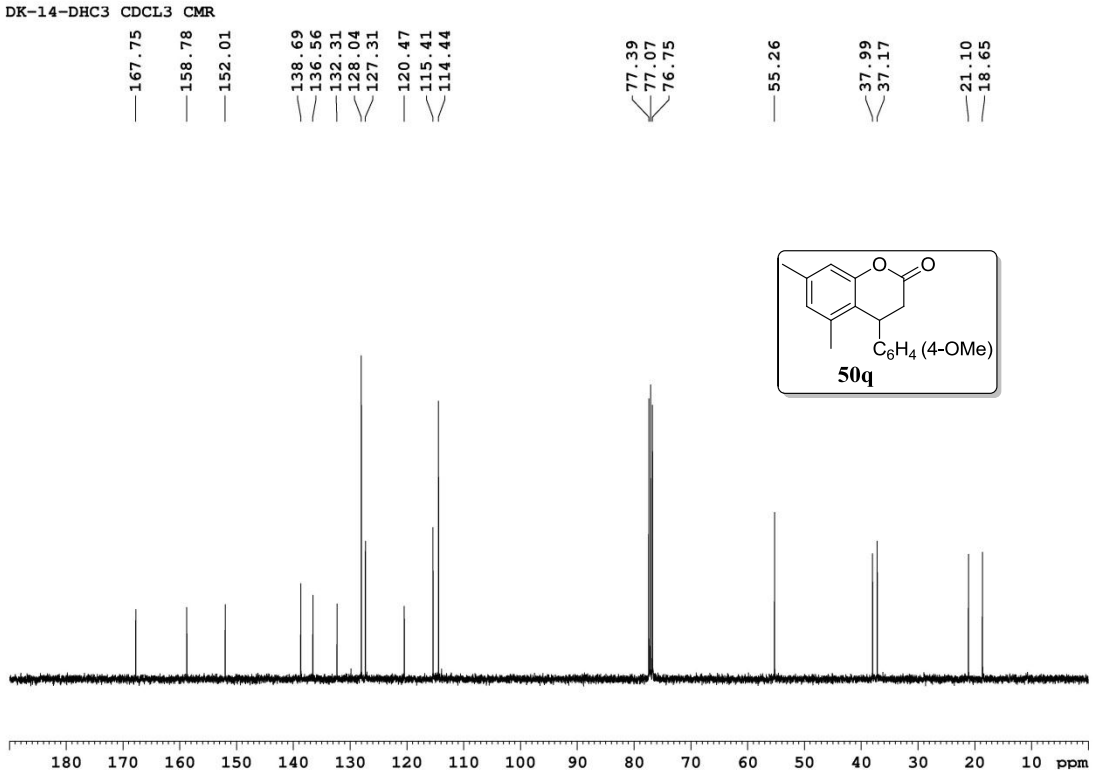

DK-11-13 CDCL3 DEPT
129.23
128.63
128.61
116.83
114.47
55.31
39.94
37.34
20.80
50o C6H4 (4-OMe)
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

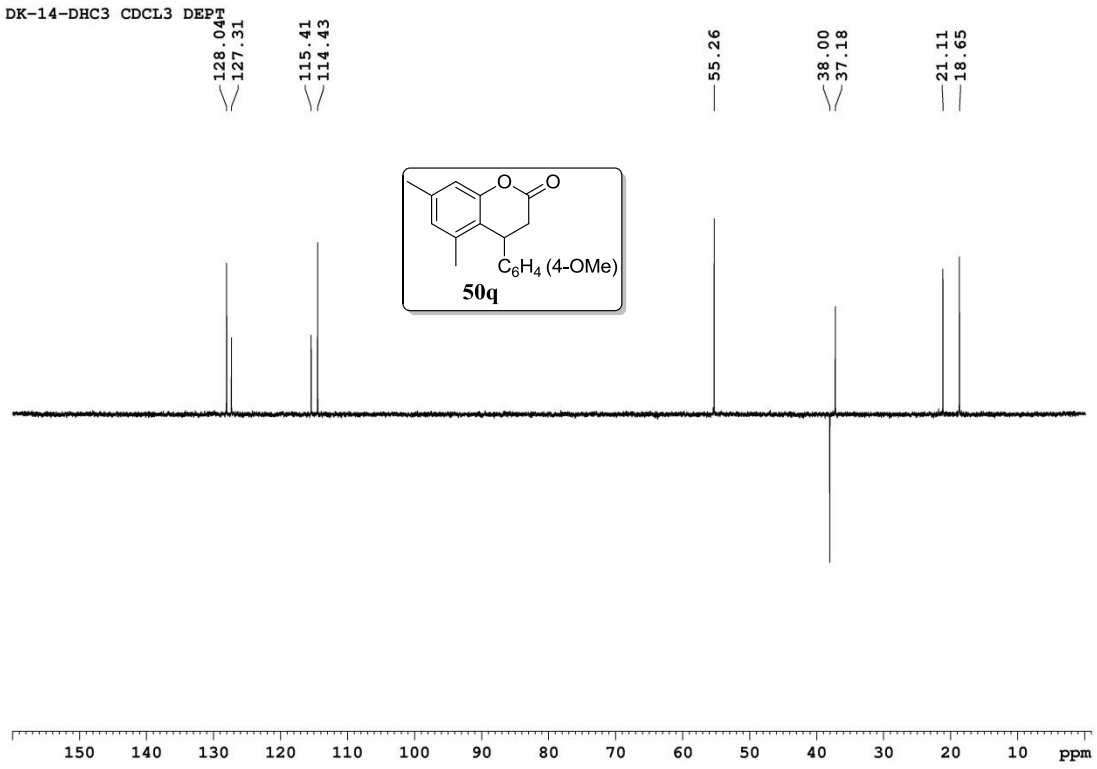

DK-14-DHC1 PMR CDCL3
7.193
7.005
6.983
6.816
6.795
6.582
6.320
5.878
4.124
4.109
4.104
4.090
3.729
2.972
2.957
2.932
2.917
2.885
2.865
2.845
2.825
1.510
-0.000
7.0
6.5
6.0
ppm
4.14
4.12
4.10
ppm
3.0
2.9
ppm
50p C6H4 (4-OMe)
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.00
0.91
0.94
1.98
0.99
3.00
0.97
1.03

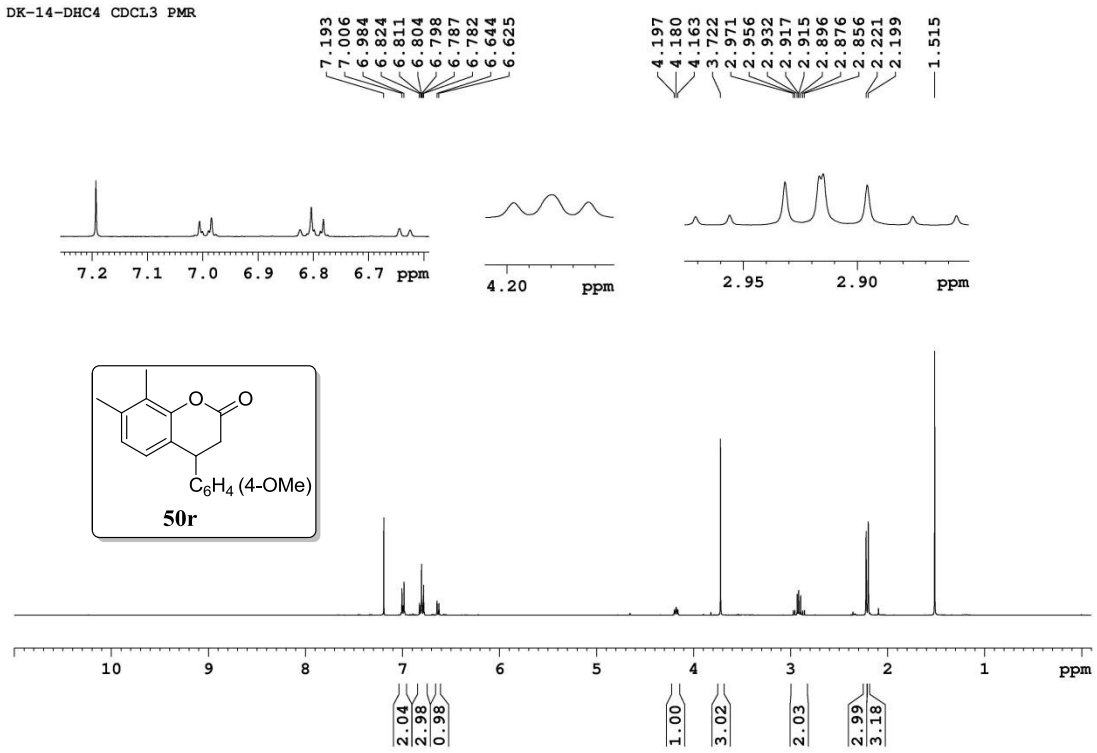

DK-14-DHC1 CDCL3 CMR
167.84
159.01
147.45
146.12
144.41
132.36
128.55
118.41
114.50
107.27
101.71
99.13
77.36
77.05
76.73
55.33
39.85
37.21
50p C6H4 (4-OMe)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

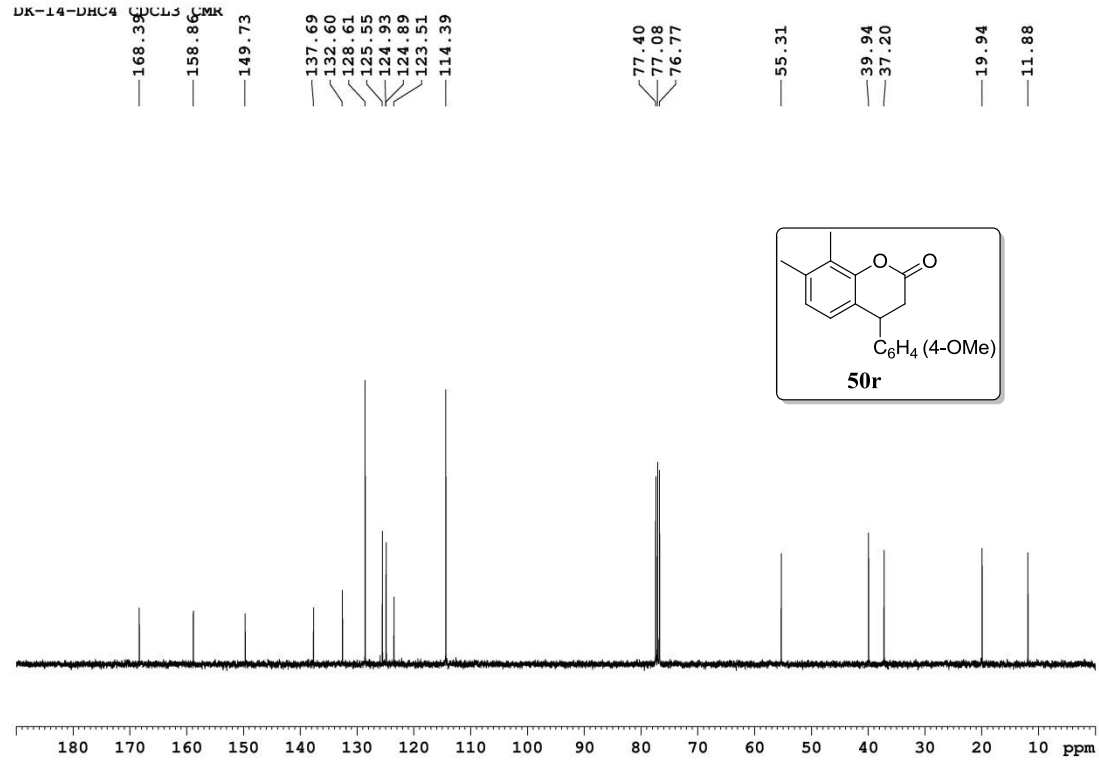

DK-14-DHC1 CDCL3 DEPT
128.56
114.50
107.27
101.71
99.13
55.33
39.84
37.21
50p C6H4 (4-OMe)
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

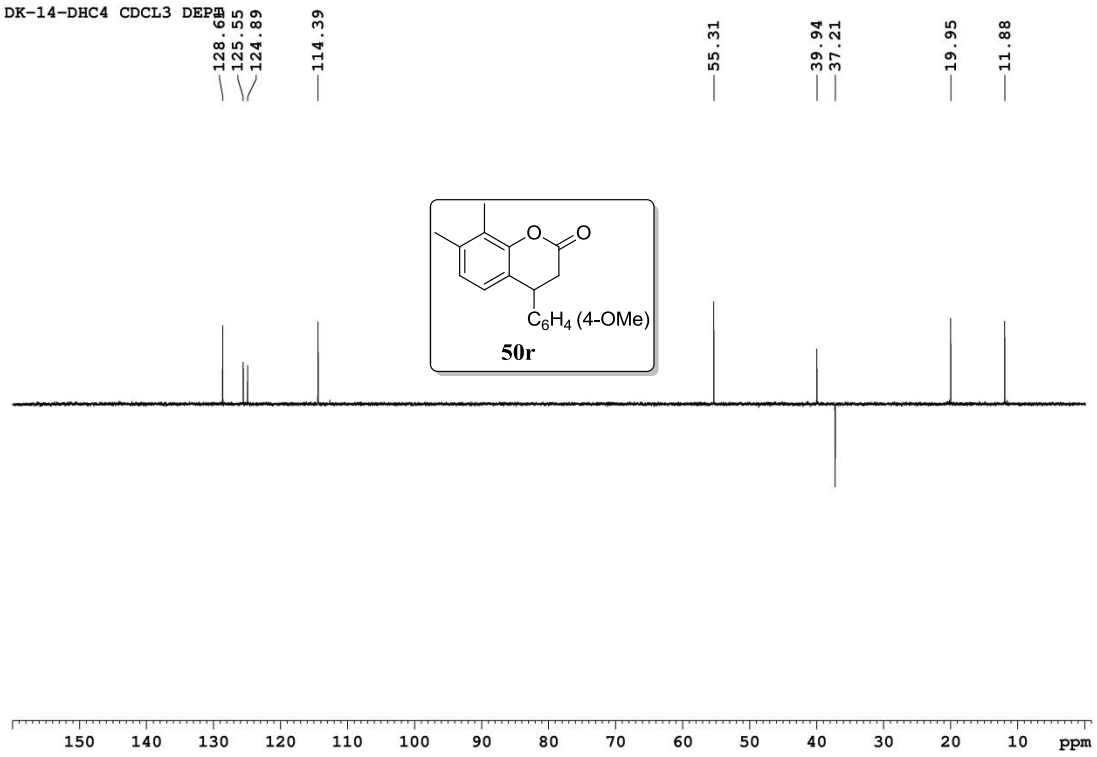

DK-14-DHC-03 CDCL3 PMR
7.193
6.893
6.888
6.876
6.872
6.765
6.757
6.733
6.728
6.717
6.711
4.265
4.259
4.250
4.244
3.683
2.989
2.974
2.950
2.935
2.930
2.924
2.891
2.885
2.273
2.076
1.511
6.90 6.85 6.80 6.75 ppm
4.26 ppm
2.95 ppm
C6H4 (4-OMe)
50q
10 9 8 7 6 5 4 3 2 1 ppm
2.11
2.00
1.95
1.00
3.03
2.04
3.04
3.04

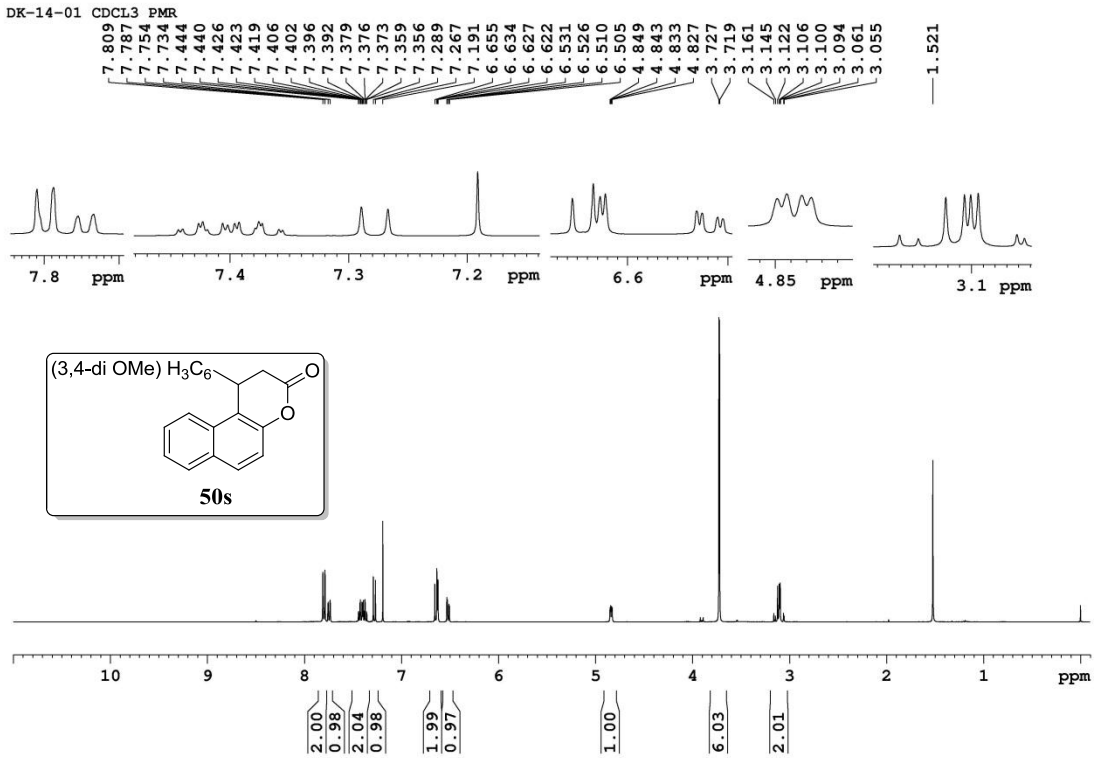

DK-14-DHC3 CDCL3 CMR
167.75
158.78
152.01
138.69
136.56
132.31
128.04
127.31
120.47
115.41
114.44
77.39
77.07
76.75
55.26
37.99
37.17
21.10
18.65
O
O
C6H4 (4-OMe)
50q
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

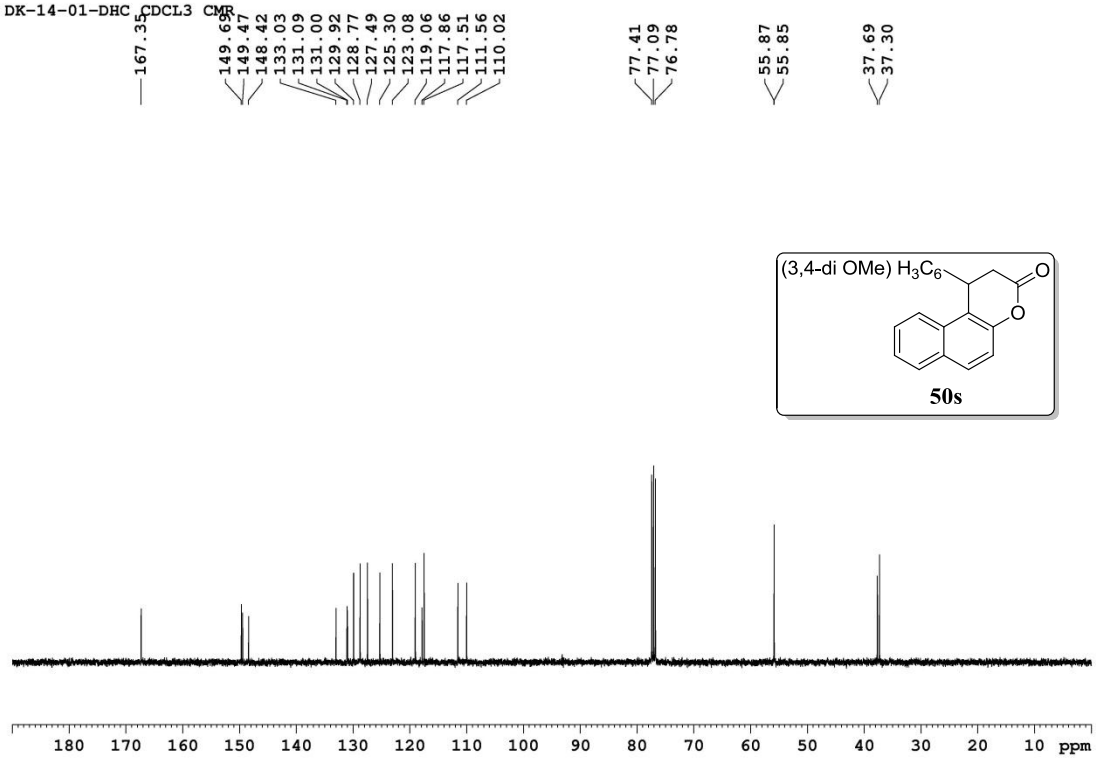

DK-14-DHC3 CDCL3 DEPT
128.04
127.31
115.41
114.43
55.26
38.00
37.18
21.11
18.65
O
O
C6H4 (4-OMe)
50q
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

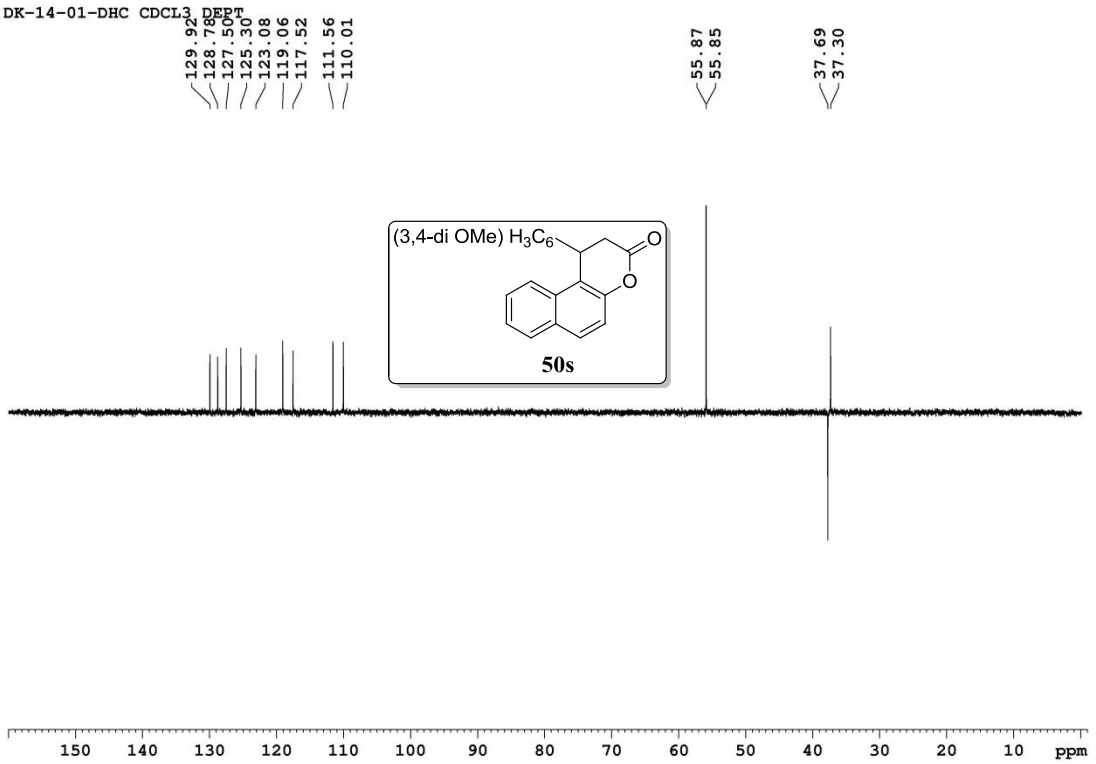

DK-14-DHC4 CDCL3 PMR
7.193
7.006
6.984
6.824
6.811
6.804
6.798
6.787
6.782
6.644
6.625
4.197
4.180
4.163
3.722
2.971
2.956
2.932
2.917
2.915
2.896
2.876
2.856
2.221
2.199
1.515
7.2 7.1 7.0 6.9 6.8 6.7 ppm
4.20 ppm
2.95 2.90 ppm
C6H4 (4-OMe)
50r
10 9 8 7 6 5 4 3 2 1 ppm
2.04
2.98
0.98
1.00
3.02
2.03
2.99
3.18

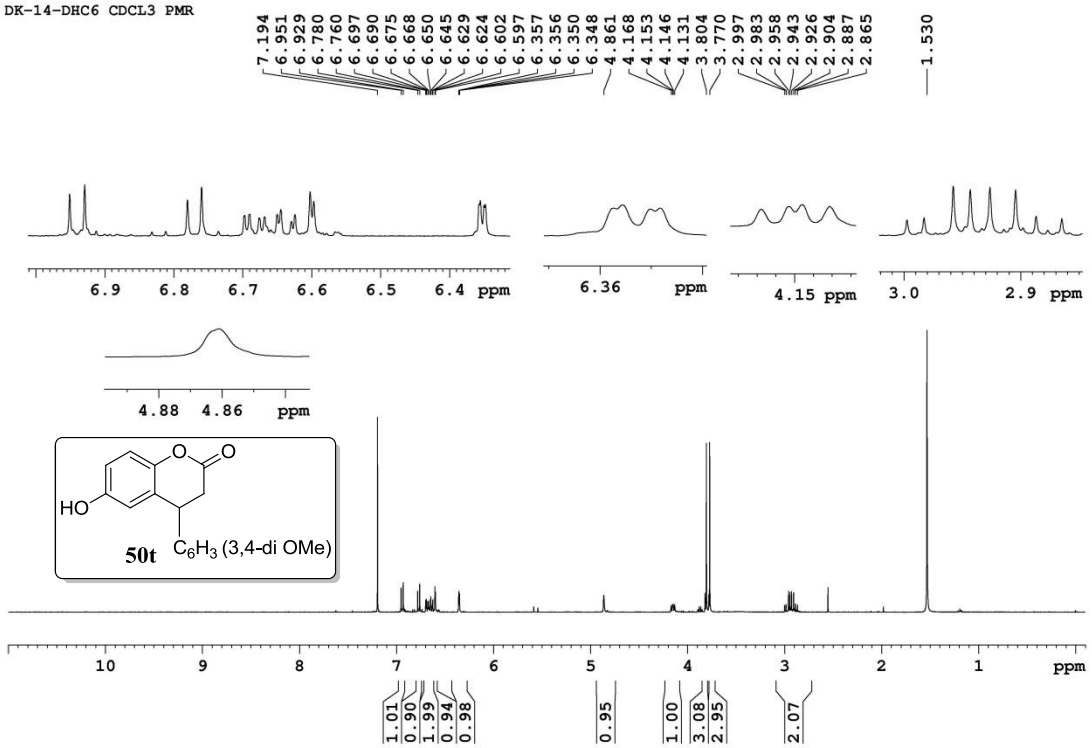

168.39
158.86
149.73
137.69
132.60
128.61
125.55
124.93
124.89
123.51
114.39
77.40
77.08
76.77
55.31
39.94
37.20
19.94
11.88
C6H4 (4-OMe)
50r
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

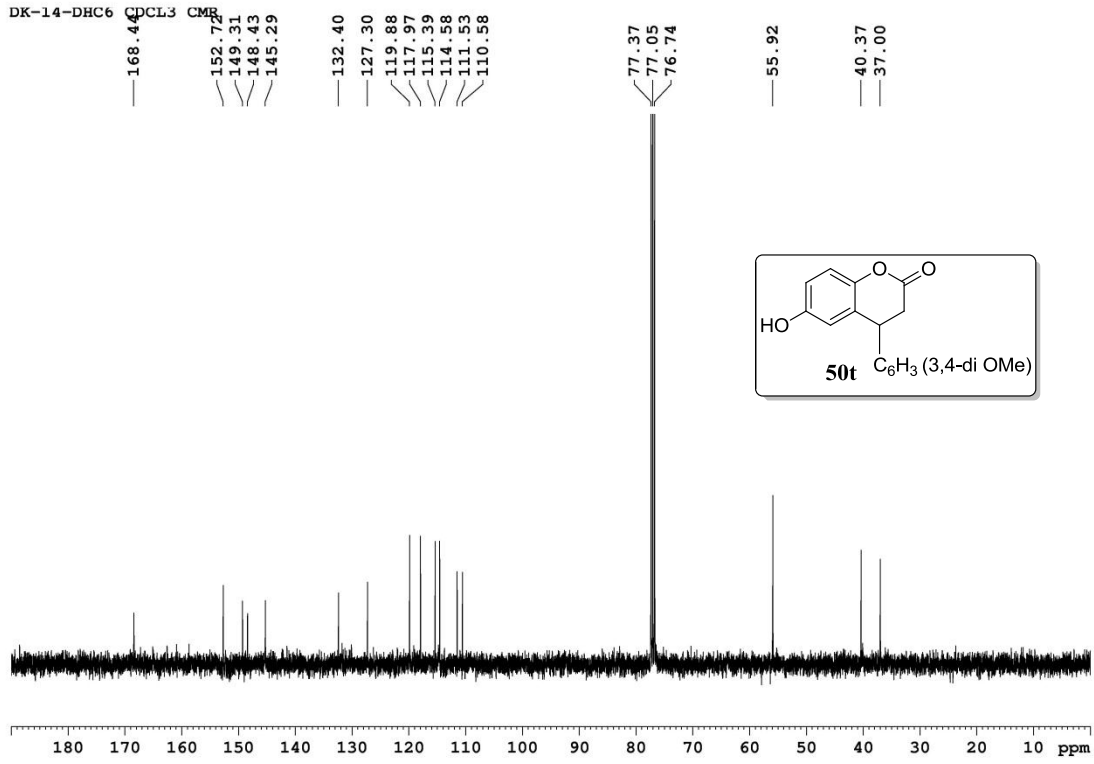

DK-14-DHC4 CDCL3 DEPT
128.61
125.55
124.89
114.39
55.31
39.94
37.21
19.95
11.88
O
O
C6H4 (4-OMe)
50r
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-14-01 CDCL3 PMR
7.809 7.787 7.754 7.734 7.444 7.440 7.426 7.423 7.419 7.406 7.402 7.396 7.392 7.379 7.376 7.373 7.359 7.356 7.289 7.267 7.191 6.655 6.634 6.627 6.622 6.531 6.526 6.510 6.505 4.849 4.843 4.833 4.827 3.727 3.719 3.161 3.145 3.122 3.106 3.100 3.094 3.061 3.055 1.521
7.8 ppm 7.4 7.3 7.2 ppm 6.6 ppm 4.85 ppm 3.1 ppm
(3,4-di OMe) H3C6
O
O
50s
10 9 8 7 6 5 4 3 2 1 ppm
2.00 0.98 2.04 0.98 1.99 0.97 1.00 6.03 2.01


DK-14-01-DHC CDCL3 CMR
167.35
149.63
149.47
148.42
133.03
131.09
131.00
129.92
128.77
127.49
125.30
123.08
119.06
117.86
117.51
111.56
110.02
77.41
77.09
76.78
55.87
55.85
37.69
37.30
(3,4-di OMe) H3C6
O
O
50s
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-14-01-DHC CDCL3 DEPT
129.92
128.78
127.50
125.30
123.08
119.06
117.52
111.56
110.01
55.87
55.85
37.69
37.30
(3,4-di OMe) H3C6
O
O
50s
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-14-DHC6 CDCL3 PMR
7.194
6.951
6.929
6.780
6.760
6.697
6.690
6.675
6.668
6.650
6.645
6.629
6.624
6.602
6.597
6.357
6.356
6.350
6.348
4.861
4.168
4.153
4.146
4.131
3.804
3.770
2.997
2.983
2.958
2.943
2.926
2.904
2.887
2.865
1.530
6.9 6.8 6.7 6.6 6.5 6.4 ppm
6.36 ppm
4.15 ppm
3.0 2.9 ppm
4.88 4.86 ppm
HO
O
O
50t
C6H3 (3,4-di OMe)
10 9 8 7 6 5 4 3 2 1 ppm
1.01
0.90
1.99
0.94
0.98
0.95
1.00
3.08
2.95
2.07


DK-14-DHC6 CDCL3 CMR
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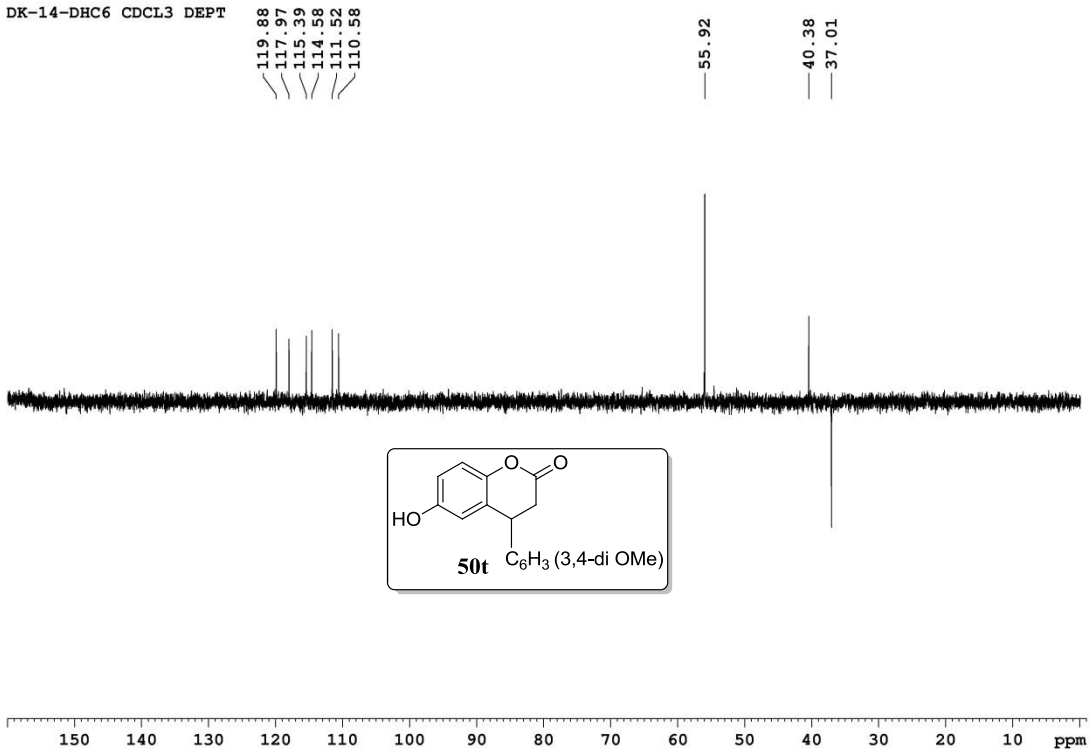
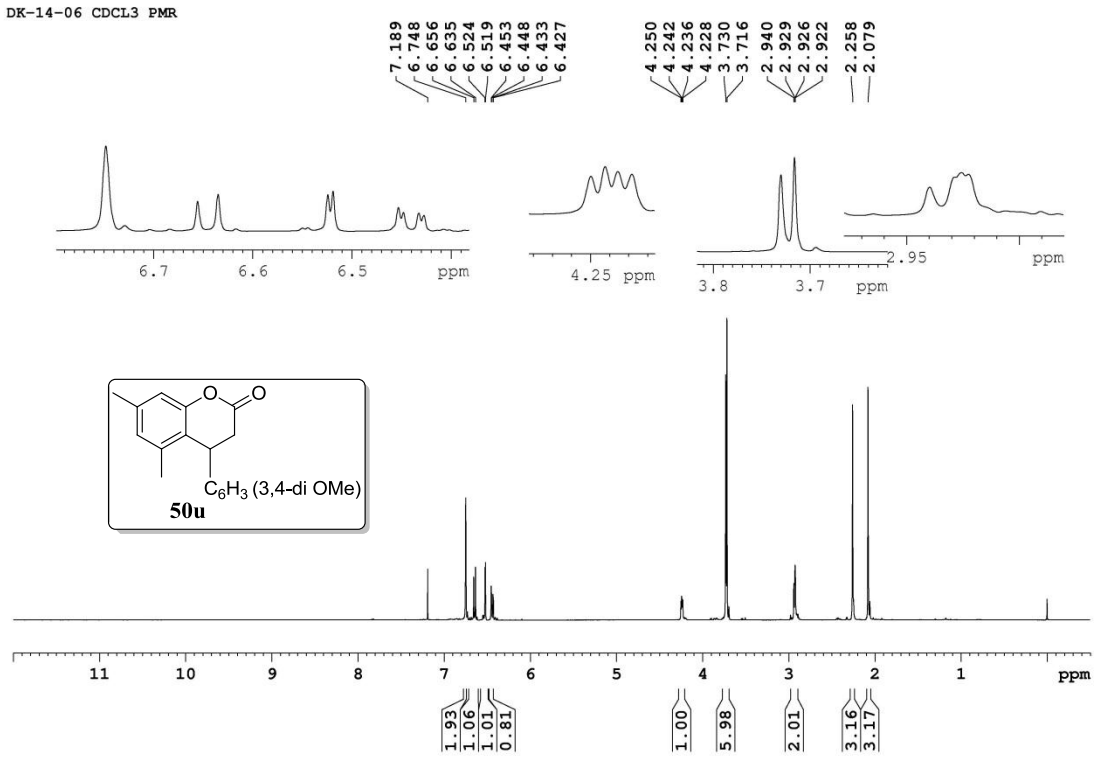
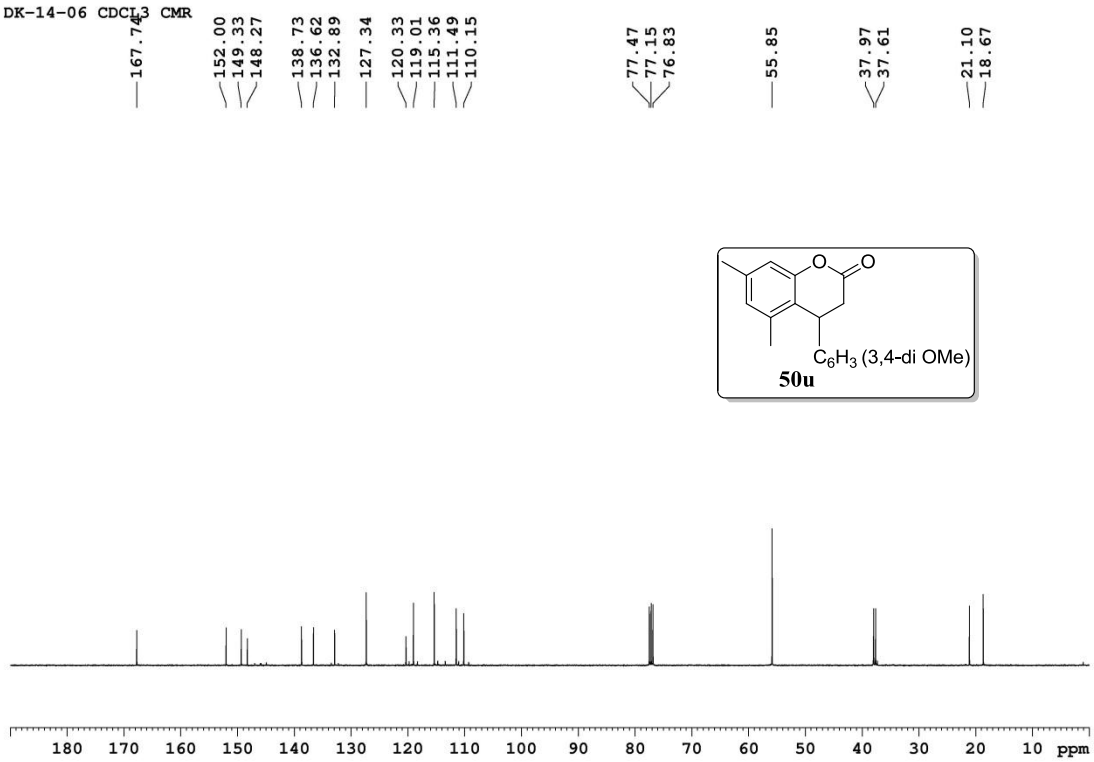
152.72
149.31
148.43
145.29
132.40
127.30
119.88
117.97
115.39
114.58
111.53
110.58
77.37
77.05
76.74
55.92
40.37
37.00
HO
O
O
50t
C6H3 (3,4-di OMe)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-14-DHC6 CDCL3 DEPT
119.88
117.97
115.39
114.58
111.52
110.58
55.92
40.38
37.01
HO
O
O
50t
C6H3 (3,4-di OMe)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


DK-14-06 CDCL3 PMR
7.189
6.748
6.656
6.635
6.524
6.519
6.453
6.448
6.433
6.427
4.250
4.242
4.236
4.228
3.730
3.716
2.940
2.929
2.926
2.922
2.258
2.079
6.7
6.6
6.5
ppm
4.25 ppm
3.8
3.7
ppm
2.95
ppm
O
O
C6H3 (3,4-di OMe)
50u
11
10
9
8
7
6
5
4
3
2
1
ppm
1.93
1.06
1.01
0.81
1.00
5.98
2.01
3.16
3.17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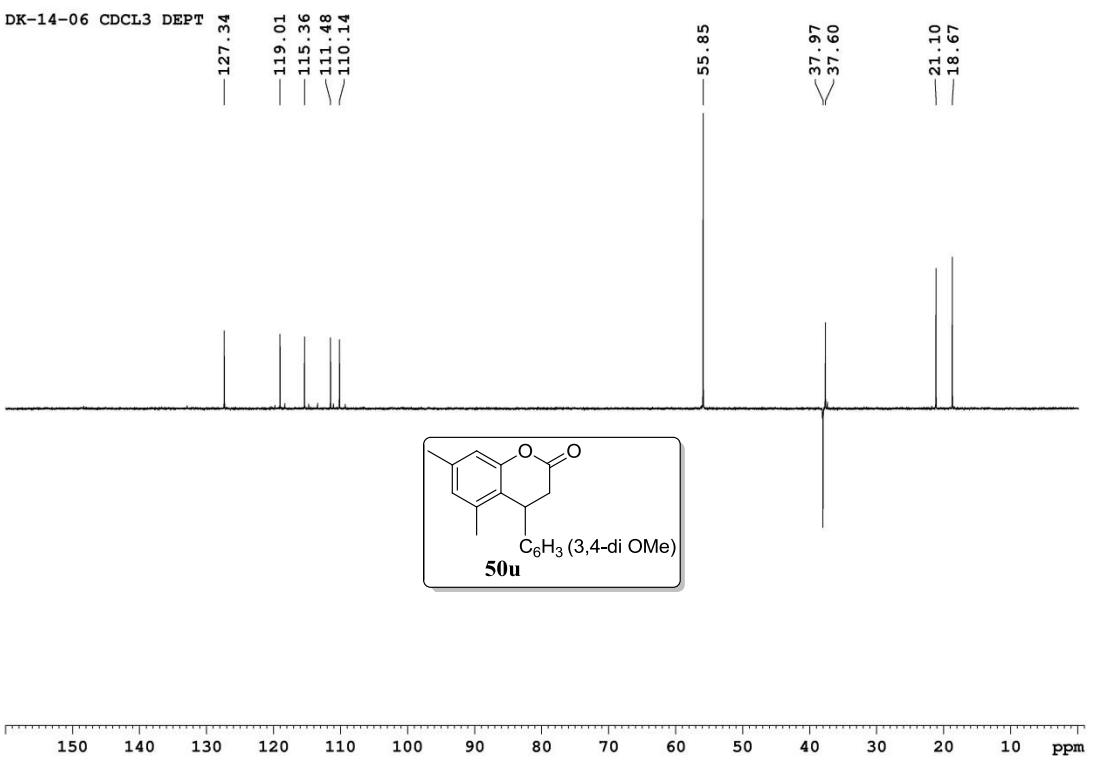
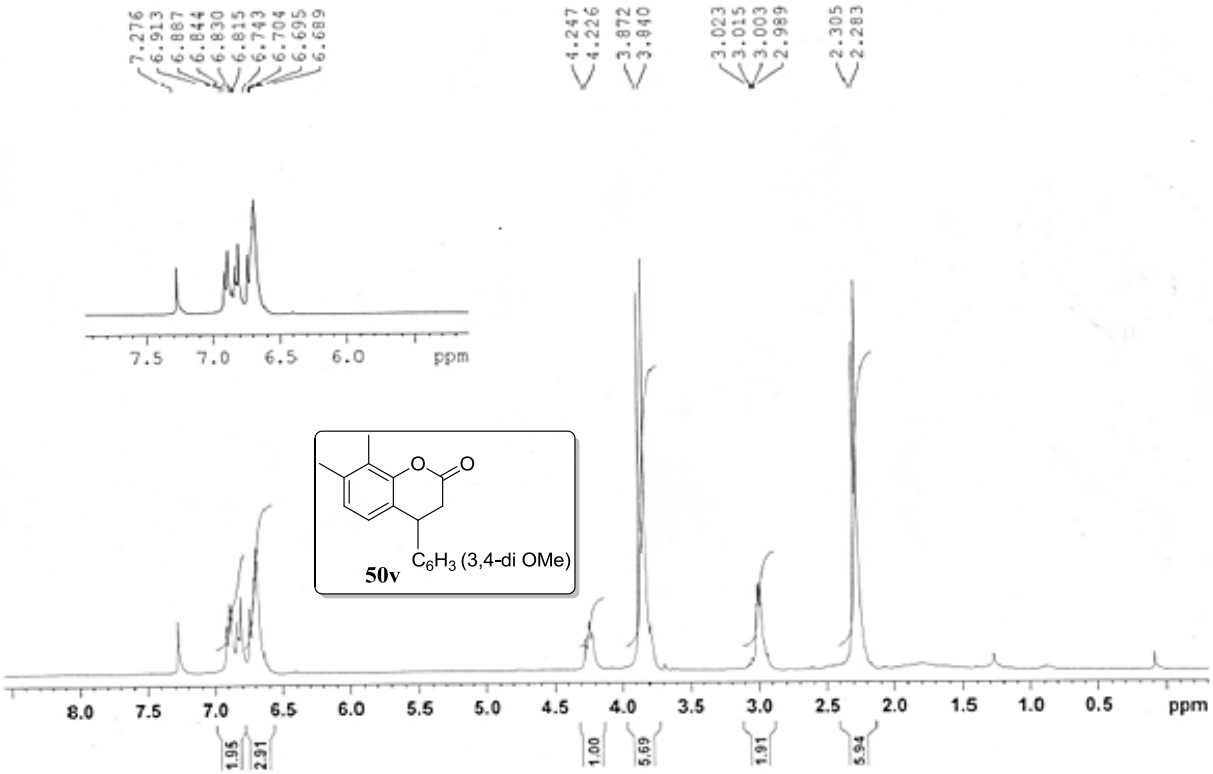
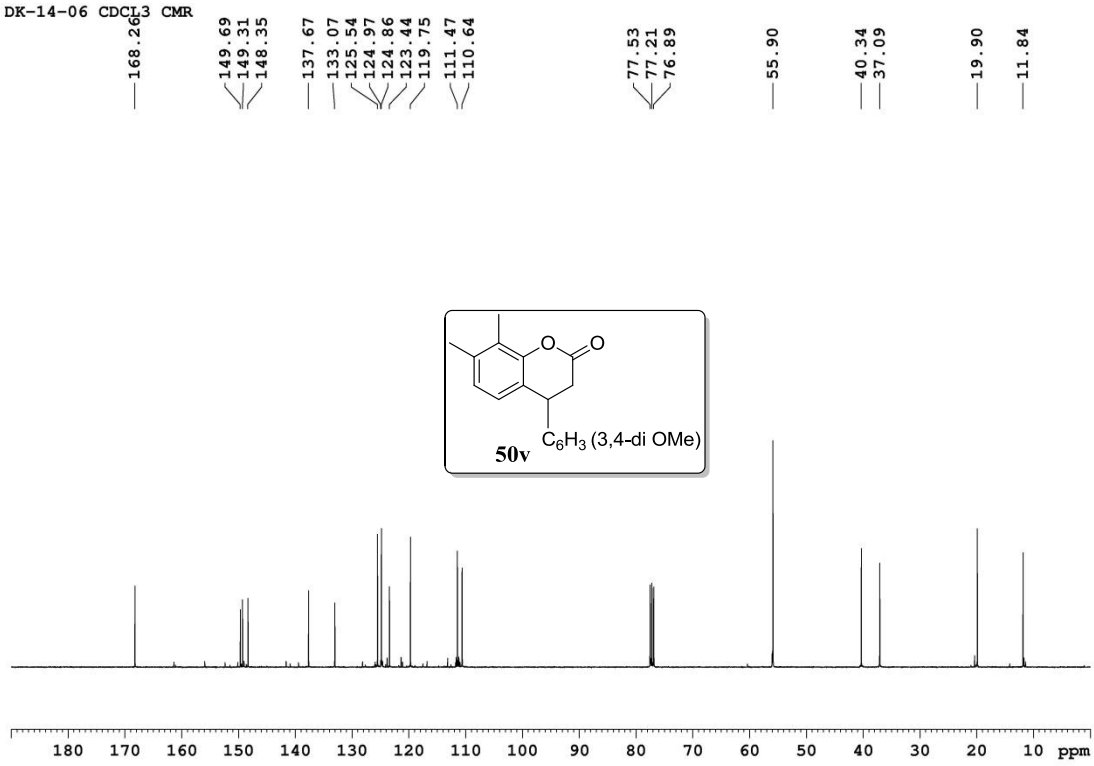
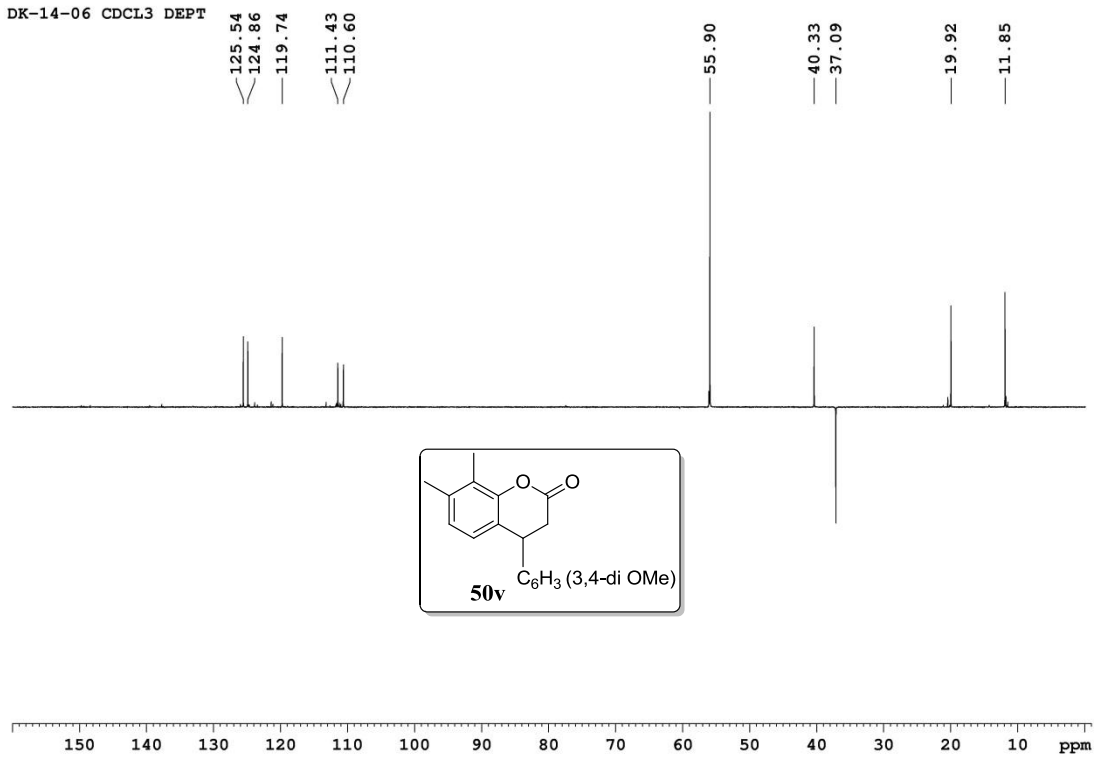
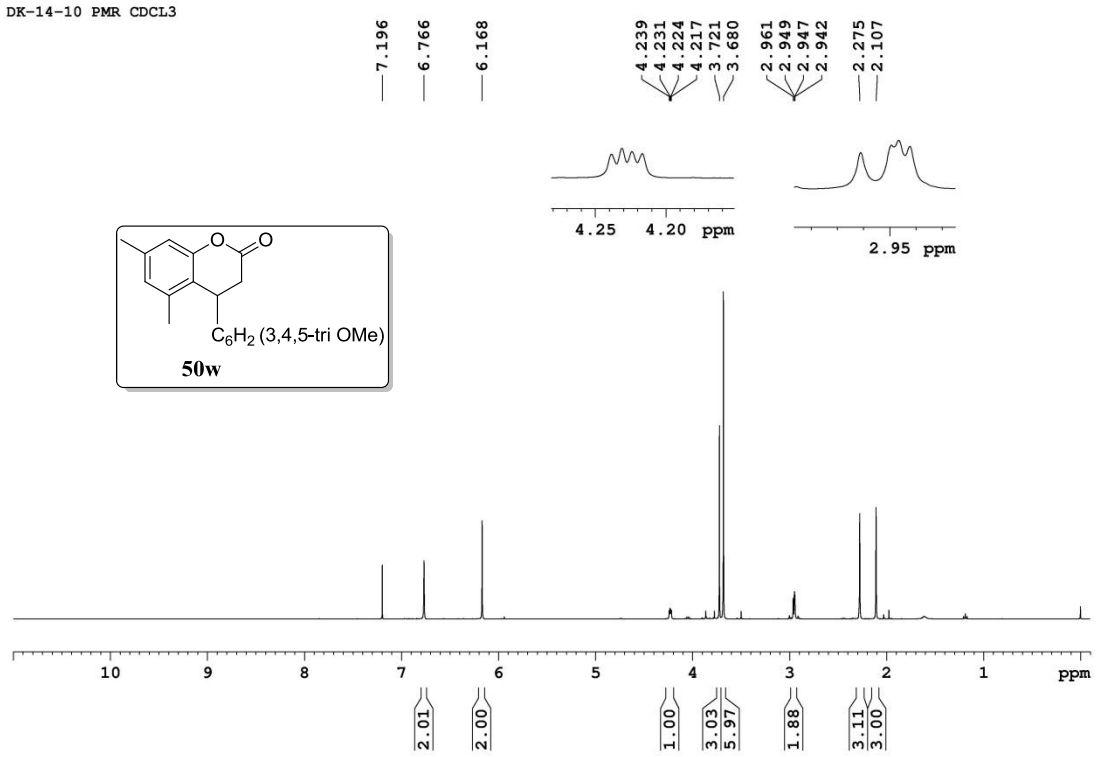
152.00
149.33
148.27
138.73
136.62
132.89
127.34
120.33
119.01
115.36
111.49
110.15
77.47
77.15
76.83
55.85
37.97
37.61
21.10
18.67
O
O
C6H3 (3,4-di OMe)
50u
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

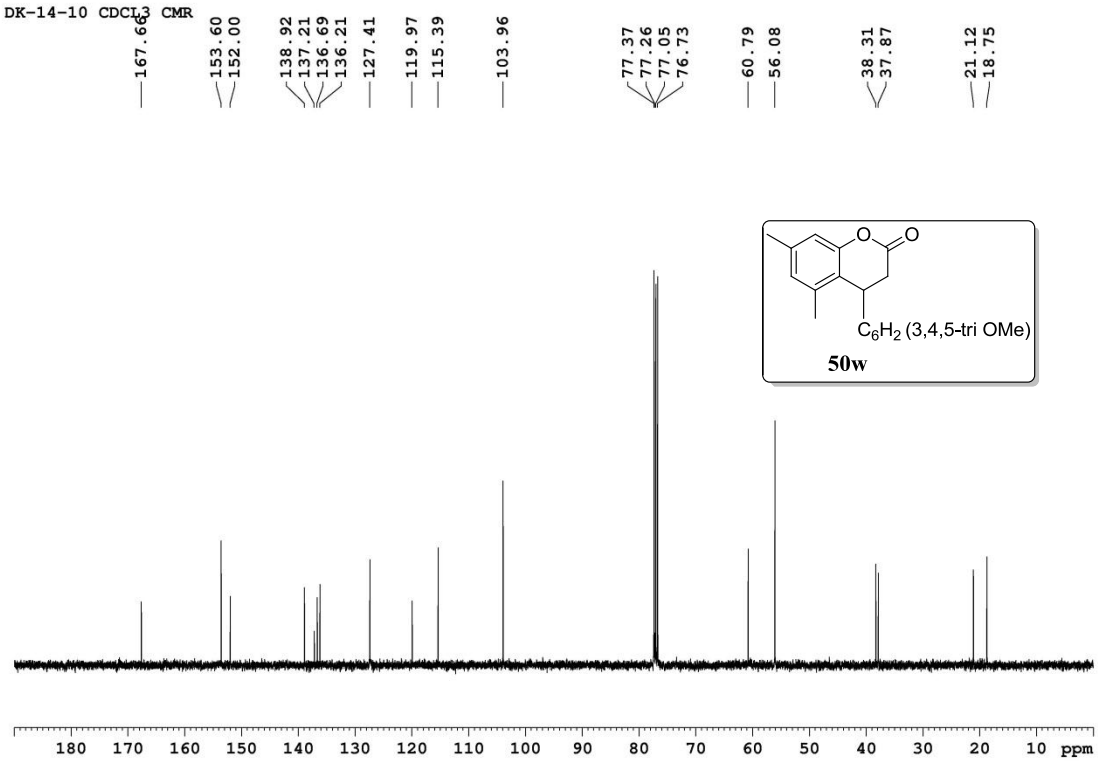

DK-14-06 CDCL3 DEPT
127.34
119.01
115.36
111.48
110.14
55.85
37.97
37.60
21.10
18.67
O
O
C6H3 (3,4-di OMe)
50u
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

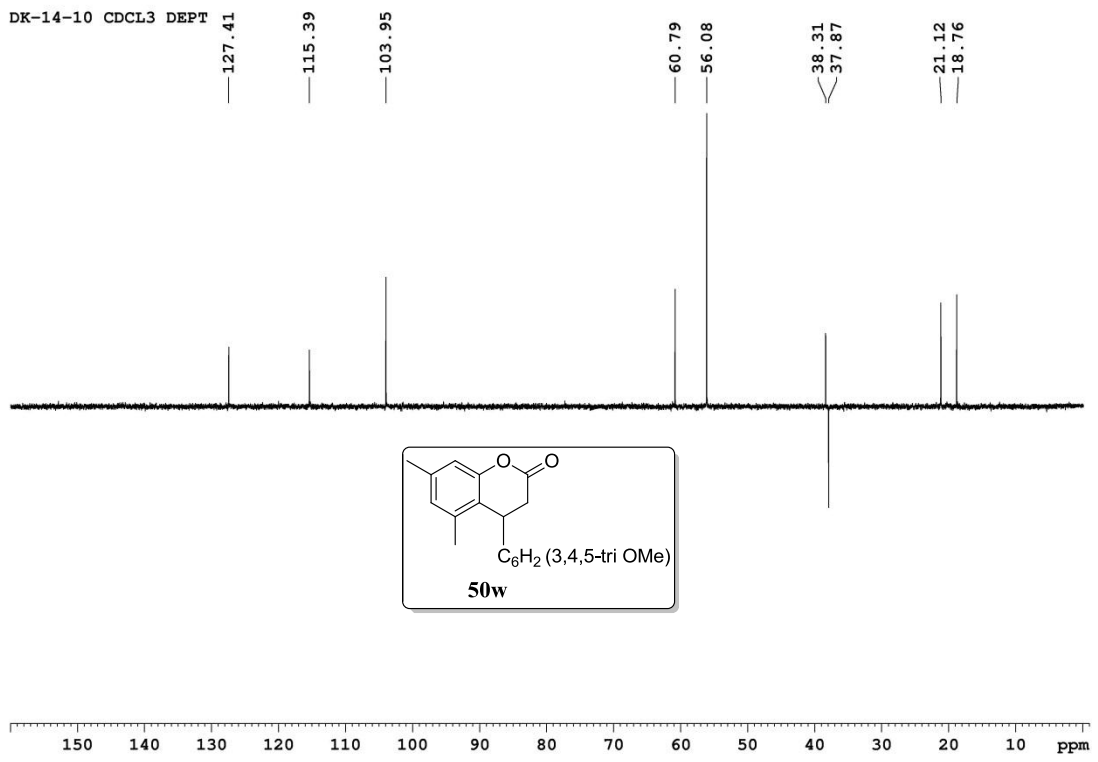

7.276
6.913
6.887
6.844
6.830
6.815
6.743
6.704
6.695
6.689
4.247
4.226
3.872
3.840
3.023
3.015
3.003
2.989
2.305
2.283
7.5
7.0
6.5
6.0
ppm
O
O
C6H3 (3,4-di OMe)
50v
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.95
2.91
1.00
5.69
1.91
5.94

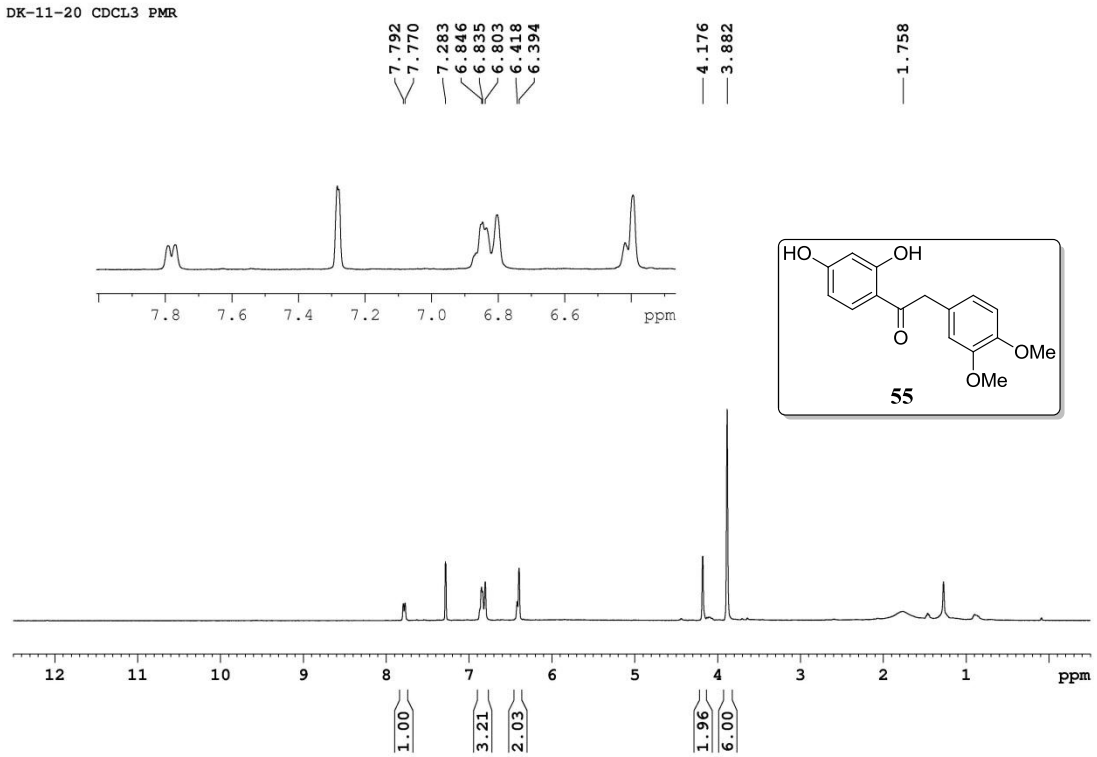

DK-14-06 CDCL3 CMR
168.26
149.69
149.31
148.35
137.67
133.07
125.54
124.97
124.86
123.44
119.75
111.47
110.64
77.53
77.21
76.89
55.90
40.34
37.09
19.90
11.84
O
O
C6H3 (3,4-di OMe)
50v
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

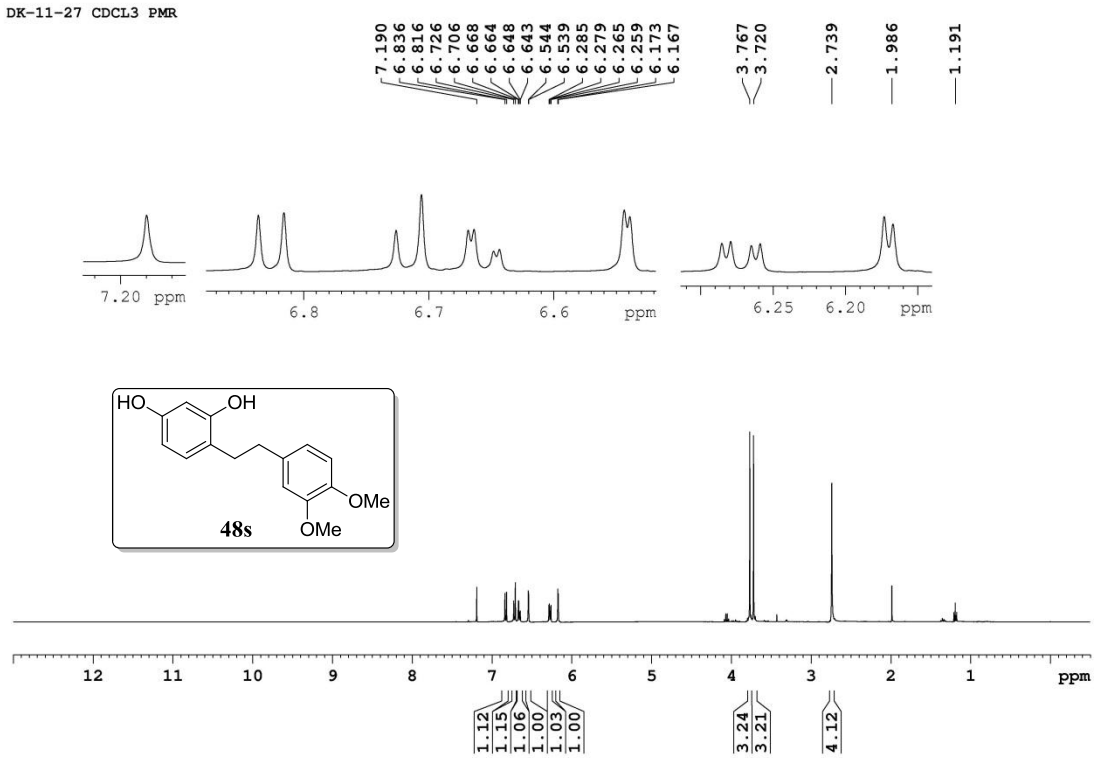

DK-14-06 CDCL3 DEPT
125.54
124.86
119.74
111.43
110.60
55.90
40.33
37.09
19.92
11.85
C6H3 (3,4-di OMe)
50v
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

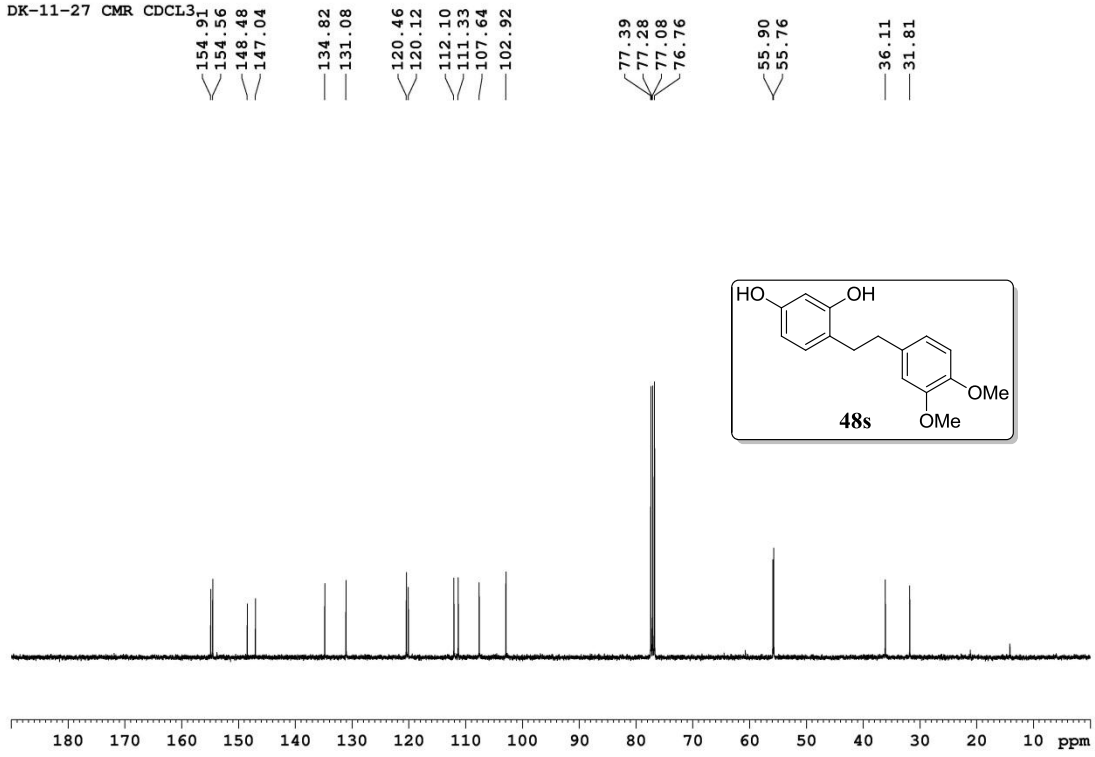

DK-14-10 PMR CDCL3
7.196
6.766
6.168
4.239
4.231
4.224
4.217
3.721
3.680
2.961
2.949
2.947
2.942
2.275
2.107
4.25 4.20 ppm
2.95 ppm
C6H2 (3,4,5-tri OMe)
50w
10 9 8 7 6 5 4 3 2 1 ppm
2.01
2.00
1.00
3.03
5.97
1.88
3.11
3.00

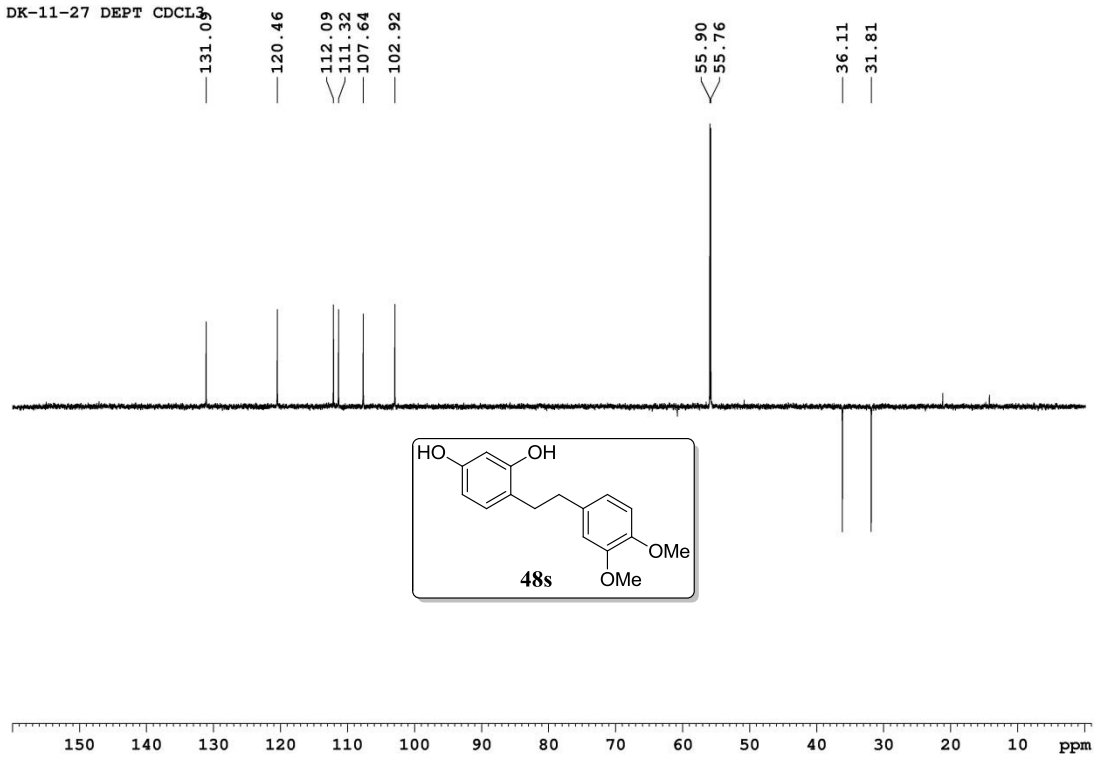

DK-14-10 CDCL3 CMR
167.66
153.60
152.00
138.92
137.21
136.69
136.21
127.41
119.97
115.39
103.96
77.37
77.26
77.05
76.73
60.79
56.08
38.31
37.87
21.12
18.75
C6H2 (3,4,5-tri OMe)
50w
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

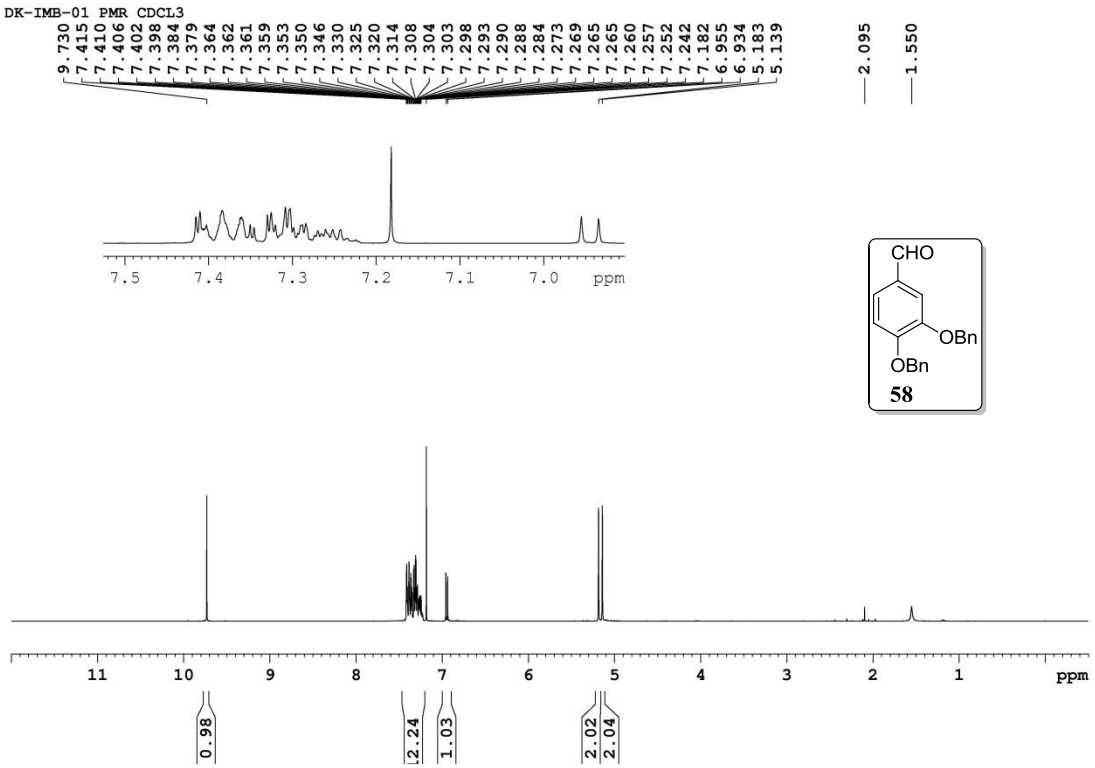

DK-14-10 CDCL3 DEPT
127.41
115.39
103.95
60.79
56.08
38.31
37.87
21.12
18.76
C6H2 (3,4,5-tri OMe)
50w
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

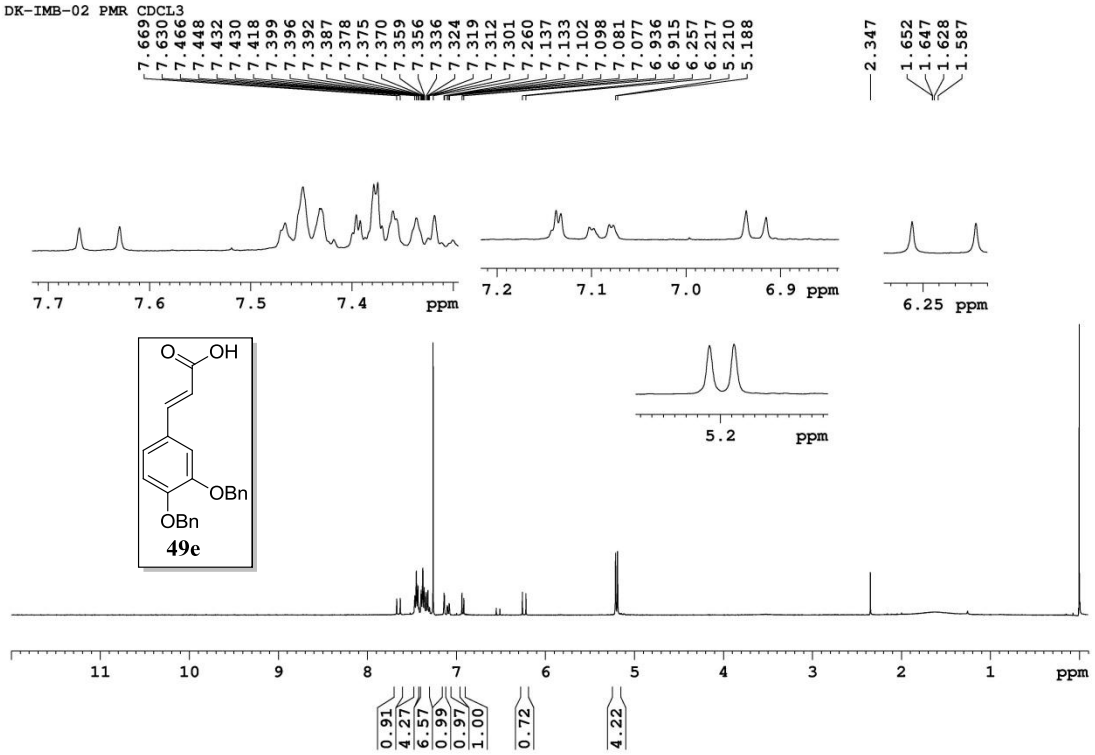

DK-11-20 CDCL3 PMR
7.792
7.770
7.283
6.846
6.835
6.803
6.418
6.394
4.176
3.882
1.758
HO
OH
O
OMe
OMe
55
ppm
1.00
3.21
2.03
1.96
6.00


DK-11-27 CDCL3 PMR
7.190
6.836
6.816
6.726
6.706
6.668
6.664
6.648
6.643
6.544
6.539
6.285
6.279
6.265
6.259
6.173
6.167
3.767
3.720
2.739
1.986
1.191
7.20 ppm
6.8
6.7
6.6
ppm
6.25
6.20
ppm
HO
OH
OMe
OMe
48s
ppm
1.12
1.15
1.06
1.00
1.03
1.00
3.24
3.21
4.12


DK-11-27 CMR CDCL3
154.91
154.56
148.48
147.04
134.82
131.08
120.46
120.12
112.10
111.33
107.64
102.92
77.39
77.28
77.08
76.76
55.90
55.76
36.11
31.81
HO
OH
OMe
OMe
48s
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-11-27 DEPT CDCL3
131.09
120.46
112.09
111.32
107.64
102.92
55.90
55.76
36.11
31.81
HO
OH
OMe
OMe
48s
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-IMB-01 PMR CDCL3
9.730
7.415
7.410
7.406
7.402
7.398
7.384
7.379
7.364
7.362
7.361
7.359
7.353
7.350
7.346
7.330
7.325
7.320
7.314
7.308
7.304
7.303
7.298
7.293
7.290
7.288
7.284
7.273
7.269
7.265
7.265
7.260
7.257
7.252
7.242
7.182
6.955
6.934
5.183
5.139
2.095
1.550
7.5
7.4
7.3
7.2
7.1
7.0
ppm
CHO
OBn
OBn
58
11
10
9
8
7
6
5
4
3
2
1
ppm
0.98
2.24
1.03
2.02
2.04


DK-IMB-02 PMR CDCL3
7.669
7.630
7.466
7.448
7.432
7.430
7.418
7.399
7.396
7.392
7.387
7.378
7.375
7.370
7.359
7.356
7.336
7.324
7.319
7.312
7.301
7.260
7.137
7.133
7.102
7.098
7.081
7.077
6.936
6.915
6.257
6.217
5.210
5.188
2.347
1.652
1.647
1.628
1.587
7.7
7.6
7.5
7.4
ppm
7.2
7.1
7.0
6.9 ppm
6.25 ppm
5.2
ppm
O
OH
OBn
OBn
49e
11
10
9
8
7
6
5
4
3
2
1
ppm
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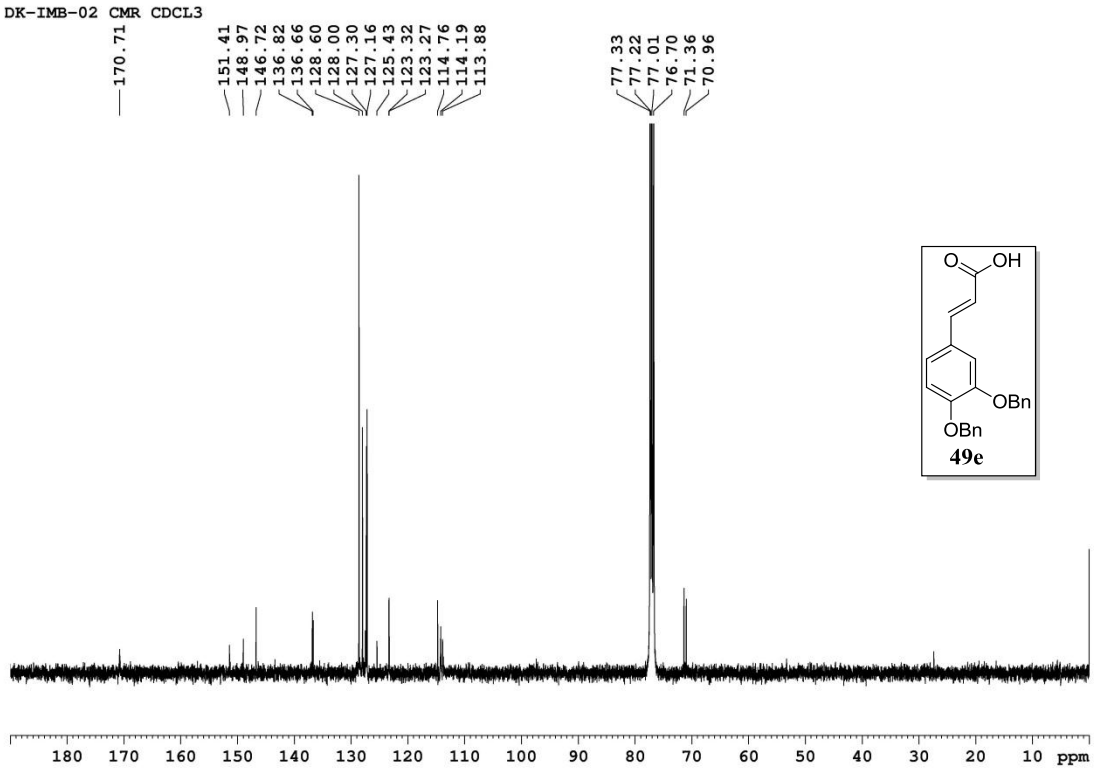
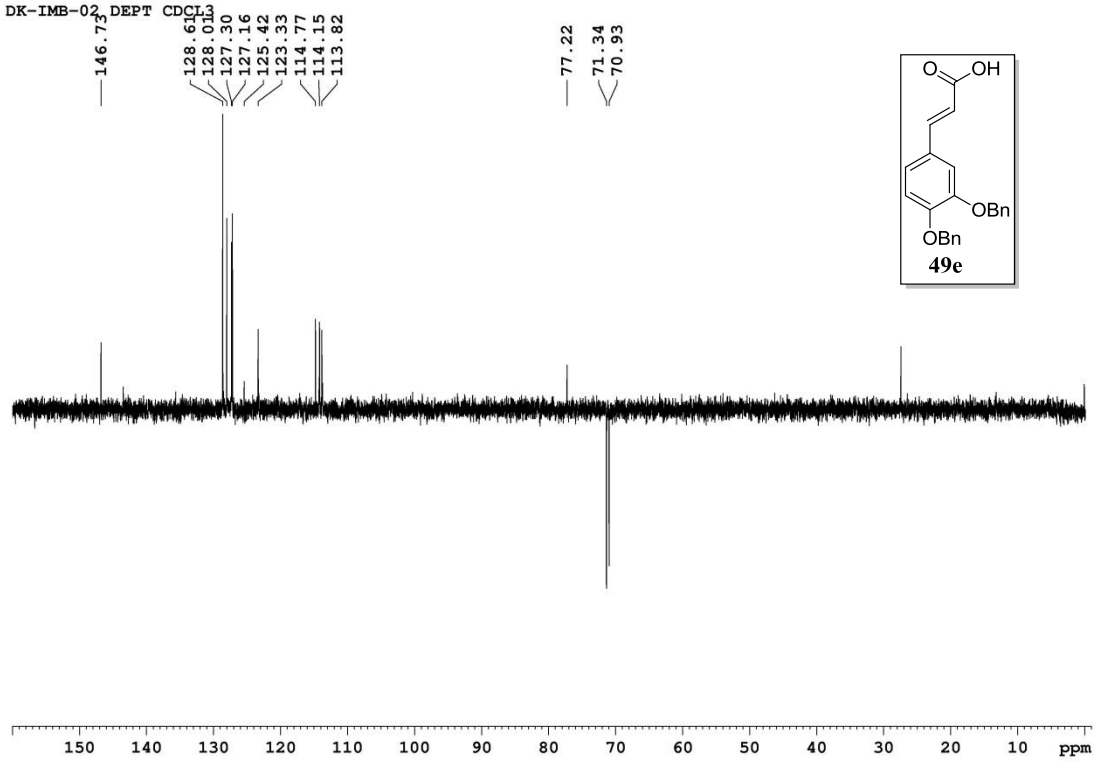
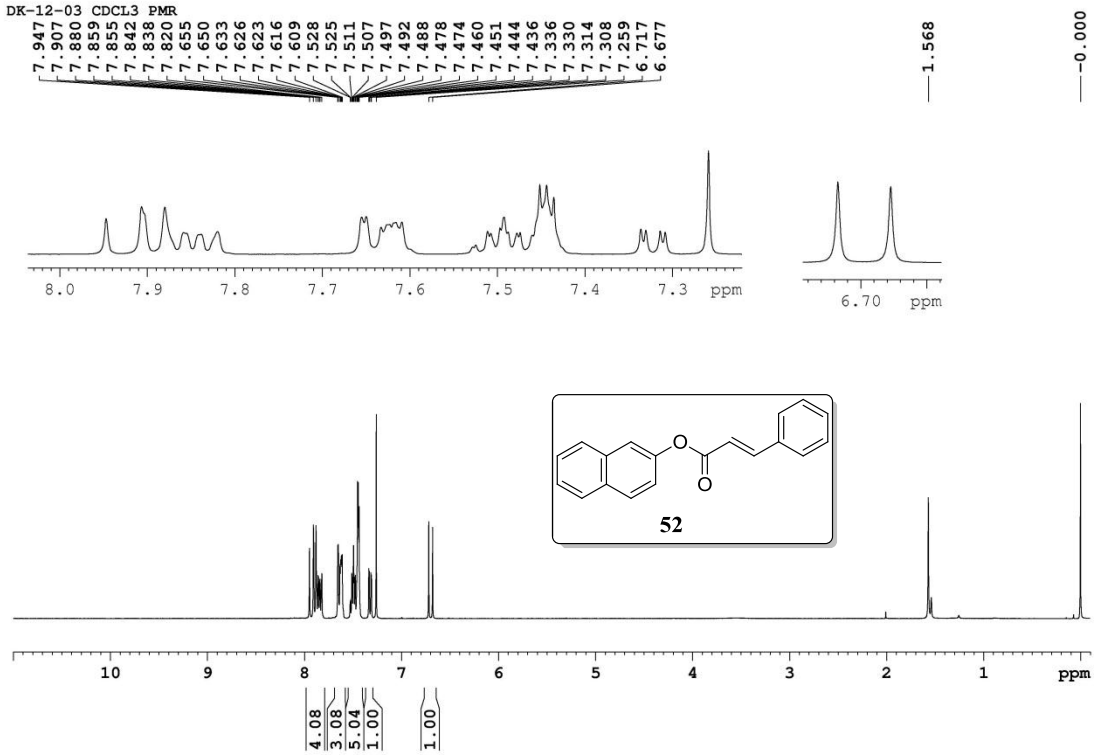
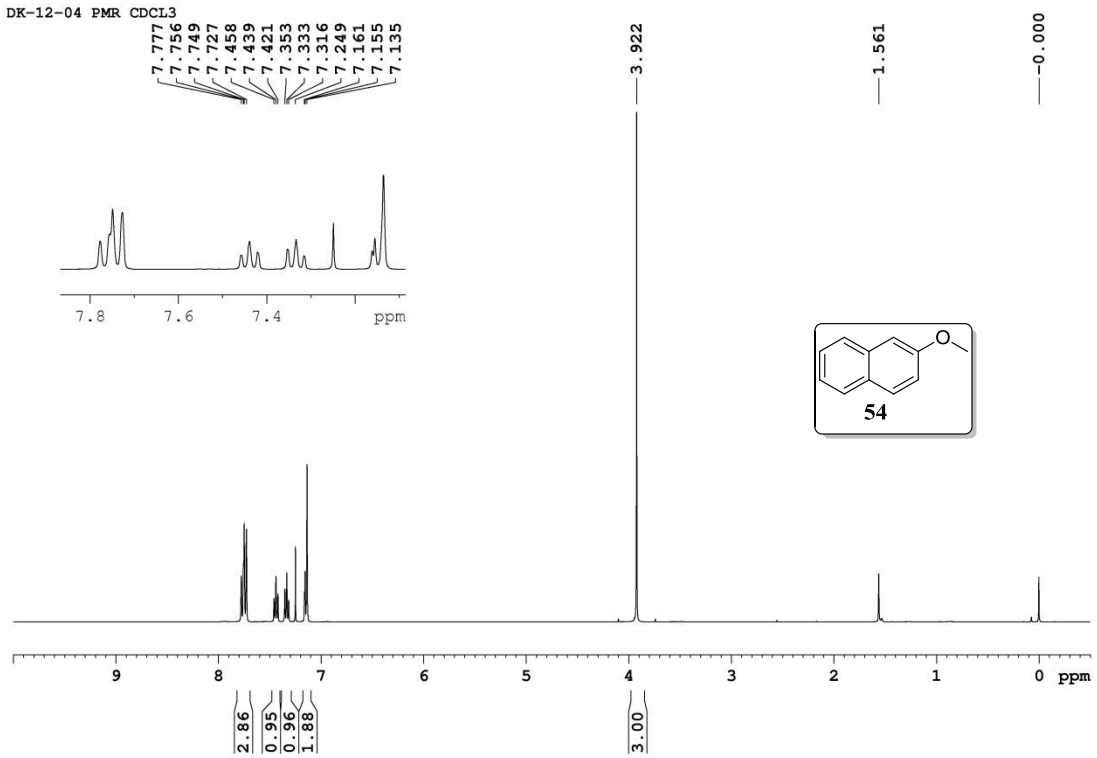
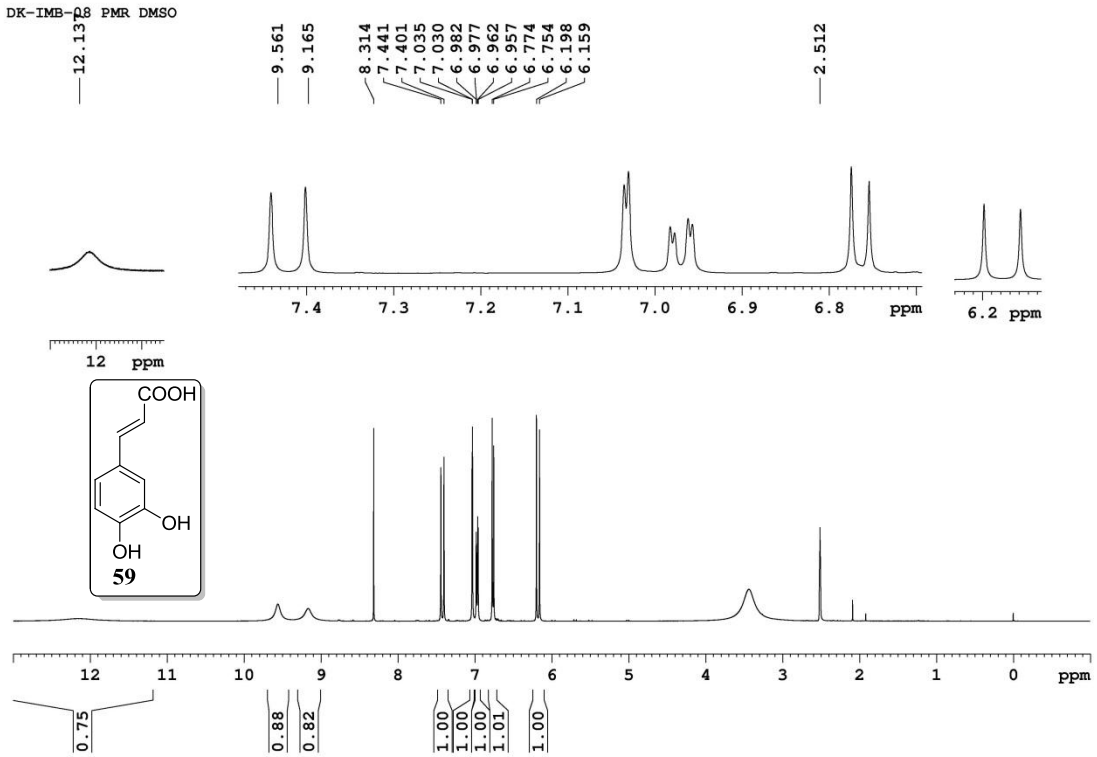
4.27
6.57
0.99
0.97
1.00
0.72
4.22

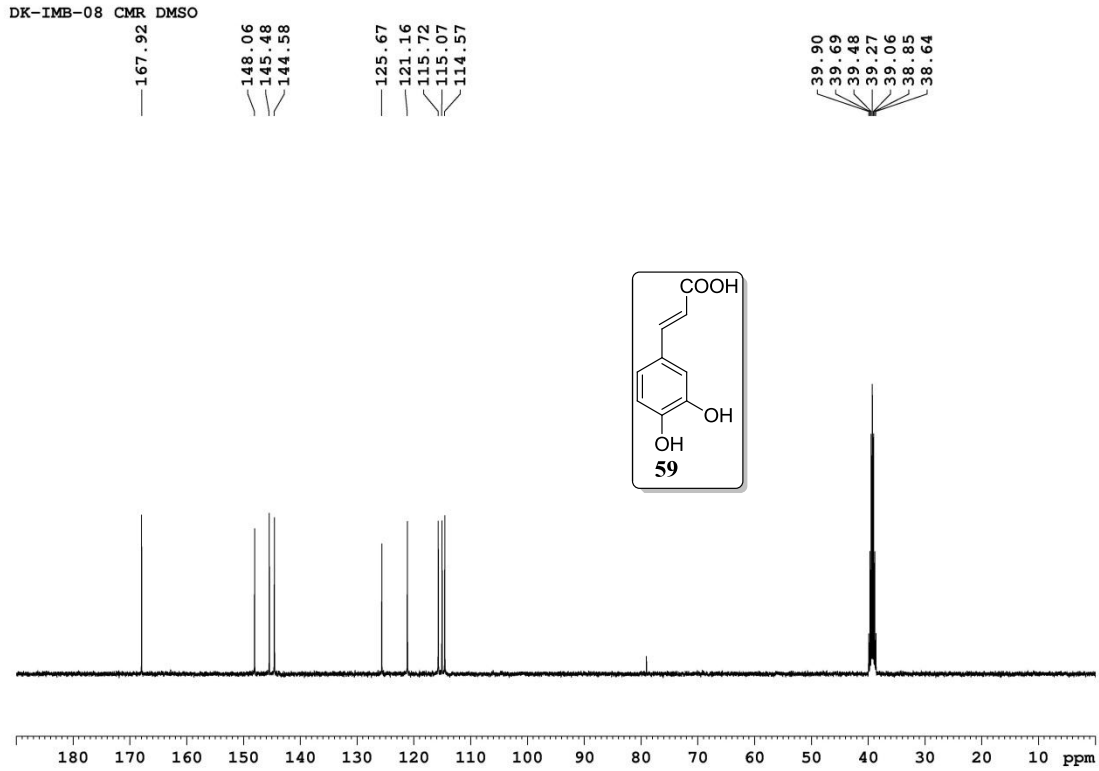

DK-IMB-02 CMR CDCL3
170.71
151.41
148.97
146.72
136.82
136.66
128.60
128.00
127.30
127.16
125.43
123.32
123.27
114.76
114.19
113.88
77.33
77.22
77.01
76.70
71.36
70.96
O
OH
OBn
OBn
49e
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

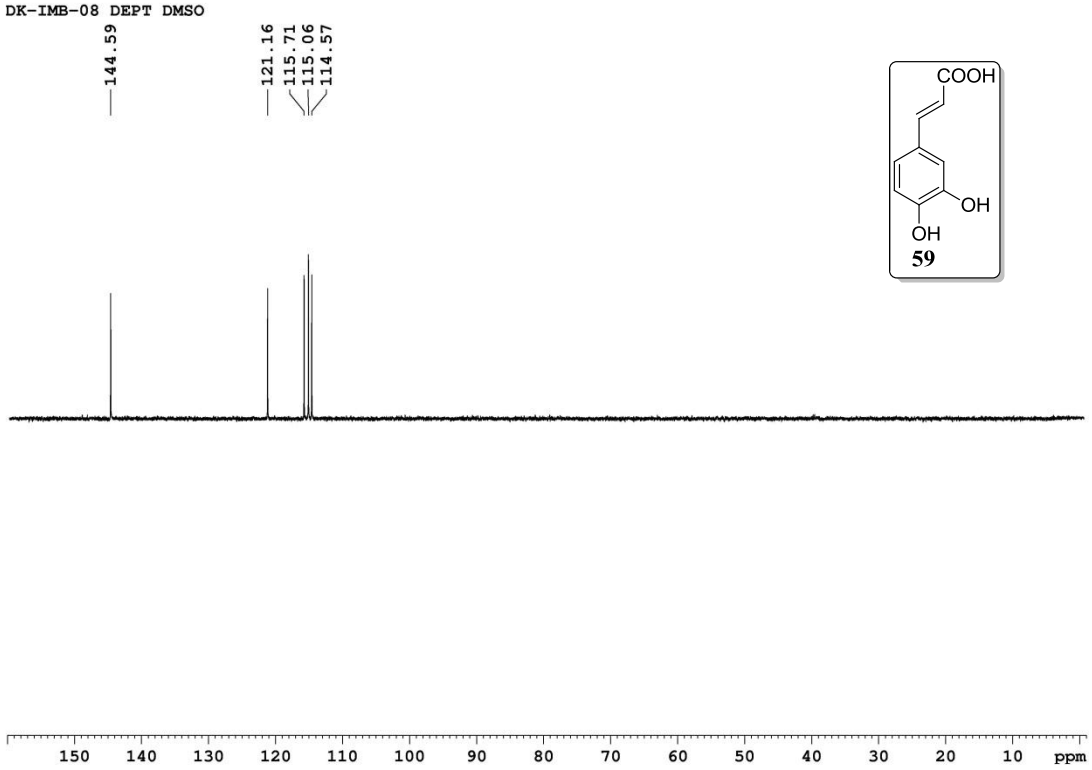

DK-IMB-02 DEPT CDCL3
146.73
128.63
128.01
127.30
127.16
125.42
123.33
114.77
114.15
113.82
77.22
71.34
70.93
O
OH
OBn
OBn
49e
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-12-03 CDCL3 PMR
7.947
7.907
7.880
7.859
7.855
7.842
7.838
7.820
7.655
7.650
7.633
7.626
7.623
7.616
7.609
7.528
7.525
7.511
7.507
7.497
7.492
7.488
7.478
7.474
7.460
7.451
7.444
7.436
7.336
7.330
7.314
7.308
7.259
6.717
6.677
1.568
0.000
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
ppm
6.70
ppm
O
O
52
10
9
8
7
6
5
4
3
2
1
ppm
4.08
3.08
5.04
1.00
1.00


DK-12-04 PMR CDCL3
7.777
7.756
7.749
7.727
7.458
7.439
7.421
7.353
7.333
7.316
7.249
7.161
7.155
7.135
3.922
1.561
0.000
7.8
7.6
7.4
ppm
O
54
9
8
7
6
5
4
3
2
1
0
ppm
2.86
0.95
0.96
1.88
3.00


DK-IMB-08 PMR DMSO
12.137
9.561
9.165
8.314
7.441
7.401
7.035
7.030
6.982
6.977
6.962
6.957
6.774
6.754
6.198
6.159
2.512
7.4
7.3
7.2
7.1
7.0
6.9
6.8
ppm
6.2 ppm
12 ppm
COOH
OH
OH
59
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.75
0.88
0.82
1.00
1.00
1.00
1.01
1.00


DK-IMB-08 CMR DMSO
167.92
148.06
145.48
144.58
125.67
121.16
115.72
115.07
114.57
39.90
39.69
39.48
39.27
39.06
38.85
38.64
COOH
OH
OH
59
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


DK-IMB-08 DEPT DMSO
144.59
121.16
115.71
115.06
114.57
COOH
OH
OH
59
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Chapter 3

Synthesis of naturally occurring carbazole alkaloids and evaluation of antioxidant activity of selected compounds

3.1: Introduction

More than 100 years ago, Graebe and Glaser described the first isolation of the parent compound 9*H*-carbazole **1** (*Figure 1*), obtained from the anthracene fraction of coal tar distillate.[1] Ninety years later, in 1965, Chakraborty *et al.*[2] described the isolation of murrayanine (**7)** from *Murraya koenigii* Spreng, which was the first report of a naturally occurring carbazole alkaloid. Carbazole alkaloids are classified into two main groups based on their natural origin. Carbazole alkaloids isolated from the higher plants constitute the first group, generally featuring a C1-substituent at C-3 (a methyl group or its oxidized equivalents). The carbazoles constituting the second group usually lack such a carbon substituent at C-3 which are isolated from other natural sources like microorganisms (for both the groups exceptions are known). Most of the carbazole alkaloids belong to the first group.[3]

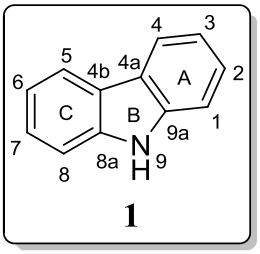


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Figure 1

According to the systematic classification of tricyclic carbazole alkaloids suggested by Knölker and co-workers, carbazoles are classified based on their oxygenation pattern as non-oxygenated carbazole alkaloids, monooxygenated carbazole alkaloids, dioxygenated carbazole alkaloids, trioxygenated carbazole alkaloids, carbazole-1,4-quinone alkaloids, carbazole-1,4-quinol alkaloids and carbazole-3,4-quinone alkaloids.[3] Carbazole alkaloids fused to a furan ring are classified as furocarbazole alkaloids. This group is further divided on the basis of the annulation mode of the furan ring at the carbazole framework.

In India, the leaves of *Murraya koenigii* (known as currypatta or curry-leaf tree) are used in curry. The discovery of antibiotic properties of murrayanine developed a strong interest amongst the chemists and biologists leading to enormous growth in the field of isolation, biological activity studies and synthesis of carbazole alkaloids.[3]

The higher plants of the genus *Murraya* (family Rutaceae) and the trees growing in southern Asia represent the chief source of 1-oxygenated carbazole alkaloids. In 1983, Furukawa and

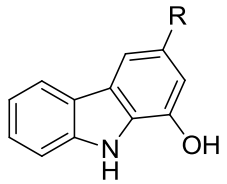
co-workers isolated murrayafoline-A (**5**) from the ethanol extract of the root bark of *Murraya euchrestifolia* collected in Taiwan *(Figure 2).*[4, 5] Two decades later, murrayafoline-A was isolated from *Glycosmis stenocarpa* Guillaumin by Cuong *et al.* in Northern Vietnam.[6] Koenoline (**6**), was isolated by Fiebig *et al.* from the root bark of *Murraya koenigii*.[7] Murrayanine (**7**) was isolated from two different genera of the Rutaceae family, *Murraya koenigii* [2c] and *Clausena heptaphylla*.[8] Cuong *et al.* isolated murrayanine (**7**) from another genus of the Rutaceae family, *Glycosmis stenocarpa* Guillaumin.[6]

Mukoeic acid (**8**), the first carbazole carboxylic acid obtained from a plant, was isolated from the alcoholic extract of the stem bark of *Murraya koenigii*.[9, 10] Mukonine (**9**)[11] and 1-hydroxy-3-methylcarbazole (**4**)[12] were also isolated from the same plant source. Connolly and co-workers described the isolation of *O*-demethylmurrayanine (**3**) from the combined extracts of the stem bark and roots of *Clausena anisata*.[13] Mukoline (**10**) and mukolidine (**11**) were isolated from *Murraya koenigii* Spreng.[14]

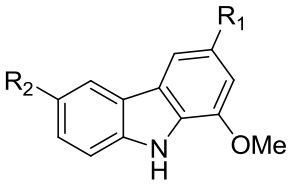
In 1992, Wu and Huang isolated clausine D (1-hydroxy-4-prenylcarbazole, **14**) from *Clausena excavata*, which showed inhibition of platelet aggregation.[15] Ito *et al.* isolated clausamine D (**13**),[16a] clausamine E (**19**),[16a] clausamine G (**21**),[16a] ekeberginine (**12**),[16a] clausamine A-C (**31**, **32**, **27**),[16b] furanoclausamine A-B (**36**, **37**),[16c] from *Clausena anisata*. Claulansine C, D, G, I (**35**, **44**, **43**, **18**),[17] claulamine C-E (**25-26**, **45**),[18] claulansine M (**47**),[19] claulamine A (**42**),[20] mafaicheenaine A (**38**),[17] mafaicheenamine B-C (**39**, **40**),[21] mafaicheenamine E (**41**),[22] claulansine A-B (**23**, **24**),[17] clausenaline B-D (**33, 34**, **22**),[18] were isolated from *Clausena lansium*. Clausevatine D-G (**28-30**, **46**),[23] were isolated from *Clausena excavata*.

Carbazoles exhibit promising biological activities such as anti-microbial,[2b] anti-inflammatory,[18] antitumor,[16a, 21] cytotoxic,[16c] neuroprotective[17] activities.

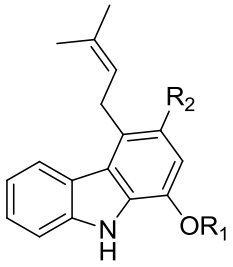
Murrayanine (**7**) is known to exhibit antimicrobial properties against human pathogenic fungi.[2b] Clausine D (**14**) showed inhibition of platelet aggregation. *O*-Demethylmurrayanine (**3**), clausine D (**14**) and murrayanine (**7**), inhibited elastase release with IC_{50} values in the range from 2.0 to 6.9 μM.[18]



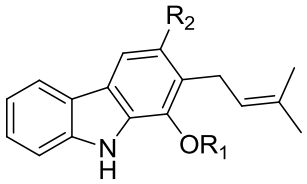
Clausine E (**2**) R= COOMe
O-Demethylmurrayanine (**3**) R = CHO
1-Hydroxy-3-methylcarbazole (**4**) R = Me



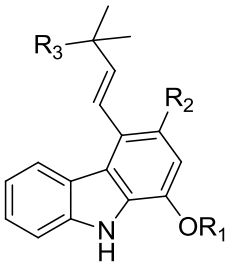
Murrayafoline A (**5**) R_1= Me, R_2 = H
Koenoline (**6**) R_1= CH_2OH, R_2 = H
Murrayanine (**7**) R_1= CHO, R_2 = H
Mukoeic acid (**8**) R_1= COOH, R_2 = H
Mukonine (**9**) R_1= COOMe, R_2 = H
Mukoline (**10**) R_1= H, R_2 = CH_2OH
Mukolidine (**11**) R_1= H, R_2 = CHO



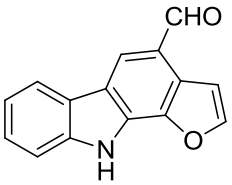
Ekeberginine (**12**) R_1= Me, R_2 = CHO
Clausamine D (**13**) R_1= Me, R_2 = COOMe
Clausine D (**14**) R_1= H, R_2 = CHO
Clausine F (**15**) R_1= H, R_2 = COOMe



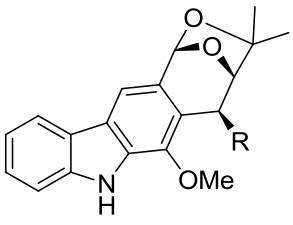
Clausenapin (**16**) R_1= Me, R_2 = Me
Indizoline (**17**) R_1= Me, R_2 = CHO
Claulansine I (**18**) R_1= H, R_2 = CHO



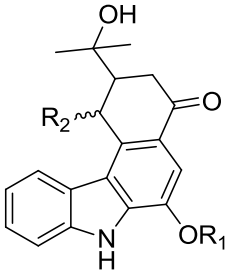
Clausamine E (**19**) R_1= Me, R_2 = COOMe, R_3 = OH
Clausamine F (**20**) R_1= H, R_2 = COOMe, R_3 = OH
Clausamine G (**21**) R_1= Me, R_2 = COOMe, R_3 = OOH



Clausenaline D (**22**)



Claulansine A (**23**) R = H
Claulansine B (**24**) R = OH
Claulamine C (**25**) R = OMe
Claulamine D (**26**) R = OAc



Clausamine C (**27**) R_1= Me, R_2 = H
Clausevatine D (**28**) R_1= R_2 = H
Clausevatine E (**29**) R_1= H, R_2 = *cis*-OH
Clausevatine F (**30**) R_1= H, R_2 = *tras*-OH

Figure 2: Structures of some naturally occurring carbazole alkaloids.

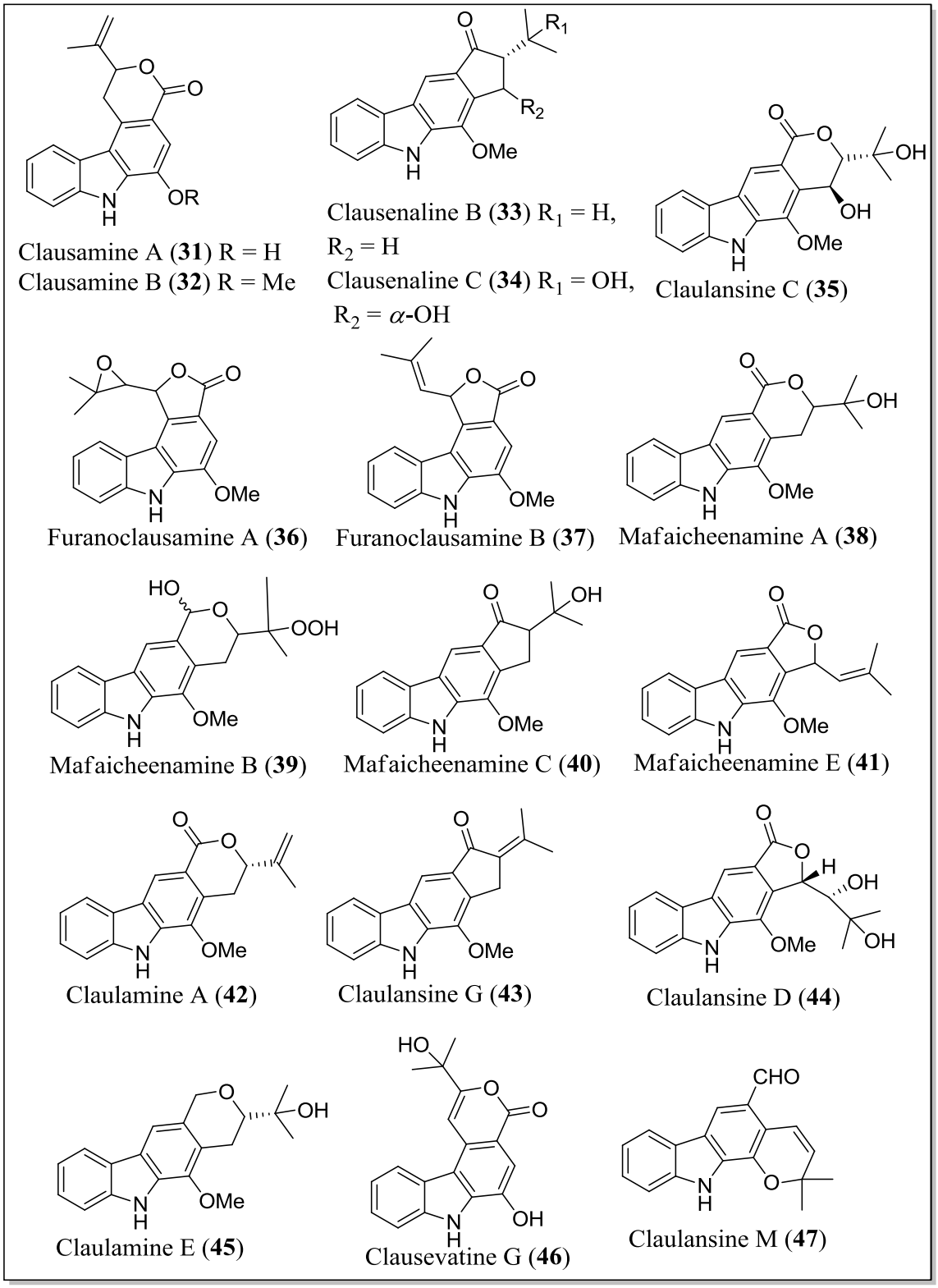


Figure 2: Structures of some naturally occurring carbazole alkaloids.

Clausamines D (**13)**, E-G **(19-21**) have showed potent inhibitory effects on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA) activation in Raji cells.[16a] Claulansine A (**23**), claulansine I (**18**) and murrayanine (**7**) exhibited selective neuroprotective effects on neuron-like PC12 cells at the concentration of 10 μM.[17] Clausamine E (**19**) showed cytotoxic activity against the human leukemia cell line HL-60.[16c] Mafaicheenamine A-B (**38-39**),[21] indizoline (**17**)[21] and murrayanine (**7**)[21, 24] were found to be active against three human cancer cell lines namely, oral cavity cancer (KB), breast cancer (MCF7) and small cell lung cancer (NCI-H187).

These interesting biological activities of carbazole alkaloids attracted our attention towards development of new synthetic routes for the synthesis of some of these carbazole alkaloids.

The synthetic strategies employed for building of the carbazole frameworks have been periodically reviewed by Knölker and co-workers.[3] Recent advances and trends involved in synthesis of carbazoles have also been reviewed by Yaqub[25] *et al.* and Mal[26] and co-workers.

The Fischer indolization,[27, 28] intramolecular cyclization of indole,[29] Graebe-Ullmann synthesis,[30] an allene-mediated electrocyclic reaction involving the indole 2,3-bond,[31] [2+2+2] cycloaddition,[32] Diels-Alder reaction between an imine quinone and cyclic diene,[33] Suzuki-Miyaura coupling,[34] Lewis acid promoted intramolecular amination and oxylation of biaryl triazenes,[35] ring closing metathesis,[36] [4+2] annulation process,[37] transition metal-catalyzed C-C or C-N bond forming reactions have been examined widely.[38] Knölker and co-workers have also reported numerous iron-mediated synthesis of carbazole alkaloids over the past two decades.[39]

Section A: Total synthesis of Clausine E

3.A.1: Occurrence and biological activities of clausine E

Clausine E (**2**) also known as clauszoline I was isolated from various plant sources like stem bark of *Clausena excavata*,[40,41] from *Clausena harmandiana*[42-44] and *Clausena emarginata*.[45] Clausine E showed inhibition of rabbit platelet aggregation and vasocontraction.[41] Its growth inhibitory activity against several cancer cell lines by inhibiting PKC$^{\delta}$ phosphorylation as well as decreasing F-actin staining RhoA activity has been reported.[46] Clausine E exhibited cytotoxicity against three human cancer cell lines, oral cavity cancer (KB), breast cancer (MCF7) and small cell lung cancer (NCI-H187).[24] Clausine E is also known to possess antioxidant property.[43]

3.A.2: Literature synthetic methods

The synthetic methods for carbazole alkaloid **2** are divided into two categories based on the way to construct the carbazole core. One way is to form the pyrrolyl ring and other way involves construction of the benzene ring starting from an indole derivative. There are nine literature reports on the synthesis of clausine E. Furthermore, we have classified these methods based on the formation of the final carbazole framework *(Figure 3).*

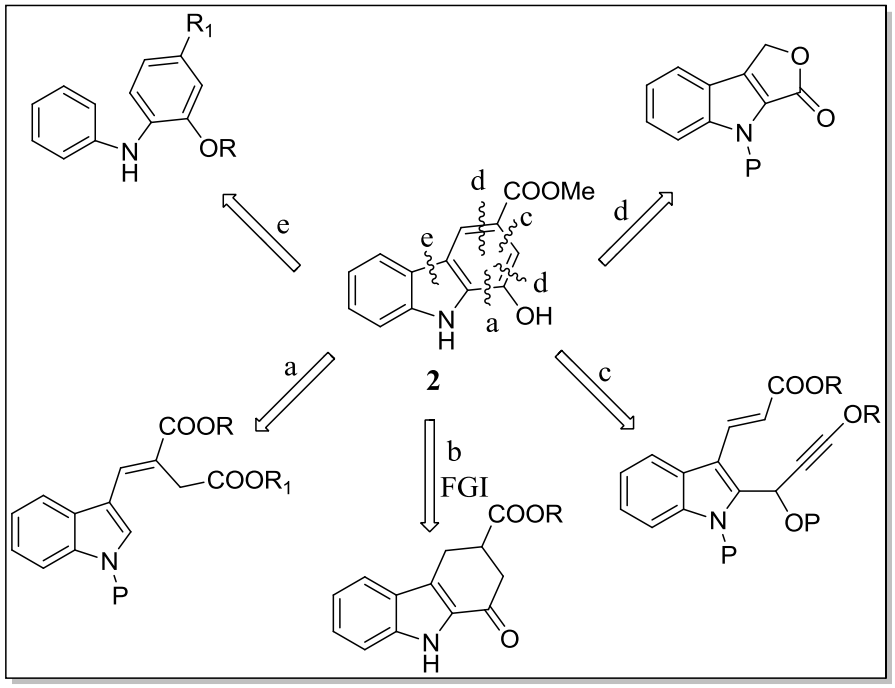
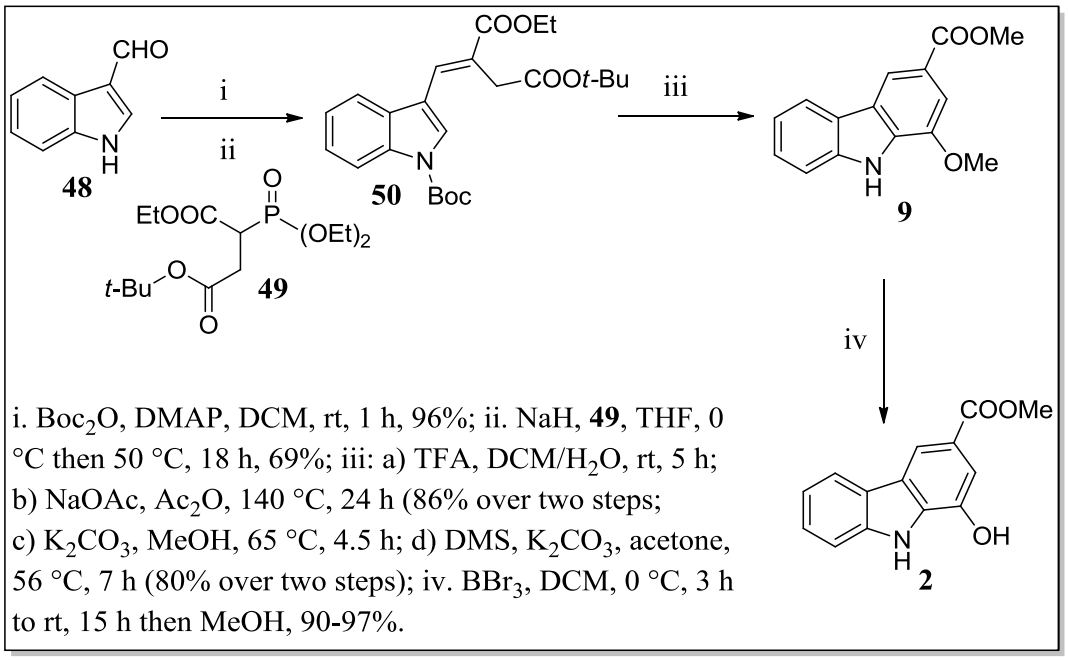


Figure 3: Common synthetic disconnections of clausine E.

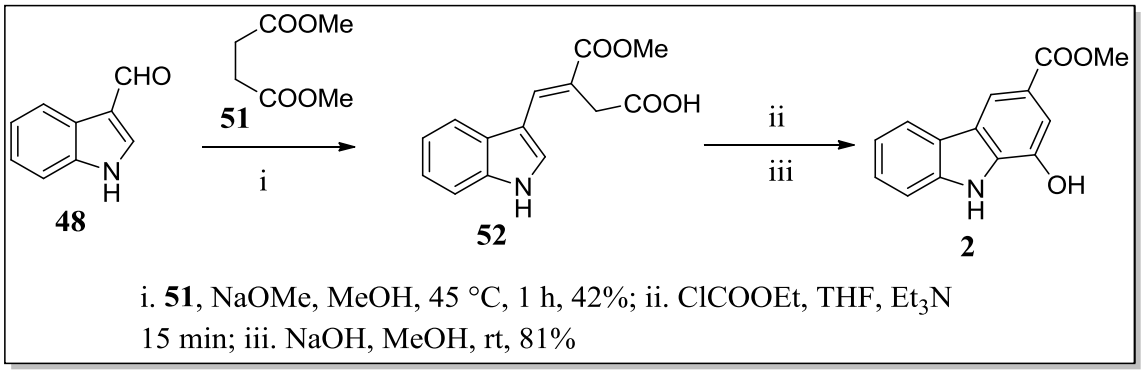
3.A.2.1: By intramolecular cyclization (Route a)

The first synthesis of clausine E was described by Bringmann *et al.*[29c] in the year 1998, starting from indole-3-carbaldehyde using Horner-Emmons reaction and intramolecular cyclization as the crucial steps. Olefination of the *N*-protected indole-3-carbaldehyde was carried out using phosphonate **49** with a Horner-Emmons reaction in 69% yield. *N*-Deprotection as well as *t*-butyl ester cleavage of compound **50** was accomplished using TFA, followed by cyclization of the resulting intermediate with sodium acetate in acetic anhydride. Subsequent methanolysis directly yielded clausine E. However it was not purified at this stage. The product was methylated with dimethyl sulfate to give mukonine (**9**). Treatment of **9** with boron tribromide in dichloromethane gave clausine E (**2**) *(Scheme 1)*.



Scheme 1

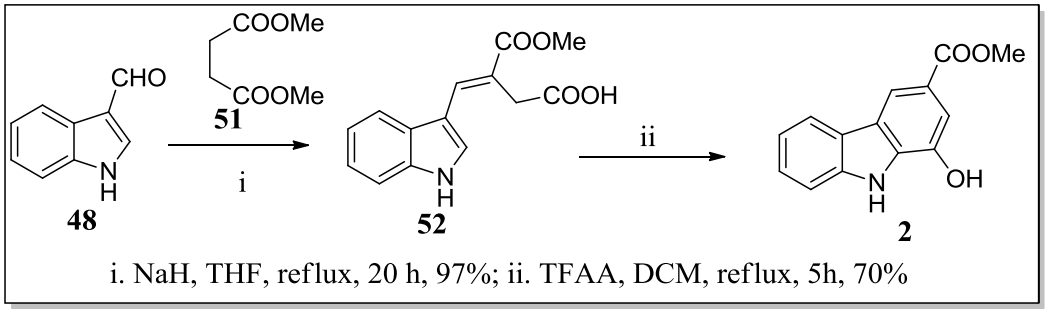
In the same year Brenna *et al.*[29b] reported the synthesis of clausine E starting from indole-3-carbaldehyde *via* a base-promoted cyclization. Reaction of indole-3-carbaldehyde with dimethyl succinate (**51**) and sodium methoxide in methanol afforded the Stobbe condensation product **52**. In a one- pot operation the compound **52** was converted to a mixed anhydride and cyclized to the aromatic derivative by reacting with ethyl chloroformate in presence of triethylamine. The aromatic derivative was deacetylated with sodium hydroxide in methanol to give clausine E in 81% yield *(Scheme 2)*.



i. **51**, NaOMe, MeOH, 45 °C, 1 h, 42%; ii. ClCOOEt, THF, Et_3N 15 min; iii. NaOH, MeOH, rt, 81%

Scheme 2

Recently Liu *et al.*[29e] reported an efficient synthesis of clausine E *via* the TFAA-mediated intramolecular cyclization of the succinic monoester **52**. The starting monoester **52** was obtained from Stobbe condensation of indole-3-carbaldehyde with dimethyl succinate (**51**) using sodium hydride as a base *(Scheme 3)*.

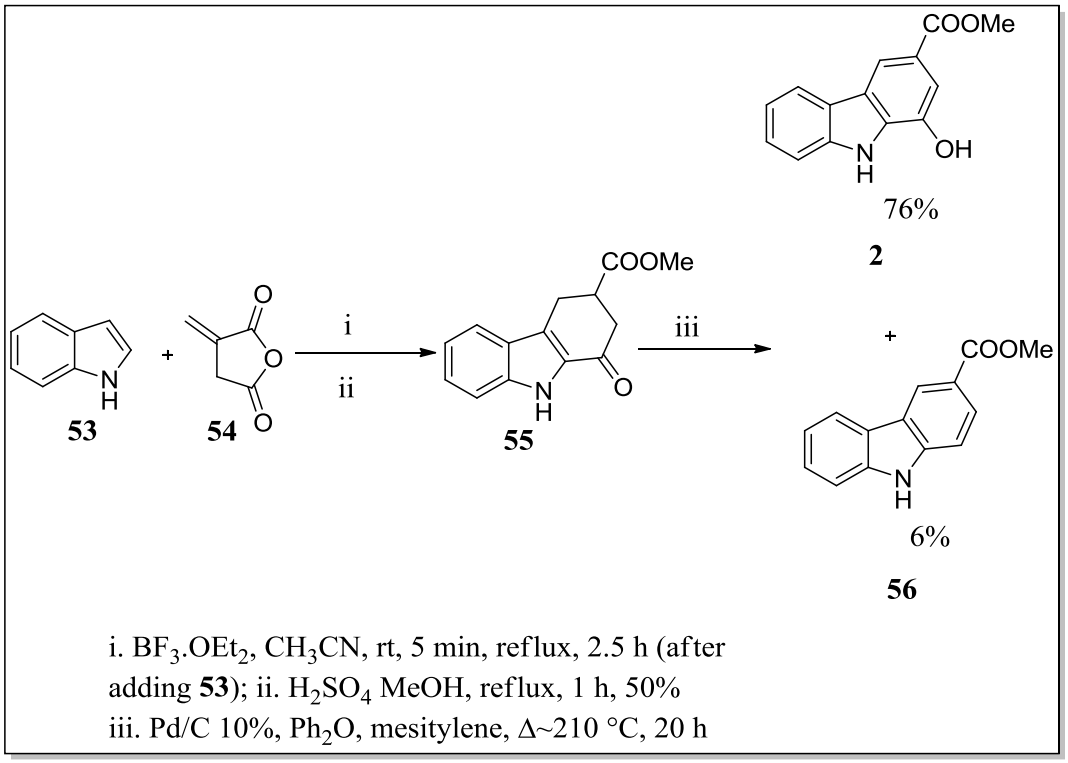


i. NaH, THF, reflux, 20 h, 97%; ii. TFAA, DCM, reflux, 5h, 70%

Scheme 3

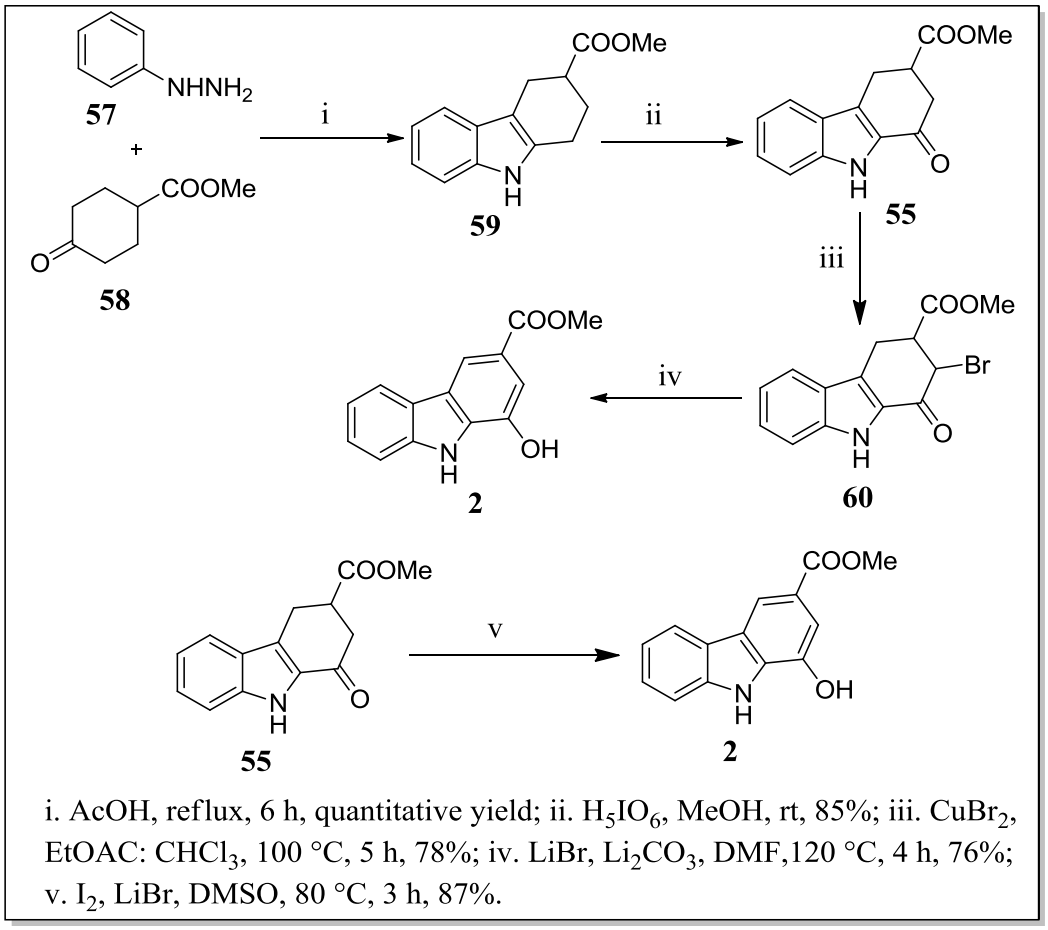
3.A.2.2: By aromatization (*via* 1-oxotetrahydrocarbazole, Route b)

Bergman and Johnson reported the synthesis of clausine E by utilizing a Michael addition type reaction between itaconic anhydride (**54**) and indole (**53)** in the presence of Lewis acid catalyst ($BF_3.OEt_2$).[29d] The 1-oxotetrahydrocarbazole **55** was subjected to Pd/C catalyzed aromatization to give clausine E as the major product *(Scheme 4)*.



Scheme 4

Recently, Humne *et al.* synthesized clausine E using Fischer-Borsche method and aromatization of 1-oxotetrahydrocarbazole using molecular iodine.[28a] The tetrahydrocarbazole **59**, obtained by Fischer indolization was treated with periodic acid in methanol to give 1-oxotetrahydrocarbazole derivative **55** in good yield. Initially introduction of bromo group at the *α*-position of **55** using $CuBr_2$ followed by aromatization using $LiBr/Li_2CO_3$ in DMF was carried out to give clausine E in 76% yield. Improved yield of clausine E was obtained when 1-oxotetrahydrocarbazole **55** was subjected to a combination of LiBr and molecular iodine in DMSO at 80 °C *(Scheme 5)*.

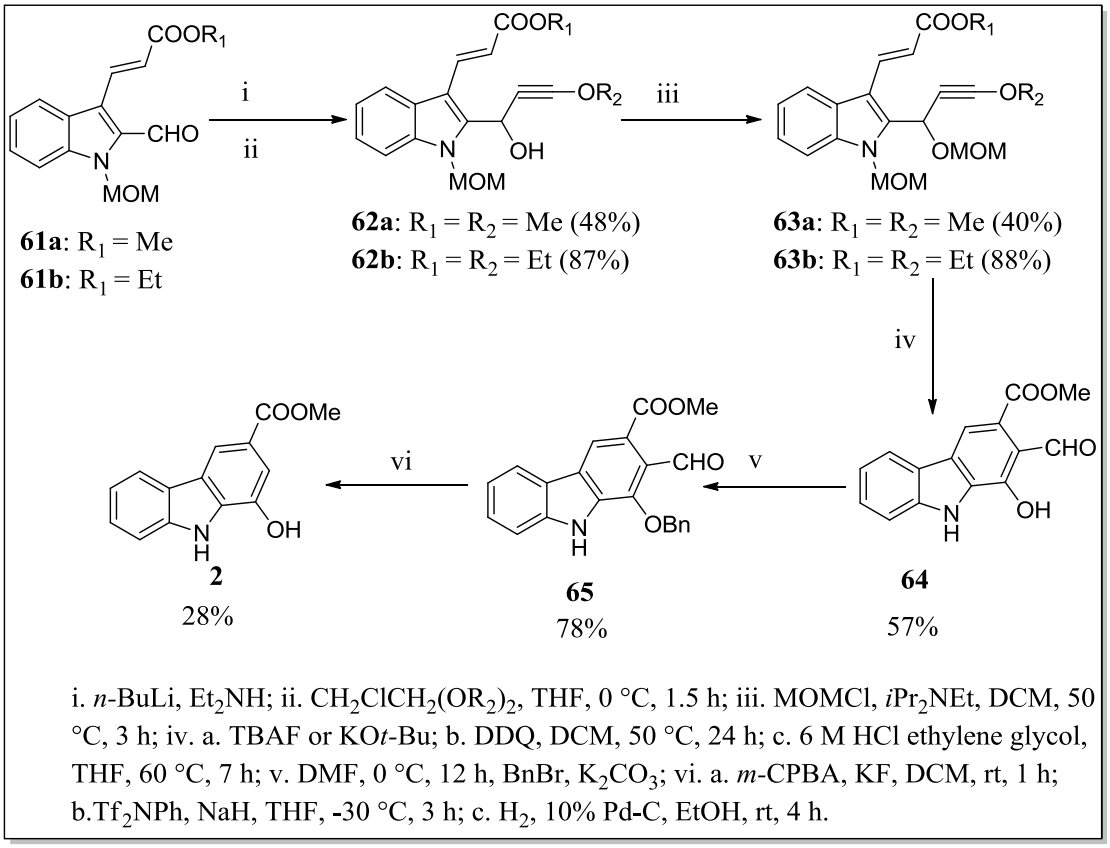


i. AcOH, reflux, 6 h, quantitative yield; ii. H_5IO_6, MeOH, rt, 85%; iii. $CuBr_2$, EtOAC: $CHCl_3$, 100 °C, 5 h, 78%; iv. LiBr, Li_2CO_3, DMF,120 °C, 4 h, 76%; v. I_2, LiBr, DMSO, 80 °C, 3 h, 87%.

Scheme 5

3.A.2.3: By Electrocyclization (Route c)

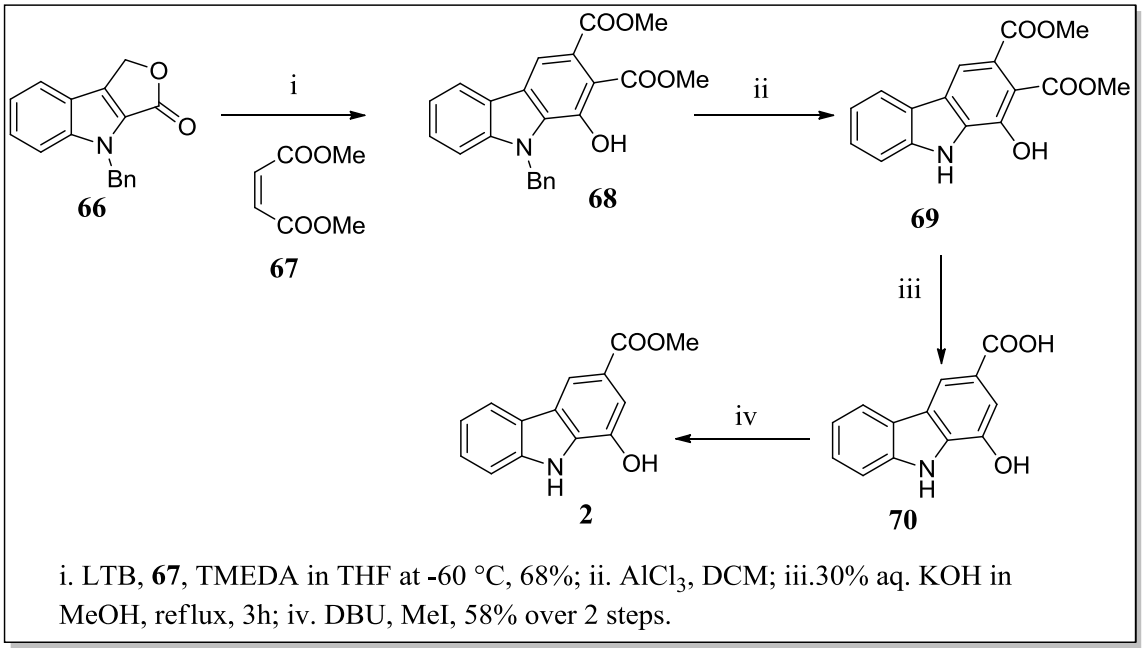
Hibino and co-workers developed the synthesis of clausine E *via* an allene mediated electrocyclization.[31] Nucleophilic addition to **61a** and **61b** with lithium methoxyacetylide or ethoxyacetylide, was carried out to give the propargyl alcohols **62a** and **62b** respectively. The propargyl ethers **63a** and **63b** obtained after protection with chloromethyl methyl ether were transformed into the cyclized derivative **64** *via* a base promoted electrocyclization followed by oxidation of alkoxymethyl group with DDQ and subsequent deprotection of methoxy methyl group. Further benzylation of **64** yielded **65** in 78% yield. Baeyer-Villiger oxidation of **65** followed by treatment with *N*-phenyl bistrifluoromethanesulfonylamide in presence of sodium hydride gave the corresponding triflate, which was subjected to hydrogenolysis to give clausine E *(Scheme 6)*.



Scheme 6

3.A.2.4: By Benzannulation (Route d)

Mal and co-workers have described a lateral lithiation initiated annulations for the synthesis of various 1-oxygenated carbazole alkaloids, including clausine E.[37d] *N*-Benzylfuroroindolone (**66)** was subjected to annulation with dimethyl maleate (**67**) in the presence of lithium *t*-butoxide and TMEDA to give product **68** in 68% yield. Further the *N*-deprotected product **69** was subjected to selective C-2 hydrolytic demethoxycarbonylation followed by esterification to furnish clausine E *(Scheme 7).*



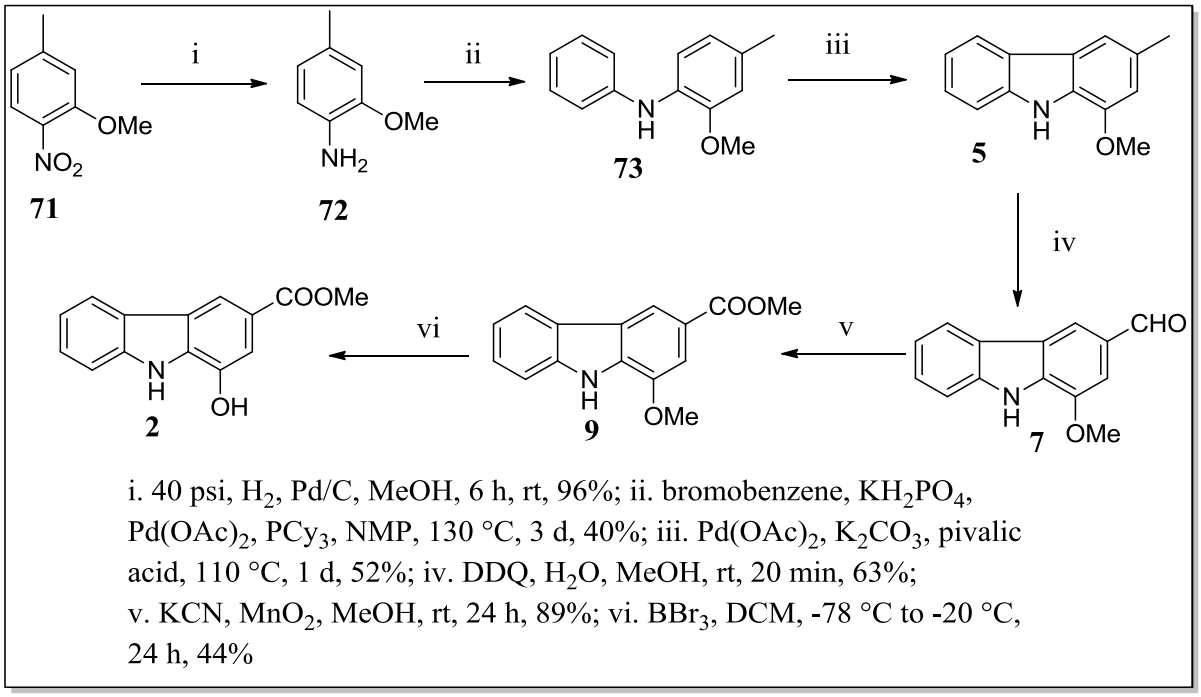
i. LTB, **67**, TMEDA in THF at -60 °C, 68%; ii. $AlCl_3$, DCM; iii.30% aq. KOH in MeOH, reflux, 3h; iv. DBU, MeI, 58% over 2 steps.

Scheme 7

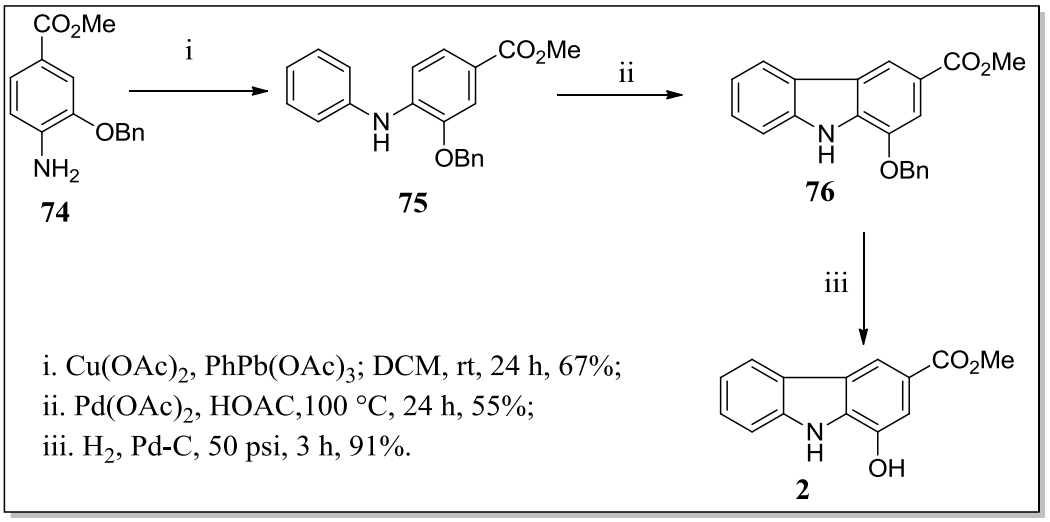
3.A.2.5: By Cyclodehydrogenation (Route e)

In the year 2013, Song *et al.* utilized cyclodehydrogenation as the key step for the synthesis of clausine E.[47] *N*-Arylation of aniline **72**, followed by Palladium (II) acetate catalyzed cyclodehydrogenation gave the product **5**. Further functional group transformation of the methyl group present at C-3 carbon followed by deprotection of the C-1 methoxy group gave clausine E *(Scheme 8)*.

Ullah and co-workers synthesized clausine E using palladium acetate catalyzed cyclodehydrogenation of methyl 3-(benzyloxy)-4-(phenylamino)benzoate as the key step.[48] *N*-Arylation of ester **74** with phenyl lead triacetate under Barton conditions gave the product **75** in 67% yield. Palladium (II) acetate catalyzed cyclodehydrogenation was performed on **75** to furnish the product **76** in good yield. Deprotection of *O*-benzyl group of **76** with catalytic hydrogenation furnished clausine E *(Scheme 9)*.



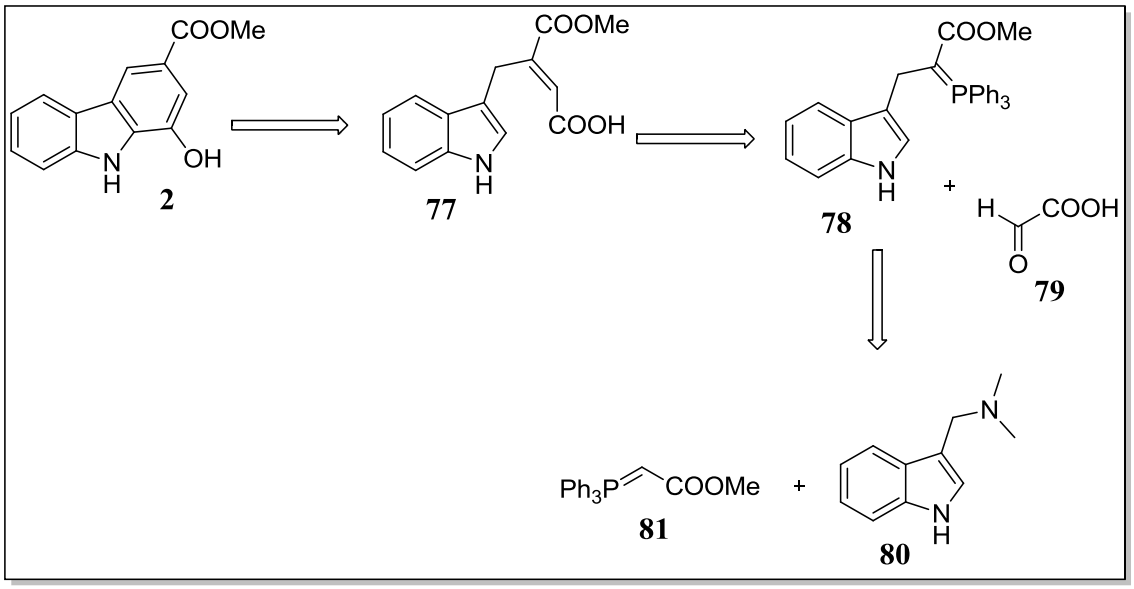
Scheme 8



Scheme 9

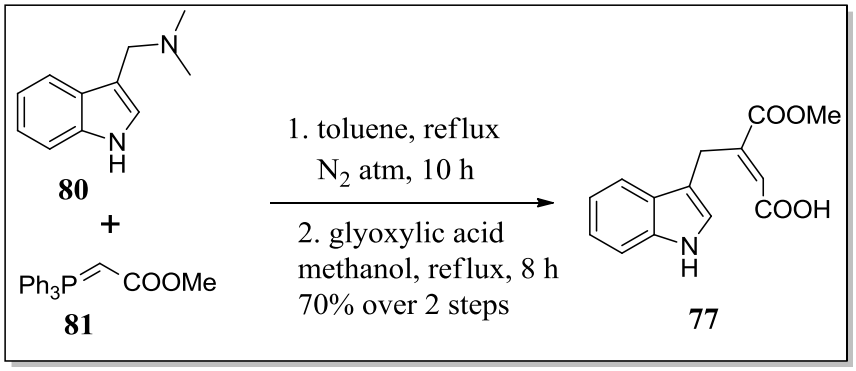
3.A.3: Results and Discussion

The important biological activities associated with clausine E generated an interest in designing new synthetic pathway for its synthesis. Our retrosynthetic analysis of clausine E indicated that it could be prepared from annulation of acid **77**, which in turn, could be derived from a Wittig reaction between phosphorane **78** and glyoxylic acid (**79**) *(Scheme 10)*. The desired phosphorane **78** could be synthesized from alkylation of phosphorane **81** by gramine (**80**).



Scheme 10

Accordingly, we started with the synthesis of acid **77**. Alkylation of the stable phosphorane [methyl(triphenylphospharanylidene)acetate] (**81**) with gramine (**80**) in refluxing toluene under nitrogen atmosphere gave a white solid **78**,[49] after ten hours. This solid compound was filtered and without characterization, directly subjected to reaction with glyoxylic acid in refluxing methanol. TLC of the reaction mixture showed appearance of new spot along with a spot corresponding for triphenylphosphine oxide. Corresponding workup for carboxylic acid followed by column chromatographic purification yielded a brown gummy mass over two steps *(Scheme 11).*



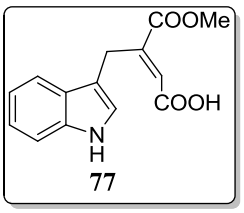
Scheme 11

Its IR spectrum showed two strong bands one at 1691 cm^{-1} and another at 1710 cm^{-1} indicating the presence of an acid carbonyl group and an ester carbonyl group respectively. The broad band at 3057 cm^{-1} corresponding to the hydroxyl group of acid was observed. Also, a strong band at 3408 cm^{-1} indicating the presence of N-H bond of indole ring was observed. In its ^{1}H NMR spectrum the singlet at δ 3.66 for three protons was assigned to the protons of carbomethoxy group while the singlet at δ 4.29 integrating for two protons was attributed to the methylene protons ($-CH_2-$) attached to the third carbon of indole ring. The vinylic proton was observed at δ 6.74 (s, 1H). The downfield chemical shift of the vinylic proton indicated it to be *cis* to the methyl ester.[50] Hence, *E*-geometry was assigned to this double bond. The peaks between δ 6.96-7.63 were attributed to the aromatic protons of indole ring and the proton attached to nitrogen showed a broad singlet at δ 7.94 in the ^{1}H NMR spectrum.

The structure of this compound was further confirmed by recording its ^{13}C NMR, DEPT and HRMS spectra. The detailed spectroscopic data is given below.

Spectroscopic data

(2*E*)-4-Methoxy-3-(1*H*-indol-3-ylmethyl)-4-oxobut-2-enoic acid (77)



IR (neat): υ_{max} 1273, 1454, 1643, 1691, 1710, 2600, 3057, 3408 cm^{-1}.

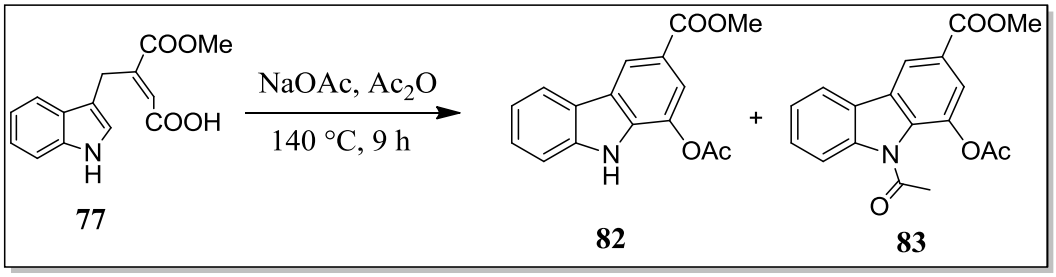
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 4.29 (s, 2H), 6.74 (s, 1H), 6.96 (s, 1H), 7.02-7.12 (m, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.94 (br s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.32 (CH_2), 52.70 (CH_3), 111.07 (CH), 112.00 (Cq), 119.19 (CH), 119.51(CH), 122.01 (CH), 122.98 (CH), 125.02(CH), 127.26 (Cq), 136.02 (Cq), 148.53 (Cq), 167.32 (Cq), 170.29 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{14}H_{13}NO_4Na$: 282.0742, found: 282.0746.

Thus based on the mode of formation and spectral data mentioned above, structure **77** was assigned to the compound. This compound was obtained in 70% yield over the two steps.

Once we had sufficient amount of compound **77** in hand, the next step was to carry out the intramolecular cyclization of **77** to get the carbazole framework. Accordingly, we refluxed compound **77** with sodium acetate in acetic anhydride *(Scheme 12)*.[29C]

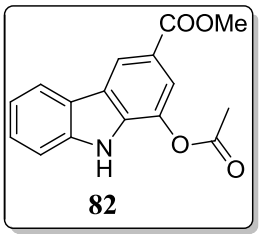


Scheme 12

After nine hours, the TLC of the reaction mixture showed two new spots and the spot corresponding to the starting had disappeared. Column chromatographic purification of the reaction mixture helped in isolation of two compounds. One of which was a brown gummy mass and the other was a white solid. The IR spectrum of the former compound, showed presence of two strong bands at 1710 cm^{-1} and 1766 cm^{-1} indicating the presence of two carbonyl groups. Also, a band due to N-H stretching was observed at 3334 cm^{-1}. The complete structure elucidation was done based on the spectroscopic data (provided below) and structure **82** was assigned to this compound.

Spectroscopic data

Methyl-1-acetoxy-carbazole-3-carboxylate (82)



82

IR (neat): υ_{max} 1433, 1610, 1710, 1766, 2924, 2953, 3334 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.90 (s, 3H), 7.22-7.41 (m, 3H), 7.87 (s, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 8.25 (br s, 1H), 8.62 (s, 1H) ppm.

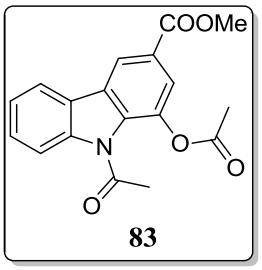
^{13}C NMR (100 MHz, $CDCl_3$): δ 21.11 (CH_3), 52.15 (CH_3), 111.30 (CH), 119.41 (CH), 120.46 (CH), 120.80 (2 x CH), 121.86 (Cq), 123.49 (Cq), 125.80 (Cq), 127.06 (CH), 134.51 (Cq), 135.03 (Cq), 139.97 (Cq), 167.15 (Cq), 168.84 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{16}H_{13}NO_4Na$: 306.0742, found: 306.0744.

The white solid obtained showed absence of N-H stretching band in its IR spectrum. And the three bands observed at 1714 cm^{-1}, 1722 cm^{-1} and 1770 cm^{-1} indicated the presence of three carbonyl groups. The structure of this compound was confirmed by comparing its physical properties and spectral data with literature[51] and structure **83** was assigned to it.

Spectroscopic data

Methyl-1-acetoxy-9-acetyl-carbazole-3-carboxylate (83)



83

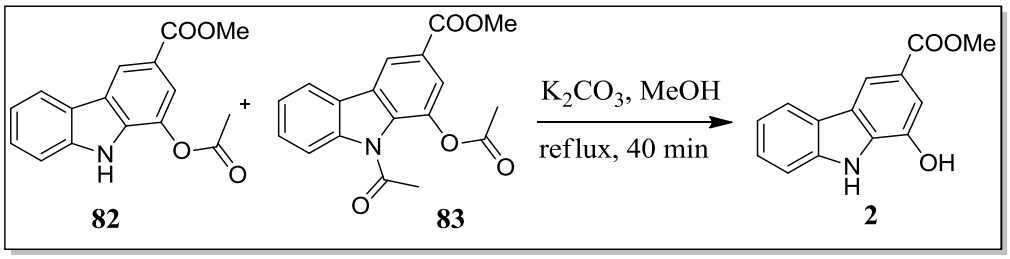
IR (KBr): υ_{max} 1485, 1581, 1714, 1722, 1770, 2398, 2439, 2924 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.72 (s, 3H), 3.92 (s, 3H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.86 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 8.53 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.88 (CH_3), 25.94 (CH_3), 51.39 (CH_3), 113.21 (CH), 118.21(CH), 119.61(CH), 122.06 (CH), 122.81 (CH), 124.28 (Cq), 125.31 (Cq), 127.22 (CH), 128.34 (Cq), 132.17 (Cq), 136.74 (Cq), 138.33 (Cq), 165.24 (Cq), 167.21(Cq), 169.06 (Cq) ppm.

m.p.: 108-110 ^{O}C; lit.[51] 110 ^{O}C.

Further the mixture of compounds **82** and **83** was subjected to deprotection with potassium carbonate in methanol to yield a white solid *(Scheme 13)*.

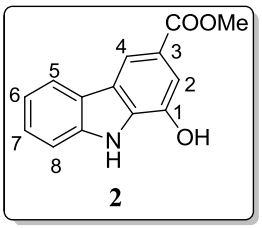


Scheme 13

Its IR spectrum showed a strong band at 1655 cm^{-1} indicating the presence of a carbonyl group. Broadening of the N-H band of indole ring at 3360 cm^{-1} was observed due to the presence of a phenolic hydroxyl group. In its ^{1}H NMR spectrum the singlet at δ 3.86 for three protons was assigned to the protons of carbomethoxy group. The peaks between δ 7.16-8.30 were attributed to the aromatic protons of the carbazole ring. A doublet at δ 8.17 and a singlet at δ 8.30 were attributed to the C-5 proton and C-4 proton respectively. The C-8 proton showed a doublet at δ 7.51. A broad singlet at δ 10.28 and a singlet at δ 11.57 were attributed to proton attached to indole nitrogen and the phenolic hydrogen respectively.

Spectroscopic data

Methyl-1-hydroxy-9*H*-carbazole-3-carboxylate (clausine E, 2)



IR (KBr): υ_{max} 1367, 1496, 1600, 1651, 1655, 2848, 2951, 3051, 3360 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H), 7.19 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.46 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 7.6 Hz, 1H), 8.30 (s, 1H), 10.28 (s, 1H), 11.57 (s, 1H) ppm.

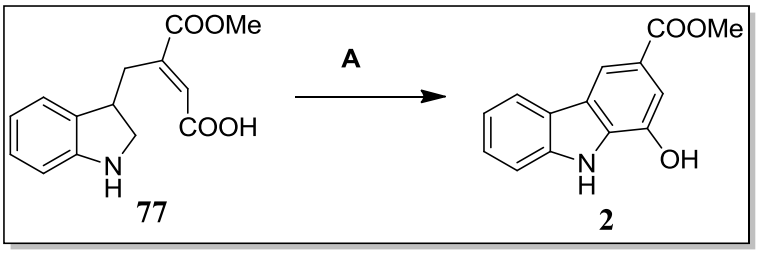
^{13}C NMR (100 MHz, DMSO-d_6): δ 51.74 (CH_3), 110.00 (CH), 111.66 (CH), 113.99 (CH), 119.36 (CH), 120.46 (CH), 120.51 (Cq), 122.83 (Cq), 123.31(Cq), 126.04 (CH), 132.66 (Cq), 140.07 (Cq), 142.80 (Cq), 167.12 (Cq) ppm.

m.p.: 214-215 ^{O}C; lit.[29d] 215-216.5 ^{O}C.

With the help of complete spectral analysis structure **2** was assigned to it. The compound **2** was obtained in 55% yield (over two steps) starting from compound **77**.

Although compound **2** was obtained in moderate yield, we were more interested in getting the final product (clausine E) directly by annulation of acid **77**. Hence we attempted the annulation of acid **77** by heating with polyphosphoric acid in the absence of solvent *(Scheme 14, Table 1)*. Very little product (clausine E) formation was observed at 80 ^{O}C with much of the starting remaining intact. When the reaction temperature was increased to 100-110 ^{O}C clausine E was obtained in 20% yield in 3 hours. Prolonging the reaction resulted in decrease in the yield due to decomposition of the reaction mass. Similar results were observed when the temperature was increased beyond 110 ^{O}C. Various other reaction conditions were tried (entry 5-9) which either failed to give the desired product or delivered only trace amount.

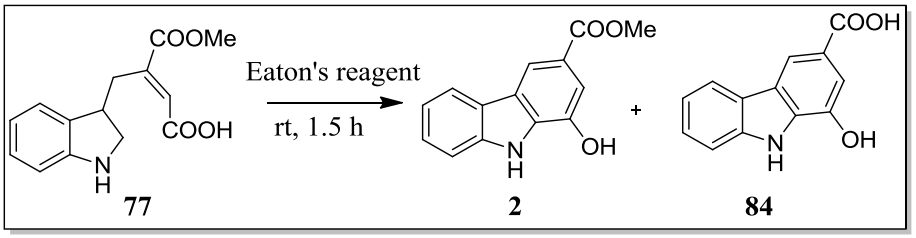
When freshly prepared Eaton's reagent[52] (1:10 phosphorus pentoxide-methanesulfonic acid solution) was used the desired product **2** was obtained in 60% yield after 1.5 hours at room temperature (entry 10). Use of Eaton's reagent helped in decreasing the reaction time, improved the product yield and also allowed for an easy and clean workup procedure. We also tried this reaction either only with methanesulfonic acid or just with phosphorus pentoxide (entry 11-12). However the combination of the two (Eaton's reagent) gave the best result *(Scheme 15)*.



Scheme 14

Table 1: Screening of reaction conditions for direct annulation of acid **77**.

Sr No.	Reaction conditions (**A**)	Observation
1	PPA, no solvent, Δ 80 °C, 1-3 h	5% of **2** obtained
2	PPA, no solvent, Δ 100-110 °C, 3 h	20% of **2** obtained
3	PPA, no solvent, Δ 110 °C, 8 h	8% of **2** obtained
4	PPA, no solvent, Δ 130-150 °C, 3 h	5% of **2** obtained
5	*p*-TsOH, Δ 130-140 °C, upto 48 h	No product (starting **77** observed on TLC)
6	Iodine (1-4 equiv.), no solvent, Δ 120-140 °C, upto 48 h	No product (starting 77 observed on TLC)
7	DCC (1-2 equiv.), TFA, rt, upto 48 h	**2** obtained in trace amount (starting **77** observed on TLC)
8	DCC (1-2 equiv.), TFA, Δ 80-110 °C	No product (decomposition of reaction mass)
9	H_3PO_4, Δ 100-120 °C, upto 24 h	**2** obtained in trace amount (starting **77** observed on TLC)
10	**Eaton's reagent, rt, 1.5 h**	**60% of 2 obtained**
11	Methanesulfonic acid, rt, 3h	50% of **2** obtained
12	P_2O_5 (3-5 equiv.), DCE, rt, 2-5 h	15-20% of **2** obtained



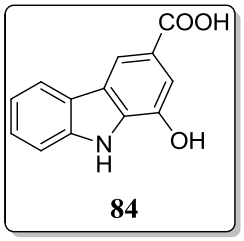
Scheme 15

When Eaton's reagent was used, along with desired product **2** trace amount of side product **84** was obtained. This side product was formed due to acidic hydrolysis of methoxycarbonyl group. Prolonging the reaction time resulted in increase in the yield of side-product **84**. The IR spectrum of compound **84** showed a strong band at 1698 cm^{-1} indicating the presence of

an acid carbonyl group. The broad band at 3200 cm^{-1} and a strong band at 3425 cm^{-1} corresponding to the hydroxyl group of acid and N-H bond of indole ring, respectively were observed. Structure of compound **84** was confirmed based on complete spectral analysis.

Spectroscopic data

1-Hydroxy-9H-carbazole-3-carboxylic acid (84)



84

IR (KBr): υ_{max} 1698, 3200, 3425 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18 (t, J = 8.0 Hz, 1H), 7.38-7.44 (m, 2H), 7.52 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.26 (s, 1H), 10.36 (br s, 1H), 11.48 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 110.34 (CH), 111.63 (CH), 114.07 (CH), 119.29 (CH), 120.36 (CH), 121.59 (Cq), 122.86 (Cq), 123.24 (Cq), 125.94 (CH), 132.49 (Cq), 140.03 (Cq), 142.62 (Cq), 168.27 (Cq) ppm.

m.p.: 228-230 ^{O}C; lit.[53] 228 ^{O}C.

3.A.4: Conclusion

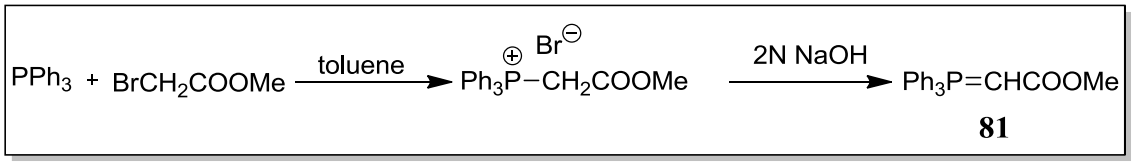
In conclusion we have developed an efficient total synthesis of clausine E involving Wittig reaction and annulation as the key steps. Use of Eaton's reagent helped in increasing the yield of the annulation step.

Furthermore, this synthesis constitutes a formal synthesis of naturally occurring mukonine and related naturally occurring carbazoles such as koenoline, mukoeic acid, murrayanine, mukoline, mukolidine, murrayafoline A and *O*-demethylmurrayanine.

The highlight of our approach was the non-requirement of protection of the indole nitrogen.

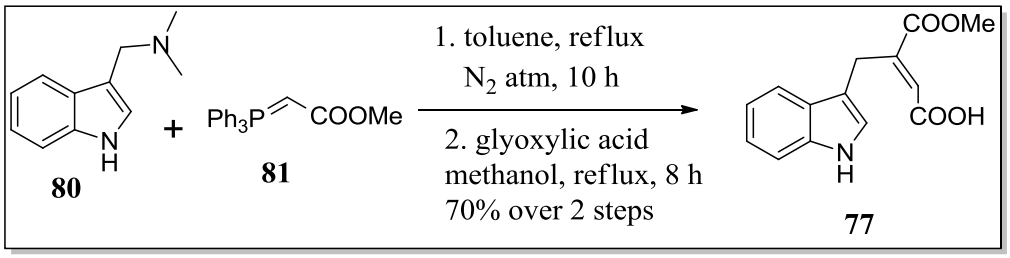
3.A.5: Experimental

3.A.5.1: Preparation of methyl 2-(triphenylphosphoranylidene)acetate (81)



To a solution of triphenylphosphine (15.67 g, 59.8 mmol) in dry toluene (50 mL) methyl bromoacetate (5 mL, 54.3 mmol) was added dropwise, over a period of five minutes with constant stirring and stirring was continued for 12 hours at room temperature. The white solid obtained was filtered and washed with toluene. Further it was dissolved in water (100 ml) and toluene (50 × 2 mL) was added to it. It was neutralized with 2N sodium hydroxide using phenolphthalein as indicator. The toluene layer was separated, dried over anhyd. sodium sulphate and concentrated under reduced pressure. Addition of hexanes (40-60 °C) resulted in the separation of product **81**, as a white crystalline solid in 85% (15.5 g) yield (**m.p.:** 163-164 ^{O}C; lit.[55] 162-163 ^{O}C).

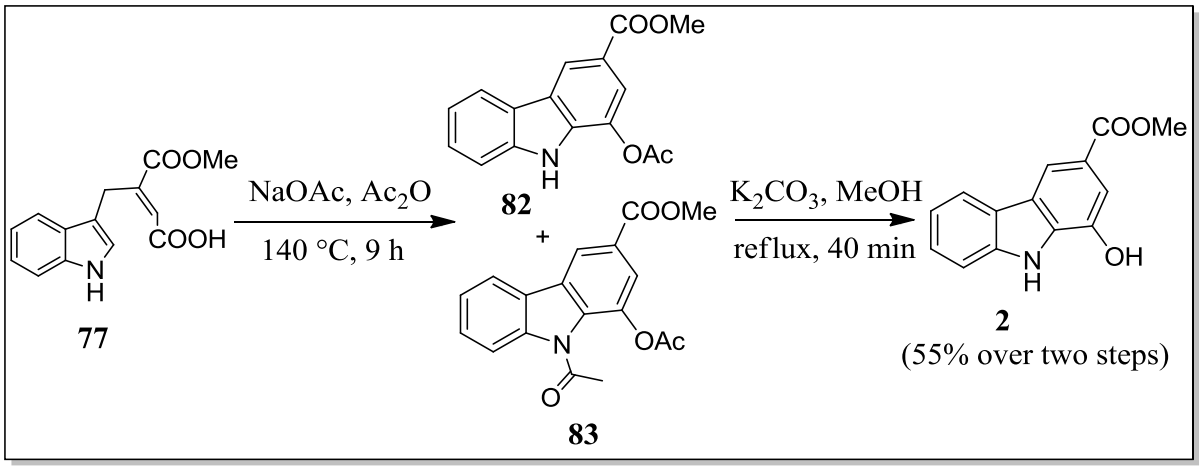
3.A.5.2: Synthesis of (*E*)-3-((1*H*-indol-3-yl)methyl)-4-methoxy-4-oxobut-2-enoic acid (77)



Gramine (**80**, 2.5 g, 14.34 mmol) was added to a solution of phosphorane (**81**, 4.7 g, 14.32 mmol) in dry toluene (30 mL) and subjected to reflux for 10 hours under nitrogen atmosphere to give phosphorane **78**, obtained as a white solid after filtration which without further purification was directly subjected to Wittig reaction with glyoxylic acid (50% solution in water, 2.242 g, 15.15 mmol) in refluxing methanol (30 mL) for 8 hours. Methanol was evaporated and the residue was dissolved in EtOAc (30 mL). The EtOAc layer was extracted with sat. sodium bicarbonate solution (3 x 30 mL). The sodium bicarbonate extract was cooled, acidified with aq. HCl solution to pH 2-3 and extracted with EtOAc (3 x 30 mL). The crude product was further purified by column chromatography using hexanes-

EtOAc (8:2) as an eluent to give compound **77** as brown gummy mass in 70% (2.597 g) yield.

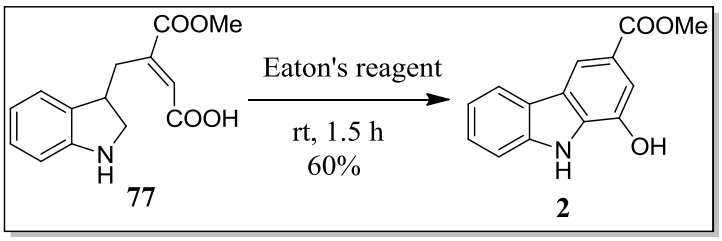
3.A.5.3: Synthesis of clausine E *via* mixture of acetylated carbazoles.



Acid **77** (0.6 g, 2.316 mmol) was refluxed in acetic anhydride (6mL) with freshly fused sodium acetate (0.38 g, 4.632 mmol) for 9 hours. The acetic anhydride was removed by vacuum distillation and remaining residue containing a mixture of differently acetylated carbazoles was subjected to flash column chromatography (hexanes-EtOAc, 8:2) to give **82** as a brown gummy mass in 29% (0.189 g) yield and **83** as a white solid in 40% (0.298 g) yield (**m.p.:** 108-110 ^{O}C; lit.[51] 110 ^{O}C).

Further the mixture containing acetylated products was treated with K_2CO_3 (0.25 g) in refluxing methanol (30 mL) for 40 minutes. Methanol was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with 10 % aq. HCl (3 × 10 mL). The organic extracts were dried over sodium sulphate and concentrated. The crude product was then subjected to column chromatography using hexanes-EtOAc (7.5:2.5) as an eluent to give **2**. Recrystallization of the obtained solid from toluene provided white crystals (**m.p.:** 214-215 ^{O}C; lit.[29d] 215-216.5 ^{O}C). The product was obtained in 55% yield, starting from **77** over the two steps.

3.A.5.4: Synthesis of clausine E using Eaton's reagent.



Freshly prepared Eaton's reagent (1:10 phosphorus pentoxide-methanesulfonic acid solution, 2.5 mL)[52] was added to (*E*)-3-((1*H*-indol-3-yl)methyl)-4-methoxy-4-oxobut-2-enoic acid (**77**, 0.8 g, 3.08 mmol) and stirred at ambient temperature for 90 minutes. To the resulting reaction mixture water (20 mL) was added and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude residue obtained was subjected to column chromatographic purification on silica gel using hexanes-EtOAc (7.5:2.5) as an eluent to give **2** as a white solid in 60% (0.449 g) yield.

Section B: Synthesis of naturally occurring carbazoles starting from clausine E

3.B.I: Synthesis of clausine F

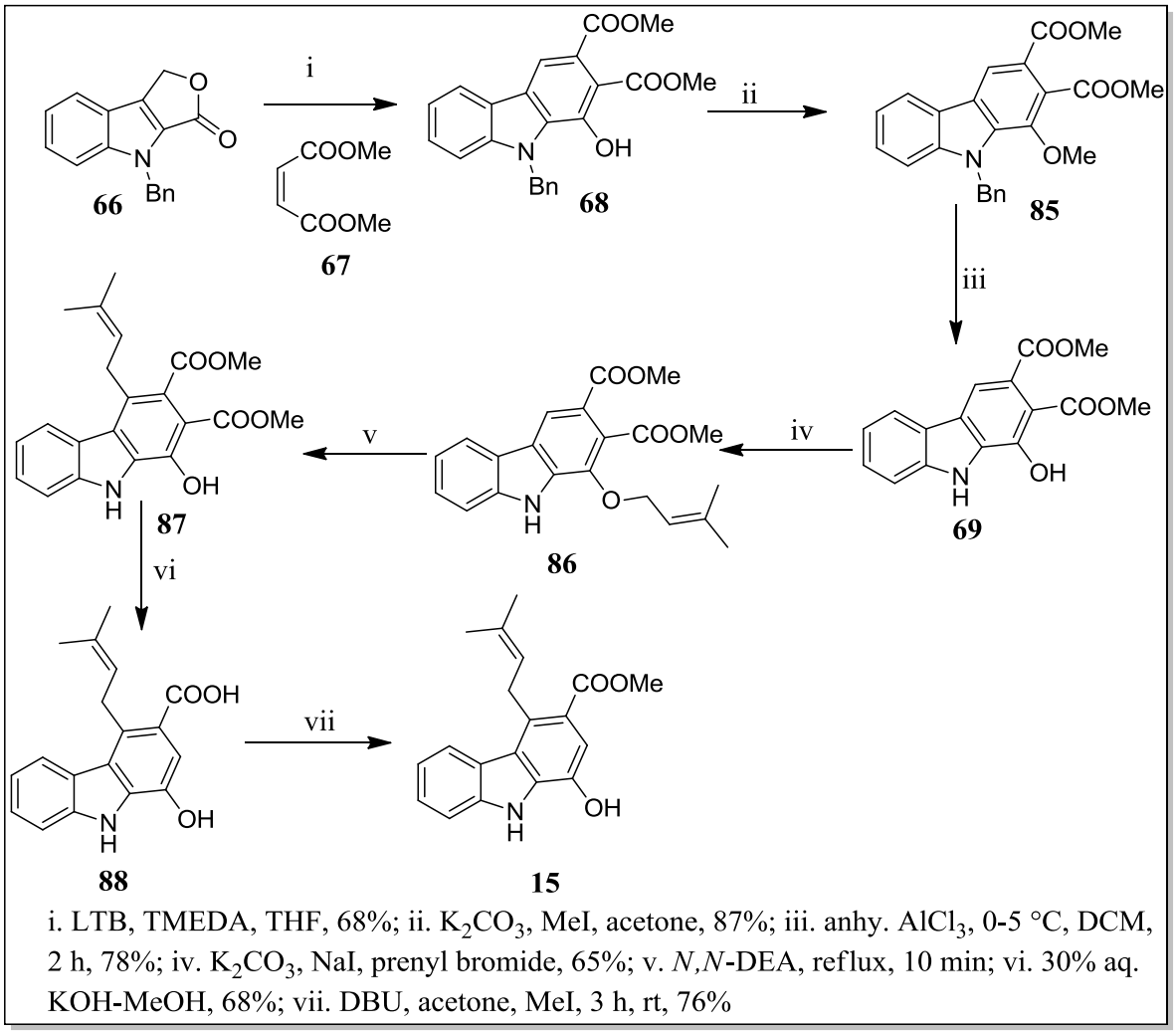
3.B.I.1: Occurrence and biological activities of clausine F

Clausine F (**15**) was isolated from stem bark[15] and roots[24] of clausena excavata. It was also isolated from branches[16a] and stems[16c] of clausena anisata, twigs of *Clausena harmandiana*[42] and stems of *Clausena emarginata*.[45] Clausine F showed inhibition of platelet aggregation[15] and posesses antitumor properties.[16a]

Clausine F showed strong antibacterial activity against MRSA SK1 and S. aureus TISTR 1466 with MIC value of 4 μg/mL.[42] Clausine F also displayed hepatoprotective effects against DL-galactosamine-induced damage in WB-F344 cells.[45]

3.B.I.2: Literature synthetic methods

First total synthesis of clausine F was reported by Mal and co-workers.[37c] Annulation of **66** with dimethyl maleate using lithium *t*-butoxide (LTB) in combination with TMEDA gave the carbazole **68** in 68% yield. Debenzylation as well as demethylation in **85** using $AlCl_3$, gave the carbazole **69** in 78% yield. Chemoselective prenylation of the free hydroxyl group in **69** using prenyl bromide in presence of K_2CO_3 gave **86** in 65% yield. The *para*-Claisen rearrangement of *O*-prenylated carbazole **86** in refluxing diethylaniline gave carbazole **87**. The hydroxy acid **88** was obtained from **87** using 30% aq. KOH in refluxing methanol. Clausine F **15** was obtained by treatment of **88** with DBU-MeI *(Scheme 16)*.

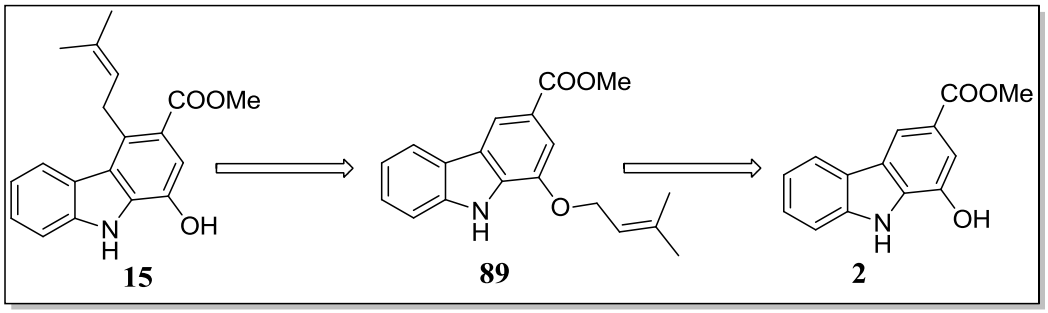


i. LTB, TMEDA, THF, 68%; ii. K_2CO_3, MeI, acetone, 87%; iii. anhy. $AlCl_3$, 0-5 °C, DCM, 2 h, 78%; iv. K_2CO_3, NaI, prenyl bromide, 65%; v. *N,N*-DEA, reflux, 10 min; vi. 30% aq. KOH-MeOH, 68%; vii. DBU, acetone, MeI, 3 h, rt, 76%

Scheme 16

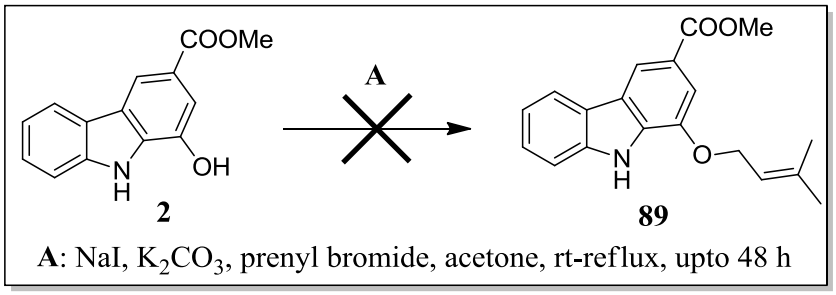
3.B.I.3: Results and Discussion

In view of the only report towards the synthesis of biologically important clausine F, we designed a new retrosynthetic pathway for its synthesis, as enunciated in *Scheme 17*. Since we already had clausine E in hand, we envisaged that clausine F (**15**) could be synthesized starting from clausine E (**2**) *via p*-Claisen rearrangement of its *O*-prenyl ether **89**.



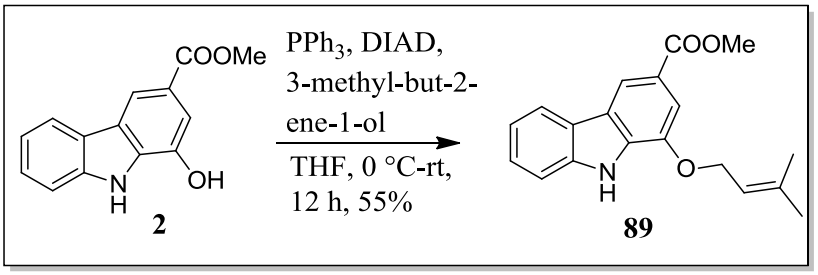
Scheme 17

For the synthesis of *O*-prenyl ether **89**, clausine E (**2**) was subjected to reaction with prenyl bromide in presence of potassium carbonate and sodium iodide in anhyd. acetone at room temperature. However when progress of the reaction was followed by TLC, it was observed that there was no change in the reaction mass even after continuing the reaction for 48 hours *(Scheme 18)*. Prenylation failed to occur even after subjecting the reaction mixture to reflux.



Scheme 18

Hence we decided to attempt the *O*-prenylation of clausine E using the classical Mitsunobu reaction.[54] Thus the carbazole **2** was condensed with 3-methyl-2-buten-1-ol in the presence of diisopropylazodicarboxylate and triphenylphosphine in dry THF under nitrogen atmosphere. The reaction mixture was stirred at 0 ^{O}C for an hour and then stirring was continued at ambient temperature *(Scheme 19)*.

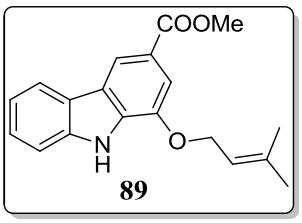


Scheme 19

The reaction was complete in 11 hours (monitored by TLC). Column chromatographic purification of the reaction mixture yielded a white solid, with melting point 166-168 ^{O}C. Sharpening of the N-H band of indole ring at 3358 cm^{-1} indicated the disappearance of the hydroxyl group in its IR spectrum. Also, a strong absorbance at 1687 cm^{-1} was observed indicating the presence of a carbonyl group. In its ^{1}H NMR spectrum the two methyl groups of the prenyl moiety appeared as singlets at δ 1.75 and 1.78 while the methylene group showed a doublet at δ 4.70 (J = 6.8 Hz). The olefinic proton adjacent to methylene group appeared as triplet at δ 5.53. The singlet at δ 3.91 for three protons was assigned to the protons of carbomethoxy group. The peaks between δ 7.22-8.40 were attributed to the aromatic protons of the carbazole ring. A singlet at δ 8.40 and a doublet at δ 8.03 were attributed to the C-4 and C-5 protons respectively. A broad singlet at δ 8.47 was attributed to proton attached to indole nitrogen. The structure was further supported by its ^{13}C NMR, DEPT experiment and HRMS data.

Spectroscopic data

Methyl-1-(3-methyl-2-butenyloxy)-9*H*-carbazole-3-carboxylate (89)



89

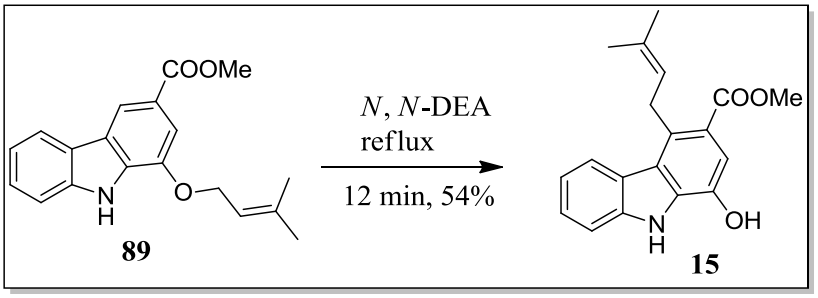
IR (neat): υ_{max} 1240, 1350, 1377, 1431, 1440, 1583, 1629, 1687, 2918, 2956, 3358 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (s, 3H), 1.78 (s, 3H), 3.91 (s, 3H), 4.70 (d, J = 6.80 Hz, 2H), 5.53 (t, J = 6.8 Hz, 1H), 7.21-7.23 (m, 1H), 7.36-7.42 (m, 2H), 7.54 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.40 (s, 1H), 8.47 (br s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.32 (CH_3), 25.91 (CH_3), 52.06 (CH_3), 65.32 (CH_2), 107.66 (CH), 111.21 (CH), 116.10 (CH), 119.27 (CH), 120.22 (CH), 120.75 (CH), 121.79 (Cq), 123.58 (Cq), 123.77 (Cq), 126.32 (CH), 133.16 (Cq), 139.02 (Cq), 139.47 (Cq), 144.34 (Cq), 168.07 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{19}H_{19}NO_3Na$: 332.1263, found: 332.1263.

Thus, based on mode of formation and spectral data, structure **89** was assigned to it. The yield of the product was found to be 55%.

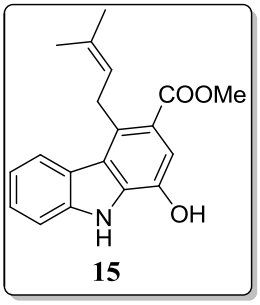


Scheme 20

Once sufficient amount of compound **89** was in hand, it was subjected to reflux in *N*, *N*-diethylaniline *(Scheme 20)*. The *p*-Claisen rearrangement[37c] product was formed in just 12 minutes (monitored by TLC). The *p*-Claisen rearrangement product, clausine F (**15**) was obtained as a white solid, on column chromatographic purification of the reaction mixture, melting in the range 195-196 ^{O}C (lit.[37c] 196-198 ^{O}C). Its IR spectrum showed a strong band at 1674 cm^{-1} indicating the presence of a carbonyl group. Broadening of the N-H band of indole ring at 3350 cm^{-1} was observed due to the presence of a phenolic hydroxyl group. In its ^{1}H NMR spectrum the two methyl groups of the prenyl moiety appeared as singlets at δ 1.71 and 1.91 while the methylene group showed a doublet at δ 4.29 (J = 4.8 Hz). The olefinic proton adjacent to methylene group appeared as multiplet at δ 5.28. The singlet at δ 3.92 for three protons was assigned to the protons of carbomethoxy group. The broad singlet corresponding to phenolic hydroxyl proton was observed at δ 5.84. The peaks between δ 7.29-8.14 were attributed to the aromatic protons of the carbazole ring. A doublet at δ 8.14 was attributed to the C-5 proton of the carbazole ring. A broad singlet at δ 8.59 was attributed to proton attached to indole nitrogen. The ^{13}C NMR and DEPT experiments were also in well agreement with the structure.

Spectroscopic data

Methyl-1-hydroxy-4-(3-methyl-but-2-enyl)-9*H*-carbazole-3-carboxylate (15)



IR (neat): υ_{max} 1024, 1091, 1255, 1342, 1444, 1620, 1674, 3350 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 3H), 1.91 (s, 3H), 3.92 (s, 3H), 4.29 (d, J = 4.8 Hz, 2H), 5.28 (s, 1H), 5.84 (br s, 1H), 7.29 (s, 1H), 7.43-7.51 (m, 3H), 8.14 (d, J = 8.4 Hz, 1H), 8.59 (br s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.44 (CH_3), 25.69 (CH_3), 29.38 (CH_2), 52.03 (CH_3), 111.06 (CH), 112.81 (CH), 120.13 (CH), 120.52 (Cq), 122.90 (CH), 123.08 (Cq), 123.38 (CH), 123.93 (Cq), 125.78 (CH), 131.87 (Cq), 132.31 (Cq), 133.54 (Cq), 138.72 (Cq), 139.69 (Cq), 169.13 (Cq) ppm.

Thus, formation of compound **15** was confirmed on the basis of detailed spectroscopic data. The product was obtained in 54% yield.

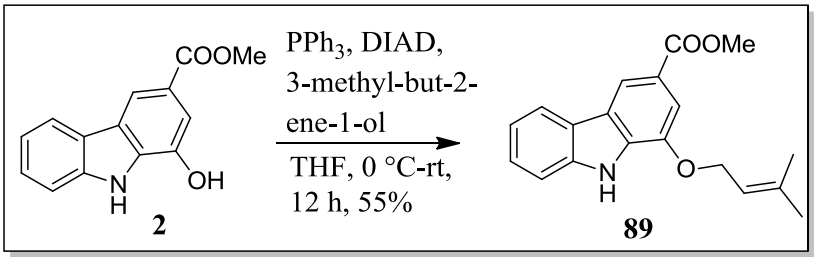
3.B.I.4: Conclusion

The synthesis of clausine F was successfully implemented *via* a *p*-Claisen rearrangement of *O*-prenylated clausine E, which also completes the formal synthesis of naturally occurring carbazole alkaloids clausevatine D, clausamine C and clausamine D.

The highlight of our approach was the non-requirement of protection of the indole nitrogen and the *para* selectivity of the Claisen rearrangement.

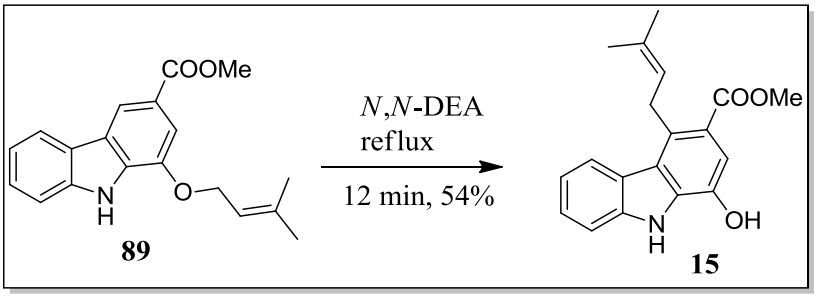
3.B.I.5: Experimental

3.B.I.5.1: Synthesis of methyl-1-(3-methyl-2-butenyloxy)-9*H*-carbazole-3-carboxylate (89)



A solution of diisopropylazodicarboxylate (0.7 mL, 3.566 mmol) in THF was added dropwise to a well stirred suspension of clausine E (**2**, 0.430 g, 1.784 mmol), triphenylphosphine (0.701 g, 2.676 mmol) and 3-methyl-2-buten-1-ol (0.230 g, 2.676 mmol) in anhyd. THF (20 mL) at 0 ^{O}C under nitrogen atmosphere. The suspension was stirred at 0 ^{O}C for an hour and then stirred at ambient temperature for 11 hours. After removal of the solvent under reduced pressure the reaction mixture was subjected to column chromatography on silica gel using hexanes-EtOAc (9:1) as an eluent to give **89** in 55% (0.305 g) yield. Recrystallization of the obtained solid from hexanes-EtOAc (9:1) provided white crystals (**m.p.:** 166-168 ^{O}C).

3.B.I.5.2: Synthesis of methyl-1-hydroxy-4-(3-methyl-but-2-enyl)-9*H*-carbazole-3-carboxylate (15)



A solution of compound **89** (0.05 g, 0.161 mmol) in *N*, *N*- diethylaniline (3 mL) was heated at reflux for 12 minutes. After cooling the reaction mixture was acidified with 10% aq. HCl (10 mL) and extracted with EtOAc (3 X 10 mL). The combined organic extracts were dried over anhyd. sodium sulfate and concentrated under reduced pressure. The crude product was

subjected to column chromatography using hexanes-EtOAc (7.5:2.5) as an eluent to give **15** as a white solid in 54% (0.027 g) yield. Recrystallization of the obtained solid from hexanes-EtOAc (8:2) provided white crystals. (**m.p.:** 195-196 ^{O}C (lit.[37c] 196-198 ^{O}C).

3.B.II: Formal synthesis of Clausenaline D

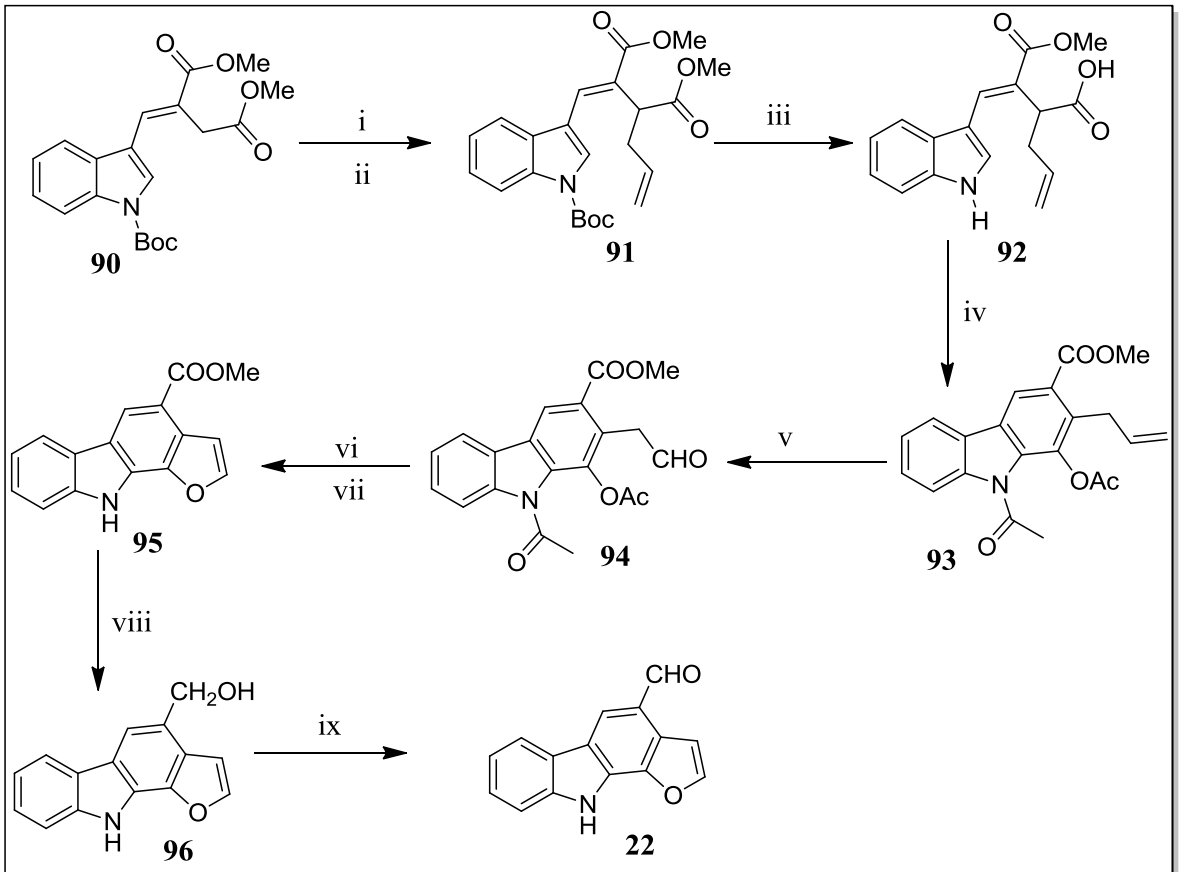
3.B.II.1: Occurrence and biological activities of Clausenaline D

Clausenaline D (**22**) was isolated from the roots of *Clausena lansium*.[18] The biological activities pertaining to this molecule are not yet reported.

3.B.II.2: Literature synthetic methods

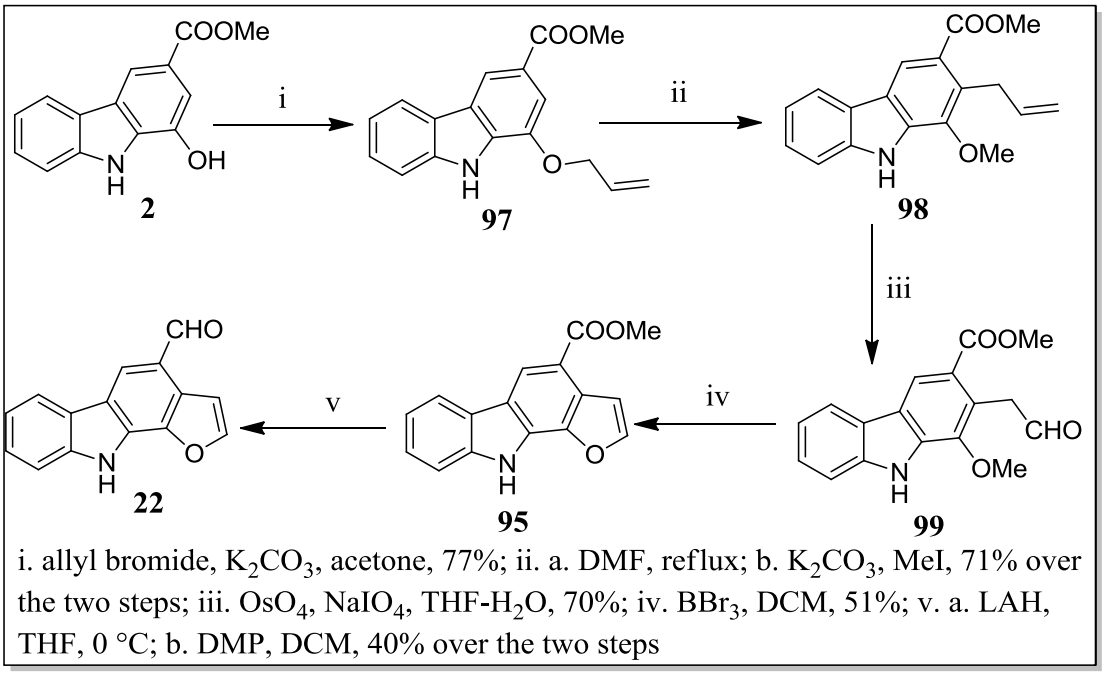
Argade and co-worker accomplished the first total synthesis of clausenaline D.[29f] Compound **90** was subjected to NaHMDS induced regioseletive allylation at an activated methylene carbon to furnish compound **91** in 73% yield. The monoacid **92** was obtained by controlled potassium hydroxide catalyzed regioselective hydrolysis of the unconjugated ester unit in **91**. The monoacid **92** was then subjected to Ac_2O – NaOAc stimulated dehydrative intramolecular cyclization to give the carbazole **93**. The transformation of terminal alkene in carbazole **93**, into the desired aliphatic aldehyde **94** was achieved by an in situ oxidative cleavage of the double bond, *via* the diol using OsO_4 and $NaIO_4$. A one pot *p*-TsOH mediated double deacylation of **94** was achieved followed by dehydrative intramolecular cyclization to furnish the furocarbazole **95** in 94% yield. Clausenaline D **22** was synthesized by carrying out DIBALH reduction of the aromatic ester unit in **95** followed by PCC oxidation of the corresponding alcohol *(Scheme 21)*.

Recently Liu *et al.* reported the synthesis of clausenaline D (**22**) *via* clausine E.[29e] Clausine E was obtained by TFAA-mediated annulation of (*E*)-4-(1′*H*-indol-3′-yl)-3-(methoxycarbonyl)but-3-enoic acid, obtained from Stobbe condensation of indole-3-carbaldehyde, with dimethyl succinate using sodium hydride as a base. Allylation of clausine E followed by *o*-Claisen rearrangement and methylation furnished the intermediate **98**. Oxidative cleavage of **98** followed by boron tribromide mediated cyclization gave the furocarbazole **95**. On reduction of the methyl ester group in **95** using LAH and subsequent Dess-Martin periodinane oxidation gave clausenaline D *(Scheme 22)*.



i. NaHMDS, THF, -78 °C, 30 min; ii. allyl bromide, -78 °C, 45 min, 73%; iii. KOH aq. MeOH, 25 °C, 15h, 92%; iv. Ac_2O, NaOAC, reflux, 12 h, 88 %; v. OsO_4, $NaIO_4$ THF: H_2O (3:1), 25 °C, 4 h, 93%; vi. *p*-TsOH, MeOH, 25 °C, 3 h; vii. *p*-TsOH, toluene, reflux, 94%; viii. DIBALH, THF, -78 °C to 25 °C, 2 h, 96%; ix. PCC, celite, DCM, 25 °C, 30 min, 98%

Scheme 21

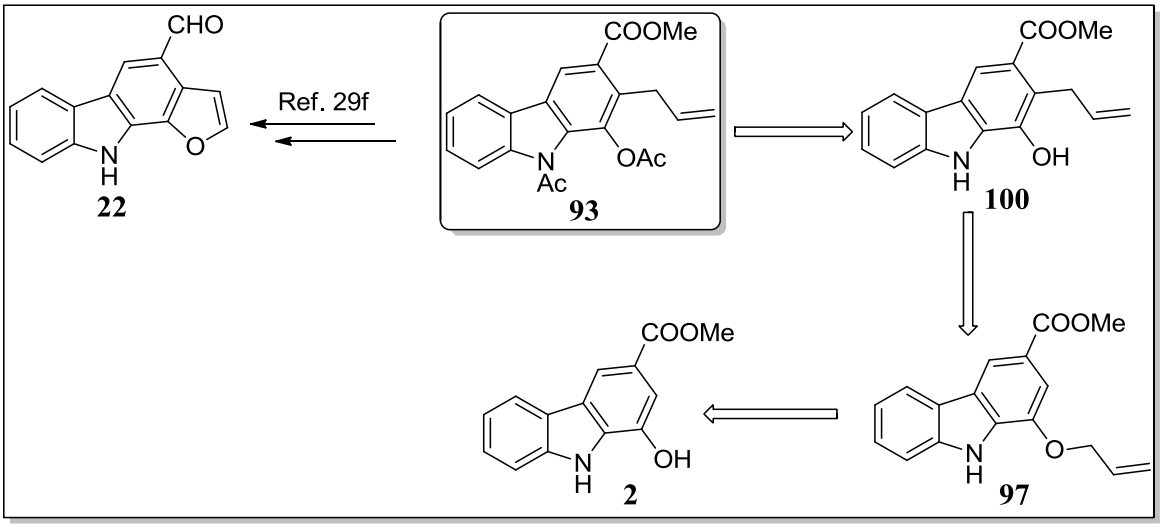


i. allyl bromide, K_2CO_3, acetone, 77%; ii. a. DMF, reflux; b. K_2CO_3, MeI, 71% over the two steps; iii. OsO_4, $NaIO_4$, THF-H_2O, 70%; iv. BBr_3, DCM, 51%; v. a. LAH, THF, 0 °C; b. DMP, DCM, 40% over the two steps

Scheme 22

3.B.II.3: Results and Discussion

We realized that the formal synthesis of clausenaline D (**22**) could be accomplished through intermediate **93** *(Scheme 21)*.[29f] With clausine E in hand, we planned a synthetic strategy for intermediate **93** as depicted in *Scheme 23*.



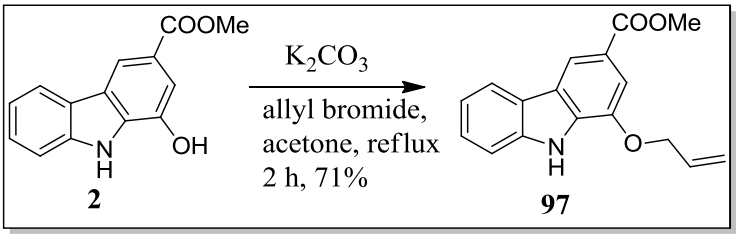
Scheme 23

It was expected that clausine E on allylation would form the *O*-allyl carbazole **97** which on Claisen rearrangement would form the *o*-Claisen rearrangement product **100**. Acetylation of

100 would form the desired intermediate **93**.

Accordingly, Clausine E was reacted with allyl bromide using K_2CO_3 as base in refluxing acetone *(Scheme 24)*. Flash chromatographic purification of the reaction mixture yielded a white solid, melting in the range 178-180 ^{O}C. Its IR spectrum showed a strong band at 1687 cm^{-1} indicating the presence of a carbonyl group. Asymmetric C-O-C stretch near 1217 cm^{-1} and a symmetric stretch near 1024 cm^{-1} characteristic of the aryl alkyl ether were observed. A sharp band at 3369 cm^{-1} representing the N-H band of indole ring was also observed. In its ^{1}H NMR spectrum the singlet at δ 3.99 for three protons was accounted for the protons of the carbomethoxy group. A doublet of triplet at δ 4.80 (2H, J = 5.6, 1.2 Hz) was assigned to the allylic methylene group (–OC**H**$_2$-CH=CH_2). A doublet of doublet at δ 5.39 (1H, J = 10.4, 1.2 Hz) and at δ 5.53 (1H, J = 17.6, 1.6 Hz) corresponding to the terminal olefinic protons of the allylic group (–OCH_2-CH=C**H**$_2$) were also observed. The single olefinic proton (–OCH_2-C**H**=CH_2) appeared as a multiplet at δ 6.14-6.24.

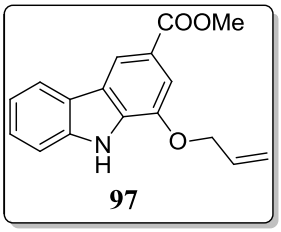
The peaks between δ 7.28-8.50 were attributed to the aromatic protons of the carbazole ring. A singlet at δ 8.50 and a doublet at δ 8.12 (J = 8.0 Hz) were attributed to the C-4 and C-5 protons respectively. A broad singlet at δ 8.59 was attributed to proton attached to indole nitrogen. The structure was further supported by its ^{13}C NMR, DEPT experiment and HRMS data. This product was obtained in 71% yield.



Scheme 24

Spectroscopic data

Methyl 1-(allyloxy)-9*H*-carbazole-3-carboxylate (97)



97

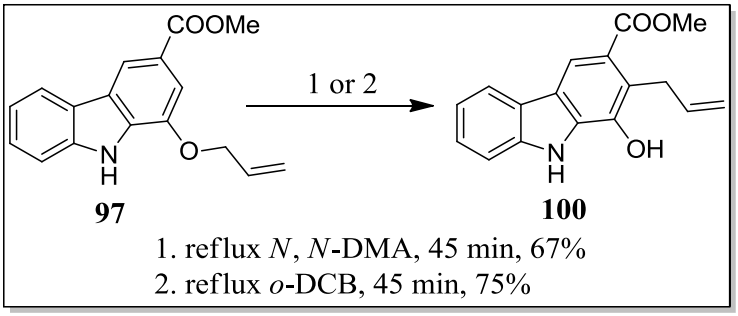
IR (KBr): υ_{max} 1024, 1217, 1311, 1687, 3369 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 3H), 4.80 (dt, *J* = 4.0, 1.2 Hz, 2H), 5.39 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.53 (dd, *J* = 17.6, 1.6 Hz, 1H), 6.14-6.24 (m, 1H), 7.28-7.33 (m, 1H), 7.46-7.53 (m, 2H), 7.62 (d, *J* = 1.2 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.50 (s, 1H), 8.59 (br s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 52.07 (CH_3), 69.39 (CH_2), 107.84 (CH), 111.25 (CH), 116.36 (CH), 118.42 (CH_2), 120.29 (CH), 120.76 (CH), 121.82 (Cq), 123.74 (Cq), 123.76 (Cq), 126.40 (CH), 132.84 (CH), 133.06 (Cq), 139.52 (Cq), 143.98 (Cq), 167.95 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{17}H_{15}NO_3Na$: 304.0950, found: 304.0951.

Next, the compound **97** was refluxed in *N*, *N*-dimethylaniline (*N*, *N*-DMA) for 45 minutes (monitored by TLC) *(Scheme 25)*. Flash chromatographic separation of the reaction mass furnished a white solid (**m.p.:** 147-149 °C).



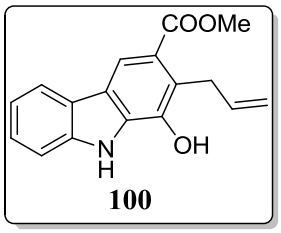
Scheme 25

In its IR Spectrum the peak corresponding to carbonyl stretching of the carbomethoxy group was observed at 1658 cm^{-1}. Broadening of the N-H band of indole ring at 3346 cm^{-1} indicated the presence of the hydroxyl group in its IR spectrum. In its ^{1}H NMR spectrum the singlet at δ 3.94 for three protons was attributed to the protons of the carbomethoxy group. A

doublet at δ 4.02 for two protons (J = 5.6 Hz) was assigned to the allylic methylene group (–C**H$_2$**-CH=CH$_2$). A doublet at δ 5.18 (1H, J = 5.2 Hz) and a singlet at δ 5.21 (1 H) were attributed to the terminal olefinic protons of the allylic group (–CH$_2$-CH=C**H$_2$**). A singlet corresponding to the phenolic hydrogen was also observed at δ 5.60. The single olefinic proton (–CH$_2$-C**H**=CH$_2$) appeared as a multiplet at δ 6.11-6.21. The aromatic protons appeared between δ 7.25-8.37. A singlet at δ 8.37 and a doublet at δ 8.05 (J = 7.6 Hz) could be attributed to the C-4 and C-5 protons respectively. A broad singlet at δ 8.44 was attributed to proton attached to indole nitrogen. The structure was further confirmed by ^{13}C NMR, DEPT experiment and HRMS data. The product was obtained in 67% yield.

Spectroscopic data

Methyl 2-allyl-1-hydroxy-9*H*-carbazole-3-carboxylate (100)



100

IR (KBr): υ_{max} 1280, 1307, 1620, 1658, 3057, 3346 cm^{-1}.

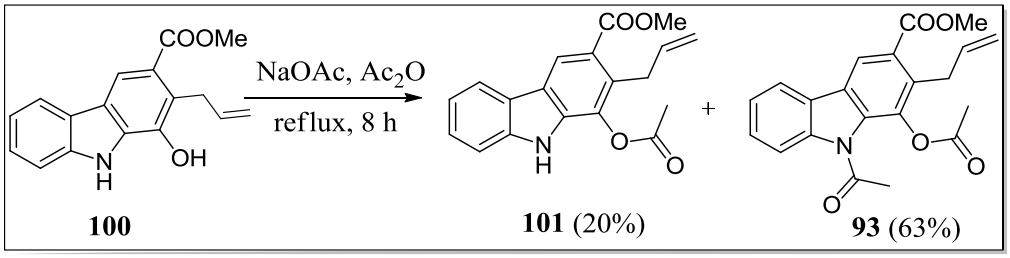
^{1}H NMR (400 MHz, CDCl$_3$): δ 3.94 (s, 3H), 4.02 (d, J = 5.6 Hz, 2H), 5.18 (d, J = 5.2 Hz, 1H), 5.21 (s, 1H), 5.60 (s, 1H), 6.11-6.21 (m, 1H), 7.25 (t, J = 4.8 Hz, 1H), 7.41-7.47 (m, 2H), 8.05 (d, J = 7.6 Hz, 1H), 8.37 (s, 1H), 8.44 (br s, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 31.74 (CH$_2$), 52.03 (CH$_3$), 111.18 (CH), 116.01 (CH$_2$), 117.26 (CH), 120.18 (CH), 120.60 (CH), 121.81 (Cq), 122.52 (Cq), 123.69 (Cq), 126.36 (CH), 132.28 (2 × Cq), 136.93 (CH), 139.79 (Cq), 140.51 (Cq), 168.82 (Cq) ppm.

HRMS: *m/z* [M+Na]$^+$ calculated for $C_{17}H_{15}NO_3Na$: 304.0950, found: 304.0950.

The product yield could be improved by replacing the solvent. When the compound **97** was refluxed in *o*-dichlorobenzene for 45 minutes, the product was obtained in 75% yield *(Scheme 25)*.

When the intermediate **100** was subjected to acetylation with sodium acetate in refluxing acetic anhydride formation of two products (monitored by TLC) was observed after 8 hours, while the spot due to intermediate **100** had completely disappeared *(Scheme 26)*.

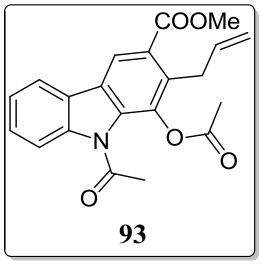


Scheme 26

Flash chromatographic separation of the reaction mass provided two products. We assumed these two products to be **93** (diacetylated compound) and **101 (**monoacetylated compound). The former compound was a white solid melting in the range 119-120 °C. Its IR spectrum showed absence of N-H stretching band and the three bands observed at 1697 cm^{-1}, 1732 cm^{-1} and 1755 cm^{-1} indicated the presence of three carbonyl groups. The structure of this compound was confirmed by comparing its physical properties and spectral data with literature[29f] and structure **93** was assigned to it.

Spectroscopic data

Methyl 1-acetoxy-9-acetyl-2-allyl-9*H*-carbazole-3-carboxylate (93)



IR (KBr): υ_{max} 1224, 1427, 1607, 1697, 1732, 1755 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 2.40 (s, 3H), 2.78 (s, 3H), 3.90 (d, J = 5.6 Hz, 2H), 3.94 (s, 3H), 4.94-5.05 (m, 2H), 5.89-5.99 (m, 1H), 7.45 (t, J = 7.2 Hz, 1H), 7.57 (td, J = 7.9, 1.2 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 8.58 (s, 1H) ppm.

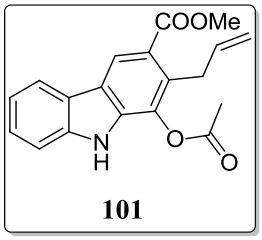
^{13}C NMR (100 MHz, acetone-d_6): δ 20.63 (CH_3), 26.98 (CH_3), 32.35 (CH_2), 52.57 (CH_3), 115.14 (CH), 115.66 (CH_2), 120.87 (CH), 121.30 (CH), 124.48 (CH), 125.61 (Cq), 127.39 (Cq), 127.88 (Cq), 128.96 (CH), 133.73 (Cq), 134.18 (Cq), 137.44 (CH), 137.96 (Cq), 140.54 (Cq), 168.05 (Cq), 168.26 (Cq), 171.38 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{21}H_{19}NO_5Na$: 388.1161, found: 388.1161.

In the IR spectrum of the second isolated compound, appearing as a white solid (Melting point 137-139 °C), presence of two strong bands at 1720 cm^{-1} and 1735 cm^{-1} indicated the presence of two carbonyl groups. Also, a band due to N-H stretching was observed at 3338 cm^{-1}. The complete structure elucidation was done based on the spectroscopic data (provided below) and structure **101** was assigned to this compound.

Spectroscopic data

4. <u>Methyl 1-acetoxy-2-allyl-9*H*-carbazole-3-carboxylate (101)</u>



101

IR (KBr): υ_{max} 1213, 1431, 1720, 1735, 3338 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 2.43 (s, 3H), 3.89 (s, 2H), 3.90 (s, 3H), 4.93 (d, J = 10.0 Hz, 1H), 5.05 (d, J = 17.2 Hz, 1H), 5.94-5.99 (m, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.42-7.50 (m, 2H), 8.20 (d, J = 8.0 Hz, 1H), 8.66 (s, 1H), 10.79 (br s, 1H) ppm.

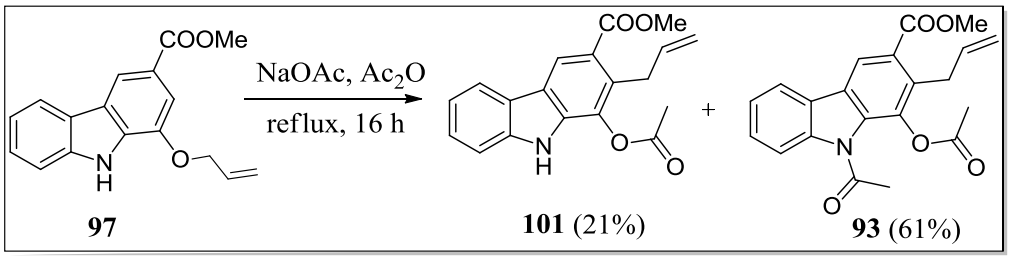
^{13}C NMR (100 MHz, acetone-d_6): δ 20.89 (CH_3), 32.08 (CH_2), 52.14 (CH_3), 112.20 (CH), 115.25 (CH_2), 120.97 (CH), 121.33 (CH), 122.18 (CH), 122.37 (Cq), 123.63 (Cq), 124.06 (Cq), 127.47 (CH), 131.33 (Cq), 135.66 (Cq), 136.27 (Cq), 137.92 (CH), 141.60 (Cq), 168.43 (Cq), 169.21 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{19}H_{17}NO_4Na$: 346.1055, found: 346.1055.

The compound **93** and compound **101** were obtained in 63% and 20%yield respectively.

We envisaged that the synthesis of desired intermediate **93** could be also achieved directly from compound **97** *via* a one-pot Claisen rearrangement and acetylation reaction. Accordingly, compound **97** was subjected to reflux in acetic anhydride in presence of sodium acetate *(Scheme 27).* After 16 hours the desired diacetylated product **93** was formed as indicated by TLC, involving a one pot *o*-Claisen rearrangement and acetylation sequence. The monoacetylated compound **101** was also formed as indicated by TLC. Flash chromatographic separation of the reaction mass provided carbazole **93** and carbazole **101** in

61% and 21% yield respectively. Prolonging the reaction time did not have any significant effect on the yield of the product **93**.



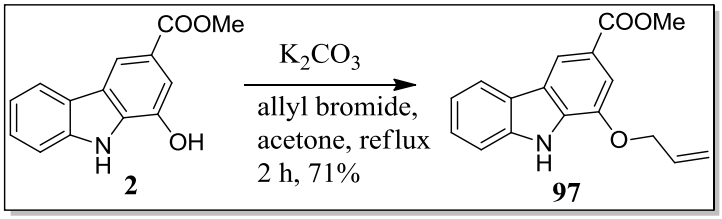
Scheme 27

3.B.II.4: Conclusion

A formal synthesis of a naturally occurring carbazole, clausenaline D was achieved through intermediate **93**. The synthesis of intermediate **93** could be accomplished by employing a one pot *o*-Claisen rearrangement and acetylation sequence.

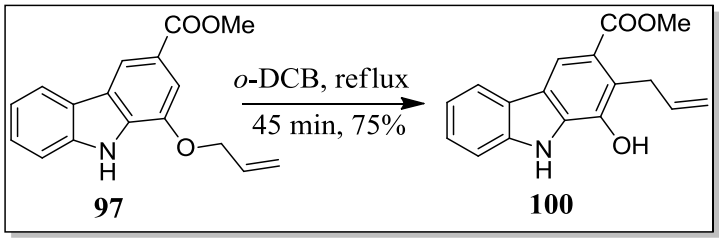
3.B.II.5: Experimental

3.B.II.5.1: Synthesis of methyl 1-(allyloxy)-9*H*-carbazole-3-carboxylate (97)



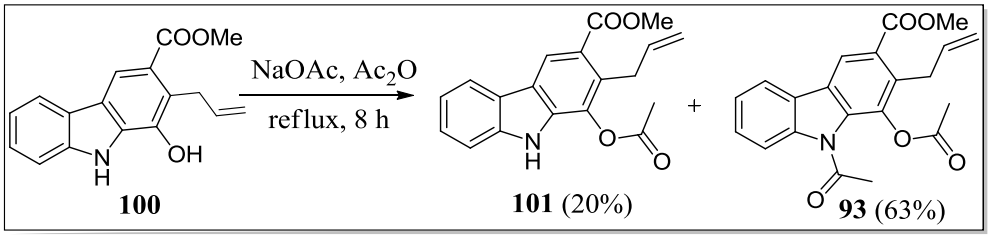
To a suspension of **2** (0.6 g, 2.48 mmol) in K_2CO_3 (0.68 g, 4.97 mmol) and acetone (15 mL), was added allyl bromide (0.21 mL, 2.48 mmol) at room temperature under argon atmosphere and the reaction mixture was subjected to reflux for 2 hours. The mixture was filtered, the filtrate was concentrated under vacuum and the remaining residue was purified by flash chromatography on silica gel using hexanes- EtOAc (9:1) as an eluent to give **97** as a white solid in 71% (0.499 g) yield (**m.p.:** 178-180 °C).

3.B.II.5.2: Synthesis of methyl 2-allyl-1-hydroxy-9*H*-carbazole-3-carboxylate (100)



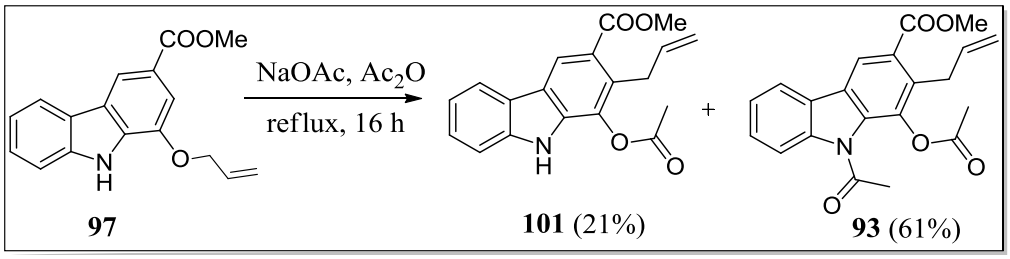
A solution of **97** (0.4 g, 1.42 mmol) in *ortho* dichlorobenzene (5 mL) under an argon atmosphere was heated at reflux for 45 minutes. The reaction mixture was purified by flash chromatography on silica gel using hexanes-EtOAc (7.5:2.5) as an eluent to give **100** as a white solid in 75% (0.3 g) yield. (**m.p.:** 147-149 °C).

3.B.II.5.3: Synthesis of methyl 1-acetoxy-9-acetyl-2-allyl-9*H*-carbazole-3-carboxylate (93) and methyl 1-acetoxy-2-allyl-9*H*-carbazole-3-carboxylate (101)



To a solution of **100** (0.2 g, 0.71 mmol) in acetic anhydride (7 mL) under argon atmosphere was added sodium acetate (0.116 g, 1.42 mmol) and the reaction mixture was refluxed for 8 hours. The reaction mixture was cooled and the solvent was removed under reduced pressure. This crude residue was dissolved in EtOAc (40 mL) washed with brine, (2 × 10 mL) and water (2 × 10 mL). The organic layer was dried over anhyd. sodium sulphate, concentrated and the residue was subjected to flash column chromatography on silica gel using hexanes- EtOAc (9:1) as an eluent to give **93** as a white solid in 63% (0.163 g) yield (**m.p.:** 119-121 °C; lit.[29f] 120-122 °C); and **101** as a white solid in 20% (0.045 g) yield (**m.p.:** 137-139 °C).

3.B.II.5.4: Synthesis of methyl 1-acetoxy-2-allyl-9*H*-carbazole-3-carboxylate (93) and methyl 1-acetoxy-2-allyl-9*H*-carbazole-3-carboxylate (101)



To a solution of **97** (0.11 g, 0.39 mmol) in acetic anhydride (5 mL) under argon atmosphere was added sodium acetate (0.096 g, 1.17 mmol) and the reaction mixture was refluxed for 16 hours. The reaction mixture was cooled and the solvent was removed under reduced pressure. This crude residue was dissolved in EtOAc (25 mL) washed with brine, (2 × 5 mL) and water (2 × 5 mL). The organic layer was dried over anhyd. sodium sulphate, concentrated and the residue was subjected to flash column chromatography on silica gel using hexanes- EtOAc (9:1) as an eluent to give **93** as a white solid in 61% (0.087 g) yield (**m.p.:** 119-121 °C; lit.[29f] 120-122 °C); and **101** as a white solid in 21% (0.026 g) yield (**m.p.:** 137-139 °C).

3.B.III: Total synthesis of Indizoline and Clausenapin

3.B.III.1: Occurrence and biological activities of Indizoline and Clausenapin

Indizoline (**17**) was first isolated from the roots of *Clausena indica* Oliv. by Joshi and Gawad in the year 1974.[56] Later it was isolated from the roots,[57,22] root bark,[58] twigs[21] and stems of *Clausena lansium*.[19, 20]

Clausenapin (**16**) was isolated from the leaves of *Clausena heptaphylla*.[59]

Various constituents of *Clausena lansium* along with indizoline showed a significant concentration dependent inhibition of nitrite production in the case of RAW264.7, a mouse macrophage cell line which was used to model macrophage-mediated inflammatory events *in vitro*. Further studies showed that indizoline was also effective in causing significant concentration dependent inhibition of tumor necrosis factor-α (TNF-α) which mediates the production of many cytokines during inflammation.[20] It also exhibited antitumor activity against three human cancer cell lines including oral cavity cancer (KB), breast cancer (MCF7) and small cell lung cancer (NCI-H187).[21]

The biological activities pertaining to clausenapin are not yet reported.

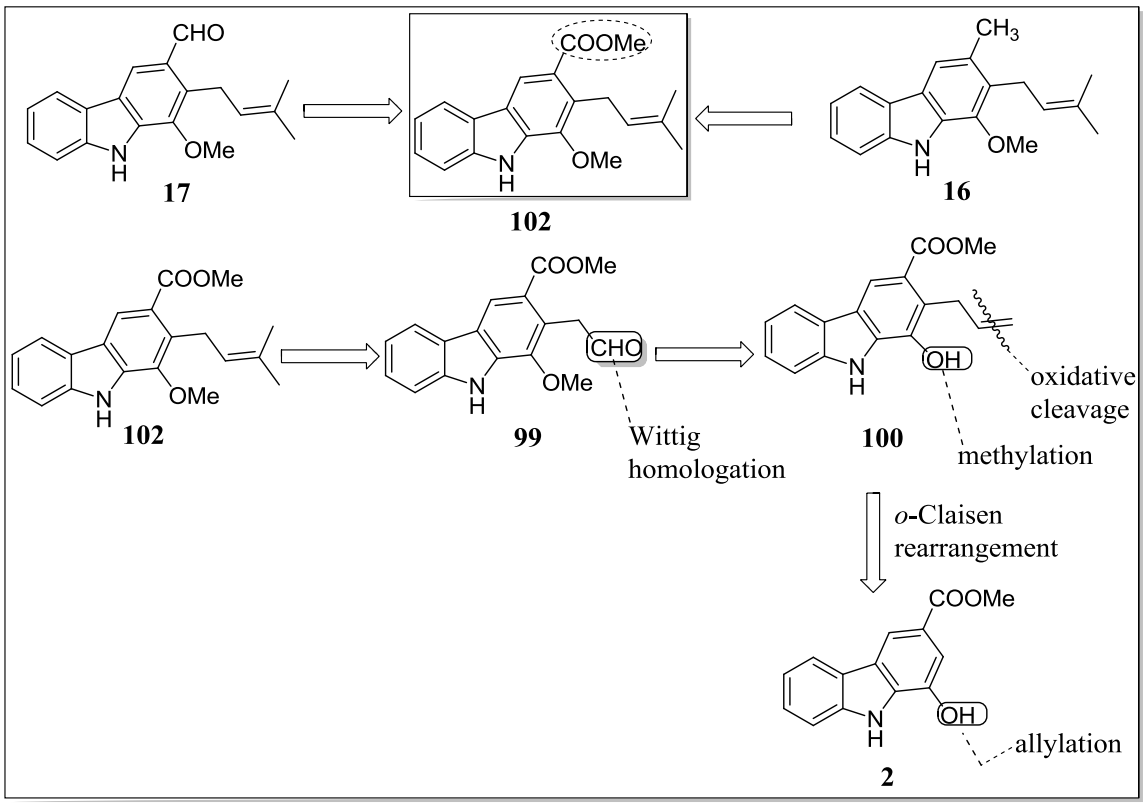
3.B.III.2: Literature synthetic methods

When we undertook the synthesis of the 2-prenylated carbazole alkaloids, indizoline and clausenapin starting from clausine E, there were no reports on their synthesis. Prior to its isolation clausenapin was synthesized as Huang Minlon reduction product of indizoline.[56] Unsuccessful attempts were made in the past to synthesize indizoline as well as clausenapin.[60]

3.B.III.3: Results and Discussion

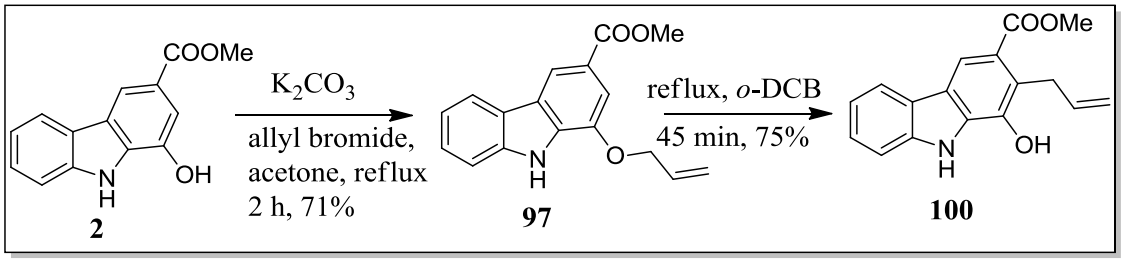
As mentioned in the introduction part, we presented our preliminary work on the successful conversion of clausine E to clausenapin *via* the key ester intermediate (**methyl 1-methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carboxylate) 102**, at the NFCFA2015 conference in December 2015.[61]

We envisioned a rapid entry into indizoline (**17**) and clausenapin (**16**) from the elaboration of a common intermediate **102** involving transformation of the ester function. A brief retrosynthetic strategy for the synthesis of intermediate **102** is shown below *(Scheme 28)*. Intermediate **102** would be accessible *via* Wittig homologation of the aldehyde **99**. Intermediate **99** would in turn come from carbazole **100** *via* methylation of the phenolic hydroxyl group and oxidative cleavage of the terminal double bond. Carbazole **100** could be obtained from *O*-allylation and concomitant *o*-Claisen rearrangement of clausine E.



Scheme 28

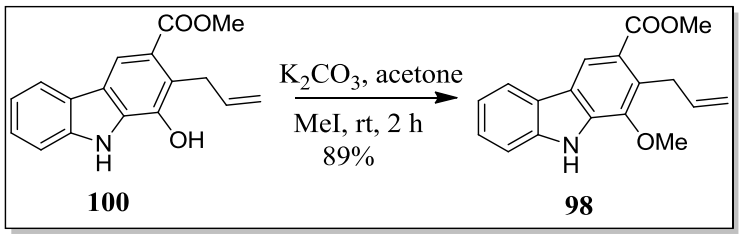
As mentioned in section **3.B.II**, carbazole **100** was synthesized *via o*-allylation of clausine E (**2**) followed by *O*-Claisen rearrangement *(Scheme 29).*



Scheme 29

Next, the carbazole **100** was subjected to methylation using K_2CO_3- MeI in acetone[37d] for two hours at room temperature *(Scheme 30)*. Column chromatographic purification of the reaction mass furnished a white solid (**m.p.:** 115-118 °C). Its IR spectrum showed a strong band at 1681 cm^{-1} indicating the presence of a carbonyl group. Asymmetric C-O-C stretch near 1263 cm^{-1} and a symmetric stretch near 1047 cm^{-1} characteristic of the aryl alkyl ether were observed. Sharpening of the N-H band of indole ring at 3346 cm^{-1} indicated the disappearance of the hydroxyl group in its IR spectrum.

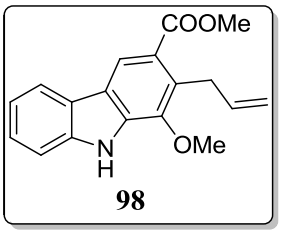
In its ^{1}H NMR spectrum the singlet at δ 3.96 for three protons was assigned to the protons of methoxy group at C-1. The singlet at δ 3.99 for three protons was attributed to the protons of the carbomethoxy group. A doublet of triplet at δ 4.05 for two protons (J = 5.6, 1.6 Hz) was assigned to the allylic methylene group (–C**H$_2$**-CH=CH_2). A multiplet between δ 4.95-5.05 integrating for two protons were attributed to the terminal olefinic protons of the allylic group (–CH_2-CH=C**H$_2$**). The single olefinic proton (–CH_2-C**H**=CH_2) appeared as a multiplet at δ 6.11-6.18. The aromatic protons appeared between δ 7.28-8.55. A singlet at δ 8.55 and a doublet at δ 8.09 (J = 7.6 Hz) could be attributed to the C-4 and C-5 protons respectively. A broad singlet at δ 8.40 was attributed to proton attached to indole nitrogen. The structure was further confirmed by ^{13}C NMR, DEPT experiment and HRMS data. The product was obtained in 89% yield.



Scheme 30

Spectroscopic data

Methyl 2-allyl-1-methoxy-9*H*-carbazole-3-carboxylate (98)



IR (KBr): υ_{max} 1047, 1263, 1346, 1606, 1681, 3346 cm^{-1}.

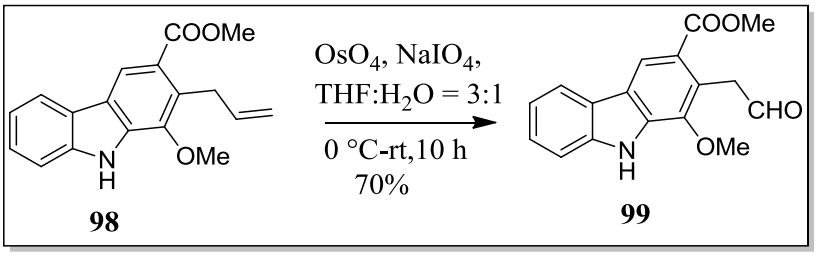
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H), δ 3.99 (s, 3H), 4.05 (dt, *J* = 4.0, 1.6 Hz, 2H), 4.95-5.05 (m, 2H), 6.11-6.18 (m, 1H), 7.28-7.32 (m, 1H), 7.45-7.52 (m, 2H), 8.09 (d, *J* = 7.6 Hz, 1H), 8.40 (br s, 1H), 8.55 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 30.68 (CH_2), 51.92 (CH_3), 61.43 (CH_3), 111.13 (CH), 114.60 (CH_2), 120.29 (CH), 120.39 (CH), 120.58 (CH), 122.37 (Cq), 122.92 (Cq), 123.92 (Cq), 126.46 (CH), 131.19 (Cq), 135.51 (Cq), 138.26 (CH), 139.83 (Cq), 143.43 (Cq), 168.38 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{18}H_{17}NO_3Na$: 318.1106, found: 318.1106.

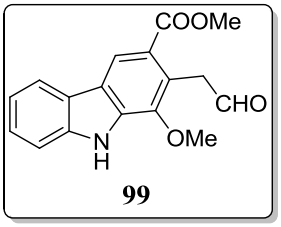
The above chemoselective methylation product **98** was transformed into the desired aliphatic aldehyde **99** by an in situ oxidative cleavage of the double bond, *via* the diol using OsO_4 and $NaIO_4$.[29f] The reaction was complete in 10 hours *(Scheme 31)*. Flash chromatographic separation of the reaction mass gave a white solid (**m.p.:** 170-172 °C). Its IR spectrum showed a strong band at 1712 cm^{-1} indicating the presence of a carbonyl group of aldehyde and a strong band at 1703 cm^{-1} indicating the presence of a carbonyl group of the ester moiety. Asymmetric C-O-C stretch near 1240 cm^{-1} and a symmetric stretch near 1058 cm^{-1} characteristic of the aryl alkyl ether were observed. A sharp band at 3338 cm^{-1} representing the N-H band of indole ring was also observed.

In its ^{1}H NMR spectrum the singlet at δ 3.81 for three protons was assigned to the protons of methoxy group at C-1. The singlet at δ 3.84 for three protons was attributed to the protons of the carbomethoxy group. A singlet at δ 4.25 for two protons was assigned to the methylene group adjacent to the aldehyde group (–C**H$_2$**-CHO). The aromatic protons appeared between δ 7.18-8.35. A singlet at δ 8.35 and a doublet at δ 7.91 (*J* = 7.6 Hz) could be attributed to the C-4 and C-5 protons respectively. A broad singlet at δ 8.60 was attributed to proton attached to indole nitrogen. The aldehydic proton was observed at δ 9.88 as a singlet. The structure was further confirmed by ^{13}C NMR, DEPT experiment and HRMS data. Compound **99** was obtained in 70% yield.



Scheme 31

Methyl 1-methoxy-2-(2-oxoethyl)-9*H*-carbazole-3-carboxylate (99)



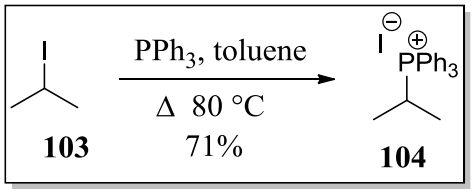
IR (KBr): υ_{max} 1058, 1240, 1703, 1712, 3338 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), δ 3.84 (s, 3H), 4.25 (s, 2H), 7.18-7.22 (m, 1H), 7.31-7.38 (m, 2H), 7.91 (d, J = 7.6 Hz, 1H), 8.35 (s, 1H), 8.60 (br s, 1H), 9.88 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 41.79 (CH_2), 51.96 (CH_3), 61.34 (CH_3), 111.31 (CH), 120.41 (CH), 120.51 (CH), 120.57 (CH), 120.72 (Cq), 123.62 (Cq), 123.70 (Cq), 124.76 (Cq), 126.62 (CH), 135.40 (Cq), 140.03 (Cq), 144.00 (Cq), 167.79 (Cq), 200.44 (CHO) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{17}H_{15}NO_4Na$: 320.0899, found: 320.0899.

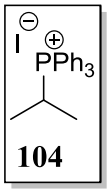
Next, the Wittig salt, triphenyl(propan-2-ylidene)phosphorane (**104**) was required in order to carry out Wittig homologation of the aldehyde **99**. This preparation of salt **104** by reaction of isopropyl iodide with triphenylphosphine in toluene at 80 °C was carried out as reported in literature *(Scheme 32)*.[62]



Scheme 32

The white solid obtained after 20 hours was filtered, washed with diethyl ether and dried under vacuum. The product was obtained in 71% yield (**m.p.:** 194-197 °C).

Triphenylphosphonium isopropyl iodide (104)

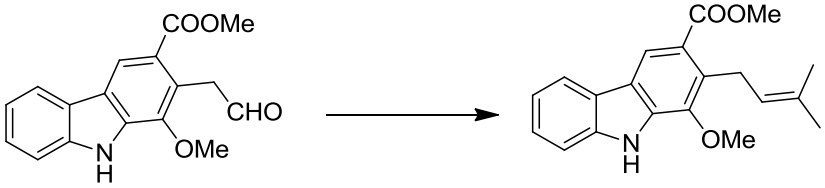


104

IR (KBr): υ_{max} 530, 694, 756, 995, 1107, 1435, 1477, 1583, 2985, 3045 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.8 Hz, 3H), 1.41 (d, J = 6.8 Hz, 3H), 5.15-5.25 (m, 1H), 7.70-7.82 (m, 9H), 7.94-7.98 (m, 6H) ppm.

The carbazole **99** was then treated with triphenyl(propan-2-ylidene)phosphorane,[33] obtained *in situ* by the reaction of triphenylphosphonium isopropyl iodide (**104**) with base such as *n*-BuLi or NaHMDS *(Scheme 33)*.



99 **102**

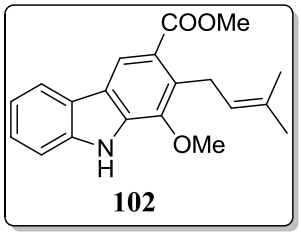
Entry	Reaction Conditions	Yield
1	**104**, *n*-BuLi, THF, -10°C-rt, 1 h	10%
2	**104**, *n*-BuLi, THF, -78°C-rt, 1 h	60%
3	**104**, NaHMDS, THF, -78°C-rt, 1 h	70%
4	**104**, NaHMDS, THF, -10°C-rt, 1 h	70%

Scheme 33

When the addition of *n*-BuLi was carried out at -10 °C followed by addition of aldehyde, the reaction was complete in one hour (as monitored by TLC). Flash chromatographic purification of the crude product gave a white solid (**m.p.:** 140-142 °C). Its IR spectrum showed a strong band at 1687 cm^{-1} indicating the presence of a carbonyl group of ester moiety. Asymmetric C-O-C stretch near 1261 cm^{-1} and a symmetric stretch near 1049 cm^{-1} characteristic of the aryl alkyl ether were observed. A sharp band at 3342 cm^{-1} representing the N-H band of indole ring was also observed.

In its ^{1}H NMR spectrum the two methyl groups of the prenyl moiety appeared as singlets at δ 1.66 and 1.81 while the methylene group showed a doublet at δ 3.93 (J = 6.4 Hz). The olefinic proton adjacent to methylene group appeared as triplet at δ 5.24 (J = 6.4 Hz). The singlets at δ 3.88 and at δ 3.95 for three protons were assigned to the protons of mehoxy group (attached to C-1) and carbomethoxy group respectively. The peaks between δ 7.21-8.48 were assigned to the aromatic protons of the carbazole ring. A singlet at δ 8.48 and a doublet at δ 8.16 (J = 8.0 Hz) could be attributed to the C-4 and C-5 protons respectively. A broad singlet at δ 10.74 was attributed to proton attached to the indole nitrogen. The structure was further confirmed by ^{13}C NMR, DEPT experiment and HRMS data.

Methyl 1-methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carboxylate (102)



102

IR (KBr): υ_{max} 1049, 1261, 1608, 1687, 3342 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d$_6$): δ 1.66 (s, 3H), δ 1.81 (s, 3H), 3.88 (s, 3H), 3.93 (d, J = 6.4 Hz, 2H), 3.95 (s, 3H), 5.24 (t, J = 6.4 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 10.74 (br s, 1H) ppm.

^{13}C NMR (100 MHz, acetone-d$_6$): δ 18.19 (CH_3), 25.91 (CH_3), 26.33 (CH_2), 52.02 (CH_3), 61.25 (CH_3), 112.34 (CH), 120.37 (CH), 120.64 (CH), 121.10 (CH), 122.95 (Cq), 123.36 (Cq), 124.45 (Cq), 125.49 (CH), 127.05 (CH), 131.14 (Cq), 133.42 (Cq), 136.49 (Cq), 141.58 (Cq), 144.43 (Cq), 168.96 (Cq) ppm.

HRMS: *m/z* $[M+Na]^+$ calculated for $C_{20}H_{21}NO_3Na$: 346.1419, found: 346.1419.

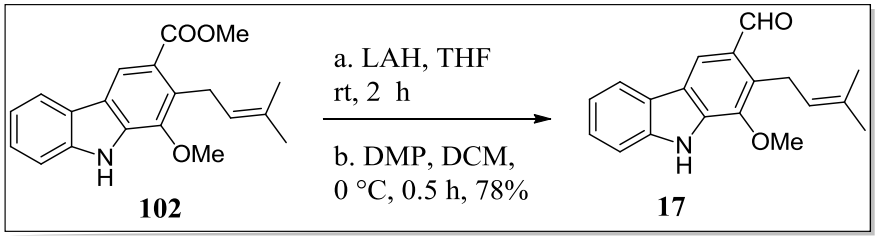
However, the product was obtained in only 10% yield. Addition of *n*-BuLi at -78 °C resulted in improvement of the product yield. Furthermore, when NaHMDS was used instead of *n*-BuLi, the yield of the product further increased to 70% (even when the addition was done at -10 °C).

Next, in order to transform the ester function in intermediate **102** into an aldehyde, it was treated with LAH in THF followed by Dess-Martin periodinane mediated oxidation *(Scheme 34)*.[63]

Flash chromatographic separation of the reaction mass gave a white solid (**m.p.:** 168-170 °C; lit.[56] 170-171 ^{O}C).

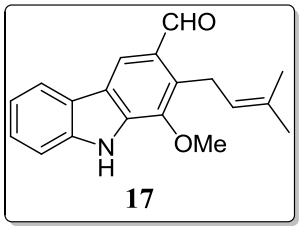
Its IR spectrum showed a strong band at 1724 cm^{-1} corresponding to an aldehydic carbonyl group. Asymmetric C-O-C stretch near 1242 cm^{-1} and a symmetric stretch near 1066 cm^{-1} characteristic of the aryl alkyl ether were observed. A sharp band at 3315 cm^{-1} representing the N-H band of indole ring was also observed.

In its ^{1}H NMR spectrum the two methyl groups of the prenyl moiety appeared as singlets at δ 1.67 and 1.85 ppm. The methylene group showed a doublet at δ 4.00 (J = 6.8 Hz). The olefinic proton adjacent to the methylene group appeared as multiplet at δ 5.23-5.27 ppm. The singlet at δ 3.98 for three protons was assigned to the protons of the methoxy group (attached to C-1). The peaks between δ 7.26-8.48 were assigned to the aromatic protons of the carbazole ring. A singlet at δ 8.48 and a doublet at δ 8.21 (J = 7.6 Hz) could be attributed to the C-4 and C-5 protons respectively. The aldehydic proton was observed as a singlet at δ 10.27 ppm. A broad singlet at δ 10.93 was attributed to proton attached to the indole nitrogen. The ^{13}C NMR and DEPT experiments were also in well agreement with the structure.



Scheme 34

1-Methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carbaldehyde (17)



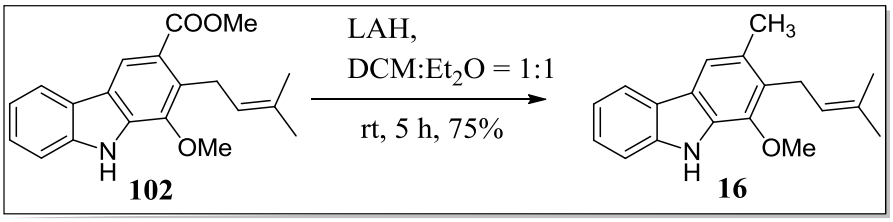
17

IR (KBr): υ_{max} 1066, 1242, 1666, 1724, 3315 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.67 (s, 3H), 1.85 (s, 3H), 3.98 (s, 3H), 4.00 (d, J = 6.8 Hz, 2H), 5.23-5.27 (m, 1H), 7.26-7.30 (m, 1H), 7.44-7.48 (m, 1H), 7.60 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 7.6 Hz, 1H), 8.48 (s, 1H), 10.27 (s, 1H), 10.93 (br s, 1H) ppm.

^{13}C NMR (100 MHz, acetone-d_6): δ 18.18 (CH_3), 24.62 (CH_2), 25.82 (CH_3), 61.51 (CH_3), 112.53 (CH), 121.05 (CH), 121.30 (CH), 122.61 (CH), 123.98 (Cq), 124.62 (Cq), 125.24 (CH), 127.33 (CH), 128.54 (Cq), 131.73 (Cq), 133.90 (Cq), 137.77 (Cq), 141.62 (Cq), 144.19 (Cq), 192.06 (CHO) ppm.

Having successfully transformed the intermediate **102** into indizoline (**17)** in 78% yield, the intermediate **102** was treated with excess LAH in order to synthesize clausenapin (**16**) *(Scheme 35)*.



102 **16**

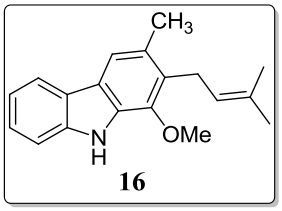
Scheme 35

Flash chromatographic separation of the reaction mass gave a pale red solid (**m.p.:** 83-85 °C; lit.[29e] 81-83 ^{O}C). Its IR spectrum showed an asymmetric C-O-C stretch near 1255 cm^{-1} and a symmetric stretch near 1062 cm^{-1} characteristic of the aryl alkyl ether. A sharp band at 3325 cm^{-1} representing the N-H band of indole ring was also observed.

In its ^{1}H NMR spectrum the two methyl groups of the prenyl moiety appeared as singlets at δ 1.69 and 1.83 ppm. The methylene group showed a doublet at δ 3.54 (J = 6.4 Hz). The olefinic proton adjacent to the methylene group appeared as a triplet at δ 5.14 (J = 6.4 Hz). The singlets at δ 2.43 and at δ 3.93 for three protons each was assigned to the protons of the

methyl group (attached to C-3) and methoxy group (attached to C-1) respectively. The peaks between δ 7.11-8.01 were attributed to the aromatic protons of the carbazole ring. A singlet at δ 7.66 and a doublet at δ 8.01 (J = 8.0 Hz) could be attributed to the C-4 and C-5 protons respectively. A broad singlet at δ 10.27 was attributed to the proton attached to the indole nitrogen. The structure was further confirmed by ^{13}C NMR and DEPT experiment.

Methoxy-3-methyl-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole (16)



16

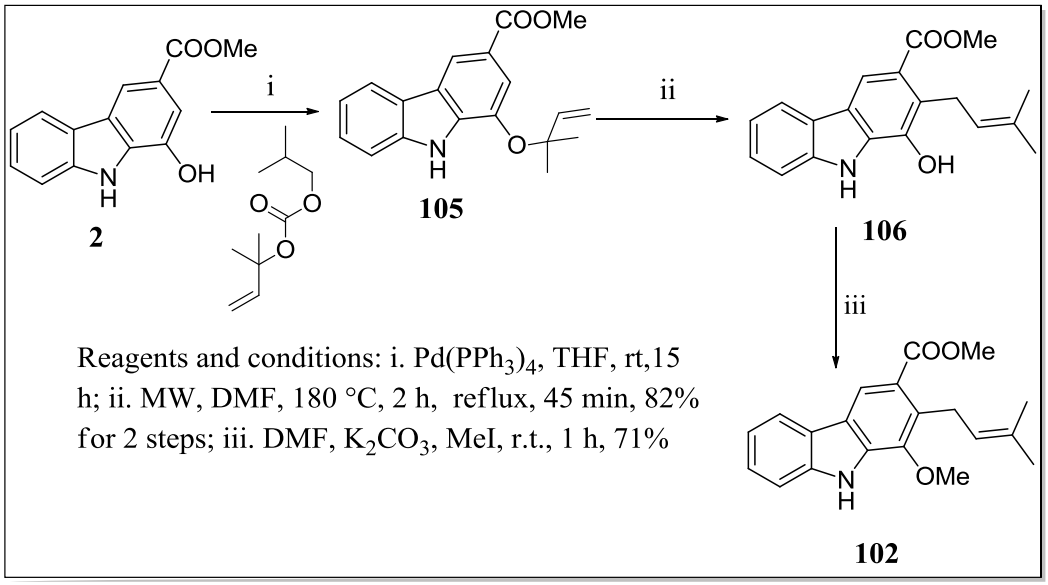
IR (KBr): υ_{max} 1062, 1255, 1338, 1612, 3325 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d$_6$): δ 1.69 (s, 3H), 1.83 (s, 3H), 2.43 (s, 3H), 3.54 (d, J = 6.4 Hz, 2H), 3.93 (s, 3H), 5.14 (t, J = 6.4 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 10.27 (br s, 1H) ppm.

^{13}C NMR (100 MHz, acetone-d$_6$): δ 18.07 (CH_3), 20.15 (CH_3), 25.83 (CH_3), 26.46 (CH_2), 61.09 (CH_3), 111.88 (CH), 117.50 (CH), 119.52 (CH), 120.64 (CH), 123.94 (Cq), 124.37 (Cq), 124.40 (CH), 125.99 (CH), 129.05 (Cq), 130.58 (Cq), 131.58 (Cq), 132.70 (Cq), 141.17 (Cq), 144.21 (Cq) ppm.

HRMS: *m/z* $[M+H]^+$ calculated for $C_{19}H_{22}NO$: 280.1701, found: 280.1701.

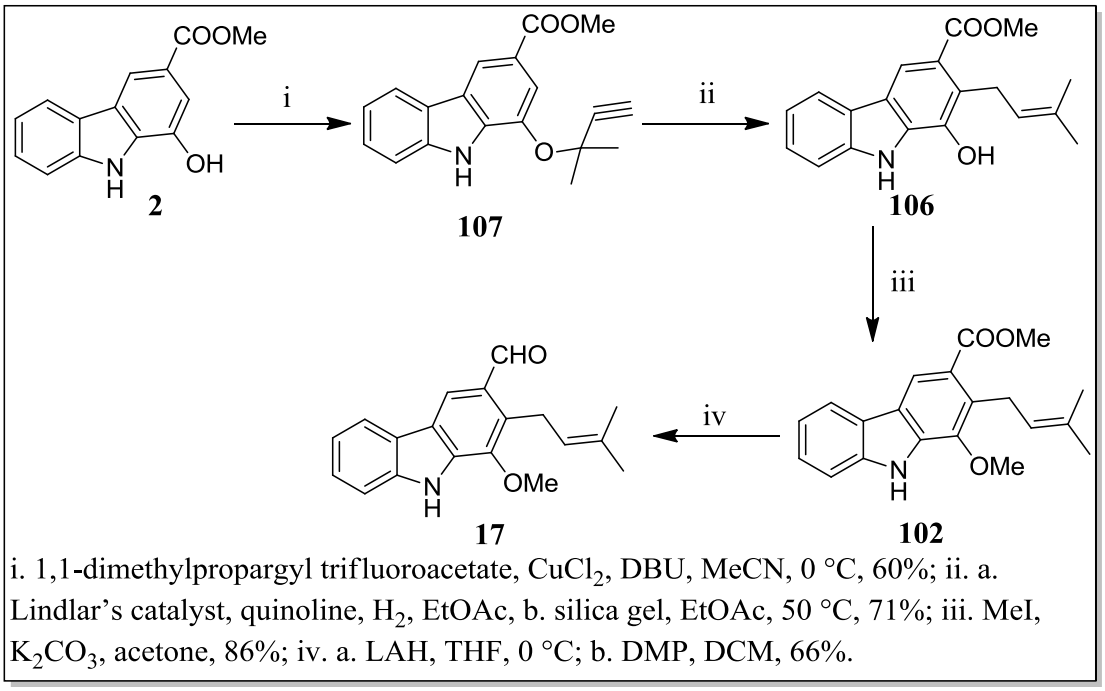
Hence we were successful in accomplishing the first total synthesis of indizoline and clausenapin. Immediately, in the year 2016, Ullah and co-workers reported the synthesis of this key ester intermediate **102** using palladium catalysed *O*-prenylation of clausine E and subsequent microwave assisted *o*-Claisen rearrangement *(Scheme 36)*. This intermediate was used for accomplishing the first total synthesis of (±)-mafaicheenamine A (**38**).[48]



Scheme 36

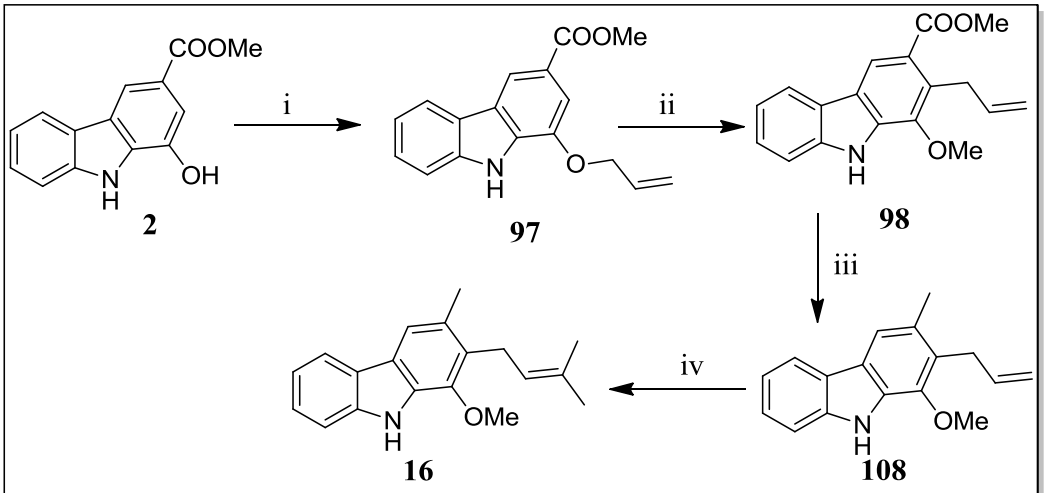
Following this report, Chang and co-workers described synthesis of the key ester intermediate **102** using *O*-allylation of clausine E and olefin metathesis as the key steps and used it as a precursor for getting indizoline.[29e] Propargylation of clausine E (**2**) with 1,1-dimethylpropargyl trifluoroacetate provided the propargyl ether **107** in 60% yield. Selective hydrogenation of the triple bond in propargyl ether **107** in the presence of Lindlar's catalyst followed by Claisen rearrangement gave the intermediate **106**. Methylation of the phenolic hydroxyl group in **106** furnished the intermediate **102**. The ester function in the intermediate **102** was transformed into an aldehyde, on treatment with lithium aluminium hydride in THF followed by Dess-Martin periodinane mediated oxidation resulting in the total synthesis of indizoline (**17**) *(Scheme 37).*

Furthermore they have also synthesized clausenapin from clausine E. Allylation of clausine E followed by *O*-Claisen rearrangement and methylation furnished the intermediate **98**. Transformation of the methyl ester functional group in **98** by LAH in refluxing 1,4-dioxane provided **108** in 94% yield. Olefin metathesis of **108** with 2,3-dimethyl-2-butene gave clausenapin (**16**) *(Scheme 38).*



i. 1,1-dimethylpropargyl trifluoroacetate, $CuCl_2$, DBU, MeCN, 0 °C, 60%; ii. a. Lindlar's catalyst, quinoline, H_2, EtOAc, b. silica gel, EtOAc, 50 °C, 71%; iii. MeI, K_2CO_3, acetone, 86%; iv. a. LAH, THF, 0 °C; b. DMP, DCM, 66%.

Scheme 37

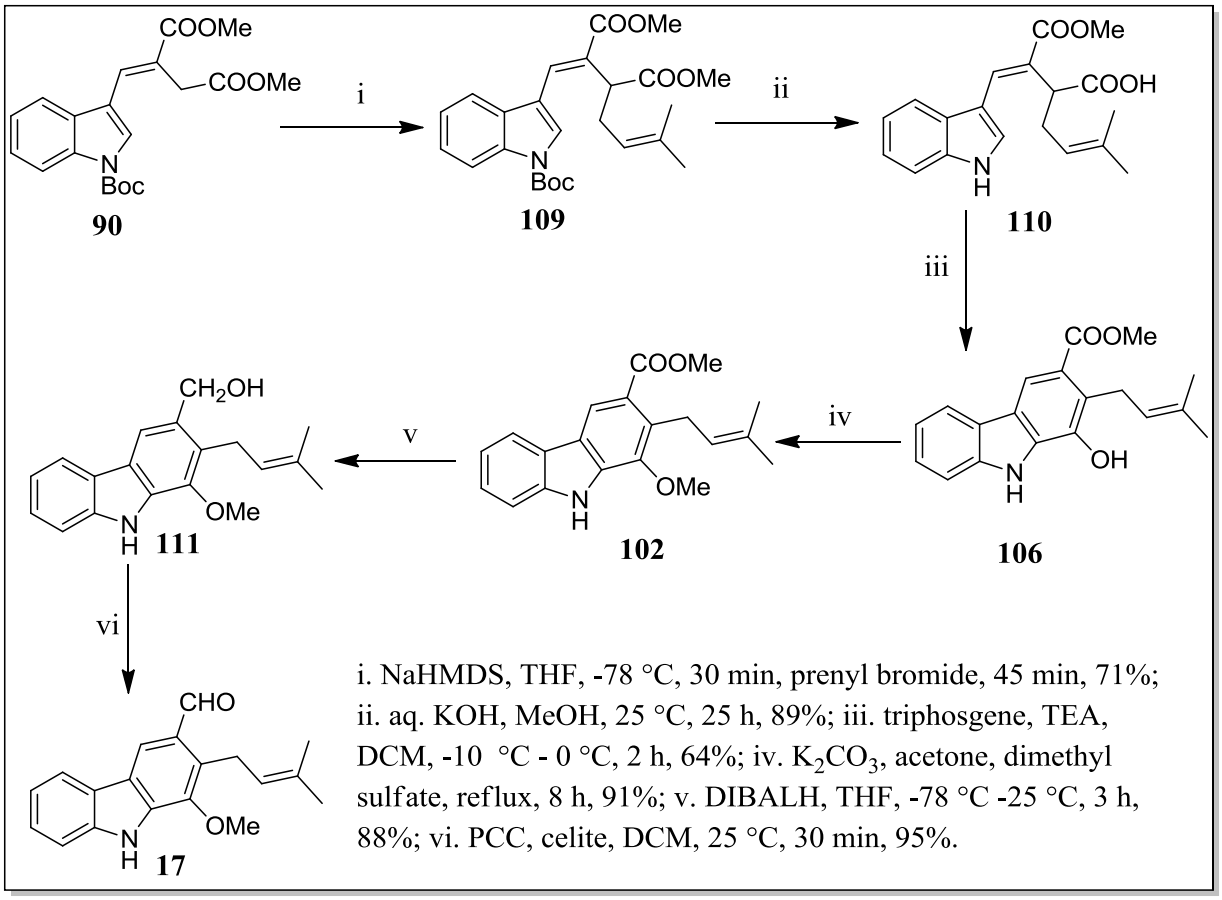


i. allyl bromide, K_2CO_3, acetone, 77%; ii. a. DMF, reflux; b. K_2CO_3, MeI, 71% over the two steps; iii. LAH, 1,4-dioxane, reflux, 94%; iv. 2,3-dimethyl-2-butene, Grubbs 2nd generation catalyst, DCM, reflux, 84%.

Scheme 38

This report was rapidly followed by a publication from Argade's group involving the synthesis of the key ester intermediate **102** and its conversion to indizoline.[29g] The Wittig product **90** upon treatment with NaHMDS/prenyl bromide provided the monoprenylated product **109** in good yield. One pot *N*-Boc-deprotection and regioselective base-induced

hydrolysis of the diester **109** delivered the carboxylic acid **110** in 89% yield. Triphosgene induced intramolecular acylation provided the carbazole **106** in moderate yield. Methylation of the phenolic hydroxyl group in **106** gave the desired intermediate **102**. Intermediate **102** on DIBALH reduction of carbomethoxy unit gave alcohol **111** in 88% yield, which upon oxidation with PCC provided indizoline (**17**) in 95% yield *(Scheme 39)*.



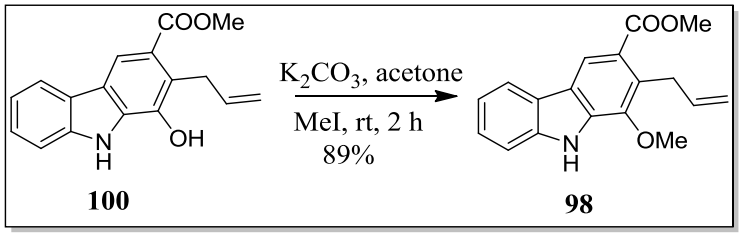
Scheme 39

3.B.III.4: Conclusion

Total synthesis of two 2-prenylated carbazole alkaloids, indizoline and clausenapin was achieved *via* a facile functional group transformation of the ester functionality at the C-3 carbon of the key ester intermediate **102**, derived from clausine E by employing *o*-Claisen rearrangement and Wittig homologation as the key steps.

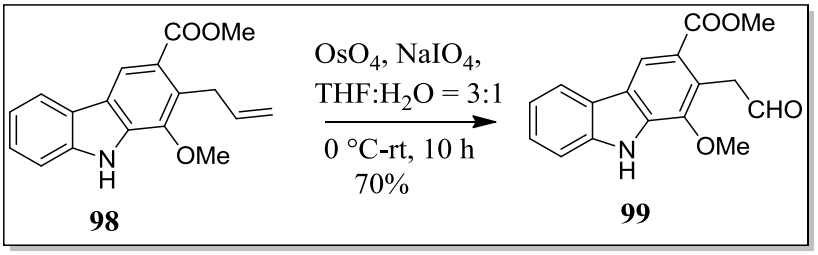
3.B.III.5: Experimental

3.B.III.5.1: Synthesis of Methyl 2-allyl-1-methoxy-9*H*-carbazole-3-carboxylate (98)



To a solution of **100** (0.3 g, 1.06 mmol) in acetone (10 mL) was added K_2CO_3 (0.339 g, 2.45 mmol) and stirred for 5 minutes at ambient temperature, iodomethane (0.47 mL, 7.46 mmol) was added and the reaction mixture was further stirred for two hours. Acetone was evaporated under reduced pressure. The mixture was dissolved in ethyl acetate (30 mL), washed with water (10 mL) and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude residue was subjected to column chromatographic purification on silica gel using hexanes- EtOAc (9:1) as an eluent to give **98** as a white solid in 89% (0.28 g) yield (**m.p.:** 115-118 °C).

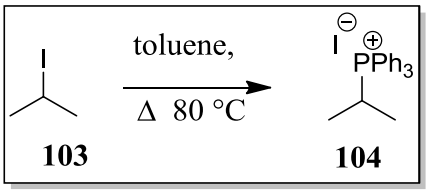
3.B.III.5.2: Synthesis of Methyl 1-methoxy-2-(2-oxoethyl)-9*H*-carbazole-3-carboxylate (99)



To a suspension of **98** (0.27 g, 0.914 mmol) in a mixture of THF (7.5 mL) and water (2.5 mL) was added 1% aq. OsO_4 solution (1.6 mL, 0.063 mmol) at 0-5 °C and the reaction mixture was stirred. After 10 minutes, $NaIO_4$, (0.879 g, 4.11 mmol) was added to the reaction mixture and stirring was continued for 10 hours at ambient temperature. THF was evaporated under vacuum and water (15 mL) was added to the residue. The reaction mixture was extracted with ethyl acetate (3 × 15 mL) and the combined extract was washed with

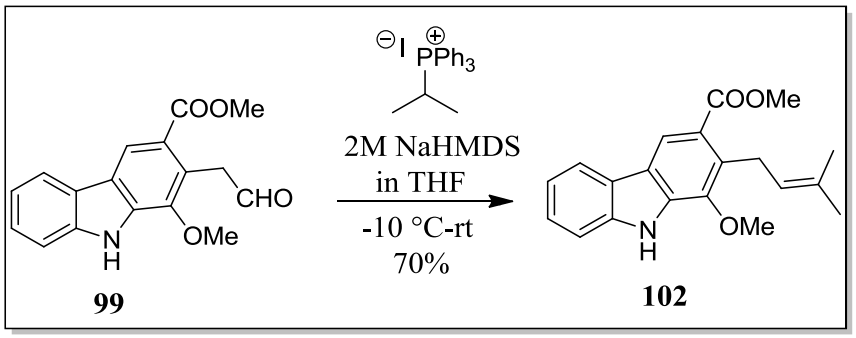
water, brine and dried over anhyd. sodium sulfate. The organic layer was concentrated in vacuo and the crude residue was purified by flash chromatography on silica gel using hexanes- EtOAc (7:3) as an eluent to give **99** as a white solid in 70% (0.19 g) yield (**m.p.:** 170-172 °C).

3.B.III.5.3: Synthesis of triphenylphosphonium isopropyl iodide (104)



Triphenylphosphine (7.02 g, 26.75 mmol) and isopropyl iodide **103** (25 g, 9.5 mmol) in toluene (30 mL) were subjected to heating at 80 °C for 20 hours under argon atmosphere. The reaction mixture was cooled and the white solid obtained was filtered. The solid was washed with Et_2O (2 × 25 mL) and vacuum dried for 45 minutes under vacuum to give triphenylphosphonium isopropyl iodide in 71% (8.2 g) yield (**m.p.:** 194-197 °C).

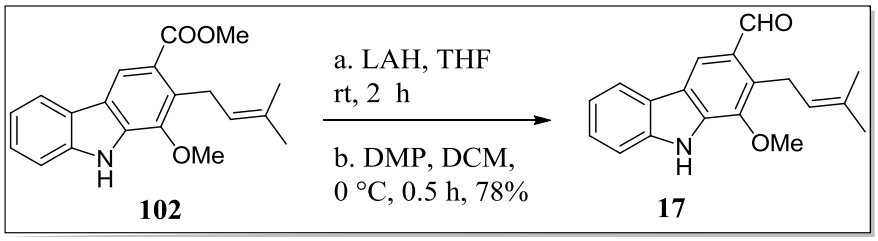
3.B.III.5.4: Synthesis of Methyl 1-methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carboxylate (102)



A flame-dried, 2-necked round bottomed flask under argon atmosphere was charged with triphenylphosphonium isopropyl iodide **104** (0.58 g, 1.34 mmol) and anhyd. THF (10 mL). The solution was cooled to -10 °C and 2M NaHMDS in THF (0.67 mL, 1.34 mmol) was added drop wise (till the dark red colour persisted). After ten minutes, a solution of compound **99** (0.2 g, 0.67 mmol) in anhyd. THF (5mL) was added drop wise at -10 °C to the reaction mixture. The reaction mixture was then allowed to gradually warm to room temperature and stirred for about one hour. The reaction mixture was quenched with aq. sat.

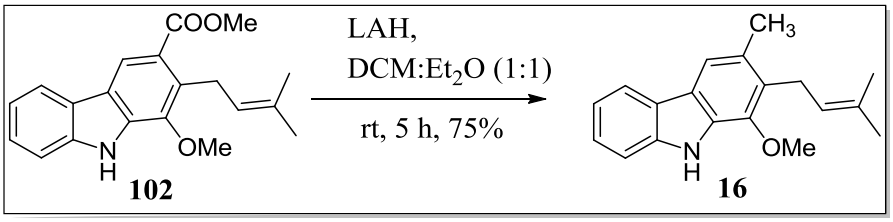
NH_4Cl solution (10 mL). THF was removed under vacuum and the crude mixture was extracted with Et_2O (3 × 15 mL). The combined organic extract was washed with water (10 mL), brine (10 mL) and dried over anhyd. sodium sulfate. The organic layer was concentrated in vacuo and the crude residue was purified by flash chromatography on silica gel using hexanes- EtOAc (8:2) as an eluent to give **102** as a white solid in 70% (0.152 g) yield (**m.p.:** 140-142 °C).

3.B.III.5.5: Synthesis of 1-Methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carbaldehyde (17)



To a suspension of LAH (0.025 g, 0.649 mmol) in anhyd. THF (4 mL) was added drop wise compound **102** (0.07 g, 0.216 mmol) dissolved in anhyd. THF (4 mL) under an argon atmosphere. The reaction was stirred for 2 hours at ambient temperature. The reaction mixture was quenched with water (3 mL) at 0 °C and filtered. The solvent of the filtrate was removed under vacuum. The crude residue was dissolved in dry DCM (5 mL) and DMP (0.0918 g, 0.216 mmol) was added to it under argon atmosphere at 0 °C. After stirring for 0.5 hours, DCM was evaporated under vacuum and the reaction mixture was diluted with Et_2O (30 mL) and washed with 10% Na_2CO_3 solution (10 mL) and water (10 mL). The organic layer was dried over anhyd. sodium sulfate and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using hexanes- EtOAc (8:2) as an eluent to give **17** as a white solid in 78% (0.049 g) yield (**m.p.:** 168-170 °C; lit.[56] 170-171 ^{O}C).

3.B.III.5.6: Synthesis of Methoxy-3-methyl-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole (16)



To a suspension of LAH (0.126 g, 3.3 mmol) in anhyd. DCM: Et_2O (6 mL, 1:1) was added drop wise compound **102** (0.09 g, 0.278 mmol) dissolved in anhyd. DCM: Et_2O (4 mL, 1:1) under an argon atmosphere at ambient temperature and stirring was continued for 5 hours. The reaction mixture was quenched with water (2 mL) at 0 °C and filtered. The solvent of the filtrate was removed under vacuum; the resulting residue was dissolved in chloroform (30 mL) and washed with water (10 mL). The organic layer was dried over anhyd. sodium sulphate, concentrated under vacuum and the residue was subjected to flash column chromatography on silica gel using hexanes- EtOAc (9:1) as an eluent to give **16** as a pale red solid in 75% (0.058 g) yield (**m.p.:** 83-85 °C; lit.[29e] 81-83 ^{O}C).

3.C: Evaluation of antioxidant activity of selected 1-Oxygenated carbazoles

3.C.1: Introduction

(1) An antioxidant is a substance that in small quantities is able to prevent or greatly retard the oxidation of easily oxidisable molecules. The role of an antioxidant is to intercept a free radical (responsible for initiating oxidation) before it can react with the substrate.

(2) High concentration of free radicals and reactive oxygen species (ROS), which include hydrogen peroxide, extremely reactive hydroxyl, and several other free radicals produced by cells, are responsible for initiating various diseases such as carcinogenesis, inflammation, atherogenesis and aging in aerobic organisms.[64] Antioxidants are considered as the drug candidates to combat these conditions.

Primary sources of naturally occurring antioxidants include whole grains, fruits and vegetables. Antioxidants like vitamin C, vitamin E, carotenes, phenolic acids, polyphenols, flavonoids etc. have the potential to reduce disease risk.

There are a number of mechanistic ways in which phenolics could act as antioxidants.

Owing to the presence of phenolic hydroxyl groups these compounds are good proton donors and hence can react with reactive oxygen and nitrogen species[65] in a termination reaction, resulting in the breaking of the cycle of generation of new free radicals. A radical form of the antioxidant which is produced on interaction with the initial reactive species, has a much greater chemical stability compared to the initial radical. The formation of such long-lived radicals results in the modification of the radical-mediated oxidation processes.[66]

This ability of the phenolic compounds to generate free radicals is attributed to the interaction of the hydroxyl groups with the pi-electrons of the benzene ring (the radical is stabilized by delocalization).

The phenolic compounds also have the ability to chelate metal ions which are involved in the production of free radicals.[65] The phenolic compounds can act as antioxidants, also by inhibiting some enzymes involved in radical generation, such as lipoxygenases, xanthine oxidase, cytochrome P450 isoforms and xanthine oxidase.[65-66]

A simple, rapid and most accepted method to evaluate the antioxidant activity of compounds involve the use of the free radical, 2, 2-Diphenyl-1-picrylhydrazyl (DPPH). The DPPH assay method is based on the reduction of DPPH, a stable free radical.[67] The DPPH free radical

with an odd electron shows a maximum absorption at 517 nm. DPPH free radical is reduced to the DPPH-H in the presence of a hydrogen donor (antioxidant) resulting in decolorization and decrease in absorbance with respect to the number of electrons captured. More the decolorization and less the absorbance better is the reducing ability.

There are several reports on antioxidant activities of the carbazole alkaloids.[68-74]

In this section, previously reported antioxidant activities of carbazole alkaloids and evaluation of antioxidant activities of selected 1-oxygenated carbazoles *via* the DPPH radical scavenging method has been described.

3.C.2: Literature Report

In 1984, Searle *et al.* tested several carbazoles for antioxidant activity in peroxidizing rat liver microsomes and human erythrocyte ghosts.[68] 6-Hydroxy-1,4-dimethylcarbazole (**112**, *Figure 4*) showed the highest inhibitory effect on lipid peroxidation. Figure 4 provides structures of some carbazole alkaloids evaluated for their possible potential to antioxidant action. Although the mechanism of action of **112** was not very clear, it was partly attributed to high rates of reaction with hydroxy and peroxy radicals, high lipid solubility and a substituted indole-type structure.

In 1989, Kato *et al.* discovered a 3-hydroxycarbazole alkaloid, carazostatin (**113**), isolated from *Streptomyces chromofuscus* DC 118 as a new free radical- scavenging substance.[69] Carazostatin (**113**) exhibited strong inhibitory effect on lipid peroxidation induced free radicals in rat brain homogenate.

Although α-tocopherol was a stronger antioxidant against free radical-induced lipid peroxidation than carazostatin (**113**) in homogeneous solution, carazostatin was more active than α-tocopherol in the liposomal membranes.[70]

The antioxidative activity of carbazomadurins A (**114**) and B (**115**) and carquinostatin A (**116**) was studied by testing the inhibition of the *L*-glutamate toxicity in N18-RE-105 cells.[71]

The antioxidant activities of various natural and synthetic carbazoles were evaluated by Iwatsuki *et al.* in the oxidation of methyl linoleate in homogeneous solution and soybean phosphatidyl choline (PC) liposomes in aqueous dispersion induced by free radicals.[72] Carazostatin (**113**) was found to be a strong antioxidant in both oxidation systems.

Carbazomycin B (**117**) exhibited a moderate antioxidant activity. Carbazole derivatives without a free hydroxyl group could not suppress the oxidation appreciably.

Oleoresin of *Murraya koenigii* Spreng (curry leaves) obtained using acetone, along with the other extracts obtained using methanol, water and volatile oil were evaluated for antioxidant activity using a *β*-carotene–linoleic acid model system.[73] Among all the extracts, the oleoresin showed maximum activity of 83.2% at 100 ppm in comparison to butylated hydroxyl anisole (synthetic antioxidant), which exhibited 90.2% activity at the same concentration. Among the five isolated compounds, two compounds which exhibited maximum antioxidant activity were characterized as mahanimbine (**118**) and koenigine (**119**). Koenigine showed a highest degree of radical scavenging activity.

Yenjai and co-workers evaluated antioxidant activity of carbazoles isolated from *Clausena harmandiana* using DPPH and lipid peroxidation assay.[44] 7-Methoxyheptaphylline (**120**) and 7-methoxymukonal (**121**) showed high lipid peroxidation inhibitory activity with an IC_{50} value of 3.61 μM and1.42 μM respectively. However these compounds showed weak antioxidant activity on DPPH assay. 7-Hydroxyheptaphylline (**122**) (IC_{50} = 56.82 μM) showed stronger ability to DPPH assay than compound **120** (IC_{50} = 843.42 μM). Clausine E (**2**) showed higher DPPH (IC_{50} = 57.54 μM) and lipid peroxidation inhibitory activity (IC_{50} = 1.69 μM) than Clausine C (**123**). Infact, compound **123** was inactive for the DPPH assay showing that the hydroxyl group at C-1 might be responsible for the antioxidant activity. Similarly, compound **121** showed high DPPH (IC_{50} = 649.13 μM) and lipid peroxidation inhibitory activity (IC_{50} = 1.42 μM), whereas Lansine (**124**) was inactive against DPPH and lipid peroxidation assay confirming that the hydroxyl group played an important role for this activity.

The antioxidative activity of naturally occurring 3-hydroxy- and 3,4-dioxygenated carbazole alkaloids along with their synthetic precursors was described by Hibino and co-workers using DPPH-radical and $ABTS^+$ radical scavenging assays. Furthermore, antioxidant activity was evaluated using a test kit for potential antioxidant in oil solution (PAO-SO).[74] In DPPH-radical and $ABTS^+$ radical scavenging assays, the dihydroxy compounds, carbazomadurins A (**114**) and B (**115**), and their synthetic precursors **114a** and **115a** exhibited better antioxidant activities than carazostatin (**113**) and the synthetic precursors **116a** and **116b** of

carquinostatin A (**116**). 3,8-Dihydroxycarbazoles, carbazomadurin A (**114**) and B (**115**) and their synthetic precursors **114a** and **115a** showed better total potential capacity than all 3-monohydroxycarbazoles in the PAO-SO assay. Carquinostatin A (**116**, carbazole-3,4-quinone) displayed the lowest total potential antioxidant capacity of all the carbazoles tested. The radical scavenging activities of 3-hydroxy- and 3,8-dihydroxycarbazoles could be attributed to the contribution of a nitrogen atom located at the pyrrole ring to form an iminoquinone structure by donating an electron or a hydrogen radical to the free radical.

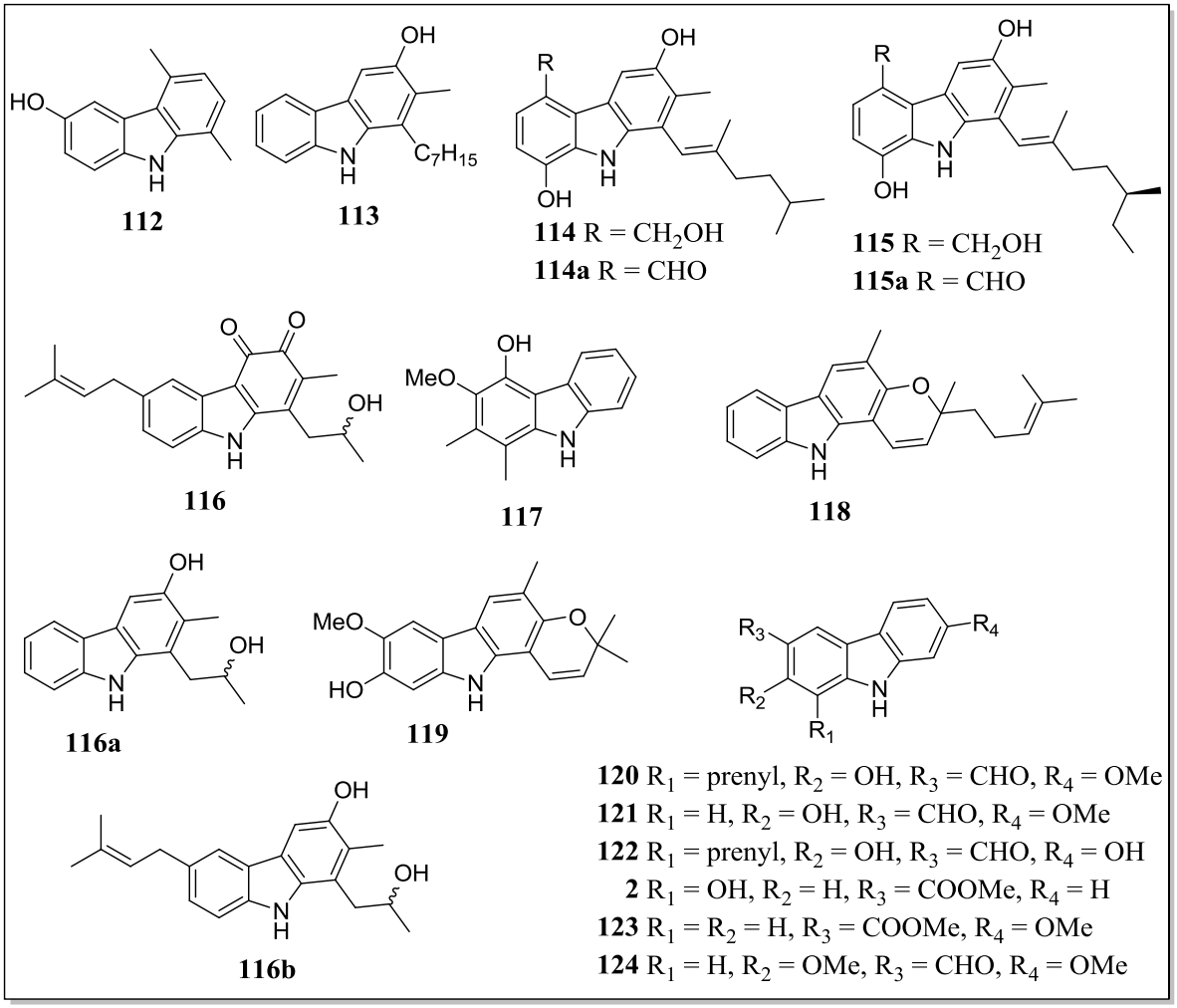


Figure 4: Structures of some carbazole alkaloids evaluated for their possible potential to antioxidant action.

3.C.3: Results and Discussion

As evident from literature report, clausine E is known to possess antioxidant property and presence of hydroxyl group plays an important role for this activity. Therefore a study was undertaken to evaluate selected carbazoles, synthesized in our laboratory, having phenolic hydroxyl group for their possible potential to antioxidant action by DPPH radical scavenging method.

Clausine E (**C-1**), 1-hydroxy-9*H*-carbazole-3-carboxylic acid (**C-2**), methyl 2-allyl-1-hydroxy-9*H*-carbazole-3-carboxylate (**C-3**) and clausine F (**C-4**) were used as the test compounds (*Figure 5*).

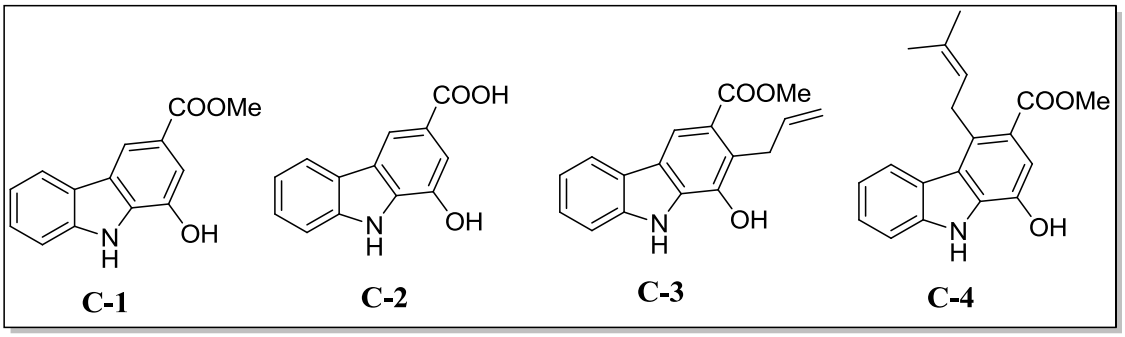


Figure 5: Structures of some carbazole alkaloids evaluated for their possible potential to antioxidant action.

Various concentrations of the compounds in methanol were treated with 0.2 mM DPPH radical solution in methanol and kept in dark at room temperature for 30 minutes. Thereafter, the absorbance of the resulting solution was measured at 517 nm using a spectrophotometer.

The decreased absorbance value of reaction mixture corresponded to an increased percentage inhibition or percentage of free radical scavenging activity (% Inhibition).

Methanol was used as blank and *L*-ascorbic was used as standard. Control comprised of only methanol and DPPH solution. All the reactions were monitored in triplicate and the values were expressed as the mean ± standard deviation (S.D.).

The % Inhibition was calculated by using the following formula;

% Inhibition = [(Acontrol – Atest) / Acontrol] x 100

Where Acontrol is the absorbance of the control reaction (containing all reagents except the test compound) and Atest is the absorbance of the test compound.

The detailed results are provided below.

Table 1: DPPH radical scavenging activities of *L*-Ascorbic acid

Concentration of L-Ascorbic acid (μg/mL)	Optical Density (517 nm)			Mean	S. D.	% Inhibition
10	0.559	0.561	0.560	0.560	0.001	45
20	0.305	0.308	0.314	0.309	0.0045	70
30	0.255	0.262	0.257	0.258	0.0036	75
40	0.225	0.227	0.225	0.226	0.0012	78
50	0.195	0.199	0.201	0.198	0.059	80
60	0.142	0.140	0.140	0.140	0.0014	86
70	0.129	0.129	0.127	0.128	0.0012	87
80	0.117	0.117	0.114	0.116	0.0017	89
90	0.105	0.103	0.103	0.104	0.0012	90
100	0.0912	0.091	0.0912	0.091	0.0003	91
Control (0.5 mL methanol)	1.015	1.011	1.015	1.014	0.0023	

Table 2: DPPH radical scavenging activities of Clausine E (**C-1**)

Concentration of (C-1) (μg/mL)	Optical Density (517 nm)			Mean	S. D.	% Inhibition
10	0.645	0.649	0.645	0.646	0.0023	36
20	0.611	0.612	0.617	0.613	0.0032	40
30	0.560	0.559	0.558	0.559	0.001	45
40	0.475	0.470	0.468	0.471	0.0036	54
50	0.398	0.403	0.402	0.401	0.0026	60
60	0.225	0.227	0.225	0.226	0.0012	78
70	0.213	0.210	0.217	0.213	0.0035	79
80	0.201	0.202	0.200	0.201	0.001	80
90	0.197	0.197	0.193	0.196	0.0023	81

100	0.185	0.183	0.185	0.184	0.0012	82
Control (0.5 mL methanol)	1.015	1.011	1.015	1.014	0.0023	

Table 3: DPPH radical scavenging activities of 1-hydroxy-9*H*-carbazole-3-carboxylic acid (**C-2**)

Concentration of (C-2) (µg/mL)	Optical Density (517 nm)			Mean	S. D.	% Inhibition
10	0.563	0.559	0.558	0.560	0.0026	45
20	0.305	0.314	0.308	0.309	0.0045	70
30	0.260	0.259	0.261	0.260	0.001	74
40	0.229	0.230	0.235	0.231	0.0032	77
50	0.200	0.201	0.202	0.201	0.001	80
60	0.160	0.165	0.158	0.161	0.0036	84
70	0.147	0.148	0.146	0.147	0.001	86
80	0.108	0.109	0.108	0.108	0.0007	89
90	0.097	0.099	0.097	0.098	0.0012	90
100	0.0825	0.0829	0.0825	0.0826	0.0002	92
Control (0.5 mL methanol)	1.015	1.011	1.015	1.014	0.0023	

Table 4: DPPH radical scavenging activities of methyl 2-allyl-1-hydroxy-9*H*-carbazole-3-carboxylate (**C-3**)

Concentration of (C-3) (µg/mL)	Optical Density (517 nm)			Mean	S. D.	% Inhibition
10	0.645	0.649	0.646	0.647	0.0021	36
20	0.599	0.596	0.598	0.598	0.0015	41
30	0.558	0.559	0.563	0.560	0.0026	45
40	0.453	0.454	0.457	0.455	0.0021	55

50	0.379	0.378	0.379	0.379	0.0007	63
60	0.246	0.245	0.246	0.246	0.0007	76
70	0.237	0.239	0.237	0.238	0.0012	77
80	0.221	0.227	0.221	0.223	0.0035	78
90	0.207	0.207	0.209	0.208	0.0012	79
100	0.198	0.194	0.198	0.197	0.0023	81
Control (0.5 mL methanol)	1.015	1.011	1.015	1.014	0.0023	

Table 5: DPPH radical scavenging activities of clausine F (**C-4**)

Concentration of (C-4) (μg/mL)	Optical Density (517 nm)			Mean	S. D.	% Inhibition
10	0.867	0.863	0.867	0.865	0.0024	15
20	0.827	0.829	0.832	0.829	0.0025	18
30	0.817	0.810	0.811	0.813	0.0038	20
40	0.710	0.709	0.711	0.710	0.001	30
50	0.614	0.618	0.620	0.617	0.0030	39
60	0.507	0.505	0.502	0.505	0.0025	50
70	0.457	0.458	0.458	0.458	0.0007	55
80	0.443	0.443	0.442	0.443	0.0007	56
90	0.425	0.425	0.425	0.425	0	58
100	0.395	0.391	0.397	0.394	0.003	61
Control (0.5 mL methanol)	1.015	1.011	1.015	1.014	0.0023	

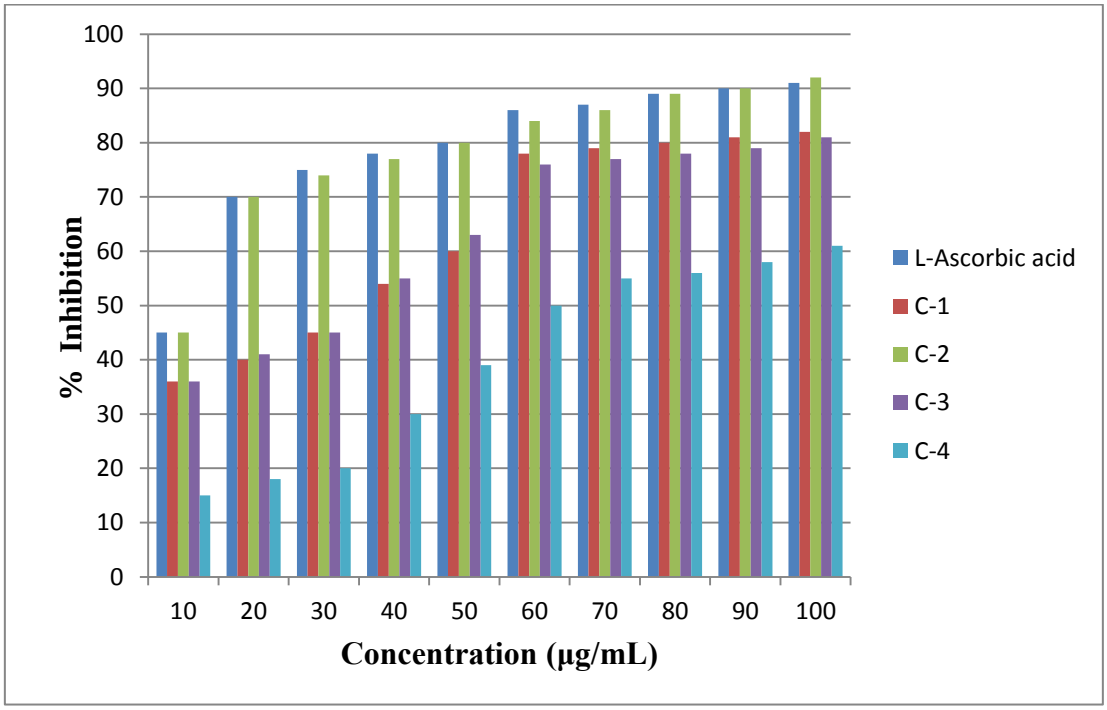


Figure 6: DPPH radical scavenging activities of Ascorbic acid and Carbazoles (**C-1** to **C-4**).

The concentration of the compounds which reduces the DPPH free radical to about 50% i.e. the IC_{50} values were calculated by using regression analysis from graphpad prism software.

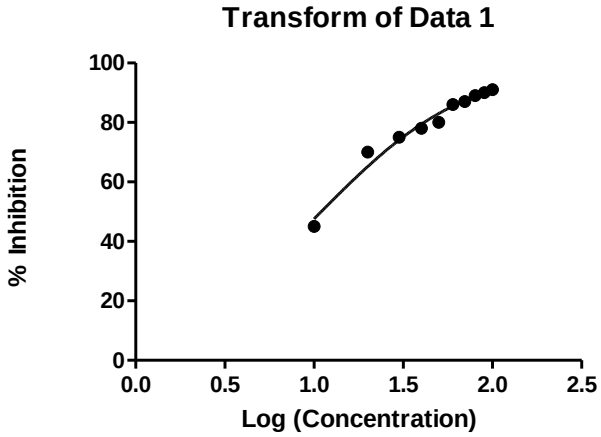


Figure 7: Graph of % Inhibition *v/s* Log of concentration of *L*-Ascorbic acid in µg/mL.

Log IC_{50} = 1.040

IC_{50} = 10.97

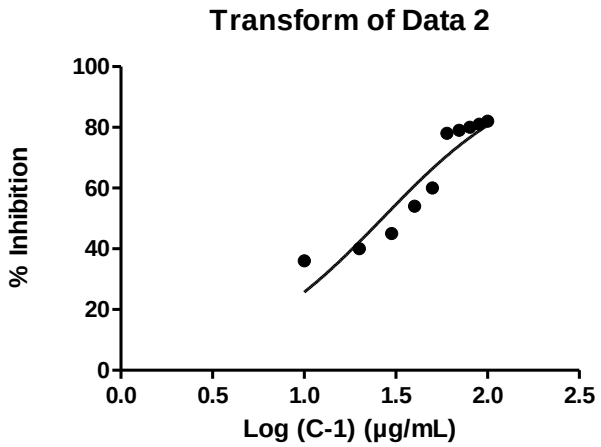


Figure 8: Graph of % Inhibition *v/s* Log of concentration of Clausine E (**C-1**) in µg/mL.

Log IC_{50} = 1.426

IC_{50} = 26.66

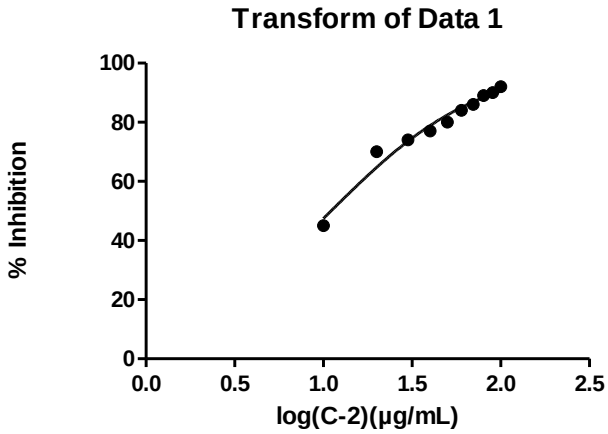


Figure 9: Graph of % Inhibition *v/s* Log of concentration of 1-hydroxy-9*H*-carbazole-3-carboxylic acid (**C-2**).

Log IC_{50} = 1.043

IC_{50} = 11.05

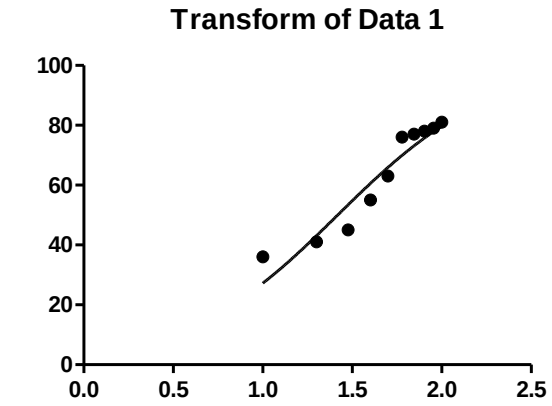


Figure 10: Graph of % Inhibition *v/s* Log of concentration of methyl 2-allyl-1-hydroxy-9*H*-carbazole-3-carboxylate (**C-3**).

Log IC_{50} = 1.419

IC_{50} = 26.23

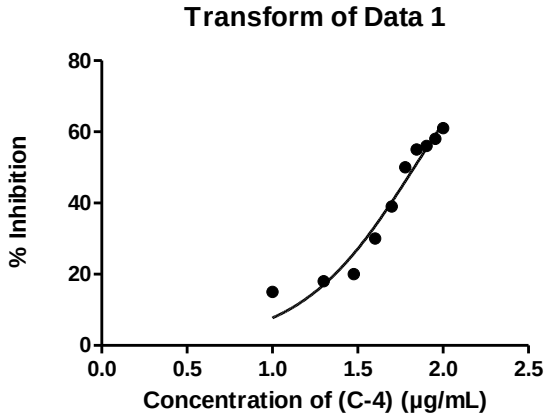


Figure 11: Graph of % Inhibition *v/s* Log of concentration of clausine F (**C-4**).

Log IC_{50} = 1.831

IC_{50} = 67.78

The results suggest that amongst the carbazoles, **C-2** showed highest percentage inhibition or free radical scavenging activity and the lowest value of IC_{50} (IC_{50} = 11.05 µg/mL). Clausine F showed lowest percentage inhibition or free radical scavenging activity (IC_{50} = 67.78

μg/mL). The ascending order of the antioxidant activity exhibited by the carbazoles was **C-4**< **C-1**< **C-3**< **C-2**.

3.C.4: Conclusion

From the order of the antioxidant activity exhibited by the carbazoles (**C-4**< **C-1**< **C-3**< **C-2**) it can be concluded that replacing the ester group at C-3 carbon in clausine E (**C-1**) by carboxylic acid group, as in the case of **C-2** enhanced the antioxidant property. Infact, **C-2** was as potent as the standard, *L*-ascorbic acid. There was not much difference in the IC_{50} values for the compounds **C-1** and **C-3**, suggesting that the presence of an allyl group in the *ortho* position did not affect the antioxidant property. However the presence of prenyl group in the para position hampered the antioxidant property.

3.C.5: Experimental

3.C.5.1: Materials and methods

2,2-diphenyl-1-picrylhydrazyl and *L*-ascorbic acid were purchased from Sigma-Aldrich and Spectrochem respectively. HPLC grade Methanol was purchased from S.D. Fine Chemicals Ltd.

Preparation of 0.2 mM DPPH solution: 4 mg of DPPH was dissolved in methanol and diluted upto 100 mL to make a final concentration of 0.2 mM.

The % Inhibition was calculated by using the following formula;

% Inhibition = [(Acontrol – Atest) / Acontrol] x 100

Where Acontrol is the absorbance of the control reaction (containing all reagents except the test compound) and Atest is the absorbance of the test compound.

The concentration of the compounds which reduces the DPPH free radical to about 50% i.e. the IC_{50} values were calculated by using regression analysis from graphpad prism software.

3.C.5.2: DPPH Assay

0.5 mL of various concentrations (10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 μg/mL) of the test sample in methanol was added to 1mL of 0.2 mM DPPH radical solution in methanol. The mixture was shaken vigorously and kept at room temperature in dark for 30 minutes. The absorbance of the resulting solution was measured at 517 nm using a spectrophotometer.

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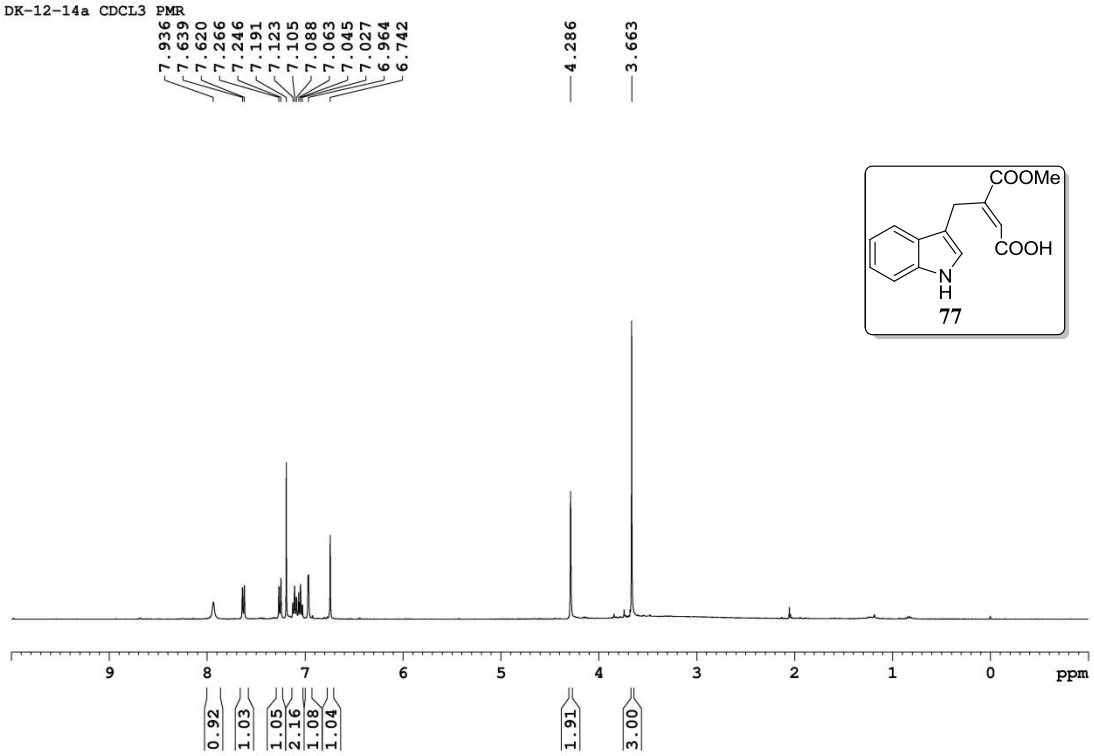
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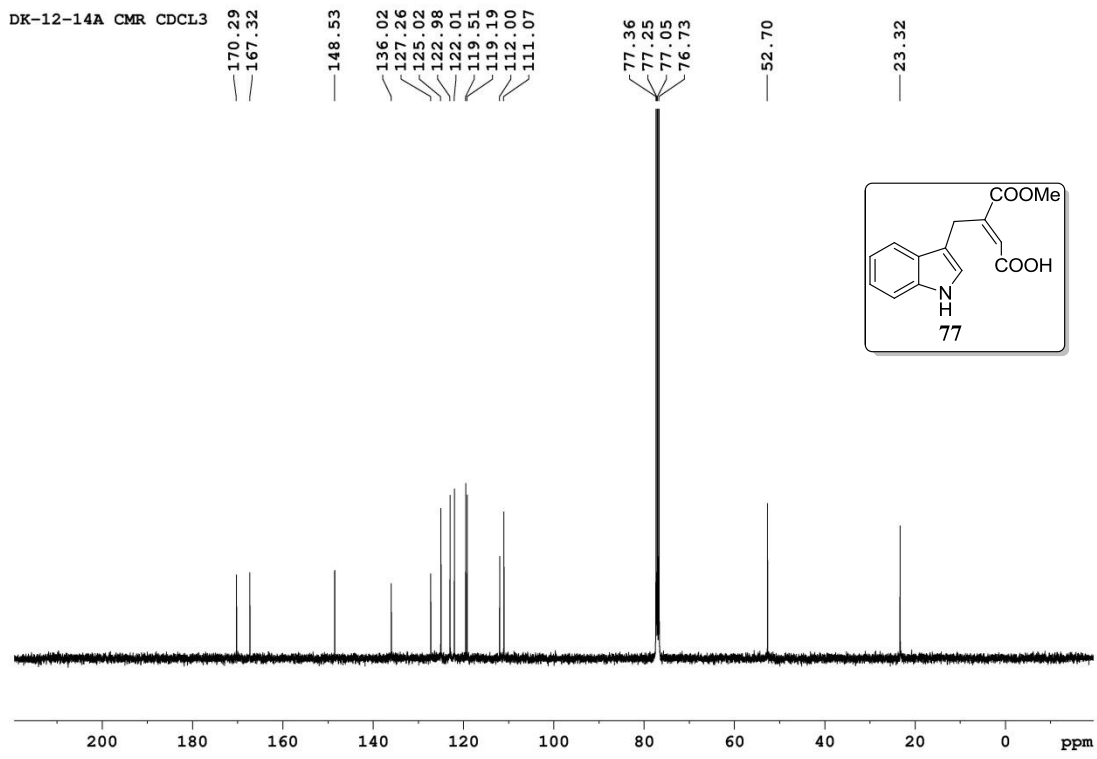
7.639
7.620
7.266
7.246
7.191
7.123
7.105
7.088
7.063
7.045
7.027
6.964
6.742
4.286
3.663
COOMe
COOH
N
H
77
9
8
7
6
5
4
3
2
1
0
ppm
0.92
1.03
1.05
2.16
1.08
1.04
1.91
3.00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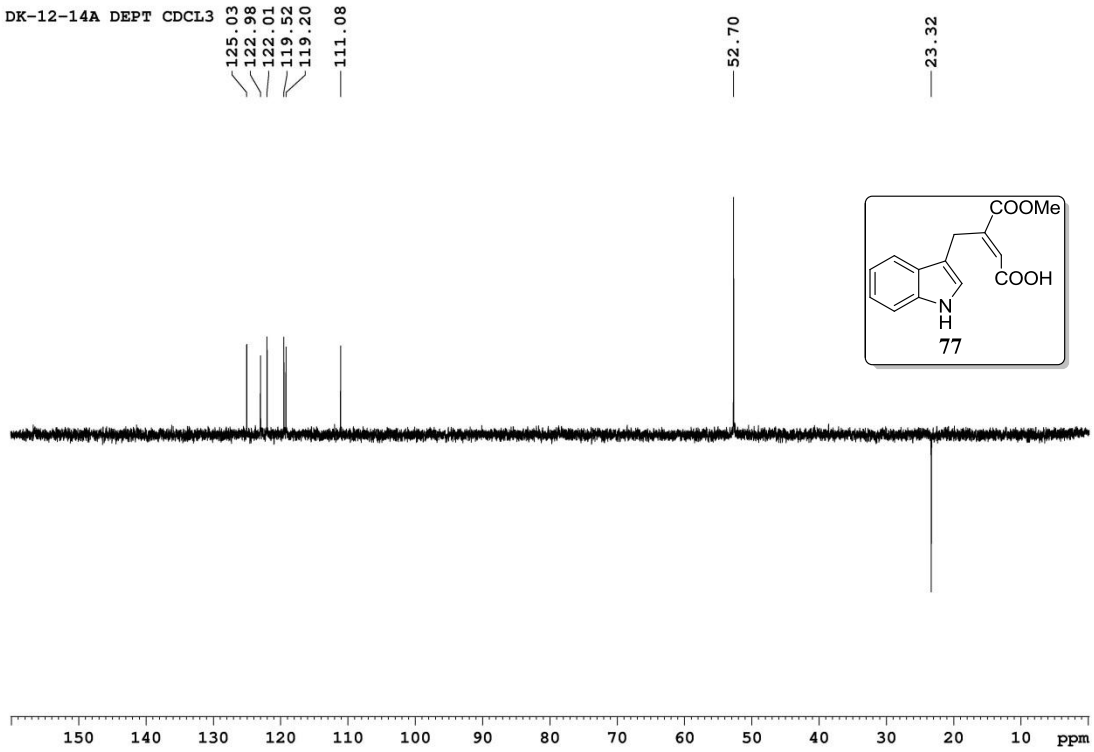
167.32
148.53
136.02
127.26
125.02
122.98
122.01
119.51
119.19
112.00
111.07
77.36
77.25
77.05
76.73
52.70
23.32
COOMe
COOH
N
H
77
200
180
160
140
120
100
80
60
40
20
0
ppm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122.01
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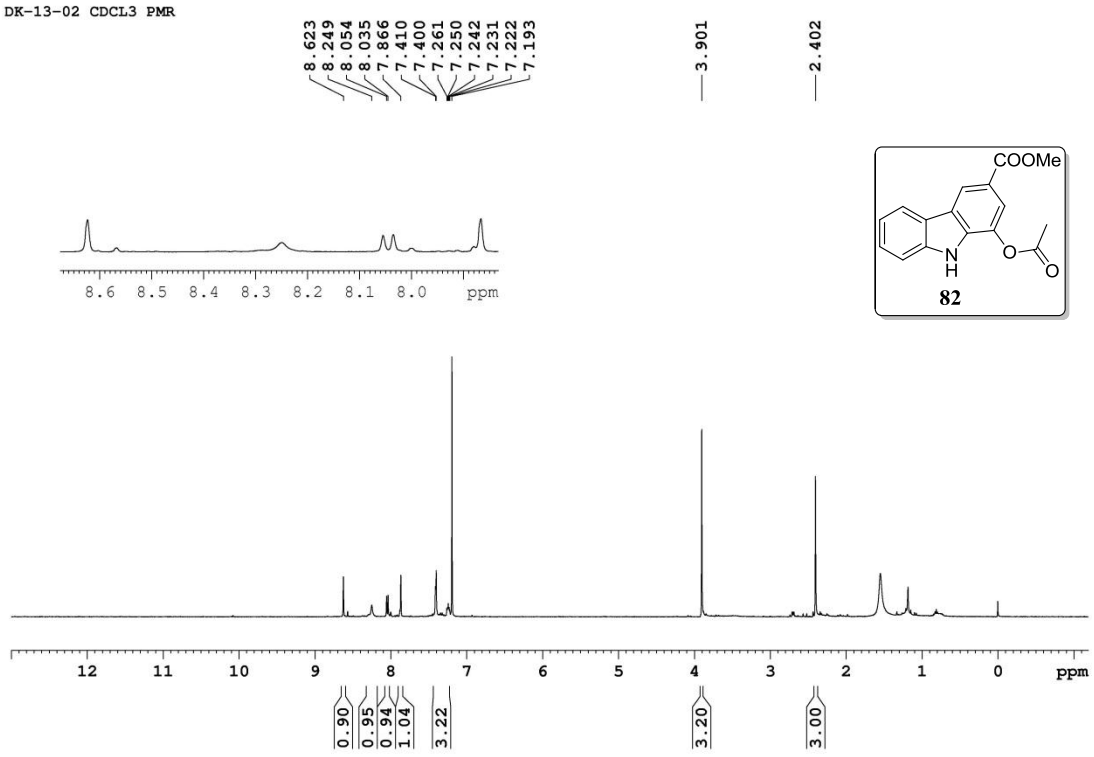
23.32
COOMe
COOH
N
H
77
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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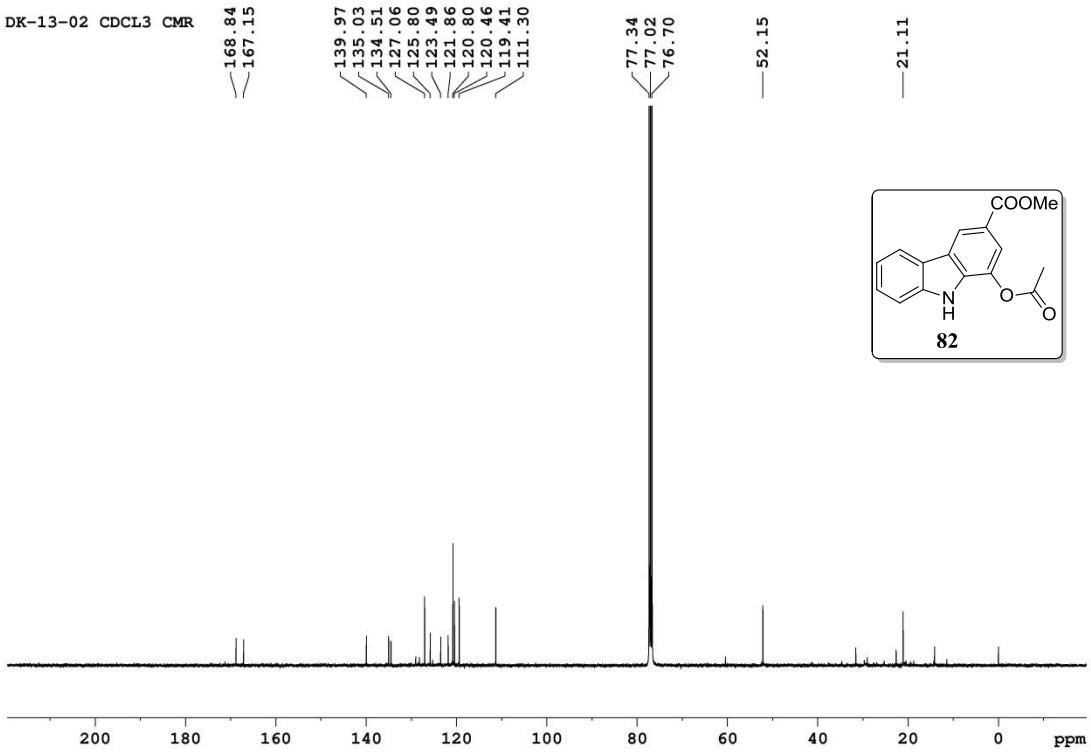
8.249
8.054
8.035
7.866
7.410
7.400
7.261
7.250
7.242
7.231
7.222
7.193
3.901
2.402
COOMe
O
O
N
H
82
8.6 8.5 8.4 8.3 8.2 8.1 8.0 ppm
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.90
0.95
0.94
1.04
3.22
3.20
3.00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167.15
139.97
135.03
134.51
127.06
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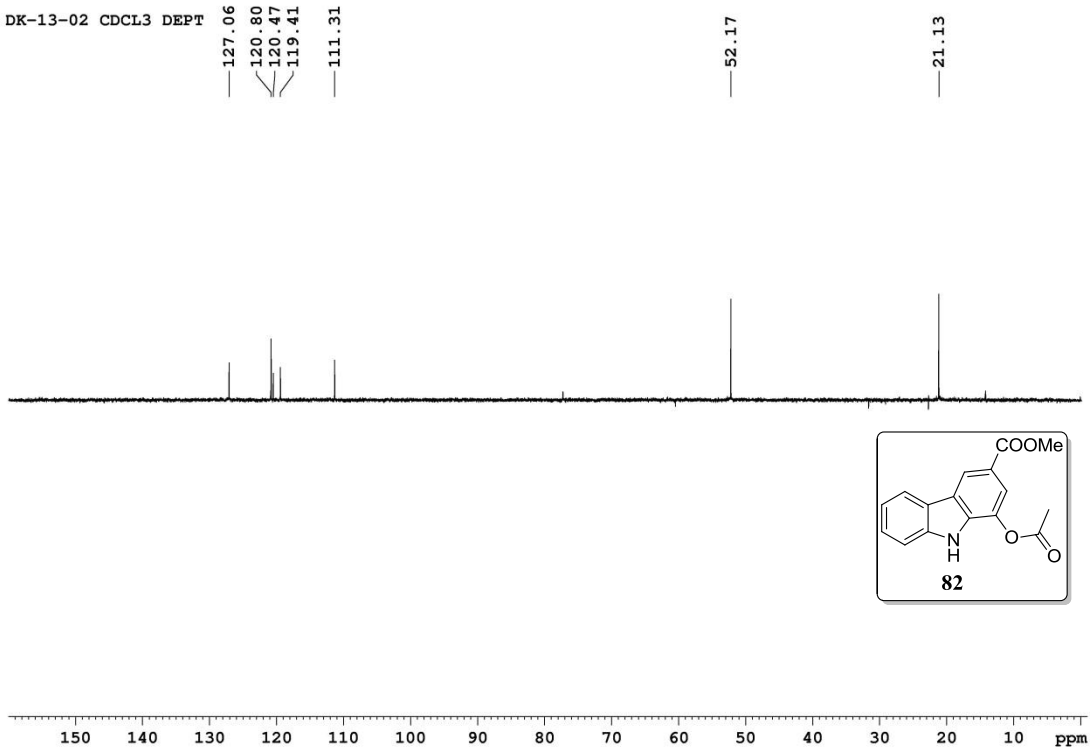
123.49
121.86
120.80
120.46
119.41
111.30
77.34
77.02
76.70
52.15
21.11
COOMe
N
H
O
O
82
200
180
160
140
120
100
80
60
40
20
0
ppm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119.41
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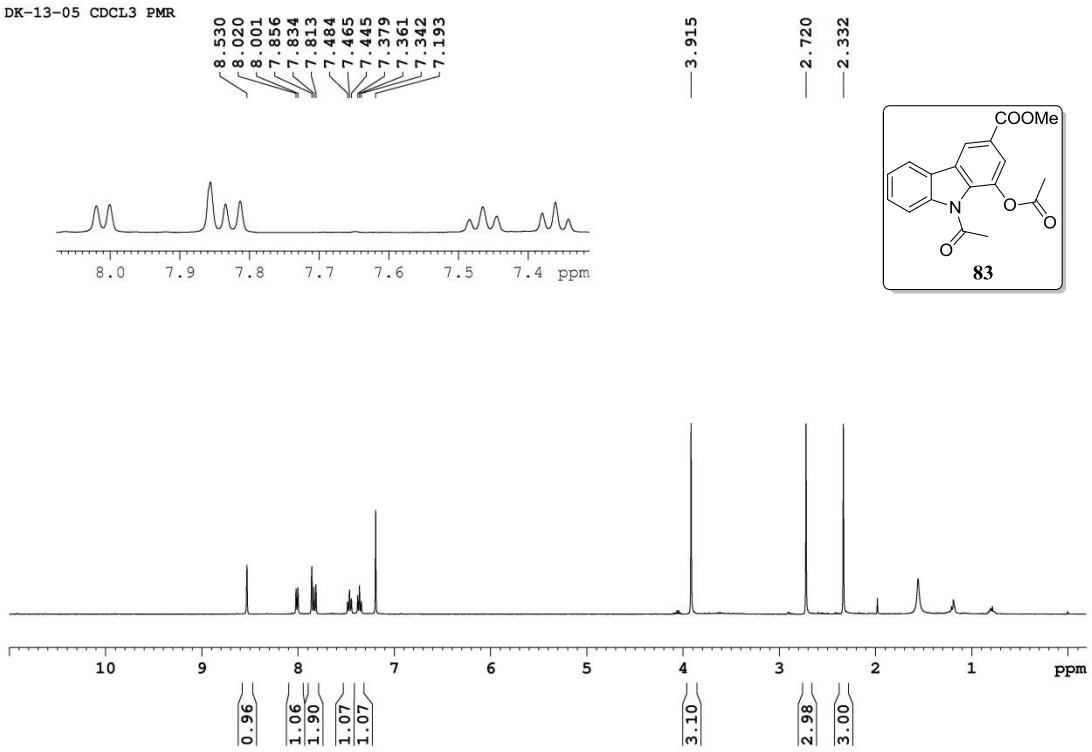
COOMe
N
H
O
O
82
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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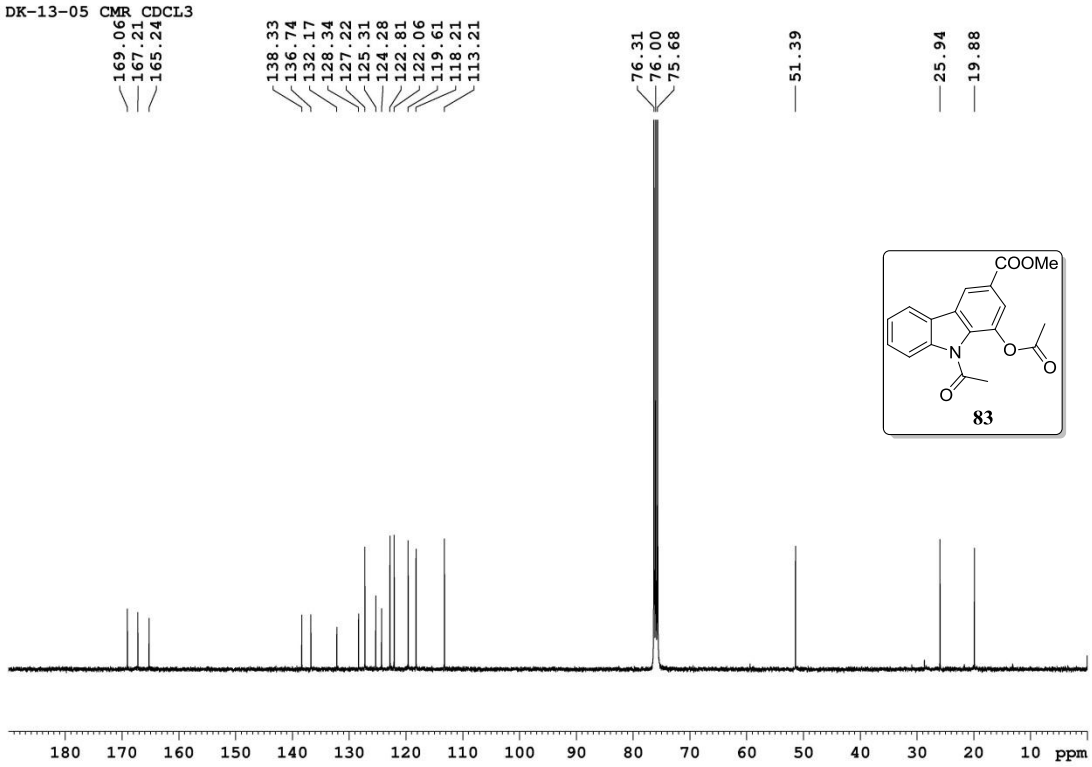
8.020
8.001
7.856
7.834
7.813
7.484
7.465
7.445
7.379
7.361
7.342
7.193
3.915
2.720
2.332
COOMe
O
N
O
O
83
8.0
7.9
7.8
7.7
7.6
7.5
7.4 ppm
10
9
8
7
6
5
4
3
2
1
ppm
0.96
1.06
1.90
1.07
1.07
3.10
2.98
3.00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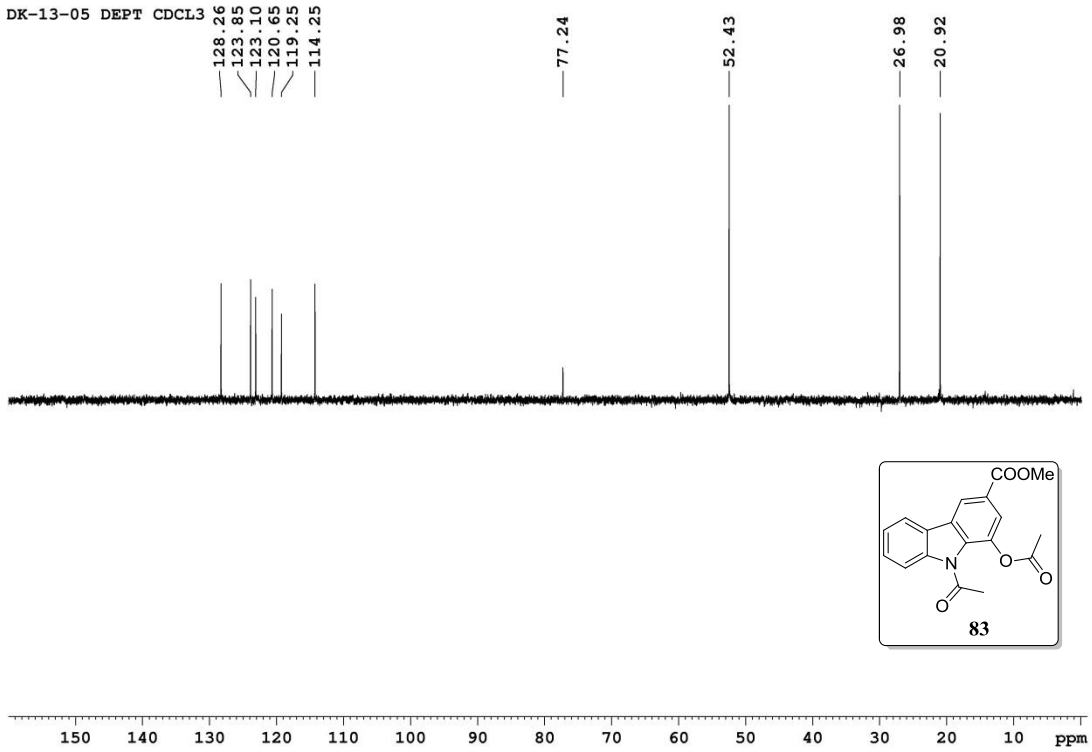
169.06
167.21
165.24
138.33
136.74
132.17
128.34
127.22
125.31
124.28
122.81
122.06
119.61
118.21
113.21
76.31
76.00
75.68
51.39
25.94
19.88
COOMe
O
N
O
O
83
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm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128.26
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120.65
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114.25
77.24
52.43
26.98
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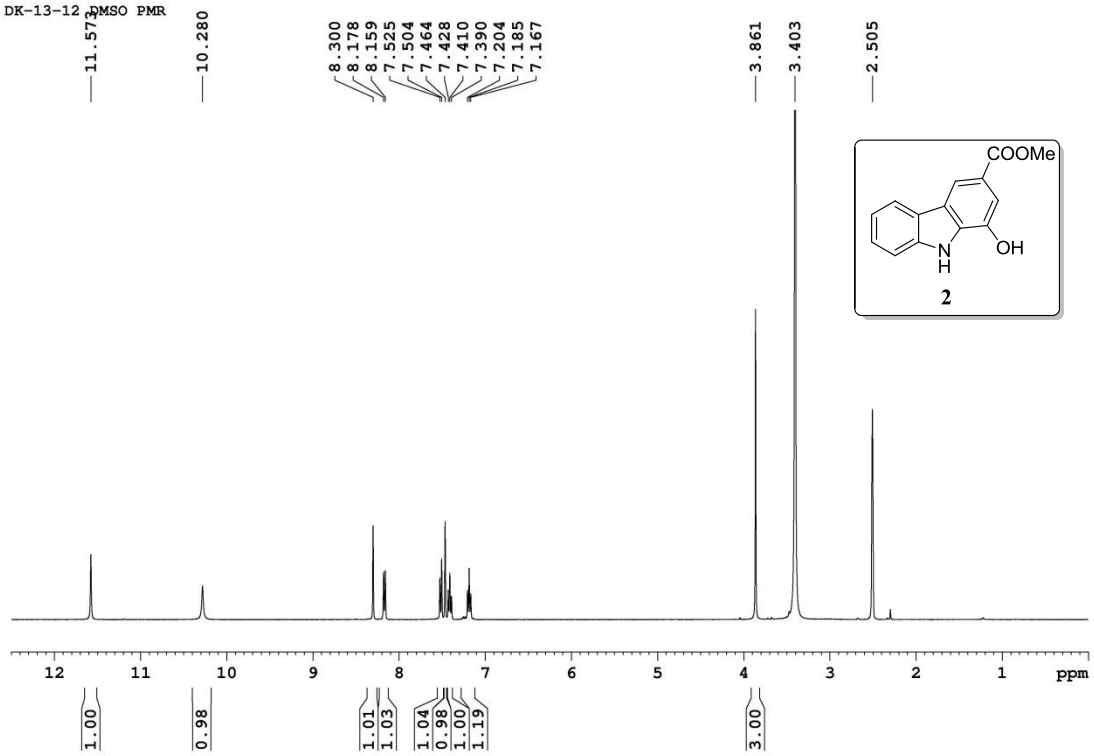
COOMe
N
O
O
O
O
83
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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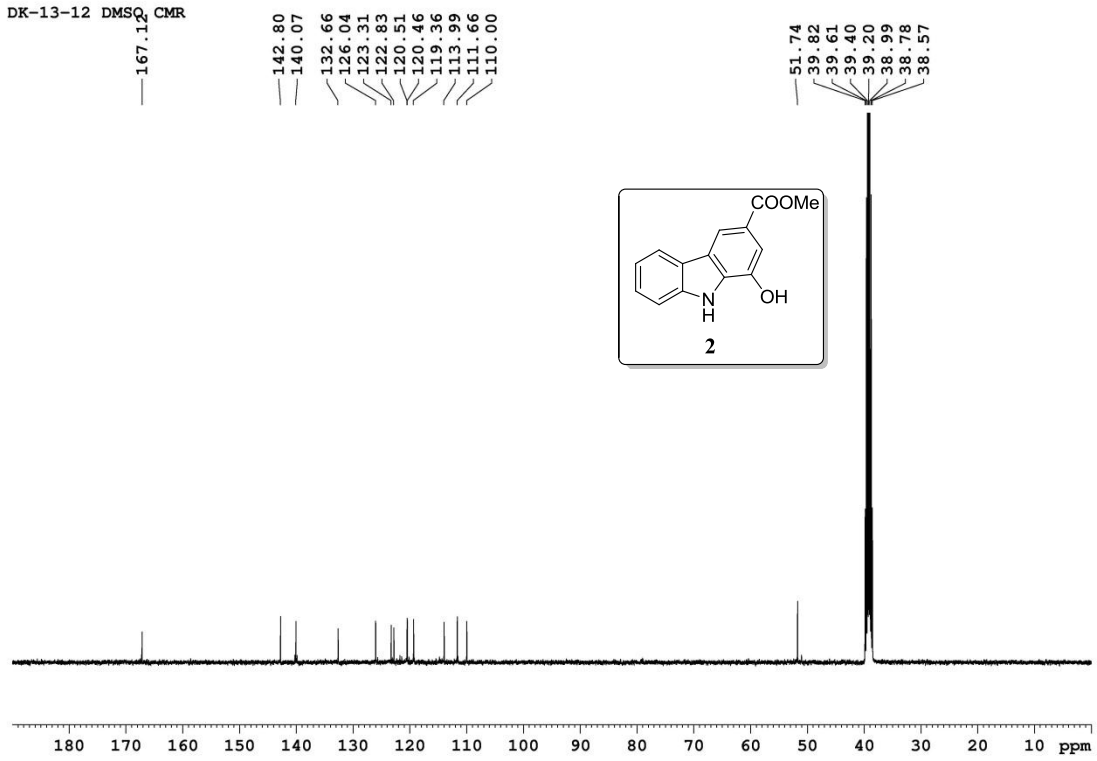
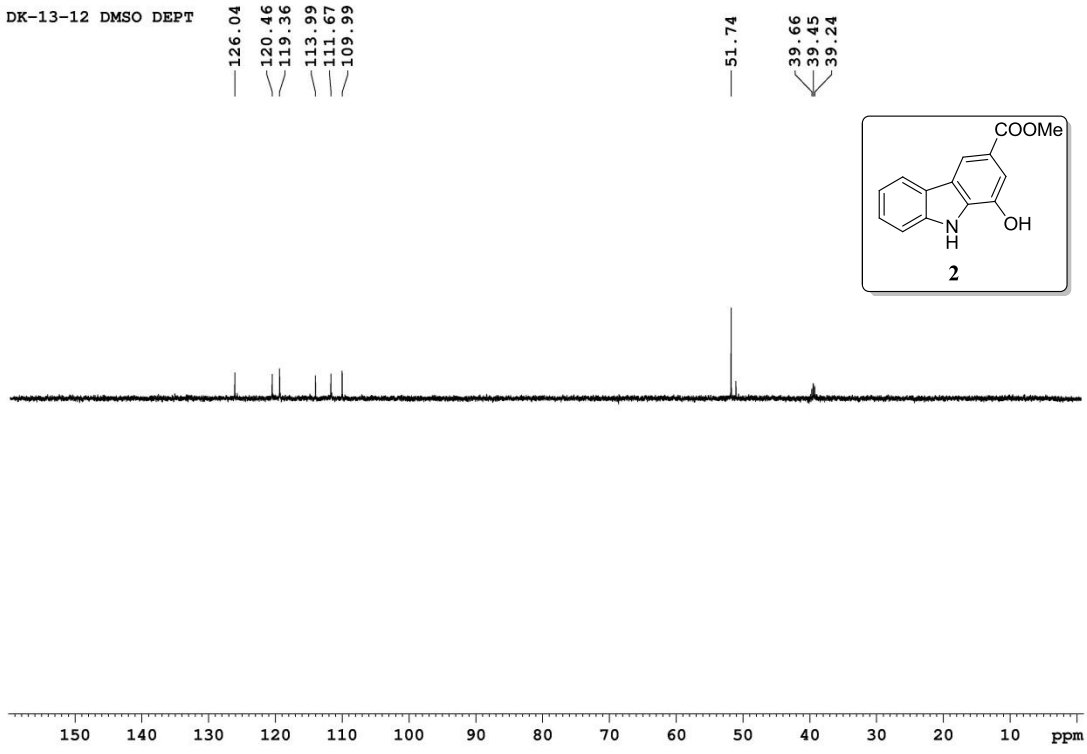
8.300
8.178
8.159
7.525
7.504
7.464
7.428
7.410
7.390
7.204
7.185
7.167
3.861
3.403
2.505
COOMe
N
H
OH
2
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.98
1.01
1.03
1.04
0.98
1.00
1.19
3.00


DK-13-12 DMSO CMR
167.12
142.80
140.07
132.66
126.04
123.31
122.83
120.51
120.46
119.36
113.99
111.66
110.00
51.74
39.82
39.61
39.40
39.20
38.99
38.78
38.57
COOMe
OH
N
H
2
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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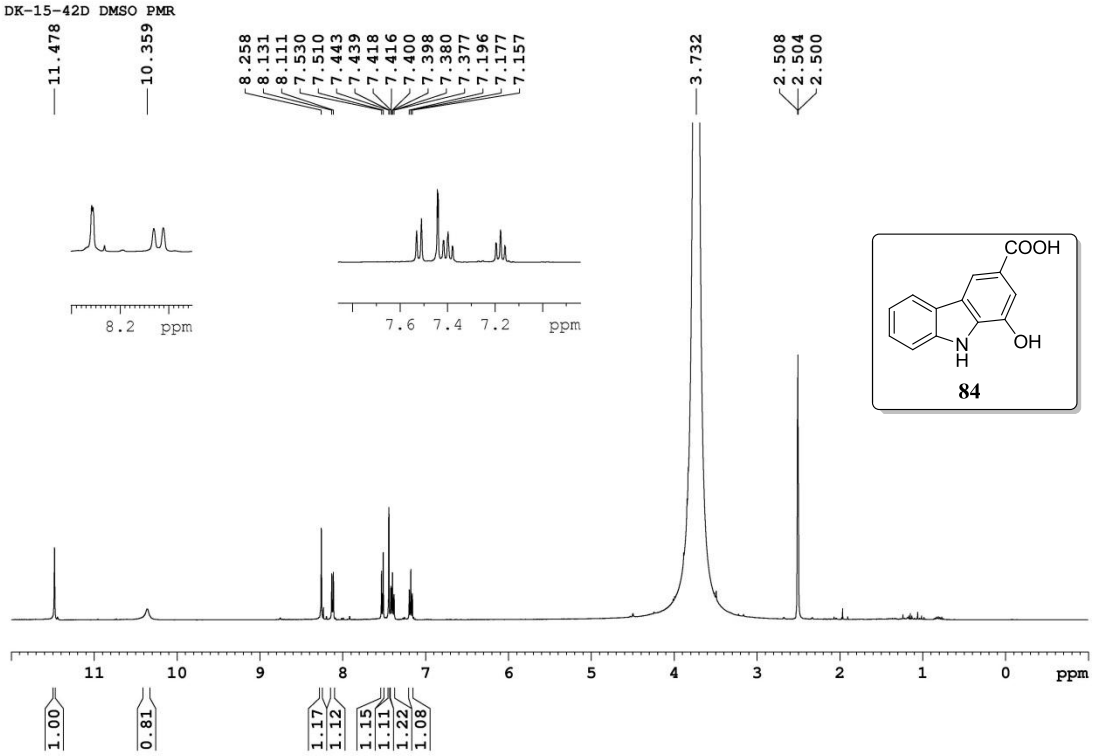
120.46
119.36
113.99
111.67
109.99
51.74
39.66
39.45
39.24
COOMe
OH
N
H
2
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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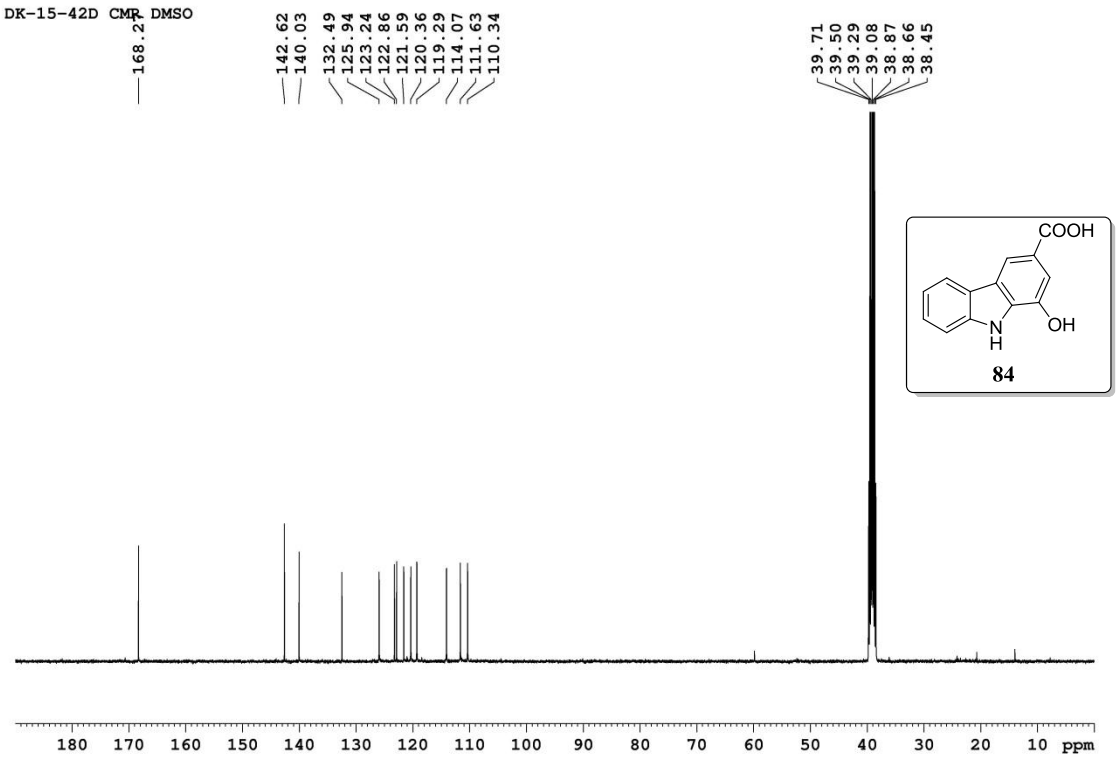
8.258
8.131
8.111
7.530
7.510
7.443
7.439
7.418
7.416
7.400
7.398
7.380
7.377
7.196
7.177
7.157
3.732
2.508
2.504
2.500
8.2 ppm
7.6 7.4 7.2 ppm
COOH
OH
N
H
84
11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
0.81
1.17
1.12
1.15
1.11
1.22
1.08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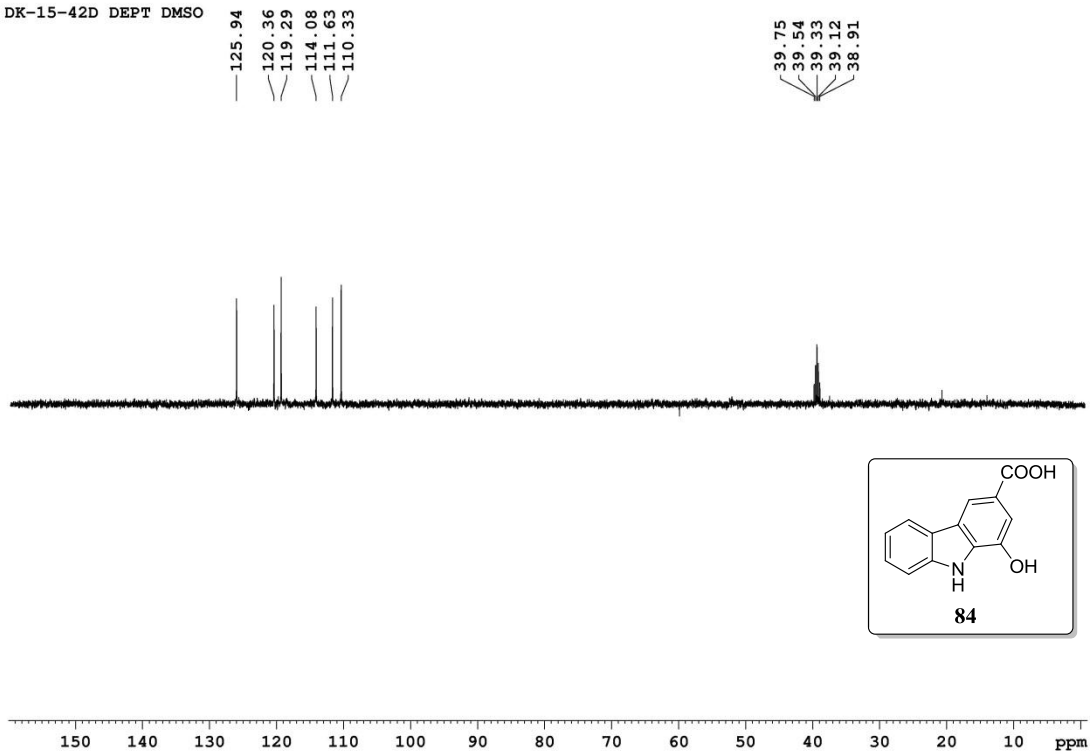
168.21
142.62
140.03
132.49
125.94
123.24
122.86
121.59
120.36
119.29
114.07
111.63
110.34
39.71
39.50
39.29
39.08
38.87
38.66
38.45
COOH
OH
N
H
84
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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125.94
120.36
119.29
114.08
111.63
110.33
39.75
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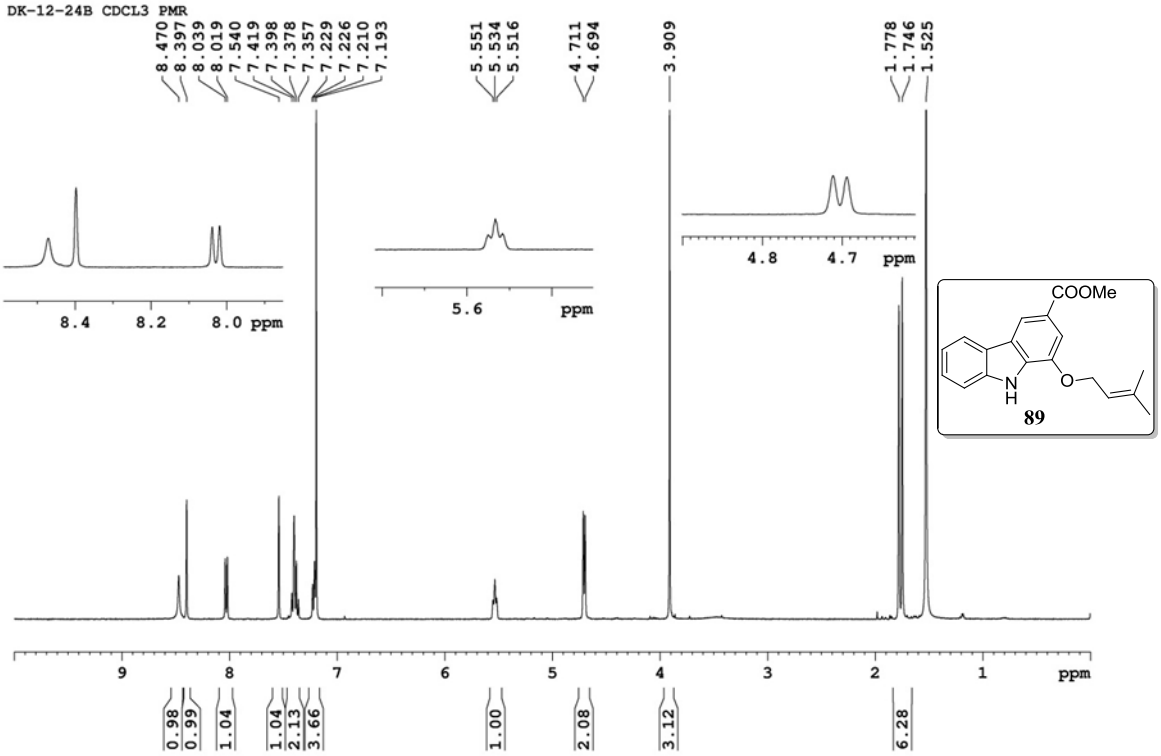
39.33
39.12
38.91
COOH
OH
N
H
84
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-12-24B CDCL3 PMR
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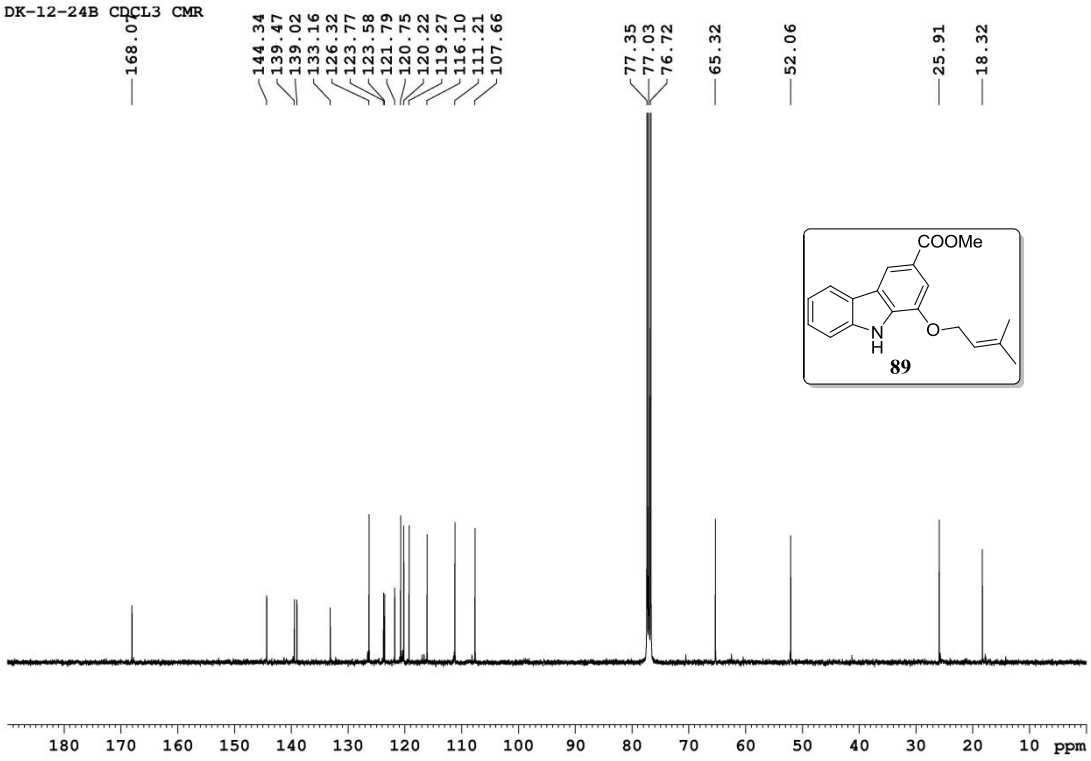
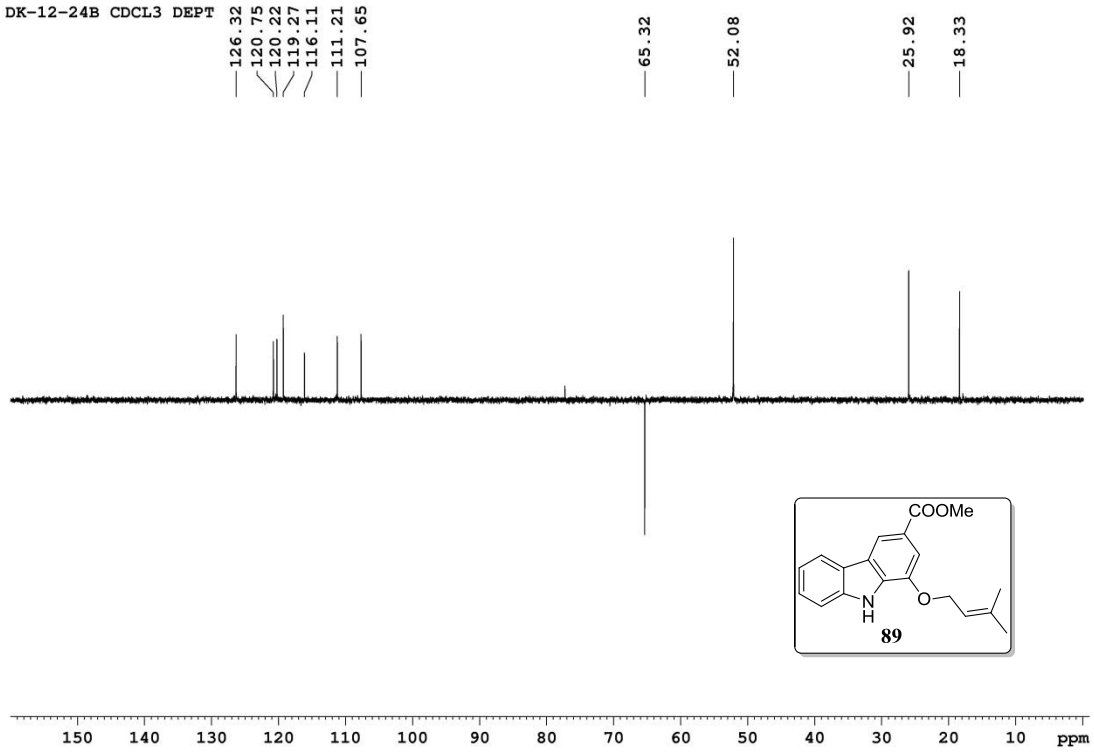
8.397
8.039
8.019
7.540
7.419
7.398
7.378
7.357
7.229
7.226
7.210
7.193
5.551
5.534
5.516
4.711
4.694
3.909
1.778
1.746
1.525
8.4 8.2 8.0 ppm
5.6 ppm
4.8 4.7 ppm
COOMe
O
N
H
89
9 8 7 6 5 4 3 2 1 ppm
0.98
0.99
1.04
1.04
2.13
3.66
1.00
2.08
3.12
6.28


DK-12-24B CDCL3 CMR
168.01
144.34
139.47
139.02
133.16
126.32
123.77
123.58
121.79
120.75
120.22
119.27
116.10
111.21
107.66
77.35
77.03
76.72
65.32
52.06
25.91
18.32
COOMe
N
H
O
89
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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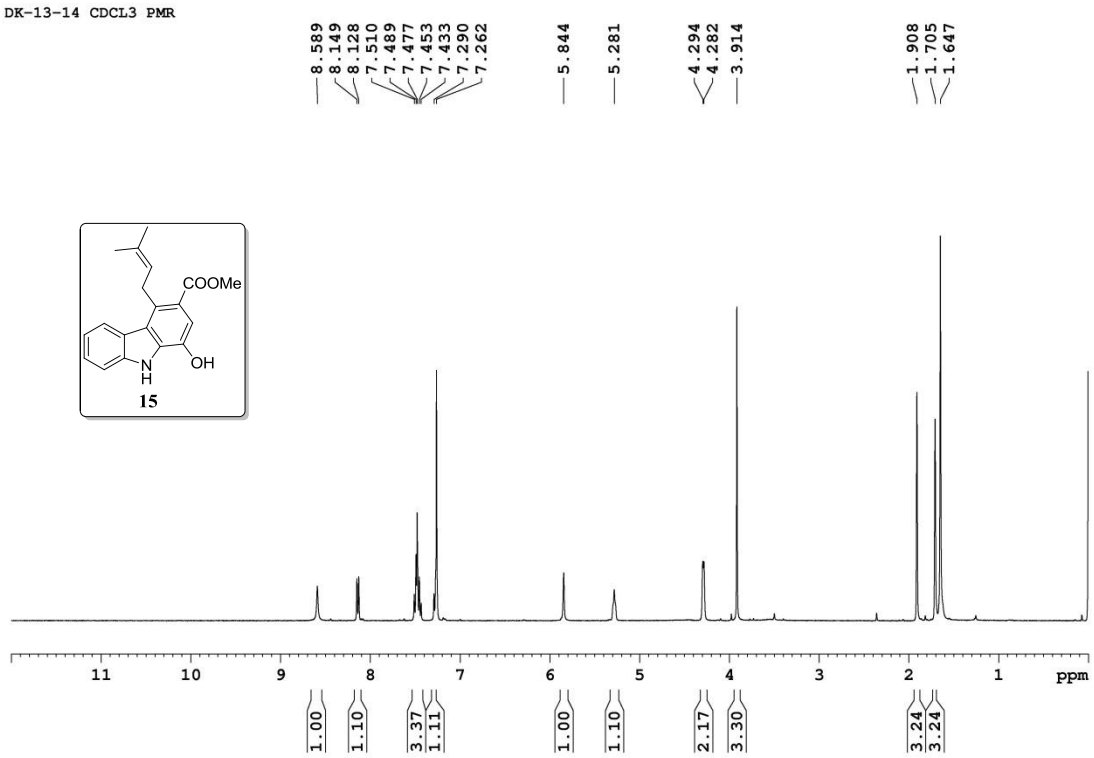
120.75
120.22
119.27
116.11
111.21
107.65
65.32
52.08
25.92
18.33
COOMe
N
H
O
89
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.149
8.128
7.510
7.489
7.477
7.453
7.433
7.290
7.262
5.844
5.281
4.294
4.282
3.914
1.908
1.705
1.647
COOMe
OH
N
H
15
11
10
9
8
7
6
5
4
3
2
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1.10
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1.10
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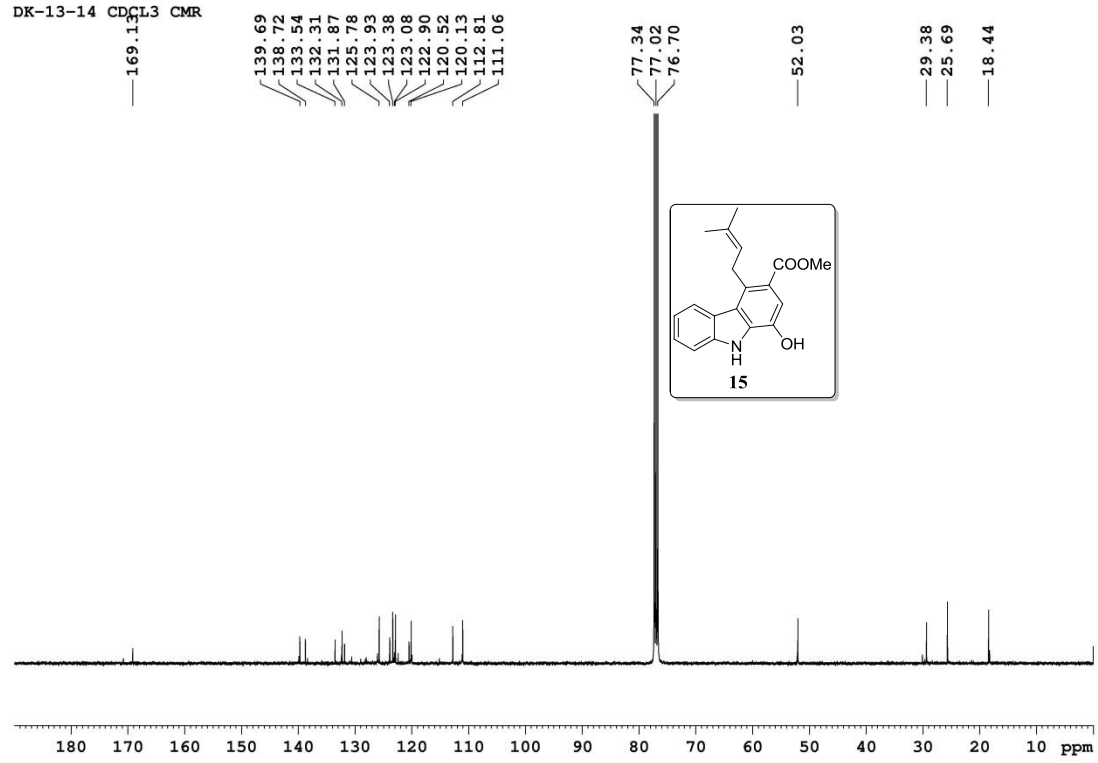
3.30
3.24
3.24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169.13
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138.72
133.54
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131.87
125.78
123.93
123.38
123.08
122.90
120.52
120.13
112.81
111.06
77.34
77.02
76.70
52.03
29.38
25.69
18.44
COOMe
OH
N
H
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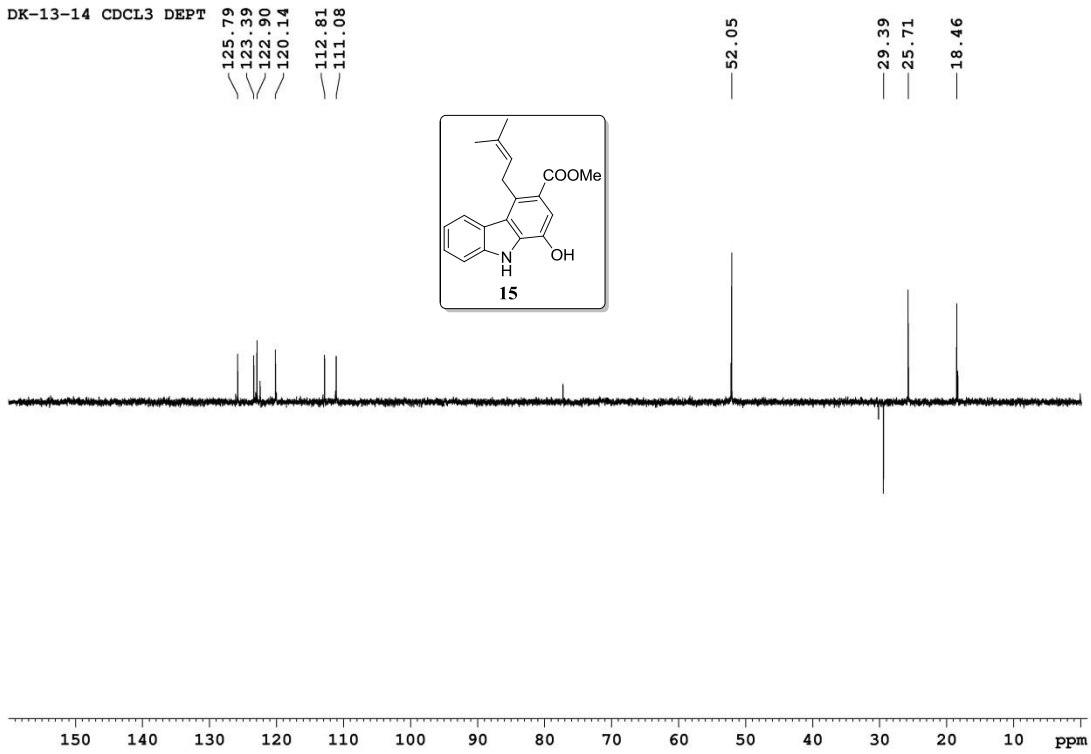
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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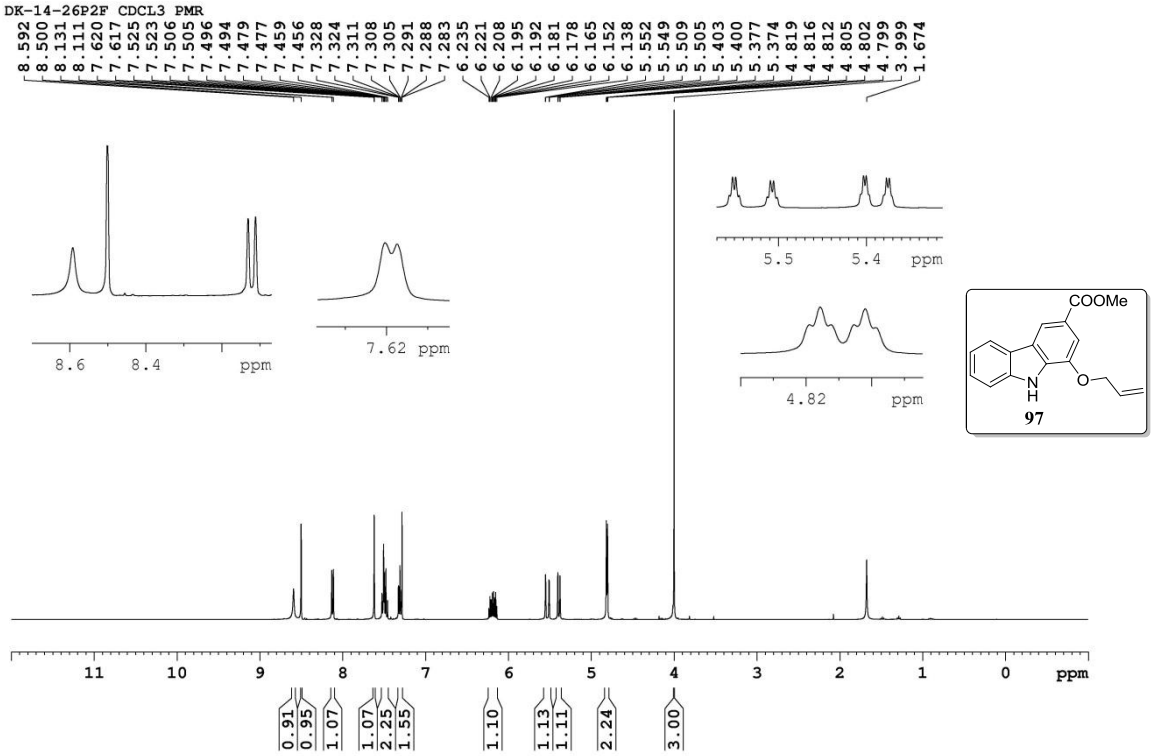
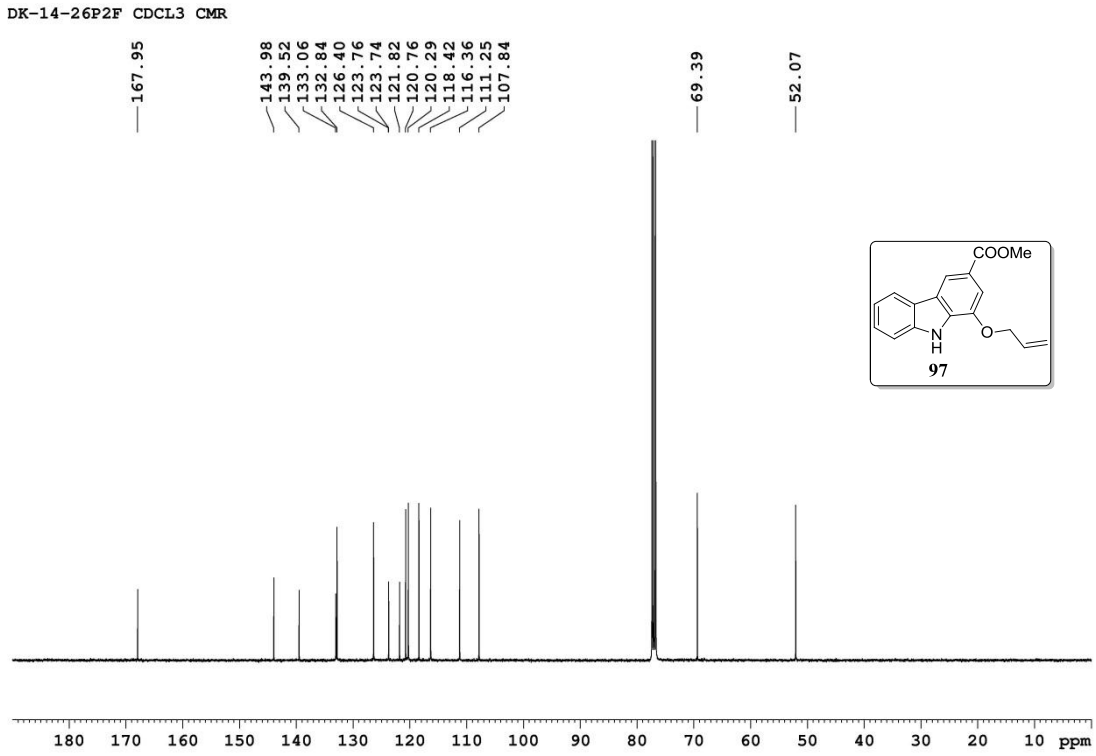
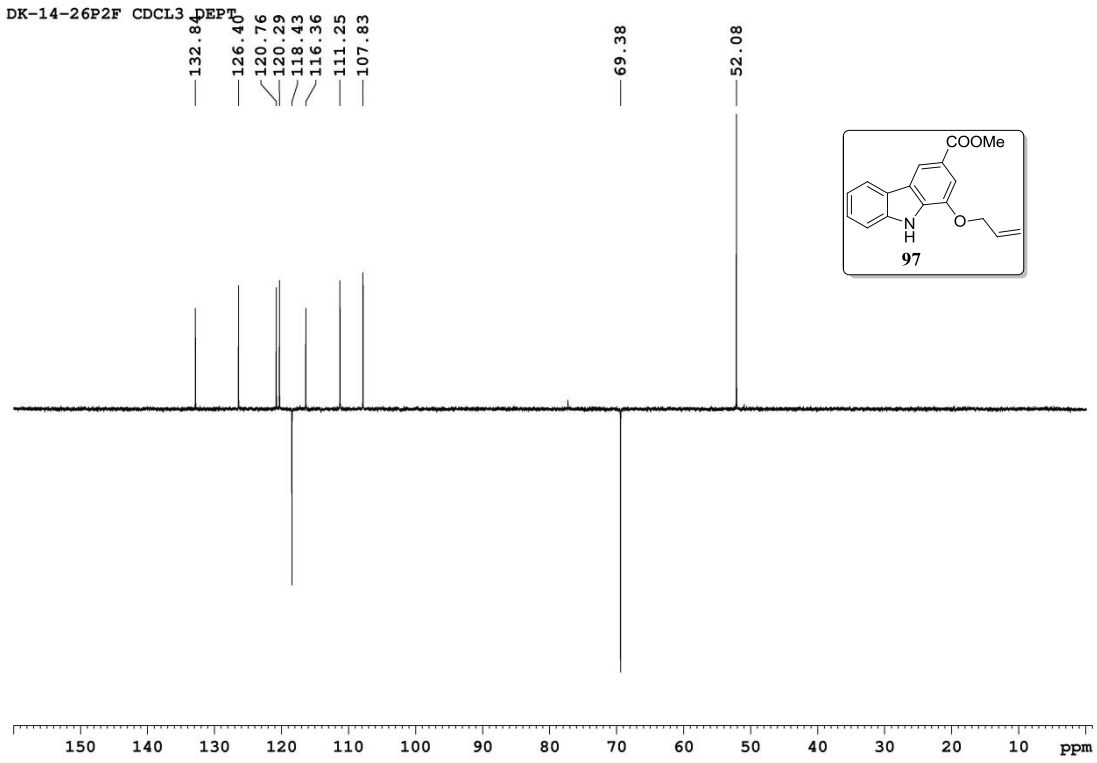
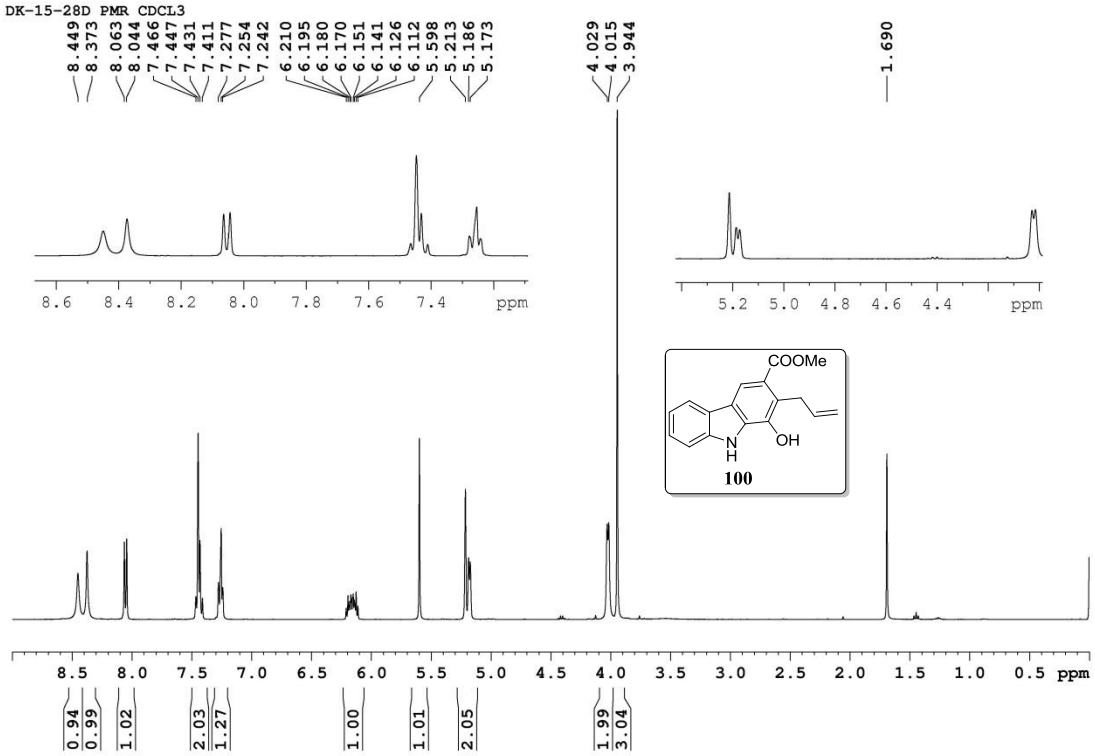
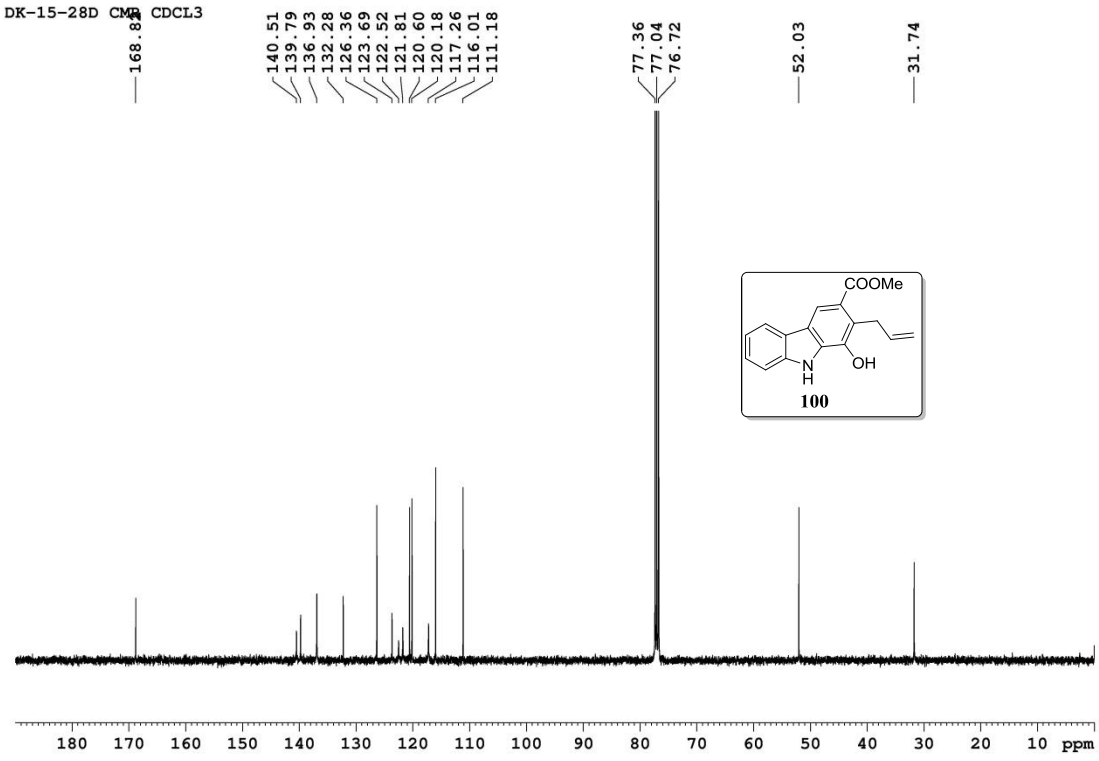
122.90
120.14
112.81
111.08
52.05
29.39
25.71
18.46
COOMe
OH
N
H
15
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

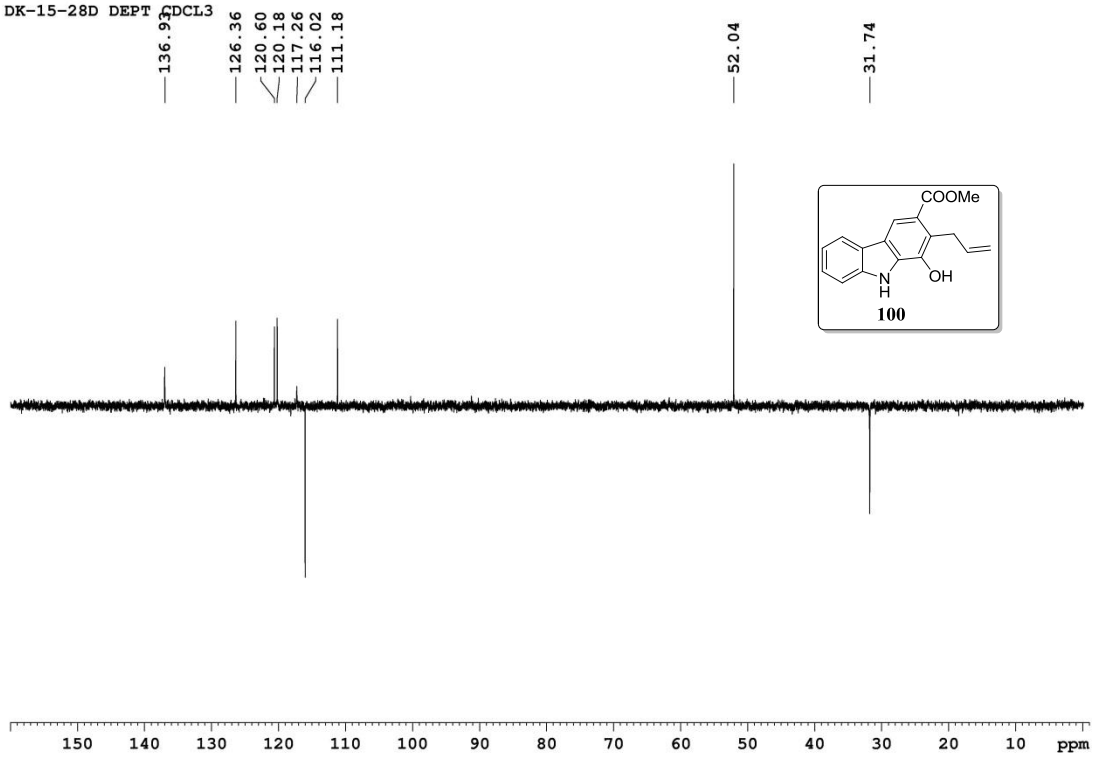

DK-14-26P2F CDCL3 PMR
8.592 8.500 8.131 8.111 7.620 7.617 7.525 7.523 7.506 7.505 7.496 7.494 7.479 7.477 7.459 7.456 7.328 7.324 7.311 7.308 7.305 7.291 7.288 7.283 6.235 6.221 6.208 6.195 6.192 6.181 6.178 6.165 6.152 6.138 5.552 5.549 5.509 5.505 5.403 5.400 5.377 5.374 4.819 4.816 4.812 4.805 4.802 4.799 3.999 1.674
8.6 8.4 ppm
7.62 ppm
5.5 5.4 ppm
4.82 ppm
COOMe
O
N
H
97
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.91 0.95 1.07 1.07 2.25 1.55 1.10 1.13 1.11 2.24 3.00

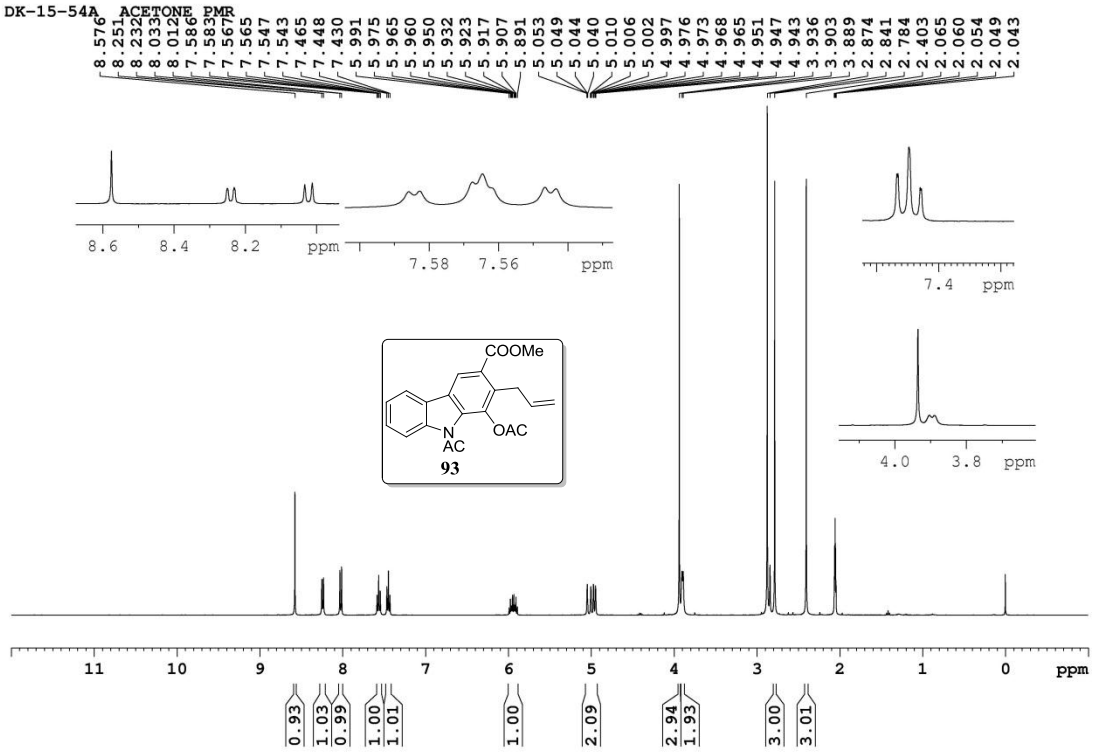

DK-14-26P2F CDCL3 CMR
167.95
143.98
139.52
133.06
132.84
126.40
123.76
123.74
121.82
120.76
120.29
118.42
116.36
111.25
107.84
69.39
52.07
COOMe
N
H
O
97
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

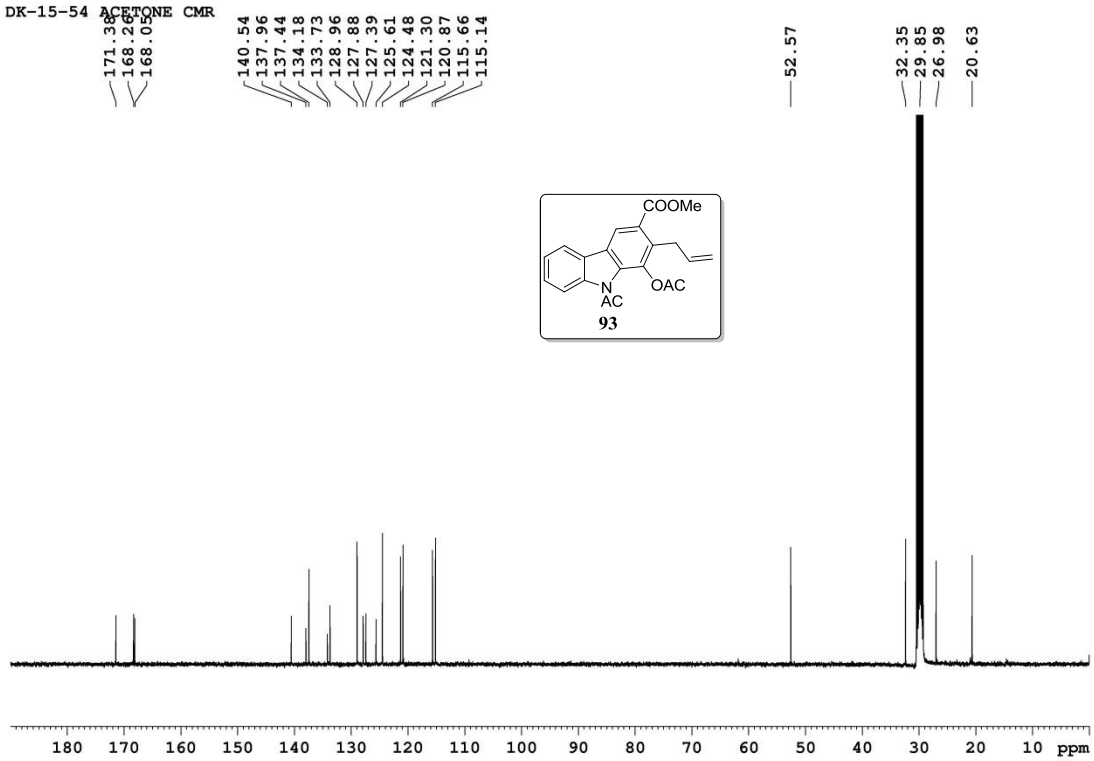

DK-14-26P2F CDCL3 DEPT
132.84
126.40
120.76
120.29
118.43
116.36
111.25
107.83
69.38
52.08
COOMe
N
H
O
97
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

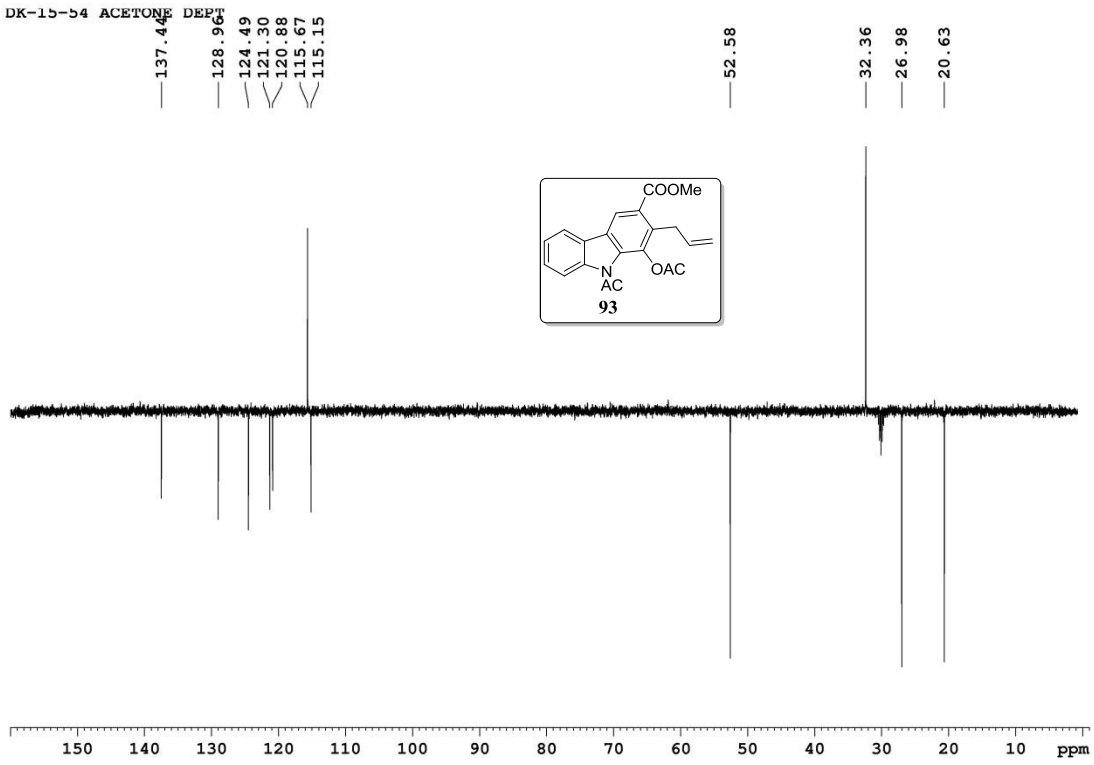

DK-15-28D PMR CDCL3
8.449
8.373
8.063
8.044
7.466
7.447
7.431
7.411
7.277
7.254
7.242
6.210
6.195
6.180
6.170
6.151
6.141
6.126
6.112
5.598
5.213
5.186
5.173
4.029
4.015
3.944
1.690
8.6 8.4 8.2 8.0 7.8 7.6 7.4 ppm
5.2 5.0 4.8 4.6 4.4 ppm
COOMe
OH
N
H
100
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.94
0.99
1.02
2.03
1.27
1.00
1.01
2.05
1.99
3.04

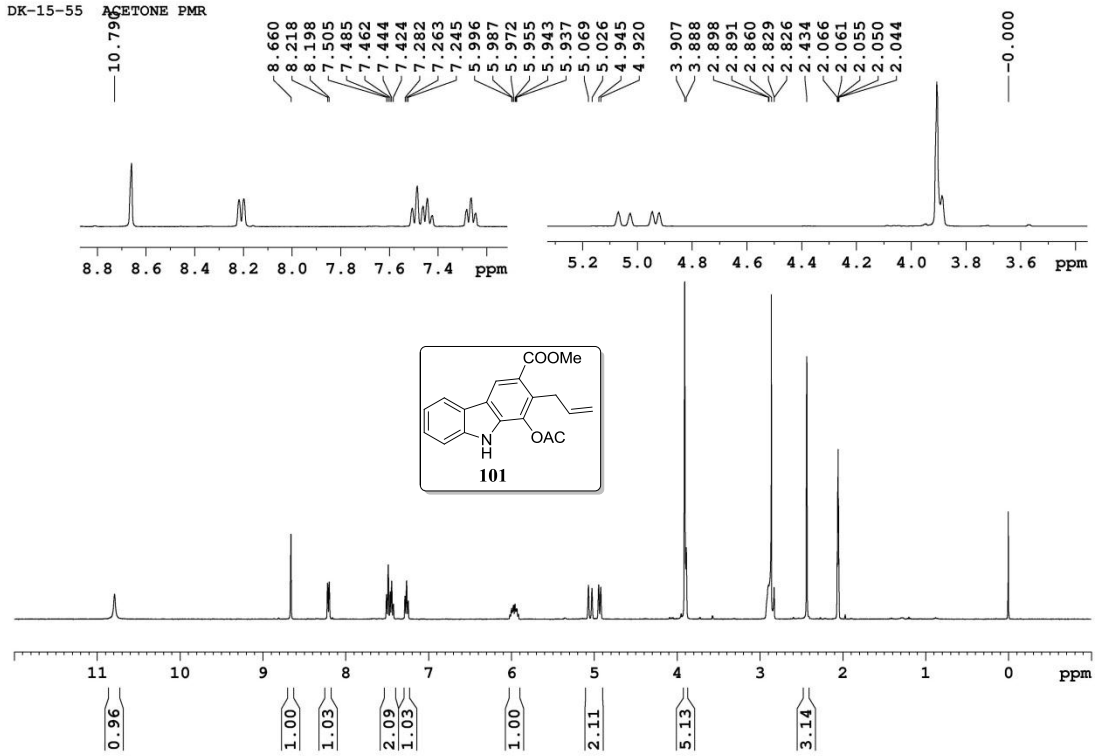

DK-15-28D CMR CDCL3
168.8
140.51
139.79
136.93
132.28
126.36
123.69
122.52
121.81
120.60
120.18
117.26
116.01
111.18
77.36
77.04
76.72
52.03
31.74
COOMe
OH
N
H
100
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

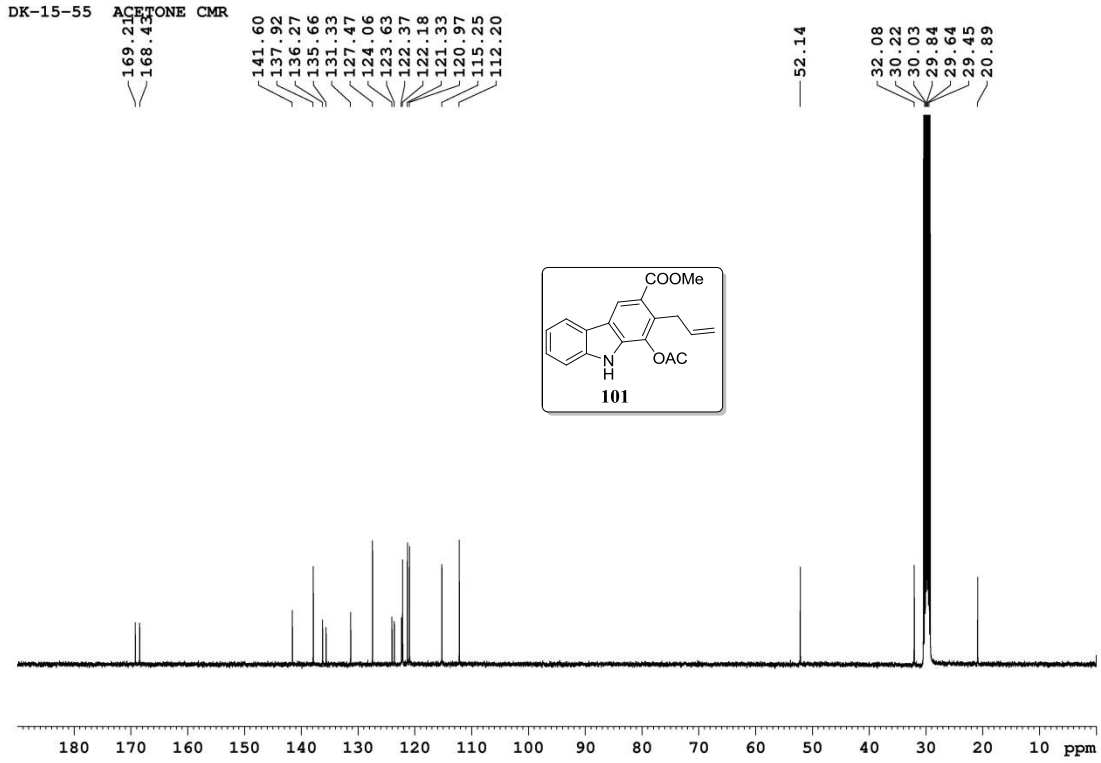

DK-15-28D DEPT CDCL3
136.93
126.36
120.60
120.18
117.26
116.02
111.18
52.04
31.74
COOMe
OH
N
H
100
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

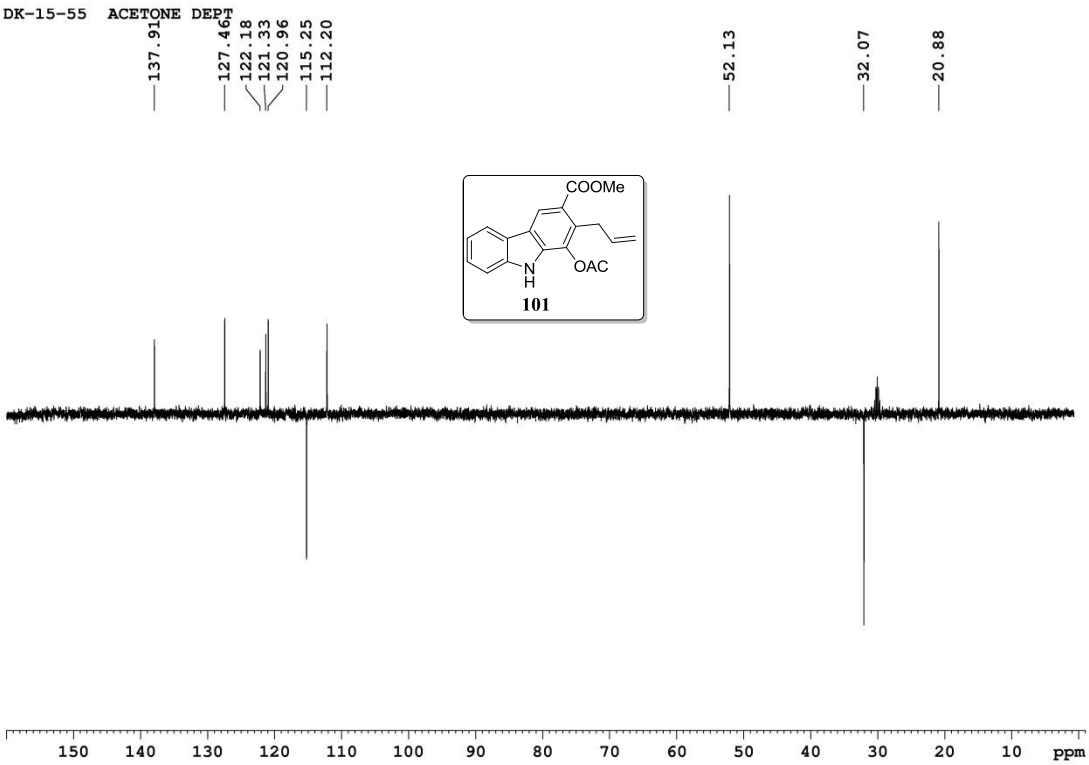

DK-15-54A ACETONE PMR
8.576
8.251
8.232
8.033
8.012
7.586
7.583
7.567
7.565
7.547
7.543
7.465
7.448
7.430
5.991
5.975
5.965
5.960
5.950
5.932
5.923
5.917
5.907
5.891
5.053
5.049
5.044
5.040
5.010
5.006
5.002
4.997
4.976
4.973
4.968
4.965
4.951
4.947
4.943
3.936
3.903
3.889
2.874
2.841
2.784
2.403
2.065
2.060
2.054
2.049
2.043
8.6 8.4 8.2 ppm
7.58 7.56 ppm
7.4 ppm
4.0 3.8 ppm
COOMe
OAC
N
AC
93
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.93
1.03
0.99
1.00
1.01
1.00
2.09
2.94
1.93
3.00
3.01

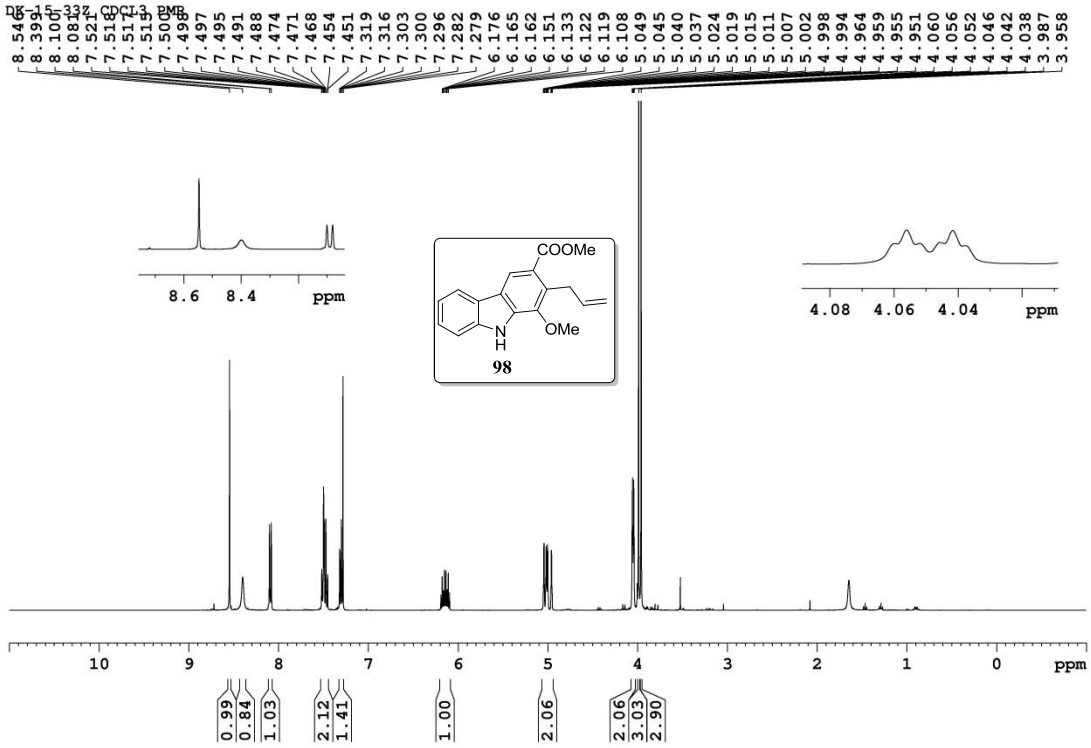

DK-15-54 ACETONE CMR
171.38
168.25
168.05
140.54
137.96
137.44
134.18
133.73
128.96
127.88
127.39
125.61
124.48
121.30
120.87
115.66
115.14
52.57
32.35
29.85
26.98
20.63
COOMe
OAC
N
AC
93
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

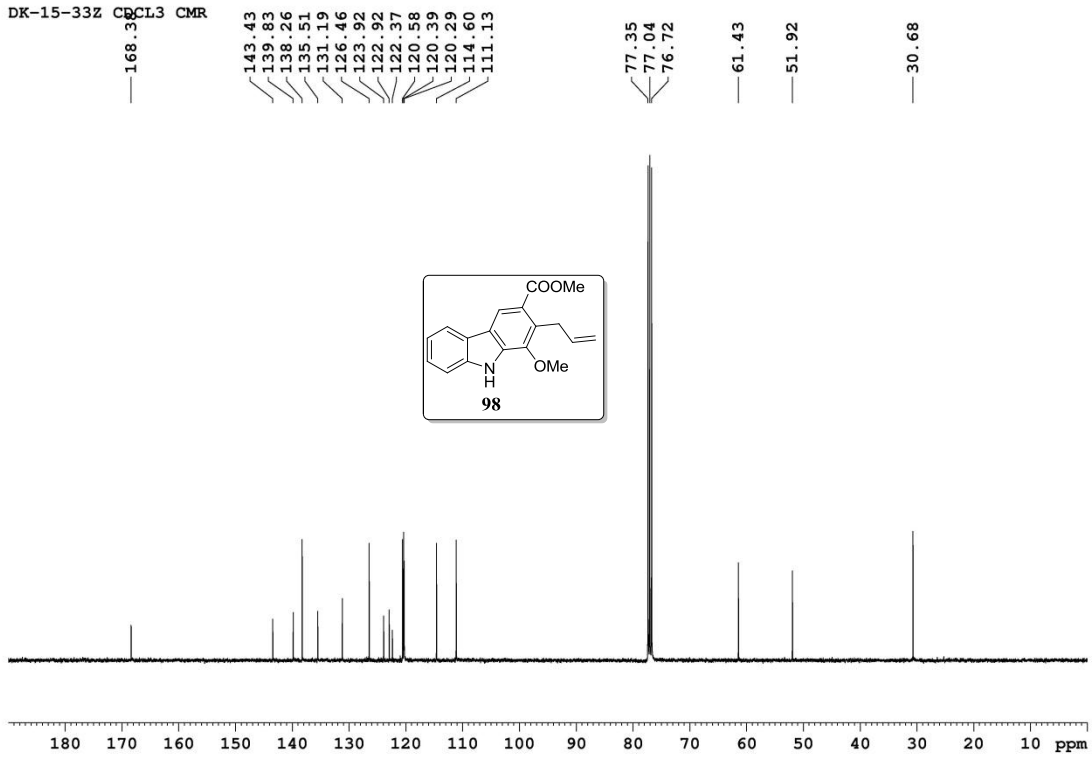

DK-15-54 ACETONE DEPT
137.44
128.96
124.49
121.30
120.88
115.67
115.15
52.58
32.36
26.98
20.63
COOMe
OAC
N
AC
93
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

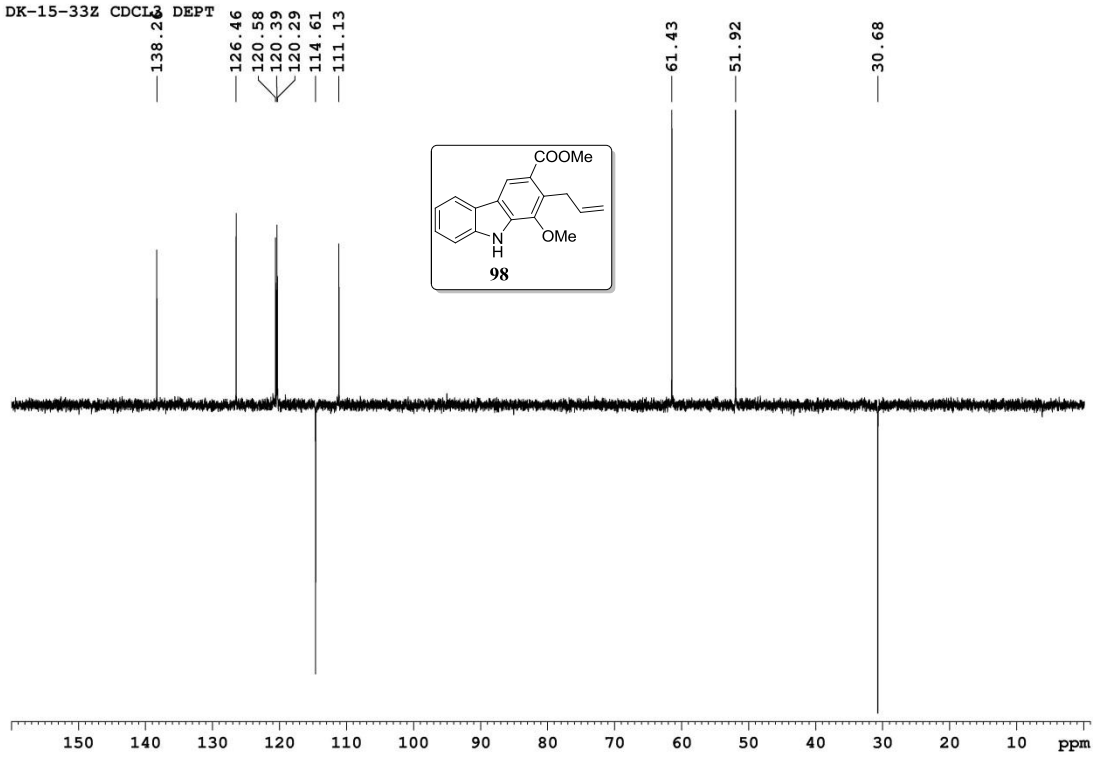

DK-15-55 ACETONE PMR
10.796
8.660
8.218
8.198
7.505
7.485
7.462
7.444
7.424
7.282
7.263
7.245
5.996
5.987
5.972
5.955
5.943
5.937
5.069
5.026
4.945
4.920
3.907
3.888
2.898
2.891
2.860
2.829
2.826
2.434
2.066
2.061
2.055
2.050
2.044
0.000
COOMe
OAC
N
H
101
0.96
1.00
1.03
2.09
1.03
1.00
2.11
5.13
3.14
ppm

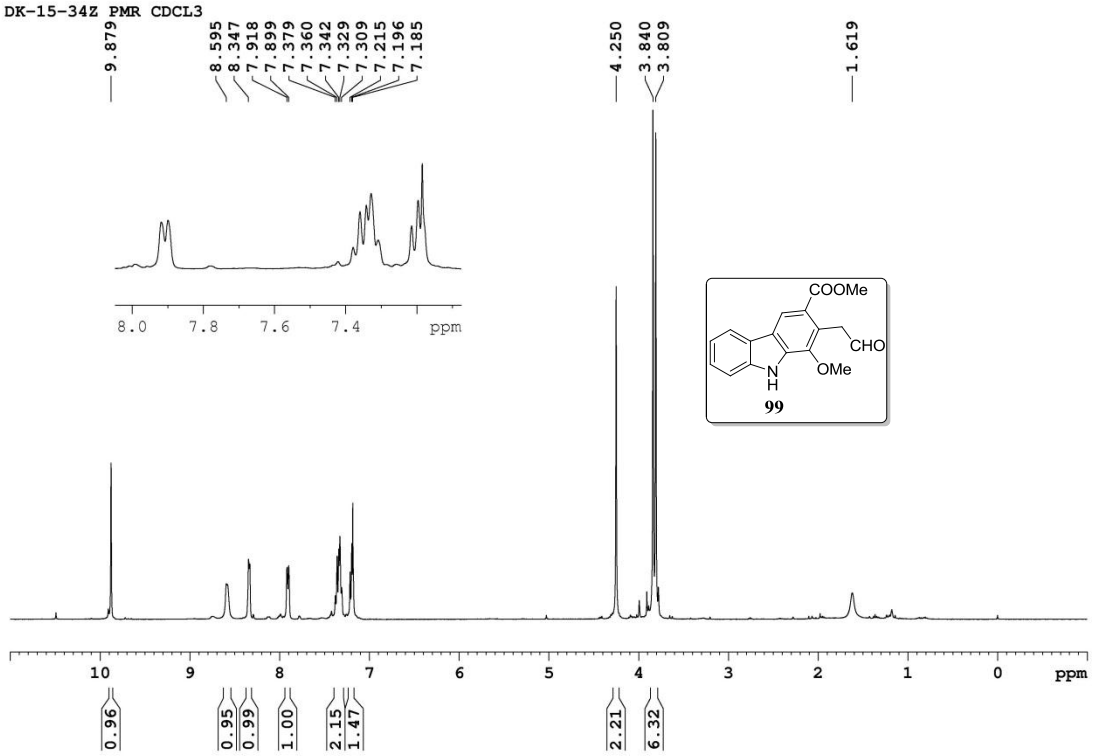

DK-15-55 ACETONE CMR
169.21
168.43
141.60
137.92
136.27
135.66
131.33
127.47
124.06
123.63
122.37
122.18
121.33
120.97
115.25
112.20
52.14
32.08
30.22
30.03
29.84
29.64
29.45
20.89
COOMe
OAC
N
H
101
ppm

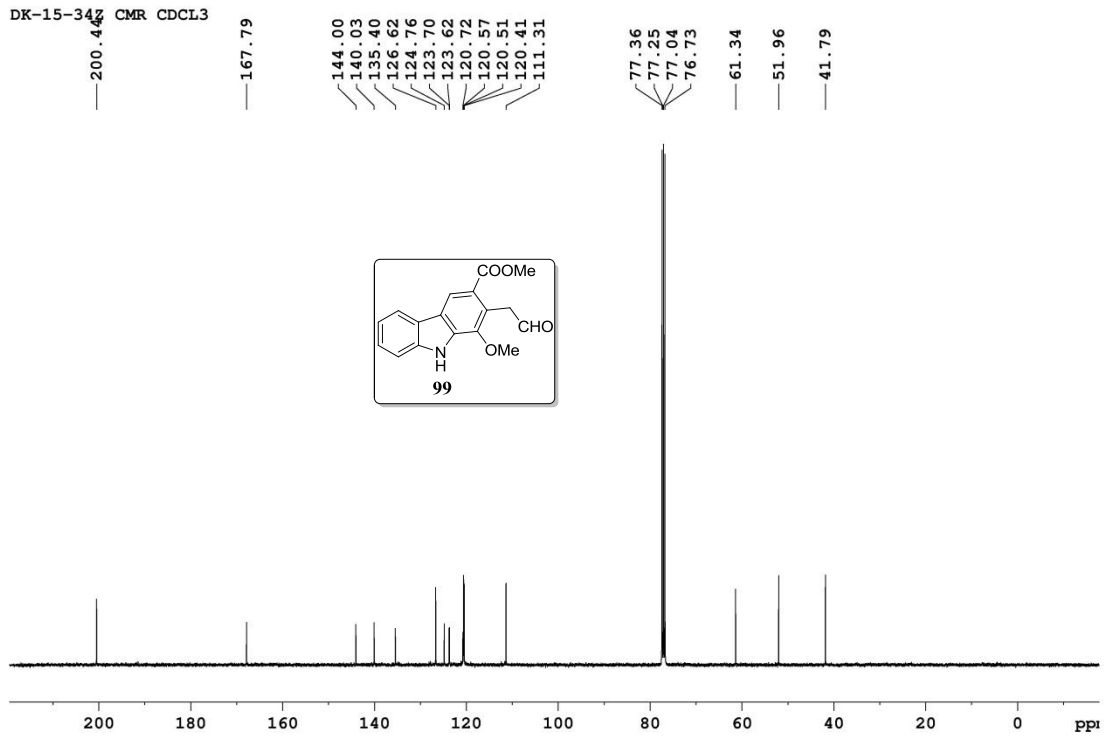

DK-15-55 ACETONE DEPT
137.91
127.46
122.18
121.33
120.96
115.25
112.20
52.13
32.07
20.88
COOMe
OAC
N
H
101
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

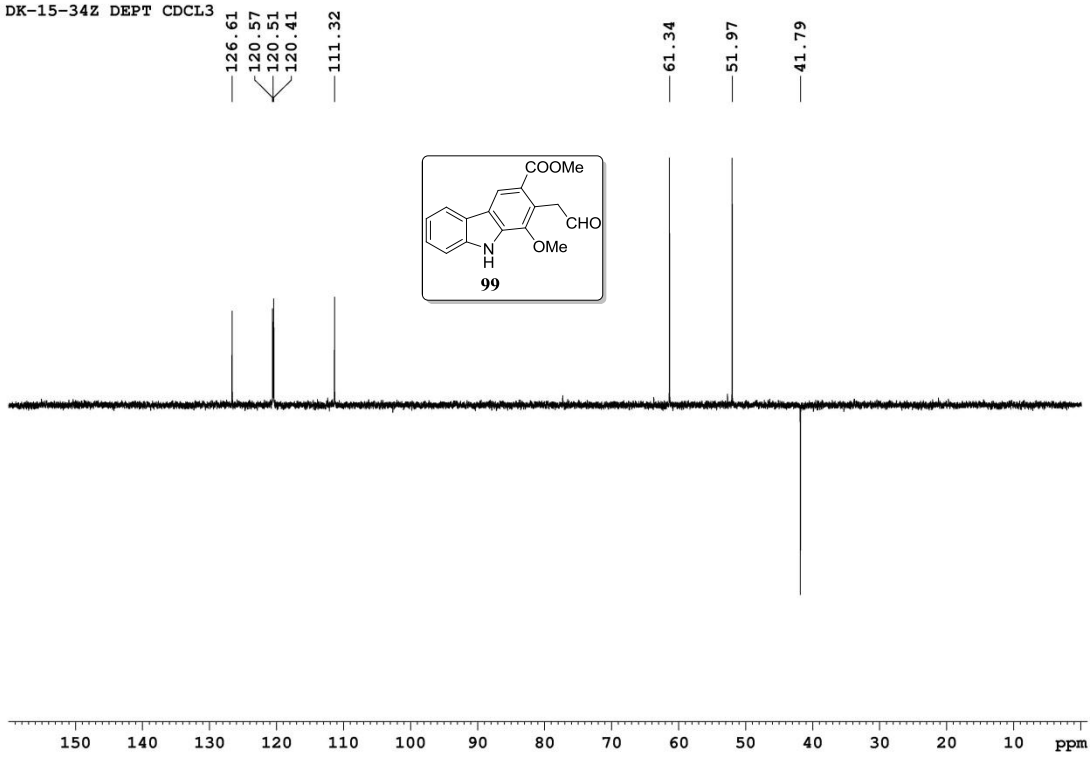

DK-15-33Z CDCl3 PMB
8.546
8.393
8.100
8.082
7.521
7.515
7.513
7.500
7.498
7.497
7.495
7.491
7.488
7.474
7.471
7.468
7.454
7.451
7.319
7.316
7.303
7.300
7.296
7.282
7.279
6.176
6.165
6.162
6.151
6.133
6.122
6.119
6.108
5.049
5.045
5.040
5.037
5.024
5.019
5.015
5.011
5.007
5.002
4.998
4.994
4.964
4.959
4.955
4.951
4.060
4.056
4.052
4.046
4.042
4.038
3.987
3.958
8.6 8.4 ppm
4.08 4.06 4.04 ppm
COOMe
OMe
N
H
98
10 9 8 7 6 5 4 3 2 1 0 ppm
0.99
0.84
1.03
2.12
1.41
1.00
2.06
2.06
3.03
2.90

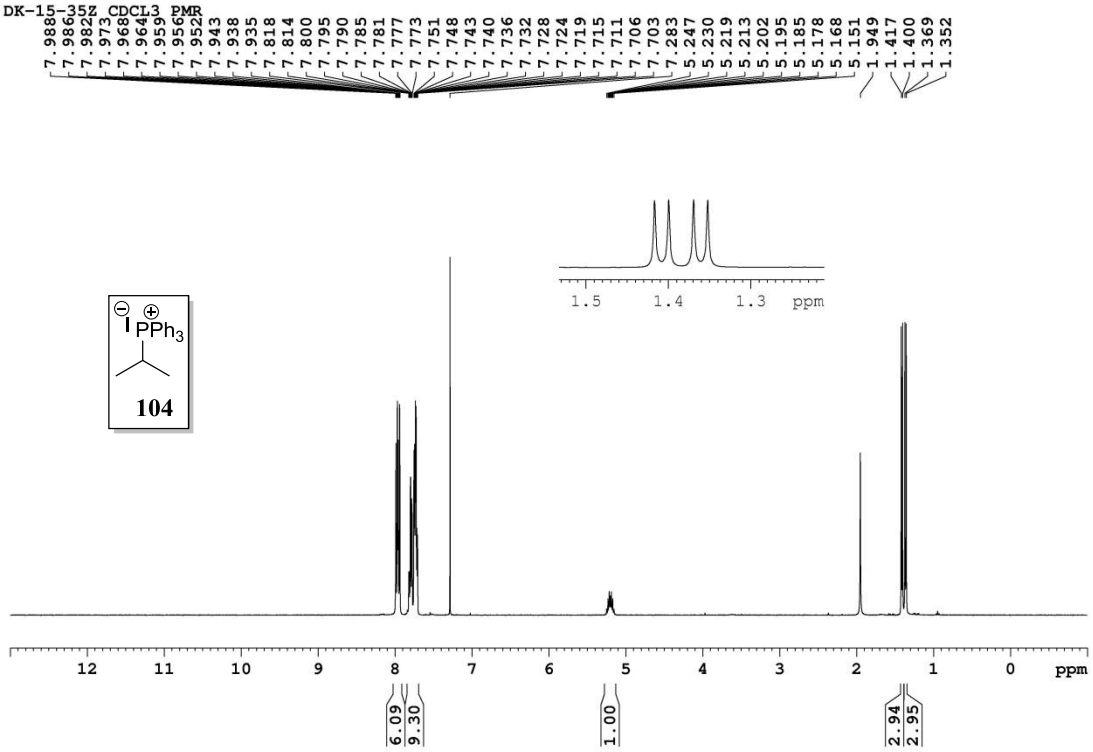

DK-15-33Z CDCL3 CMR
168.38
143.43
139.83
138.26
135.51
131.19
126.46
123.92
122.92
122.37
120.58
120.39
120.29
114.60
111.13
77.35
77.04
76.72
61.43
51.92
30.68
COOMe
OMe
N
H
98
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

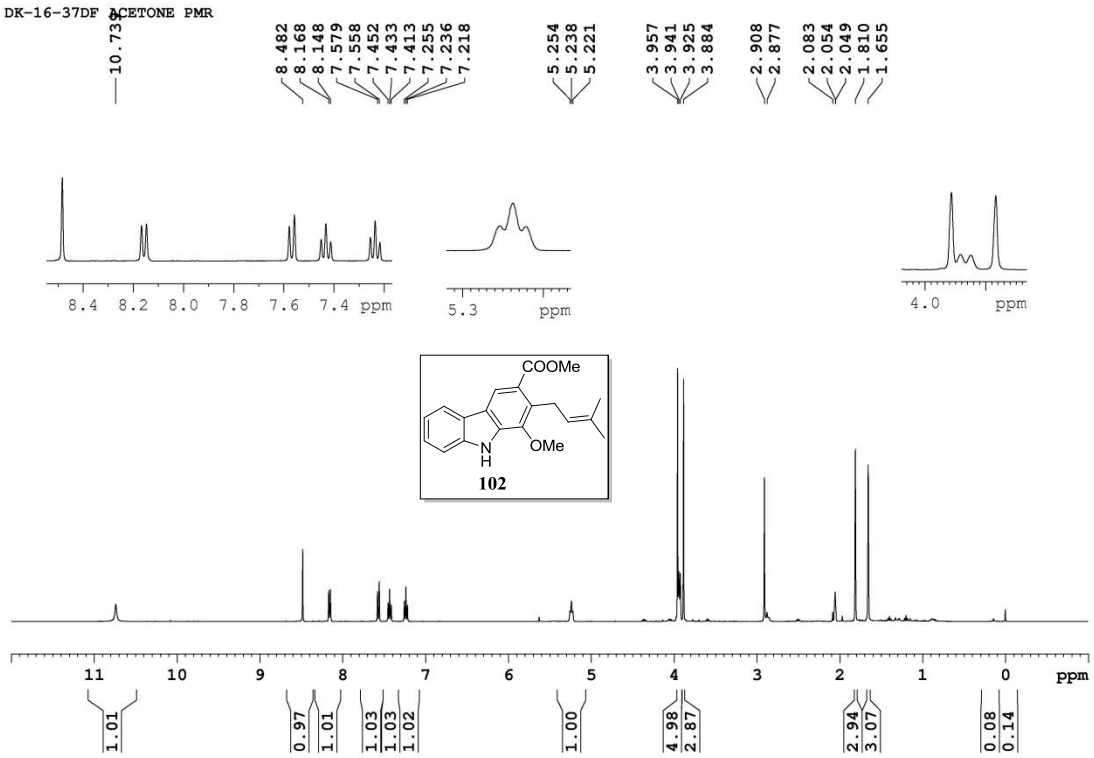

DK-15-33Z CDCL3 DEPT
138.28
126.46
120.58
120.39
120.29
114.61
111.13
61.43
51.92
30.68
COOMe
OMe
N
H
98
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

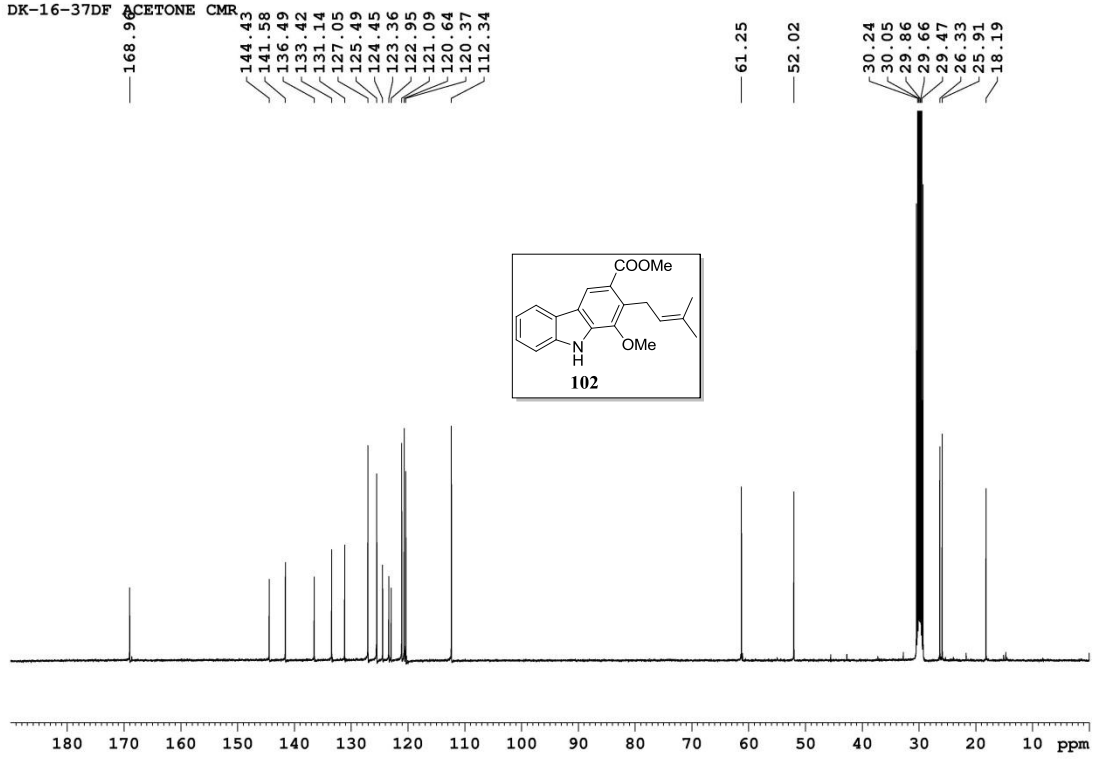

DK-15-34Z PMR CDCL3
9.879
8.595
8.347
7.918
7.899
7.379
7.360
7.342
7.329
7.309
7.215
7.196
7.185
4.250
3.840
3.809
1.619
8.0
7.8
7.6
7.4
ppm
COOMe
CHO
OMe
N
H
99
10
9
8
7
6
5
4
3
2
1
0
ppm
0.96
0.95
0.99
1.00
2.15
1.47
2.21
6.32

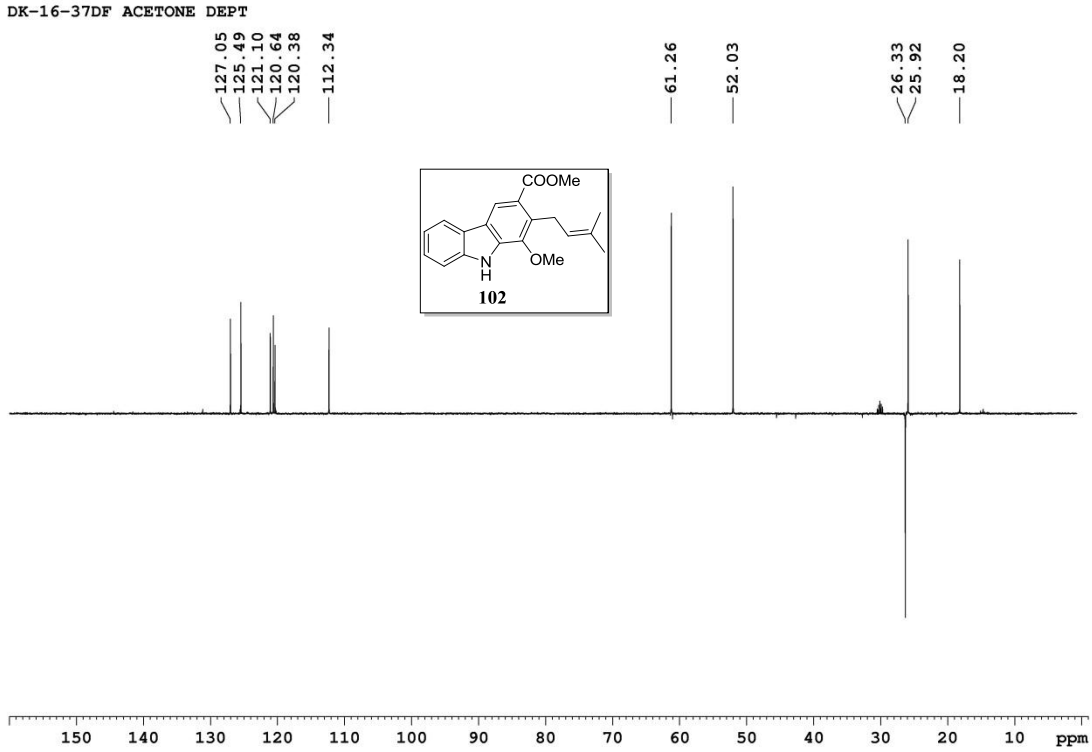

DK-15-34Z CMR CDCL3
200.44
167.79
144.00
140.03
135.40
126.62
124.76
123.70
123.62
120.72
120.57
120.51
120.41
111.31
77.36
77.25
77.04
76.73
61.34
51.96
41.79
COOMe
CHO
OMe
N
H
99
200
180
160
140
120
100
80
60
40
20
0
ppı

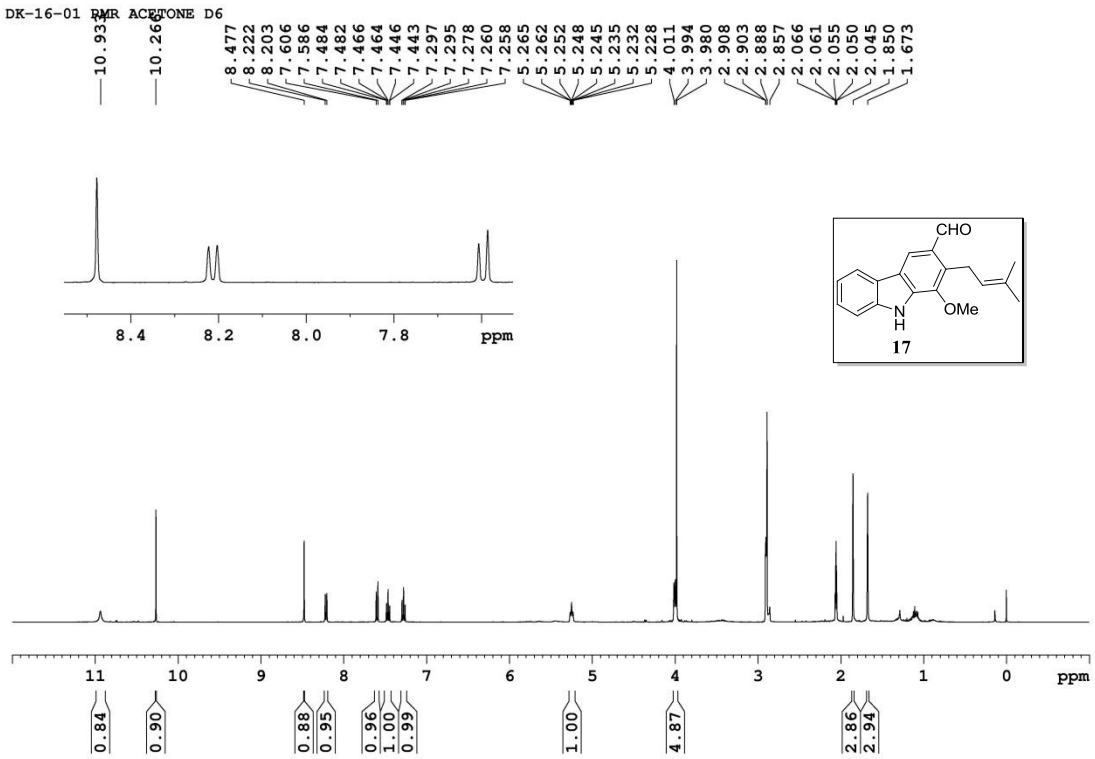

DK-15-34Z DEPT CDCL3
126.61
120.57
120.51
120.41
111.32
61.34
51.97
41.79
COOMe
CHO
OMe
N
H
99
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

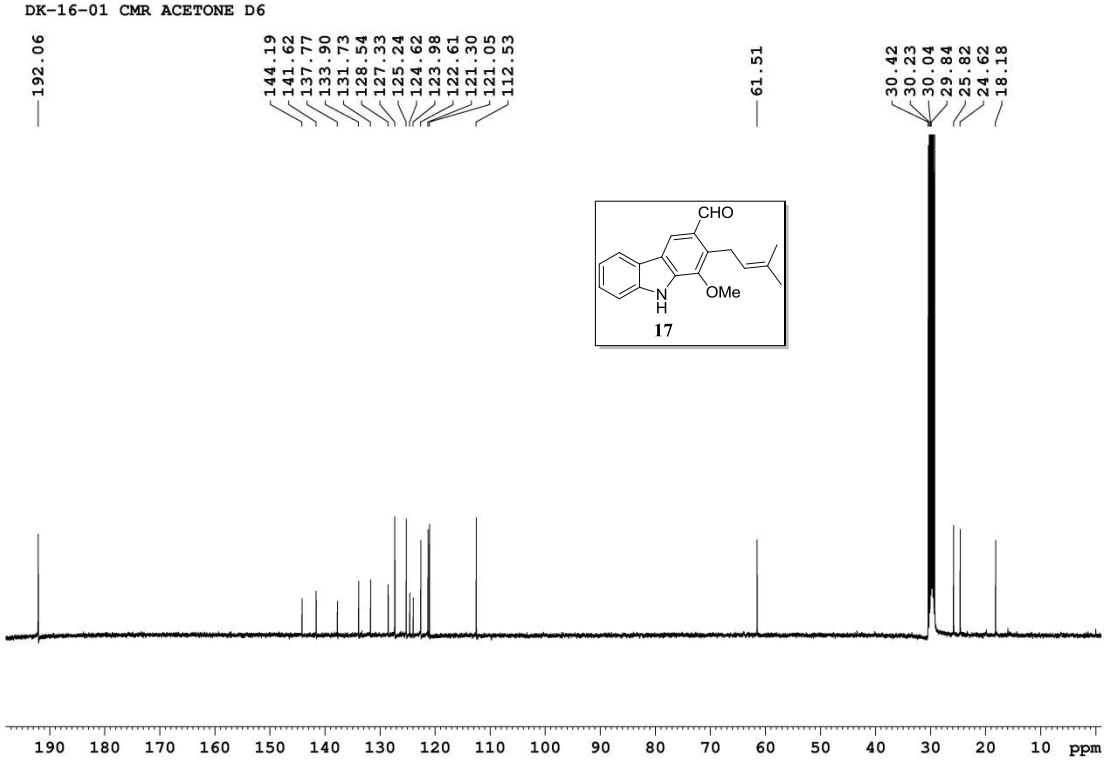

DK-15-35Z CDCL3 PMR
7.988
7.986
7.982
7.973
7.968
7.964
7.959
7.956
7.952
7.943
7.938
7.935
7.818
7.814
7.800
7.795
7.790
7.785
7.781
7.777
7.773
7.751
7.748
7.743
7.740
7.736
7.732
7.728
7.724
7.719
7.715
7.711
7.706
7.703
7.283
5.247
5.230
5.219
5.213
5.202
5.195
5.185
5.178
5.168
5.151
1.949
1.417
1.400
1.369
1.352
PPh3
104
1.5 1.4 1.3 ppm
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
6.09
9.30
1.00
2.94
2.95

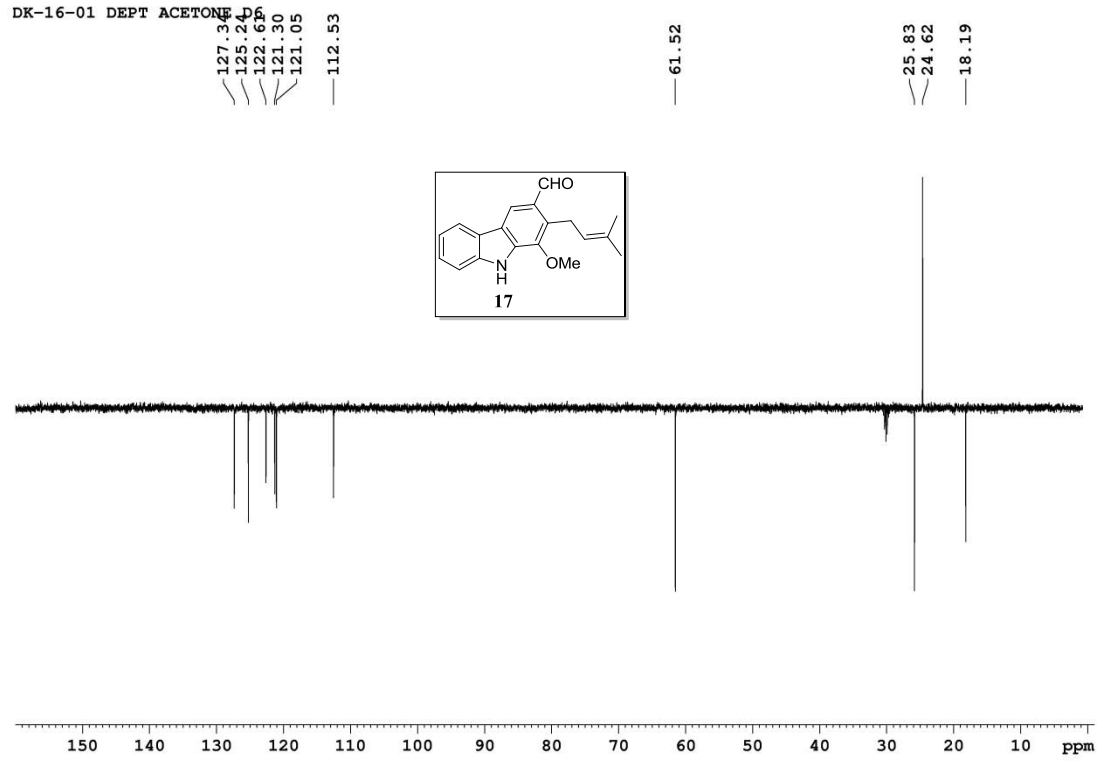

DK-16-37DF ACETONE PMR
10.731
8.482
8.168
8.148
7.579
7.558
7.452
7.433
7.413
7.255
7.236
7.218
5.254
5.238
5.221
3.957
3.941
3.925
3.884
2.908
2.877
2.083
2.054
2.049
1.810
1.655
8.4 8.2 8.0 7.8 7.6 7.4 ppm
5.3 ppm
4.0 ppm
COOMe
OMe
N
H
102
11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.01
0.97
1.01
1.03
1.03
1.02
1.00
4.98
2.87
2.94
3.07
0.08
0.14

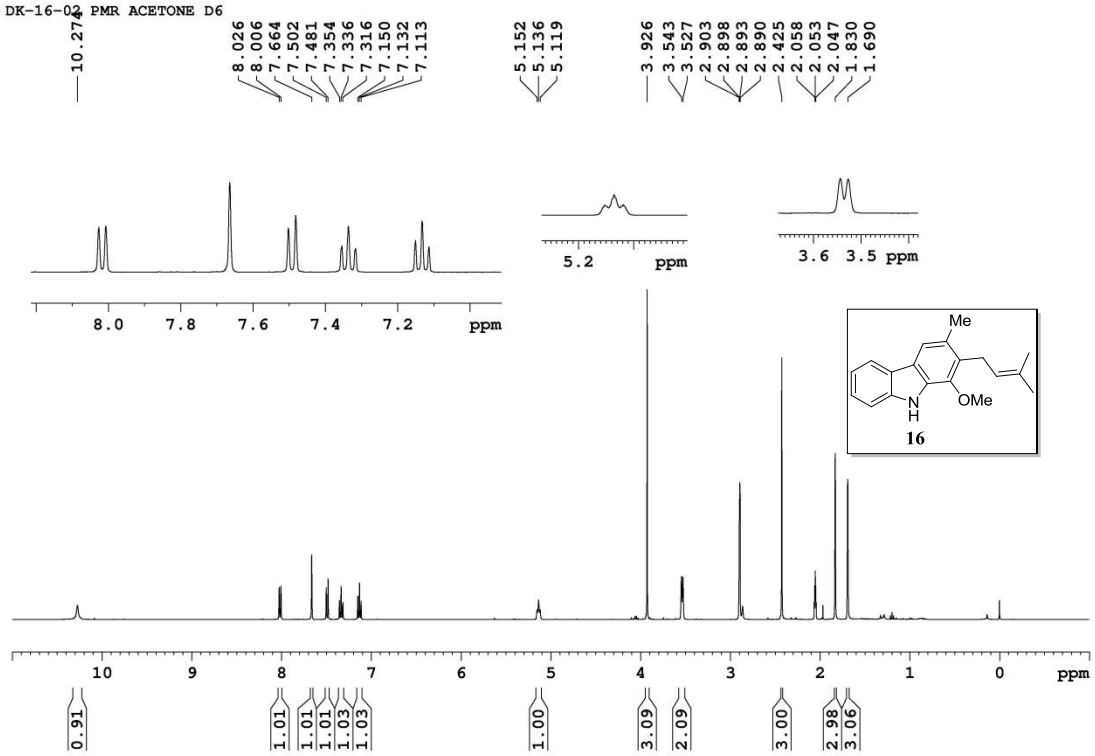

DK-16-37DF ACETONE CMR
168.96
144.43
141.58
136.49
133.42
131.14
127.05
125.49
124.45
123.36
122.95
121.09
120.64
120.37
112.34
61.25
52.02
30.24
30.05
29.86
29.66
29.47
26.33
25.91
18.19
COOMe
OMe
N
H
102
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

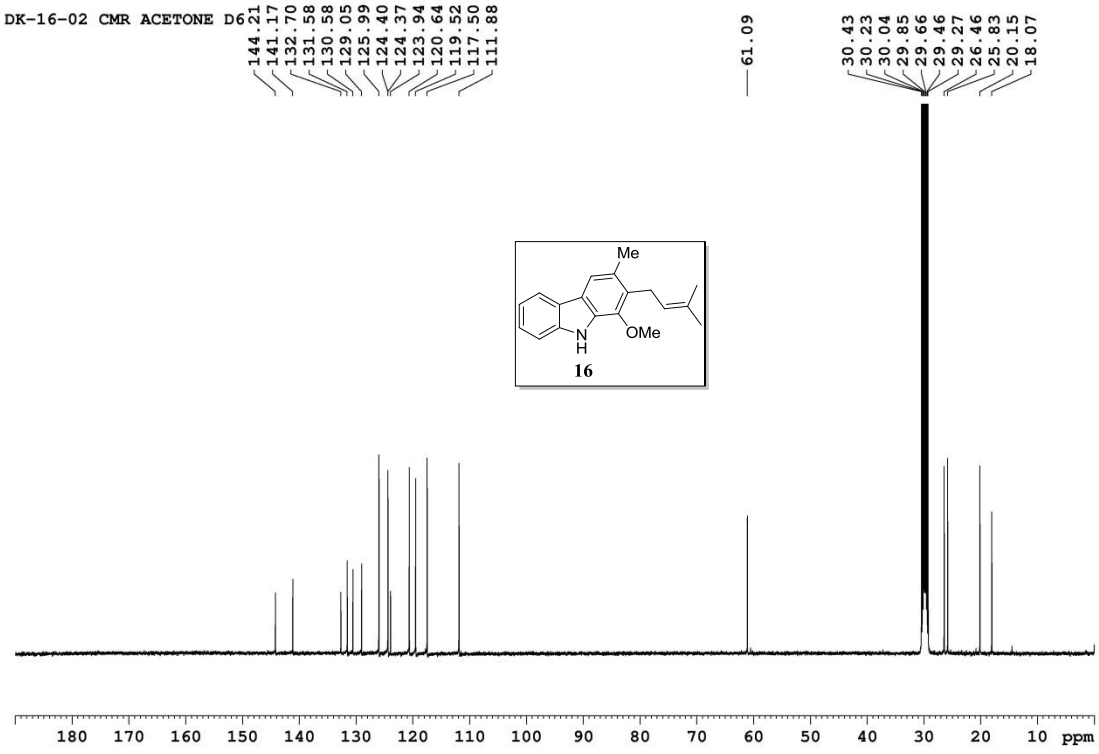

DK-16-37DF ACETONE DEPT
127.05
125.49
121.10
120.64
120.38
112.34
61.26
52.03
26.33
25.92
18.20
COOMe
OMe
N
H
102
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

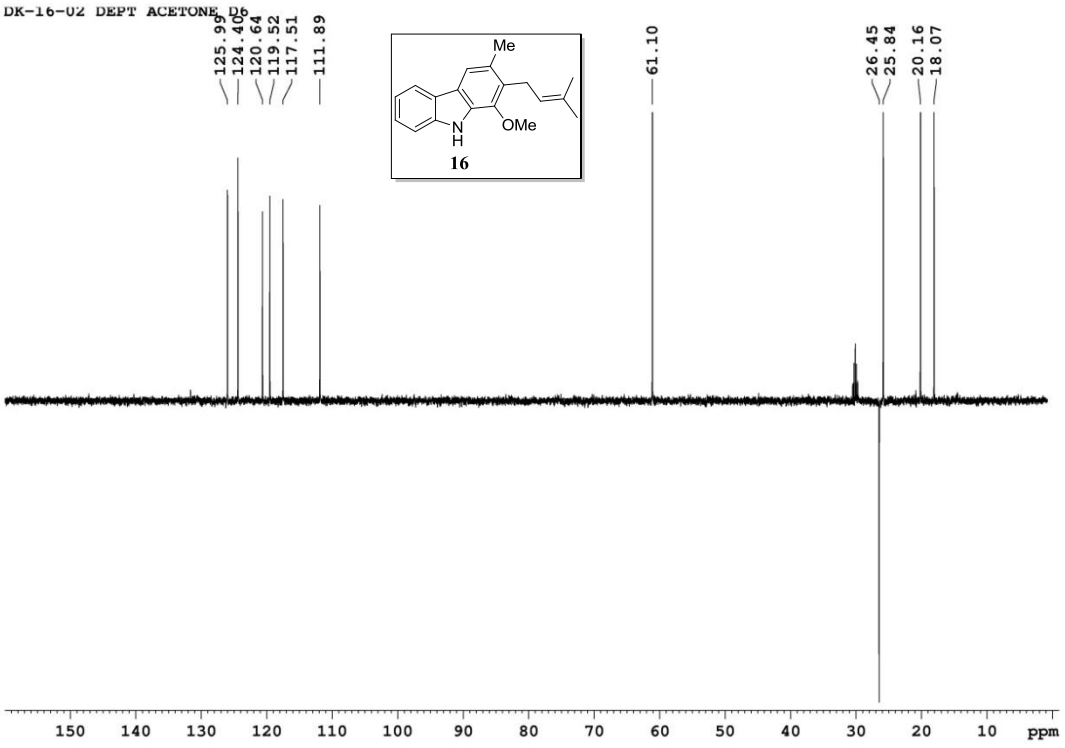

DK-16-01 PMR ACETONE D6
10.93
10.26
8.477
8.222
8.203
7.606
7.586
7.484
7.482
7.466
7.464
7.446
7.443
7.297
7.295
7.278
7.260
7.258
5.265
5.262
5.252
5.248
5.245
5.235
5.232
5.228
4.011
3.994
3.980
2.908
2.903
2.888
2.857
2.066
2.061
2.055
2.050
2.045
1.850
1.673
8.4
8.2
8.0
7.8
ppm
CHO
OMe
N
H
17
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.84
0.90
0.88
0.95
0.96
1.00
0.99
1.00
4.87
2.86
2.94

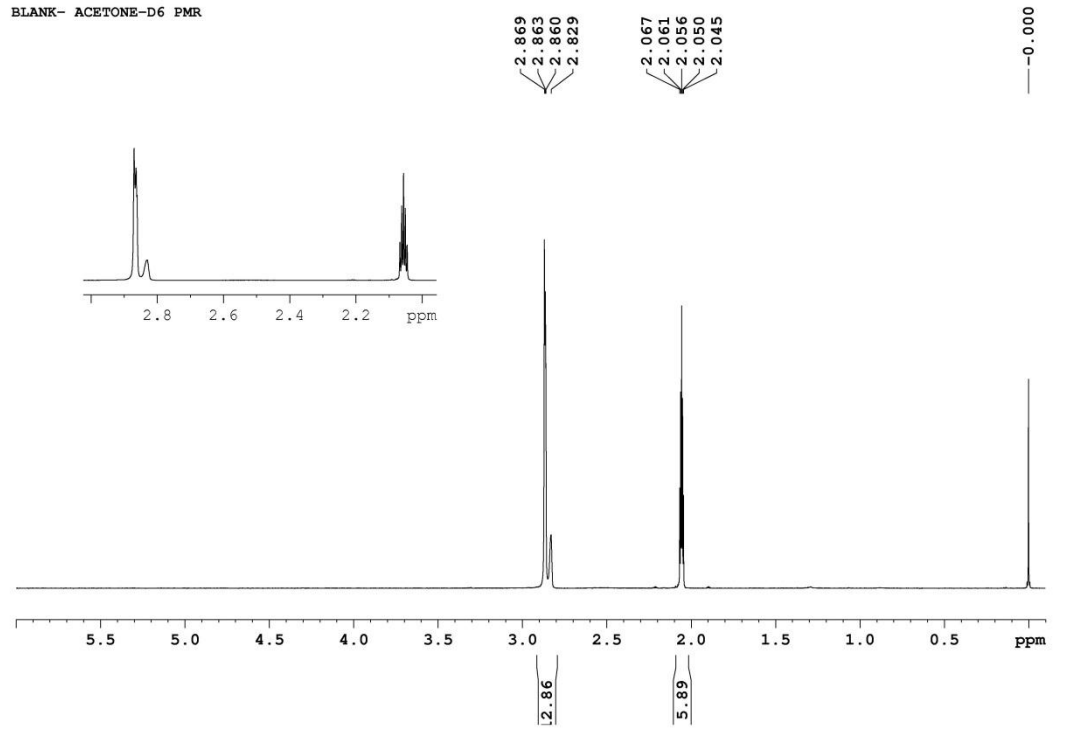

DK-16-01 CMR ACETONE D6
192.06
144.19
141.62
137.77
133.90
131.73
128.54
127.33
125.24
124.62
123.98
122.61
121.30
121.05
112.53
61.51
30.42
30.23
30.04
29.84
25.82
24.62
18.18
CHO
OMe
N
H
17
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-16-01 DEPT ACETONE D6
127.34
125.24
122.62
121.30
121.05
112.53
61.52
25.83
24.62
18.19
CHO
OMe
N
H
17
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-16-02 PMR ACETONE D6
10.274
8.026
8.006
7.664
7.502
7.481
7.354
7.336
7.316
7.150
7.132
7.113
5.152
5.136
5.119
3.926
3.543
3.527
2.903
2.898
2.893
2.890
2.425
2.058
2.053
2.047
1.830
1.690
8.0 7.8 7.6 7.4 7.2 ppm
5.2 ppm
3.6 3.5 ppm
Me
OMe
N
H
16
10 9 8 7 6 5 4 3 2 1 0 ppm
0.91
1.01
1.01
1.01
1.03
1.03
1.00
3.09
2.09
3.00
2.98
3.06


DK-16-02 CMR ACETONE D6
144.21
141.17
132.70
131.58
130.58
129.05
125.99
124.40
124.37
123.94
120.64
119.52
117.50
111.88
61.09
30.43
30.23
30.04
29.85
29.66
29.46
29.27
26.46
25.83
20.15
18.07
Me
OMe
N
H
16
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DK-16-02 DEPT ACETONE D6
125.99
124.40
120.64
119.52
117.51
111.89
61.10
26.45
25.84
20.16
18.07
Me
OMe
N
H
16
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


BLANK- ACETONE-D6 PMR
2.869
2.863
2.860
2.829
2.067
2.061
2.056
2.050
2.045
0.000
2.8 2.6 2.4 2.2 ppm
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.86
5.89