Studies on Total Synthesis of Bioactive Carbazole Alkaloids

Thesis Submitted to AcSIR

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In

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BY

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Dedicated to

My Parents and Teachers

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Studies on Total Synthesis of Bioactive Carbazole Alkaloids**" submitted by **Mr. Shivaji Bhimrao Markad** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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CSIR-NATIONAL CHEMICAL LABORATORY

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Studies on Total Synthesis of Bioactive Carbazole Alkaloids''** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D) is the outcome of experimental investigations carried out by me under the supervision of **Dr. N. P. Argade**, Senior Principal Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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…Shivaji

ABBREVATIONS

Ac_2O	Acetic anhydride
Ar	Aryl
$AlMe_3$	Trimethylaluminium
n-Bu_3P	Tributylphophine
t-BuOH	*tert*-Butyl alcohol
Boc_2O	Di-*tert*-butyl dicarbonate
DEAD	Diethyl azodicarboxylate
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulphoxide
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DIBAL-H	Diisobutylaluminium hydride
dr	*Diastereomeric ratio*
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
g	Grams
h	Hours
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
HCl	Hydrochloric acid
IR	Infra-red
K_2CO_3	Potassium carbonate
LiHMDS	Lithium hexamethyldisilazide
LAH	Lithium aluminium hydride
m-CPBA	*meta*-Chloroperoxybenzoic acid
M+	Molecular ion
Me	Methyl
min	Minute
mg	Miligram
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
NMR	Nuclear magnetic resonance
NaHMDS	Sodium hexamethyldisilazide
$NaBH_4$	Sodium borohydride
NMO	*N*-Methylmorpholine *N*-oxide
OsO_4	Osmium tetroxide
Pd/C	Palladium on activated charcoal
Ph	Phenyl
PCC	Pyridinium chlorochromate
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TFAA	Trifluoroacetic anhydride

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60–80°C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (60–120 &230–400 mesh).
5. TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol), bromocresol green (in ethanol), phosphomolybdic acid (in ethanol) and ninhydrin (in ethanol).
6. IR Spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR andabsorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}CNMR spectra were recorded on Brucker FT AC-200 MHz, BruckerAvance 400 MHz,Avance 500 MHzand JEOL ECX 400 instruments using TMS or solvent residue as an internal standard. The following abbreviationswere used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broadsinglet, dd = doublet of doublet, td = triplet of doublet, dt = doubletof triplet, dq = doublet of quartet and app = apparent.
8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25°C usingsodium D light.
9. Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a chiral column.
10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.
11. All melting points are uncorrected and the temperatures are incentigrade scale.
12. The compounds, scheme and reference numbers given in each chapter/section refers to thatparticular chapter/section only.

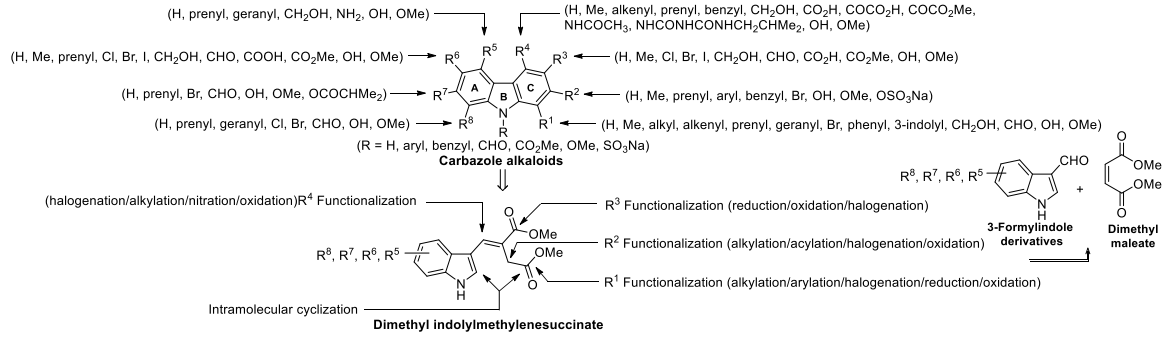
Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry

Name of the Candidate	Mr. Shivaji Bhimrao Markad
Degree Enrolment No. & Date	Ph. D. in Chemical Sciences (10CC13J26024); January 2013
Title of the Thesis	Studies on Total Synthesis of Bioactive Carbazole Alkaloids
Research Supervisor	Dr. Narshinha P. Argade (AcSIR, CSIR-NCL, Pune)

Introduction

Development of new synthetic stratagems for the collective total synthesis of different classes of natural products is a challenging task of contemporary interest.[1] A large number of carbazole alkaloids have been isolated from plant, animal, microbial and marine genesis. They are an important class of natural products from novel structural topographies and major biological activities point of view.[2] Carbazoles exhibit well proved antitumor, antibiotic, antiviral, anti-HIV, anti-inflammatory, antimalarial, psychotropic, antihistaminic, anti-oxidative and the significant anti-tuberculosis activities. Moreover, carbazoles are used in the treatment of hypertension, ischemic heart disease and congestive heart failure. They have also been used in illustrious hole-transporting electroluminescent materials and are potential building blocks in functional materials owing to their electrical and thermal properties. Therefore carbazoles have been crucial target compounds and several elegant product specific synthesis of these have been reported during the past few decades. The main steps involved in their synthesis were acid/ base/metal/heat/light-catalyzed aryl–carbon/aryl–nitrogen/aryl–aryl couplings of two suitably substituted building blocks and the specific intramolecular cyclizations. In the synthesis of carbazoles, construction of an appropriate fully functionalized aromatic ring system is the important assignment for steric and/or electronic factors and reactivity reasons. Despite tremendous synthetic efforts to develop regioselective installation of appropriate substituents on these heterocyclic structures, a general and efficient method is still limited. We reasoned that, retrosynthetically the stepwise intermolecular and intramolecular coupling reactions of three carbon units from suitably substituted 3-formylindole derivatives with three carbon unit from dimethyl maleate would constitute a general pathway to the majority of diversely substituted carbazole alkaloids (Figure 1). In the present dissertation work major synthetic strategies have been described to access the core ring system, which have resulted into the concise and efficient total synthesis of several recently isolated bioactive natural products (Figure 2).

Figure 1. General representation of known major carbazole alkaloids and their retrosynthetic analysis.



Statement of Problem

The synthesis of selected bioactive carbazole alkaloids from coupling of 3-formylindole with dimethyl maleate and alkylation, allylation, prenylation and condensation with aldehyde of the

formed coupling product leading to target compounds.

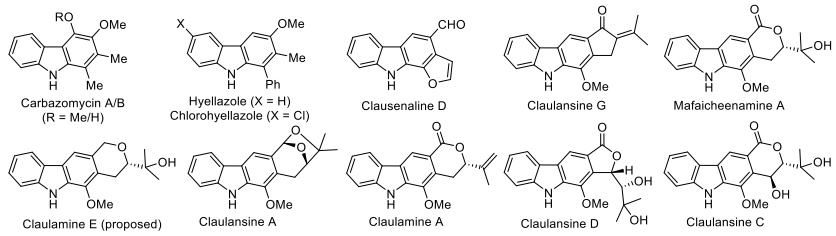


Figure 2. Bioactive carbazole natural products.

Methodology Used

1. The products were characterized by the advanced analytical and spectroscopic techniques such as high field ^{1}H & ^{13}C NMR, FT-IR, LC-MS and HRMS.

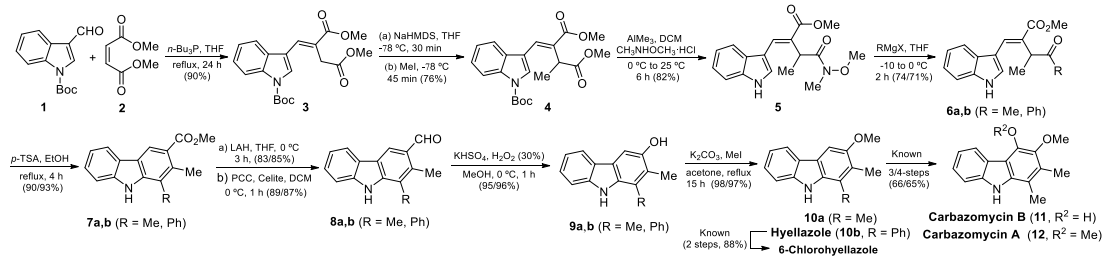
2. Single crystal X-ray crystallographic study has been carried out to determine the relative stereochemistry.

3. The optical purity of enantiomerically enriched target compounds has been determined by using chiral HPLC analysis and comparing their specific rotation with those reported in the literature.

Sample Results

1. The carbazole alkaloids carbazomycin A and carbazomycin B have been isolated from *Streptoverticillium ehimense*.[3] Hyellazole and chlorohyellazole have been isolated from *Hyella caespitose*.[4] Facile synthesis of imperative carbazole alkaloids carbazomycin A, carbazomycin B, hyellazole and chlorohyellazole have been accomplished starting from readily available Boc-protected 3-formylindole and dimethyl maleate. The suitably substituted aromatic rings have been designed comprising three/four significant carbon–carbon bond forming reactions. The competent Wittig reaction, selective mono-alkylations, one-pot regioselective Weinreb amide formation and Boc-deprotection, well designed Grignard reactions, dehydrative intramolecular cyclizations and Baeyer–Villiger rearrangement of aromatic aldehydes were the main features (Scheme 1).

Scheme 1. Synthesis of Carbazole Alkaloids from Boc-Protected 3-Formylindole and Dimethyl Maleate

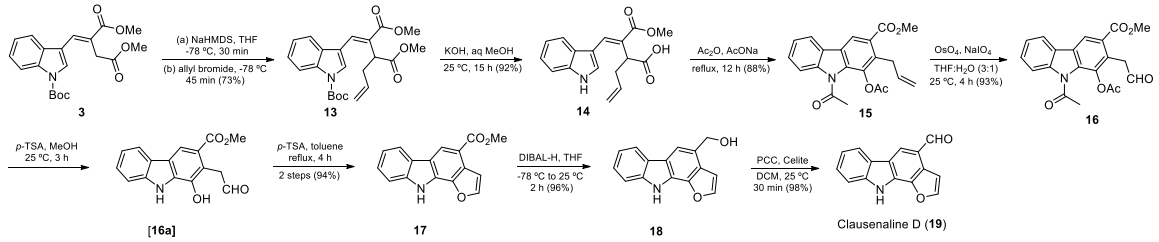


In summary, starting from easily available chemicals and reagents, we have demonstrated a diversity oriented convergent access for collective synthesis of four different carbazole alkaloids with very good overall yields. In the present approach, generation of suitably substituted basic carbazole skeleton in just 4/5-steps utilizing three carbon fragments from each 3-formylindole and dimethyl maleate is remarkable. Furthermore, the generation of biaryl systems without the aryl–aryl coupling is also noteworthy. Syntheses of these alkaloids have been completed without involving any discrete protection deprotection steps.

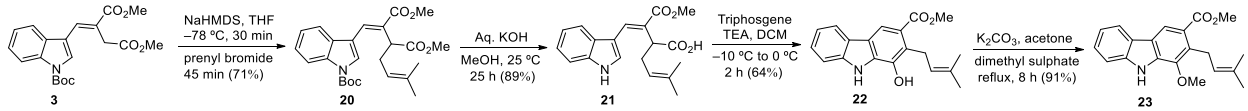
2. The carbazole alkaloids clausenaline D, indizoline, mafaicheenamine A, claulamine A, claulansine A, claulamine E and claulansine C have been isolated from *Clausena lansium*.[5] The NaHMDS induced regioselective introduction of an allyl group at an activated allylic methyelene

carbon in compound **3** with allyl bromide provided the required product **15** in 73% yield. The product **15** was transformed into clausenaline D via two different intamolecular cyclizations (Scheme 2). The common precursor 1-methoxy-2-prenyl-3-carbomethoxycarbazole was synthesized from dimethyl indolylmethylenesuccinate in four steps (Scheme 3). Well planned reductive and/or oxidative transformations and intramolecular cyclizations were performed on a pivotal common precursor to accomplish collective first total synthesis of titled natural products and the proposed claulamine E. Burgess reagent induced formation of kinetically controlled product claulamine A and intramolecular cyclizations to form bicyclic claulansine A were the key reactions (Scheme 4).

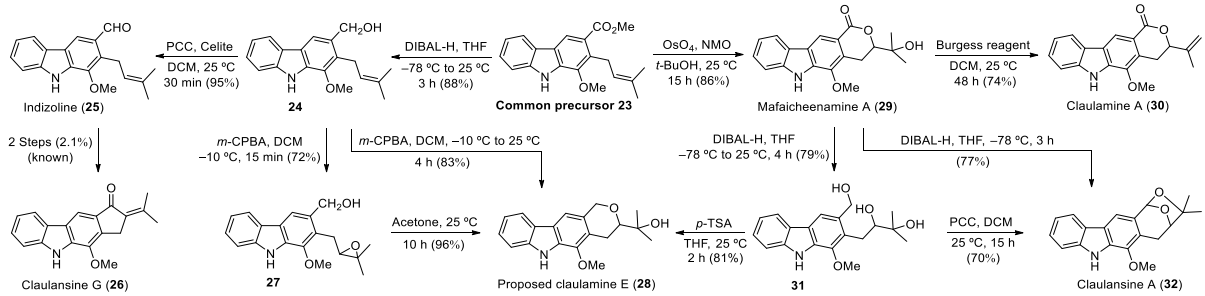
Scheme 2. First Total Synthesis of Clausenaline D



Scheme 3. A Facile Synthesis of Common Precursor 1-Methoxy-2-prenyl-3-carbomethoxycarbazole



Scheme 4. Concise and Efficient Collective Total Synthesis of Bioactive Carbazole Alkaloids

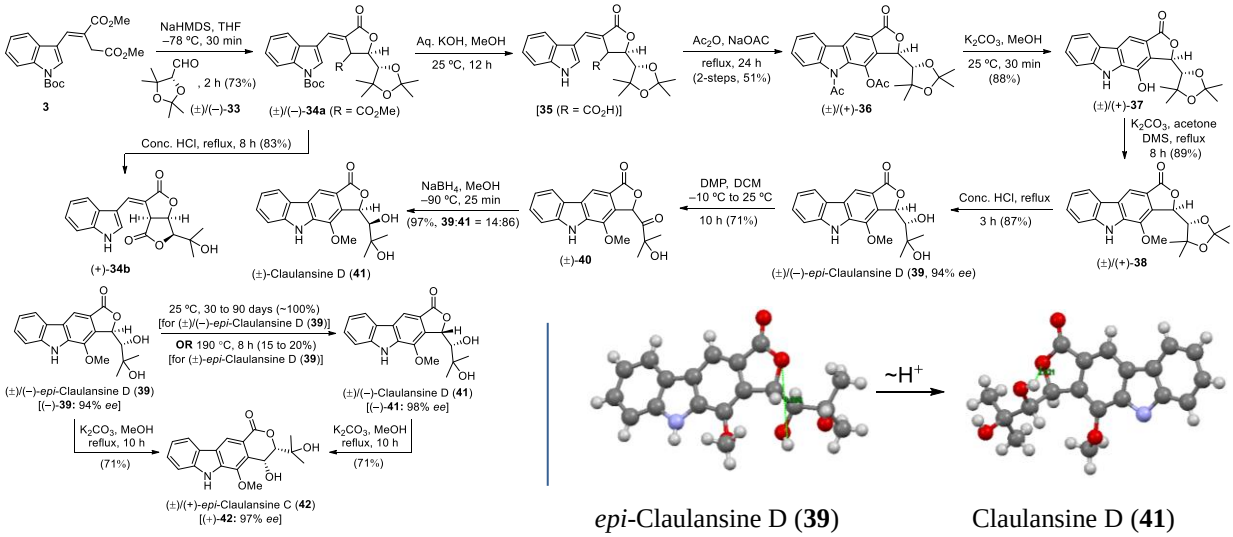


In summary, we have demonstrated a concise and efficient access to accomplish a biogenetic collective total synthesis of carbazole alkaloids from readily available simple starting materials. The involved different types of intramolecular cyclizations with the generation of new carbon–oxygen bonds selectively leading to those natural products are noteworthy from both basic chemistry and applications point of view. More specifically, remarkable cascade reaction has been demonstrated in the synthesis of claulansine A by taking the advantage of reactivity difference in three different types of alcohol units. We have accomplished an efficient total synthesis of the proposed structure of claulamine E and regioisomeric revision in structural assignment of natural product is necessary.

3. Several parts of *Clausena lansium* plant have been used as a folk medicine in China for cough, asthma and chronic ulcers. In search of potential lead compounds the phthalide unit consisting carbazoles (+)-claulansine C (3 mg) and (–)-claulansine D (2 mg) were isolated from 6.40 kilogram powdered stems of above specified plant species. Starting from dimethyl (*E*)-2-((1-*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methylene)succinate and (±)/(–)-(*R*)-2,2,5,5-tetramethyl-1,3-dioxolane-4-carbaldehyde, facile synthesis of (±)/(–)-*epi*-claulansine D has been completed via condensation and two intramolecular cyclizations. The (±)/(–)-*epi*-claulansine D in solid state exists in a metastable form and after an induction period of 30 days it underwent complete

epimerization to exclusively deliver the desired natural product (±)/(–)-claulansine D in quantitative yield. We feel that the witnessed inversion of *C*-centrochirality in solid state is conceptually new and takes place for relatively higher crystal stability reasons. Base catalysed ring expansion of both (±)/(–)-*epi*-claulansine D and (±)/(–)-claulansine D resulted into (±)/(+)-*epi*-claulansine C in very good yields (Scheme 5).

Scheme 5. Synthesis of (±)/(–)-*epi*-Claulansine D, (±)/(–)-Claulansine D and (±)/(+)-*epi*-Claulansine C



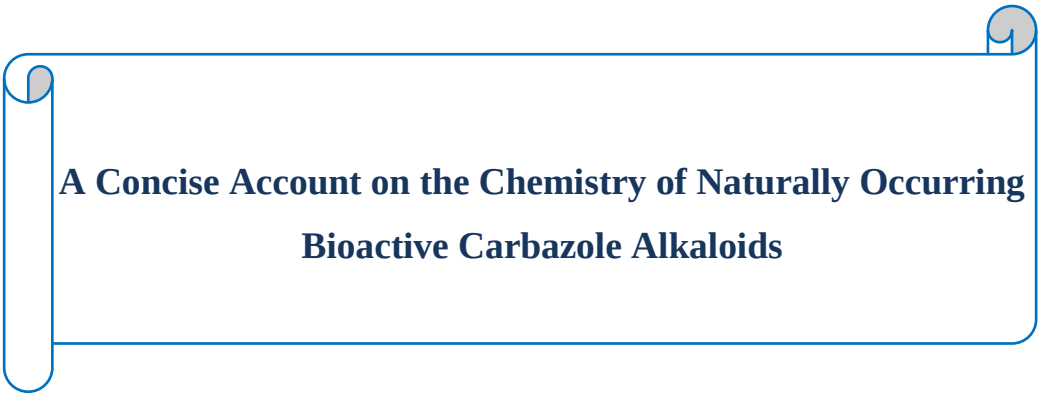
epi-Claulansine D (**39**) Claulansine D (**41**)

In summary, stereoselective total synthesis of (±)/(–)-claulansine D has been demonstrated via remarkable solid state auto epimerization of (±)/(–)-*epi*-claulansine D and it represents first example of crystal engineering driven inversion of *C*-centrochirality. The present synthesis demonstrates diastereomeric enrichment of phthalide moiety in a crystal lattice to a single isomer and we feel that it will be conceptually highly useful in future from applications point of view. Moreover further elaboration of solid state dynamic resolutions will provide the environment friendly and cost effective approaches to the enantiomerically pure essential chemical products.

Overall conclusion: Starting from 3-formylindole and dimethyl maleate, collective total synthesis of several carbazole alkaloids has been demonstrated via alkylation, allylation, prenylation and condensation with aldehyde in efficient manner.[6a–c] Stereoselective total synthesis of (±)/(–)-claulansine D has been accomplished via remarkable solid state auto epimerization of (±)/(–)-*epi*-claulansine D and it represents first example of crystal engineering driven inversion of *C*-centrochirality. The present new strategy to construct the carbazole architecture provides an avenue to natural and unnatural carbazoles for SAR studies.

References: (**1**) (a) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (b) Flyer, A. N.; Si, C.; Myers, A. G. *Nat. Chem*. **2010**, *2*, 886. (**2**) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev*. **2012**, *112*, 3193. (**3**) (a) Sakano, K. I.; Ishimaru, K.; Nakamura, S. *J. Antibiot*. **1980**, *33*, 683. (b) Sakano, K. I.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 961. (c) Kaneda, M.; Sakano, K. I.; Nakamura, S.; Kushi, Y.; Iitaka, Y. *Heterocycles* **1981**, *15*, 993. (**4**) Cardellina II, J. H.; Kirkup, M. P.; Moore, R. E.; Mynderse, J. S.; Seff, K.; Simmons, C. J. *Tetrahedron Lett*. **1979**, *20*, 4915. (**5**) (a) Li, W.-S.; Mcchesney, J. D.; El-Feraly, F. S. *Phytochemistry* **1991**, *30*, 343. (b) Maneert, W.; Laphookhieo, S. *Heterocycles* **2010**, *81*, 1261. (c) Shen, D.-Y.; Chao, C.-H.; Chan, H.-H.; Huang, G.-J.; Hwang, T.-L.; Lai, C.-Y.; Lee, K.-H.; Thang, T. D.; Wu, T.-S. *Phytochemistry* **2012**, *82*, 110. (d) Liu, H.; Li, C.-J.; Yang, J.-Z.; Ning, N.; Si, Y.-K.; Li, L.; Chen, N.-H.; Zhao, Q.; Zhang, D.-M. *J. Nat. Prod*. **2012**, *75*, 677. (e) Shen, D.-Y.; Chan, Y.-Y.; Hwang, T.-L.; Juang, S.-H.; Huang, S.-C.; Kuo, P.-C.; Thang, T.-D.; Lee, E.-J.; Damu, A.-G.; Wu, T.-S. *J. Nat. Prod*. **2014**, *77*, 1215. (**6**) (a) Markad S. B.; Argade N. P. *Org. Lett*. **2014**, *16*, 5470. (b) Markad S. B.; Argade N. P. *J. Org. Chem*. **2016**, *81*, 5222. (c) Markad S. B.; Argade N. P. *J. Org. Chem*. **2017**, revision submitted.

Chapter 1


A Concise Account on the Chemistry of Naturally Occurring
Bioactive Carbazole Alkaloids

1.1 Introduction

Carbazoles have been a building block of approximately 500 naturally occurring alkaloids isolated to date from a large number of families from the plant, animal, microbial and marine genesis. Carbazole (**1**) was isolated first from anthracene fraction of coal tar distillate in 1872 by Graebe and Glazer (Figure 1).[1] Ninety years later (in 1965), Chakraborty et al. isolated murrayanine from the plant *Murraya koenigii Spreng*.[2–4] They also described the antibiotic properties of murrayanine alkaloids. In India, the leaves of this small tree (known as currypatta or curry-leaf tree) are used in the preparation of delicious curry having high food value. The isolation of murrayanine was the first report of a naturally occurring carbazole alkaloid. Since then there has been strong interest in this area from chemists and biologists due to the structural topographies and promising biological activities exhibited by several carbazole alkaloids. Large number of carbazoles has been isolated from the genus *Murraya*, *Glycosmis* and *Clausena* belonging to the Rutaceae family. The genus *Murraya* represents the richest source of carbazole alkaloids from terrestrial plants. 3-Methylcarbazole was isolated from the genus *Clausena*;[5,6] the co-occurrence of murrayafoline A (**2**), koenoline (**3**), murrayanine (**4**) and mukoeic acid (**5**), as well as the subsequent isolation of mukonine (**6**), 2-hydroxy-3-methylcarbazole (**7**), mukonal (**8**) and mukonidine (**9**) from *M. koenigii*[7–9] support the hypothesis of biomimetic hydroxylation of 3-methylcarbazole. A rational comparison of structures of the carbazole alkaloids isolated from higher plants suggests that 3-methylcarbazole may represent the key intermediate in their biosynthesis.[10]

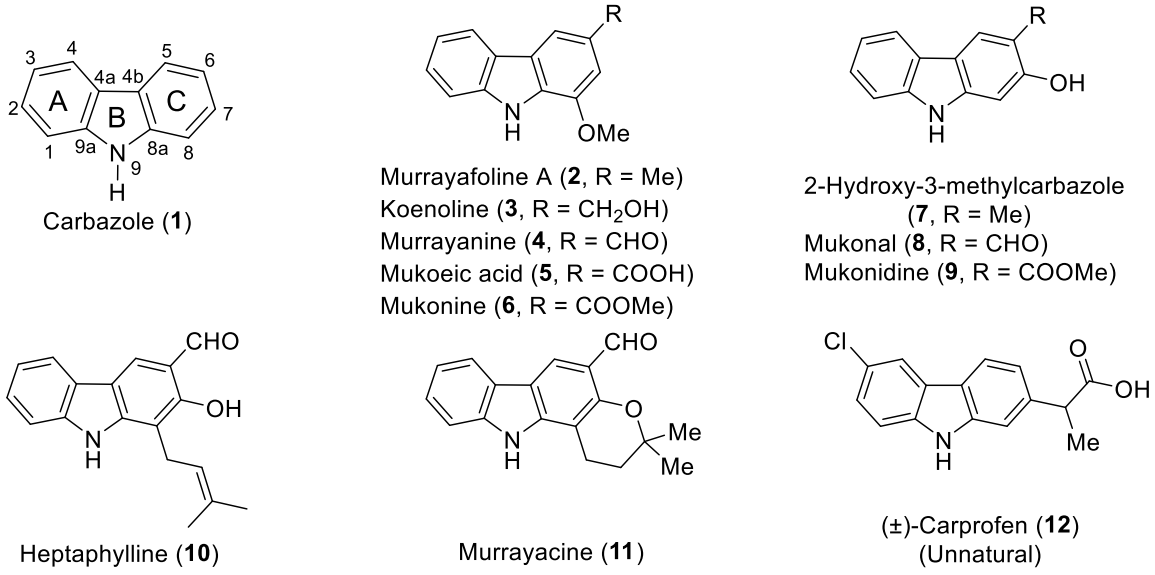


Figure 1. Bioactive Natural and Unnatural Carbazoles.

The isolation of heptaphylline (**10**)[11] and murrayacine (**11**)[12] from *Clausena heptaphylla* is circumstantial evidence for the origin of the pyran ring from the prenylated congener. This explains the formation of pyranocarbazoles from 2-hydroxy-3-methylcarbazole as shown by Popli et al.[13] The carbazole containing veterinary drug (±)-carprofen (**12**) possessing nonsteroidal anti-inflammatory activity is prescribed for supportive treatment in animals.

Carbazoles exhibit well proved antitumor, antibiotic, antiviral, anti-HIV, anti-inflammatory, antimalarial, psychotropic, antihistaminic, anti-oxidative and the significant anti-tuberculosis activities. Moreover, carbazoles are used in the treatment of hypertension, ischemic heart disease and congestive heart failure.[14–16] They have also been used in eminent hole-transporting electroluminescent materials and are potential building blocks in functional materials owing to their electrical and thermal properties.[17]

The carbzole were synthesized by classical methods such as Fischer–Borsche synthesis and the Graebe–Ullmann synthesis. The transition metal-mediated/catalyzed processes have been used for the total synthesis of biologically active carbazole alkaloids. Conventional tricyclic ring systems are denoted by A, B and C with the numbering from ring A as shown in figure 1.

1.2 Background

The chemistry of the carbazole alkaloids is well presented in a number of comprehensive

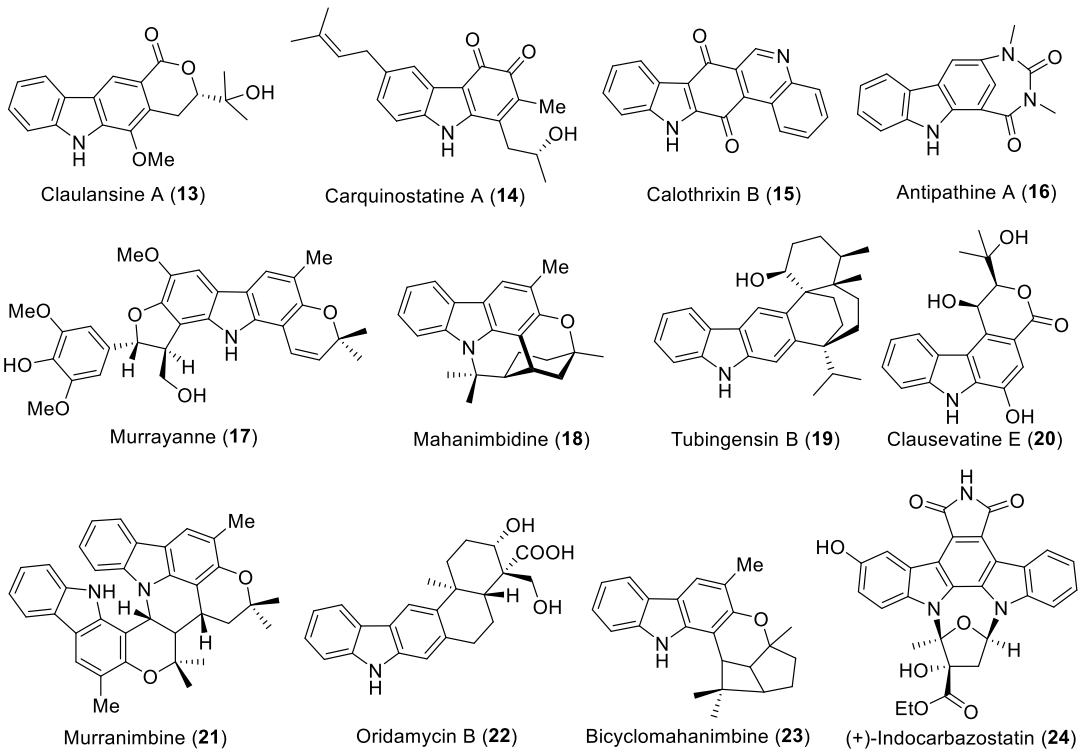
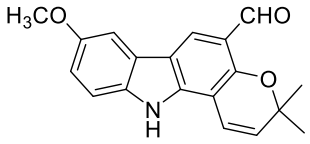


Figure 2. Representative Carbazole Alkaloids Isolated up to the Year 2012.

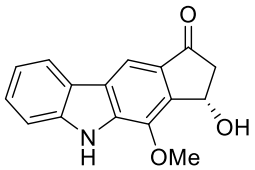
reviews, articles and is continuously updated in natural product reports.[18] In 2002 & 2012 Knölker's group has published the comprehensive reviews on the chemistry of carbazole alkaloids (Figure 2).[14] The reviews represent an authoritive account on isolation, bioactivity and synthesis of naturally occurring several carbazole alkaloids isolated up to the year 2011. They cover recent developments in the area of the complex carbazole natural products with an emphasis on classical and nonclassical methods used for their synthesis. These methods of carbazole synthesis can be further divided into two categories based on the pathway used to construct the carbazole core. One way is to form the pyrrolyl ring via coupling reaction of two building blocks and the other way starts from an indole derivative to construct the second benzene ring via electrocyclic reactions, cycloaddition reactions and so on.

1.3 New Carbazole Alkaloids Isolated After the Year 2012

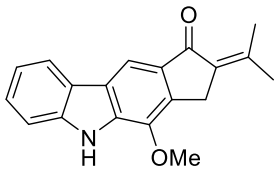
More than 45 new natural carbazoles have been isolated from various species during the period of 2012 to till date and are listed in figure 3 along with species from which they have been isolated with the details about their bioactivity and synthesis of most of them are not yet reported. We have tried our best to summarize the recent information on carbazole chemistry, however no pretension to completeness has been claimed.



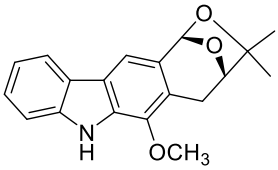
Claulansine F (**25**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: Not known



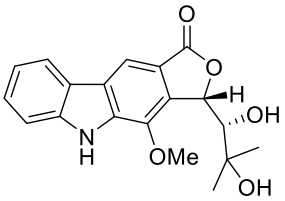
Claulansine E (**26**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: Not known



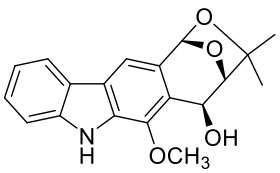
Claulansine G (**27**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: One known



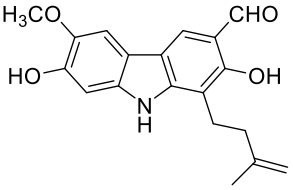
Claulamine A (**28**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: Not known



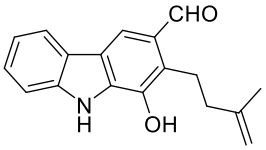
Claulansine D (**29**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: One known



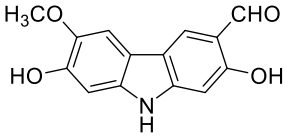
Claulamine B (**30**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: Not known



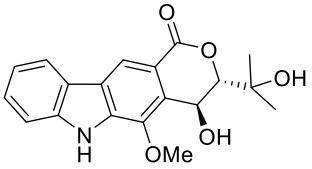
Claulansine H (**31**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: Not known



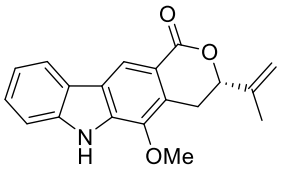
Claulansine I (**32**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: Not known



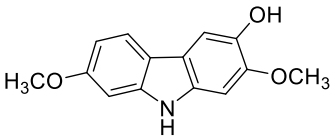
Claulansine J (**33**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: Not known



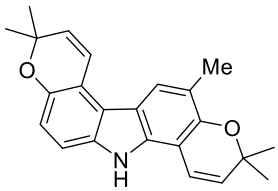
Claulansine C (**34**)
(*Clausena lansium*)[19]
Activity: Neuroprotective
Synthesis: Not known



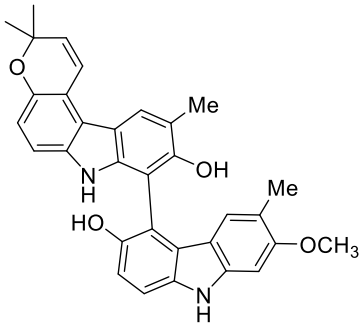
Claulamine A (**35**)
(*Clausena lansium*)[20]
Activity: Neuroprotective
Synthesis: Not known



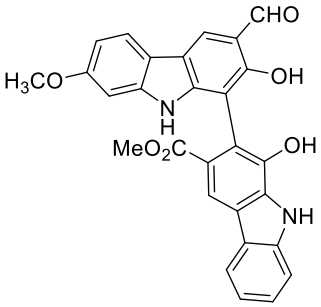
Clausenawalline D (**36**)
(*Clausena wallichii.*)[21]
Activity: Antibacterial
Synthesis: Not known



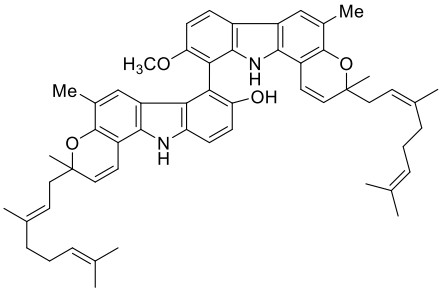
Clausenawalline C (**37**)
(*Clausena wallichii.*)[21]
Activity: Antibacterial
Synthesis: Not known



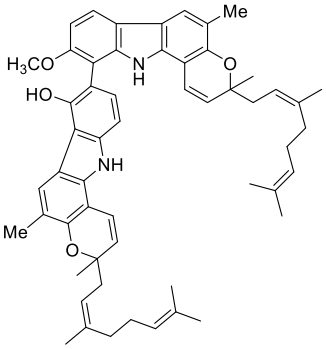
Clausenawalline E (**38**)
(*Clausena wallichii.*)[21]
Activity: Antibacterial
Synthesis: Not known



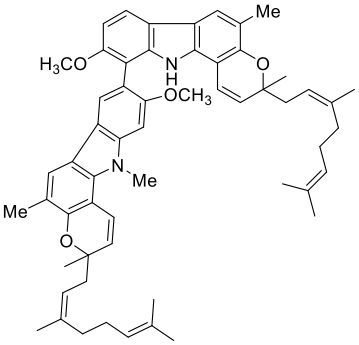
Clausenawalline F (**39**)
(*Clausena wallichii.*)[21]
Activity: Cytotoxic
Synthesis: Not known



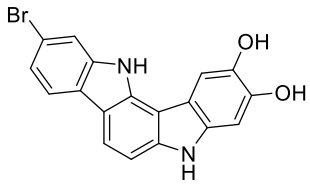
Bisgerayafolines A (**40**)
(*Murraya koenigii*)[22]
Activity: Antioxidant
Synthesis: Not known



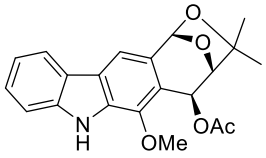
Bisgerayafolines B (**41**)
(*Murraya koenigii*)[22]
Activity: Antioxidant
Synthesis: Not known



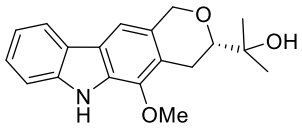
Bisgerayafolines C (**42**)
(*Murraya koenigii*)[22]
Activity: Antioxidant
Synthesis: Not known



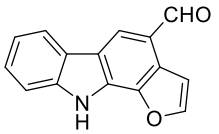
Indolo[3,2-*a*]carbazoles (**43**)
(genus *Asteropus*.)[23]
Activity: Cytotoxic
Synthesis: Not known



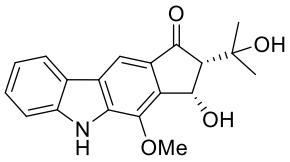
Claulamine D (**44**)
(*Clausena lansium*)[24]
Activity: Anti-inflammatory
Synthesis: Not known



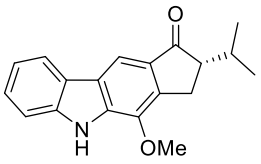
Claulamine E (**45**)
(*Clausena lansium*)[24]
Activity: Anti-inflammatory
Synthesis: Not known



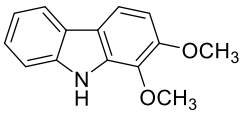
Clausenaline D (**46**)
(*Clausena lansium*)[24]
Activity: Anti-inflammatory
Synthesis: One known



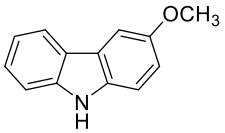
Clausenaline C (**47**)
(*Clausena lansium*)[24]
Activity: Anti-inflammatory
Synthesis: Not known



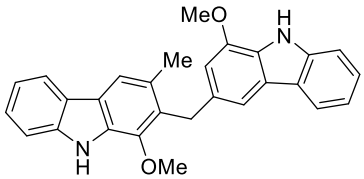
Clausenaline B (**48**)
(*Clausena lansium*)[24]
Activity: Anti-inflammatory
Synthesis: Not known



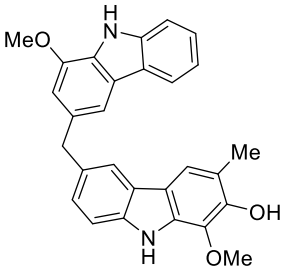
Clausenaline F (**49**)
(*Clausena lansium*)[24]
Activity: Anti-inflammatory
Synthesis: Not known



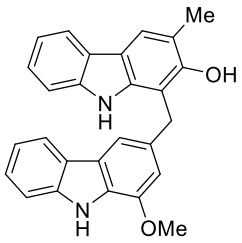
Clausenaline E (**50**)
(*Clausena lansium*)[24]
Activity: Anti-inflammatory
Synthesis: Not known



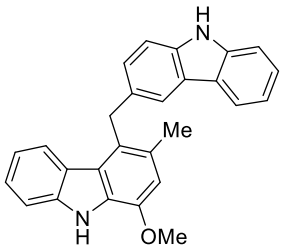
Murradines B (**51**)
(*Murraya tetramera*)[25]
Activity: Lipopolysaccharide
in BV-2 microglial cells
Synthesis: Not known



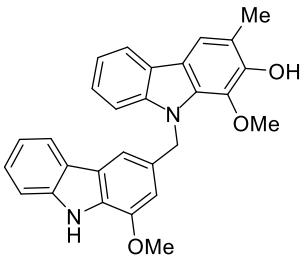
Murradines D (**52**)
(*Murraya tetramera*)[25]
Activity: Not known
Synthesis: Not known



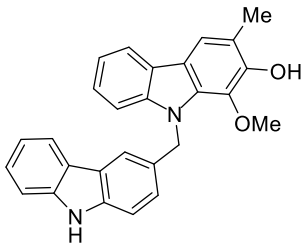
Murradines A (**53**)
(*Murraya tetramera*)[25]
Activity: Not known
Synthesis: Not known



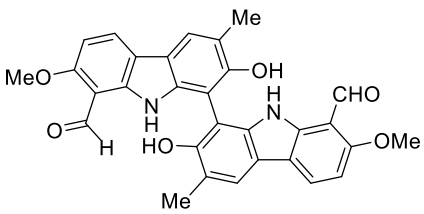
Murradines C (**54**)
(*Murraya tetramera*)[25]
Activity: Not known
Synthesis: Not known



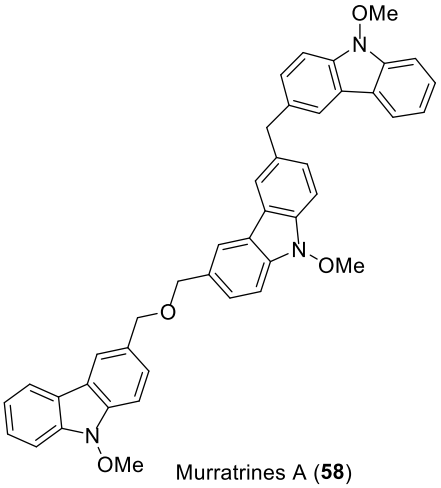
Murradines E (**55**)
(*Murraya tetramera*)[25]
Activity: Lipopolysaccharide
in BV-2 microglial cells
Synthesis: Not known



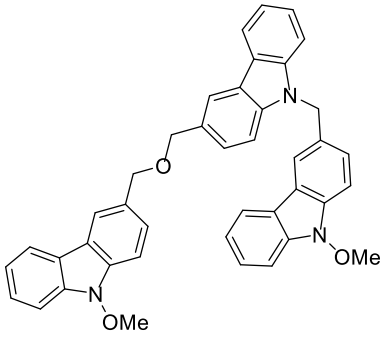
Murradines F (**56**)
(*Murraya tetramera*)[25]
Activity: Lipopolysaccharide
in BV-2 microglial cells
Synthesis: Not known



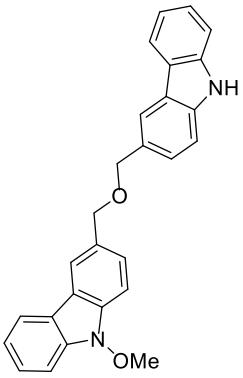
Murradines J (**57**)
(*Murraya tetramera*)[25]
Activity: Not known
Synthesis: Not known



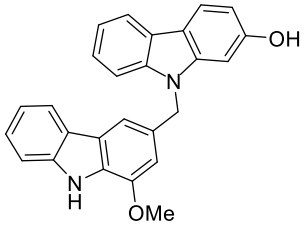
Murratrines A (**58**)
(*Murraya tetramera*)[25]
Activity: Not known
Synthesis: Not known



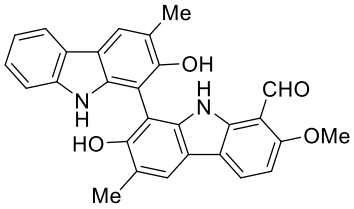
Murratrines B (**59**)
(*Murraya tetramera*)[25]
Activity: Not known
Synthesis: Not known



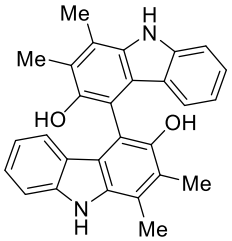
Murradines K (**60**)
(*Murraya tetramera*)[25]
Activity: Lipopolysaccharide
in BV-2 microglial cells
Synthesis: Not known



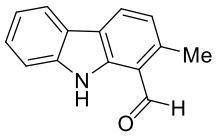
Murradines G (**61**)
(*Murraya tetramera*)[25]
Activity: Lipopolysaccharide
in BV-2 microglial cells
Synthesis: Not known



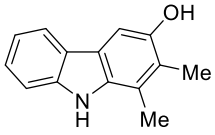
Murradines **I** (**62**)
(*Murraya tetramera*)[25]
Activity: Not known
Synthesis: Not known



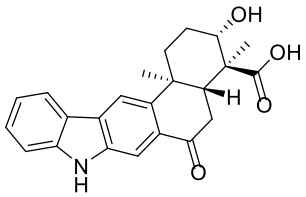
Sorazolon E2 (**63**)
(*Sorangium cellulosum*)[26]
Activity: Weak cytotoxic
Synthesis: Not known



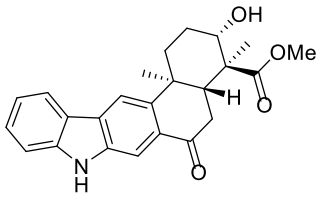
Sorazolon C (**64**)
(*Sorangium cellulosum*)[26]
Activity: Weak cytotoxic
Synthesis: Not known



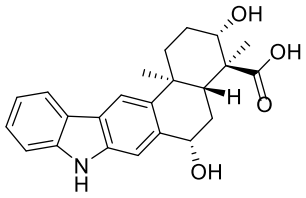
Sorazolon E (**65**)
(*Sorangium cellulosum*)[26]
Activity: Weak cytotoxic
Synthesis: Known



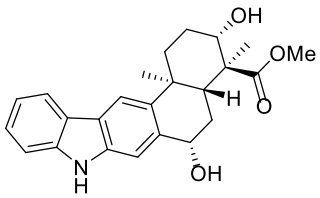
Xiamycins E (**66**)
(*Streptomyces*. sp)[27]
Activity: Weak cytotoxic
Synthesis: Not known



Xiamycins F (**67**)
(*Streptomyces*. sp)[27]
Activity: Weak cytotoxic
Synthesis: Not known



Xiamycins C (**68**)
(*Streptomyces*. sp)[27]
Activity: Weak cytotoxic
Synthesis: Not known



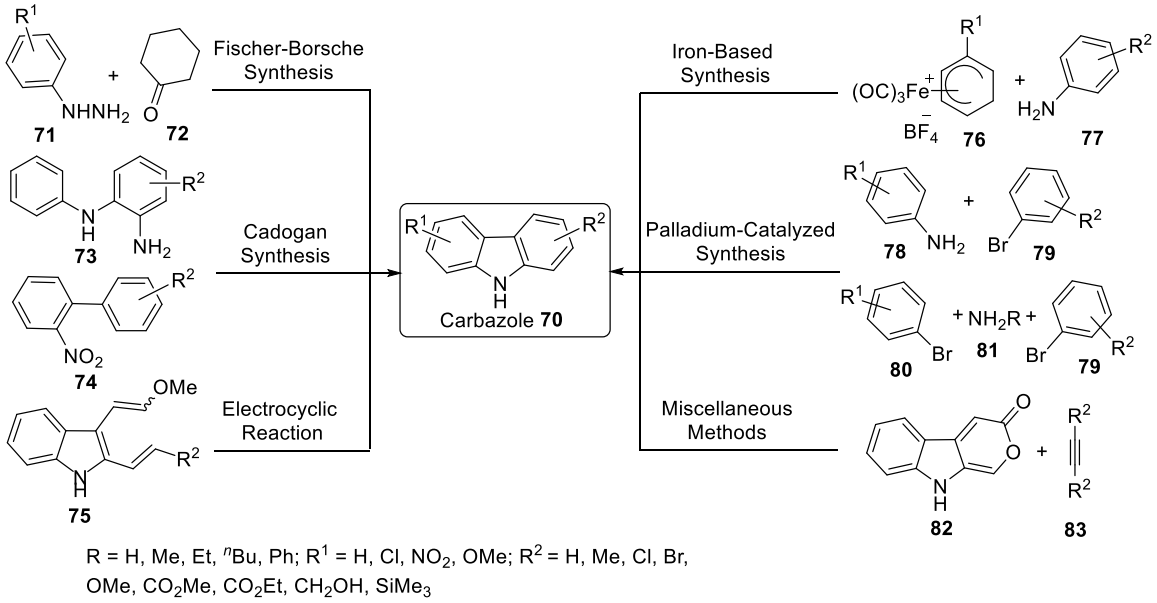
Xiamycins D (**69**)
(*Streptomyces*. sp)[27]
Activity: Weak cytotoxic
Synthesis: Not known

Figure 3. Carbazole Alkaloids Isolated from the Year 2012 Onwards.

1.4 Synthetic Methods Reported for Carbazole Constructions

A large number of classical and nonclassical methods have been developed for carbazole

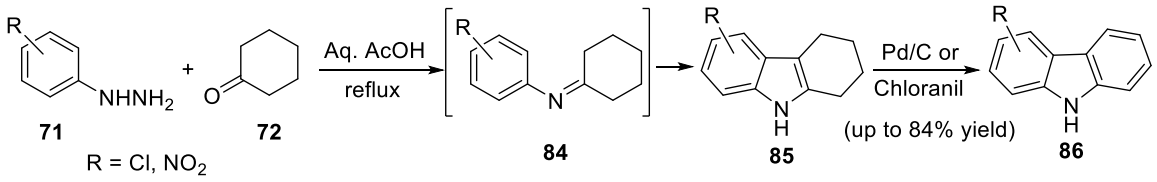
synthesis (Scheme 1).[14] Most simple way to constitute fully aromatized carbazoles is the construction of the central pyrrole ring by cyclization of either biphenyls with an *ortho*-nitrogen substituent or diarylamines.



Scheme 1. Schematic Representation of Carbazole Synthesis

The commonly used approach to carbazoles also involves dehydrogenation of a 1,2,3,4-tetrahydrocarbazole. Recently, a variety of synthetic procedures using mild reaction conditions have been developed and some of them are widely applicable. Most of these methods provide carbazoles in good to excellent yields and use starting materials that are either commercially available or can be easily prepared.

1.4.1 Fischer-Borsche Synthesis: Condensation of cyclohexanone (**72**) with phenylhydrazines **71** gives the arylhydrazones **84**. Fischer-Borsche cyclization of the arylhydrazones forms an indole moiety and thus leads to the 1,2,3,4-tetrahydrocarbazoles

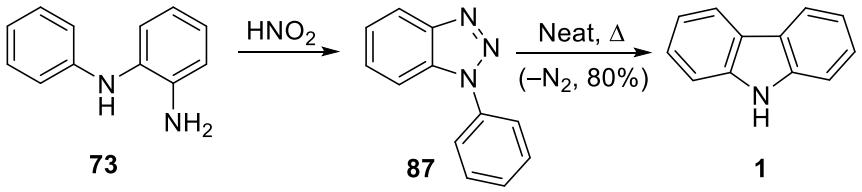


Scheme 2. Fischer-Borsche Synthesis via [3,3]-Sigmatropic Rearrangement

(Scheme 2).[28] This reaction involves protonation, formation of new C–C bond via a [3,3]-sigmatropic rearrangement and elimination of ammonia. Lastly, the tetrahydrocarbazoles **85** are easily aromatized to carbazoles **86** via dehydrogenation using palladium on activated carbon or chloranil.

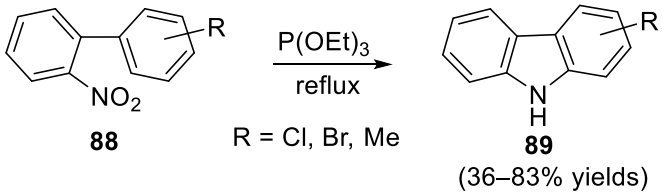
1.4.2 Graebe-Ullmann Synthesis: In 1896, Carl James Peter Graebe (1841–1927) and Fritz Ullmann (1875–1939) reported the transformation of 1-phenylbenzotriazole (**87**) to

carbazole (**1**) under thermal reaction condition and it is known as Graebe-Ullmann synthesis.[29] The 1-phenylbenzotriazole (**87**) was prepared by diazotization of *N*-(2-aminophenyl)aniline (**73**). Mechanistically, diradical intermediate is involved in the thermolysis of the triazole **87** (Scheme 3).



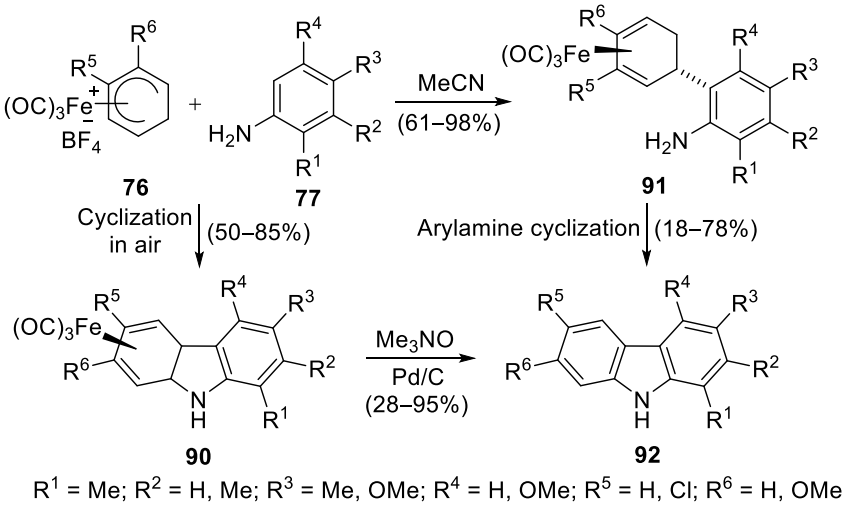
Scheme 3. Graebe-Ullmann Synthesis via Thermolysis

1.4.3 Cadogan Synthesis: The cyclization of *o*-nitrobiphenyls **88** to carbazoles **89** in triethylphosphite under the reflux conditions is known as Cadogan synthesis (Scheme 4).[30] Mechanistically, the exhaustive deoxygenation to a singlet nitrene takes place and finally that undergoes C–H insertion.



Scheme 4. Carbazoles Synthesis via Phosphite-Mediated Approach

1.4.4 Iron-Involved Carbazole Synthesis: The electrophilic aromatic substitution of ele-

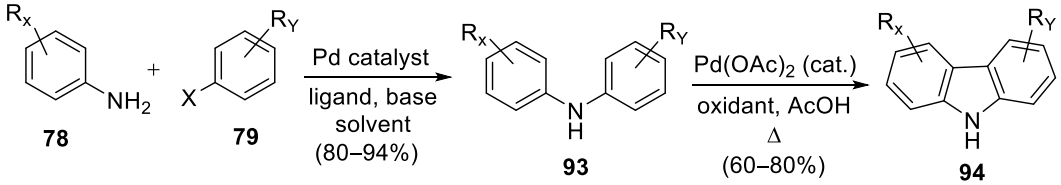


Scheme 5. Carbazoles Synthesis via Iron-Involved Approach

ctron-rich arylamines **77** with tricarbonyl iron-coordinated cyclohexadienylium ions **76** provide compounds **91** (Scheme 5).[31] The oxidative cyclization of the resulting arylamine-substituted tricarbonyl iron complexes **91** directly lead to carbazoles **92**. The overall process involves a generation of C–C and C–N bonds. Alternatively, reaction of

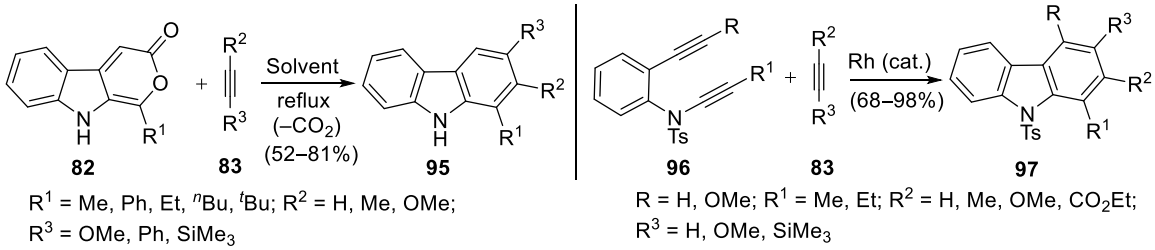
the tricarbonyl iron-coordinated cyclohexadienylium ions **76** with the arylamines **77** in the presence of air directly provide the tricarbonyl ironcoordinated 4a,9a-dihydrocarbazoles **90**. Demetalation of the complexes **90** to the corresponding free ligands and consequent aromatization provide carbazoles **92** (Scheme 5).[32]

1.4.5 Palladium-Catalyzed Carbazole Synthesis: The palladium-catalyzed Buchwald–Hartwig coupling of aryl halides, aryl triflates, aryl nonaflates and aryl tosylates with arylamines **78** provide diarylamines **93** in high yields.[33] The palladium(II) acetate catalyzed transformations of corresponding diphenyl amines **93** provide diversely substituted carbazole alkaloids **94**. Moreover these cyclizations were also catalyzed by acids such as trifluoroacetic acid or methanesulphonic acid (Scheme 6).[34]



Scheme 6. Palladium-Catalyzed Carbazoles Synthesis

1.4.6 Miscellaneous Methods: The indolo-2,3-quinodimethanes and their cyclic analogues have been of great interest because of their ability to undergo Diels–Alder reactions with a wide variety of dienophiles to give functionalized carbazoles (Scheme 7).



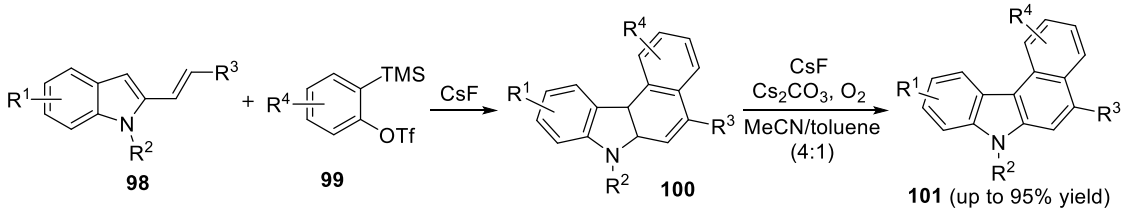
Scheme 7. Diels–Alder Approach to Carbazoles Synthesis

Diels–Alder reactions of diene indolo-2,3-quinodimethanes **82** with dienophiles **83** to afford bridged intermediates, which on exclusion of carbon dioxide give rise to the carbazoles **95**.[35a]

Witulski and Alayrac utilized the Vollhardt-type cyclotrimerization of diynes **96** and alkynes **83** in the presence of catalytic amount of Wilkinson's catalyst ($RhCl(PPh_3)_3$) for the synthesis of substituted carbazoles **97**.[35b]

1.5 Recently Reported Selected Methodologies towards the Synthesis of Carbazoles

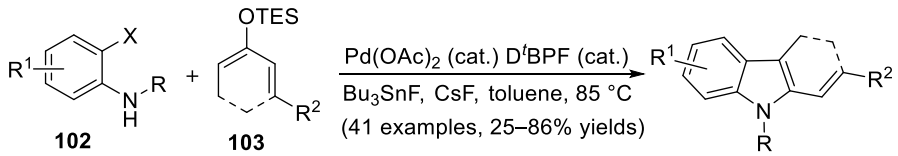
During the last few years remarkable progress on synthetic methodologies applicable to design carbazole alkaloids and related molecules has been reported in the literature. Some of the important methodologies for the synthesis of carbazole have been presented in this section by using some selected examples.



R^1 = H, 4-Me, 5-OMe, 5-Cl, 6-Cl, 7-Me; R^2 = CO_2Et, CO_2Me, Ph; R^3 = Me, Ph, Boc; R^4 = H, Me, F

Scheme 8. Synthesis of Carbazoles via Diels–Alder Reaction

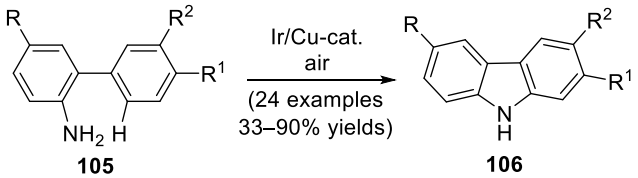
Wu and co-workers synthesized benzo[*c*]carbazoles and their antitumor derivatives by using the Diels–Alder reaction. Starting from 2-alkenylindoles **98** and arynes **99** the arylsubstituted 7,11b-dihydrobenzo[*c*]carbazoles **100** were obtained in good to excellent yields under inert atmosphere. On carrying out the same reaction under oxygen atmosphere, the corresponding in situ aromatized benzo[*c*]carbazoles **101** were directly obtained in one-pot with high selectivity and efficiency (Scheme 8).[36]



X = Cl, Br; R = H, Me, ^{i}Pr; R^1 = H, Me, NO_2, CF_3; R^2 = H, Me

Scheme 9. Palladium-Catalyzed Approach to Carbazoles

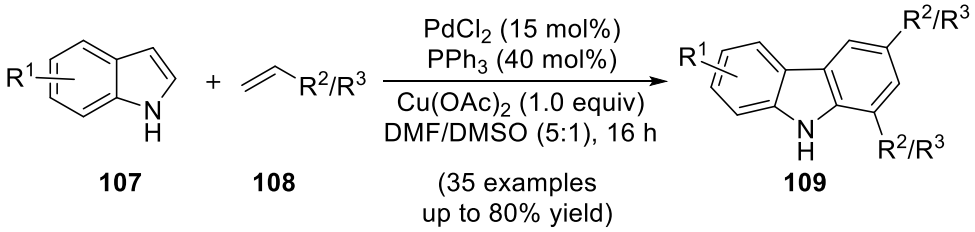
Kapur and co-workers developed a new unified palladium-catalyzed strategy for the synthesis of substituted 2-alkenylindoles and carbazoles **104**. The strategy is based on palladium-catalyzed *α*-arylation of TES-enol ethers **103** with *ortho*-haloanilines **102** as the key step. The utilized silylenol ethers of enones direct the regioselectivity and offer yet another approach towards oxidative-Heck reaction of indole derivatives. The method is highly regioselective, provides good yields and is expected to have wider applications (Scheme 9).[37]



R = H, Cl, Me, CF_3; R^1 = H, Me, OMe, F, Cl, Br, CF_3, COPh, Ph; R^2 = H, Me, F, OMe

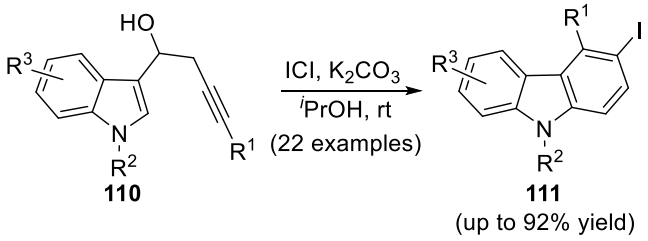
Scheme 10. Iridium-Catalyzed Approach to Carbazoles

Miura and co-workers developed iridium-catalyzed direct synthesis of *N*–H carbazoles via dehydrogenative cyclization of 2-aminobiphenyls **105**. The reaction proceeds smoothly in the presence of copper as a co-catalyst under atmospheric conditions and oxygen from air acts as a terminal oxidant for intramolecular direct C–H amination to produce *N*–H carbazoles **106**. Iridium/copper system can also catalyze the unprecedented dimerization reaction of 2-aminobiphenyl **105** involving two C−H/N−H couplings (Scheme 10).[38]



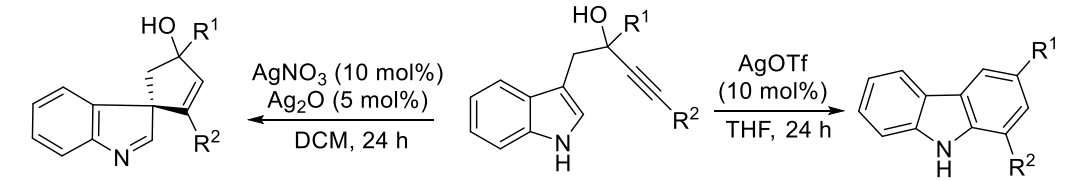
Scheme 11. Pd(II)-Catalyzed Approach to Carbazoles

Choudhary and co-workers developed a novel Pd(II)-catalyzed approach for the direct synthesis of diversely substituted carbazoles **109** from indoles **107** via regioselective triple successive oxidative Heck reaction. It has been demonstrated for the first time that both electron-deficient and electron-rich alkenes **108** can be used successively for the incorporation of two different functional groups into the product. A deuterium labelling experiment revealed that C−H activation is much faster than C−D activation (Scheme 11).[39]



Scheme 12. Tandem Iodocyclization Approach to Carbazoles

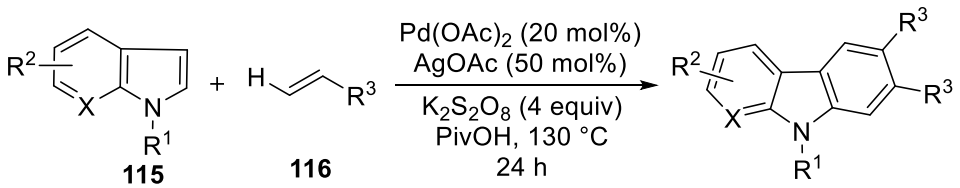
Liang and co-workers developed facile synthesis of carbazoles **111** via a tandem iodocyclization using iodine chloride with the 1,2-alkyl migration and aromatization of compound **110**. This method integrates the tandem iodocyclization, 1,2-shift on the indoles, aromatization and opens new avenue for future research. Moreover, the obtained products may serve as essential intermediates for the synthesis of natural products (Scheme 12).[40]



R^1 = H, Me, Ph; R^2 = H, C_4H_9, Ph, *p*-OMe-C_6H_4, *p*-F-C_6H_4

Scheme 13. Ag(I)-Catalyzed Approach to Carbazoles

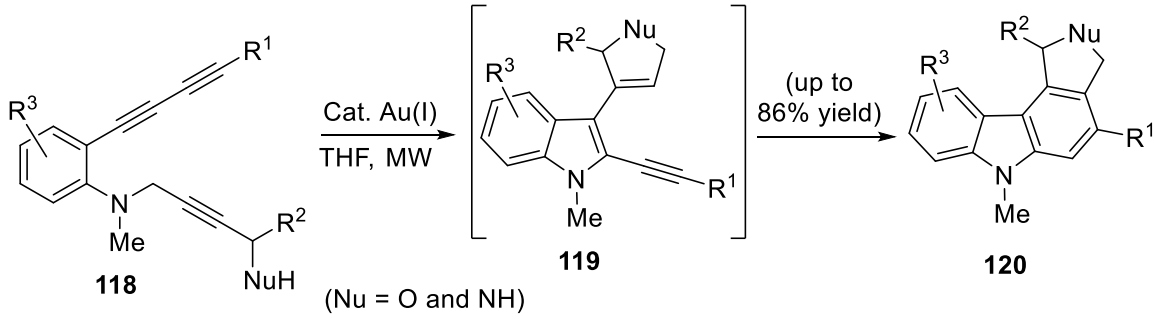
Unsworth and co-workers developed a divergent approach utilizing mild and operationally simple conditions to selectively form the spirocyclic indolenines **112** and carbazoles **114** from a common indole-tethered propargyl alcohol precursors **113**. Mechanistically indicating that the spirocyclization step involves Ag(I)-catalysis. Whereas the 1,2-migration step appears to proceed via a vinyl silver intermediate and can be promoted by Bronsted acid. Procedures typically provide high yields and have been shown to work on a range of functionalized alkyne tethered indoles (Scheme 13).[41]



R^1 = H, Ts, Ms, Bz, COEt; R^2 = H, F, Cl, OMe; R^3 = CO_2Me, Ph, *p*-Me-C_6H_4

Scheme 14. Pd(II)-Catalyzed One-Pot Approach to Carbazoles

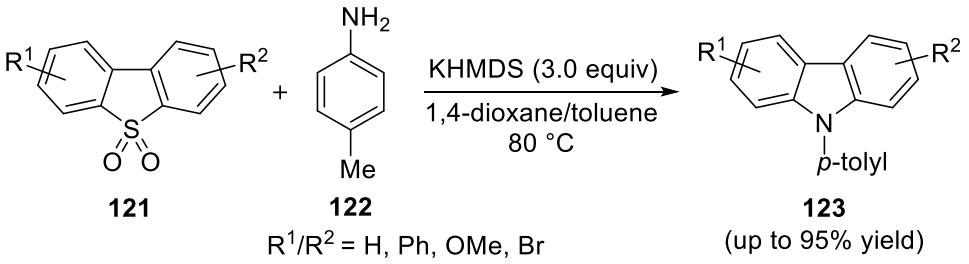
Dayal and co-workers developed a direct one-pot approach for the synthesis of mono-, di- and trisubstituted carbazoles **117** and α-carbolines via two successive regioselective oxidative heck reactions followed by thermal electrocyclization. Stoichiometric amount of a palladium catalyst together with an oxidant and readily available indoles **115** or 7-azaindoles and alkenes **116** provide functionalized carbazoles. Mechanistically, reaction proceeds through palladium-catalyzed regioselective C-3 alkenylation/palladium-catalyzed C-2 alkenylation/thermal electrocyclization (Scheme 14).[42]



R^1 = *n*-Hex, $(CH_2)_2$OBn, Ph; R^2 = Et, Ph, Bn; R^3 = H, Me, Cl; R^4 = H, OMe, Br

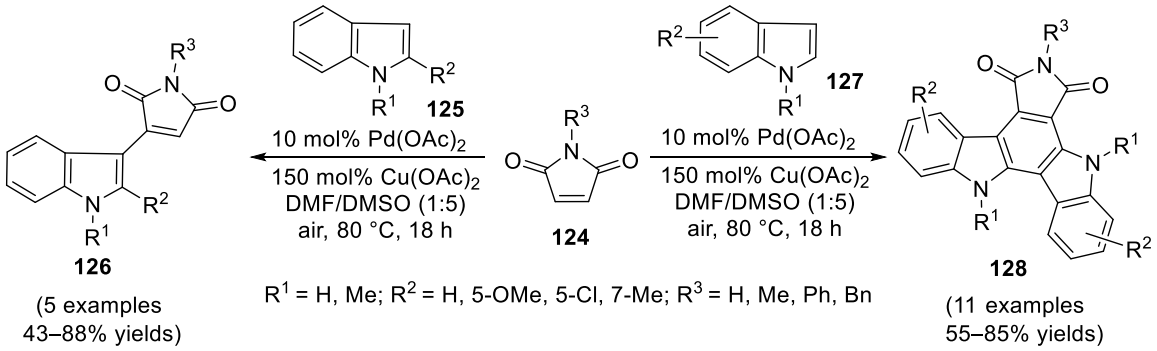
Scheme 15. Gold(I)-Catalyzed Cascade Reaction for the Synthesis of Carbazoles

Ohno and co-workers developed a one-pot fused carbazoles synthesis. Starting from various *N*-propargylanilines **118** bearing a conjugated diyne moiety at the 2-position were converted to tetracyclic fused carbazoles **120** by treatment with a homogeneous gold(I) catalyst. This cascade reaction proceeds through indole formation **119** with concomitant rearrangement of the *N*-propargyl group, intramolecular nucleophilic addition resulting in allene moiety and subsequent hydroalkenylation. This remarkable transformation proceeds with 100% atom economy (Scheme 15).[43]



Scheme 16. S_NAr-Based "Aromatic Metamorphosis" of Thiaarenes

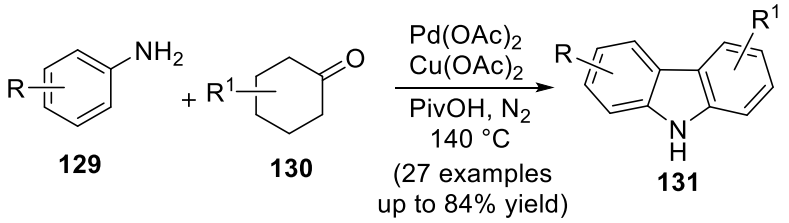
Osuka and co-workers developed a transition-metal-free synthesis of carbazoles and indoles by an S_NAr-based "aromatic metamorphosis" of thiaarenes. Dibenzothiophene dioxides **121** are readily prepared by oxidation of the parent dibenzothiophenes. Dibenzothiophene dioxide **121** derivatives undergo sequential inter/intramolecular nucleophilic aromatic substitution with aniline **122** in the presence of KHMDS to afford a wide range of carbazoles **123** in a single operation. The "aromatic metamorphosis" of dibenzothiophenes into carbazoles does not require any heavy metal. This strategy is also applicable for the synthesis of indoles. Since electron-deficient thiophene dioxide exhibit reactivity difference from that of the corresponding electron-rich azaarenes, specific use of a thiaarene-dioxide reaction for S_NAr carbazole synthesis opens up a new route to importance carbazoles (Scheme 16).[44]



Scheme 17. Pd(II)-Catalyzed Approach to Indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-diones

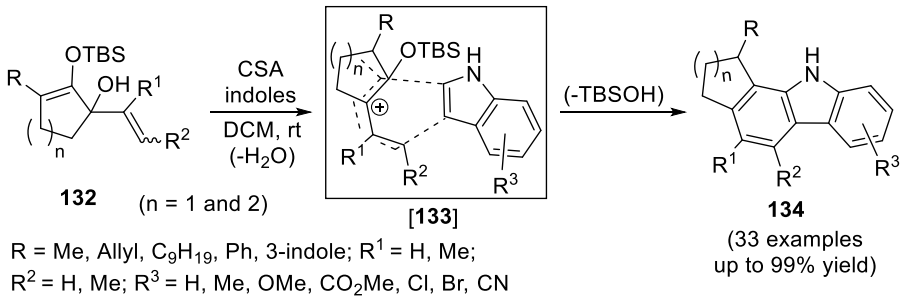
Zhao and co-workers developed an efficient Pd(II)-catalyzed approach for the direct synthesis of indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-diones **128** from both *N*-protected

and without *N*-protected indoles **127** and maleimides **124** via a regioselective tandem oxidative cross-coupling reaction. On the basis of the involved catalytic system carbazoles can be synthesized in moderate to excellent yields. The 2-substituted indoles **125** are suitable substrates for this protocol leading to the formation of indolylmaleimides **126** (Scheme 17).[45]



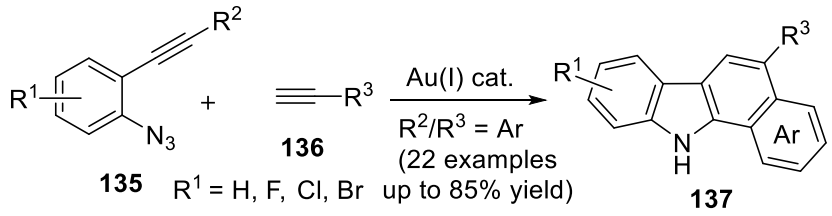
Scheme 18. Palladium-Catalyzed Domino Reaction for Synthesis of Carbazoles

Wang and co-workers developed a palladium-catalyzed domino reaction for the synthesis of carbazoles **131** in absence of ligand, which was demonstrated with good functional group tolerance. The reaction proceeds via a dehydrogenative aromatization and a dual C(sp2)−H functionalization process in the one-pot synthesis of carbazoles. On the basis of the catalytic system, carbazoles can be synthesized in moderate to good yields from arylamines **129** and cyclic ketones **130** (Scheme 18).[46]



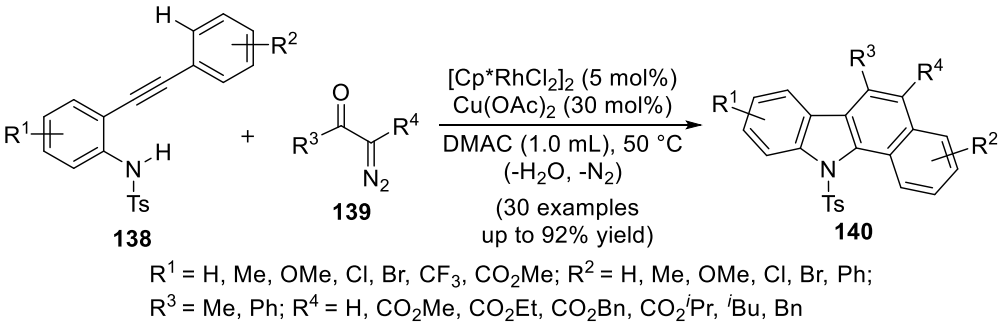
Scheme 19. Bronsted Acid Catalyzed Synthesis of Carbazoles

Kartika and co-workers developed a new strategy towards the synthesis of highly functionalized carbazoles **134** via 2-(silyloxy)pentadienyl cation intermediates **133**, which were generated upon ionization of vinylsubstituted *α*-hydroxy silyl enol ethers **132** under Bronsted acid catalysis. These electrophilic species readily undergo cascade reactions with substituted indoles to generate carbazole molecular scaffolds in good yields. The reaction proceeds via a sequence of regioselective nucleophilic additions, followed by intramolecular dehydrative cyclization (Scheme 19).[47]



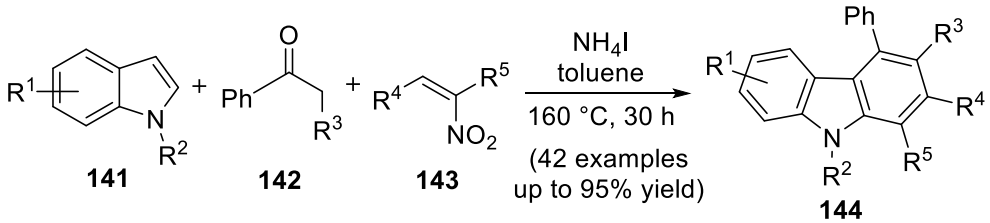
Scheme 20. Gold-Catalyzed Synthesis of Aryl-Annulated Carbazoles

Gong and co-workers have established an unprecedented gold catalyzed synthetic protocol for the direct assembly of aryl annulated carbazoles **137** from 2-alkynyl arylazides **135** and alkynes **136** (Scheme 20).[48] The gold-catalyzed reaction proceeds via a sequential cyclopropenation and intramolecular metal carbene/arene Friedel-Crafts type reaction respectively; mediated by two different gold carbene intermediates.



Scheme 21. Rh(III)-Catalyzed Cascade Annulation to Benzo[*a*]carbazoles

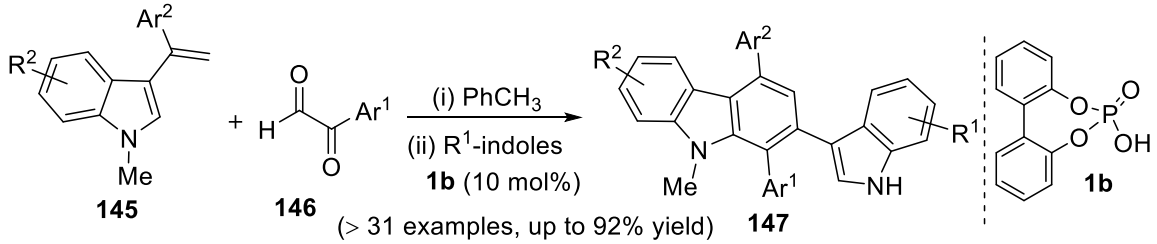
Yao and co-workers developed a Rh(III)-catalyzed cascade annulation/C–H activation of *o*-ethynylanilines **138** with diazo compounds **139**. This concise method allows rapid formation of a number of benzo[*a*]carbazoles **140** in high yields tolerating several functional groups with scalability. The reaction proceeds via a catalytic cycle through intramolecular nucleophilic addition of *o*-ethynylanilines and aryl-to-aryl 1,4-rhodium migration. In this synthesis generation of one C–N and two C–C bonds was achieved in one-pot operation (Scheme 21).[49]



Scheme 22. Carbazole Synthesis Using [2 + 2 + 2] Cycloaddition Reaction

Deng and co-workers developed an efficient indole-to-carbazole transformation strategy specifically under the metal-free conditions. This carbazole formation was highly

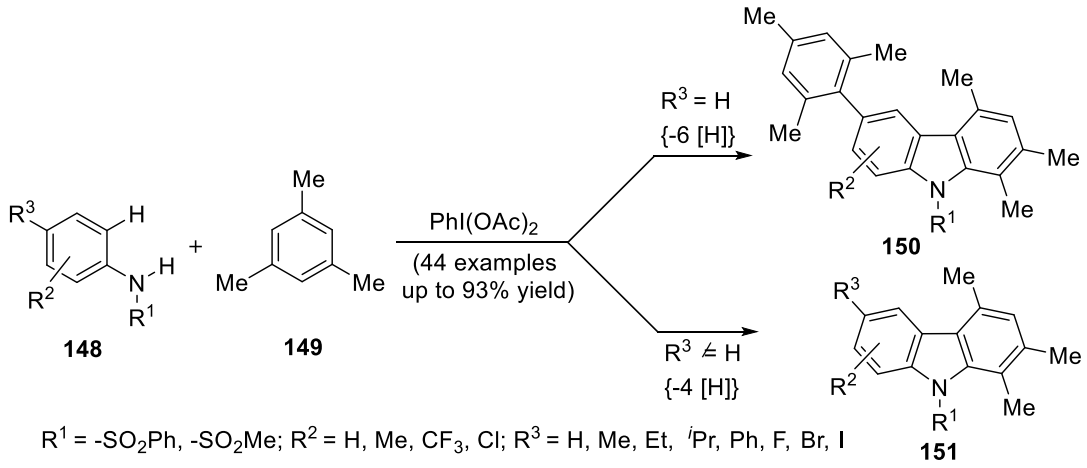
indorsed by NH_4I with high regioselectivity and it thus suitably enabled the assembly of a large number of diversified carbazoles **144**. The reaction proceeds via formal [2 + 2 + 2] annulation of indoles **141**, ketones **142** and nitro olefins **143**. Mechanistic studies indicate a condensation/nucleophilic-annulation/aromatization cascade, in which 3-vinylindole is involved as the key intermediate (Scheme 22).[50]



R^1 = H, 5-Me, 5-OMe, 5-Cl, 5-Br, 5-I, 6-F, 7-Me; R^2 = H, 5-Me, 5-Br, 6-Me;
Ar^1 = Ph, *p*-F-C_6H_4, *p*-Br-C_6H_4, *p*-CF_3-C_6H_4, *o*,*p*-F_2-C_6H_3;
Ar^2 = Ph, *o*-Me-C_6H_4, *o*-Br-C_6H_4, *m*-MeO-C_6H_4, *p*-Br-C_6H_4, *p*-Cl-C_6H_4

Scheme 23. Bronsted Acid Catalyzed Carbazoles Synthesis

Guo and co-workers developed a simple Bronsted acid catalyzed tandem reaction for the synthesis of polysubstituted carbazoles **147** from 3-vinyl indoles **145**. It involved intermolecular nucleophilic addition, substitution and intramolecular cyclization in one-pot. The simple phosphoric acid **1b** derived from 2,2′-biphenol promoted this tandem reaction and provided the polysubstituted carbazoles **147** in good to excellent yields. Applying this methodology the poly 1,4-carbazole has been prepared bearing good thermo stability with specific optical properties (Scheme 23).[51]

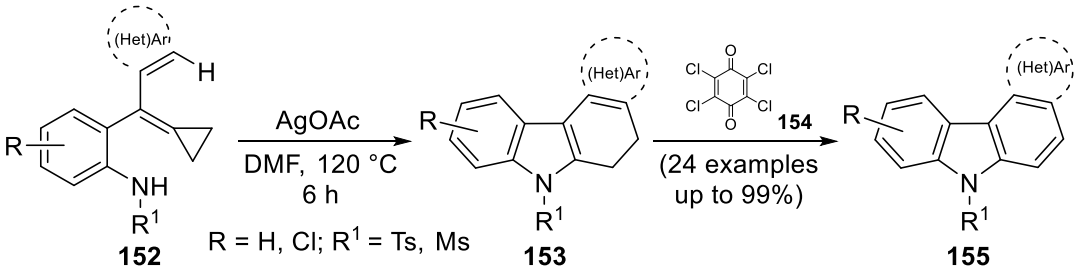


R^1 = -SO_2Ph, -SO_2Me; R^2 = H, Me, CF_3, Cl; R^3 = H, Me, Et, ^{i}Pr, Ph, F, Br, I

Scheme 24. Dehydrogenative Annulation (IDA) Approach to Carbazoles

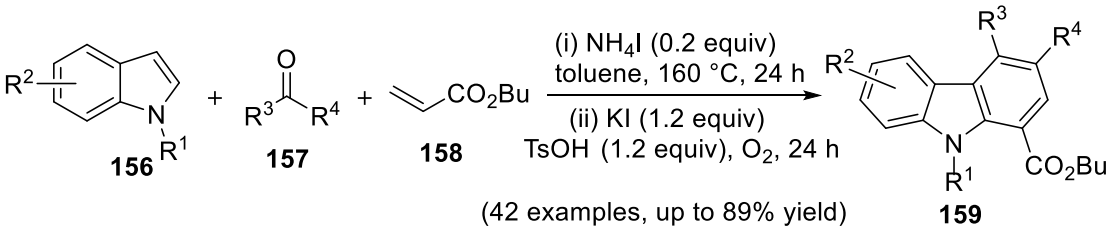
Mal and co-workers developed an intermolecular dehydrogenative annulation (IDA) for synthesis of carbazoles **150** and **151** via sequential C−C/C−N bond formations with a noteworthy selective alkyl group migration. The use of hypervalent iodine(III) reagent $PhI(OAc)_2$ (PIDA) induced one-pot generation of five C(sp2)−H bonds, one N(sp3)−H

bond functionalization and methyl group migration to yield compounds **150**/**151** from non-prefunctionalized 1,3,5-trialkylbenzene **149** and anilides **148** under ambient laboratory conditions. The cascade dehydrogenative C–C and C–N bonds formation was demonstrated under aerobic and metal-free reaction conditions to yield multisubstituted polycyclic heteroaromatic carbazole compounds (Scheme 24).[52]



Scheme 25. Silver Catalyzed Annulation Leading to Carbazoles

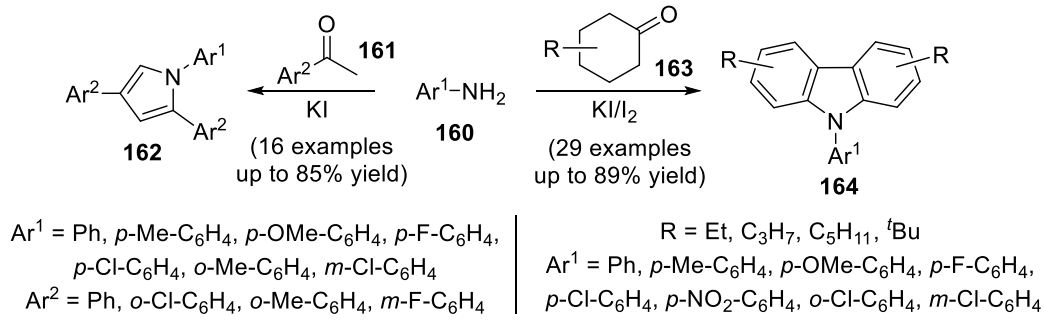
Shi and co-workers developed an intramolecular cascade reaction of functionalized alkylidenecyclopropanes leading to carbazoles. This reaction involves sequential amination/cyclization/aromatization of functionalized alkylidenecyclopropanes **152**, in the presence of silver acetate catalyst affording a variety of [2,3-*c*]dihydrocarbazoles **153** and [2,3-*c*]carbazoles **155** in moderate to excellent yields. Mechanistically, the reaction takes place via a radical process and the key intermediate in this reaction was captured by a radical trapping reagent TEMPO. The total synthesis of natural product eustifoline D proved the potential synthetic utility of this method (Scheme 25).[53]



R^1 = Me, Et, Ph; R^2 = Me, Cl, F; R^3 = Me, Ph, Et;
R^4 = *p*-Me-C_6H_4, *p*-F-C_6H_4, *p*-Br-C_6H_4, *p*-CN-C_6H_4, *p*-Ph-C_6H_4, *p*-NO_2-C_6H_4, *p*-OMe-C_6H_4

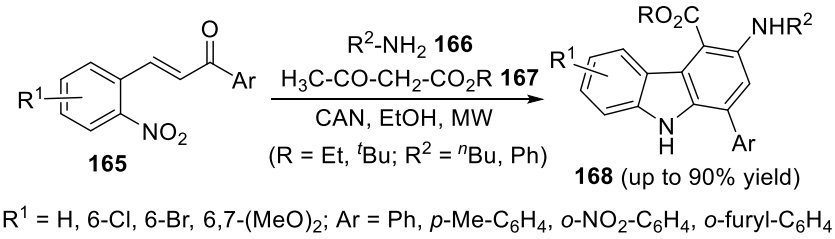
Scheme 26. Transition-Metal-Free Synthesis of Carbazoles

Deng and co-workers developed an efficient one-pot two-step indole-to-carbazole synthesis strategy (Scheme 26).[54] They have developed the transition metal-free methodology using oxygen as an oxidant and synthesis starts from cheap and readily available indoles **156**, ketones **157** and alkene **158** resulting in moderate to good yields of target compounds. This indole-to-carbazole procedure involves a cascade of condensation, [4 + 2] annulation and dehydrogenative aromatization to yield the target carbazoles **159**.



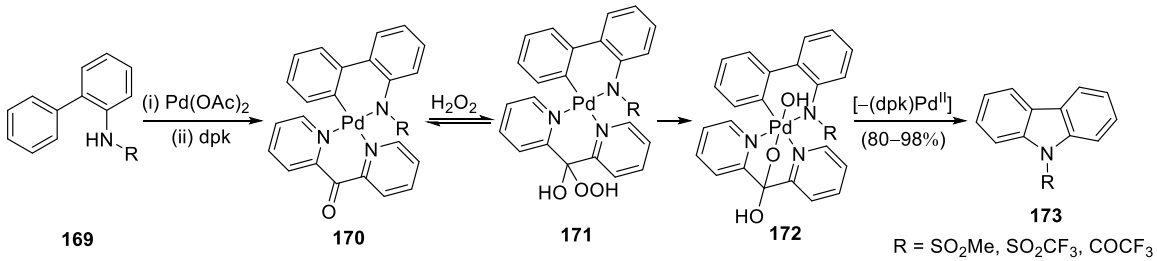
Scheme 27. Transition-Metal-Free Synthesis of Carbazoles and Triarylpyrroles

Deng and co-workers developed an efficient approach for carbazoles **164** and 1,2,4-triarylpyrroles **162** synthesis, starting from anilines **160** and cyclohexanones **163** or acetophenones **161** under transition-metal-free conditions. A variety of disubstituted 9-arylcarbazoles were synthesized in moderate to good yields. The reaction is promoted by KI/I_2 using anilines as the nitrogen and aryl source (Scheme 27).[55]



Scheme 28. CAN-Catalyzed Multicomponent Approach to Carbazoles

Menendez and co-workers developed CAN-catalyzed multicomponent process to yield carbazoles. This comprises of *ortho*-nitrochalcones **165**, primary amines **166** and *β*-dicarbonyl compounds **167** for the general access to carbazoles **168**. This reaction involves the generation of two rings, two C−C and two C−N bonds and proceeds in high atom economy with elimination of water as the only side product (Scheme 28).[56]



Scheme 29. Di-2-pyridyl Ketone (dpk)-Supported Amidoarylpallada(II)cycles to Carbazoles

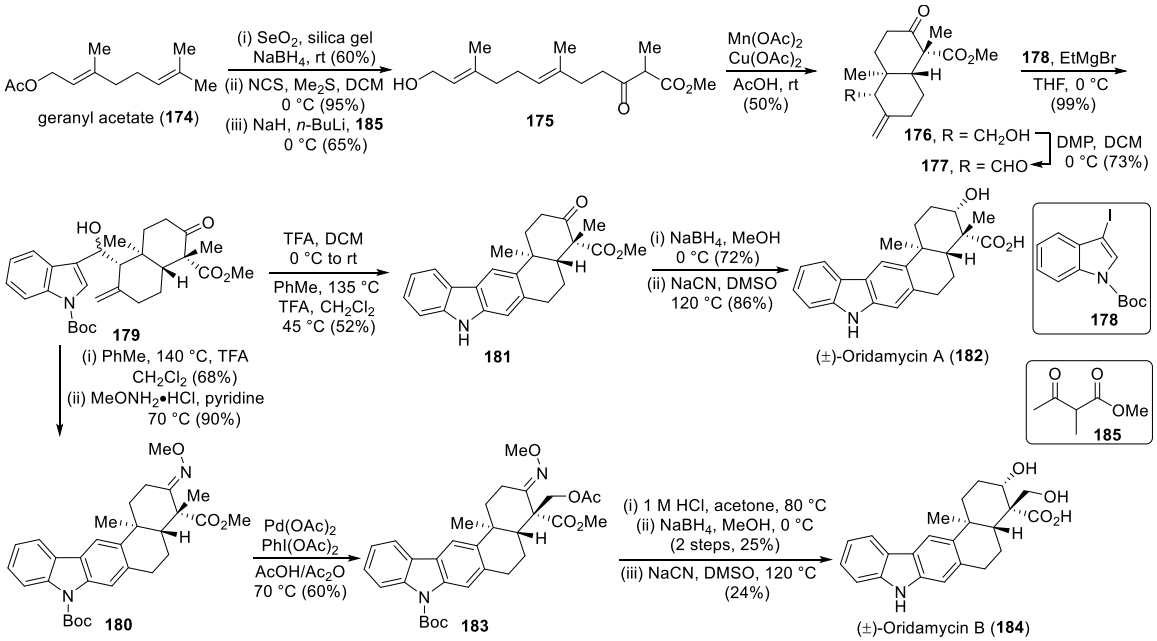
Vedernikov and co-workers developed a di-2-pyridyl ketone (dpk)-supported amidoarylpallada(II)cycles to deliver carbazoles. Starting from the 2-(*N*-R-amino)biphenyls **169** react with hydrogen peroxide in MeOH, THF, MeCN or AcOH to form the corresponding C–N coupled products, *N*–R-substituted carbazoles **173**. The reaction intermediates amidoaryl Pd(IV) complexes **170**–**172** were isolated and

characterized by single crystal X-ray diffraction and/or NMR spectroscopy. The C(sp2)–N reductive elimination from isolated amidoaryl Pd(IV) complexes has been demonstrated for the first time. These results will be useful for the development of new useful protocols for catalytic oxidative C–H amination (Scheme 29).[57]

1.6 Total Synthesis of Carbazole Alkaloids

A large number of total syntheses of imperative carbazole alkaloids have been known in the earlier and contemporary literature. In this section we have summarized few recently reported total synthesis of structurally interesting and biological importance carbazole.

Oridamycin A and Oridamycin B Synthesis: The oridamycin A (**182**) and oridamycin B (**184**) were isolated from *Streptomyces* sp. These pentacyclic molecules possess a carbazole nucleus fused to a *trans*-decalin ring system containing four contiguous stereocenters, including two quaternary centers. Adam H. Trotta reported total synthesis of both oridamycin A (**182**) and oridamycin B (**184**) starting from a common synthetic intermediate **175**, which was readily prepared from geranyl acetate (**174**) (Scheme 30).[58] Oxidative radical cyclization of multifunctional compound **175** proceeded smoothly under the standard reaction conditions to furnish the alcohol **176** as a single diastereomer. The reaction sequence utilizes an oxidative radical cyclization to construct the *trans*-decalin ring system, setting three of four contiguous stereocenters in one operation. Subsequent oxidation with Dess–Martin periodinane provided aldehyde, which was coupled with the

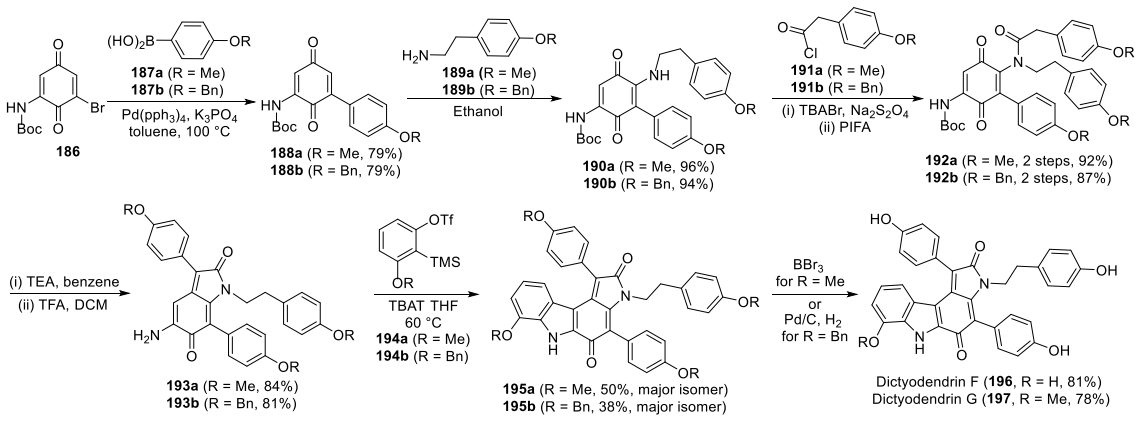


Scheme 30. Total Synthesis of Oridamycin A and Oridamycin B

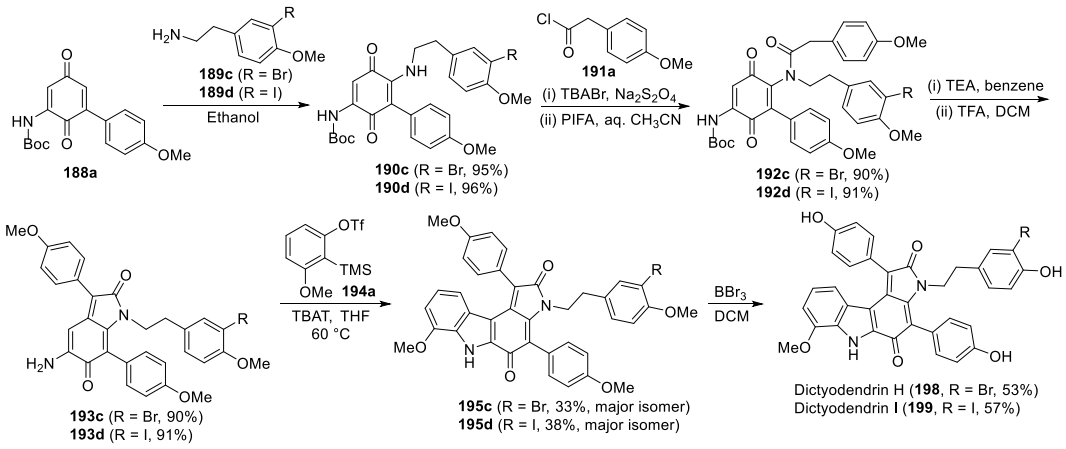
Grignard reagent generated from iodoindole **178** to produce **179** as a mixture of diastereomers. The dehydration of intermediate **179** with TFA formed a triene

intermediate without the deprotection of Boc-group and delivered compound **180**. Alternatively, treatment of **179** with TFA in DCM formed triene intermediate, which was dissolved in toluene and heated to 135 °C to induce a thermal *6π*-electrocyclization/aromatization sequence under aerobic conditions. Finally, TFA induced removal of Boc-group gave free carbazole **181**. Stereoselective reduction of **181** using $NaBH_4$ yielded oridamycin A methyl ester (*dr* > 20:1) and treatment of formed ester with NaCN provided the desired oridamycin A (**182**) in 62% yield over two steps. The same sequence of dehydration and electrocyclization was employed on **179** but the Boc group was preserved to produce the protected carbazole. The ketone was smoothly converted into *O*-methyloxime derivative **180** (62%, 2 steps). Oxidation of *O*-methyloxime **180** with $PhI(OAc)_2$ and catalytic $Pd(OAc)_2$ at elevated temperature resulted **183** in 60% yield. Deprotection using 3:1 mixture of 1.0 M HCl/acetone at 80 °C cleaved the acetate, also deprotected the Boc-group and hydrolyzed the *O*-methyloxime to ketone. The reduction of the crude ketone produced oridamycin B methyl ester and finally it was treated with NaCN in DMSO to give the oridamycin B (**184**).

Synthesis of Dictyodendrin F–I: Dictyodendrins isolated in 2003 were the first marine natural products with good telomerase inhibitory activity (100% inhibition at 50 μg/mL concentration). Dictyodendrins F−J exhibit important inhibitory activity against *β*-site amyloid-cleaving enzyme 1 (BACE1), a potential target for the treatment of Alzheeimer's disease. Guo and co-workers developed an unified modular synthetic strategy for the first total synthesis of dictyodendrin G and synthesis of dictyodendrins F, H and I. The synthesis features consecutive functionalization of the core aminoquinone by palladium-mediated Suzuki-Miyaura coupling reaction, 1,4-addition, acylation and base mediated formation of a pyrrolinone and the regioselective formation of carbazolequinone moiety through a formal [3 + 2] cycloaddition using arynes. Starting from palladium catalysed



Scheme 31. Total Synthesis of Dictyodendrin F and Dictyodendrin G

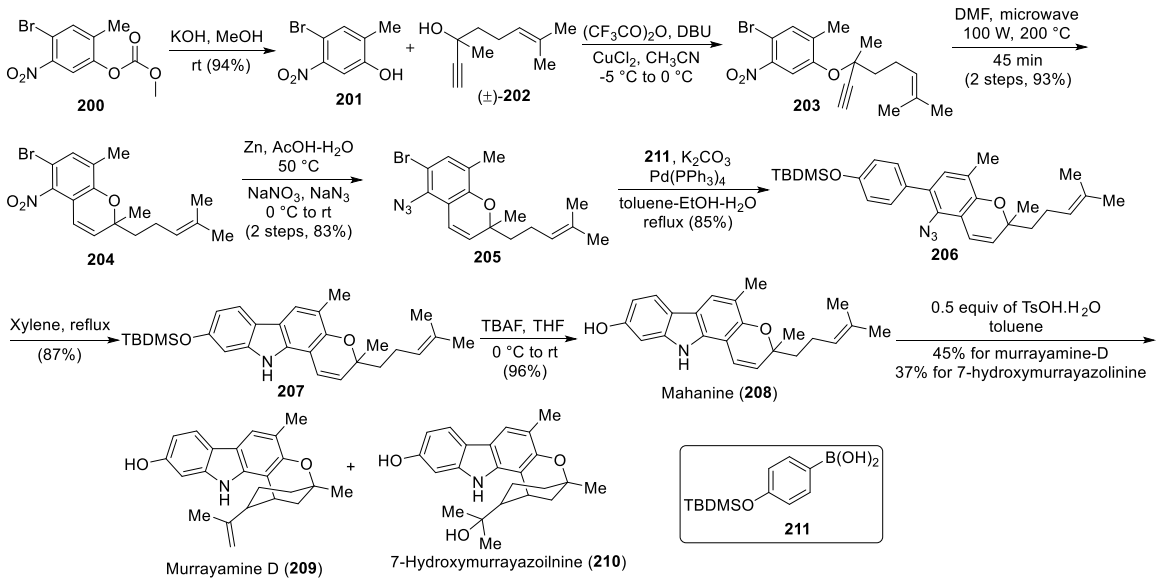


Scheme 32. Total Synthesis of Dictyodendrin H and Dictyodendrin I

Suzuki–Miyaura cross coupling of brominated aminoquinone **186** with 4-methoxyphenylboronic acid (**187a**) gave the initially functionalized aminoquinone **188a** in 79% yield. Treatment of aminoquinone **188a** with 4-methoxy phenethylamine (**189a**) in ethanol at room temperature directly furnished the desired aminoquinone **190a** in 96% yield. The regioselectivity of this 1,4-addition presumably resulted from both the electrostatic and steric-hindrance effects. Reduction of aminoquinone **190a** using sodium dithionate and acylation with acyl chloride **191a** followed by oxidation with PIFA resulted into compound **192a** in 92% yield over three steps. The compound **192a** was subjected to cyclization using triethylamine in refluxing benzene and subsequent deprotection of Boc-group provided pyrrolinone **193a** in 84% yield. The required key intermediate **193a** and aryne precursor **194a** provided desired product **195a** in good yield. The formal [3 + 2] cycloaddition catalyzed by tetrabutylammonium difluorotriphenylsilicate (TBAT) was used to construct the carbazolequinone moiety **195a** in 50% yield and complete the synthesis of pyrrolo[2,3-*c*] carbazole core of dictyodendrins. Finally, deprotection of all methyl groups in **195a** with BBr_3 afforded dictyodendrin F (**196**) in moderate yield. To complete the first total synthesis of dictyodendrin G (**197**) which contains a 10-*O*-Me group, first all methoxyl groups were replaced with benzyl groups so that they can be selectively removed in final stage of the synthesis (Scheme 31). Following the same reaction sequence and conditions as described in synthesis of dictyodendrin F (**196**), tribenzyl compound **195b** was synthesized in good overall yield. Finally, selective hydrogenation of **195b** with Pd/C under hydrogen atmosphere yielded dictyodendrin G (**197**) in 78% yield. This synthetic route was similarly extended to prepare dictyodendrins H (**198**) and I (**199**). Dictyodendrins H and I share the same core skeleton bearing an *O*-methyl tyramine side chain along with a bromo

and iodo groups respectively. Since the *O*-methyl tyramine side was introduced in the second-round of functionalization, initially functionalized aminoquinone **188a** was treated with bromo- or iodo-*O*-methyl tyramines **189c** and **189d** instead of **189a** to provide aminoquinones **190c** and **190d** in excellent yields (Scheme 32).[59] Following the same reaction sequence as for synthesis of dictyodendrins F and G, the target compound dictyodendrins H (**198**) and I (**199**) were obtained in good overall yields (8% and 10%) over 11 steps.

Synthesis of Mahanine, Murrayamine D and 7-Hydroxymurrayazolinine: Mahanine was isolated by Narasimhan et al. from the leaves of *Murraya koenigii* in 1970 and it exhibited the anticancer activities, while murrayamine D and 7-hydroxymurrayazolinine were isolated in 1995 and 2011 respectively. Brown and co-workers developed facile total synthesis of the natural products (±)-mahanine (**208**), murrayamine D (**209**) and 7-hydroxymurrayazolinine (**210**) through a nitro group activated pyran annulation via Claisen rearrangement (Scheme 33).[60] The compound 4-bromo-2-methyl-5-nitrophenyl methyl carbonate (**200**) was treated with KOH in methanol at room temperate to provide free phenol **201** in 94% yield. Coupling of phenol **201** with the propargyl alcohol **202** using a copper(II) catalyst and trifluoroacetate in the presence of DBU yielded **203**. Without further purification, the subsequent thermal cyclization was carried out by using

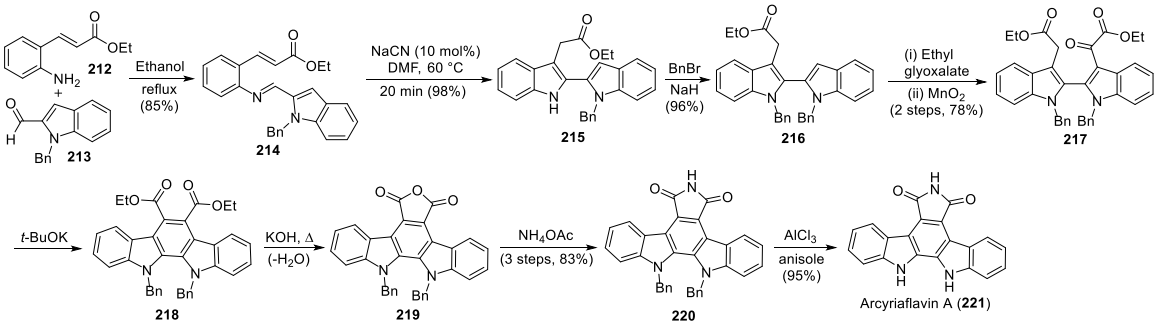


Scheme 33. Total Synthesis of Mahanine and Murrayamine D

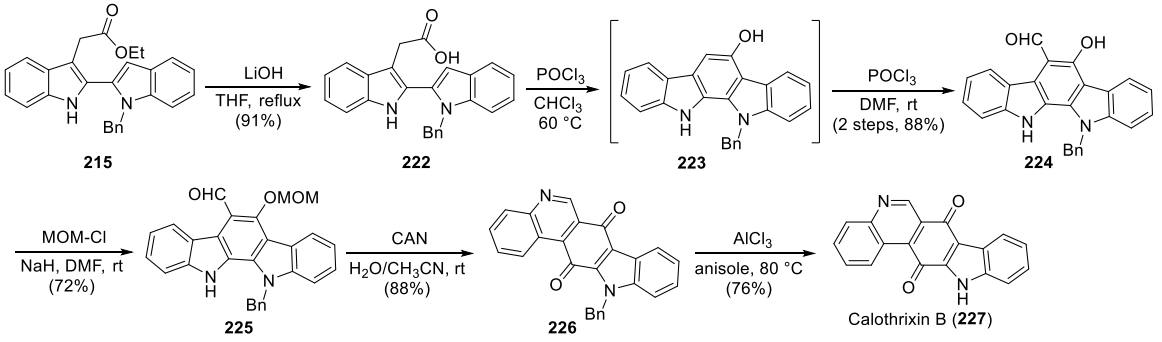
the obtained product **203** resulting in the target 2*H*-chromene **204** in 93% yield over two steps. The compound **204** was transferred to the azide diaryl **205** by reduction, diazotization and azide displacement in a continuous sequence without any intermediate isolation with 83% yield over two steps. The phenyl boronic acid **211** was used to carry

out the Suzuki coupling reaction. The biaryl adduct **206** was obtained in high yield and cyclized by a reductive Cadogan reaction to afford silyl protected mahanine **207** in 87% yield. Finally, deprotection of silyl group furnished the target molecule mahanine (**208**) in 96% yield. The acid-catalyzed cyclization of mahanine directly transformed to murrayamine D (**209**) and 7-hydroxymurrayazolinine (**210**) in the presence of a stoichiometric amount of water.

Synthesis of Arcyriaflavin A: Cheon and co-workers developed a new protocol for the total synthesis of arcyriaflavin A and calothrixin B via a cyanide-catalyzed imino-Stetter reaction (Schemes 34 and 35). The aldimine **214** was obtained from ethyl 2-aminocinnamate (**212**) and *N*-benzylindole-2-carboxaldehyde (**213**) (Scheme 34). The aldimine **214** was subjected to the imino-Stetter reaction with 10 mol% of cyanide and the desired 2,2′-bisindole product **215** was obtained in excellent yield. *N*,*N*′-Dibenzylated 2,2′-bisindole product **216** was prepared in 96% yield by the treatment of 2,2′-bisindole **215** with benzyl bromide in the presence of K_2CO_3. Friedel-Crafts reaction of **216** with



Scheme 34. Total Synthesis of Arcyriaflavin A



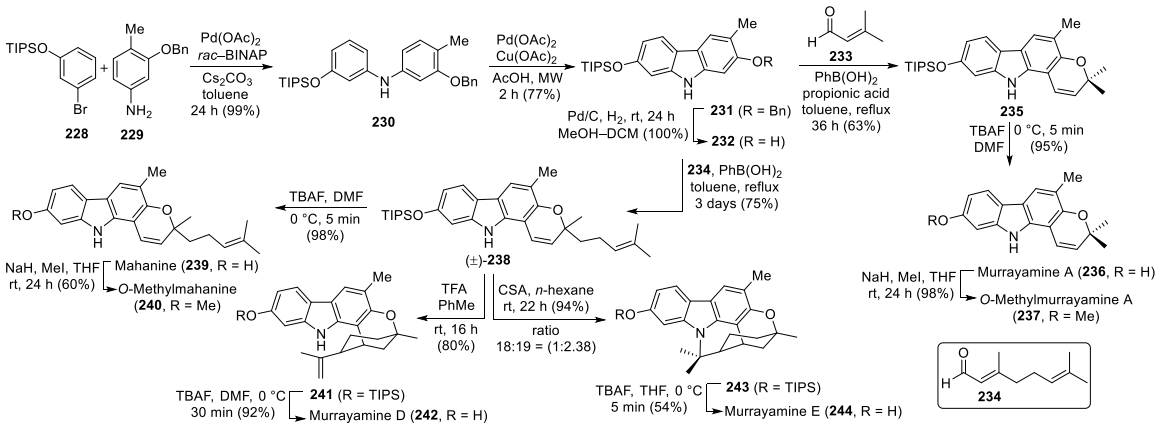
Scheme 35. Total Synthesis of Calothrixin B

ethyl glyoxylate in DCM followed by oxidation with MnO_2 yielded *N*,*N*′-dibenzylated 2,2′-bisindole product **217** in 78% yield over two steps. Treatment of **217** with *t*-BuOK provided indolocarbazole compound **218**. The compound **218** was directly subjected to hydrolysis under basic conditions to produce the corresponding anhydride **219** via thermal dehydration. Without any further purification, the anhydride **219** was treated with

ammonium acetate at 140 °C to furnish *N*,*N*′-dibenzyl-protected arcyriaflavin A **220** in 83% yield over three steps. Finally, deprotection of the benzyl groups with $AlCl_3$ in the presence of anisole provided arcyriaflavin A (**221**) in 95% yield.

Synthesis of Calothrixin B: The ester moiety in **215** was hydrolyzed in presence of aqueous LiOH solution to the corresponding carboxylic acid **222** in 91% yield (Scheme 35). Subsequent treatment of **222** with phosphorusoxychloride provided 5-hydroxyindolecarbazole **223**. The formed **223** was unstable and decomposed during the aqueous workup. Hence without the aqueous workup, indolocarbazole **223** was directly subjected to the Vilsmeier–Haack reaction condition to provide aldehyde **224**. The hydroxyl group was selectively protected with methoxymethyl chloride (MOM-Cl). The MOM-protected compound **225** was treated with CAN to afford *N*-benzylprotected calothrixin B **226** in 88% yield. Subsequent deprotection of the benzyl group with $AlCl_3$ in the presence of anisole provided the desired calothrixin B (**227**) in 76% yield.[61] Overall, the total synthesis of calithroxin B was completed from readily available starting materials in 34% overall yield in six steps.

Total Synthesis of Pyran Containing Carbazole Alkaloids: Knölker and co-workers described efficient synthetic routes to murrayamine A (mukoenine C), *O*-methylmurrayamine A, mahanine, *O*-methylmahanine and murrayamine D and also completed the first total synthesis of murrayamine E. Key steps were palladium-catalyzed construction of the carbazole framework and an annulation of pyran ring, which was eith-



Scheme 36. Total Synthesis of Pyanocarbazole Alkaloids

er catalyzed by phenylboronic acid or promoted by a Lewis acid (Scheme 36).[62] Buchwald–Hartwig amination of the silyl-protected bromophenol **228** with the aniline **229** using catalytic amount of palladium(II) acetate and racemic 2,2′-bis(diphenylphosphino)-1,1′-bi-naphthyl (*rac*-BINAP) provided the diarylamine **230** in quantitative yield. Microwave heating of **230** in the presence of catalytic amounts of

palladium(II) acetate and copper(II) acetate as re-oxidant neatly directed to the protected carbazole **231**. The desired precursor **232** was finally obtained by hydrogenolytic cleavage of the benzyl ether. Treatment of hydroxycarbazole **232** with prenal (**233**), propionic acid and catalytic amounts of phenylboronic acid in toluene at reflux provided the pyrano[3,2-*a*]carbazole **235**. Subsequent cleavage of the silyl group with TBAF transformed **235** into murrayamine A (**236**). *O*-Methylmurrayamine A (**237**) was obtained by methylation of resultant murrayamine A (**236**) under NaH/MeI condition. Following the same procedure the synthesis of mahanine (**239**) and *O*-methylmahanine (**240**) has been completed. Phenylboronic acid-catalyzed reaction of the 2-hydroxycarbazole **232** and citral (**234**) in toluene provided the silyl protected mahanine **238** in 75% yield. Cleavage of the silyl ether provided mahanine (**239**) in 98% yield. *O*-methylmahanine (**240**) was obtained by methylation to resultant mahanine (**239**) in presence of NaH/MeI. Treatment of **238** with 0.5 equiv of trifluoroacetic acid (TFA) in toluene yielded the TIPS-protected murrayamine D **241** in 80% yield. Cleavage of the silyl ether in presence of TBAF provided murrayamine D (**242**). Cyclization of compound **238** in the presence of 5 mol% camphorsulfonic acid (CSA) in *n*-hexane afforded a mixture of **241** and the silyl-protected murrayamine E **243** in a ratio of 1:2.38 (94% yield). Precipitation of **243** from the solvent prevents further proton-catalyzed transformation of **243** to **241**. Finally, cleavage of the silyl ether moiety in compounds **241** and **243** followed by their separation provided the pure murrayamine E (**244**) in 54% yield.

1.7 Summary

In summary, we have presented a concise account of the carbazole alkaloids isolated during the last five years along with their bioactivity. Almost fourty five new carbazole alkaloids have been isolated as natural products during last five years span. Selected synthetic methodologies to the carbazole motif and related derivatives reported by different research groups have been presented. Importance has been placed on modern developments of synthetic methodologies for carbazole nucleus, including microwave-assisted synthesis, multi-component one pot reactions, radical initiated C–C bond formation, enantioselective synthesis using chiral phosphoric acid, transition metal (iron, molybdenum and palladium) catalyzed C–H activation, Gold catalyzed alkyne insertion, Rh(II)-catalyzed cascade annulation, hypervalent iodine(III) N-H bond functionalization. A variety of synthetic approaches to biologically active natural/synthetic carbazoles have been reported by number of research groups. All the information collected and presented

here has been well supported by the provision of more than 62 contemporary references from the various international journals.

Given the advances in synthetic methodology and technology in recent years and the continued interest in the carbazole skeleton in medicinal chemistry and drug development, the development of efficient and economically viable methods for the building of these molecules ensures that this is an active and important area of research in alkaloid chemistry. We strongly believe that the broad carbazole alkaloid field will be of continuing interest to both the synthetic and medicinal chemists and positively there will be interminable promising advancements in the knowledge. In this context, as part of this present dissertation, we have developed new methods for synthesis of carbazole natural products. Our synthetic strategies towards the collective total synthesis of these natural products and their synthetic analogues along with new novel solid state auto-epimerization will be discussed in details in the second and third chapters of the present dissertation.

1.8 References

1. Graebe, C.; Glazer, C. *Ber. Dtsch. Chem. Ges.* **1872**, *5*, 12.
2. Chakraborty, D. P.; Barman, B. K.; Bose, P. K. *Sci. Cult.* (India) **1964**, *30*, 445.
3. Das, K. C.; Chakraborty, D. P.; Bose, P. K. *Experientia* **1965**, *21*, 340.
4. Chakraborty, D. P.; Barman, B. K.; Bose, P. K. *Tetrahedron* **1965**, *21*, 681.
5. Roy, S.; Bhattacharyya, P.; Chakraborty, D. P. *Phytochemistry* **1974**, *13*, 1017.
6. Joshi, B. S.; Gawad, D. H. *Indian J. Chem.* **1974**, *12*, 437.
7. Bhattacharyya, P.; Chowdhury, B. K. *Indian J. Chem.* **1985**, *24B*, 452.
8. Bhattacharyya, P.; Jash, S. S.; Chowdhury, B. K. *Chem. Ind.* (London) **1986**, 246.
9. Bhattacharyya, P.; Chakraborty, A. *Phytochemistry* **1984**, *23*, 471.
10. Roy, S.; Guha, R.; Ghosh, S.; Chakraborty, D. P. *Indian J. Chem.* **1982**, *21B*, 617.
11. (a) Joshi, B. S.; Kamat, V. N.; Saksena, A. K.; Govindachari, T. R. *Tetrahedron Lett.* **1967**, *8*, 4019. (b) Joshi, B. S.; Kamat, V. N.; Gawad, D. H.; Govindachari, T. R. *Phytochemistry* **1972**, *11*, 2065.
12. Ray, S.; Chakraborty, D. P. *Phytochemistry* **1976**, *15*, 356.
13. Kureel, S. P.; Kapil, R. S.; Popli, S. P. *Chem. Commun.* **1969**, 1120.

14. (a) Knölker, H.-J.; Reddy, K. R. *Chem. Rev*. **2002**, *102*, 4303. (b) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev*. **2012**, *112*, 3193.
15. (a) Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Ess, D. H.; Kurti, L. *Angew. Chem., Int. Ed*. **2014**, *53*, 2701. (b) Wang, S.; Chai, Z.; Wei, Y.; Zhu, X.; Zhou, S.; Wang, S. *Org. Lett*. **2014**, *16*, 3592. (c) Kumar, V. P.; Gruner, K. K.; Kataeva, O.; Knölker, H.-J. *Angew. Chem., Int. Ed*. **2013**, *52*, 11073.
16. (a) Rajeshwaran, G. G.; Mohanakrishnan, A. K. *Org. Lett*. **2011**, *13*, 1418. (b) Choi, T. A.; Czerwonka, R.; Forke, R.; Jäger, A.; Knöll, J.; Krahl, M. P.; Krause, T.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *Med. Chem. Res*. **2008**, *17*, 374. (c) Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *ChemMedChem* **2006**, *1*, 812.
17. (a) Morin, J.-F.; Leclerc, M.; Adés, D.; Siove, A. *Macromol. Rapid Commun*. **2005**, *26*, 761. (b) Chmielewski, M. J.; Charon, M.; Jurczak, J. *Org. Lett*. **2004**, *6*, 3501. (c) Wang, Y. Z.; Epstein, A. J. *Acc. Chem. Res*. **1999**, *32*, 217.
18. (a) Ishikura, M.; Yamada, K.; Abe, T. *Nat. Prod. Rep*. **2010**, *27*, 1630. (b) Ishikura, M.; Abe, T.; Choshib, T.; Hibinob, S. *Nat. Prod. Rep*. **2013**, *30*, 694.
19. Liu, H.; Li, C.-J.; Yang, J.-Z.; Ning, N.; Si, Y.-K.; Li, L.; Chen, N.-H.; Zhao, Q.; Zhang, D.-M. *J. Nat. Prod*. **2012**, *75*, 677.
20. Shen, D.-Y.; Chao, C.-H., Chan, H.-H.; Huang, G.-J.; Hwang, T.-L.; Lai, C.-Y.; Lee, K.-H.; Thang, T. D.; Wu, T.-S. *Phytochemistry* **2012**, *82*, 110.
21. Maneerat, W.; Ritthiwigrom, T.; Cheenpracha, S.; Promgool, T.; Yossathera, K.; Deachathai, S.; Phakhodee, W.; Laphookhieo, S. *J. Nat. Prod*. **2012**, *75*, 741.
22. Uvarani, C.; Sankaran, M.; Jaivel, N.; Chandraprakash, K.; Ata, A.; Mohan, P. S. *J. Nat. Prod*. **2013**, *76*, 993.
23. Russell, F.; Harmody, D.; McCarthy, P. J.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod*. **2013**, *76*, 1989.
24. Shen, D.-Y.; Chan, Y.-Y.; Hwang, T.-L.; Juang, S.-H.; Huang, S.-C.; Kuo, P.-C.; Thang, T.-D.; Lee, E.-J.; Damu, A. G.; Wu, T.-S. *J. Nat. Prod*. **2014**, *77*, 1215.
25. Lv, H.-N.; Wen, R.; Zhou, Y.; Zeng, K.-W.; Li, J.; Guo, X.-Y.; Tu, P.-F.; Jiang, Y. *J. Nat. Prod*. **2015**, *78*, 2432.
26. Karwehl, S.; Jansen, R.; Huch, V.; Stadler, M. *J. Nat. Prod*. **2016**, *79*, 369.

27. Kim, S.-H.; Ha, T.-K.-Q.; Oh, W. K.; Shin, J.; Oh, D.-C. *J. Nat. Prod.* **2016**, *79*, 51.
28. (a) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241. (b) Borsche, W.; Witte, A.; Bothe, W. *Liebigs Ann. Chem.* **1908**, *359*, 49.
29. Graebe, C.; Ullmann, F. *Liebigs Ann. Chem.* **1896**, *291*, 16.
30. Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, 4831.
31. (a) Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B. *Chem. Ber.* **1992**, *125*, 2783. (b) Knölker, H.-J.; Reddy, K. R. *In The Alkaloids*; Cordell, G. A., Ed.; Academic Press: Amsterdam, **2008**; Vol. *65*, p 1.
32. Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115.
33. (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (c) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23.
34. Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.
35. (a) Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.* **1989**, *89*, 1681. (b) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281.
36. Sha, F.; Tao, Y.; Tang, C.-Y.; Wu, X.-Y. *J. Org. Chem.* **2015**, *80*, 8122.
37. Kale, A. P.; Kumar, G. S.; Mangadan, A. R. K.; Kapur, M. *Org. Lett.* **2015**, *17*, 1324.
38. Suzuki, C.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2015**, *17*, 1597.
39. Verma, A. K.; Danodia, A. K.; Saunthwal, R. K.; Patel, M.; Choudhary, D. *Org. Lett.* **2015**, *17*, 3658.
40. Wang, J.; Zhu, H.-T.; Qui, Y.-F.; Niu, Y.; Chen, S.; Li, Y.-X.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2015**, *17*, 3186.
41. James, M. J.; Clubly, R. E.; Palate, K. Y.; Procter, T. J.; Wyton, A. C.; Brien, P. O.; Taylor, R. J. K.; Unsworth, W. P. *Org. Lett.* **2015**, *17*, 4372.
42. Laha, J. K.; Dayal, N. *Org. Lett.* **2015**, *17*, 4742.
43. Taguchi, M.; Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2015**, *17*, 6250.
44. Bhanuchandra, M.; Murakami, K.; Vasu, D.; Yorimitsu, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 10234.
45. An, Y.-L.; Yang, Z.-H.; Zhang, H.-H.; Zhao, S.-Y. *Org. Lett.* **2016**, *18*, 152.

46. Wen, L.; Tang, L.; Yang, Y.; Zha, Z.; Wang, Z. *Org*. *Lett*. **2016**, *18*, 1278.
47. Stepherson, J. R.; Ayala, C. E.; Tugwell, T. H.; Henry, J. L.; Fronczek, F. R.; Kartika, R. *Org*. *Lett*. **2016**, *18*, 3002.
48. Li, N.; Lian, X.-L.; Li, Y.-H.; Wang, T.-Y.; Han, Z.-Y.; Zhang, L.; Gong, L.-Z. *Org*. *Lett*. **2016**, *18*, 4178.
49. Guo, S.; Yuan, K.; Gu, M.; Lin, A.; Yao, H. *Org*. *Lett*. **2016**, *18*, 5236.
50. Chen, S.; Li, Y.; Ni, P.; Huang, H.; Deng, G.-J. *Org*. *Lett*. **2016**, *18*, 5384.
51. Huang, Y.-W.; Li, X.-Y.; Fu, L.-N.; Guo, Q.-X. *Org*. *Lett*. **2016**, *18*, 6200.
52. Maiti, S.; Mal, P. *Org*. *Lett*. **2017**, *19*, 2454.
53. Fan, X.; Yu, L.-Z.; Wei, Y.; Shi, M. *Org*. *Lett*. **2017**, *19*, 4476.
54. Chen, S.; Li, C.; Ni, P.; Yang, B.; Huang, H.; Deng, G.-J. *J*. *Org*. *Chem*. **2017**, *82*, 2935.
55. Wu, J.; Chen, X.; Xie, Y.; Guo, Y.; Zhang, Q.; Deng, G.-J. *J*. *Org*. *Chem*. **2017**, *82*, 5743.
56. Gonzalez, J. F.; Rocchi, D.; Tejero, T.; Merino, P.; Menendez, J. C. *J*. *Org*. *Chem*. **2017**, *82*, 7492.
57. Abada, E.; Zavalij, P. Y.; Vedernikov, A. N. *J*. *Am*. *Chem*. *Soc*. **2017**, *139*, 643.
58. Trotta, A. H. *Org*. *Lett*. **2015**, *17*, 3358.
59. Banne, S.; Reddy, D. P.; Li, W.; Wang, C.; Guo, J.; He, Y. *Org*. *Lett*. **2017**, *19*, 4996.
60. Hou, S.; Liu, Y.; Kong, Y.; Brown, M. *Org*. *Lett*. **2015**, *17*, 2298.
61. Lee, S.; Kim, K.-H.; Cheon, C.-H. *Org*. *Lett*. **2017**, *19*, 2785.
62. Schuster, C.; Julich-Gruner, K. K.; Schnitzler, H.; Hesse, R.; Jager, A.; Schmidt, A.; Knölker, H.-J. *J*. *Org*. *Chem*. **2015**, *80*, 5666.

Chapter 2

Facile Synthesis of Bioactive Carbazole Alkaloids

Section A

Diversity Oriented Convergent Access for Collective Total Synthesis of Bioactive Multifunctional Carbazole Alkaloids: Synthesis of Sorazolon E, Carbazomycin A, Carbazomycin B, Hyellazole and Chlorohyellazole

Note: An independent figure, table, scheme, structure and reference numbers have been used for the each section.

This chapter is divided into two sections. The first section presents diversity oriented convergent access for collective total synthesis of bioactive multifunctional carbazole alkaloids: synthesis of carbazomycin A, carbazomycin B, hyellazole and chlorohyellazole (Figure 1). The second section describes a biomimetic collective total synthesis of bioactive carbazole alkaloids clausenaline D, indizoline, mafaicheenamine A, claulamine A, claulansine A and the proposed claulamine E. The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end of each section.

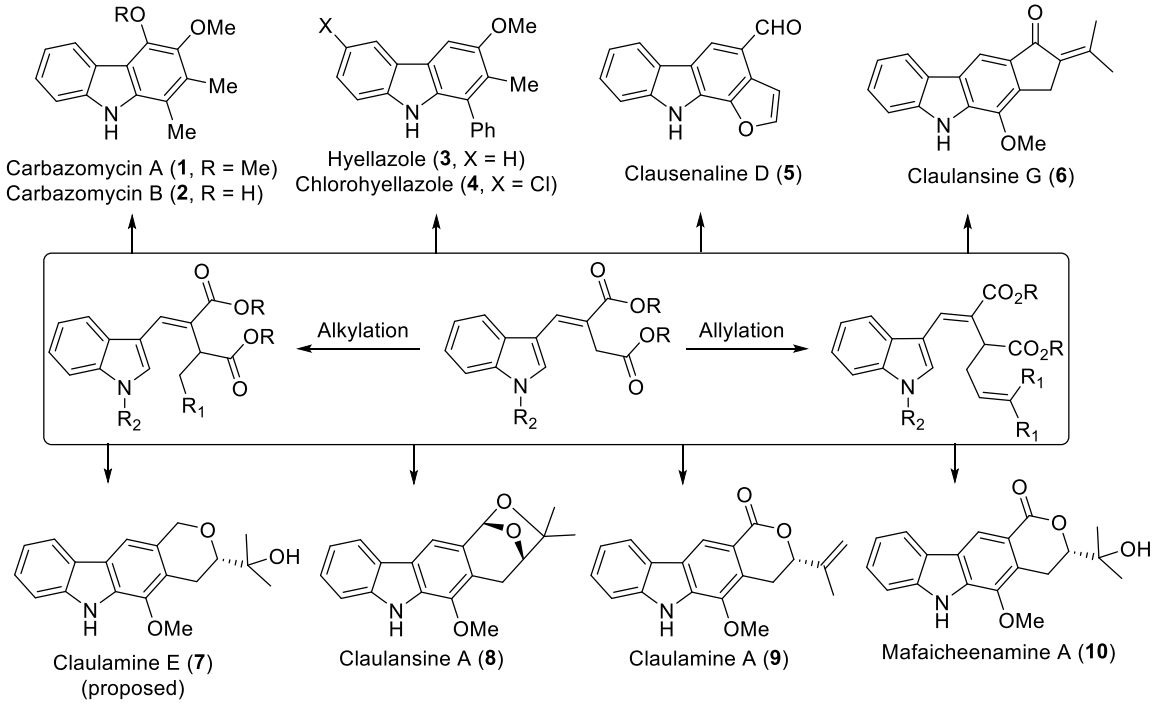


Figure 1. Bioactive Carbazole Alkaloids Synthesized.

2A.1 Background

Multisubstituted Carbazole **11** represents the basic skeleton of carbazole heterocycles (Figure 2). Development of new synthetic stratagems for the collective total synthesis of different classes of natural products is a challenging task of contemporary interest.[1] A large number of carbazole alkaloids have been isolated from plant, animal, microbial and marine genesis.[2]

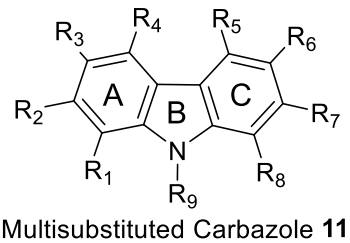


Figure 2. Basic Carbazole Skeleton.

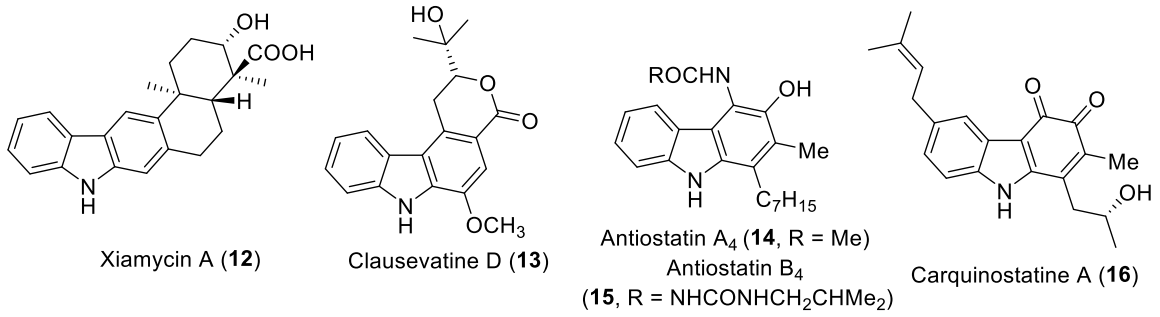


Figure 3. Bioactive Carbazole Alkaloids.

The carbazole alkaloids such as xiamycin (anti-HIV activity),[3] clausevatine D (snakebites and detoxificant activity),[4] antiostatin A_4/B_4 (activity against free radical-induced lipid peroxidation),[5] carquinostatine A (free radical scavenging activity)[6] (Figure 3) and other carbazole alkaloids such as carbazomycin A/B (antibacterial/5-lipoxygenase inhibitor), sorazolon E (weak cytotoxic),[7] mafaicheenamine A (anti-inflammatory), claulamine A (neuroprotective) and claulansine A (antitumor)[8] have attracted significant attention of chemist's community. The interesting biological activities and fascinating molecular architectures of these compounds have attracted immediate attention and became the synthetic targets as a result of their limited availability from natural sources. Many elegant total syntheses of carbazole alkaloids have been reported. In the total synthesis of these alkaloids, the formation of multifunctional aromatic scaffold is the involved important step.

2A.2 Concise Account of Sorazolon E, Carbazomycin A, Carbazomycin B, Hyellazole and Chlorohyellazole Syntheses

Several syntheses of sorazolon E, carbazomycin A, carbazomycin B, hyellazole and chlorohyellazole are known in the literature. All known 3,4-dioxygenated carbazole alkaloids were isolated from microorganisms, e.g., various *Streptomyces* species. The first 3,4-dioxygenated carbazoles carbazomycin A (**1**) and carbazomycin B (**2**) were isolated from *Streptoverticillium ehimense* H 1051-MY 10.[7] These structurally unique alkaloids have been biogenetically derived from tryptophan[1] and represent the first antibiotics with a carbazole framework. Carbazomycin A (**1**) inhibits the growth of phytopathogenic fungi and displays antibacterial and antiyeast activities. The carbazomycin B (**2**) inhibits 5-lipoxygenase and also showed inhibitory activity against lipid peroxidation induced by free radicals (Figure 4).[7a–d] In 2016, Stadler and co-workers isolated sorazolon E (**17**) from *sorangium cellulosum* strain Soce375 along with other two different type of

natural products, which possess moderate cytotoxic activity against mouse fibroblast cell line L929 with IC_{50} values between 5.0 μM and 0.09 mM.[7e]

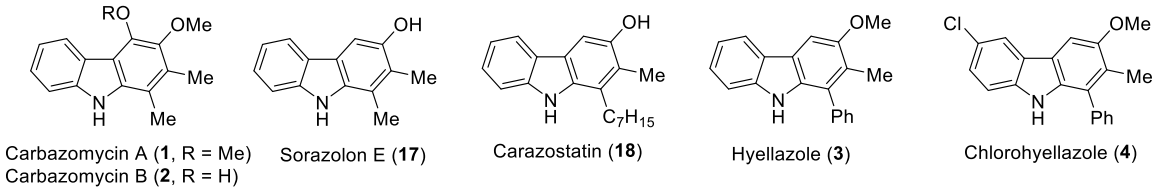
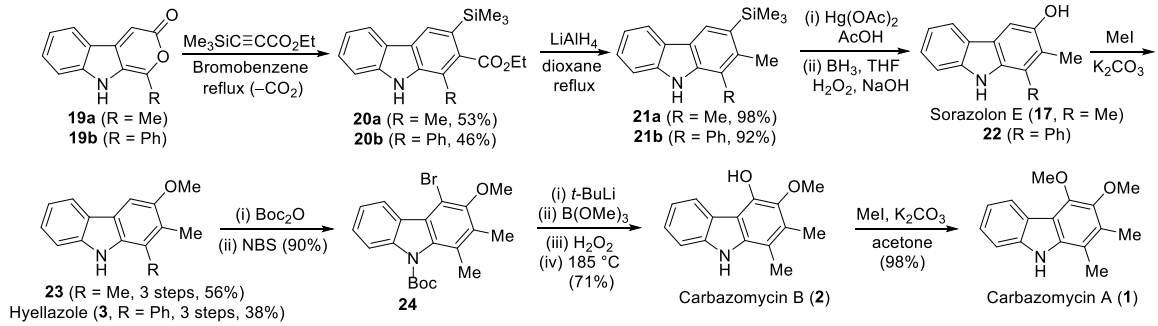


Figure 4. Diversely Substituted Carbazomycin A/B, Carazostatin, Hyellazole and Chlorohyellazole Alkaloids.

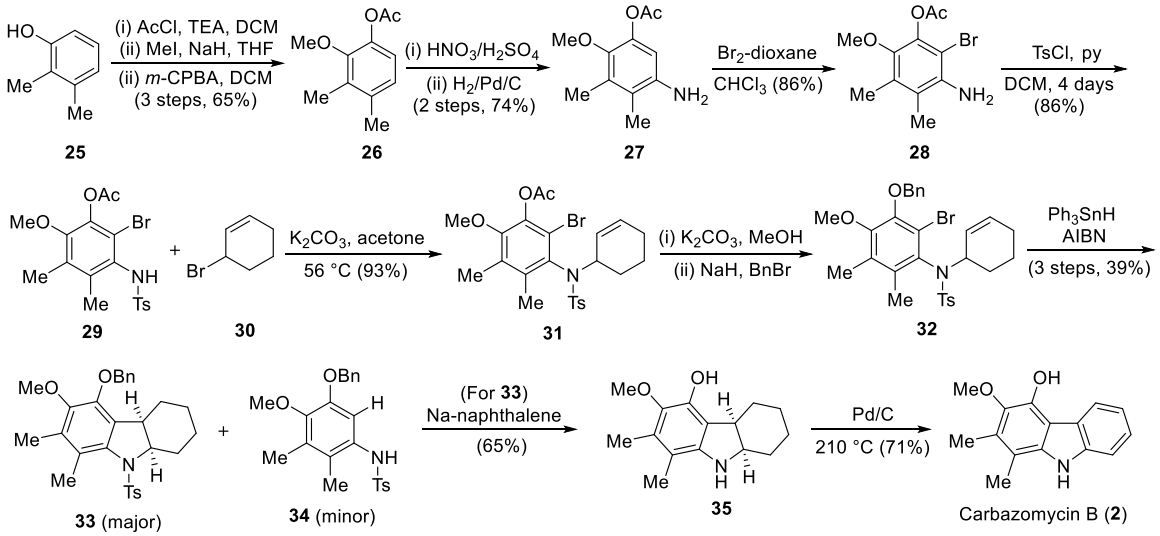
In 1979, Moore and co-workers isolated nonbasic 3-oxygenated carbazole alkaloids hyellazole (**3**) and 6-chlorohyellazole (**4**) from the blue-green algae *Hyella caespitosa*.[9] Carazostatin (**18**) is a radical scavenger and is more active than 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT).[10]



Scheme 1. Total Synthesis of Sorazolon E, Carbazomycins A and B via Diels–Alder Reaction

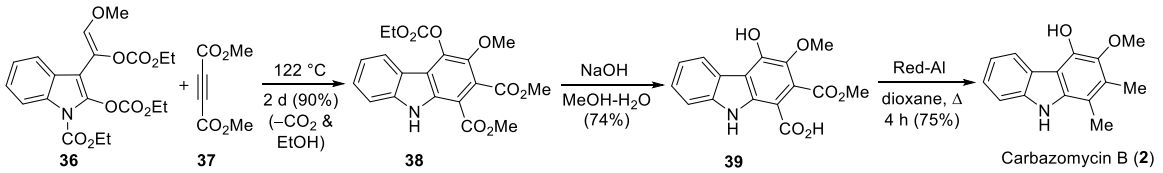
The first synthesis of carbazomycins A (**1**) and B (**2**) have been reported by Moody and Shah in 1989 via Diels–Alder reaction (Scheme 1).[11] The marine alkaloid hyellazole (**3**) was also synthesized by a similar route. Pyrano[3,4-*b*]indol-3-ones **19a**,**b** were prepared by reaction of indol-3-ylacetic acid derivatives with acetic anhydride. The Diels–Alder reactions of **19a**,**b** with ethyl 3-trimethylsilylpropynoate with associated loss of carbon dioxide yielded the carbazoles **20a**,**b** in 53% and 46% yields respectively, without any evidence of formation of the corresponding isomeric carbazoles. The esters **20a**,**b** were reduced to the 2-methylcarbazoles **21a**,**b** using lithium aluminium hydride in refluxing dioxane. Mercurio-desilylation of the **21a**,**b** gave the arylmercury compounds, which were subjected to hydroboration and oxidation to provide sorazolon E (**17**) and product **22**. Methylation of hydroxycarbazoles **17** and **22** with MeI in acetone gave compound **23** and hyellazole (**3**) in 56% and 38% yield over three steps. The bromination of carbazole **23** with *N*-bromosuccinimide (NBS) in acetonitrile gave undesired 6-bromo compound, however bromination of *N*-*t*-butoxycarbonylcarbazole under the same reaction conditions gave the required 4-bromo derivative **24** in 90% yield over two steps. Treatment of Boc-

protected bromocarbazole **24** with *t*-butyllithium in THF at –78 ºC, followed by reaction of the resulting aryllithium with trimethyl borate and alkaline hydrogen peroxide work-up gave 4-hydroxycarbazole. The *t*-butoxycarbonyl group was removed simply by heating the carbazole to 185 ºC yielding carbazomycin B (**2**) in 71% yield and methylation of the same gave carbazomycin A (**1**) in 98% yield.



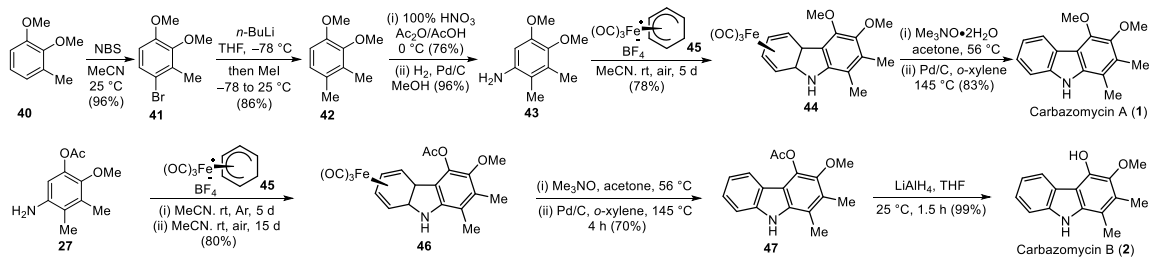
Scheme 2. Total Synthesis of Carbazomycin B via Radical Cyclization

Lown and co-workers reported synthesis of carbazomycin B (Scheme 2).[12] The second oxygen substituent in the *ortho*-position relative to the hydroxy group was introduced by *O*-acetylation of **25** followed by *ortho*-selective Fries rearrangement of the intermediate acetoxy derivative to the desired acetophenone. Methylation of the obtained phenolic compound and Baeyer–Villiger oxidation gave acetoxy derivative **26** in 65% yield over three steps. Regioselective nitration of **26** using fuming nitric acid and sulphuric acid resulted 5-nitrophenyl acetate, which was followed by catalytic hydrogenation leading to the formation arylamine **27** in very good yield. Bromination of obtained arylamine **27** with bromine-dioxane gave bromoaniline derivative **28** in 86% yield. The tosyl protection of amine **28** provided sulfonamide **29** in 86% yield. Alkylation of the resulting sulfonamide **29** with 3-bromo-1-cyclohexene gave product **31** in 93% yield. The deacetylation with K_2CO_3-MeOH followed by *O*-benzylation provided benzyl ether **32**, which underwent efficient radical cyclization with AIBN/Ph_3SnH and yielded the desired cyclized product **33** (major) in 39% yield over 3 steps along with minor product **34**. Treatment of **33** with sodium-naphthalene served to remove the *N*-tolylsulfonyl and *O*-benzyl groups (**33** to **35**; 65% yield), finally dehydrogenation with Pd/C gave carbazomycin B (**2**) in 71% yield.



Scheme 3. Total Synthesis of Carbazomycin B via Diels–Alder Reaction

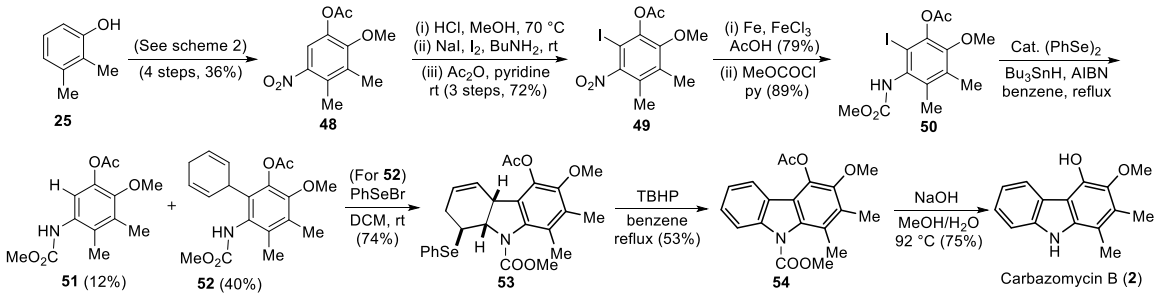
Beccalli and co-workers reported Diels–Alder approach for the synthesis of carbazole alkaloid carbazomycin B (**2**) (Scheme 3).[13] They have reported the use of (*Z*)-ethyl-3-[(1-ethoxycarbonyloxy-2-methoxy)ethenyll-2-(ethoxycarbonyloxy)indole-1-carboxylate (**36**) as a diene in the Diels–Alder reaction based synthesis of carbazomycin B. Diels–Alder reaction of the diene **36** with dimethyl acetylendicarboxylate (**37**, DMAD) gave the tetrasubtituted carbazole **38** in 90% yield. Hydrolysis of aryl ester **38** with NaOH in MeOH-H_2O resulted phenol-acid **39** in 74% yield, which was treated with Red-Al in dioxane for 4 h to provide carbazomycin B (**2**) in 75% yield.



Scheme 4. Total Synthesis of Carbazomycin A and B via Iron-Based Coupling Reaction

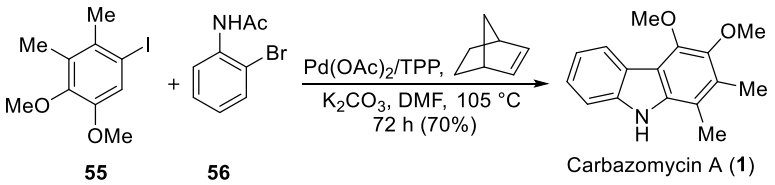
Knölker and co-workers reported the synthesis of carbazomycins A (**1**) and B (**2**) via iron-based coupling reaction (Scheme 4).[14] Electrophilic bromination of 3-methylveratrole (**40**) provided 4-bromo-3-methylveratrole (**41**). Halogen-metal exchange using *n*-butyllithium in tetrahydrofuran followed by alkylation with iodomethane gave the 3,4-dimethylveratrole (**42**) in 86% yield. Regioselective nitration of **42** with fuming nitric acid in a 3:1 mixture of acetic anhydride and glacial acetic acid led to the nitro compound and its catalytic hydrogenation over 10% palladium on activated carbon gave the arylarnine **43**. The iron-based oxidative coupling of the arylamine **43** in the presence of air formed the iron-coordinated dihydrocarbazole **44**. Finally, demetalation of **44** and aromatization led to carbazomycin A (**1**) in 65% overall yield based on the iron-complex salt **45**. 2,3-Dimethylphenol (**25**) was used as starting material to access the arylamine **27** (see scheme 2), which was required for the total synthesis of carbazomycin B (**2**). Oxidative coupling of the iron-complex salt **45** and the arylamine **27** in the presence of air afforded the iron complex **46**. Demetalation of iron-complex **46** followed by

aromatization led to *O*-acetylcarbazomycin B (**47**). Finally, ester cleavage provided carbazomycin B (**2**) in five steps and 55% overall yield based on the iron complex salt **45**.



Scheme 5. Total Synthesis of Carbazomycin B via Oxidative Aromatization

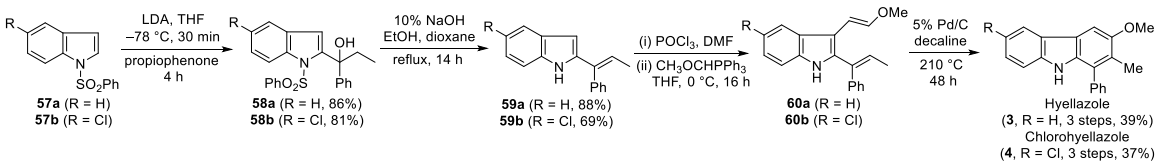
In 2004, Crich and Rumthao reported the synthesis of carbazomycin B (**2**) (Scheme 5).[15] 5-Nitrophenyl acetate **48** was prepared from **25** by following the Clive and co-workers route (see scheme 2). Deprotection of acetyl group in **48** to the corresponding hydroxyphenol followed by iodination with sodium iodide, iodine and butylamine in water and acylation of thus formed iodophenol provided nitroaryl **49** in 72% over 3 steps. The product **49** was cleanly reduced with iron and ferric chloride in acetic acid and derivatization of which provided iodocarbamate **50**. In the key radical dearomatization step, a 0.05 M solution of iodide **50** and diphenyl diselenide (20 mol%) in benzene was treated at reflux with tributyltin hydride and AIBN. The product **52** was obtained in 40% yield, together with 8% of the recovered substrate and 12% of the deiodinated product **51**. Treatment of **52** with phenylselenenyl bromide in dichloromethane led to the tetrahydrocarbazole **53** in 74% yield. Oxidative deselenation followed by aromatization with an excess of *tert*-butyl hydroperoxide led to the fully aromatized carbazole **54**. Finally, exposure of **54** to hot methanolic sodium hydroxide gave carbazomycin B (**2**) in 75% yield.



Scheme 6. Synthesis of Carbazomycin A via Palladium-catalyzed Cross-coupling Reaction

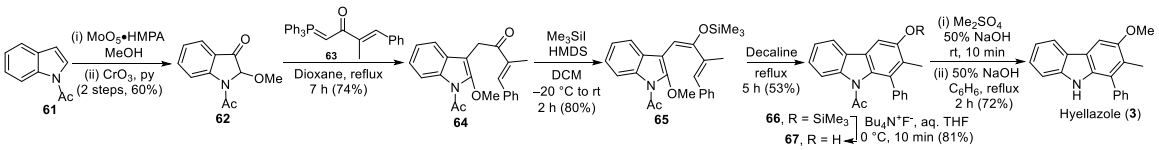
Catellani and co-workers reported the synthesis of carbazomycin A (**1**) via palladium-catalyzed reaction through sequential C–C and C–N bond formation (Scheme 6).[16] Pd-catalyzed cross-coupling reaction of *o*-substituted aryl iodide **55** and aryl bromide **56** was utilized for the synthesis of substituted carbazole. The 5-substituted aryl iodide **55** coupled with *o*-bromo-*N*-acylaniline in the presence of $Pd(OAc)_2$/TPP at 105 ºC and

provided carbazomycin A (**1**) in 70% yield. Mechanistically, oxidative addition of the aryl iodide **55** to Pd(0) followed by stereoselective insertion of norbornene and ring closure to metallacycle by electrophilic aromatic substitution was the reaction pathway.



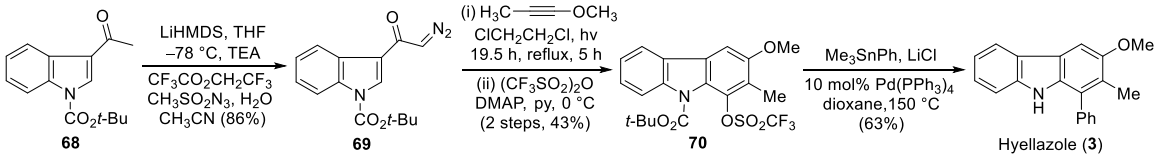
Scheme 7. Total Synthesis of Hyellazole and Chlorohyellazole via Condensation

Hibino and co-workers reported the synthesis of hyellazole and chlorohyellazole (Scheme 7).[17] Condensation of benzenesulfonylindoles **57a**,**b** with propiophenone in presence of LDA gave the 2-(l-hydroxycyclohexyl)indoles **58a**,**b**. Hydrolysis and stereoselective dehydration of both the compounds **58a**,**b** with ethanolic aqueous NaOH resulted in the formation of **59a**,**b** in 88% and 69% yields respectively. Vilsmeier reaction of **59a**,**b** followed by Wittig reaction of the formed indole 3-aldehydes with (methoxymethy1ene)triphenylphosphorane yielded the 2,3-divinylindoles **60a**,**b**. Those products were heated in decalin in the presence of 5% Pd-C at 210 ºC for 48 h to give hyellazole (**3**) and chlorohyellazole (**4**) in 39% and 37% overall yields from **59a**,**b** respectively.



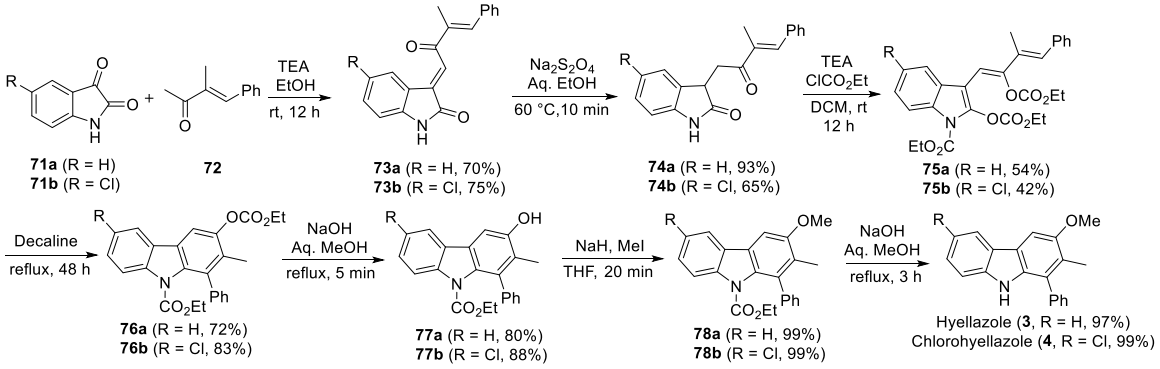
Scheme 8. Total Synthesis of Hyellazole via Electrocyclic Reaction

Sakamoto and co-workers reported an efficient synthesis of hyellazole (**3**) (Scheme 8).[18] Treatment of 1-acetylindole (**61**) with MoO_5·HMPA in MeOH gave *cis*-and *trans*-1-acetyl-3-hydroxy-2-methoxyindolines, which on oxidation with CrO_3 gave acetylmethoxyindole **62** in 60% yield over 2 steps. The phosphonium ylide **63** was prepared by usual procedure from 1-chloro-3-methyl-4-phenylbut-3-en-2-one and triphenylphosphine. Wittig reaction of ketone **62** with ylide **63** gave the 3-(2-oxobut-3-enyl)indole **64** in 74% yield and the formed product was treated with trimethylsilyl iodide in the presence of hexamethyldisilazane (HMDS) to provide the desired product **65** in 80% yield. On heating of compound **65**, an electrocyclic reaction occurred leading to carbazole **66** and it was further treated with tetrabutylammonium fluoride (TBAF) to afford **67** in 81% yield. Methylation of **67** with dimethyl sulfate and sodium hydroxide followed by deacetylation gave hyellazole (**3**) in 72% yield over two steps.



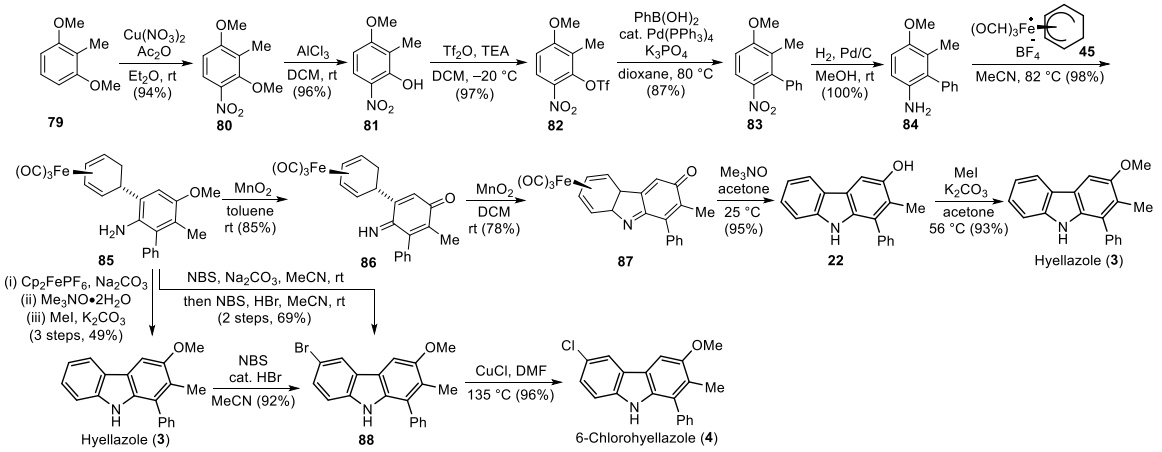
Scheme 9. Total Synthesis of Hyellazole via Stille Cross-coupling Reaction

Danheiser and co-workers reported an annulation method for the synthesis of hyellazole (Scheme 9).[19] Treatment of 3-acylindole **68** with LiHMDS and 2,2,2-trifluoroethyl trifluoroacetate provided the requisite *α*-diazo ketone **69** in 86% yield. Irradiation of a 1,2-dichloroethane solution of product **69** and 1-methoxypropyne for 19.5 h followed by refluxing for 5 h furnished the expected carbazole, which was converted to triflate derivative **70** in 43% yield over 2 steps. The installation of the C-1 phenyl group was then accomplished by using the Stille cross-coupling reaction, the triflate **70** and phenyltrimethylstannane were heated in dioxane in the presence of a catalytic amount of $(Ph_3P)_4Pd$ to afford hyellazole (**3**) in 63% yield.



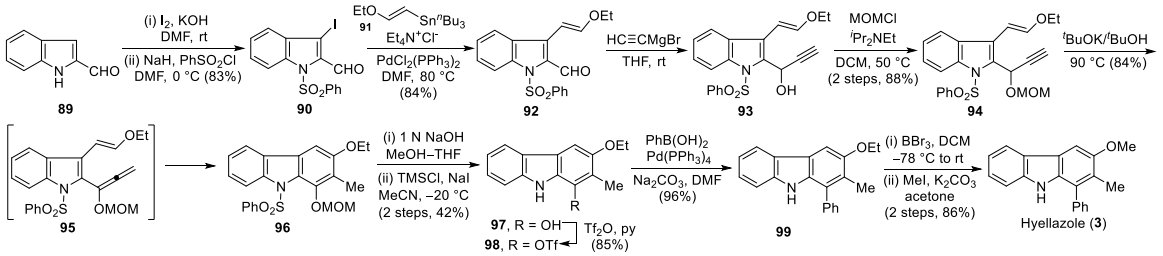
Scheme 10. Total Synthesis of Hyellazole and Chlorohyellazole via Thermal Cyclization

Pilati and co-workers reported the synthesis of hyellazole and chlorohyellazole (Scheme 10).[20] The condensation of indole-2,3-diones **71a**,**b** with the 4-phenylbutenone **72** was carried out in EtOH and in the presence of trithylamine to give the corresponding 3-hydroxy derivatives, dehydration of which stereoselectively yielded **73a**,**b** (70 and 75%). The selective reduction of the double bond in compounds **73a**,**b** was carried out with sodium hydrosulfite to give oxoindole derivatives **74a**,**b** in 93 and 65% yield. The oxoindoles **74a**,**b** were treated with an excess of ethyl chloroformate and triethylamine in DCM to form the corresponding **75a**,**b** in 54 and 42% yields respectively. Thermal cyclization and hydrolysis of the **75a**,**b** gave the corresponding carbazoles **77a**,**b**. The obtained carbazoles **77a**,**b** were transformed into the methylated derivatives **78a**,**b** using NaH/MeI. Finally, alkaline hydrolysis resulted in the formation of hyellazole (**3**) and chlorohyellazole (**4**) in 97 and 99% yields.



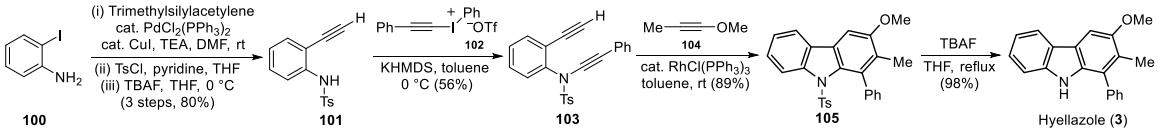
Scheme 11. Total Synthesis of Hyellazole and Chlorohyellazole via Suzuki–Miyaura Coupling

Knölker and co-workers have developed a synthetic route to the carbazole alkaloids hyellazole (**3**) and 6-chlorohyellazole (**4**) based on their iron-based approach (Scheme 11).[22] The arylamine **84** was prepared using reported route of Azzena et al. starting from 1,2-dimethoxy-3-(methoxymethyl)benzene (**79**).[21] Regioselective nitration of **79** using $Cu(NO_3)_2$ furnished the desired nitrophenyl compound **80** in 94% yield. The regioselective demethylation of methyl ether in compound **80** by using $AlCl_3$ to form the corresponding phenol **81** and then its conversion to triflate provided product **82**. The Suzuki–Miyaura cross-coupling of the triflate **82** with phenylboronic acid provided the desired biphenyl derivative **83** in 76% overall yield based on compound **79**. Catalytic hydrogenation of **83** to the arylamine **84** in quantitative yield and electrophilic substitution of the arylamine **84** by reaction with the complex salt **45** provided the iron complex **85** in excellent yield. Chemoselective oxidation of the iron complex **85** with manganese dioxide provided tricarbonyliron-coordinated **87** via the quinone imine **86**. Demetalation of tricarbonyl iron-coordinated complex to hydroxycarbazole **22** and selective *O*-methylation gave hyellazole (**3**). Treatment of iron-complex **85** with ferrocenium hexafluorophosphate in the presence of sodium carbonate provided hyellazole (**3**) in 49% yield over 3-steps. An attempted direct conversion of hyellazole (**3**) into 6-chlorohyellazole (**4**) by reaction with *N*-chlorosuccinimide (NCS) exclusively led to 4-chlorohyellazole. In contrast, bromination of **3** using NBS exclusively provided 6-bromohyellazole **88** (92% yield). A straightforward one pot transformation of the iron-complex **85** to 6-bromohyellazole **88** was also achieved by reaction of **85** with an excess of NBS in acidic reaction medium. Finally, halogen exchange in compound **88** with copper(I) chloride transformed it to 6-chlorohyellazole (**4**) in 96% yield.



Scheme 12. Total Synthesis of Hyellazole via Cross-coupling Reaction

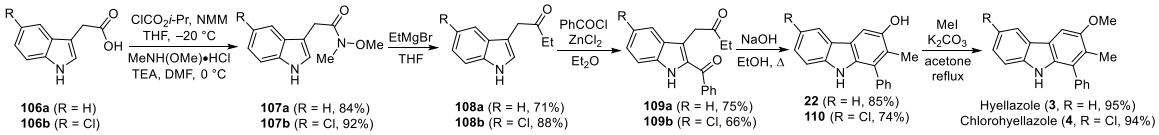
Hibino and co-workers reported one more total synthesis of hyellazole and chlorohyellazole (Scheme 12).[23] The 2-formyl-3-iodoindole prepared from 2-formylindole (**89**), which was converted into the *N*-benzenesulfonylindole **90**. The usual Cross-coupling reaction between **90** and the vinylstannane **91** in the presence of bis(triphenylphosphine)palladium(II) chloride ($Pd(PPh_3)_2Cl_2$) gave the 3-alkenylindole **92** in 84% yield. Reaction of **92** with ethynylmagnesium bromide gave propargylindole **93**, and it was followed by protection with chloromethyl methyl ether (MOM-C1) to provide 3-alkenyl-2-propargylindole **94** (88% over 2 steps). Heating of **94** in the presence of potassium *t*-butoxide yielded substituted carbazole **96** in 84% via an allene intermediate **95**. Hydrolysis of **96** with sodium hydroxide followed by subsequent cleavage of the MOM-ether with the trimethysilyl chloride (TMSCl) and sodium iodide gave the 1-hydroxycarbazole **97** in 42% yield over two steps. The phenol **97** was converted into the triflate **98** and subjected to Suzuki cross-coupling reaction with phenylboronic acid in the presence of palladium catalyst to yield the carbazole **99**. Finally, cleavage of the ethyl ether with boron tribromide (BBr_3) followed by *O*-methylation yielded hyellazole (**3**) in 86% yield over two steps.



Scheme 13. Total Synthesis of Hyellazole via Cyclotrimerization

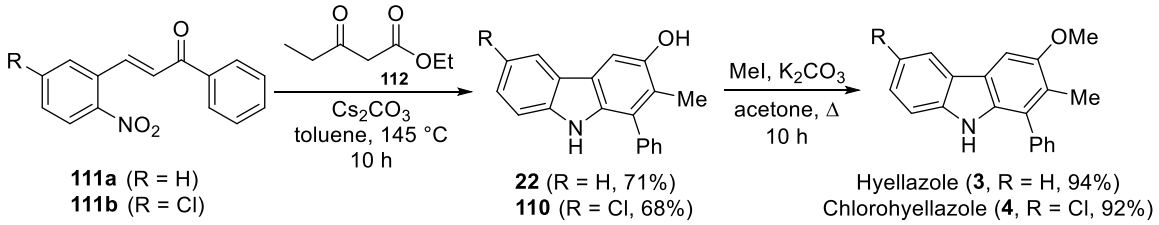
In 2002, Witulski and Alayrac reported the total synthesis of hyellazole (**3**) via a vollhardt-type rhodium-catalyzed alkyne cyclotrimerization (Scheme 13).[24] Sonogashira–Hagihara coupling of 2-iodoaniline (**100**) with trimethylsilylacetylene followed by *N*-tosylation and protodesilylation gave the alkyne **101** (80% yield in 3 steps). Alkynylation of compound **101** with the alkynyliodonium triflate (**102**) yielded diyne **103** (56%). A Vollhardt-type cyclization of the diyne **103** and 1-methoxypropyne (**104**) using Wilkinson's catalyst provided desired *N*-tosylhyellazole (**105**) in 89% yield.

Finally, hyellazole (**3**) was obtained in 98% yield by removal of the tosyl group of **105** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran under reflux conditions.



Scheme 14. Total Synthesis of Hyellazole and Chlorohyellazole via Intramolecular Cyclization

Duval and Cuny reported the synthesis of hyellazole and chlorohyellazole (Scheme 14).[25] The coupling of acids **106a**,**b** with *N*,*O*-dimethylhydroxylamine hydrochloride delivered the Weinreb amides **107a**,**b**, which were allowed to react with Grignard reagent to provide ketones **108a**,**b** in good yields. The 3-substituted indoles **108a**,**b** were subjected to Friedel–Crafts acylations with acid chloride, which were promoted by the addition of excess zinc chloride to give diketoindoles **109a**,**b** in 75% and 66% yields respectively. The base mediated cyclization of diketoindoles **109a**,**b** led to carbazoles **22** and **110**. Finally, methylation of them yielded the natural products hyellazole (**3**) and 6-chlorohyellazole (**4**) in 80 and 70% yields over 2-steps.



Scheme 15. Synthesis of Hyellazole and Chlorohyellazole via Condensation and Cyclization

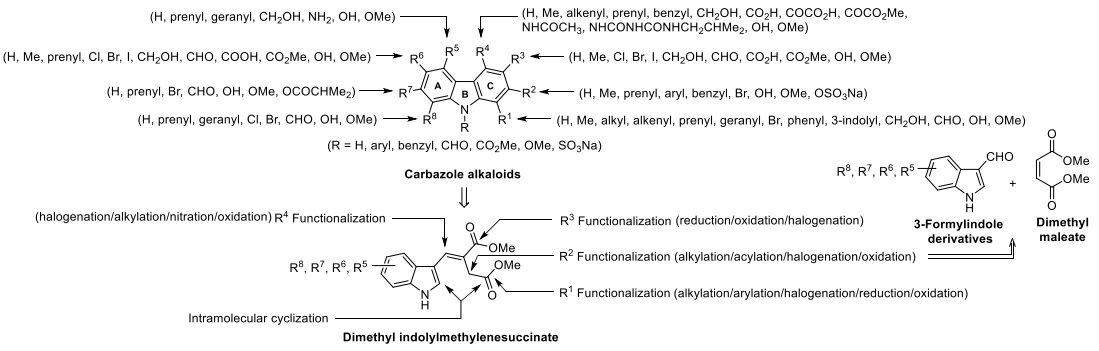
Tej Poudel and Yong Lee reported the synthesis of carbazole alkaloids via condensation of nitro aryls and *β*-ketoester (Scheme 15).[26] Condensation of 2-nitrochalcones **111a**,**b** and *β*-ketoester **112** in the presence of Cs_2CO_3 in refluxing toluene yielded hydroxycarbazoles **22** and **110** in 71 and 68% yields. Finally, methylation of hydroxycarbazoles **22** and **110** provided hyellazole (**3**) and chlorohyellazole (**4**) in excellent yields.

2A.3 Results and Discussion

Diversity Oriented Convergent Access for Collective Total Synthesis of Bioactive Multifunctional Carbazole Alkaloids: Synthesis of Sorazolon E, Carbazomycin A, Carbazomycin B, Hyellazole and Chlorohyellazole

Total synthesis of bioactive natural products leading to essential medicines is the priority area in science.[27] Development of new synthetic stratagems for the collective total synthesis of different classes of natural products is a challenging task of contemporary

interest.[1] A large number of carbazole alkaloids have been isolated from plant, animal, microbial and marine genesis (Figures 1–3).[2] They are an important class of natural products from the point of view of novel structural topographies and major biological activities.[2,28–29] Carbazoles exhibit well proved antitumor, antibiotic, antiviral, anti-HIV, anti-inflammatory, antimalarial, psychotropic, antihistaminic, anti-oxidative and the significant anti-tuberculosis activities. Moreover, carbazoles are used in the treatment of hypertension, ischemic heart disease and congestive heart failure.[2,28–29] They have also been used in illustrious hole-transporting electroluminescent materials and are potential building blocks in functional materials owing to their electrical and thermal properties.[30] Therefore carbazoles have been crucial target compounds and several elegant product specific synthesis of these have been reported during the past few decades.[2,28–29] The main steps involved in their synthesis were acid/base/metal/heat/light-catalyzed aryl–carbon/aryl–nitrogen/aryl–aryl couplings of two suitably substituted building blocks and the specific intramolecular cyclizations.[2,28–29] In the synthesis of carbazoles, construction of an appropriate fully functionalized aromatic ring system is the important assignment for steric and/or electronic factors and reactivity reasons.[31] Despite tremendous synthetic efforts to develop regioselective installation of appropriate substituents on these heterocyclic structures, general and efficient methods are still limited.[2,28–30] In the continuation of our studies on total synthesis of bioactive natural products,[32] we reasoned that the readily available suitably substituted 3-formylindole derivatives and dimethyl maleate would constitute a diversity oriented new approach to this important class of compounds. In this context we herein report the robust route to essential carbazole alkaloids (Schemes 16–18).

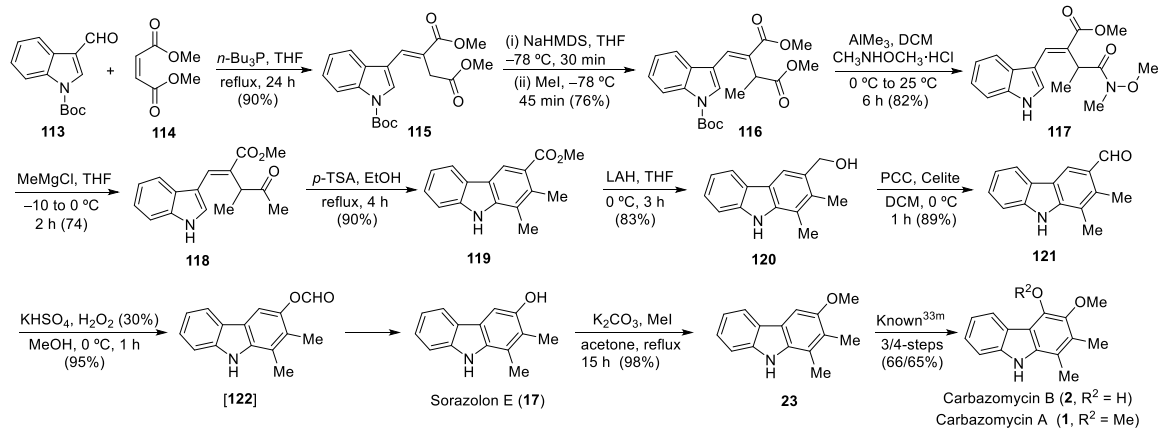


Scheme 16. General Representation of Known Major Carbazole Alkaloids and their Retrosynthetic Analysis

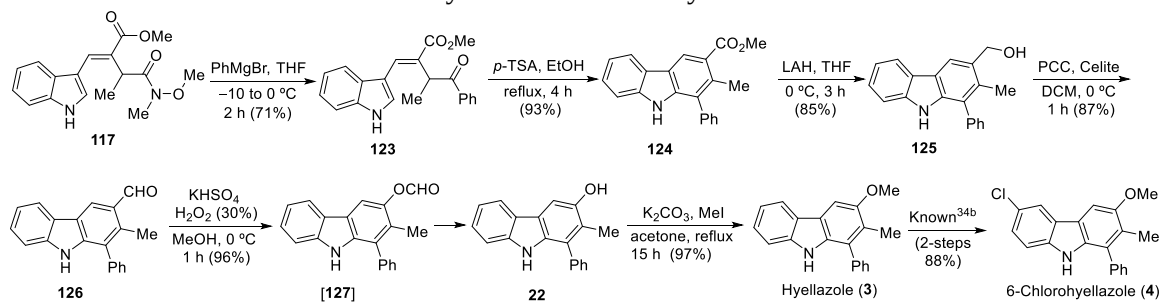
A careful search of major carbazole alkaloid structures revealed that the pathway encompassing completely open scope for introduction of broad range of substituents at appropriate positions would provide a general approach to an array of fascinating

bioactive natural and unnatural carbazole and fused carbazole architectures. A general representation and concise retrosynthetic analysis of carbazole alkaloids has been depicted in scheme 16. Retrosynthetically, the stepwise intermolecular and intramolecular coupling reactions of three carbon units from suitably substituted 3-formylindole derivatives with three carbon unit from dimethyl maleate would constitute a general pathway to the majority of diversely substituted carbazole alkaloids. As represented in scheme 16, multiple electro- and nucleophilic reactions would be possible on the potential antecedent dimethyl indolylmethylenesuccinate. Productively, it bears the correct number of electro- and nucleophilic C-atoms, accurately located to introduce the appropriate substituents and/or functional groups along with a site for dehydrative intramolecular cyclization to form the desired aromatic ring structure. Accordingly, we prepared a synthetic plan to accomplish the collective synthesis of five carbazole alkaloids namely: carbazomycin A (antibiotic) and carbazomycin B (antibiotic and 5-lipoxygenase inhibitor) isolated from *Streptoverticillium ehimense*,[7a–d] sorazolon E (moderate cytotoxic) from *sorangium cellulosum* Strain Soce375,[7e] hyellazole and chlorohyellazole from *Hyella caespitosa*.[9] Several synthesis of the five target compounds (Section 2A.2) and their closely related analogues have been known in the literature.[33–35]

The initially studied reaction of 3-formylindole with an in situ generated Wittig reagent[36] from dimethyl maleate (**114**) and tributylphophine was not very efficient and the required product was formed only in 33% yield. However, the alternatively performed reaction of Boc-protected 3-formylindole (**113**) with the same Wittig reagent stereoselectively furnished the desired potential precursor **115** in 90% yield; essentially under neutral reaction conditions (Scheme 17). The *E*-geometry of product **115** was confirmed on the basis of *peri* interaction of vinylic proton with an ester carbonyl group.[32a,36] The conjugation of 3-formyl unit with the lone pair of electrons on indole N-atom is responsible for its decline in reactivity and therefore the *N*-Boc protection activates it for the anticipated Wittig reaction. The NaHMDS induced chemo- and regioselective monomethylation of an activated allylic methyelene carbon in **115** with methyl iodide provided the necessary product **116** in 76% yield. Providentially, the formed carbanion did not endure plausible intramolecular 1,6-addition course generating a 6-5-5 heterocyclic system. Trimethylaluminium prompted regioselective coupling reaction of *N*,*O*-dimethylhydroxylamine hydrochloride with diester **116** to form the desired product **117** in 82% yield.[37] Conveniently, transformations of more reactive unconjugated ester unit to W-



Scheme 17. Synthesis of Sorazolon E, Carbazomycin A and Carbazomycin B from Boc-Protected 3-Formylindole and Dimethyl Maleate



Scheme 18. Synthesis of Carbazole Alkaloids Hyellazole and Chlorohyellazole from Boc-Protected 3-Formylindole and Dimethyl Maleate

einreb amide and *N*-Boc-deprotection took place in the presence of trimethylaluminium/*N*,*O*-dimethylhydroxylamine hydrochloride. The well-organized chemoselective reactions of methylmagnesium bromide and phenylmagnesium bromide with Weinreb amide **117** cleanly delivered corresponding ketones **118** and **123** in 74 and 71% yields respectively (Schemes 17 and 18). *p*-TSA catalyzed dehydrative intramolecular cyclization of ketones **118** and **123** provided the products **119** and **124** in 90/93% yields, efficiently constituting the rightly functionalized aromatic ring C. LAH-reduction of ester function in **119** and **124** followed by the PCC-oxidation of formed intermediate alcohols **120** and **125** yielded corresponding aromatic aldehydes **121** and **126** in very good overall yields in two-steps. The Baeyer–Villiger oxidation of aromatic aldehydes **121** and **126** formed the corresponding unisolable formate esters **122** and **127** which, upon in situ hydrolysis, transformed to the known compounds sorazolon E (**17**)[7e] and **22**[33m] in 95/96% yields. The present Baeyer–Villiger oxidation reaction was higher temperature and time sensitive. Fortunately, we did not notice any oxidation of aldehyde to the corresponding carboxylic acid under employed set of reaction conditions. The base-catalyzed chemoselective *O*-methylation of compound **17** gave the corresponding methyl ether intermediate **23** in 98% yield from which three-step synthesis of carbazomycin B (**2**) is

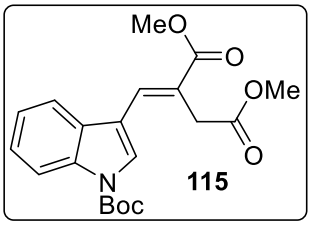
known in the literature.[33m] Carbazomycin B (**2**) on simple *O*-methylation forms carbazomycin A (**1**) in high yield.[33m] Methylation of compound **22** furnished the natural product hyellazole (**3**) in 97% yield from which two-step synthesis of yet another natural product chlorohyellazole is known in the literature.[34b] The analytical and spectral data obtained for both showed that the advanced intermediate **23** of carbazomycins and hyellazole (**3**) were in complete agreement with the reported data.[33,34]

2A.4 Summary

In summary, starting from easily available chemicals and reagents, we have demonstrated a diversity oriented convergent access for collective synthesis of five different carbazole alkaloids with very good overall yields. In the present approach, generation of suitably substituted basic carbazole skeleton in just 4/5-steps utilizing three carbon fragments from each 3-formylindole and dimethyl maleate is remarkable. Furthermore, the generation of biaryl systems without the aryl–aryl coupling is also noteworthy. Syntheses of these alkaloids have been accomplished without involving any discrete protection deprotection steps. For an appropriate functionalization of aromatic ring A, the synthesis itself can begin with suitably substituted indole derivatives; otherwise, the functionalization of aromatic ring A towards the end part of total synthesis would also be feasible. The present approach is general in nature and can provide access to a large number of carbazole alkaloids and their congeners for SAR studies.

2A.5 Experimental Section

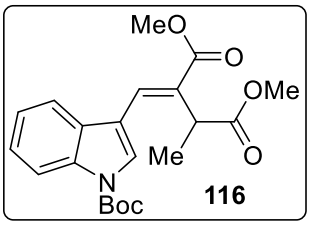
Dimethyl (*E*)-2-{[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]methylene}succinate (115).



To a stirred solution of dimethyl maleate (**114**, 5.87 g, 40.81 mmol) and 3-formylindole **113** (10.00 g, 40.81 mmol) in THF (80 mL) was added *n*-Bu_3P (10.05 mL, 40.81 mmol) in dropwise fashion at 25 °C under argon atmosphere. The reaction mixture was refluxed for 24 h and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (200 mL) and the resultant solution was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent furnished the pure product **115** as yellow thick oil (13.80 g, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.69 (s, 9H), 3.69 (s, 2H), 3.75 (s, 3H), 3.86 (s, 3H), 7.25–7.43 (m, 2H), 7.68 (dd, J = 6 and 2 Hz, 1H), 7.86 (s, 1H), 8.02 (s, 1H), 8.15 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.1, 34.5, 52.2, 52.3,

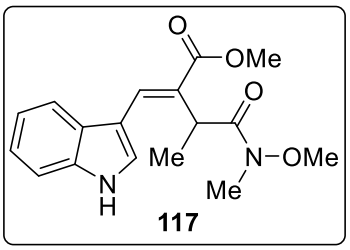
84.5, 115.3, 115.4, 119.0, 123.3, 124.7, 125.2, 126.1, 129.9, 132.0, 135.0, 149.3, 167.7, 171.3; ESIMS (*m*/*z*) 373 $[M]^+$; IR ($CHCl_3$) ν_{max} 1736, 1719, 1631 cm^{-1}.

Dimethyl (*E*)-2-{[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]methylene}-3-methylsuccinate (116). To a stirred solution of compound **115** (6.00 g, 16.08 mmol) in dry THF (30 mL) was added a solution of NaHMDS in THF (1 M, 32.17 mL, 32.17 mmol) in a dropwise mode at –78 °C under argon atmosphere. The reaction mixture was stirred for 30 min and then methyl iodide (1.20 mL, 19.30 mmol) was added dropwise. The reaction mixture was further stirred at –78 °C for 45 min and quenched with saturated aqueous NH_4Cl solution (20 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (200 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (1:9) as an eluent yielded pure **116** as a solid (4.70 g, 76%). Mp 98–100 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50 (d, J = 8 Hz, 3H), 1.70 (s, 9H), 3.68 (s, 3H), 3.84 (s, 3H), 3.98 (q, J = 6 Hz, 1H), 7.25–7.45 (m, 2H), 7.71 (dd, J = 8 and 2 Hz, 1H), 7.77 (s, 1H), 7.89 (s, 1H), 8.14 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5, 28.1, 39.0, 52.0, 52.1, 84.7, 115.3 (2 carbons), 119.2, 123.2, 125.0, 125.3, 130.0, 130.3, 132.2, 134.9, 149.4, 166.9, 173.6; ESIMS (*m*/*z*) 410 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{25}O_6NNa$ 410.1574, found 410.1563; IR ($CHCl_3$) ν_{max} 1735, 1719, 1701, 1625 cm^{-1}.



116

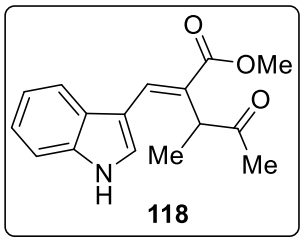
Methyl (*E*)-2-[(1*H*-Indol-3-yl)methylene]-4-[methoxy(methyl)amino]-3-methyl-4-oxobutanoate (117). To a stirred suspension of *N*,*O*-dimethylhdroxlamine hydrochloride (1.69 g, 17.44 mmol) in dry DCM (20 mL) was added Me_3Al in toluene (2 M, 17.44 mL, 34.88 mmol) in a dropwise fashion at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h at 25 °C and then again cooled to 0 °C. To the reaction mixture was added solution of compound **116** (4.50 g, 11.62 mmol) in DCM (10 mL) in a dropwise manner over 10 min. The reaction mixture was stirred at 25 °C for 6 h and the reaction was quenched by addition of saturated aqueous tartaric acid (10 mL) at 0 °C. The reaction mixture was further stirred for 30 min at 0 °C and then diluted with water. It was extracted with DCM (25 mL × 3) and the combined organic layer was washed with water, brine and dried over



117

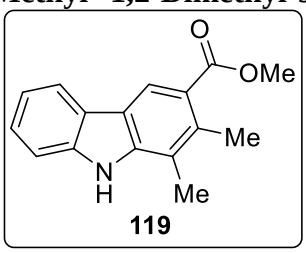
Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (4:6) as an eluent afforded Weinreb amide **117** as a yellow solid (3.00 g, 82%). Mp 152–154 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48 (d, J = 8 Hz, 3H), 3.09 (s, 3H), 3.40 (s, 3H), 3.85 (s, 3H), 4.28 (q, J = 8 Hz, 1H), 7.18–7.34 (m, 2H), 7.46 (dd, J = 6 and 2 Hz, 1H), 7.71 (d, J = 2 Hz, 1H), 7.82 (dd, J = 6 and 2 Hz, 1H), 8.09 (s, 1H), 9.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 33.0, 37.6, 52.1, 60.8, 110.8, 111.6, 118.4, 120.7, 122.9, 126.3, 127.0, 127.8, 130.0, 135.4, 168.2, 175.7; ESIMS (*m*/*z*) 339 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}O_4N_2Na$ 339.1315, found 339.1307; IR ($CHCl_3$) ν_{max} 3466, 1696, 1651 cm^{-1}.

Methyl (*E*)-2-[(1*H*-Indol-3-yl)methylene]-3-methyl-4-oxopentanoate (118). To a stirred solution of Weinreb amide **117** (1.50 g, 4.74 mmol) in THF (25 mL) was added methylmagnesium bromide solution in THF (3 M, 3.95 mL, 11.86 mmol) in a dropwise fashion at −10 °C under argon atmosphere. The reaction mixture was stirred for 2 h at −10 °C to 0 °C and the reaction was quenched by saturated aqueous NH_4Cl solution (30 mL). It was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (100 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification using ethyl acetate–petroleum ether (3:7) as an eluent afforded product **118** as a solid (950 mg, 74%). Mp 110–112 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.35 (d, J = 10 Hz, 3H), 2.00 (s, 3H), 3.77 (s, 3H), 3.94 (q, J = 10 Hz, 1H), 7.15–7.25 (m, 2H), 7.52 (d, J = 10 Hz, 1H), 7.79 (d, J = 10 Hz, 1H), 7.84 (s, 1H), 8.15 (s, 1H), 10.95 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 14.3, 27.6, 48.1, 52.0, 111.4, 112.9, 119.1, 121.5, 123.7, 124.4, 128.4, 129.0, 133.1, 137.2, 168.4, 206.4; ESIMS (*m*/*z*) 294 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{18}O_3N$ 272.1281, found 272.1277; IR ($CHCl_3$) ν_{max} 3430,1700,1680, 1650 cm^{-1}.



118

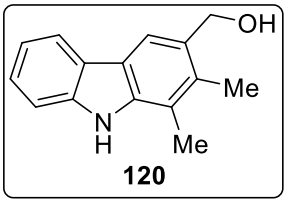
Methyl 1,2-Dimethyl-9*H*-carbazole-3-carboxylate (119). To a stirred solution of compound **118** (800 mg, 2.95 mmol) in EtOH (15 mL) was added *p*-TSA (2.24 g, 11.80 mmol) and the reaction mixture was refluxed for 4 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (50 mL) and the organic phase was



119

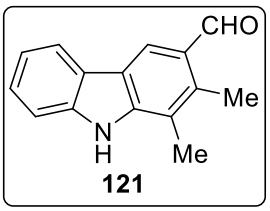
washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue by using ethyl acetate–petroleum ether (2:8) as eluent yielded pure product **119** as a white solid (675 mg, 90%). Mp 200–202 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.44 (s, 3H), 2.65 (s, 3H), 3.94 (s, 3H), 7.17–7.30 (m, 1H), 7.33–7.45 (m, 2H), 8.03 (d, J = 8 Hz, 1H), 8.11 (br s, 1H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 17.0, 51.8, 110.8, 118.7, 120.0, 120.3 (2 carbons), 121.1, 122.5, 123.9, 125.9, 135.2, 139.8, 148.4, 169.5; ESIMS (*m*/*z*) 254 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{16}O_2N$ 254.1176, found 254.1171; IR ($CHCl_3$) ν_{max} 3469, 1707, 1634 cm^{-1}.

(1,2-Dimethyl-9*H*-carbazol-3-yl)methanol (120). To a stirred solution of compound **119** (500 mg, 1.97 mmol) in THF (15 mL) was added LAH (112 mg, 2.96 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 3 h at the same temperature and the reaction was quenched with saturated aqueous sodium sulfate (10 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (80 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent furnished pure product **120** as a solid (370 mg, 83%). Mp 254–256 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 2.42 (s, 3H), 2.50 (s, 3H), 3.94 (t, J = 5 Hz, 1H), 4.80 (d, J = 5 Hz, 2H), 7.14 (t, J = 10 Hz, 1H), 7.32 (t, J = 10 Hz,1H), 7.48 (d, J = 10 Hz, 1H), 7.93 (s, 1H), 8.03 (d, J = 10 Hz, 1H), 10.11 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 13.9, 15.0, 64.8, 111.7, 118.1, 119.1, 119.6, 120.6, 121.0, 124.8, 125.7, 132.5, 133.0, 140.3, 141.2; ESIMS (*m*/*z*) 248 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{15}ONNa$ 248.1046, found 248.1043; IR ($CHCl_3$) ν_{max} 3400, 3200, 1620 cm^{-1}.



120

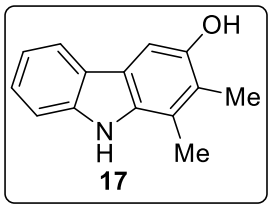
1,2-Dimethyl-9*H*-carbazole-3-carbaldehyde (121). To a mixture of compound **120** (200 mg, 0.88 mmol) and Celite (250 mg) in DCM (10 mL) was added PCC (287 mg, 1.33 mmol) at 0 °C under argon atmosphere and the reaction mixture was stirred for 1 h. The reaction mixture was filtered and concentrated in vacuo. The silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished aldehyde **121** as a solid (177 mg, 89%). Mp 218–220 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 2.54 (s, 3H), 2.75 (s, 3H), 7.25 (t, J = 10



121

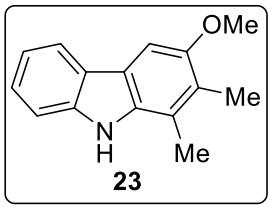
Hz, 1H), 7.42 (t, *J* = 8 Hz,1H), 7.55 (d, *J* = 8 Hz, 1H), 8.18 (d, *J* = 10 Hz, 1H), 8.47 (s, 1H), 10.31 (s, 1H), 10.66 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 13.5, 15.0, 112.3, 120.4, 120.9, 121.2, 121.5, 124.7, 125.6, 127.0, 128.6, 136.4, 141.6, 143.9, 193.1; ESIMS (*m*/*z*) 224 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{14}ON$ 224.1070, found 224.1069; IR ($CHCl_3$) ν_{max} 3430, 1680, 1600 cm^{-1}.

1,2-Dimethyl-9*H*-carbazol-3-ol (Sorazolon E, **17).** To a mixture of compound **121** (100 mg, 0.44 mmol) and $KHSO_4$ (20 mg) in MeOH (6 mL) was added 30% H_2O_2 (25 mg) at 0 °C and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished product sorazolon E (**17**) as a solid (90 mg, 95%). Mp 246–248 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 2.32 (s, 3H), 2.47 (s, 3H), 7.05 (t, *J* = 8 Hz, 1H), 7.27 (t, *J* = 8 Hz,1H), 7.30 (s, 1H), 7.40 (d, *J* = 8 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 12.6, 14.1, 103.3, 111.8, 119.0, 120.2, 120.6, 121.7, 123.4, 124.9, 125.7, 135.9, 142.0, 150.0; ESIMS (*m*/*z*) 212 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3430, 3250, 1605 cm^{-1}.



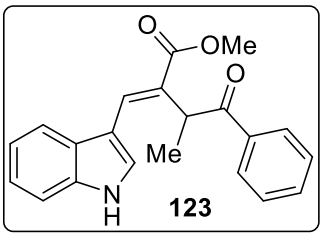
17

3-Methoxy-1,2-dimethyl-9*H*-carbazole (23). To a mixture of compound **17** (52 mg, 0.24 mmol) and K_2CO_3 (66 mg, 0.48 mmol) in acetone (10 mL) was added MeI (30μL, 0.49 mmol) under argon atmosphere and the reaction mixture was refluxed for 15 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (20 mL) and the organic phase was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent furnished product **23** as a solid (54 mg, 98%). Mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.36 (s, 3H), 2.47 (s, 3H), 3.96 (s, 3H), 7.20 (t, *J* = 10 Hz, 1H), 7.37 (t, *J* = 10 Hz, 1H), 7.40 (s, 1H), 7.43 (d, *J* = 10 Hz, 1H), 7.79 (br s, 1H), 8.01 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.3, 13.9, 56.2, 98.9, 110.7, 118.9, 119.0, 119.9, 120.1, 124.1, 124.2, 124.9, 134.1, 139.6, 152.5; ESIMS (*m*/*z*) 224 $[M-H]^+$; IR ($CHCl_3$) ν_{max} 3420 cm^{-1}.



23

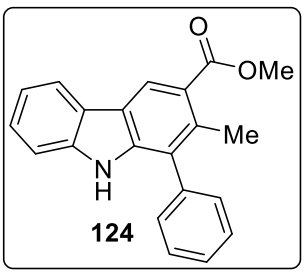
Methyl (*E*)-2-[(1*H*-Indol-3-yl)methylene]-3-methyl-4-oxo-4-phenylbutanoate (123).



123

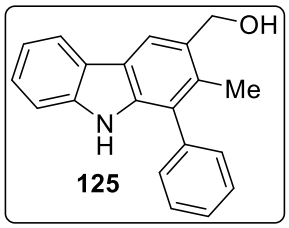
To a stirred solution of Weinreb amide **117** (1.30 g, 4.11 mmol) in THF (25 mL) was added phenylmagnesium chloride solution in THF (2 M, 5.14 mL, 10.28 mmol) in a dropwise fashion at −10 °C under argon atmosphere. The reaction mixture was stirred for 2 h at −10 °C to 0 °C and quenched by saturated aqueous NH_4Cl solution (30 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (100 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (3:7) as an eluent afforded product **123** as a white solid (980 mg, 71%). Mp 186–188 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 1.53 (d, J = 6 Hz, 3H), 3.56 (s, 3H), 4.68 (q, J = 8 Hz, 1H), 7.20–7.70 (m, 8H), 7.81 (dd, J = 8 and 2 Hz, 1H), 8.08 (d, J = 2 Hz, 1H), 8.10 (s, 1H), 11.09 (br s, 1H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 14.9, 44.5, 52.2, 111.9, 113.4, 119.5, 122.1, 124.3, 128.3, 129.0, 129.3, 129.5, 129.7, 132.6, 133.1, 137.7, 139.3, 168.3, 200.2; ESIMS (*m*/*z*) 356 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{19}O_3NNa$ 356.1257, found 356.1254; IR ($CHCl_3$) ν_{max} 3321, 1700, 1616 cm^{-1}.

Methyl 2-Methyl-1-phenyl-9*H*-carbazole-3-carboxylate (124). To a stirred solution of compound **123** (900 mg, 2.70 mmol) in EtOH (15 mL) was added *p*-TSA (2.04 g, 10.80 mmol) and the reaction mixture was refluxed for 4 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (50 mL) and the organic phase was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (2:8) as an eluent yielded pure product **124** as a white solid (795 mg, 93%). Mp 134–136 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.53 (s, 3H), 3.96 (s, 3H), 7.20–7.60 (m, 8H), 7.81 (br s, 1H), 8.09 (d, J = 8 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.7, 51.8, 110.8, 120.1, 120.3, 120.4, 122.3, 122.9, 123.6, 125.6, 126.1, 127.9, 129.2, 130.0, 135.1, 137.2, 139.8, 140.9, 169.1; ESIMS (*m*/*z*) 316 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{17}O_2NNa$ 338.1152, found 338.1149; IR ($CHCl_3$) ν_{max} 3463, 1727, 1609 cm^{-1}.



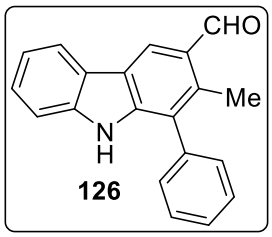
124

(2-Methyl-1-phenyl-9*H*-carbazol-3-yl)methanol (125). To a stirred solution of compound **124** (600 mg, 1.90 mmol) in THF (18 mL) was added LAH (86 mg, 2.28 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 3 h at the same temperature and the reaction was quenched with saturated aqueous sodium sulfate (10 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (80 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent furnished pure product **125** as a solid (465 mg, 85%). Mp 154–156 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 2.26 (s, 3H), 4.81 (s, 2H), 7.11 (td, J = 8 and 2 Hz, 1H), 7.27 (td, J = 8 and 2 Hz, 1H), 7.30–7.60 (m, 6H), 8.00 (d, J = 8 Hz, 1H), 8.03 (s, 1H); ^{13}C NMR (CD_3OD, 50 MHz) δ 16.4, 65.1, 112.2, 119.9, 120.5, 120.7, 122.0, 124.7, 126.2, 126.8, 128.6, 130.0, 131.4, 131.8, 132.8, 139.8, 140.1, 141.9; ESIMS (*m*/*z*) 288 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{17}ONNa$ 310.1202, found 310.1202; IR ($CHCl_3$) ν_{max} 3431, 1614 cm^{-1}.



125

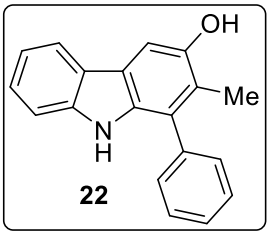
2-Methyl-1-phenyl-9*H*-carbazole-3-carbaldehyde (126). To a mixture of compound **125** (300 mg, 1.04 mmol) and Celite (350 mg) in DCM (15 mL) was added PCC (337 mg, 1.56 mmol) at 0 °C under argon atmosphere and the reaction mixture was stirred for 1 h at same temperature. The reaction mixture was filtered and concentrated in vacuo. The silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished aldehyde **126** as a solid (260 mg, 87%). Mp 212–214 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.63 (s, 3H), 7.30 (t, J = 8 Hz, 1H), 7.33–7.62 (m, 7H), 7.95 (br s, 1H), 8.13 (d, J = 4 Hz, 1H), 8.58 (s, 1H), 10.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5, 111.0, 120.6, 120.7, 121.0, 123.7, 125.4, 125.6, 126.5, 127.7, 128.2, 129.3, 130.0, 135.9, 136.4, 139.7, 142.0, 192.6; ESIMS (*m*/*z*) 286 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{15}ONNa$ 308.1046, found 308.1044; IR ($CHCl_3$) ν_{max} 3465, 2929, 1732, 1677 cm^{-1}.



126

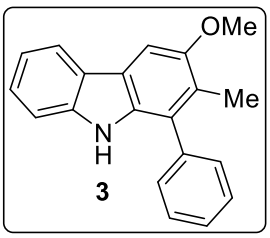
2-Methyl-1-phenyl-9*H*-carbazol-3-ol (22). To a mixture of compound **126** (150 mg, 0.52 mmol) and $KHSO_4$ (25 mg) in MeOH (8 mL) was added 30% H_2O_2 (30 mg) at 0 °C and the reaction mixture was stirred for 1 h at same temperature. It was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL). The organic phase

was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished product **22** as a white solid (138 mg, 96%). Mp 178–180 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.25 (s, 3H), 4.73 (br s, 1H), 7.18 (dd, J = 8 and 2 Hz, 1H), 7.28–7.61 (m, 8H), 7.62 (br s, 1H), 7.98 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 104.5, 110.6, 118.9, 120.2, 120.9, 121.3, 123.3, 125.4, 127.7, 129.0, 129.9, 133.6, 137.4, 139.7, 148.1; ^{1}H NMR (acetone-d_6, 500 MHz) δ 2.17 (s, 3H), 7.07 (t, J = 10 Hz, 1H), 7.25 (t, J = 10 Hz, 1H), 7.38 (d, J = 10 Hz,1H), 7.40–7.47 (m, 3H), 7.50–7.55 (m, 2H), 7.56 (s, 1H), 7.96 (d, J = 10 Hz, 1H); ^{13}C NMR (aceone-d_6, 125 MHz) δ 14.5, 105.0, 112.3, 119.4, 121.0, 122.2, 122.9, 124.5, 126.1, 126.9, 128.6, 130.1, 131.3, 134.6, 139.5, 141.9, 150.7; ESIMS (m/z) 273 $[M]^+$; IR ($CHCl_3$) ν_{max} 3430, 1638 cm^{-1}.



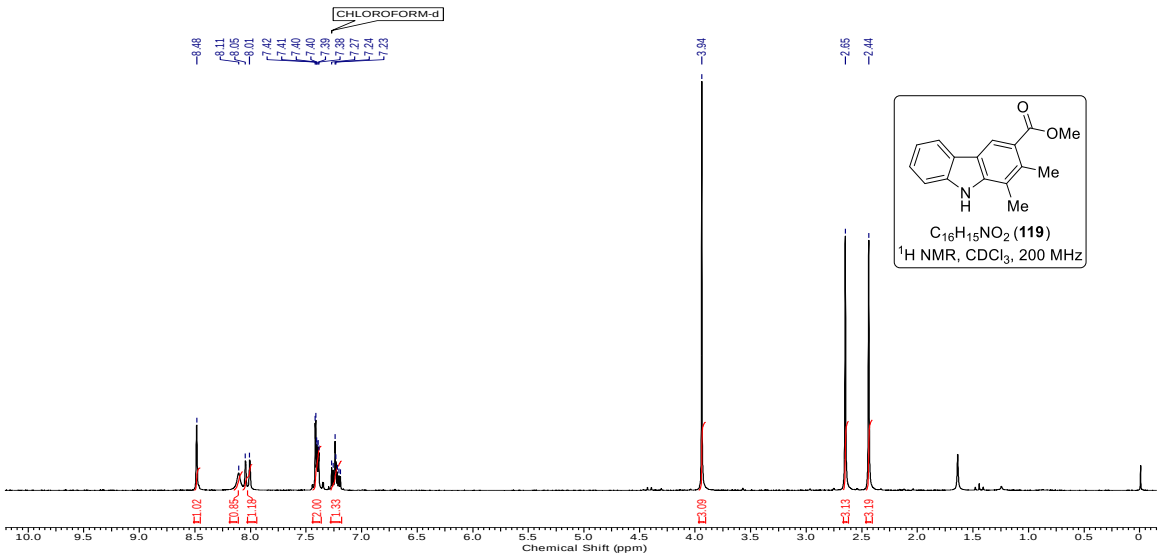
22

3-Methoxy-2-methyl-1-phenyl-9*H*-carbazole (Hyellazole, 3). To a mixture of compound **22** (100 mg, 0.36 mmol) and K_2CO_3 (101 mg, 0.73 mmol) in acetone (12 mL) was added MeI (45 μL, 0.73 mmol) under argon atmosphere and the reaction was refluxed for 15 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (20 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent yielded product hyellazole (**3**) as a solid (101 mg, 97%). Mp 132–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 3H), 4.00 (s, 3H), 7.18 (t, J = 8 Hz, 1H), 7.26–7.35 (m, 2H), 7.40–7.48 (m, 3H), 7.51–7.57 (m, 3H), 7.62 (br s, 1H), 8.03 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 56.2, 100.3, 110.6, 118.9, 119.9, 120.3, 123.7, 123.8, 125.1, 125.6, 127.6, 129.0, 129.9, 133.3, 137.6, 139.5, 152.7; ESIMS (m/z) 311 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3424, 1638 cm^{-1}.



3

2A.6 Selected Spectra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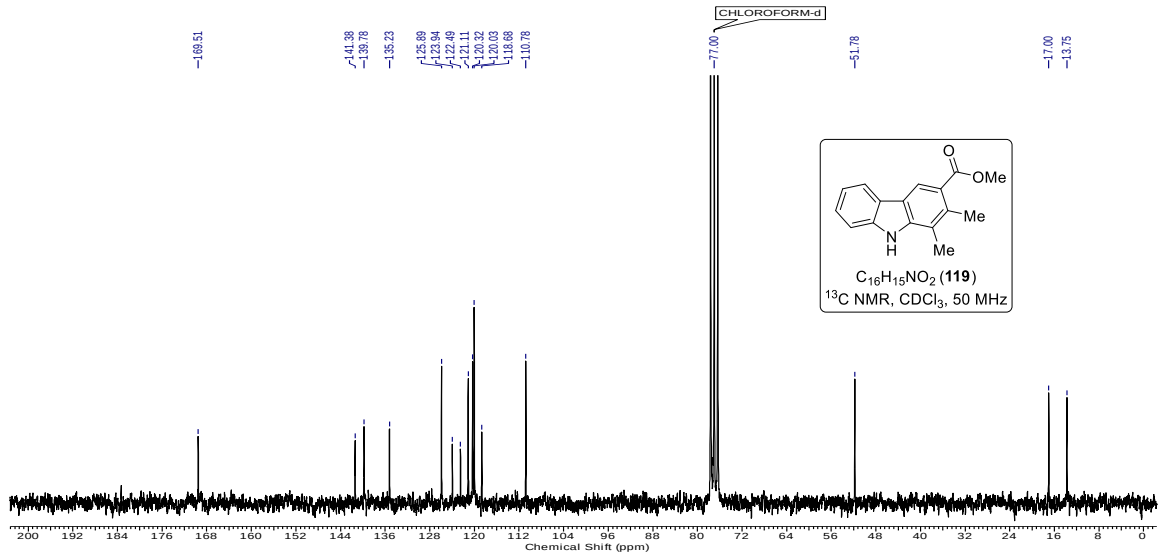
8.11
8.05
8.01
7.42
7.41
7.40
7.40
7.38
7.27
7.24
7.23
3.94
2.65
2.44
O
OMe
Me
N
H
Me
C16H15NO2 (119)
1H NMR, CDCl3, 200 MHz
1.02
0.95
1.18
2.00
1.33
3.09
3.13
3.19
Chemical Shift (ppm)


CHLOROFORM-d
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135.23
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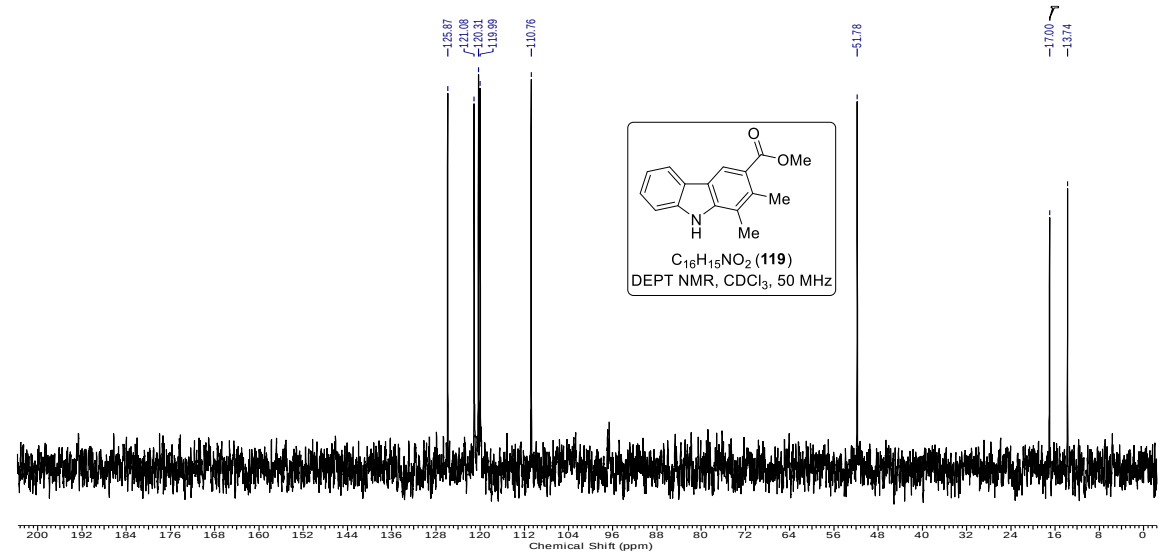
123.94
122.49
121.11
120.32
120.03
118.68
110.78
77.00
51.78
17.00
13.75
O
OMe
Me
N
H
Me
C16H15NO2 (119)
13C NMR, CDCl3, 50 MHz
Chemical Shift (ppm)


125.87
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120.31
119.99
110.76
51.78
17.00
13.74
O
OMe
Me
N
H
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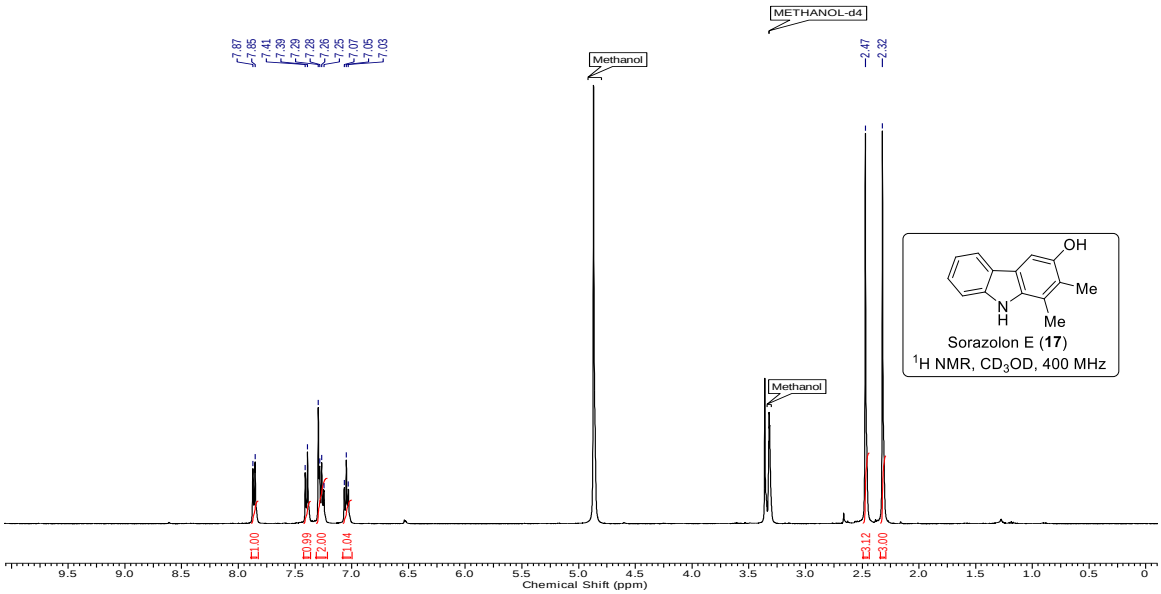
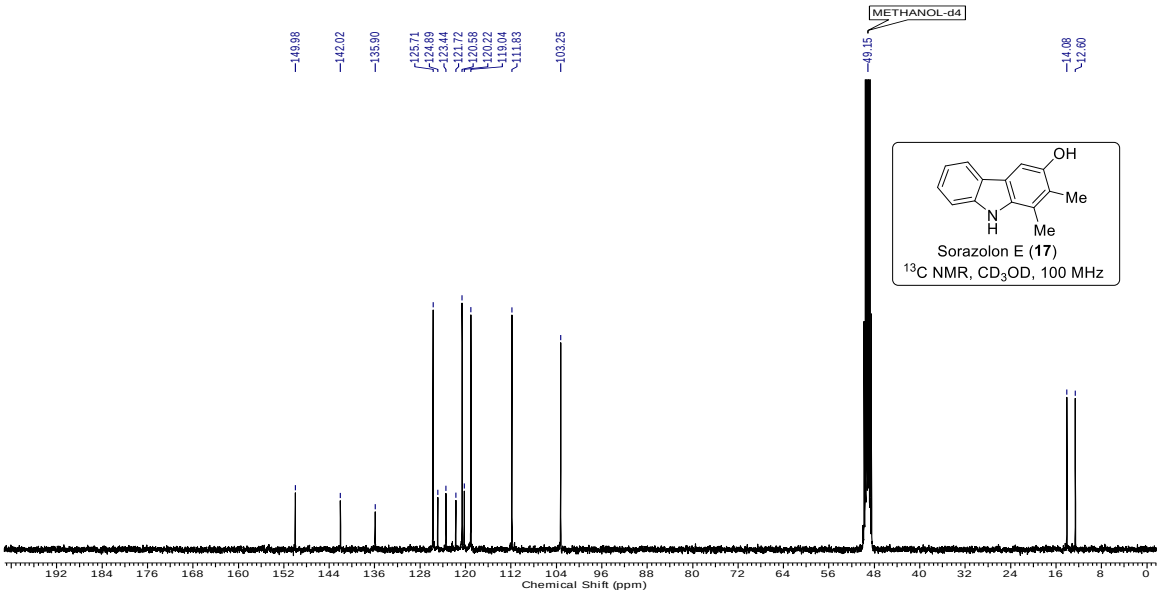
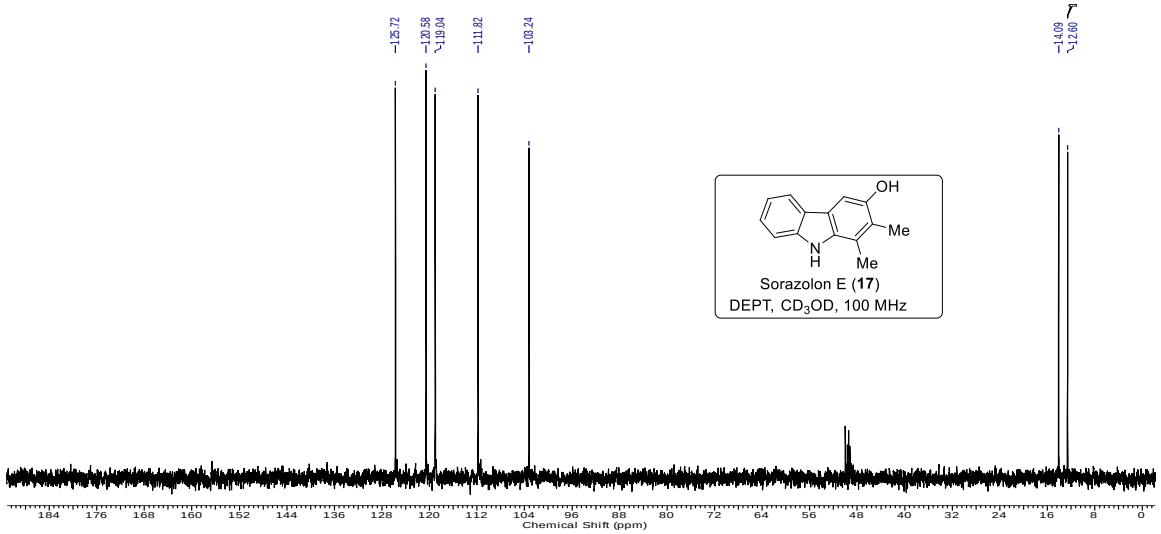
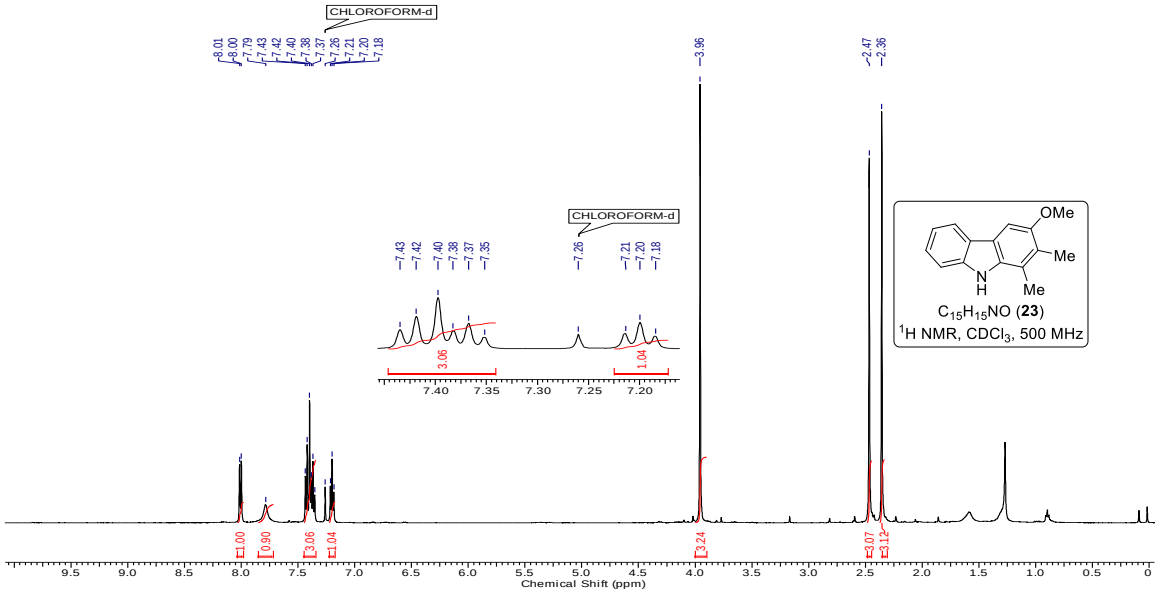
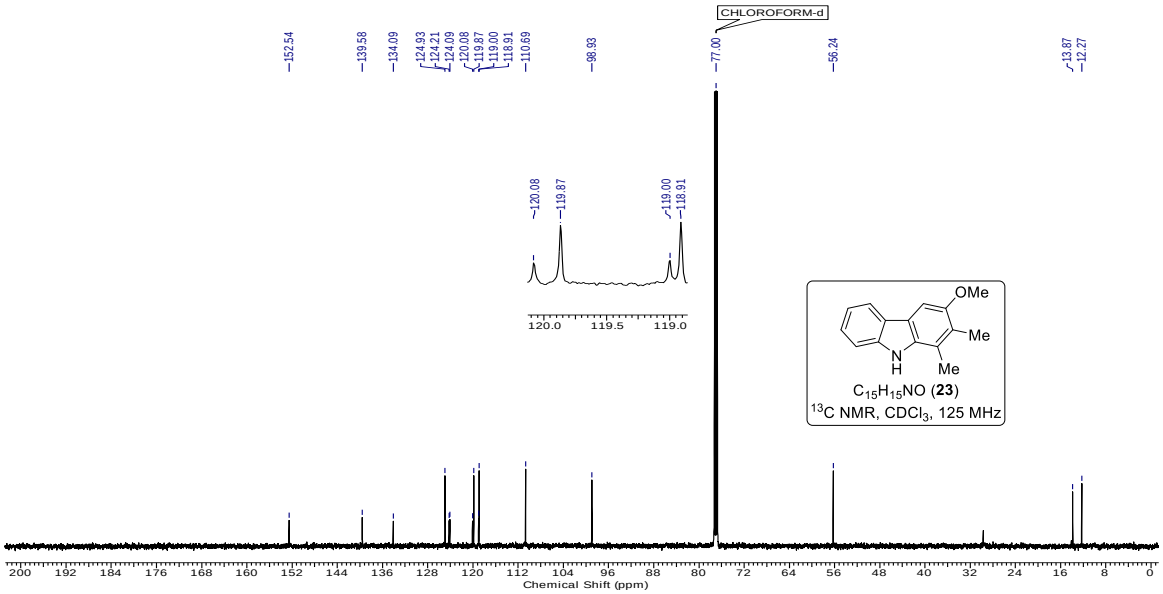
C16H15NO2 (119)
DEPT NMR, CDCl3, 50 MHz
Chemical Shift (ppm)

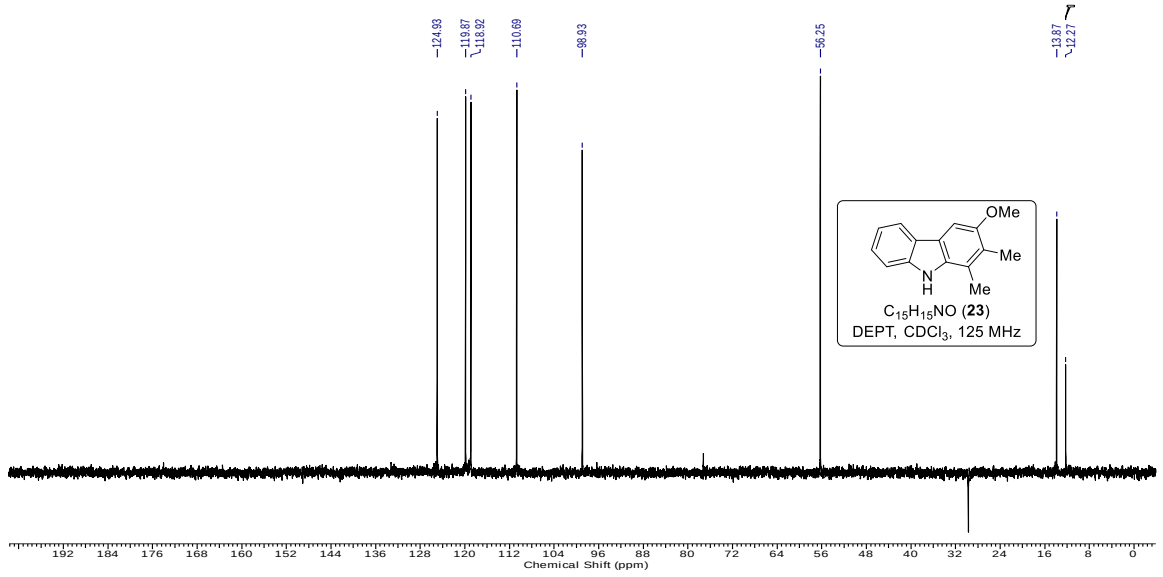

METHANOL-d4
Methanol
Methanol
Sorazolon E (17)
1H NMR, CD3OD, 400 MHz
Chemical Shift (ppm)

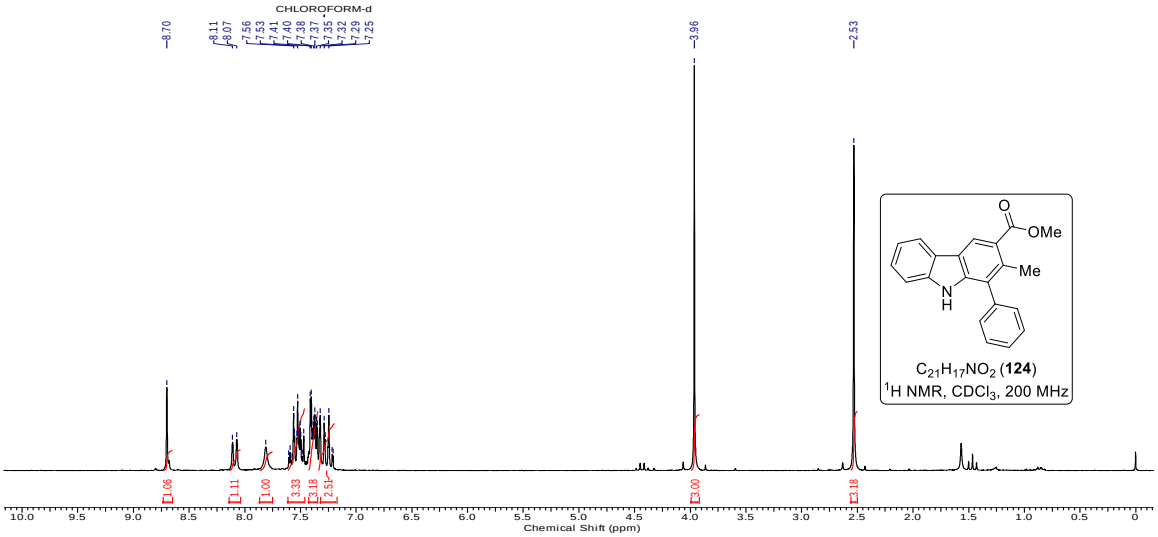

METHANOL-d4
Sorazolon E (17)
13C NMR, CD3OD, 100 MHz
Chemical Shift (ppm)

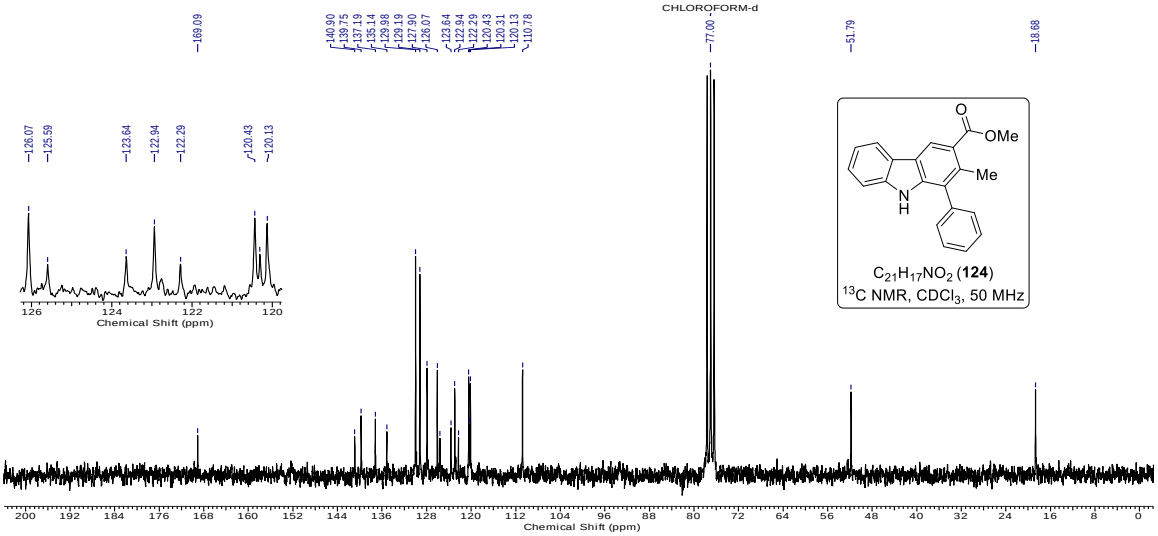

Sorazolon E (17)
DEPT, CD3OD, 100 MHz
Chemical Shift (ppm)


CHLOROFORM-d
8.01
8.00
7.79
7.43
7.42
7.40
7.38
7.37
7.26
7.21
7.20
7.18
3.96
2.47
2.36
CHLOROFORM-d
7.43
7.42
7.40
7.38
7.37
7.35
7.26
7.21
7.20
7.18
3.06
1.04
7.40
7.35
7.30
7.25
7.20
OMe
Me
N
H
Me
C15H15NO (23)
1H NMR, CDCl3, 500 MHz
1.00
0.90
3.06
1.04
3.24
5.07
3.12
Chemical Shift (ppm)


CHLOROFORM-d
152.54
139.58
134.09
124.93
124.21
124.09
120.08
119.87
119.00
118.91
110.69
98.93
77.00
56.24
13.87
12.27
120.08
119.87
119.00
118.91
120.0
119.5
119.0
OMe
Me
N
H
Me
C15H15NO (23)
13C NMR, CDCl3, 125 MHz
Chemical Shift (ppm)


124.93
119.87
118.92
110.69
98.93
56.25
13.87
12.27
OMe
Me
N
H
Me
C15H15NO (23)
DEPT, CDCl3, 125 MHz
Chemical Shift (ppm)


CHLOROFORM-d
8.70
8.11
8.07
7.56
7.53
7.41
7.40
7.38
7.37
7.35
7.32
7.29
7.25
3.96
2.53
1.06
1.11
1.00
3.33
3.18
2.51
3.00
3.18
O
OMe
Me
N
H
$C_{21}H_{17}NO_2$ (**124**)
^{1}H NMR, $CDCl_3$, 200 MHz
Chemical Shift (ppm)


CHLOROFORM-d
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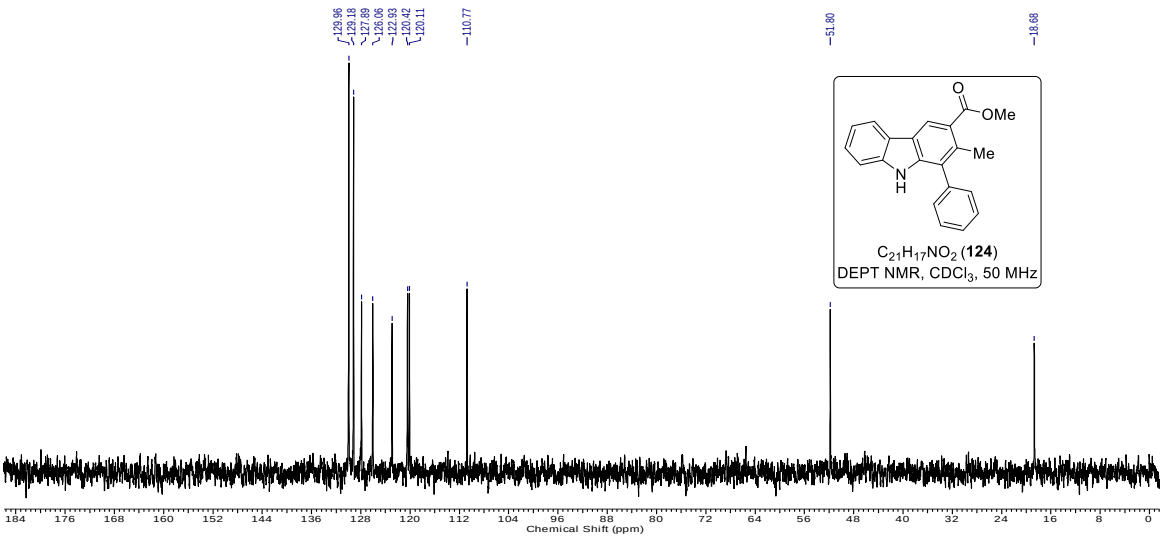
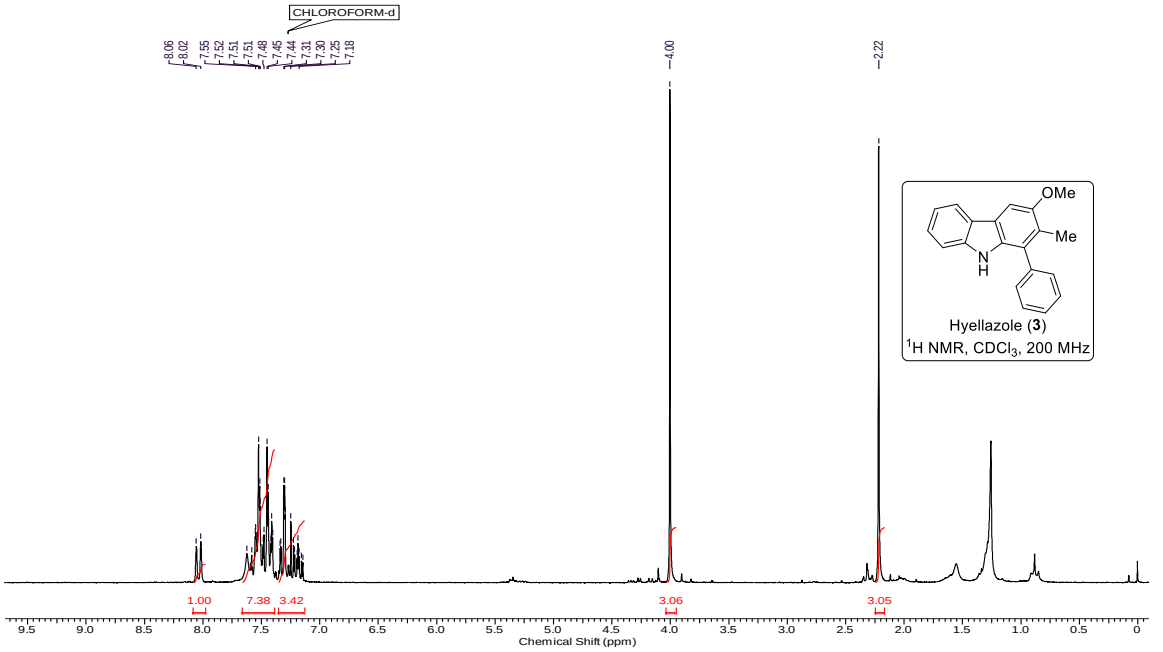
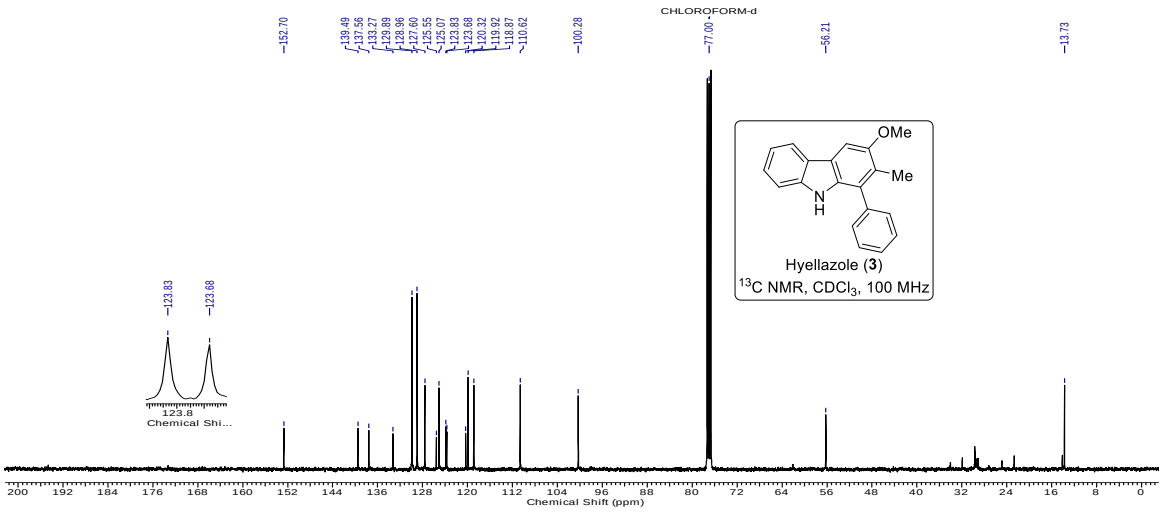
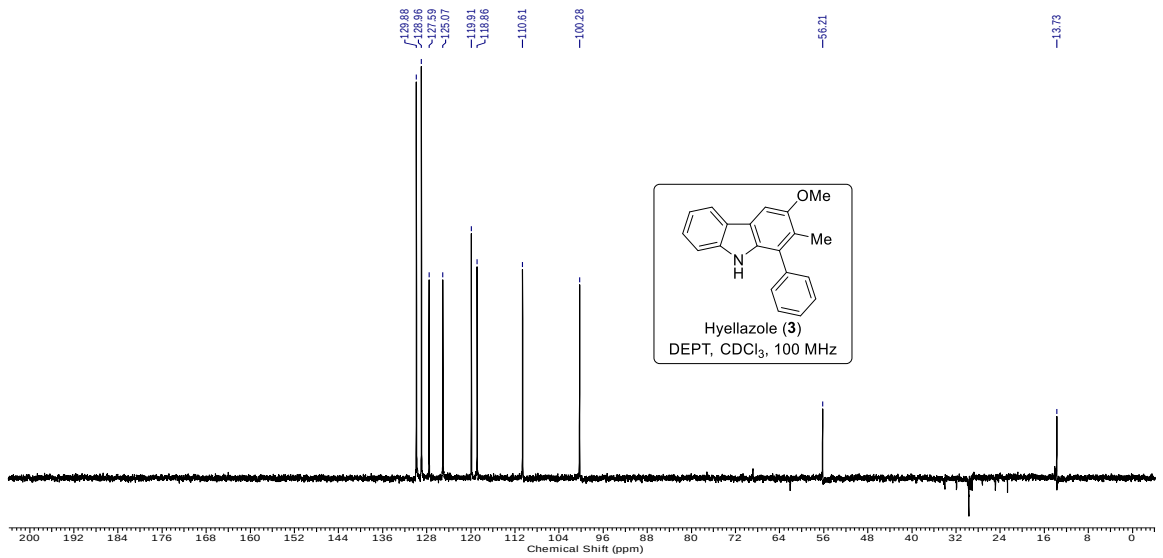
140.90
139.75
137.19
135.14
129.98
129.19
127.90
126.07
123.64
122.94
122.29
120.43
120.31
120.13
110.78
77.00
51.79
18.68
126.07
125.59
123.64
122.94
122.29
120.43
120.13
Chemical Shift (ppm)
O
OMe
Me
N
H
$C_{21}H_{17}NO_2$ (**124**)
^{13}C NMR, $CDCl_3$, 50 MHz
Chemical Shift (ppm)


129.96
129.18
127.89
126.06
122.93
120.42
120.11
110.77
51.80
18.68
O
OMe
Me
N
H
$C_{21}H_{17}NO_2$ (**124**)
DEPT NMR, $CDCl_3$, 50 MHz
Chemical Shift (ppm)


CHLOROFORM-d
8.06
8.02
7.55
7.52
7.51
7.51
7.48
7.45
7.44
7.31
7.30
7.25
7.18
4.00
2.22
OMe
Me
N
H
Hyellazole (3)
1H NMR, CDCl3, 200 MHz
1.00
7.38
3.42
3.06
3.05
Chemical Shift (ppm)


CHLOROFORM-d
152.70
139.49
137.56
133.27
129.89
128.96
127.60
125.55
125.07
123.83
123.68
120.32
119.92
118.87
110.62
100.28
77.00
56.21
13.73
123.83
123.68
OMe
Me
N
H
Hyellazole (3)
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


129.88
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127.59
125.07
119.91
118.86
110.61
100.28
56.21
13.73
OMe
Me
N
H
Hyellazole (3)
DEPT, CDCl3, 100 MHz
Chemical Shift (ppm)

2A.7 References

1. (a) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (b) Flyer, A. N.; Si, C.; Myers, A. G. *Nat. Chem.* **2010**, *2*, 886.
2. (a) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099. (b) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193. (c) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (d) Moody, C. J. *Synlett* **1994**, 681. (e) Knölker, H.-J. *Synlett* **1992**, 371 and references cited in ref 2a–e.
3. Zhang, A.; Lin, G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1021.
4. Wu, T.-S.; Huang, S.-C.; Wu, P.-L. *Chem. Pharm. Bull.* **1998**, *46*, 1459.
5. Iwatsuki, M.; Niki, E.; Kato, S.; Nishikori, K. *Chem. Lett.* **1992**, *21*, 1735.
6. Grammel, H.; Wolf, H.; Gilles, E.-D.; Huth, F.; Laatsch, H. Z. *Naturforsch., C* **1998**, *53*, 325.
7. (a) Sakano, K.-I.; Ishimaru, K.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 683. (b) Sakano, K.-I.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 961. (c) Kaneda, M.; Sakano, K.-I.; Nakamura, S.; Kushi, Y.; Iitaka, Y. *Heterocycles* **1981**, *15*, 993. (d) Hook, D. J.; Yacobucci, J. J.; O'Connor, S.; Lee, M.; Kerns, E.; Krishnan, B.; Matson, J.; Hesler, G. *J. Antibiot.* **1990**, *43*, 1347. (e) Karwehl, S.; Jansen, R.; Huch, V.; Stadler, M. *J. Nat. Prod.* **2016**, *79*, 369.
8. (a) Sakano, K.-I.; Liu, H.; Li, C.-J.; Yang, J.-Z.; Ning, N.; Si, Y.-K.; Li, L.; Chen, N.-H.; Zhao, Q.; Zhang, D.-M. *J. Nat. Prod.* **2012**, *75*, 677. (b) Shen, D.-Y.; Chan, Y.-Y.; Hwang, T.-L.; Juang, S.-H.; Huang, S.-C.; Kuo, P.-C.; Thang, T.-D.; Lee, E.-J.; Damu, A.-G.; Wu, T.-S. *J. Nat. Prod.* **2014**, *77*, 1215.
9. Cardellina, J. H., II; Kirkup, M. P.; Moore, R. E.; Mynderse, J. S.; Seff, K.; Simmons, C. J. *Tetrahedron Lett.* **1979**, *20*, 4915.
10. Kato, S.; Kawai, H.; Kawasaki, T.; Toda, Y.; Urata, T.; Hayakawa, Y. *J. Antibiot.* **1989**, *42*, 1879.
11. Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 376.
12. Clive, D. L. J.; Etkin, N.; Joseph, T.; Lown, W. *J. Org. Chem.* **1993**, *58*, 2442.
13. Tullio, P.; Marchesini, A.; Beccalli, E. M. *Tetrahedron* **1996**, *52*, 3029.
14. (a) Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett.* **1999**, *40*, 6915. (b) Knölker, H.-J.; Bauermeister, M.; Bläser, D.; Boese, R.; Pannek, J.-B. *Angew. Chem., Int. Ed.* **1989**, *28*, 223. (c) Knölker, H.-J.; Bauermeister, M.; Bläser, D.; Boese, R.; Pannek, J.-B. *Angew. Chem., Int. Ed.* **1989**, *101*, 225. (d) Knölker, H.-J.; Bauermeister, M.

J. Chem. Soc., Chem. Commun. **1989,** 1468. (e) Knölker, H.-J.; Bauermeister, M. *Helv. Chim. Acta* **1993**, *76*, 2500.

15. Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513.
16. (a) Ca, N. D.; Sassi, G.; Catellani, M. *Adv. Synth. Catal.* **2008**, *350*, 2179. (b) Catellani, M.; Motti, E.; Della Ca', N. *Top. Catal.* **2010**, *53*, 991.
17. Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 3856.
18. Kawasaki, T.; Nonaka, Y.; Sakamoto, M. *J. Chem. Soc., Chem. Commun.* **1989**, 43.
19. Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.
20. Beccalli, E. M.; Marchesini, A.; Pilati, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 579.
21. Azzena, U.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1993**, *34*, 5635.
22. (a) Knölker, H.-J.; Hopfmann, T. *Synlett* **1995**, 981. (b) Knölker, H.-J.; Hopfmann, T. *Tetrahedron* **2002**, *58*, 8937.
23. (a) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535. (b) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1996**, *37*, 2593.
24. Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281.
25. Duval, E.; Cuny, G. D. *Tetrahedron Lett.* **2004**, *45*, 5411 and references cited therein.
26. Poudel, T. N.; Lee, Y. R. *Chem. Sci.* **2015**, *6*, 7028.
27. (a) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109*, 3012. (b) Li, J. W.-H.; Vederas, J. C. *Science* **2009**, *325*, 161. (c) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451 and references cited in ref 27a–c.
28. (a) Zheng, X.; Lv, L.; Lu, S.; Wang, W.; Li, Z. *Org. Lett.* **2014**, *16*, 5156. (b) Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Ess, D. H.; Kurti, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2701. (c) Wang, S.; Chai, Z.; Wei, Y.; Zhu, X.; Zhou, S.; Wang, S. *Org. Lett.* **2014**, *16*, 3592. (d) Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 2892. (e) Zhu, C.; Ma, S. *Org. Lett.* **2014**, *16*, 1542. (f) Guney, T.; Lee, J. J.; Kraus, G. A. *Org. Lett.* **2014**, *16*, 1124. (g) Trosien, S.; Böttger, P.; Waldvogel, S. R. *Org. Lett.* **2014**, *16*, 402. (h) Hernandez-Perez, A. C.; Collins, S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 12696. (i) Kumar, V. P.; Gruner, K. K.; Kataeva, O.; Knölker, H.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 11073. (j) Shu, D.; Winston-

McPherson, G. N.; Song, W.; Tang, W. *Org*. *Lett*. **2013**, *15*, 4162. (k) Louillat, M.-L.; Patureau, F. W. *Org*. *Lett*. **2013**, *15*, 164.

29. (a) Qiu, Y.; Kong, W.; Fu, C.; Ma, S. *Org*. *Lett*. **2012**, *14*, 6198. (b) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew*. *Chem*., *Int*. *Ed*. **2011**, *50*, 8605. (c) Cho, S. H.; Yoon, J.; Chang, S. *J*. *Am*. *Chem*. *Soc*. **2011**, *133*, 5996. (d) Wang, L.; Li, G.; Liu, Y. *Org*. *Lett*. **2011**, *13*, 3786. (e) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org*. *Lett*. **2011**, *13*, 3738. (f) Tsvelikhovsky, D.; Buchwald, S. L. *J*. *Am*. *Chem*. *Soc*. **2010**, *132*, 14048. (g) Rajeshwaran, G. G.; Mohanakrishnan, A. K. *Org*. *Lett*. **2011**, *13*, 1418. (h) Chen, C.-C.; Chin, L.-Y.; Yang, S.-C.; Wu, M.-J. *Org*. *Lett*. **2010**, *12*, 5652. (i) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J*. *Am*. *Chem*. *Soc*. **2008**, *130*, 16184. (j) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Nagase, Y.; Miyamura, T.; Shirakawa, E. *J*. *Am*. *Chem*. *Soc*. **2008**, *130*, 15823. (k) Choi, T. A.; Czerwonka, R.; Forke, R.; Jäger, A.; Knöll, J.; Krahl, M. P.; Krause, T.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *Med*. *Chem*. *Res*. **2008**, *17*, 374. (l) Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *ChemMedChem* **2006**, *1*, 812.

30. (a) Levick, M. T.; Grace, I.; Dai, S.-Y.; Kasch, N.; Muryn, C.; Lambert, C.; Turner, M. L.; Procter, D. J. *Org*. *Lett*. **2014**, *16*, 2292. (b) Yang, W.; Zhang, Z.; Han, C.; Zhang, Z.; Xu, H.; Yan, P.; Zhao, Y.; Liu, S. *Chem*. *Commun*. **2013**, *49*, 2822. (c) Tsvelikhovsky, D.; Buchwald, S. L. *J*. *Am*. *Chem*. *Soc*. **2011**, *133*, 14228. (d) Morin, J.-F.; Leclerc, M.; Adés, D.; Siove, A. *Macromol*. *Rapid Commun*. **2005**, *26*, 761. (e) Chmielewski, M. J.; Charon, M.; Jurczak, J. *Org*. *Lett*. **2004**, *6*, 3501. (f) Wang, Y. Z.; Epstein, A. J. *Acc*. *Chem*. *Res*. **1999**, *32*, 217 and references cited in ref 30a–f.

31. (a) Carrillo, R.; Martin, T.; Lopez-Rodriguez, M.; Crisostomo, F. P. *Org*. *Lett*. **2014**, *16*, 552. (b) Janvier, P.; Bienaymé, H.; Zhu, J. *Angew*. *Chem*., *Int*. *Ed*. **2002**, *41*, 4291. (c) Geng, Y.; Fechtenkötter, A.; Müllen, K. *J*. *Mater*. *Chem*. **2001**, *11*, 1634. (d) Thomaides, J.; Maslak, P.; Breslow, R. *J*. *Am*. *Chem*. *Soc*. **1988**, *110*, 3970. (e) Pastor, S. D.; Hyun, J. L.; Odorisio, P. A.; Rodebaugh, R. K. *J*. *Am*. *Chem*. *Soc*. **1988**, *110*, 6547 and references cited therein.

32. (a) Deore, P. S.; Argade, N. P. *J*. *Org*. *Chem*. **2014**, *79*, 2538. (b) Deore, P. S.; Argade, N. P. *Org*. *Lett*. **2013**, *15*, 5826. (c) Vaidya, S. D.; Argade, N. P. *Org*. *Lett*.

2013, *15*, 4006. (d) Mondal, P.; Argade, N. P. *J. Org. Chem.* **2013**, *78*, 6802. (e) Patel, R. M.; Argade, N. P. *Org. Lett.* **2013**, *15*, 14.

33. (a) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (b) Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2007**, 4516. (c) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (d) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (e) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (f) Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759. (g) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (h) Knölker, H.-J. *Curr. Org. Synth.* **2004**, *1*, 309. (i) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78. (j) Knölker, H.-J.; Knöll, J. *Chem. Commun.* **2003**, 1170. (k) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310. (l) Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B.; Bläser, D.; Boese, R. *Tetrahedron* **1993**, *49*, 841. (m) Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2463.

34. (a) Agarwal, S.; Cammerer, S.; Filali, S.; Frohner, W.; Knoll, J.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601. (b) Knölker, H.-J.; Fröhner, W.; Heinrich, R. *Synlett* **2004**, 2705. (c) Knölker, H.-J.; Baum, E.; Hopfmann, T. *Tetrahedron* **1999**, *55*, 10391. (d) Knölker, H.-J.; Baum, E.; Hopfmann, T. *Tetrahedron Lett.* **1995**, *36*, 5339. (e) Kano, S.; Sugino, E.; Hibino, S. *J. Chem. Soc., Chem. Commun.* **1980**, 1241.

35. (a) Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Eur. J. Org. Chem.* **2003**, 740. (b) Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Synthesis* **2002**, 557. (c) Knölker, H.-J.; Fröhner, W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 173. (d) Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett.* **1997**, *38*, 4051. (e) Knölker, H.-J.; Schlechtingen, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 349. (f) Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B. *Chem. Ber.* **1992**, *125*, 2783. (g) Knölker, H.-J.; Bauermeister, M. *Heterocycles* **1991**, *32*, 2443.

36. (a) Kshirsagar, U. A.; Argade, N. P. *Synthesis* **2011**, 1804. (b) Desai, S. B.; Argade, N. P. *J. Org. Chem.* **1997**, *62*, 4862. (c) Hedaya, E.; Theodoropulos, S. *Tetrahedron* **1968**, *24*, 2241. (d) Bringmann, G.; Tasler, S.; Endress, H.; Peters, K.; Peters, E.-M. *Synthesis* **1998**, 1501.

37. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.

Chapter 2

Section B

Biomimetic Collective Total Synthesis of Bioactive Carbazole Alkaloids Clausenaline D, Indizoline, Mafaicheenamine A, Claulamine A, Claulansine A and the Proposed Claulamine E

Note: An independent figure, table, scheme, structure and reference numbers have been used for the each section.

2B.1 Background

Carbazoles possess broad spectrum of promising biological activities.[1–6] The carbazole alkaloids claulansine G, clausenaline D, indizoline, mafaicheenamine A, claulamine A, claulansine A and claulamine E have been recently isolated from *Clausena lansium* and they exhibit potent anti-inflammatory, neuroprotective and antitumor activities against human cancer cell lines (Figure 1).[7–11] One synthesis of each clausenaline D (**3**) and indizoline (**7**) have been recently reported in the literature.[12] The synthesis of natural products mafaicheenamine A, claulamine A, claulansine A and claulamine E were awaited.

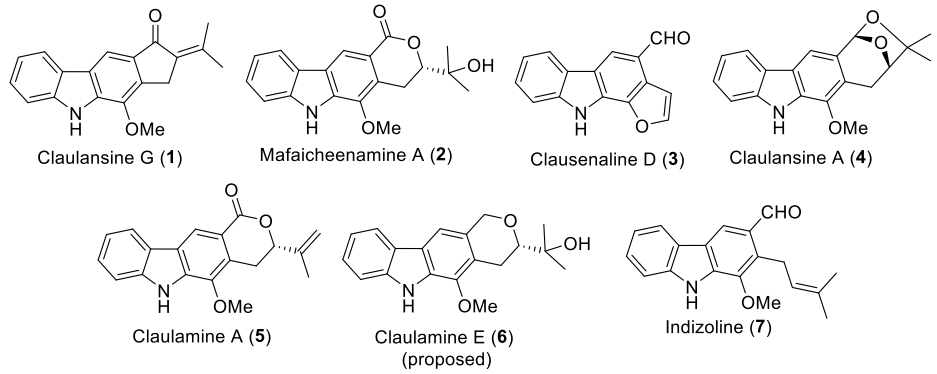
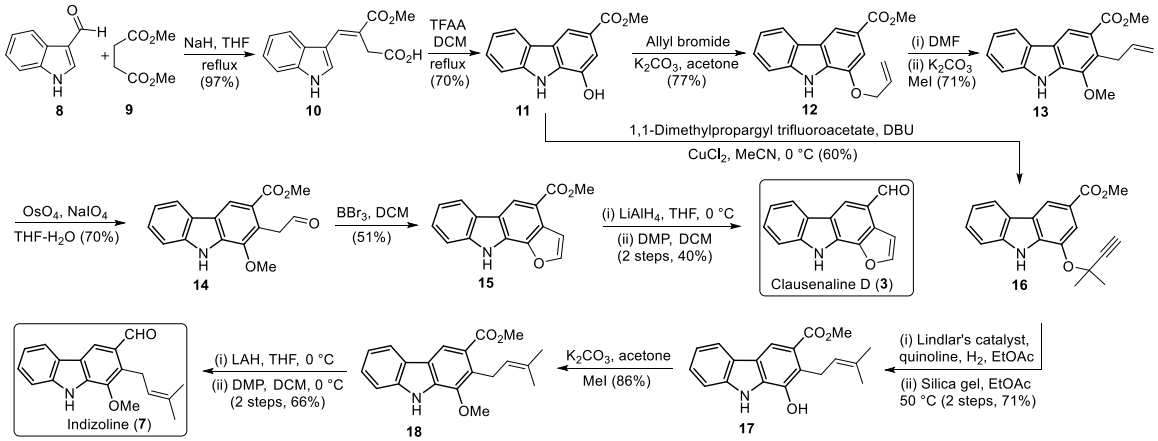


Figure 1. Representative Carbazole Alkaloids.

2B.2 Reported Synthesis of Indizoline and Clausenaline D

In 2016, Chang and co-workers have reported the second total synthesis of clausenaline D (**3**) and indizoline (**7**) (Scheme 1).[12] Stobbe condensation of indole-3-carbaldehyde (**8**) with dimethyl succinate (**9**) in the presence of sodium hydride delivered indole derivative **10** in 97% yield.



Scheme 1. Total Synthesis of Indizoline and Clausenaline D

The compound **10** was obtained in only 42% yield when sodium methoxide was used as a base.[13] TFAA-mediated intramolecular acylation of **10** delivered the desired carbazole **11**,

O-allylation of which followed by Claisen rearrangement and methylation gave the key intermediate **13** in very good yield. Dihydroxylation of **13** followed by sodium periodate oxidation furnished aldehyde **14** in 70% yield. Treatment of **14** with boron tribromide resulted in the formation of furocarbazole **15** in 51% yield via demethylation and concomitant intramolecular dehydrative furan ring formation. The methyl ester **15** on lithium aluminum hydride reduction followed by Dess–Martin oxidation gave clausenaline D (**3**) in 40% yield over the two steps. Propargylation of **11** with 1,1-dimethylpropargyl trifluoroacetate provided **16** in 60% yield. Hydrogenation of the triple bond in **16** in the presence of Lindlar's catalyst followed by Claisen rearrangement of the resulting allyl ether afforded **17** in 71% yield over the two steps. Methylation of free phenolic moiety in carbazole **17** furnished product **18** in 86% yield. Reduction of methyl ester unit in compound **18** with lithium aluminum hydride followed by Dess–Martin oxidation yielded indizoline (**7**) in 66% yield.

2B.3 Results and Discussion

Biomimetic Collective Total Synthesis of Bioactive Carbazole Alkaloids Clausenaline D, Indizoline, Mafaicheenamine A, Claulamine A, Claulansine A and the Proposed Claulamine E

Carbazoles are an important class of alkaloids and a large number of them have been isolated from plant, animal, microbial and marine origin.[1–3] Carbazoles display a wide range of biological activities and also find applications in electroluminescent materials owing to their electrical and thermal properties.[1–6] Clausenaline D, indizoline, mafaicheenamine A, claulamine A, claulansine A and claulamine E have been recently isolated from *Clausena lansium* and they exhibit potent anti-inflammatory, neuroprotective and antitumor activities against human cancer cell lines (Figure 1).[7–11] In the synthesis of carbazoles, regioselective installation of appropriate substituents on the eight different available sites in the aromatic ring systems is a challenging task.[1–3,14] Total synthesis of bioactive natural products has very successfully completed ample significant achievements. A collective total synthesis of bioactive natural products is of contemporary interest from the point of view of strategic flexibility and dedicated SAR studies.[15–22] The synthesis of structurally interesting and biologically important selected target compounds, however, merits further investigation. On the basis of retrosynthetic analysis we reasoned that the combination of readily available *N*-boc-protected-3-formylindole, dimethyl maleate and allyl/prenyl bromide would constitute a diversity

oriented convergent access to these important carbazole based natural products (Figure 2). In the continuation of our studies on cyclic anhydrides and their conversion to bioactive natural products[18,23–27] we herein present the collective total synthesis of target compounds (Schemes 2–6).

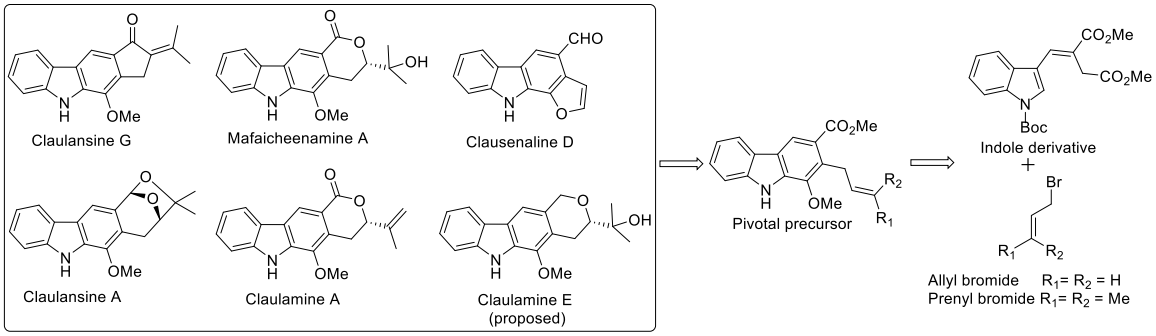
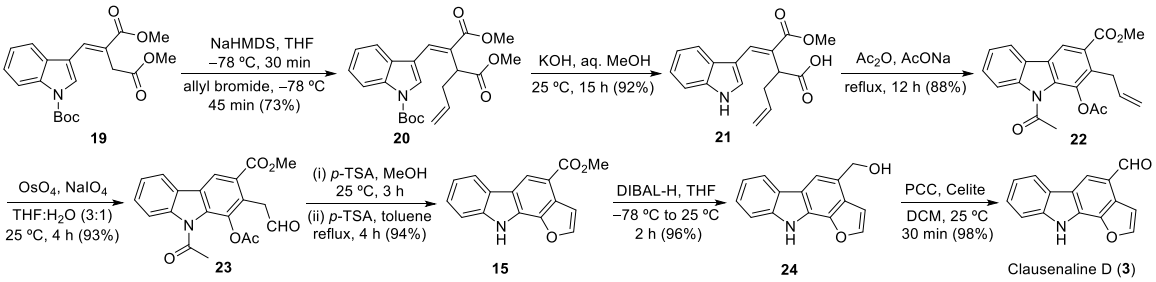


Figure 2. Representative Bioactive Carbazole Alkaloids and Their Concise Retrosynthetic Analysis.

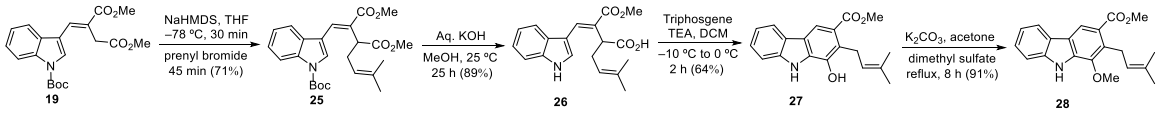


Scheme 2. First Total Synthesis of Clausenaline D

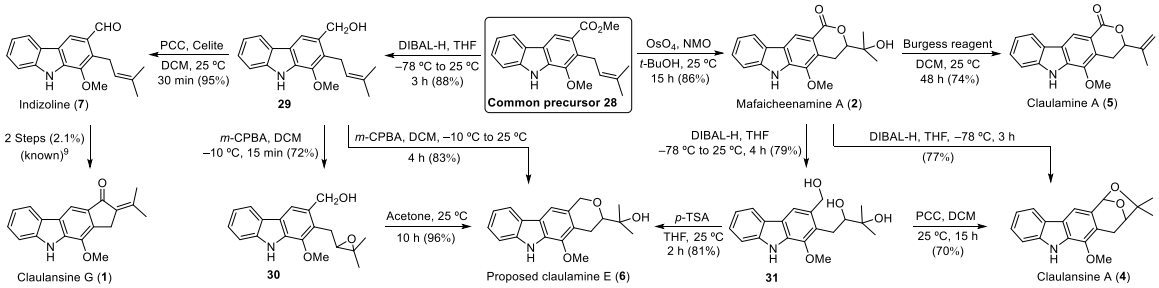
The NaHMDS induced regioselective introduction of an allyl group at an activated allylic methyelene carbon in **19** with allyl bromide provided the required product **20** in 73% yield (Scheme 2). Controlled base-catalyzed regioselective hydrolysis of more reactive unconjugated ester unit in **20** was feasible under ambient reaction conditions and directly formed the Boc-deprotected mono-acid **21** in 92% yield. The witnessed in situ *N*-boc-deprotection under basic conditions was plausibly due to the conjugation of the nitrogen lone pair with the *α,β,γ,δ*-unsaturated ester moiety. The Ac_2O-AcONa stimulated dehydrative intramolecular cyclization of product **21** directly delivered the corresponding *N*– and *O*–acylated carbazole derivative **22** in 88% yield. The transformation of C–C double bond in compound **22** to the corresponding diol followed by an in situ oxidative cleavage using OsO_4 and $NaIO_4$ delivered the desired aliphatic aldehyde **23** in 93% yield. The use of diacyl-protection in substrate **22** was essential, as the corresponding free phenolic compound on treatment with OsO_4/$NaIO_4$ resulted in a complex reaction mixture. A one-pot *p*-TSA/MeOH mediated double de-acylation of compound **23** followed by dehydrative intramolecular cyclization in refluxing *p*-TSA/toluene yielded the furocarbazole **15** in 94% yield. The DIBAL-H reduction of aromatic ester unit in **15** to

the corresponding alcohol **24** followed by its PCC-oxidation delivered the desired natural product clausenaline D (**3**) in 94% yield over two-steps. The analytical and spectral data obtained for clausenaline D were in complete agreement with the reported data.[11]

The Wittig adduct dimethyl (*E*)-2-{[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]methylene}succinate (**19**)[18] upon treatment with NaHMDS/prenyl bromide delivered expected mono-prenylated product **25** in 71% yield. Diester **25** on selective base-induced hydrolysis of the more reactive saturated ester moiety exclusively provided desired carboxylic acid **26** in 89% yield (Scheme 3). Both the *N*-boc-deprotection and regioselective ester hydrolysis took place in one-pot. Acid **26** on triphosgene induced intramolecular acylation followed by *O*-methylation of the formed phenol **27** resulted in the suitably trisubstituted requisite carbazole **28** in 58% yield over two steps. An appropriately designed 20-carbon-bearing versatile single precursor **28** can then be neatly tailored to each of the five target compounds via various reductive and/or oxidative regio- and stereoselective intramolecular cyclization pathways.



Scheme 3. A Facile Synthesis of Common Precursor 1-Methoxy-2-prenyl-3-carbomethoxycarbazole



Scheme 4. Concise and Efficient Collective Total Synthesis of Bioactive Carbazole Alkaloids

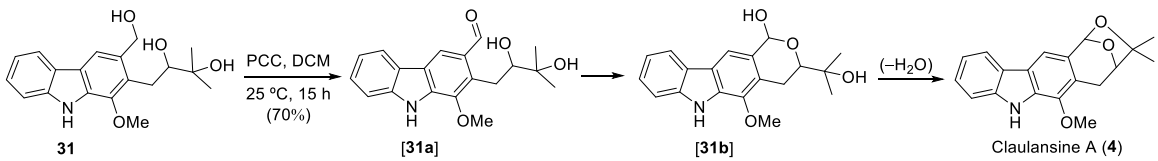
The potential precursor carbazole **28** on DIBAL-H reduction of carbomethoxy unit provided alcohol **29** in 88% yield; which upon PCC-oxidation furnished the first natural product indizoline (**7**) in 95% yield (Scheme 4). The two-step transformation of natural sample of indizoline (**7**) to yet another natural product claulansine G (**1**) is known but in very low overall yield,[9] plausibly due to the poor stability and inherent polymerization issues. The prenyl group bearing carbazole **29** upon treatment with *m*-CPBA at –10 °C resulted in the expected epoxide **30** in 72% yield in 15 min. Epoxide **30** was highly prone to further intramolecular ring closure and hence it was characterized without purification. Isolated epoxide **30** upon simple stirring in acetone at room temperature, underwent regioselective intramolecular cyclization with a cleavage of the oxirane moiety to provide

desired product **6** in 96% yield. The above-mentioned *m*-CPBA epoxidation of carbazole **29** at room temperature directly furnished the planned product **6** in 83% yield. Unfortunately, the obtained analytical and spectral data for compound **6** was not in agreement with reported data for the natural product claulamine E (Table 1). Finally, the structural assignment of synthetic product **6** was unequivocally confirmed by X-ray crystallography. Hence what we have accomplished is the total synthesis of the structure initially proposed as claulamine E (**6**) and an appropriate revision in structural assignment for the natural product is therefore recommended. In principle, several regioisomeric unknown structures are possible and the X-ray crystallographic analysis of the natural product would be most appropriate for the proper structural assignment.

Table 1. NMR Data of Natural and Proposed Claulamine E in Acetone-d_6

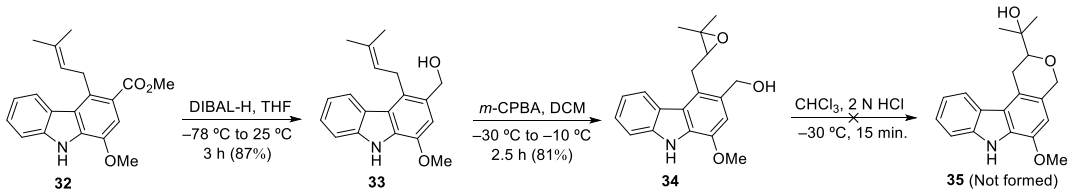
Natural (Ref. 11)		**Proposed 6**	
^{1}H (400 MHz)	^{13}C (100 MHz)	^{1}H (500 MHz)	^{13}C (125 MHz)
1.32 (s, 3H)	19.7	1.28 (s, 3H)	24.2
1.36 (s, 3H)	27.6	1.29 (s, 3H)	25.7
3.29 (dd, 1H)	31.3	2.80–2.90 (m, 1H)	26.4
3.39 (dd, 1H)	61.4	3.10 (dd, 1H)	60.4
	66.5	3.44 (br s, 1H)	70.0
3.55 (dd, 1H)	75.7	3.49 (dd, 1H)	72.0
3.92 (s, 3H)	79.6	3.96 (s, 3H)	82.7
4.60 (d, 1H)	111.9	4.92 (d, 1H)	111.7
4.84 (d, 1H)	115.7	5.05 (d, 1H)	112.0
7.15 (dd, 1H)	119.7	7.14 (t, 1H)	119.7
7.35 (dd, 1H)	120.7	7.36 (t, 1H)	120.9
7.51 (d, 1H)	123.4	7.50 (d, 1H)	124.35
7.66 (s, 1H)	124.4	7.55 (s, 1H)	124.43
8.03 (d, 1H)	126.1	8.02 (d, 1H)	124.7
10.39 (br s, 1H)	128.1	10.31 (br s, 1H)	126.5
	133.6		127.8
	134.6		132.8
	141.1		141.5
	144.4		143.9

Common precursor carbazole **28** upon osmium tetraoxide induced *cis*-dihydroxylation directly delivered natural product mafaicheenamine A (**2**) in 86% yield via an anticipated in situ regioselective lactonization (Scheme 4). The reactions of mafaicheenamine A (**2**) with $SOCl_2/P_2O_5/POCl_3$ were not selective and resulted in a mixture of products. However, the reaction of mafaicheenamine A (**2**) with the Burgess reagent[28] was completely selective and provided the kinetically controlled desired natural product claulamine A (**5**) in 74% yield. We propose that both the steric bulk and higher reactivity of Burgess reagent are responsible for the exclusive formation of kinetically controlled product **5**. Mafaicheenamine A (**2**) upon DIBAL-H reduction at –78 to 25 °C formed the corresponding triol **31** in 79% yield in 4 hours. In a cascade reaction, the triol **31** upon treatment with PCC directly yielded yet another natural product claulansine A (**4**) in 70% yield. Mechanistically, the stepwise selective oxidation of the primary alcohol to the corresponding aldehyde, an in situ cyclic *trans*-hemiacetal formation with the secondary alcohol and an associated instantaneous diastereoselective intramolecular dehydrative ring closure utilizing the tertiary alcohol took place to form desired product **4** in one pot (Scheme 5). Similarly, an osmium tetraoxide induced *cis*-dihydroxylation of indizoline (**7**) at room temperature also directly furnished claulansine A (**4**) in good yield. The temperature controlled DIBAL-H reduction of mafaicheenamine A (**2**) at –78 °C also directly delivered claulansine A (**4**) in 77% yield in 3 h. During the DIBAL-H reductions, the intermediate lactol was fairly stable at –78 °C and further underwent a concomitant diastereoselectve intramolecular dehydrative cyclization to provide claulansine A (**4**). Either the DIBAL-H reduction of **2** directly forms the *trans*-hemiacetal intermediate or the formed *cis*-hemiacetal could be rearranging to the *trans*-hemiacetal via ring-chain tautomerism making the formation of corresponding desired acetal **4** feasible. Triol **31** upon treatment with *p*-TSA again provided the proposed claulamine E (**6**) in 81% yield via protonation of benzylic alcohol followed by regioselective intramolecular dehydrative cyclization. The obtained analytical and spectral data for all target compounds except for claulamine E were in complete agreement for the reported data.[7–11,30]



Scheme 5. Synthesis of Claulansine A via Cascade Reaction

To address the inconsistencies between the structure of proposed claulamine E and compound **6**, we proposed a revised structure for claulamine E. On the basis of structural features of all the carbazoles depicted in Figure 2, we presumed that the assigned positions of the –OMe group and the cyclic benzyl ether unit in the proposed claulamine E are accurate. Therefore alternatively the prenyl moiety could be at the para position of methoxy group. Accordingly, we planned the synthesis of corresponding isomeric compound **35** as a potential revised structure of claulamine E (Scheme 6). Thus, desired precursor **32** was synthesized using known literature procedures.[29] Compound **32** upon DIBAL-H reduction resulted in benzylic alcohol **33** in 87% yield, which upon treatment with *m*-CPBA delivered compound **34** in 81% yield. Epoxide **34** remained unreacted in refluxing acetone, whereas it decomposed in the presence of 2 N HCl in chloroform at –30 °C. Unfortunately, epoxide **34** failed to undergo intramolecular cyclization to provide the desired regioisomeric product **35**.



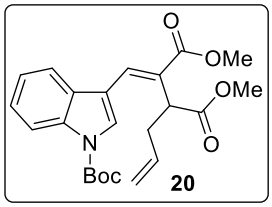
Scheme 6. An Attempted Synthesis of Regioisomer of the Proposed Claulamine E

2B.4 Summary

In summary, we have demonstrated a concise and efficient access to accomplish a biogenetic collective total synthesis of carbazole alkaloids from readily available simple starting materials. The involved different types of intramolecular cyclizations with the generation of new carbon–oxygen bonds selectively leading to those natural products are noteworthy from the point of view of both basic chemistry and applications. More specifically, a remarkable cascade reaction has been demonstrated in the synthesis of claulansine A by taking the advantage of the reactivity difference in three different types of alcohol units. We have accomplished an efficient total synthesis of the proposed structure of claulamine E and regioisomeric revision in the structural assignment of the natural product is necessary. Sharpless asymmetric dihydroxylation reactions will provide access to the enantiomerically pure target compounds and their antipodes. The present approach provides an avenue to natural and unnatural carbazoles for SAR studies.

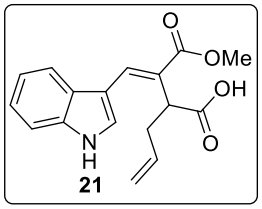
2B.5 Experimental Section

Dimethyl (*E*)-2-Allyl-3-{[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]methylene}succinate (20). To a stirred solution of compound **19** (7.00 g, 18.76 mmol) in dry THF (35 mL) was added a solution of NaHMDS in THF (1 M, 37.53 mL, 37.53 mmol) in a dropwise mode at –78 °C under argon atmosphere. The reaction mixture was stirred for 30 min and allyl bromide (2.37 mL, 28.1 mmol) was added dropwise. It was stirred for 45 min at –78 °C and the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The solvent was removed under vacuo and the obtained residue was dissolved in EtOAc (150 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (1:9) as an eluent yielded pure **20** as thick oil (5.65 g, 73%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.68 (s, 9H), 2.45–2.65 (m, 1H), 2.89–3.07 (m, 1H), 3.69 (s, 3H), 3.84 (s, 3H), 3.97 (t, *J* = 8 Hz, 1H), 4.97–5.07 (m, 1H), 5.12 (dq, *J* = 18 and 2 Hz, 1H), 5.70–5.93 (m, 1H), 7.31 (td, *J* = 8 and 2 Hz, 1H), 7.39 (td, *J* = 8 and 2 Hz, 1H), 7.70 (dd, *J* = 8 and 2 Hz, 1H), 7.87 (s, 1H), 7.97 (s, 1H), 8.17 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.1, 34.4, 44.2, 52.0, 52.1, 84.6, 115.2, 115.3, 117.0, 119.1, 123.2, 125.1, 125.2, 130.0, 130.1, 131.8, 135.1, 135.8, 149.3, 166.9, 172.7; ESIMS (*m*/*z*) 436 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{28}O_6N$ 414.1911, found 414.1899; IR ($CHCl_3$) ν_{max} 3460, 1739, 1634 cm^{-1}.



20

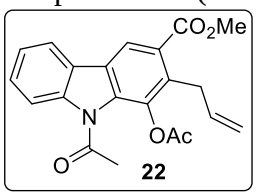
(*E*)-2-[1-(1*H*-Indol-3-yl)-3-methoxy-3-oxoprop-1-en-2-yl]pent-4-enoic Acid (21). To a solution of compound **20** (5.00 g, 12.10 mmol) in MeOH:H_2O (3:1, 20 mL) was added KOH (1.69 g, 30.2 mmol) at 25 °C and the reaction mixture was stirred for 15 h at same temperature. The reaction mixture was concentrated in vacuo and obtained residue was acidified by 2 N HCl (10 mL) and extracted with ethyl acetate (50 mL × 3). The combined extract was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:1) as an eluent to yield acid **21** as a white solid (3.35 g, 92%). Mp 186–188 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.48 (dt, *J* = 15 and 10 Hz, 1H), 2.83 (dt, *J* = 15 and 10 Hz, 1H), 3.72 (s, 3H), 4.01 (dd, *J* = 10 and 10 Hz, 1H), 4.88 (d, *J* = 10 Hz, 1H), 5.00 (d, *J* = 15 Hz, 1H), 5.70–5.81 (m, 1H), 7.14 (td, *J* = 15 and 5 Hz, 1H), 7.20 (t, *J* = 10 Hz, 1H), 7.46 (d, *J* = 10 Hz, 1H), 7.69 (d, *J* = 10 Hz, 1H), 7.83 (s, 1H), 7.98 (s, 1H), 11.78 (s, 1H), 12.21 (br s, 1H);



21

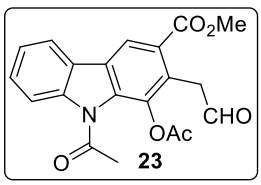
^{13}C NMR (DMSO-d_6, 125 MHz) δ 34.1, 43.5, 51.5, 109.6, 112.0, 116.2, 117.9, 120.3, 122.4, 124.4, 126.7, 127.5, 132.2, 135.7, 136.6, 167.2, 173.6; ESIMS (*m*/*z*) 322 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{18}O_4N$ 300.1230, found 300.1223; IR ($CHCl_3$) ν_{max} 3297, 1718 cm $^{-1}$.

Methyl 1-Acetoxy-9-acetyl-2-allyl-9*H*-carbazole-3-carboxylate (22). To a solution of compound **21** (3.00 g, 10.00 mmol) in acetic anhydride (15 mL) was added sodium acetate (1.40 g, 20.00 mmol) and the reaction mixture was refluxed for 12 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (100 mL) and washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed silica gel (60–120 mesh) column chromatographic purification using ethyl acetate–petroleum ether (2:8) as an eluent provided product **22** as a solid (3.24 g, 88%). Mp 120–122 $^{\circ}$C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.38 (s, 3H), 2.77 (s, 3H), 3.92 (dt, *J* = 6 and 2 Hz, 2H), 3.97 (s, 3H), 4.88–5.05 (m, 2H), 5.84–6.09 (m, 1H), 7.40 (td, *J* = 8 and 2 Hz, 1H), 7.51 (td, *J* = 8 and 2 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 8.03 (d, *J* = 8 Hz, 1H), 8.50 (s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 20.7, 27.1, 32.4, 52.6, 115.2, 115.7, 121.0, 121.4, 124.6, 125.7, 127.5, 128.0, 129.1, 133.8, 134.3, 137.5, 138.1, 140.6, 168.2, 168.4, 171.5; ESIMS (*m*/*z*) 388 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{19}O_5NNa$ 388.1155, found 388.1147; IR ($CHCl_3$) ν_{max} 1762, 1719 cm^{-1}.



22

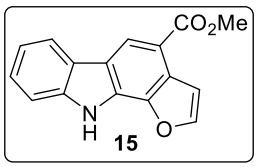
Methyl 1-Acetoxy-9-acetyl-2-(2-oxoethyl)-9*H*-carbazole-3-carboxylate (23). To a stirred solution of compound **22** (1.60 g, 4.38 mmol) in THF:H_2O (3:1, 16 mL) was added OsO_4 solution in *t*-BuOH (1 M, 4.38 mL, 4.38 mmol) and $NaIO_4$ (1.86 g, 8.76 mmol) at 25 $^{\circ}$C. The reaction mixture was further stirred for 4 h at same temperature. The reaction was quenched with aqueous 10% $Na_2S_2O_4$ (10 mL) and stirred for 30 min. The reaction mixture was extracted with diethyl ether (50 mL × 3) and the combined extract was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (3:7) as eluent yielded pure product **23** as a white solid (1.49 g, 93%). Mp 150–152 $^{\circ}$C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.38 (s, 3H), 2.78 (s, 3H), 3.96 (s, 3H), 4.21 (s, 2H), 7.42 (t, *J* = 10 Hz, 1H), 7.53 (t, *J* = 10 Hz, 1H), 7.85 (d, *J* = 10 Hz, 1H), 8.06 (d, *J* = 10 Hz, 1H), 8.63 (s, 1H), 9.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 50



23

MHz) δ 20.5, 26.9, 42.5, 52.4, 114.1, 120.5, 120.7, 123.8, 124.9, 126.0, 127.3, 127.8, 128.3, 133.3, 137.5, 139.4, 166.9, 167.6, 170.1, 198.5; ESIMS (*m*/*z*) 390 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{17}O_6NNa$ 390.0948, found 390.0943; IR ($CHCl_3$) ν_{max} 1769, 1717, 1606 cm^{-1}.

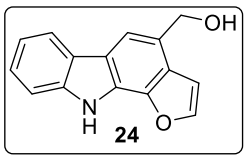
Methyl 10*H*-Furo[2,3-a]carbazole-4-carboxylate (15). To a stirred solution of



15

compound **23** (250 mg, 0.68 mmol) in MeOH (8 mL) was added *p*-TSA (295 mg, 3.40 mmol) at 25 °C. The reaction mixture was further stirred for 3 h at same temperature and MeOH was distilled off in vacuo. The obtained residue was dissolved in toluene (8 mL) and once again *p*-TSA (295 mg, 3.40 mmol) was added to the reaction mixture. The reaction mixture was refluxed for 4 h and then it was allowed to reach room temperature. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished pure product **15** as a solid (140 mg, 94%). Mp 186–188 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 3.98 (s, 3H), 7.30 (td, *J* = 8 and 2 Hz, 1H), 7.47 (td, *J* = 8 and 2 Hz, 1H), 7.59 (d, *J* = 2 Hz, 1H), 7.66 (d, *J* = 8 Hz, 1H), 8.03 (d, *J* = 2 Hz, 1H), 8.26 (d, *J* = 8 Hz, 1H), 8.77 (s, 1H), 11.33 (br s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 52.0, 110.0, 112.7, 115.0, 120.3, 121.1, 121.3, 121.5, 124.8, 126.8, 129.1, 141.1, 141.3, 141.6, 146.6, 167.8; ESIMS (*m*/*z*) 265 $[M]^+$; HRMS (ESI) calcd for $C_{16}H_{11}O_3NNa$ 288.0631, found 288.0626; IR ($CHCl_3$) ν_{max} 3524, 1737 cm^{-1}.

[10*H*-Furo(2,3-*a*)carbazol-4-yl]methanol (24). To a stirred solution of compound **15**

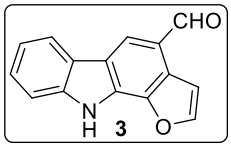


24

(120 mg, 0.45 mmol) in THF (5 mL) was added solution of DIBAL-H in toluene (1 M, 1.35 mL, 1.35 mmol) at −78 °C under argon atmosphere. The reaction mixture was stirred at −78 °C to 25 °C for 2 h. The reaction was quenched by saturated sodium–potassium tartarate solution (10 mL) and stirred for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in diethyl ether (30 mL). The organic phase was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent furnished pure product **24** as gummy solid (103 mg, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.99 (s, 2H), 7.05 (d, *J* = 4

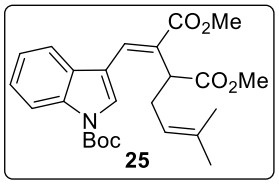
Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.44 (t, *J* = 8 Hz, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.71 (d, *J* = 4 Hz, 1H), 7.94 (s, 1H), 8.09 (d, *J* = 8 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.5, 107.0, 111.1, 115.8, 120.0, 120.1, 120.9, 122.6, 124.1, 124.7, 125.2, 125.4, 139.1, 140.9, 143.9; ESIMS (*m*/*z*) 237 $[M]^+$; HRMS (ESI) calcd for $C_{15}H_{11}O_2NNa$ 260.0682, found 260.0679; IR ($CHCl_3$) ν_{max} 3421, 1642 cm^{-1}.

10*H*-Furo[2,3-a]carbazole-4-carbaldehyde (Clausenaline D, 3). To a mixture of



compound **24** (70 mg, 0.295 mmol) and Celite (100 mg) in DCM (10 mL) was added PCC (95.2 mg, 0.44 mmol) at 25 °C under argon atmosphere and the reaction mixture was stirred for 30 min at same temperature. The reaction mixture was filtered and concentrated in vacuo. The silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished aldehyde **3** as a colorless solid (67 mg, 98%). Mp 184–186 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (t, *J* = 10 Hz, 1H), 7.50 (t, *J* = 10 Hz, 1H), 7.58 (d, *J* = 10 Hz, 1H), 7.74 (d, *J* = 5 Hz, 1H), 7.85 (d, *J* = 5 Hz, 1H), 8.16 (d, *J* = 10 Hz, 1H), 8.44 (s, 1H), 8.83 (br s, 1H), 10.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 108.3, 111.5, 120.3, 120.9, 121.3, 122.9, 124.0, 124.1, 124.5, 126.3, 128.4, 139.3, 140.8, 146.3, 191.4; ESIMS (*m*/*z*) 236 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3252, 2927, 1718, 1680, 1655 cm^{-1}.

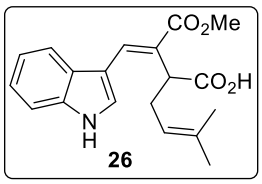
Dimethyl (*E*)-2-{[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]methylene}2-3-(3-methylbut-2-en-1-yl)succinate (25). To a stirred solution of compound **19** (10.00 g,



26.66 mmol) in dry THF (70 mL) was dropwise added a solution of NaHMDS in THF (1 M, 53.3 mL, 53.33 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred for 30 min and prenyl bromide (4.64 mL, 40.21 mmol) was added dropwise. It was further stirred for 45 min at –78 °C and the reaction was quenched with saturated aqueous NH_4Cl. Solvent was removed in vacuo and the obtained residue was dissolved in EtOAc (300 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (1:9) as an eluent yielded pure **25** as thick oil (8.38 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 3H), 1.59 (s, 3H), 1.68 (s, 9H), 2.47–2.57 (m, 1H), 2.83–2.93 (m, 1H), 3.68 (s, 3H), 3.82 (s, 3H), 3.89 (dd, *J* = 8 and 8 Hz, 1H), 5.06 (t, *J* = 8 Hz, 1H), 7.28 (t, *J* = 8 Hz, 1H), 7.36 (t, *J* = 8 Hz, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.81 (s, 1H), 7.93 (s, 1H), 8.14 (d, *J* = 8 Hz, 1H); ^{13}C

NMR ($CDCl_3$, 100 MHz) δ 17.7, 25.6, 28.0, 28.4, 44.5, 51.8, 51.9, 84.3, 115.1, 115.3, 119.0, 121.1, 123.0, 124.8, 125.0, 129.9, 130.6, 131.7, 133.6, 134.9, 149.2, 166.9, 172.9; ESIMS (*m*/*z*) 464 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{31}O_6NNa$ 464.2044, found 464.2036; IR ($CHCl_3$) ν_{max} 1736, 1636 cm^{-1}.

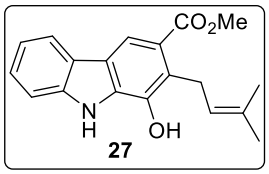
(*E*)-2-[1-(1*H*-Indol-3-yl)-3-methoxy-3-oxoprop-1-en-2-yl]-5-methylhex-4-enoic Acid (26). To a solution of compound **25** (7.50 g, 17.00 mmol) in MeOH:H_2O (3:1, 40 mL) was added KOH (2.09 g, 37.41 mmol) at 25 °C and the reaction mixture was stirred for 25 h. The reaction mixture was concentrated in vacuo and obtained residue was acidified by 2 N HCl and extracted with ethyl acetate (70 mL × 3). The combined extract was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (8:2) as an eluent to yield acid **26** as a white solid (4.94 g, 89%).



26

Mp 188–190 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.50 (s, 6H), 2.07–2.55 (m, 1H), 2.60–2.80 (m, 1H), 3.71 (s, 3H), 3.93 (dd, *J* = 10 and 6 Hz, 1H), 5.06 (t, *J* = 8 Hz, 1H), 7.05–7.25 (m, 2H), 7.46 (d, *J* = 8 Hz, 1H), 7.69 (d, *J* = 8 Hz, 1H), 7.78 (d, *J* = 2 Hz, 1H), 7.97 (s, 1H), 11.77 (br s, 1H), 12.16 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 17.6, 25.6, 28.3, 44.0, 51.5, 109.8, 112.1, 118.0, 120.3, 122.2, 122.4, 124.9, 126.7, 127.5, 131.9, 132.4, 135.8, 167.3, 174.0; ESIMS (*m*/*z*) 350 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_4NNa$ 350.1363, found 350.1357; IR (nujol) ν_{max} 3372, 1704, 1613 cm^{-1}.

Methyl 1-Hydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carboxylate (27). To a solution of compound **26** (4.00 g, 12.23 mmol) in DCM (25 mL) at –10 °C was added triethylamine (1.70 mL, 12.23 mmol) and triphosgene (5.43 g, 18.34 mmol) and the reaction mixture was stirred at –10 to 0 °C for 2 h. Reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (3:7) as an eluent provided product **27** as gummy solid (2.42 g, 64%).

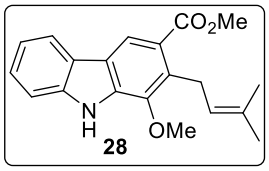


27

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (s, 3H), 1.91 (s, 3H), 4.00 (br s, 5H), 5.40 (t, *J* = 8 Hz, 1H), 5.98 (s, 1H), 7.22–7.30 (m, 1H), 7.40–7.48 (m, 2H), 8.07 (d, *J* = 8 Hz, 1H), 8.34 (br s, 1H), 8.56 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 25.7, 26.5, 52.0, 111.1, 116.7, 120.0, 120.5, 121.7, 122.2, 122.4, 123.65,

123.74, 126.1, 132.1, 134.8, 139.8, 140.5, 169.3; ESIMS (*m*/*z*) 332 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_3NNa$ 332.1257, found 332.1270; IR ($CHCl_3$) ν_{max} 3362, 1701, 1646 cm^{-1}.

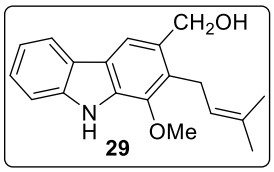
Methyl 1-Methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carboxylate (28). To a



28

stirred solution of compound **27** (2.00 g, 6.47 mmol) in dry acetone (20 mL) was added K_2CO_3 (893 mg, 6.47 mmol) and dimethyl sulfate (494 μL, 5.17 mmol) at 25 °C and the reaction mixture was refluxed for 8 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (100 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (2:8) as eluent yielded pure product **28** as a white solid (1.91 g, 91%). Mp 130–132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 3H), 1.84 (s, 3H), 3.94 (s, 2H), 3.96 (s, 6H), 5.27 (t, J = 8 Hz, 1H), 7.28 (t, J = 8 Hz, 1H), 7.40–7.50 (m, 2H), 8.07 (d, J = 8 Hz, 1H), 8.38 (br s, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1, 25.7, 25.9, 51.9, 61.1, 111.0, 120.1, 120.3, 120.5, 122.5, 122.6, 123.9, 124.1, 126.3, 131.3, 133.3, 135.5, 139.8, 143.2, 168.7; ESIMS (*m*/*z*) 346 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{21}O_3NNa$ 346.1414, found 346.1409; IR ($CHCl_3$) ν_{max} 3468, 1706, 1608 cm^{-1}.

[1-Methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazol-3-yl]methanol (29). To a stirred

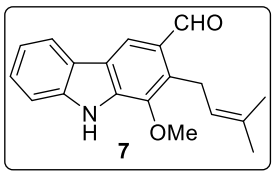


29

solution of compound **28** (120 mg, 0.37 mmol) in THF (5 mL) was added solution of DIBAL-H in toluene (1 M, 1.11 mL, 1.11 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred at –78 to 25 °C for 3 h. The reaction was quenched by saturated sodium–potassium tartarate solution and stirred for 1 h. The reaction mixture was concentrated in vacuo and obtained residue was dissolved in diethyl ether (30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent furnished pure product **29** as a white solid (96 mg, 88%). Mp 142–144 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.73 (s, 3H), 1.87 (s, 3H), 3.67 (d, J = 6 Hz, 2H), 3.97 (s, 3H), 4.83 (s, 2H), 5.15–5.27 (m, 1H), 7.24 (t, J = 8 Hz, 1H), 7.35–7.50 (m, 2H), 7.87 (s, 1H), 8.03 (d, J = 6 Hz, 1H), 8.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0, 25.1, 25.7, 61.1, 64.2, 110.9, 116.8, 119.7,

120.3, 123.3, 123.9, 124.0, 125.7, 130.0, 131.9, 132.1, 132.8, 139.6, 143.2; ESIMS (*m*/*z*) 318 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_2NNa$ 318.1465, found 318.1477; IR ($CHCl_3$) ν_{max} 3451 cm^{-1}.

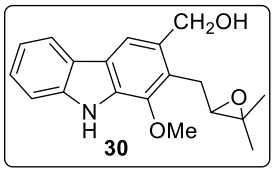
1-Methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carbaldehyde (Indizoline, 7).



7

To a mixture of compound **29** (70 mg, 0.237 mmol) and Celite (100 mg) in DCM (10 mL) was added PCC (102 mg, 0.47 mmol) at 25 °C under argon atmosphere and the reaction mixture was stirred for 30 min at same temperature. The reaction mixture was filtered and the filtrate was concentrated in vacuo. Direct silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished aldehyde **7** as gummy solid (66 mg, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 3H), 1.85 (s, 3H), 3.95 (s, 2H), 3.97 (s, 3H), 5.24 (t, *J* = 8 Hz, 1H), 7.30 (t, *J* = 8 Hz, 1H), 7.40–7.52 (m, 2H), 8.08 (d, *J* = 8 Hz, 1H), 8.44 (s, 1H), 8.52 (br s, 1H), 10.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1, 24.1, 25.7, 61.4, 111.2, 120.7, 120.8, 121.1, 123.3, 123.8, 124.0, 126.7, 127.8, 132.0, 134.0, 136.9, 139.8, 142.8, 191.9; ESIMS (*m*/*z*) 294 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_2NNa$ 316.1308, found 316.1304; IR ($CHCl_3$) ν_{max} 3302, 1725, 1659 cm^{-1}.

{2-[(3, 3-Dimethyloxiran-2-yl) methyl]-1-methoxy-9*H*-carbazol-3-yl}methanol (30).

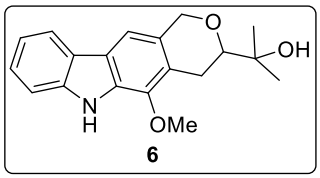


30

To a solution of compound **29** (60 mg, 0.203 mmol) in DCM (5 mL) was added *m*-CPBA (34.98 mg, 0.203 mmol) at –10 °C under argon atmosphere and the reaction mixture was stirred for 15 min. The reaction was quenched with saturated solution of $NaHCO_3$ at 0 °C. The reaction mixture extracted with DCM (15 mL) and organic layer was immediately concentrated in vacuo to obtain epoxide **30** as a white solid (43 mg, 72%). It was immediately characterized without any purification for stability issues. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.29 (s, 3H), 1.47 (s, 3H), 2.99 (dd, *J* = 20 and 4 Hz, 2H), 3.34 (dd, *J* = 12 and 4 Hz, 1H), 3.95–4.10 (br s, 1H), 4.01 (s, 3H), 4.80 (d, *J* = 4 Hz, 2H), 7.17 (t, *J* = 8 Hz, 1H), 7.37 (t, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.91 (s, 1H), 8.07 (d, *J* = 8 Hz, 1H), 10.41 (br s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 19.4, 25.0, 26.5, 59.9, 61.1, 64.1, 65.4, 112.1, 117.2, 119.9, 120.9, 124.55, 124.57, 126.4, 127.5, 133.4, 133.9, 141.4, 144.9; ESIMS (*m*/*z*); HRMS (ESI) calcd for $C_{19}H_{21}O_3NNa$ 334.1414, found 334.1410; IR ($CHCl_3$) ν_{max} 3453 cm^{-1}.

2-(5-Methoxy-1,3,4,6-tetrahydropyrano[4,3-*b*]carbazol-3-yl)propan-2-ol (Proposed Claulamine E, 6).

***Method A*:** To a solution of compound **29** (60 mg, 0.203 mmol) in DCM (5 mL) was



6

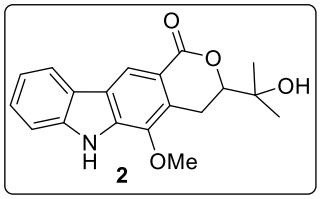
added *m*-CPBA (34.98 mg, 0.203 mmol) at –10 °C under argon atmosphere and the reaction mixture was stirred for 4 h at 25 °C. The reaction was quenched with saturated solution of $NaHCO_3$ at 25 °C. The reaction mixture was extracted with DCM (10 mL x 2) and combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished product **6** as a white solid (53 mg, 83%).

***Method B*:** The solution of compound **30** (20 mg, 0.064 mmol) in acetone (1 mL) was stirred at 25 °C for 10 h. The reaction mixture was concentrated in vacuo and silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished product **6** as a white solid (19 mg, 96%).

***Method C*:** Mixture of compound **31** (50 mg, 0.15 mmol) and *p*-TSA (52 mg, 0.30 mmol) in THF (5 mL) was stirred at 25 °C for 2 h. The reaction mixture was concentrated in vacuo and obtained residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent furnished product **6** as a white solid (38 mg, 81%). Mp 160–162 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.28 (s, 3H), 1.29 (s, 3H), 2.80–2.90 (m, 1H), 3.10 (dd, J = 15 and 5 Hz, 1H), 3.44 (br s, 1H), 3.49 (dd, J = 10 and 5 Hz, 1H), 3.96 (s, 3H), 4.92 (d, J = 15 Hz, 1H), 5.05 (d, J = 15 Hz, 1H), 7.14 (t, J = 10 Hz, 1H), 7.36 (t, J = 10 Hz, 1H), 7.50 (d, J = 10 Hz, 1H), 7.55 (s, 1H), 8.02 (d, J = 10 Hz, 1H), 10.31 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 24.2, 25.7, 26.4, 60.4, 70.0, 72.0, 82.7, 111.7, 112.0, 119.7, 120.9, 124.35, 124.43, 124.7, 126.5, 127.8, 132.8, 141.5, 143.9; ESIMS (*m*/*z*) 334 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_3NNa$ 334.1414, found 334.1409; IR ($CHCl_3$) ν_{max} 3685, 3468 cm^{-1}.

3-(2-Hydroxypropan-2-yl)-5-methoxy-4,6-dihydropyrano[4,3-*b*]carbazol-1(3*H*)-one (Mafaicheenamine A, 2). To a stirred solution of compound **28** (500 mg, 1.54 mmol) in *t*-BuOH (15 mL) was added OsO_4 in *t*-BuOH (1 M, 308 μL, 0.308 mmol) and 50%

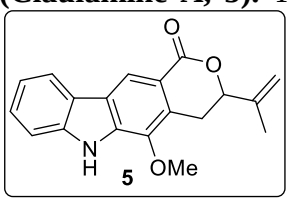
aqueous NMO solution (540 μL) at 25 °C and the reaction mixture was stirred for 15 h.



2

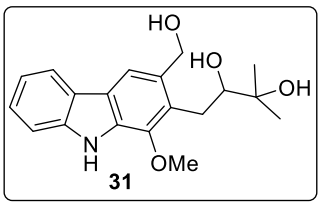
The reaction was quenched with saturated solution of $NaHSO_3$ and stirred at 25 °C for next 1 h. The reaction mixture was extracted with ethyl acetate (3 × 10 mL) and combined organic layer washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (8:2) as eluent yielded pure product **2** as a colorless solid (435 mg, 86%). Mp 236–238 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.38 (s, 6H), 3.04 (dd, J = 15 and 15 Hz, 1H), 3.46 (dd, J = 15 and 5 Hz, 1H), 3.92 (br s, 1H), 4.00 (s, 3H), 4.30 (dd, J = 10 and 5 Hz, 1H), 7.27 (t, J = 10 Hz, 1H), 7.46 (t, J = 10 Hz, 1H), 7.59 (d, J = 10 Hz, 1H), 8.23 (d, J = 10 Hz, 1H), 8.60 (s, 1H), 10.86 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 23.3, 25.5, 26.9, 61.4, 71.3, 85.2, 112.5, 118.1, 119.9, 121.0, 121.5, 124.5, 124.9, 127.5, 129.6, 137.5, 141.7, 142.1, 166.3; ESIMS (*m*/*z*) 326 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{20}O_4N$ 326.1387, found 326.1383; IR ($CHCl_3$) ν_{max} 3687, 3462, 1707, 1614 cm^{-1}.

5-Methoxy-3-(prop-1-en-2-yl)-4,6-dihydropyrano[4,3-*b*]carbazol-1(3*H*)-one (Claulamine A, 5). To a stirred solution of compound **2** (50 mg, 0.153 mmol) in dry DCM (5 mL) was added Burgess reagent (72.82 mg, 0.306 mmol) at 25 °C under argon atmosphere and the reaction mixture was stirred for 48 h. The reaction mixture was diluted with EtOAc (20 mL) and organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (3:7) as an eluent yielded pure **5** as a white solid (35 mg, 74%). Mp 170–174 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.95 (s, 3H), 3.14 (dd, J = 18 and 6 Hz, 1H), 3.38 (dd, J = 16 and 4 Hz, 1H), 3.99 (s, 3H), 4.96 (dd, J = 12 and 4 Hz, 1H), 5.07 (s, 1H), 5.21 (s, 1H), 7.27–7.35 (m, 1H), 7.43–7.55 (m, 2H), 8.08 (d, J = 8 Hz, 1H), 8.56 (br s, 1H), 8.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.4, 26.9, 61.2, 81.0, 111.2, 113.9, 117.2, 120.0, 120.8, 120.9, 123.7, 124.4, 126.9, 127.7, 136.2, 139.8, 140.6, 142.1, 166.5; ESIMS (*m*/*z*) 308 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{18}O_3N$ 308.1281, found 308.1275; IR ($CHCl_3$) ν_{max} 3460, 1709, 1615 cm^{-1}.



5

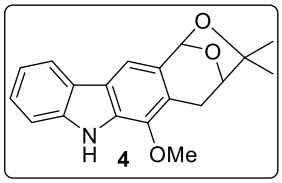
1-[3-(Hydroxymethyl)-1-methoxy-9*H*-carbazol-2-yl]-3-methylbutane-2,3-diol (31). To a stirred solution of compound **2** (80 mg, 0.246 mmol) in THF (8 mL) was added



solution of DIBAL-H in toluene (1 M, 984 μL, 0.984 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred at –78 to 25 °C for 4 h. The reaction was quenched by saturated sodium–potassium tartarate solution and stirred for 1 h. The reaction mixture was concentrated in vacuo and obtained residue was stirred with diethyl ether (25 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent furnished pure product **31** as gummy solid (64 mg, 79%). ^{1}H NMR (CD_3OD, 500 MHz) δ 1.32 (s, 3H), 1.33 (s, 3H), 2.84 (dd, J = 15 and 10 Hz, 1H), 3.30 (dd, J = 10 and 5 Hz, 1H), 3.71 (dd, J = 10 and 5 Hz, 1H), 4.00 (s, 3H), 4.67 (d, J = 15 Hz, 1H), 4.90 (d, J = 15 Hz, 1H), 7.13 (t, J = 10 Hz, 1H), 7.34 (t, J = 10 Hz, 1H), 7.47 (d, J = 10 Hz, 1H), 7.78 (s, 1H), 7.99 (d, J = 10 Hz, 1H), 10.68 (br s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 25.5, 25.6, 29.8, 60.8, 64.8, 74.3, 79.8, 112.2, 118.2, 120.1, 121.0, 124.9, 125.0, 126.7, 129.5, 132.9, 134.4, 142.0, 145.4; ESIMS (*m*/*z*) 352 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{23}O_4NNa$ 352.1519, found 352.1513; IR ($CHCl_3$) ν_{max} 3438, 1660 cm^{-1}.

6-Methoxy-3,3-dimethyl-3,4,5,7-tetrahydro-1*H*-1,4-epoxyoxepino[4,3-*b*]carbazole (Claulansine A, 4).

***Method A*:** To a stirred solution of compound **2** (60 mg, 0.184 mmol) in THF (6 mL) was

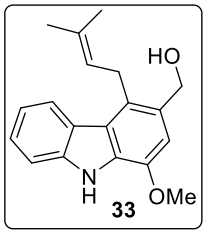


added solution of DIBAL-H in toluene (1 M, 553 μL, 0.553 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred at –78 °C for 3 h. The reaction was quenched by saturated sodium–potassium tartarate solution and stirred for 1 h. The reaction mixture was concentrated in vacuo and obtained residue was dissolved in diethyl ether (25 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent provided product **4** as a white solid (44 mg, 77%).

***Method B*:** To a solution of compound **31** (30 mg, 0.091 mmol) in DCM (5 mL) was added PCC (39.13 mg, 0.182 mmol) at 25 °C and the reaction mixture was stirred for 15 h. The reaction mixture was filtered and concentrated in vacuo. Silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl

acetate–petroleum ether (3:7) as an eluent provided product **4** as a white solid (20 mg, 70%). Mp 180–182 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.15 (s, 3H), 1.27 (s, 3H), 3.01 (d, J = 16 Hz, 1H), 3.22 (dd, J = 16 and 4 Hz, 1H), 3.91 (s, 3H), 4.49 (s, 1H), 6.10 (s, 1H), 7.14 (t, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 7.61(s, 1H), 8.02 (d, J = 8 Hz, 1H), 11.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.7, 25.6, 29.4, 59.8, 79.2, 79.9, 100.4, 111.3, 111.8, 118.8, 119.9, 120.2, 122.2, 122.9, 125.4, 130.1, 132.4, 139.9, 142.5; ESIMS (*m*/*z*) 310 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{20}O_3N$ 310.1438, found 310.1433; IR ($CHCl_3$) ν_{max} 3417, 1603 cm^{-1}.

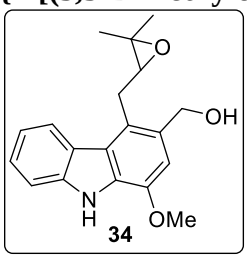
[1-Methoxy-4-(3-methylbut-2-en-1-yl)-9*H*-carbazol-3-yl]methanol (33). To a stirred



33

solution of compound **32** (100 mg, 0.30 mmol) in THF (5 mL) was added solution of DIBAL-H in toluene (1 M, 900 μL, 0.90 mmol) at –78 °C under argon atmosphere and the reaction mixture was stirred at –78 to 25 °C for 3 h. The reaction was quenched by saturated sodium–potassium tartarate solution and stirred for 1 h. The reaction mixture was concentrated in vacuo and obtained residue was dissolved in diethyl ether (30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent furnished pure product **33** as gummy solid (80 mg, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 3H), 1.94 (s, 3H), 4.00 (s, 2H), 4.01 (s, 3H), 4.85 (s, 2H), 5.33 (t, J = 8 Hz, 1H), 6.96 (s, 1H), 7.25 (t, J = 8 Hz, 1H), 7.43 (t, J = 8 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.38 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 25.7, 28.1, 55.6, 64.0, 107.7, 110.9, 119.5, 122.8, 123.0, 123.2, 123.7, 125.3, 127.8, 129.7, 129.9, 132.5, 139.6, 143.6; ESIMS (*m*/*z*) 318 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_2NNa$ 318.1465, found 318.1466; IR ($CHCl_3$) ν_{max} 3595, 3468 cm^{-1}.

{4-[(3,3-Dimethyloxiran-2-yl)methyl]-1-methoxy-9*H*-carbazol-3-yl}methanol (34). To

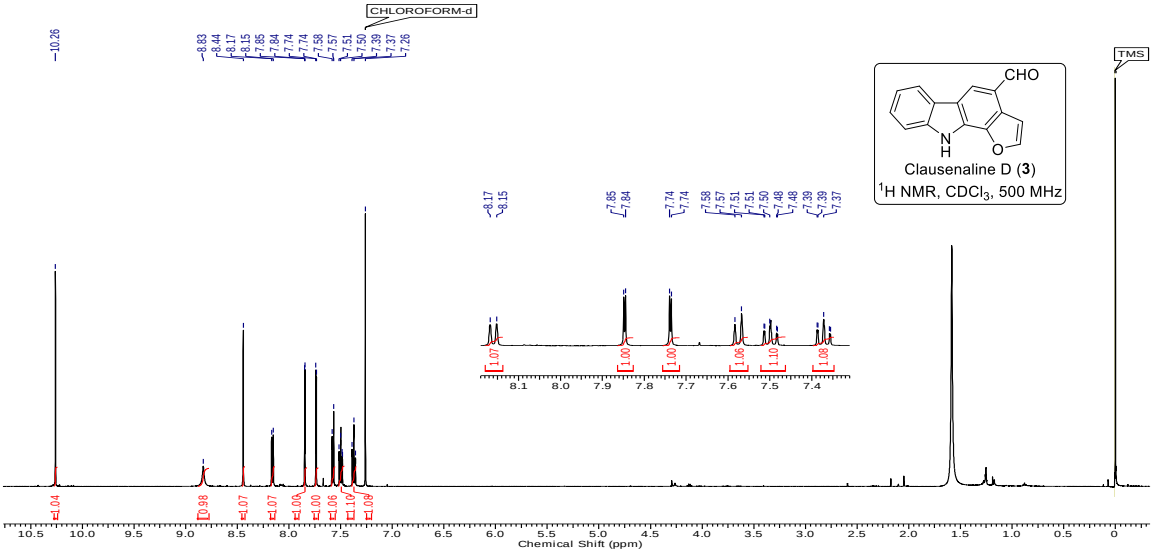


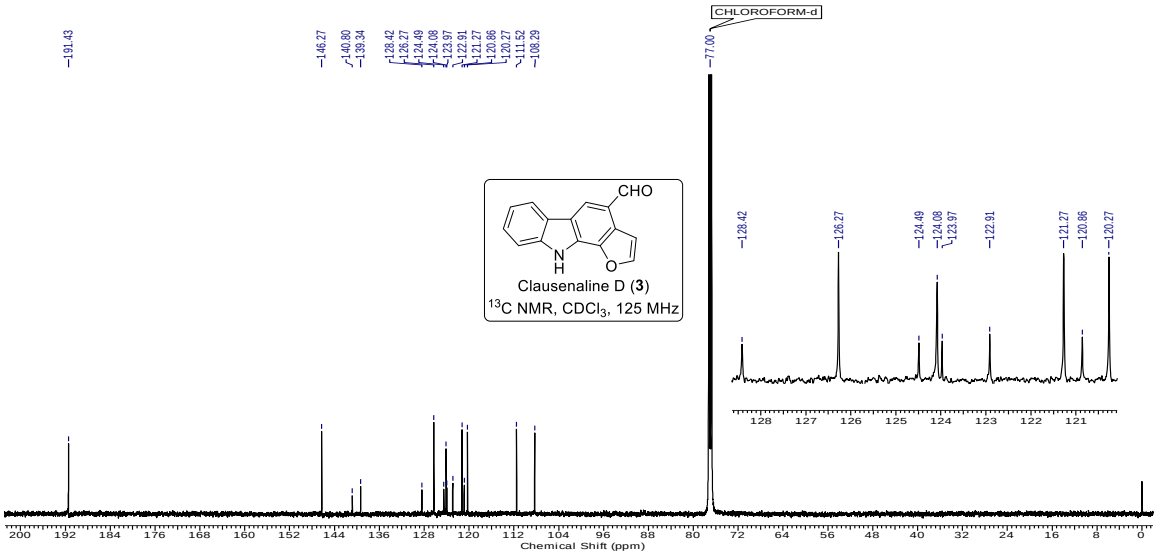
34

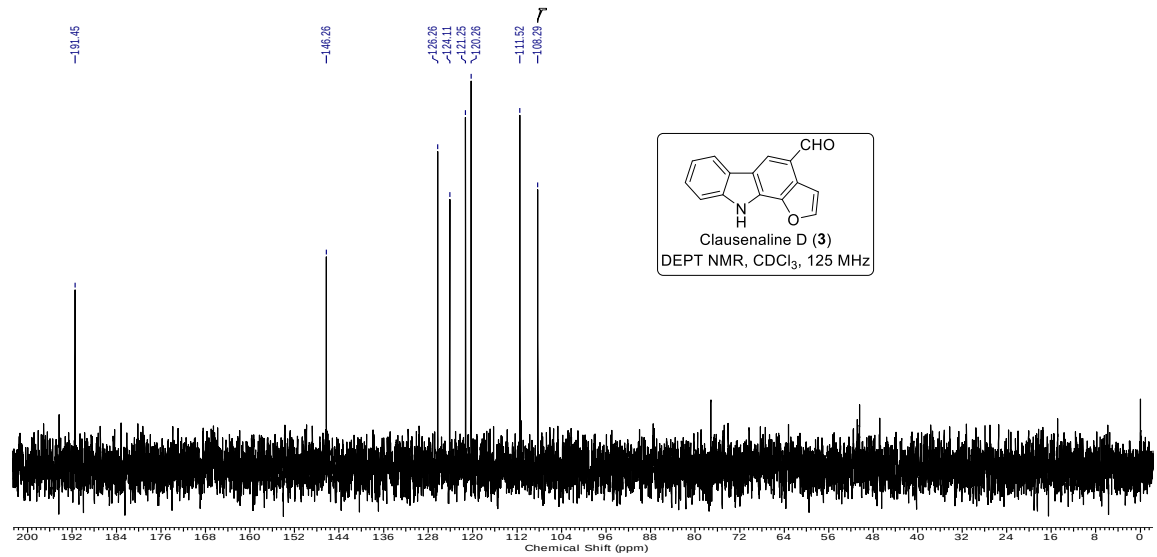
a solution of compound **33** (70 mg, 0.237 mmol) in DCM (5 mL) was added *m*-CPBA (40 mg, 0.237 mmol) at –30 °C under argon atmosphere and the reaction mixture was stirred for 2.5 h below –10 °C. The reaction was quenched with saturated solution of $NaHCO_3$ at 25 °C. The reaction mixture was extracted with DCM (10 mL × 2) and combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic

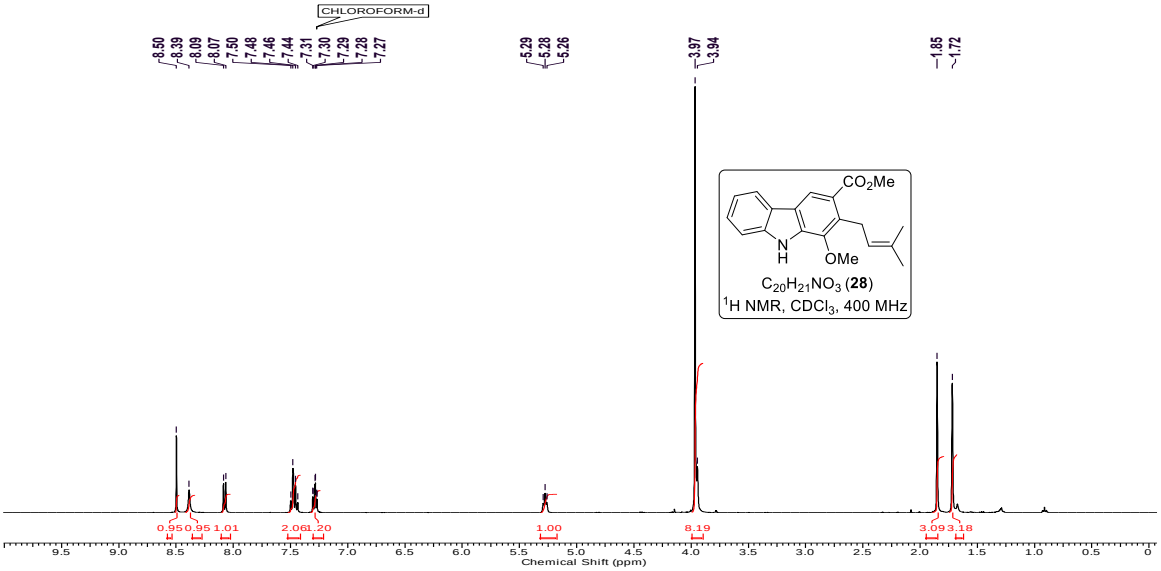
purification of resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent furnished product **34** as a white solid (60 mg, 81%). Mp 166–168 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.29 (s, 3H), 1.56 (s, 3H), 3.11 (dd, J = 5 and 5 Hz, 1H), 3.27 (dd, J = 15 and 10 Hz, 1H), 3.84 (dd, J = 15 and 5 Hz, 1H), 3.86 (br s, 1H), 4.00 (s, 3H), 4.68 (d, J = 10 Hz, 1H), 4.82 (d, J = 10 Hz, 1H), 7.06 (s, 1H), 7.20 (t, J = 10 Hz, 1H), 7.40 (t, J = 10 Hz, 1H), 7.62 (d, J = 10 Hz, 1H), 8.27 (d, J = 10 Hz, 1H), 10.45 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 19.5, 25.1, 29.1, 56.0, 60.6, 63.5, 64.8, 109.0, 112.4, 119.9, 123.1, 123.6, 124.3, 124.8, 125.9, 131.0, 132.9, 141.4, 145.1; ESIMS (m/z) 334 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_3NNa$ 334.1414, found 334.1412; IR ($CHCl_3$) ν_{max} 3424, 1640 cm^{-1}.

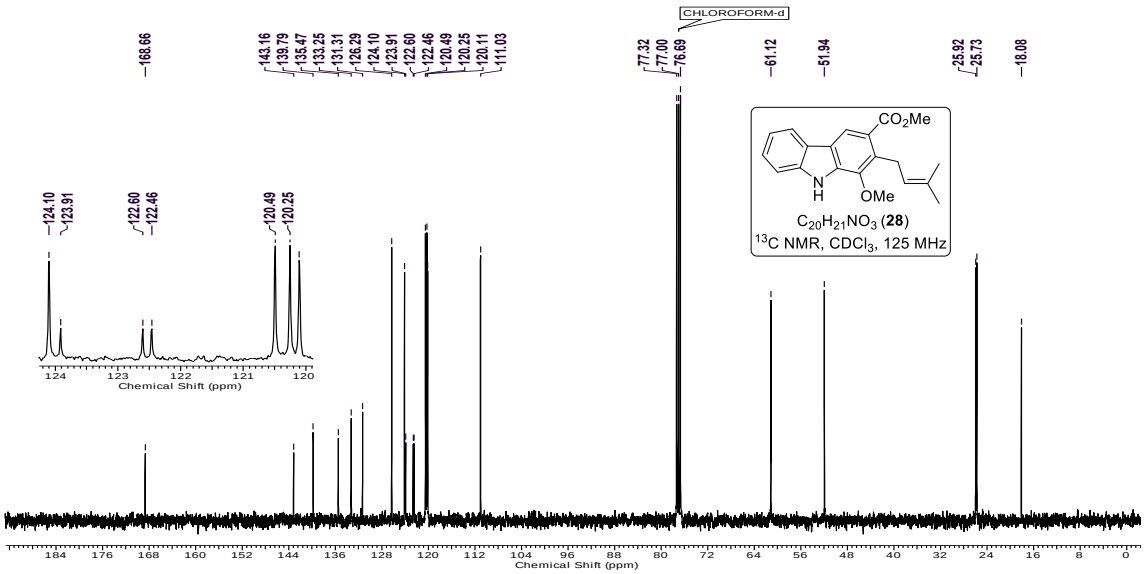
2B.6 Selected Spectra

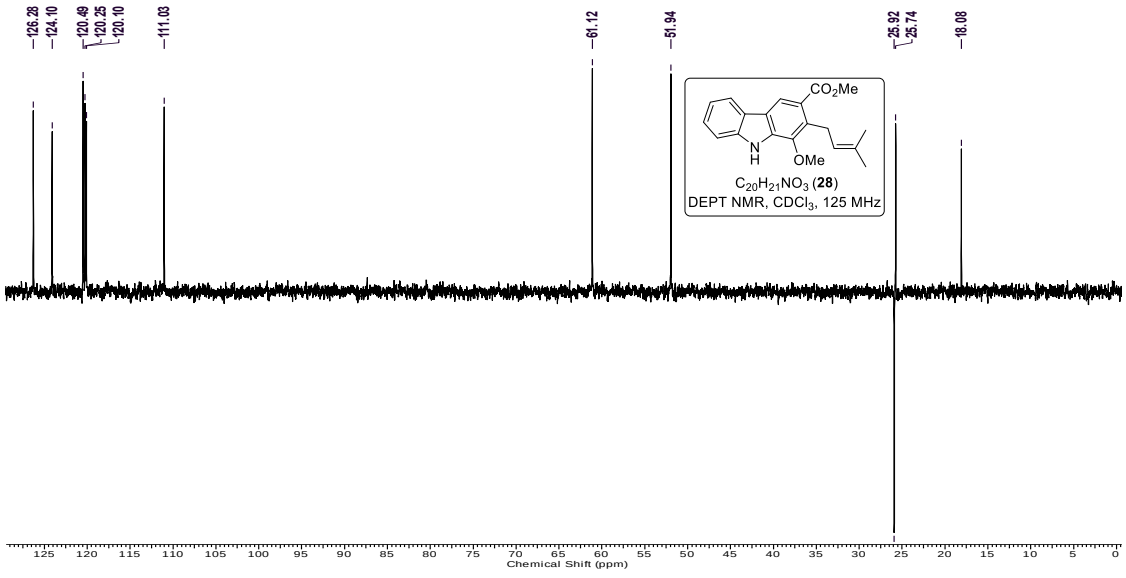

CHLOROFORM-d
TMS
CHO
N
H
O
Clausenaline D (3)
1H NMR, CDCl3, 500 MHz
Chemical Shift (ppm)

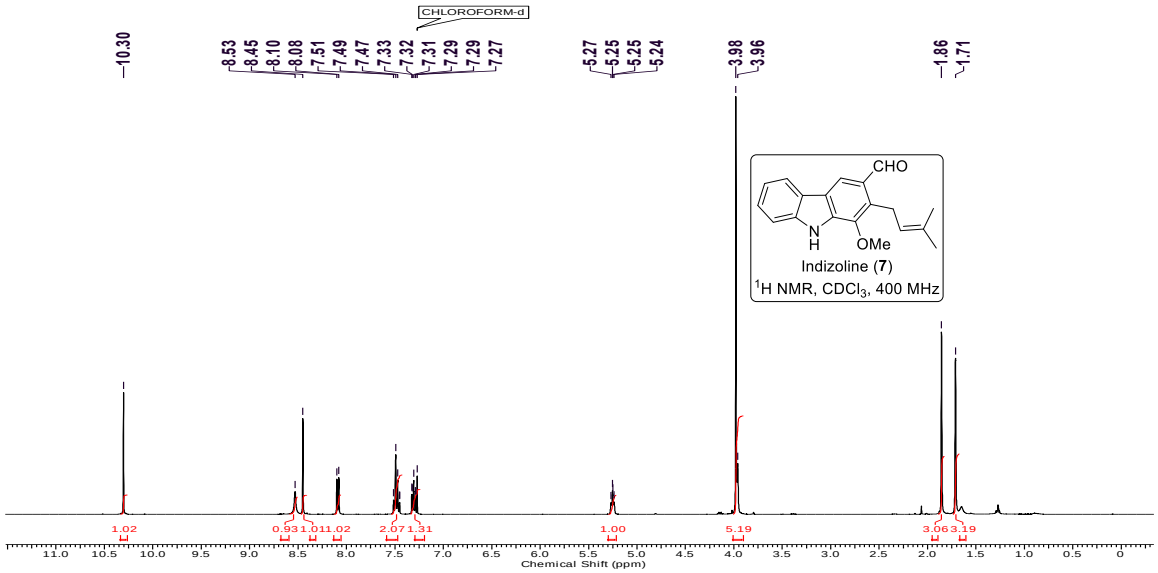

CHLOROFORM-d
CHO
N
H
O
Clausenaline D (3)
13C NMR, CDCl3, 125 MHz
Chemical Shift (ppm)

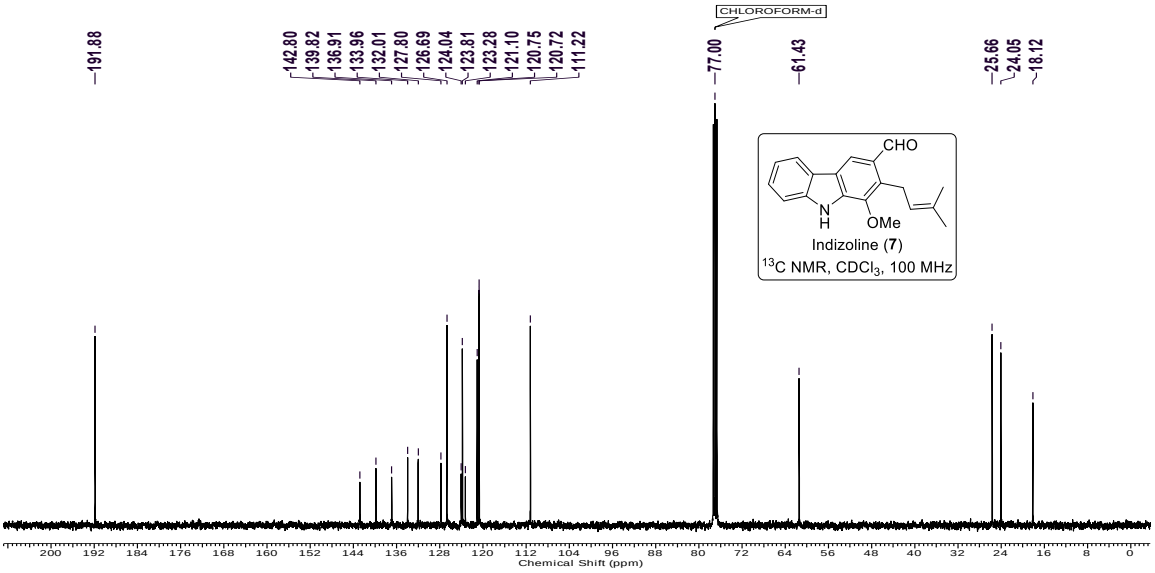

CHO
N
H
O
Clausenaline D (3)
DEPT NMR, CDCl3, 125 MHz
Chemical Shift (ppm)

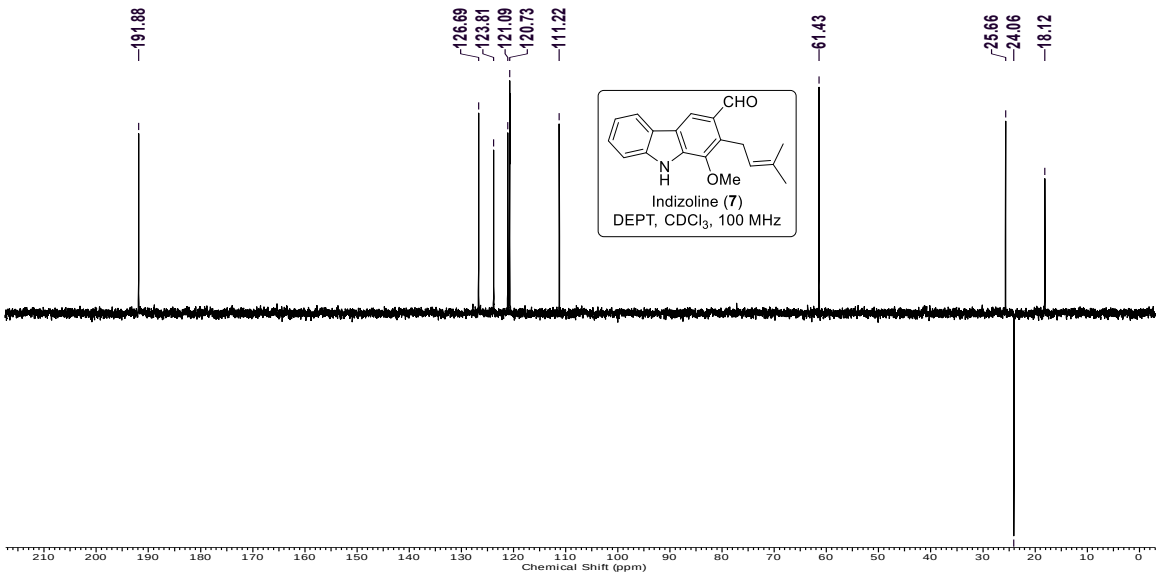

CHLOROFORM-d
8.50
8.39
8.09
8.07
7.50
7.48
7.46
7.44
7.31
7.30
7.29
7.28
7.27
5.29
5.28
5.26
3.97
3.94
1.85
1.72
CO2Me
N
H
OMe
C20H21NO3 (28)
1H NMR, CDCl3, 400 MHz
0.95 0.95 1.01 2.06 1.20 1.00 8.19 3.09 3.18
Chemical Shift (ppm)

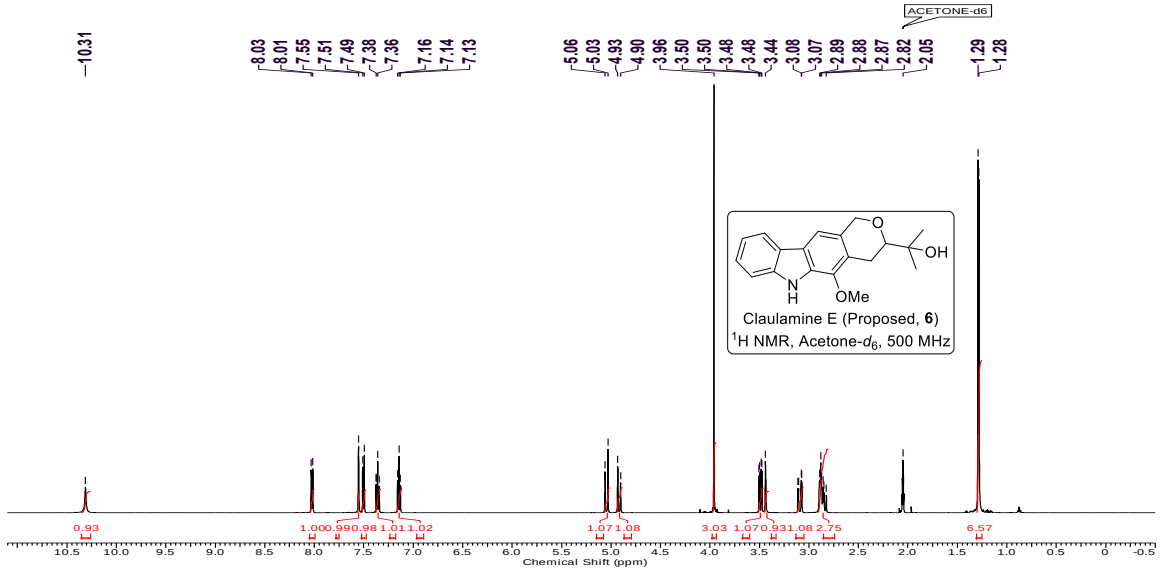

CHLOROFORM-d
168.66
143.16
139.79
135.47
133.25
131.31
126.29
124.10
123.91
122.60
122.46
120.49
120.25
120.11
111.03
77.32
77.00
76.69
61.12
51.94
25.92
25.73
18.08
CO2Me
N
H
OMe
C20H21NO3 (28)
13C NMR, CDCl3, 125 MHz
Chemical Shift (ppm)

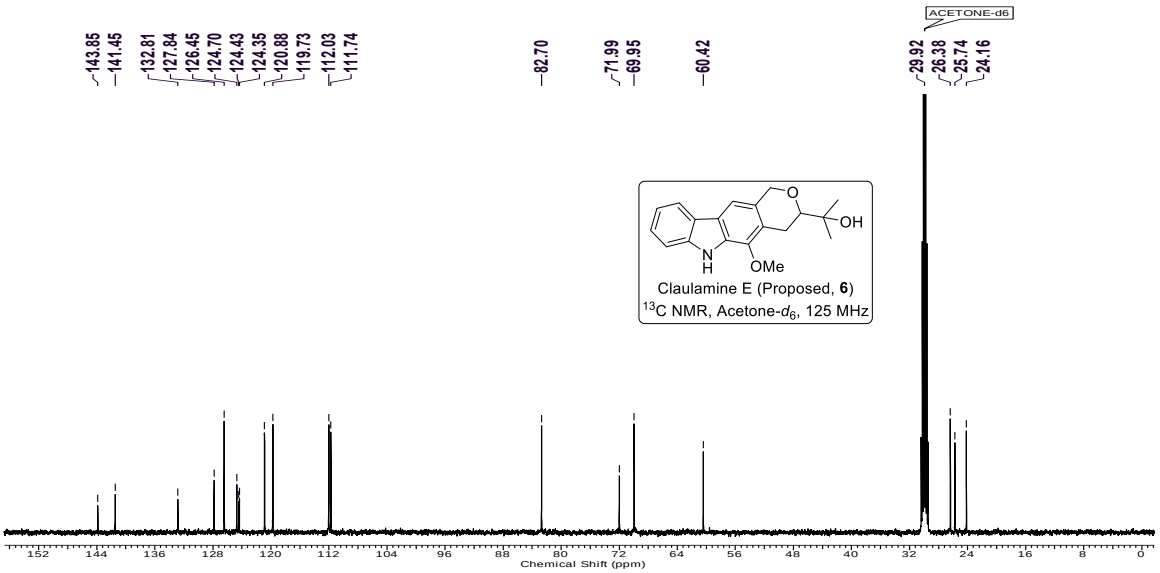

126.28
124.10
120.49
120.25
120.10
111.03
61.12
51.94
25.92
25.74
18.08
CO2Me
N
H
OMe
C20H21NO3 (28)
DEPT NMR, CDCl3, 125 MHz
Chemical Shift (ppm)

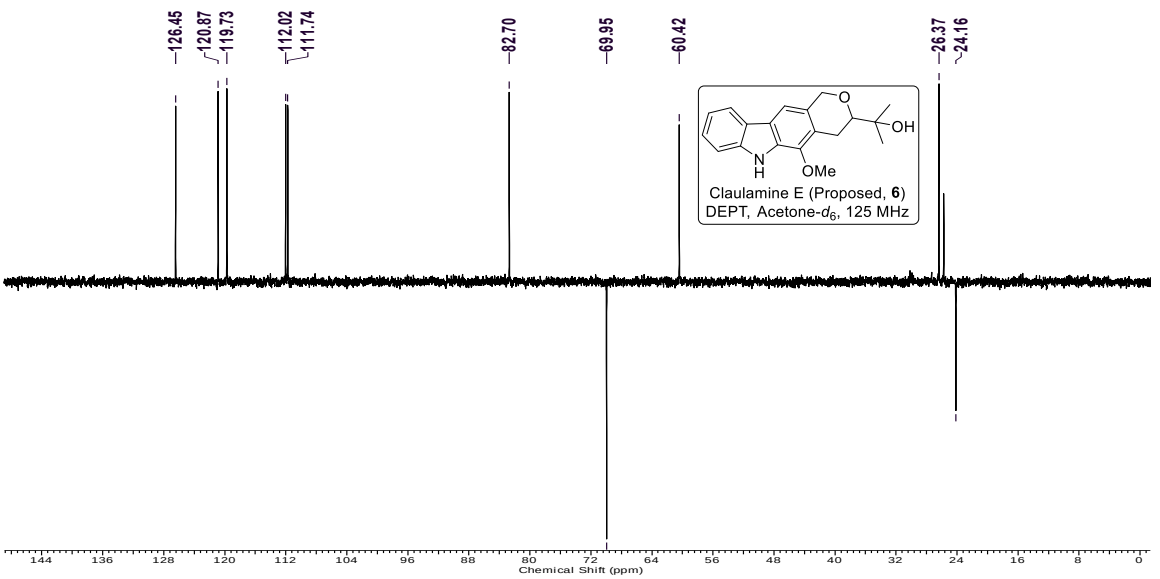

CHLOROFORM-d
10.30
8.53
8.45
8.10
8.08
7.51
7.49
7.47
7.33
7.32
7.31
7.29
7.29
7.27
5.27
5.25
5.25
5.24
3.98
3.96
1.86
1.71
CHO
N
H
OMe
Indizoline (7)
1H NMR, CDCl3, 400 MHz
1.02
0.93
1.00
1.02
2.07
1.31
1.00
5.19
3.06
3.19
Chemical Shift (ppm)

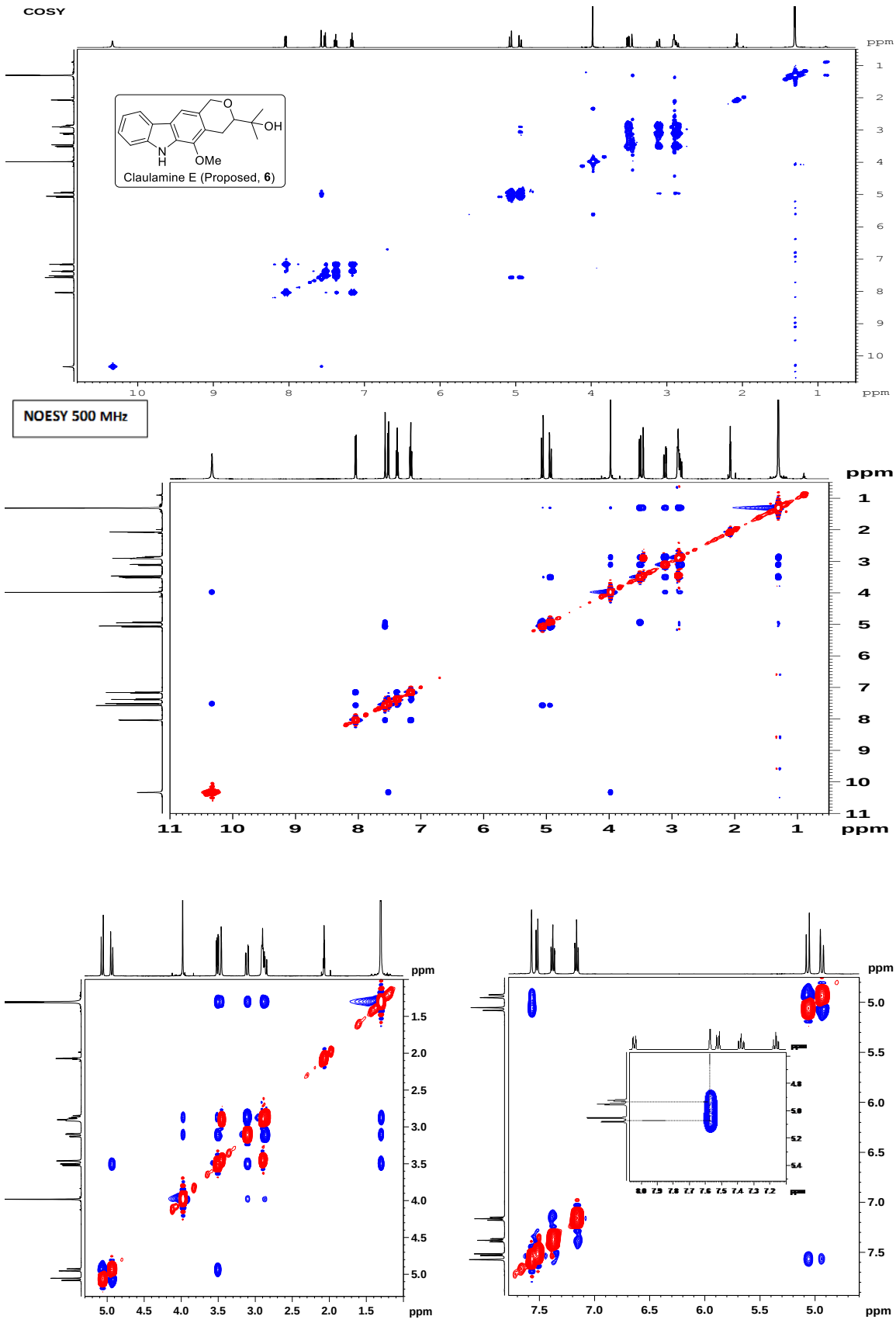

CHLOROFORM-d
191.88
142.80
139.82
136.91
133.96
132.01
127.80
126.69
124.04
123.81
123.28
121.10
120.75
120.72
111.22
77.00
61.43
25.66
24.05
18.12
CHO
N
H
OMe
Indizoline (7)
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)

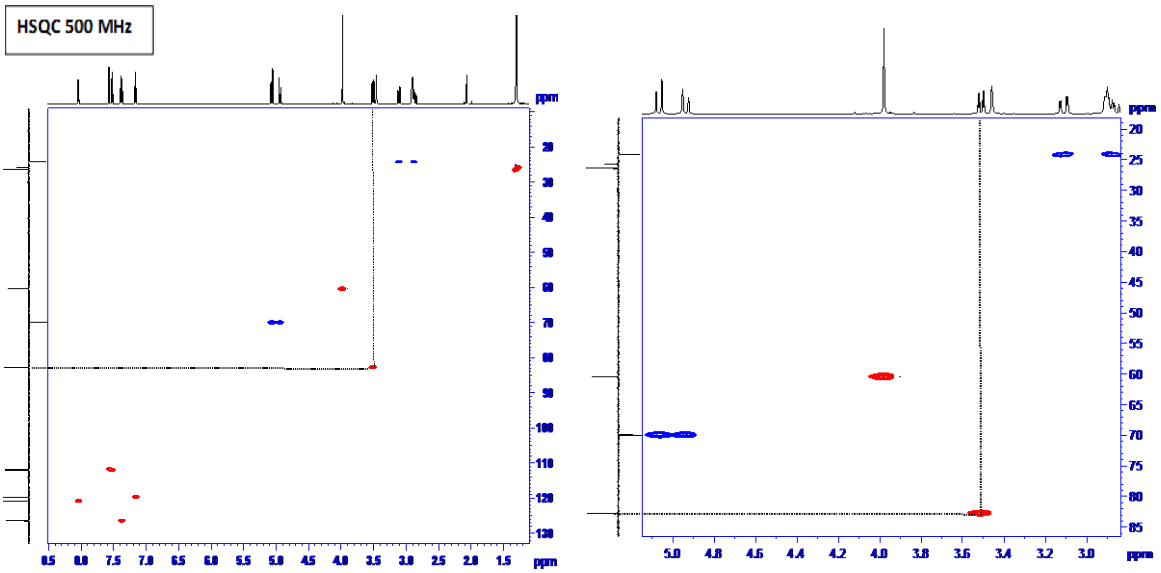

191.88
126.69
123.81
121.09
120.73
111.22
61.43
25.66
24.06
18.12
CHO
N
H
OMe
Indizoline (7)
DEPT, CDCl3, 100 MHz
Chemical Shift (ppm)

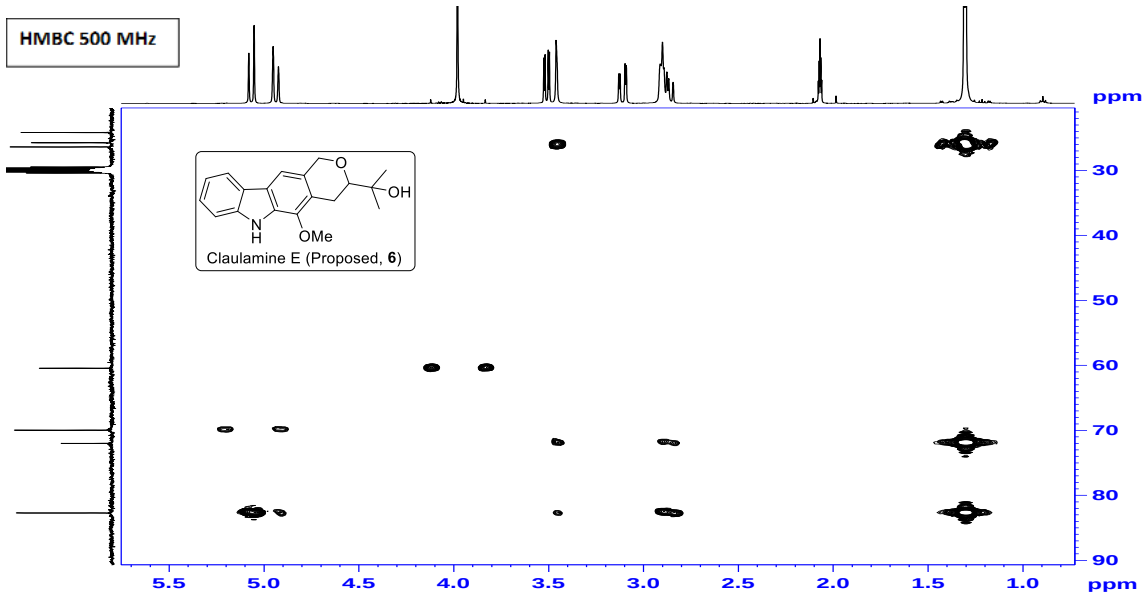

ACETONE-d6
10.31
8.03
8.01
7.55
7.51
7.49
7.38
7.36
7.16
7.14
7.13
5.06
5.03
4.93
4.90
3.96
3.50
3.50
3.48
3.48
3.44
3.08
3.07
2.89
2.88
2.87
2.82
2.05
1.29
1.28
OH
N
H
OMe
Claulamine E (Proposed, 6)
1H NMR, Acetone-d6, 500 MHz
0.93
1.00
0.99
0.98
1.01
1.02
1.07
1.08
3.03
1.07
0.93
1.08
2.75
6.57
Chemical Shift (ppm)

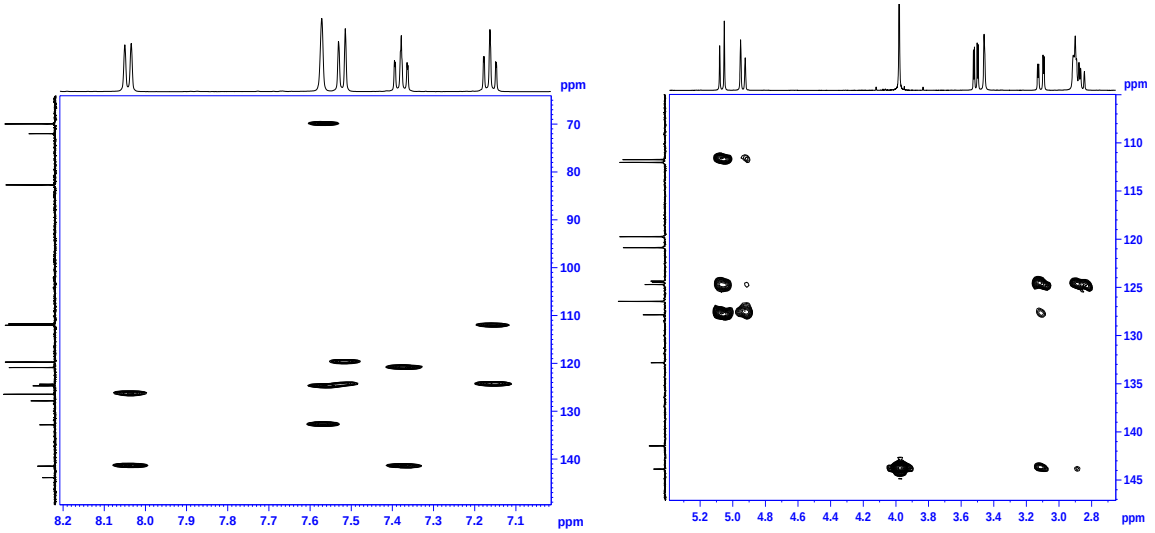

ACETONE-d6
143.85
141.45
132.81
127.84
126.45
124.70
124.43
124.35
120.88
119.73
112.03
111.74
82.70
71.99
69.95
60.42
29.92
26.38
25.74
24.16
OH
N
H
OMe
Claulamine E (Proposed, 6)
13C NMR, Acetone-d6, 125 MHz
Chemical Shift (ppm)

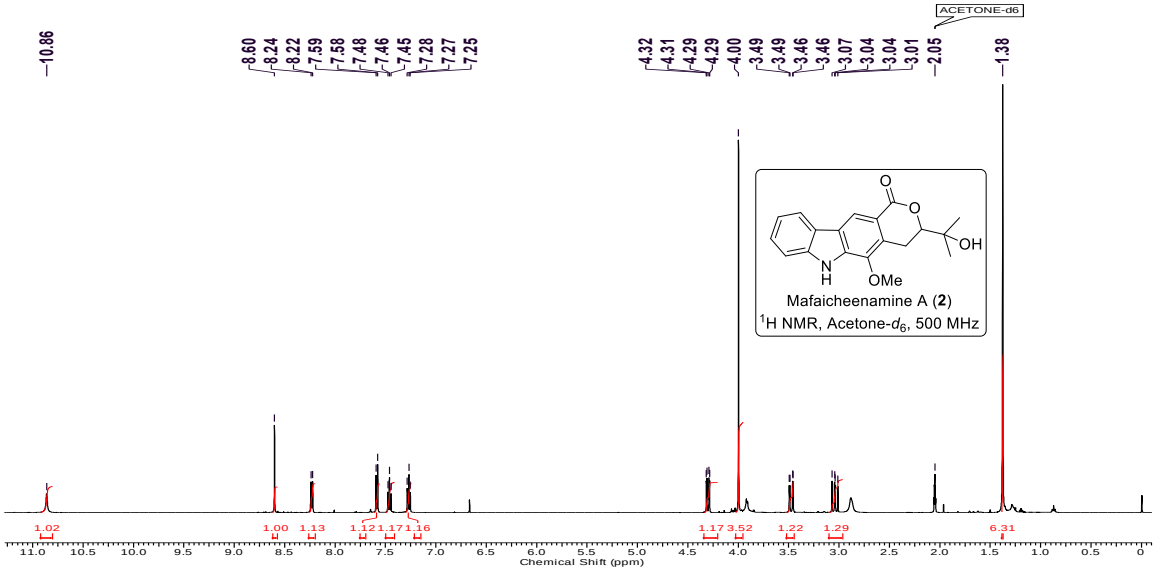

126.45
120.87
119.73
112.02
111.74
82.70
69.95
60.42
26.37
24.16
OH
N
H
OMe
Claulamine E (Proposed, 6)
DEPT, Acetone-d6, 125 MHz
Chemical Shift (ppm)


COSY
ppm
Claulamine E (Proposed, 6)
NOESY 500 MHz
ppm


HSQC 500 MHz
ppm


HMBC 500 MHz
OH
N
H
OMe
Claulamine E (Proposed, 6)
ppm


ppm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8.22
7.59
7.58
7.48
7.46
7.45
7.28
7.27
7.25
4.32
4.31
4.29
4.29
4.00
3.49
3.49
3.46
3.46
3.07
3.04
3.04
3.01
2.05
1.38
Mafaicheenamine A (2)
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1.12
1.17
1.16
1.17
3.52
1.22
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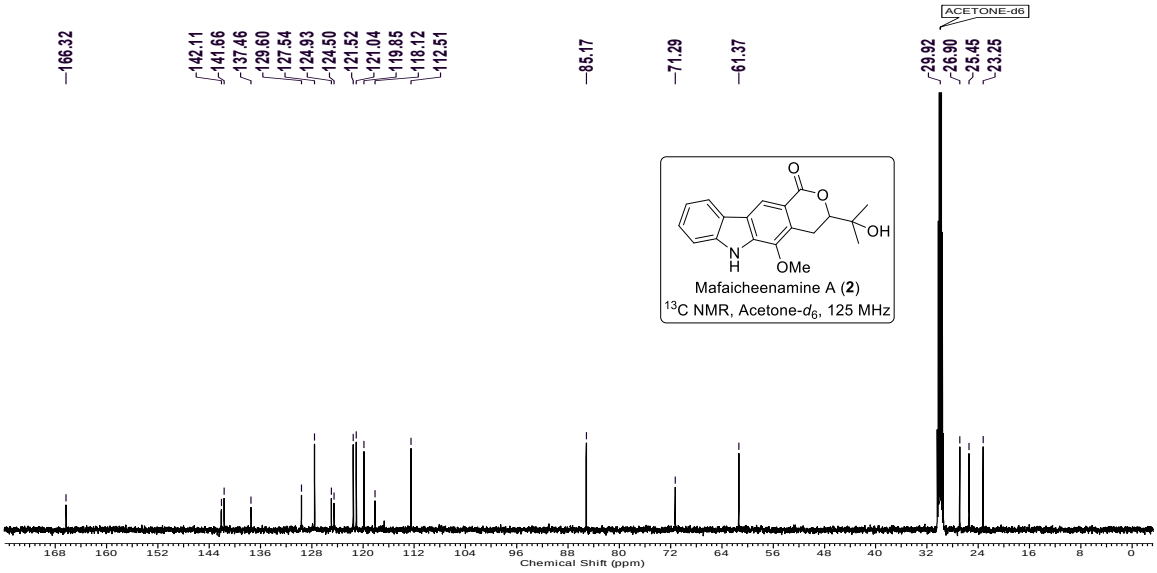
6.31
Chemical Shift (ppm)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121.04
119.85
118.12
112.51
85.17
71.29
61.37
29.92
26.90
25.45
23.25
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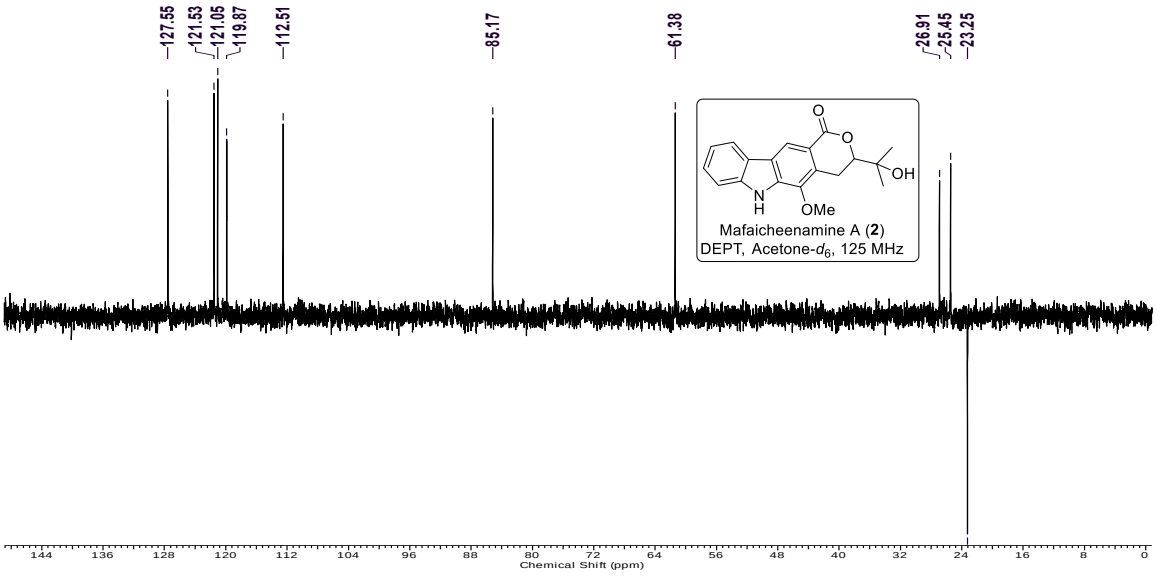
13C NMR, Acetone-d6, 125 MHz
Chemical Shift (ppm)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121.53
121.05
119.87
112.51
85.17
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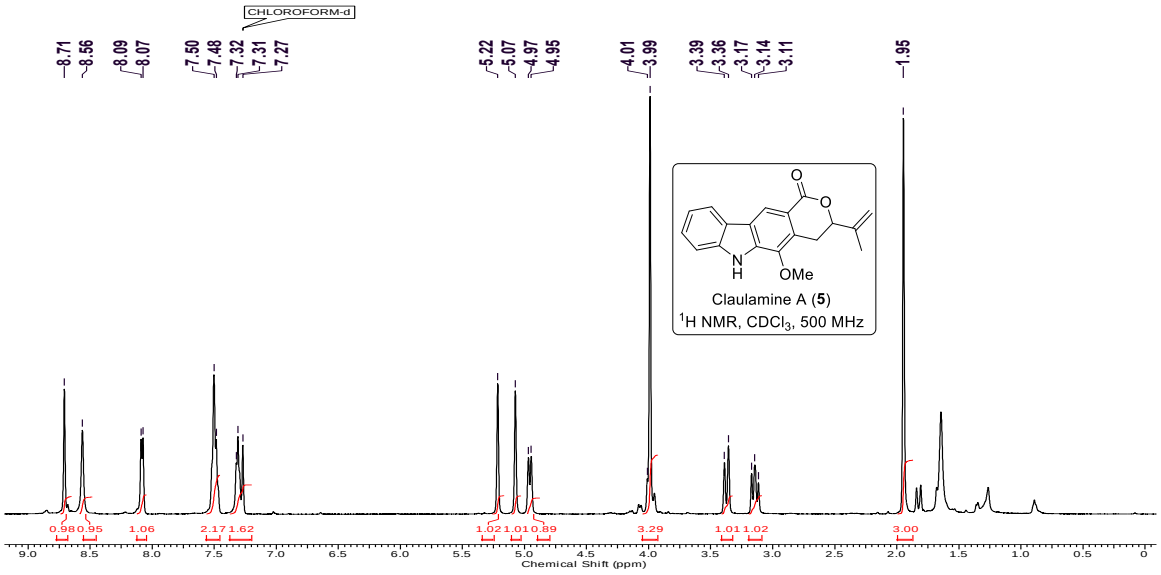
26.91
25.45
23.25
Mafaicheenamine A (2)
DEPT, Acetone-d6, 125 MHz
Chemical Shift (ppm)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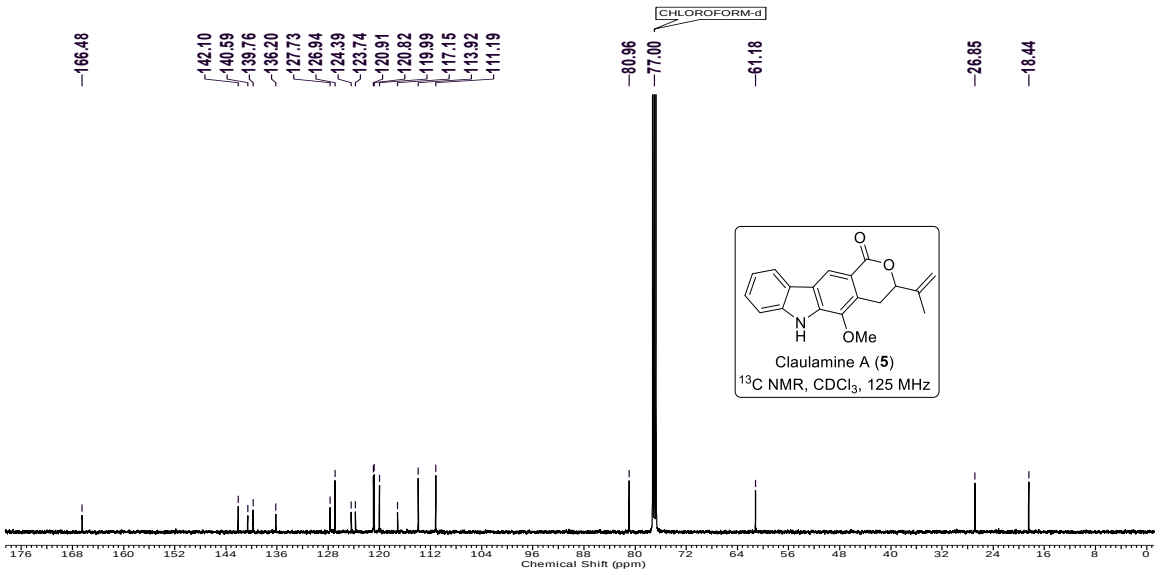
5.07
4.97
4.95
4.01
3.99
3.39
3.36
3.17
3.14
3.11
1.95
0.98 0.95
1.06
2.17 1.62
1.02 1.01 0.89
3.29
1.01 1.02
3.00
Chemical Shift (ppm)
Claulamine A (5)
1H NMR, CDCl3, 500 MHz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120.82
119.99
117.15
113.92
111.19
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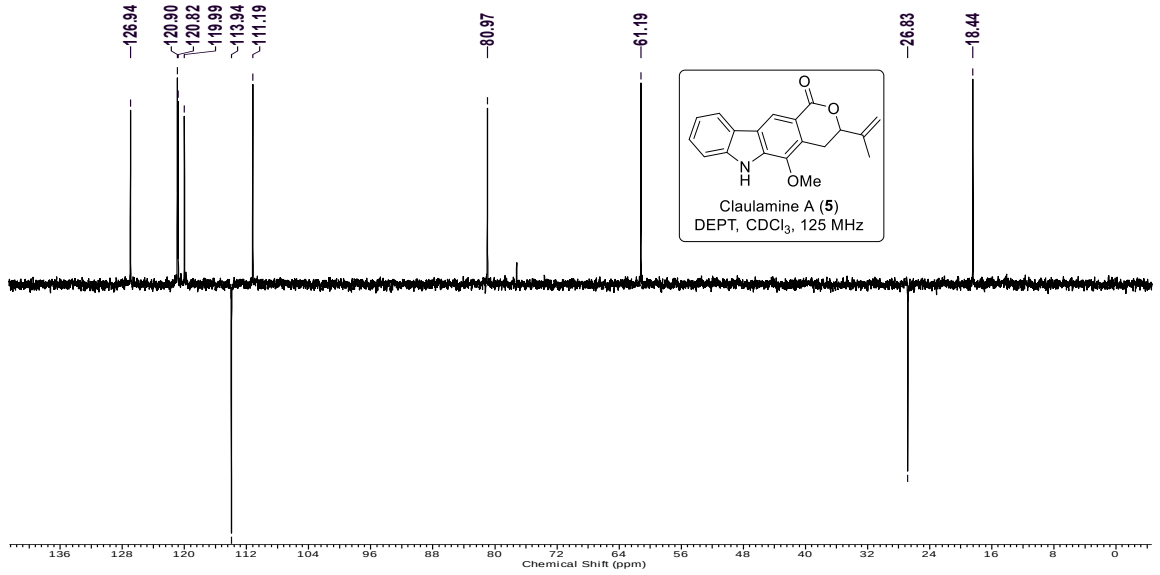
77.00
61.18
26.85
18.44
Chemical Shift (ppm)
Claulamine A (5)
13C NMR, CDCl3, 125 MHz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120.82
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80.97
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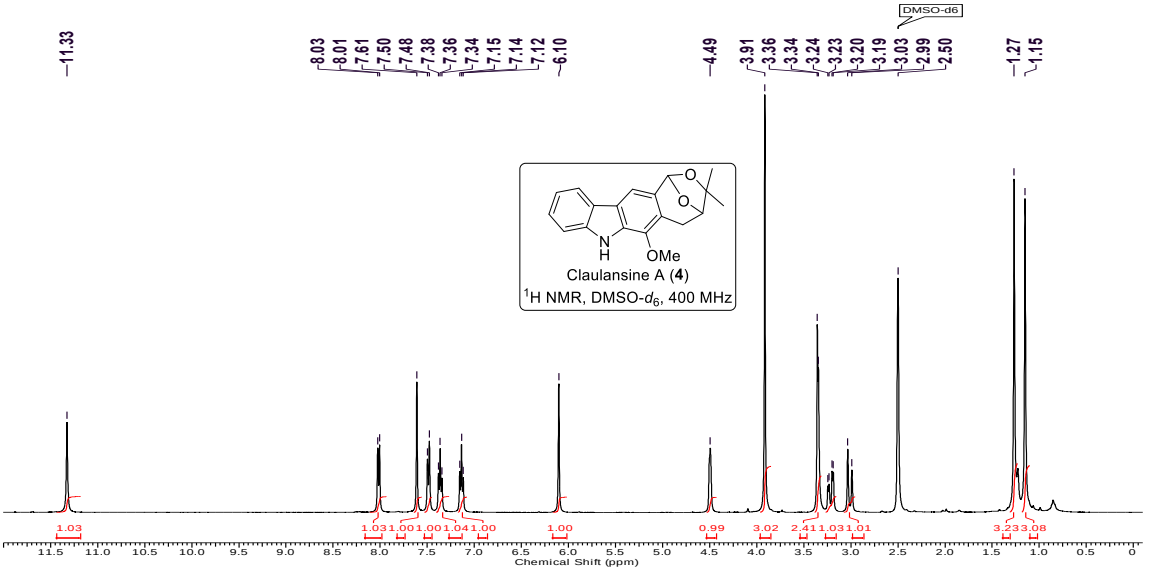
18.44
Chemical Shift (ppm)
Claulamine A (5)
DEPT, CDCl3, 125 MHz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7.14
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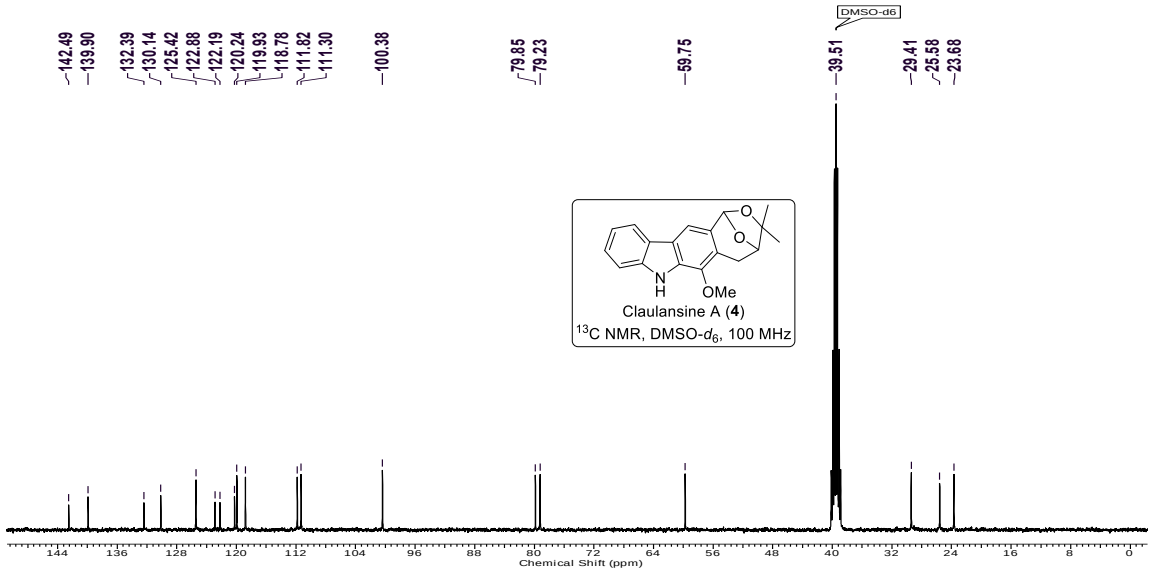
6.10
4.49
3.91
3.36
3.34
3.24
3.23
3.20
3.19
3.03
2.99
2.50
1.27
1.15
Claulansine A (4)
1H NMR, DMSO-d6, 400 MHz
Chemical Shift (ppm)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100.38
79.85
79.23
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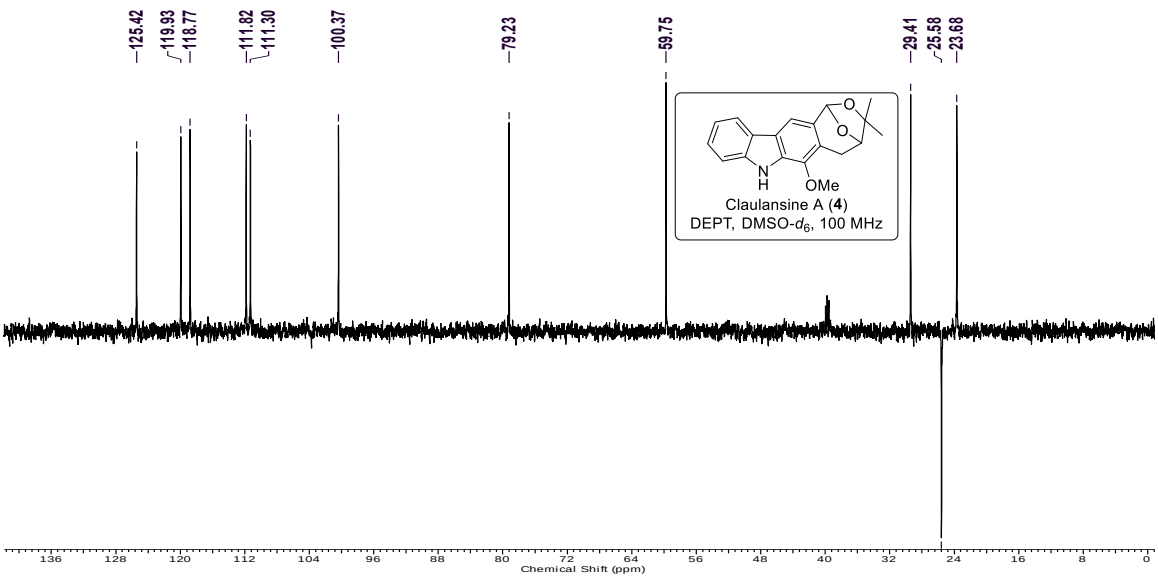
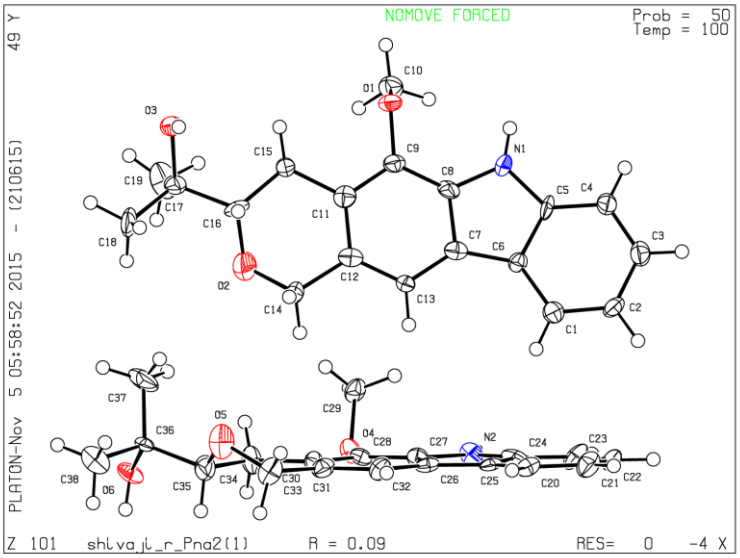
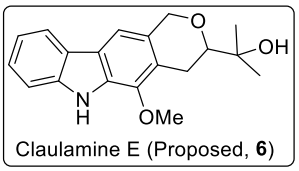
23.68
Claulansine A (4)
13C NMR, DMSO-d6, 100 MHz
Chemical Shift (ppm)


125.42
119.93
118.77
111.82
111.30
100.37
79.23
59.75
29.41
25.58
23.68
Claulansine A (4)
DEPT, DMSO-d6, 100 MHz
Chemical Shift (ppm)

2B.7 X-ray of claulamine E (proposed)





Claulamine E (Proposed, **6**)

2B.8 References

1. Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099.
2. Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193.
3. Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.
4. Levick, M. T.; Grace, I.; Dai, S.-Y.; Kasch, N.; Muryn, C.; Lambert, C.; Turner, M. L.; Procter, D. J. *Org. Lett.* **2014**, *16*, 2292.
5. Yang, W.; Zhang, Z.; Han, C.; Zhang, Z.; Xu, H.; Yan, P.; Zhao, Y.; Liu, S. *Chem. Commun.* **2013**, *49*, 2822.
6. Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 14228.
7. Li, W.-S.; Mcchesney, J. D.; El-Feraly, F. S. *Phytochemistry* **1991**, *30*, 343.
8. Maneert, W.; Laphookhieo, S. *Heterocycles* **2010**, *81*, 1261.
9. Shen, D.-Y.; Chao, C.-H.; Chan, H.-H.; Huang, G.-J.; Hwang, T.-L.; Lai, C.-Y.; Lee, K.-H.; Thang, T. D.; Wu, T.-S. *Phytochemistry* **2012**, *82*, 110.
10. Liu, H.; Li, C.-J.; Yang, J.-Z.; Ning, N.; Si, Y.-K.; Li, L.; Chen, N.-H.; Zhao, Q.; Zhang, D.-M. *J. Nat. Prod.* **2012**, *75*, 677.
11. Shen, D.-Y.; Chan, Y.-Y.; Hwang, T.-L.; Juang, S.-H.; Huang, S.-C.; Kuo, P.-C.; Thang, T.-D.; Lee, E.-J.; Damu, A.-G.; Wu, T.-S. *J. Nat. Prod.* **2014**, *77*, 1215.
12. Liu, Y.; Guo, Y.; Ji, F.; Gao, D.; Song, C.; Chang, J. *J. Org. Chem.* **2016**, *81*, 4310.
13. (a) Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron* **1998**, *54*, 1585. (b) Gordaliza, M.; del Corral, J. M. M.; Castro, M. A.; Salinero, M. A.; Feliciano, A. S.; Valle, F. *Synlett* **1996**, 1201.

14. Lebold, T. P.; Kerr, M. A. *Org*. *Lett*. **2008**, *10*, 997.
15. Batwal, R. U.; Argade, N. P. *Org*. *Biomol*. *Chem*. **2015**, *13*, 11331.
16. Han, J.-C.; Li, F.; Li, C.-C. *J*. *Am*. *Chem*. *Soc*. **2014**, *136*, 13610.
17. Jiang, S.-Z.; Lei, T.; Wei, K.; Yang, Y.-R. *Org*. *Lett*. **2014**, *16*, 5612.
18. Markad, S. B.; Argade, N. P. *Org. Lett.* **2014**, *16*, 5470.
19. Zheng, Y.; Liu, Y.; Wang, Q. *J*. *Org*. *Chem*. **2014**, *79*, 3348.
20. Li, H.; Wang, X.; Hong, B.; Lei, X. *J*. *Org*. *Chem*. **2013**, *78*, 800.
21. Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183.
22. Flyer, A. N.; Si, C.; Myers, A. G. *Nat*. *Chem*. **2010**, *2*, 886.
23. Deore, P. S.; Argade, N. P. *J. Org. Chem.* **2014**, *79*, 2538.
24. Deore, P. S.; Argade, N. P. *Org. Lett.* **2013**, *15*, 5826.
25. Mondal, P.; Argade, N. P. *J. Org. Chem.* **2013**, *78*, 6802.
26. Patel, R. M.; Argade, N. P. *Org. Lett.* **2013**, *15*, 14.
27. Deore, P. S.; Argade, N. P. *J. Org. Chem.* **2012**, *77*, 739.
28. Atkins, G. M.; Burgess, E. M. *J*. *Am*. *Chem*. *Soc*. **1968**, *90*, 4744.
29. Kamat, D. P.; Parsekar, S. B.; Kamat, V. P.; Tilve, S. G. *Synthesis* **2014**, *46*, 2789.
30. Inadvertent typographical errors were noticed in the tabulated ^{13}C NMR data for natural product claulamine A (**5**); please see the actual ^{13}C NMR spectrum provided in the supporting information part of ref. 9.

Chapter 3

Solid State Auto Inversion of *C*-Centrochirality: Enantioselective Total Synthesis of Furocarbazolones (–)-*epi*-Claulansine D and (–)-Claulansine D and Pyranocarbazolone (+)-*epi*-Claulansine C

3.1 Introduction

Most of the organic reactions have been studied in solution, reason for this might be Aristotle's famous philosophy "No Coopora nisi Fluida", which means "No reaction occurs in the absence of solvent." This philosophy had a big influence on the evolution of the modern sciences in Europe. In the ancient period of Aristotle, it was not realized that many reactions occur in the absence of solvent. Many biological reactions such as digestion of food in the stomach and bowels, the reaction between cells such as ovum and spermatid and the multiplication of the cells are more solid state than solution reactions. Nevertheless, it is very curious that almost all reactions are still carried out in solution. The quite a few reactions proceed well in the solid state. In some cases, the solid state organic reaction occurs more efficiently and selectively than does in the solution reaction, since molecules in a crystal are arranged tightly and regularly. Some selected reactions in the solid state require the host-guest chemistry technique. Reaction of the guest compound as its inclusion complex crystal with a chiral host compound in the solid state gives an optically active reaction product. The solid state complexation even occurs selectively, for example mixing of racemic guest and optically active host in the solid state gives an inclusion complex of one enantiomer of the guest with the host, from which optically active guest is obtained. Organic solid state reactions are usually carried out by keeping a mixture of finely powdered reactant and reagent at room temperature. In some cases, solid state reactions are accelerated by heating, shaking, irradiation with ultrasound or grinding of the reaction mixture using a mortar and pestle. Although both thermal and photochemical reactions can be carried out selectively in inclusion crystals, the selectivity of the latter reaction is usually higher than that of the former. The reaction rate in solid state depends on particle size of reactants and reagents used. For example, Baeyer-Villiger oxidation of benzophenone derivatives with *m*-chloroperbenzoic acid in the solid state proceeds 10 times faster when the particle diameter of both components is 50 μm compared to 100 μm, which clearly proves that smaller the particle size, faster the reaction rate. However in some cases the size of the particle is not related to reaction rate.[1–3]

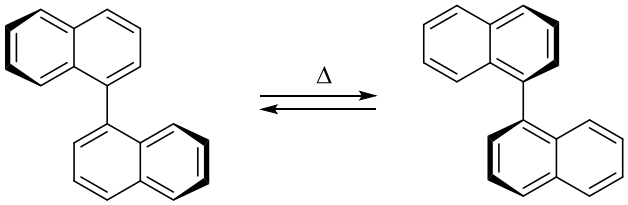
The examples in which crystalline lattice determines the course of reaction have been termed "topochemically controlled reactions". Topochemical reaction is a chemical

reaction that occurs at the boundary of solid phases. Examples of topochemical reactions are the dehydration of crystal hydrates, the reduction of oxides and the thermal decomposition of azides of heavy metals. Asymmetric synthesis through reactions in chiral crystals involves two aspects: generating chiral crystals and performing topochemically controlled solid-state reactions which essentially yield chiral products. The crystallization process itself may be considered as an elementary form of reaction, since molecules which may populate an infinite number of conformations in solution or in the melt are transformed to a finite number (generally one or two) of unique conformations in the solid. There are 230 unique space groups which describe the modes in which equivalent (i.e. congruent and enantiomeric species) may be arranged in infinite lattices. These space groups may be divided into two categories achiral and chiral, their assignment can often be made by examination of several X-ray diffraction photographs without requirement for full structure determination.[4]

Asymmetric synthesis using frozen chirality generated by spontaneous crystallization of achiral materials was performed in the year 2003.[5] If crystals can be made to order, solid-state asymmetric synthesis will be extended to a variety of new systems and this field will then be established as an important branch of organic chemistry.[6] Investigations of the photochemical and photophysical behaviour of organic compounds dispersed in a variety of solid environments represent a well-defined and relatively new area of research.[7] Crystallization-induced dynamic resolution (CIDR) is an adaptation of dynamic resolution, a process that can afford a quantitative yield of chiral product from a racemic starting material through in situ resolution. Crystallization-induced asymmetric transformation (CIAT) includes CIDR and the preparation of diastereomers and olefins that are driven by crystallization. To efficiently develop rugged CIDR and CIAT processes, it is necessary to optimize parameters for both racemization and crystallization; development time may be shortened by high-throughput screening and design of experiments.[8]

Since the chemistry of solid state organic reactions has only a very short history, it is not easy to interpret such reactions uniformly. Theoretical treatments of solid state reactions is not possible, because theory which has been developed to describe solution reactions is not simply applicable to solid state reactions.

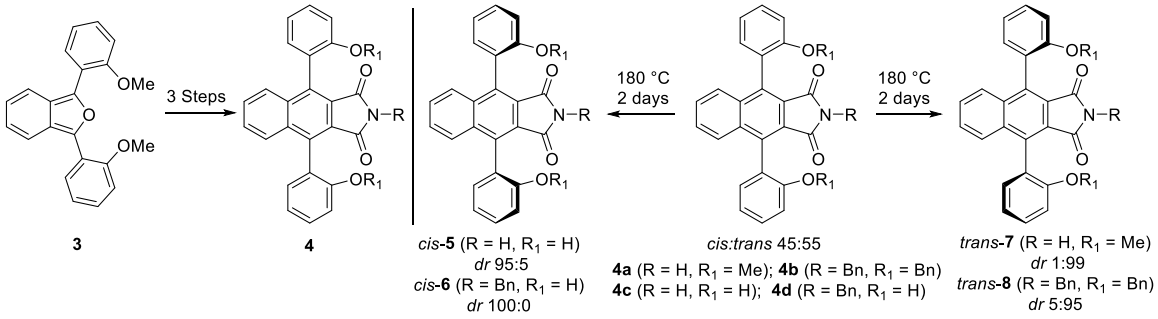
3.2 Background



(*R*)-(–)-1,1'-Binaphthalene (**1**) (*S*)-(+)-1,1'-Binaphthalene (**2**)

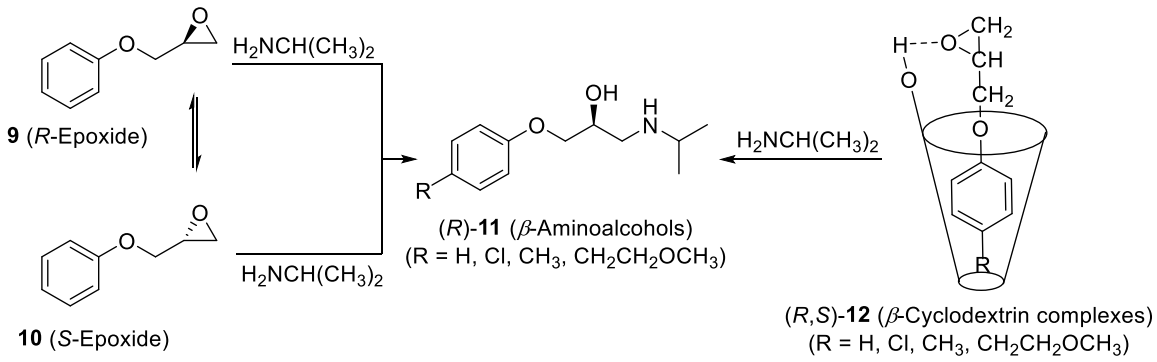
Scheme 1. Solid State Resolution of (±)-1,l'-Binaphthyl to Single Enantiomer

Thermal transformation of racemic 1,1'-binaphthalene to stable enantiomeric crystals has been depicted in scheme 1. The development of optical activity in racemic samples of 1,l'-binaphthyl can occur simply on heating polycrystalline samples. This unusual solid-state resolution is made by a phase transformation from a racemic compound (MP 145 ºC) to an unequal eutectic mixture (MP 158 ºC) of enantiomorphic crystals, with the necessary enantiomer conversion occurring in the reactant-product interface. At 150 ºC these samples resolve via a racemate–melt–eutectic phase transition, from $[\alpha]^D$ 1–10º to $[\alpha]^D$ >200º in the desired positive or negative direction within a few minutes.[9]



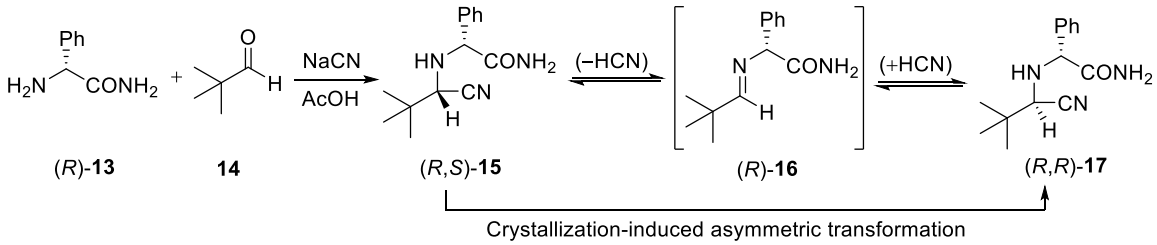
Scheme 2. Solid State Thermal Resolution to Single Isomer

Solid-state thermal isomerization of compounds **4**, which presents such a type of atropisomerism (Scheme 2).[10] None of these showed noticeable interconversion of **4a** in solution after one day at 20 ºC. On the other hand fast equilibration occurred in boiling toluene, after 15 hours at 180 ºC the ratio was 10:90 in favour of the *trans*-isomer. Further heating at 180 ºC for two days led to an almost complete isomerization of the sample (*cis*:*trans* 1:99). A similarly *cis*:*trans* 100:0 ratio for **6** was obtained after heating a 45:55 mixture of *cis*-**4d**:*trans*-**4d** in the solid state for two days at 180 ºC.



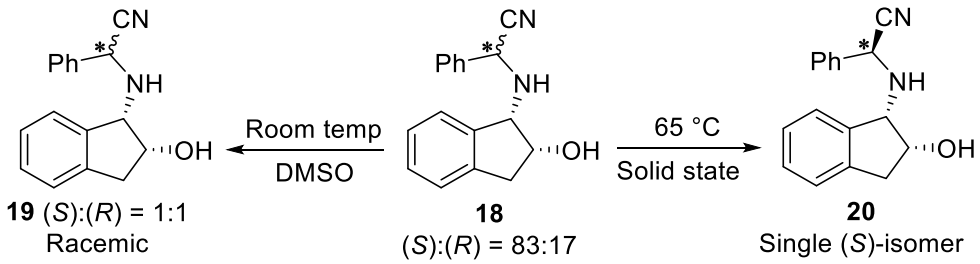
Scheme 3. Solid State Kinetic Resolution to Single Enantiomer

The enantiopuric *β*-aminoalcohols **11** of high potential can be prepared from racemic epoxides **12** by dynamic kinetic resolution involving enantio-differentiating racemization in *β*-cyclodextrin complexes under solid state conditions (Scheme 3).[11] Both *R*- and *S*-epoxides (**9** and **10**) gave the mainly *R*-enantiomer of aminoalcohol **11** (R = H, 90% ee).



Scheme 4. Solid State Epimerization to Single Diastereomer

(*R*)-Phenylglycine amide **13** is an excellent chiral auxiliary in the asymmetric Strecker reaction with pivaldehyde **14** (Scheme 4).[12] The Strecker reaction is accompanied by an in situ crystallization-induced asymmetric transformation, whereby one diastereomer selectively precipitates in good yield and *dr* >99:1. The (*S*)-phenylglycine amide is also used if the other enantiomer of a target molecule is required.



Scheme 5. Solid State Epimerization to Single Diastereomer

Yamaura and co-workers reported solid state epimerization of diastereomeric *α*-amino nitriles to a single stereoisomer via elimination-addition pathway (Scheme 5).[13] A

diastereomeric mixture of the α-amino nitrile **18** thermally epimerizes in the solid state to give a single diastereomer **20** with (*S*)-configuration at the α-position to the nitrile moiety, while in solvent DMSO at room temperature gives a 1:1 mixture of (*S*)- and (*R*)-isomers **19**.

Irradiating the racemic (1-cyanoethyl)(piperidine)cobaloxime crystal with X-rays at 343 K causes racemization of the *S*-enantiomer while the *R*-enantiomer remains unaltered. This racemization is thought to be due solely to the different volume constraints on the two enantiomers in their different crystal environments. The result is that the number of "*R*" molecules is increased at the expense of "*S*" and so the overall composition of the crystal changes from racemic to enriched in the *R*-enantiomer.[14]

The enantiomeric/diastereomeric improvement in (1-cyanoethyl)cobaloxime crystals has been studied. The diastereomeric [(*R*,*S*)-1-cyanoethyl][methyl(*S*)-alaninate]cobaloxime complex cannot be separated by the fractional crystallization method. When the crystal was irradiated with a Xenon lamp, the cell dimensions gradually changed. After about 70 h of exposure, the change became insignificantly small. Crystal structure analysis after irradiation indicated that only the (*R*)-1-cyanoethyl complex was epimerized and the (*S*)-1-cyanoethyl complex remained unaltered.[15]

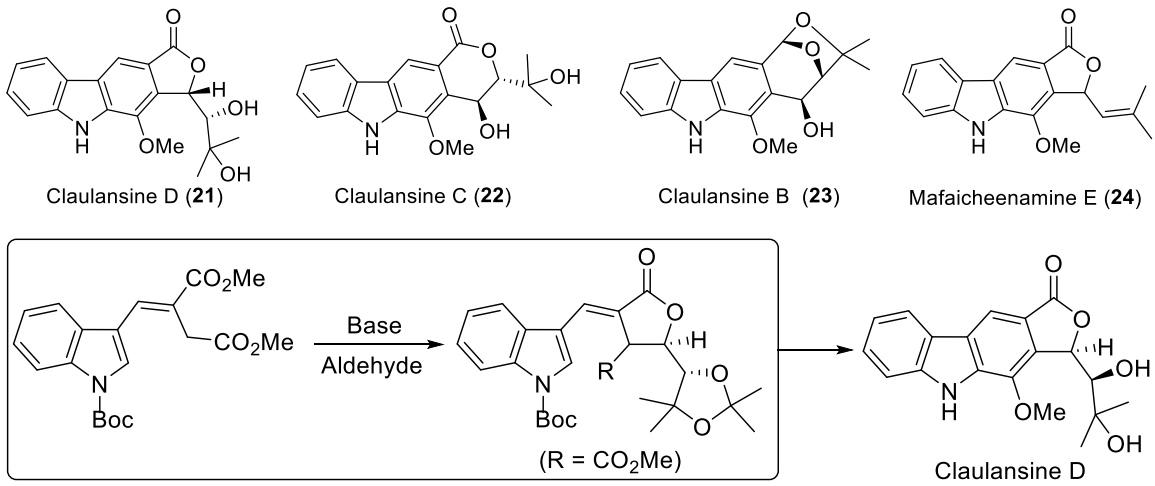
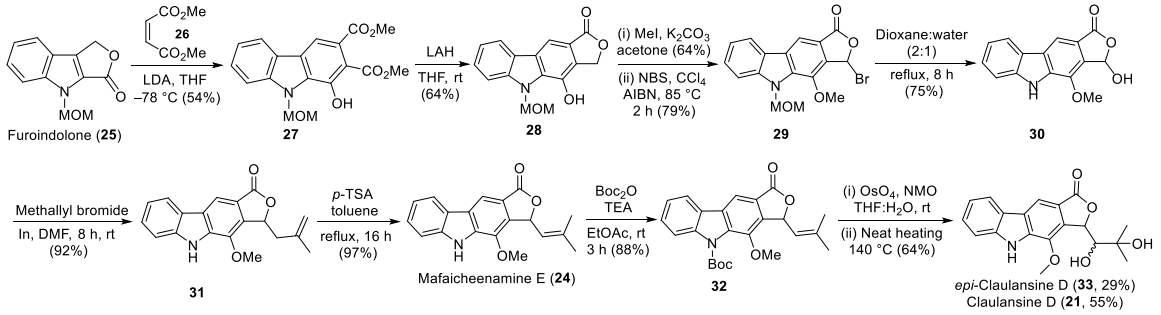


Figure 1. Representative Carbazole Alkaloids.

Carbazole alkaloids have occupied a central place in organic synthesis due to their wide range of pharmacological and biological activities. Carbazole alkaloids with linearly fused lactone rings display promising biological activities (Figure 1).[16,17]



Scheme 6. Total Synthesis of Claulansine D

Mal and Roy reported the synthesis of carbazole alkaloid claulansine D (Scheme 6).[18] Anionic annulation of furoindolone **25** with dimethyl maleate (**26**) in the presence of LDA in THF at –78 °C yielded the corresponding carbazole diester **27** in 54% yield. Phenol driven regioselective reduction of diester **27** with LAH in THF at room temperature formed furocarbazolone **28** in 64% yield. Methylation of the crude product **28** with K_2CO_3/CH_3I in acetone, followed by bromination with NBS in refluxing CCl_4 yielded product **29**. Without any purification compound **29** was treated with dioxane–water to afford hydroxyfurocarbazolone **30** via an associated deprotection of the MOM-group. Treatment of **30** with methallylindium bromide generated in situ from methallyl bromide and metal indium provided the furocarbazole **31** in 92% yield. Isomerization of the methallyl group in **31** to the propenyl group using *p*-toluenesulfonic acid in refluxing toluene furnished the mafaicheenamine E (**24**) in 97% yield. Indole nitrogen of the product **24** was protected with Boc-anhydride/trimethylamine in ethyl acetate to obtain compound **32**. The furocarbazolone **32** was subjected to dihydroxylation with OsO_4/NMO and provided a diastereomeric mixture. Neat heating of this sample at 140 °C and then purification of diastereomeric mixture by column chromatography provided (±)-claulansine D (**21**, 55%) and (±)-unnatural isomer **33** (29%) in a 2:1 ratio.

3.3 Results and Discussion

Solid State Auto Inversion of *C*-Centrochirality: Enantioselective Total Synthesis of Furocarbazolones (–)-*epi*-Claulansine D and (–)-Claulansine D and Pyranocarbazolone (+)-*epi*-Claulansine C

Synthesis of optical isomers comprising well-ordered crystal engineering has been a subject of contemporary interest. The enrichment of enantiomeric/diastereomeric excess in a crystal lattice is feasible via deracemization/epimerization.[1–8] A few such examples

on solid state transformations have been known till date viz. the thermal transformation of racemic 1,1'-binaphthalene to stable enantiomeric crystals,[9] epimerization of atropodiastereomeric teraryls,[10] enantiomeric/diastereomeric improvement in (1-cyanoethyl)cobaloxime crystals,[11,12] a crystallization induced asymmetric transformation in the Strecker reaction,[13] dynamic kinetic resolution of epoxides by means of aminolysis in the *β*-cyclodextrin inclusion complex[14] and solid state epimeriztion of diastereomeric *α*-amino nitriles to a single stereoisomer via elimination-addition pathway.[15] The stability driven stereoselective migration of an atom or a group from one face to another face with the transformation of anti-bonding orbital into bonding orbital is termed as atoms flip mechanism, overall leading to inversion of *C*-centrochirality. To the best of our knowledge, a diastereomeric enrichment of organic molecules in crystal involving inversion of *C*-centrochirality via atom flip mechanism has yet to be discovered.

The carbazole alkaloids have been isolated from several plant, animal, microbial and marine sources.[16,17] Carbazoles exhibit broad spectrum of potential biological activities and they also possess very important electrical and thermal properties which are useful for the preparation of electroluminescent materials.[16–21] Several parts of *Clausena lansium* plant have been used as a folk medicine in China for cough, asthma and chronic ulcers. In search of potential lead compounds the phthalide unit consisting carbazoles (–)-claulansine B (5 mg), (+)-claulansine C (3 mg) and (–)-claulansine D (2 mg) were isolated from 6.40 kg powdered stems of above specified plant species (Figure 1).[22,23] A large number of enantiomerically pure phthalide based bioactive natural products have been known and are prone for racemization due to the inherent acidity of methine proton.[24,25] First synthesis of (±)-claulansine D has been recently reported by Mal and Roy via chemoselective addition of an allylic organoindium reagent to the corresponding lactonol.[18] In continuation of our studies on the total synthesis of recently isolated bioactive natural products;[26–28] we herein describe total synthesis of (±)/(–)-*epi*-claulansine D and remarkable solid state auto epimerization of (±)/(–)-*epi*-claulansine D to (±)/(–)-claulansine D along with base catalysed ring expansion of both to (±)/(+)-*epi*-claulansine C (Schemes 7 and 8).

A brief retrosynthetic analysis of selected carbazole based natural products has been depicted in figure 2 and dimethyl (*E*)-2-{[(1-*tert*-butoxycarbonyl)-1*H*-indol-3-

yl]methylene}succinate (**34**)[27,28] and (*R*)-2,2,5,5-tetramethyl-1,3-dioxolane-4-carbaldehyde (**35**)[29] would constitute a diversity oriented stereoselective convergent access to those natural products essential for biological screenings. Conceptually, the 3-position methylene succinate moiety in indole **34** and the suitably functionalized aldehyde **35** will be useful to generate the appropriately substituted rings C and D in a concise pathway via condensation and intramolecular cyclization's. Base induced condensation of ester **34** with the known aldehyde (–)-**35** at –78 ºC took place in a highly diastereoselective fashion and directly furnished the lactone (–)-**36a** as a single product in 73% yield via an in situ intramolecular cyclization (Scheme 7). Initially the lactone-ester (–)-**36a** was treated with concentrated hydrochloric acid expecting one-pot *N*-Boc and ketal deprotections, and the generation of ring C via intramolecular cyclization. However, lactone-ester (–)-**36a** on treatment with refluxing concentrated hydrochloric acid underwent desired *N*-Boc and ketal deprotections along with concomitant second lactonization to furnish the bicyclic product (+)-**36b** in 83% yield. The formation of five membered bicyclic product (+)-**36b** proved that the ester moiety and ketal unit in compound (–)-**36a** are having *cis*-orientations. Base promoted hydrolysis of ester (–)-**36a** provided intermediate acid **37**; which was used for the next step without any purification for high polarity, instability and yields related issues. Acid **37** on Ac_2O/NaOAc mediated intramolecular cyclization delivered the diacyl-carbazole derivative (+)-**38** in 51% yield over 2-steps. Base induced deacylations of (+)-**38** to phenol (+)-**39** in 88% yield and its chemoselective *O*-methylation with dimethyl sulfate yielded the corresponding methyl ether (+)-**40** in 89% yield. Ketal (+)-**40** in refluxing concentrated hydrochloric acid underwent deprotection and resulted in an unnatural isomer (–)-*epi*-claulansine D (**33**) in 87% yield. The obtained analytical and spectral data for (–)-*epi*-claulansine D (**33**) was in complete agreement with reported data.[18] The coupling constants for methine proton in a lactone moiety of compounds (–)-**26a** to (–)-**33** and the subsequent formation of known (–)-*epi*-claulansine D (**33**) confirmed their stereochemical assignments.

All attempts to transform (–)-*epi*-claulansine D to (–)-claulansine D using Mitsonubo inversion met with failure and the starting material was isolated back. PCC-oxidation of (–)-*epi*-claulansine D (**33**) was also not successful and ended up in excessive decomposition. Dess-Martin periodinane (DMP) oxidation of (–)-*epi*-claulansine D (**33**)

furnished the ketone (±)-**41** in 71% yield with an anticipated complete racemization via the keto-enol tautomerism. At this stage synthesis of (±)-claulansine D (**21**) was planned and the repetition of scheme 1 using racemic aldehyde (±)-**35** provided sufficient amount of ketone (±)-**41** for the systematic study of diastereoselective reduction reactions. Selected results on reduction of ketone (±)-**41** have been summarized in table 1. The $NaBH_4$ reduction of ketone (±)-**41** at –90 °C resulted in silica gel column chromatographically inseparable mixture of major (±)-claulansine D (**21**) and minor (±)-*epi*-claulansine D (**33**) in 97% yield with 86:14 ratio (Table 1, entry 5). HPLC separation of above diastereomeric mixture quantitatively provided the analytically pure natural product (±)-claulansine D (**21**) and its obtained analytical and spectral data was in complete agreement with reported data.[18,22,23]

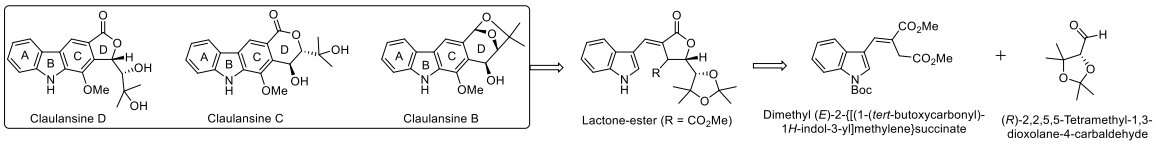
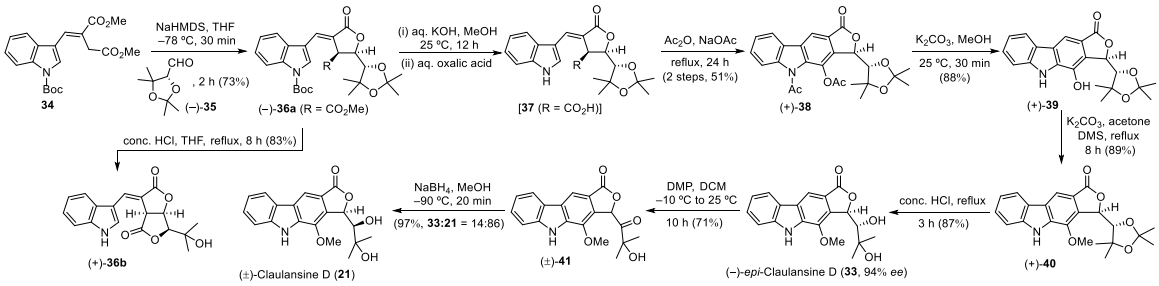
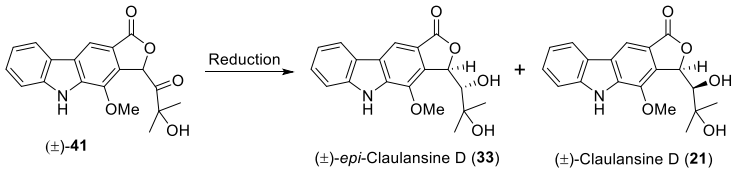


Figure 2. Concise Retrosynthetic Analysis of Targeted Carbazole Alkaloids.



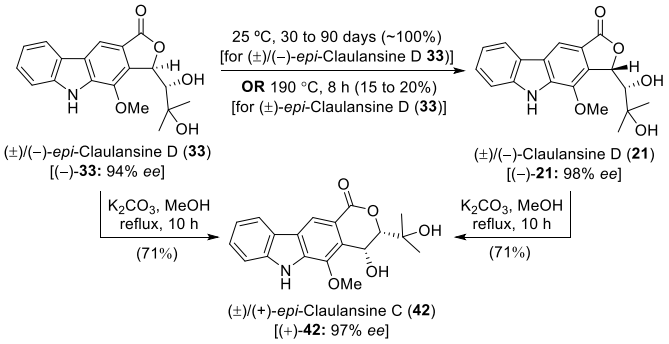
Scheme 7. Enantioselective Synthesis of (–)-*epi*-Claulansine D and Diastereoselective Synthesis of (±)-Claulansine D

Table 1. Selected Results on Diastereoselective Reduction of Ketone



Entry	Reduction Conditions	Yield (33:21)[a]
1	$NaBH_4$ (4.00 equiv), MeOH, –10 °C, 20 min	96% (53:47)
2	DIBAL-H (5.00 equiv), THF, –78 °C, 20 min	91% (84:16)
3	$LiBH_4$ (4.00 equiv), MeOH, –78 °C, 20 min	95% (30:70)
4	$NaBH_4$ (4.00 equiv), MeOH, –78 °C, 20 min	95% (29:71)
5	$NaBH_4$ (4.00 equiv), MeOH, –90 °C, 20 min	97% (14:86)

[a] The ratio was determined by ^1H NMR



Scheme 8. Solid State Auto Epimerization of (±)/(–)-*epi*-Claulansine D to (±)/(–)-Claulansine D and their Ring Expansion to (±)/(+)-*epi*-Claulansine C

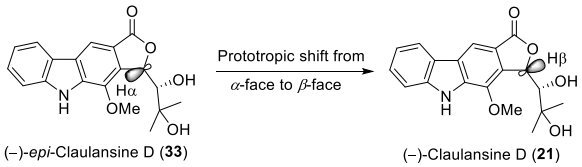
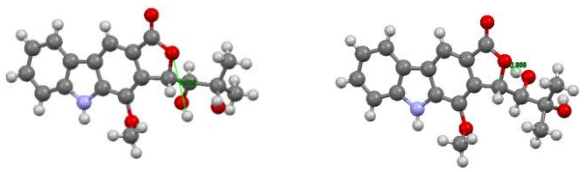
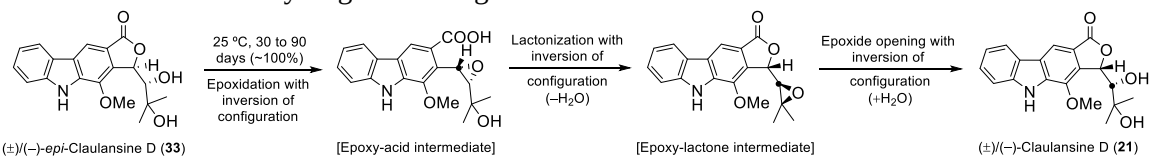


Figure 3. Solid State Inversions of *C*-Centrochirality via Ring-Atom Flip Mechanism.



epi-Claulansine D (**33**) Claulansine D (**21**)
(O–H---O bond (4.058 Å) (O–H---O bond (2.869 Å)

Figure 4. X-Ray Crystal Structures of *epi*-Claulansine D to Claulansine D and the Intramolecular Hydrogen Bondings shown with Green Dotted Lines.



Scheme 9. Plausibly Inaccessible Mechanistic Pathway for Solid State Auto Epimerization of (±)/(–)-*epi*-Claulansine D to (±)/(–)-Claulansine D

Since both analytically pure (±)-*epi*-claulansine D (**33**) and (–)-*epi*-claulansine D (**33**) were available, it was planned to check the enantiomeric purity of final product (–)-*epi*-claulansine D (**33**) by using chiral HPLC. Surprisingly the chiral HPLC data of freshly prepared (±)-*epi*-claulansine D (**33**) and approximately two month old room temperature stored solid sample of (–)-*epi*-claulansine D (**33**) were not in agreement with each other. Immediately collected analytical and spectral data of above specified samples revealed that the freshly prepared (±)-*epi*-claulansine D (**33**) is in its authentic form, while the nearly two month old (–)-*epi*-claulansine D (**33**) has been quantitatively transformed into

the natural product (–)-claulansine D (**21**) (98% *ee* by HPLC) (Scheme 8). In the next one month (±)-*epi*-claulansine D (**33**) stored in solid form also got completely transformed to (±)-claulansine D (**21**). Thus the freshly prepared neat solid samples of (±)- and (–)-*epi*-claulansine D (**33**) (94% *ee* by HPLC) were stored at room temperature and the changes were monitored by HPLC with the interval of few days and finally confirmed by ^{1}H NMR. The samples of (±)- and (–)-*epi*-claulansine D (**33**) did not indicate any noticeable changes in HPLC pattern till 18th day; the 30th days HPLC of both the solid samples showed a clean quantitative transformations into (±)- and (–)-claulansine D (**21**) (98% *ee* by HPLC). At this point three different reactions were performed and column chromatographically purified (±)-*epi*-claulansine D (**33**) were prepared to confirm the reproducibility of obtained results. Two of the samples underwent clean quantitative epimerization in 30 to 45 days; however the third one underwent epimerization only after 75 to 90 days. Overall all our samples underwent very clean quantitative conversion into (±)-claulansine D (**21**) ranging in minimum 30 to maximum 90 days incubation time. The incubation time might be dependent on several factors such as temperature, moisture content in the sample, amount of sample, crystal size, crystal shape, crystal packing, enantiomeric/diastereomeric purity and the levels of other organic/inorganic impurities.[30] The above mentioned product (±)-*epi*-claulansine D (**33**) was stable in neat form at 50 °C for two weeks and remained completely unchanged (by HPLC). Finally, we heated the (±)-*epi*-claulansine D (**33**) at 190 °C for 8 h and noticed the formation of desired product (±)-claulansine D (**21**) to the extent of 15 to 20% along with unreacted starting material (45 to 55%) and some decomposition products (by HPLC and ^{1}H NMR). In the above specified reaction increase in time and/or temperature resulted into further decline in yield of the desired product. The freshly prepared (±)/(–)-*epi*-claulansine D (**33**) and (±)/(–)-claulansine D (**21**) were quite stable in ethanol solution at room temperature for two months and did not show any signs of interconversions into each other (by HPLC). These facts indicate that the observed inversion of configuration takes place only in the solid state form and neat heating of solid also does the inversion of configuration in much shorter time but with lower yields.

The solid state auto epimerization of (±)/(–)-*epi*-claulansine D to (±)/(–)-claulansine D can take place via (i) simple epimerization at the benzylic position or (ii) via set of

unusual intramolecular and intermolecular reactions as depicted in scheme 9. Above specified serendipitously witnessed transformations of (±)/(–)-*epi*-claulansine D (**33**) to (±)/(–)-claulansine D (**21**) clearly indicated that the stereoselective auto epimerization involving migration of methine proton takes place in the solid state. The driving force for epimerization process in solid form could be the more stable three dimensional spatial arrangement in (–)-claulansine D due to the effective intramolecular and intermolecular hydrogen bondings. As expected the (–)-claulansine D (**21**) (MP 252 to 254 °C) was having higher melting point than the (–)-*epi*-claulansine D (**33**) (MP 208 to 210 °C) representing more compact crystal packing. The X-ray crystallographic data of both *epi*-claulansine D (**33**) and claulansine D (**21**) were collected to confirm the structural assignments and also to reason the epimerization process. Effective five membered intramolecular hydrogen bonding with ring oxygen atom in claulansine D (**21**) (hydrogen bond length 2.869 Å) imparts extra stability and hence in solid state the *epi*-claulansine D (**33**) (hydrogen bond length 4.058 Å) undergoes auto epimerization via an intramolecular face selective prototropic shift (Figures 3 and 4). On the basis of higher melting point, effective intramolecular and intermolecular hydrogen bondings, required induction period of 30 to 90 days involving rapid epimerization in the last few days, the strictly forbidden inversion of (±)/(–)-*epi*-claulansine D (**33**) to (±)/(–)-claulansine D (**21**) in solution form and finally the remote possibility of solid form intramolecular and intermolecular multiple reactions leading to the inversion of configuration as represented in scheme 9; we state that these results have demonstrated the first example of inversion of *C*-centrochirality via atom flip mechanism in solid state with an auto transformation of (±)/(–)-*epi*-claulansine D (**33**) to (±)/(–)-claulansine D (**21**). We feel that the sequential chemical transformations in scheme 9, such as lactone opening, subsequent epoxide formations and final intermolecular reaction of epoxide ring opening with water in the solid state simply stand as plausible theoretical proposal and can be ruled out. Both (±)/(–)-*epi*-claulansine D (**33**) and (±)/(–)-claulansine D (**21**) on treatment with K_2CO_3/methanol[31] formed the ring expansion product (±)/(+)-*epi*-claulansine C (**42**) in 71% yield [(+)-**42:** 97% *ee* by HPLC]. Mechanistically in solution phase, first the (–)-claulansine D (**21**) slowly epimerizes to thermodynamically more stable (–)-*epi*-claulansine D (**33**) and then transforms into (+)-*epi*-claulansine C (**42**); hence the (–)-

claulansine D to (–)-claulansine C conversion was not feasible. Above specified results clearly reveal that in the solid state (±)/(–)-claulansine D (**21**) is thermodynamically more stable while in the solution form (±)/(–)-*epi*-claulansine D (**33**) is thermodynamically more stable.

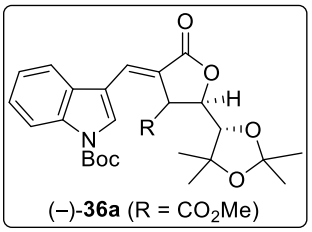
3.4 Summary

In summary, enantioselective total synthesis of (–)-claulansine D has been demonstrated via remarkable solid state auto epimerization of (–)-epi-claulansine D and it represents first example of crystal engineering driven inversion of C-centrochirality. The present synthesis demonstrates diastereomeric enrichment of phthalide moiety in a crystal lattice to a single isomer and we feel that it will be conceptually highly useful in future from applications point of view. Moreover further elaboration of solid state dynamic resolutions will provide the environment friendly and cost effective approaches to some of the enantiomerically pure essential chemical products.

3.5 Experimental Section

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR and 500 MHz NMR spectrometers using solvent residue signal as an internal standard [^{1}H NMR: $CDCl_3$ (7.27), CD_3COCD_3 (2.05), DMSO-d_6 (2.50); ^{13}C NMR: $CDCl_3$ (77.00), CD_3COCD_3 (29.84), DMSO-d_6 (39.51)]. The ^{13}C NMR spectra were recorded on 400 NMR (100 MHz) and 500 NMR (125 MHz) spectrometers. Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. (*R*)-2,2,5,5-Tetramethyl-1,3-dioxolane-4-carbaldehyde was prepared by using known procedure.[29] Commercially available starting materials and reagents were used.

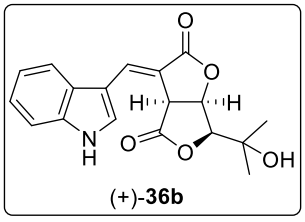
(–)-*tert*-Butyl 3-(*E*)-{[(5*S*)-4-(Methoxycarbonyl)-2-oxo-5-[(*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]dihydrofuran-3(2*H*)-ylidene]methyl}-1*H*-indole-1-carboxylate (36a).



(–)-**36a** (R = CO_2Me)

To a stirred solution of compound **34** (10.00 g, 26.66 mmol) in dry THF (60 mL) was dropwise added a solution of NaHMDS in THF (1 M, 53.3 mL, 53.33 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred for 30 min and solution of aldehyde **35** (21.00 g, 134 mmol) in THF (20 mL) was added dropwise. Reaction mixture was further stirred for 2 h at –78 °C and the reaction was quenched with saturated aqueous NH_4Cl. Solvent was removed in vacuo and the obtained residue was dissolved in EtOAc (150 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent yielded pure (–)-**36a** as a white solid (9.49 g, 73%). Mp 164–166 °C; $[\alpha]^{25}_D$ –4.89 (*c* 0.15 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.44 (s, 3H), 1.74 (s, 9H), 3.50 (d, *J* = 8 Hz, 1H), 3.80 (s, 3H), 4.18 (s, 1H), 4.86 (d, *J* = 12 Hz, 1H), 7.37 (t, *J* = 8 Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 8.01 (s, 1H), 8.14 (d, *J* = 8 Hz, 1H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2, 27.2, 27.4, 28.1, 28.5, 49.1, 53.0, 77.6, 80.8, 82.6, 85.6, 108.6, 114.6, 115.4, 118.7, 119.6, 123.7, 125.5, 128.5, 129.6, 130.7, 134.9, 149.3, 170.1 (2 C); ESIMS (*m*/*z*) 500 $[M+H]^+$; HRMS (ESI) calcd for $C_{27}H_{34}O_8N$ 500.2279, found 500.2272; IR ($CHCl_3$) ν_{max} 1740, 1723 cm^{-1}.

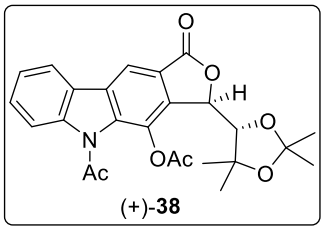
(+)-(3a*R*,6*S*,6a*S*,*E*)-3-[(1*H*-Indol-3-yl)methylene]-6-(2-hydroxypropan-2-yl)tetrahydrofuro[3,4-*b*]furan-2,4-dione (36b). To a stirred solution of compound **36a** (200 mg, 0.40 mmol) in THF (10 mL) was added conc. HCl (0.30 mL) at 25 °C and the reaction mixture was refluxed for 8 h. The reaction mixture was allowed to reach room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with saturated solution of $NaHCO_3$, water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent furnished pure product (+)-**36b** as a white solid (108 mg, 83%). Mp 224–226 °C; $[\alpha]^{25}_D$ +91.30 (*c* 0.02 $CHCl_3$); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.22 (s, 3H), 1.29 (s, 3H), 4.48 (d, *J* = 6 Hz, 1H), 4.56 (s, 1H), 5.19 (br s, 1H), 5.38 (d, *J* = 6 Hz,



(+)-**36b**

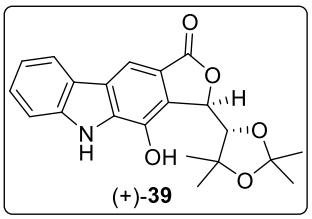
1H), 7.12–7.30 (m, 2H), 7.52 (d, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.93 (s, 1H), 8.44 (d, J = 2 Hz, 1H), 12.08 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 25.3, 25.6, 46.1, 69.8, 77.9, 89.2, 109.8, 112.4, 112.8, 118.0, 121.0, 122.6, 127.2, 129.2, 131.8, 136.1, 169.9, 173.9; ESIMS (m/z) 328 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{18}O_5N$ 328.1179, found 328.1195; IR (Nujol) ν_{max} 3370, 1727, 1595 cm^{-1}.

(+)-(*S*)-5-Acetyl-1-oxo-3-[(*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]-3,5-dihydro-1*H*-furo[3,4-*b*]carbazol-4-yl Acetate (38). To a solution of compound **36a** (8.50 g, 17.03 mmol) in MeOH:H_2O (3:1, 50 mL) was added KOH (1.90 g, 34.06 mmol) at 25 °C and the reaction mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo and obtained residue was acidified by saturated solution of oxalic acid and extracted with ethyl acetate (50 mL × 3). The combined extract was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and obtained acid **37** (4.58 g) was further used without any purification. To a solution of compound **37** (4.00 g, 10.38 mmol) in acetic anhydride (15 mL) was added sodium acetate (1.40 g, 20.00 mmol) and the reaction mixture was refluxed for 24 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (100 mL) and the organic layer was washed with saturated solution of $NaHCO_3$, water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting reside using ethyl acetate–petroleum ether (3:7) as an eluent provided product (+)-**38** as a white solid (3.41 g, 51%, two steps). Mp 144–146 °C; $[\alpha]^{25}_D$ +176.10 (*c* 0.02 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 1.54 (s, 3H), 2.39 (s, 3H), 2.82 (s, 3H), 3.55 (d, J = 10 Hz, 1H), 5.67 (d, J = 8 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.59 (t, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 23.1, 26.8, 26.9, 27.0, 28.6, 78.6, 81.9, 84.3, 108.2, 113.9, 115.0, 120.9, 122.4, 124.0, 124.4, 128.9, 131.7, 133.2, 135.1, 139.5, 139.9, 167.4, 169.0, 170.3; ESIMS (m/z) 474 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{25}O_7NNa$ 474.1523, found 474.1544; IR ($CHCl_3$) ν_{max} 1720, 1706 cm^{-1}.



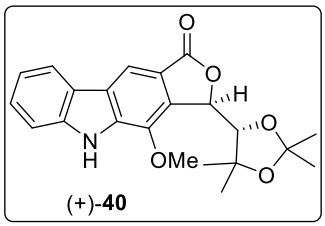
(+)-**38**

(+)-(*S*)-4-Hydroxy-3-[(*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]-3,5-dihydro-1*H*-furo[3,4-*b*]carbazol-1-one (39). To a solution of compound **38** (2.00 g, 4.43 mmol) in MeOH (20 mL) at 25 °C was added K_2CO_3 (1.22 g, 8.86 mmol) and the reaction mixture was stirred at same temperature for 30 min. Reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent provided product (+)-**39** as a white solid (1.43 g, 88%). Mp 230–232 °C; $[\alpha]^{25}_{D}$ +84.98 (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 3H), 1.53 (s, 3H), 1.55 (s, 3H), 1.66 (s, 3H), 3.84 (d, *J* = 12 Hz, 1H), 5.52 (d, *J* = 12 Hz, 1H), 7.32 (t, *J* = 8 Hz, 1H), 7.48–7.55 (m, 2H), 8.11 (d, *J* = 8 Hz, 1H), 8.25 (s, 1H), 8.35 (s, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1, 27.1, 27.4, 28.5, 76.3, 82.2, 84.3, 109.6, 111.2, 111.4, 117.4, 120.6, 121.0, 123.2, 126.9, 127.2, 127.5, 133.8, 136.4, 140.2, 170.5; ESIMS (*m*/*z*) 368 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{22}O_5N$ 368.1492, found 368.1490; IR ($CHCl_3$) ν_{max} 3412, 1738, 1596 cm^{-1}.



(+)-**39**

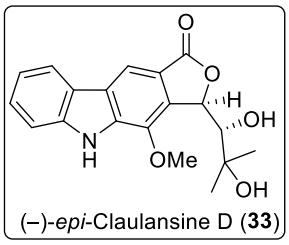
(+)-(*S*)-4-Methoxy-3-[(*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]-3,5-dihydro-1*H*-furo[3,4-*b*]carbazol-1-one (40). To a stirred solution of compound **39** (1.00 g, 2.72 mmol) in dry acetone (20 mL) was added K_2CO_3 (564 mg, 4.08 mmol) and dimethyl sulfate (0.22 mL, 2.44 mmol) at 25 °C and the reaction mixture was refluxed for 8 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (40 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as eluent yielded pure product (+)-**40** as a white solid (923 mg, 89%). Mp 254–256 °C; $[\alpha]^{25}_{D}$ +43.00 (*c* 0.05 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H), 1.44 (s, 3H), 1.49 (s, 3H), 1.58 (s, 3H), 3.63 (d, *J* = 12 Hz, 1H), 4.19 (s, 3H), 5.80 (d, *J* = 12 Hz, 1H), 7.30–7.37 (m, 1H), 7.48–7.55 (m, 2H), 8.12 (d, *J* = 8 Hz, 1H), 8.38 (s, 1H), 8.64 (s, 1H); ^{13}C



(+)-**40**

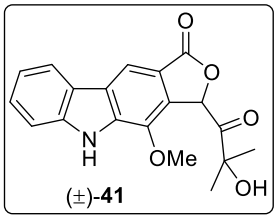
NMR ($CDCl_3$, 100 MHz) δ 23.6, 26.9, 27.3, 28.4, 60.1, 77.3, 81.6, 85.0, 108.2, 111.3, 113.8, 118.4, 120.8, 121.1, 123.2, 126.8, 127.4, 131.7, 136.8, 140.1, 140.3, 170.4; ESIMS (*m*/*z*) 404 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{23}O_5NNa$ 404.1468, found 404.1467; IR ($CHCl_3$) ν_{max} 3621, 1743, 1599 cm^{-1}.

(–)-(*S*)-3-[(*R*)-1,2-Dihydroxy-2-methylpropyl]-4-methoxy-3,5-dihydro-1*H*-furo[3,4-*b*]carbazol-1-one (*epi*-Claulansine D, 33). To a stirred solution of compound **40** (300 mg, 0.78 mmol) in THF (4 mL) was added conc. HCl (0.50 mL) at 25 °C. The reaction mixture was refluxed for 3 h, allowed to reach room temperature and diluted with ethyl acetate (25 mL). The organic layer was washed with saturated solution of $NaHCO_3$, water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent furnished pure product (–)-**33** as a white solid (233 mg, 87%). Mp 208–210 °C; $[\alpha]^{25}_D$ –22.80 (*c* 0.13 MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.05 (s, 3H), 1.19 (s, 3H), 3.60 (t, *J* = 8 Hz, 1H), 4.11 (s, 3H), 4.32 (s, 1H), 5.32 (d, *J* = 4 Hz, 1H), 5.99 (d, *J* = 4 Hz, 1H), 7.23 (t, *J* = 8 Hz, 1H), 7.46 (t, *J* = 8 Hz, 1H), 7.56 (d, *J* = 8 Hz, 1H), 8.27 (d, *J* = 8 Hz, 1H), 8.38 (s, 1H), 11.77 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.4, 27.1, 59.8, 71.8, 78.8, 81.2, 111.7, 112.7, 117.9, 119.7, 121.0, 122.6, 125.9, 126.8, 133.2, 136.3, 140.1, 140.8, 170.4; ESIMS (*m*/*z*) 364 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_5NNa$ 364.1155, found 364.1152; IR (Nujol) ν_{max} 3386, 1738, 1595 cm^{-1}.



(–)-*epi*-Claulansine D (**33**)

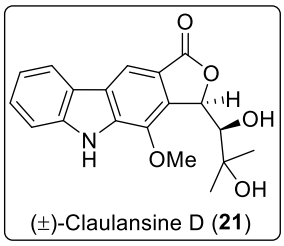
(±)-3-(2-Hydroxy-2-methylpropanoyl)-4-methoxy-3,5-dihydro-1*H*-furo[3,4-*b*]carbazol-1-one (41). To a stirred solution of compound **33** (70 mg, 0.205 mmol) in DCM (10 mL) was added DMP (174 mg, 0.41 mmol) at –10 °C under argon atmosphere and the reaction mixture was stirred for 10 h allowing to reach 25 °C. The reaction was quenched with saturated solution of $NaHCO_3$ at 0 °C and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (20 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed silica gel (60–120 mesh) column chromatographic purification of the resulting



(±)-**41**

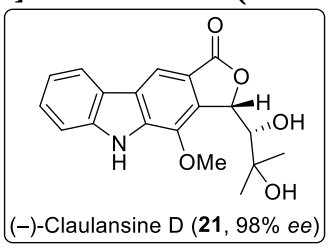
residue using ethyl acetate–petroleum ether (1:1) as an eluent furnished ketone (±)-**41** as a solid (49.4 mg, 71%). Mp 180–182 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.49 (s, 6H), 4.08 (s, 3H), 4.79 (s, 1H), 6.81 (s, 1H), 7.31 (t, J = 10 Hz, 1H), 7.51 (t, J = 10 Hz, 1H), 7.62 (d, J = 10 Hz, 1H), 8.31 (d, J = 10 Hz, 1H), 8.41 (s, 1H), 11.00 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 26.9, 27.3, 61.0, 76.8, 78.0, 112.6, 114.2, 119.2, 121.2, 121.8, 124.0, 128.1, 128.6, 133.4, 137.5, 140.1, 142.1, 170.8, 208.8; ESIMS (m/z) 340 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{17}O_5NNa$ 362.0999, found 362.0997; IR (Nujol) ν_{max} 3354, 1748, 1725, 1596 cm^{-1}.

(±)-1,2-Dihydroxy-2-methylpropyl-4-methoxy-3,5-dihydro-1*H*-furo[3,4-*b*]carbazol-1-one (Claulansine D, 21). To a stirred solution of compound **41** (20 mg, 0.05 mmol) in MeOH (4 mL) was added $NaBH_4$ (8.73 mg, 0.23 mmol) at –90 °C. The reaction mixture was stirred at the same temperature for 20 min and the reaction was quenched with saturated aq. NH_4Cl (2 mL). The reaction mixture was extracted with ethyl acetate (5 mL × 3) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent afforded mixture of (±)-claulansine D (**21**, major) and *epi*-claulansine D (**33**, minor) as a white solid (19 mg, 97%); HPLC separation of above mixture provided the desired analytically pure (±)-claulansine D (**21**) (15 mg, 79%). Mp 252–254 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.23 (s, 3H), 1.27 (s, 3H), 3.90 (d, J = 8 Hz, 1H), 4.07 (s, 3H), 4.79 (s, 1H), 4.80 (d, J = 8 Hz, 1H), 6.17 (s, 1H), 7.23 (t, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 8.28 (d, J = 8 Hz, 1H), 8.38 (s, 1H), 11.80 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.7, 28.6, 60.4, 71.6, 75.9, 77.6, 111.7, 112.7, 118.8, 119.6, 121.0, 122.6, 126.3, 126.7, 135.1, 136.3, 138.6, 140.8, 170.9; ESIMS (m/z) 342 $[M+H]^+$; IR (Nujol) ν_{max} 3386, 1747, 1596 cm^{-1}.



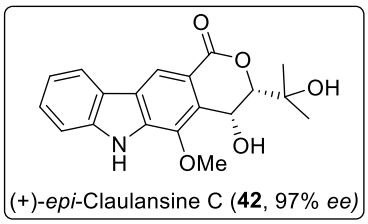
(±)-Claulansine D (**21**)

(–)-(*S*)-3-[(*S*)-1,2-Dihydroxy-2-methylpropyl]-4-methoxy-3,5-dihydro-1*H*-furo[3,4-*b*]carbazol-1-one (Claulansine D, 21). The freshly prepared pure neat solid sample of (–)-*epi*-claulansine D (**33**) was stored under atmospheric conditions for minimum 30 days to maximum 90 days. After the induction period of 30 to 90 days (–)-*epi*-claulansine D (**33**) underwent clean quantitative transformation into (–)-claulansine D (**21**). Mp 252–254 °C (MeOH); $[\alpha]^{25}_{D}$ –34.35 (*c* 0.2 MeOH).



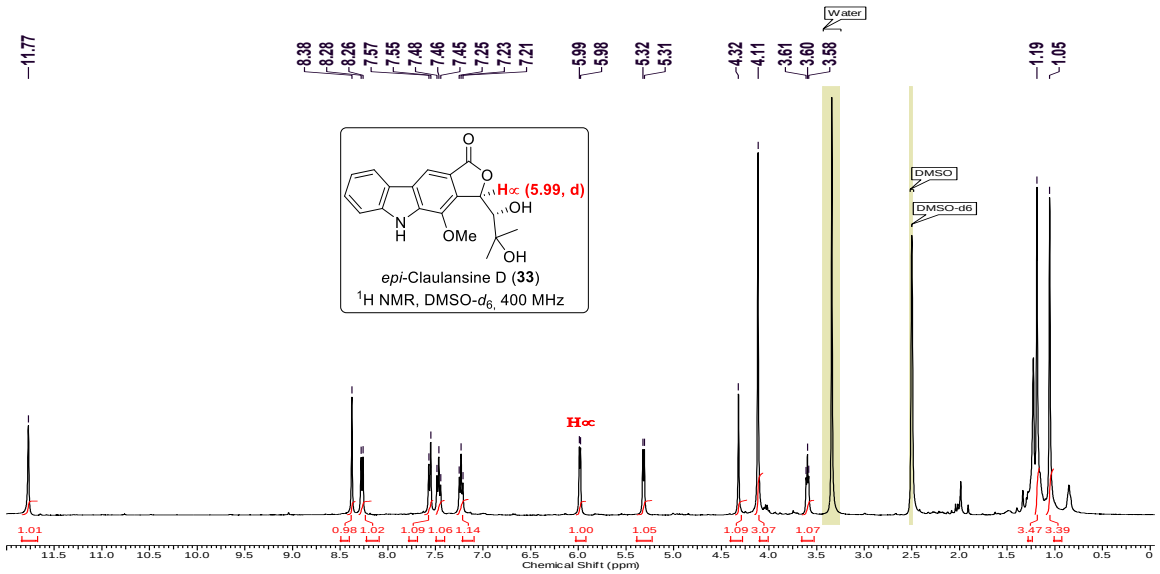
(–)-Claulansine D (**21**, 98% *ee*)

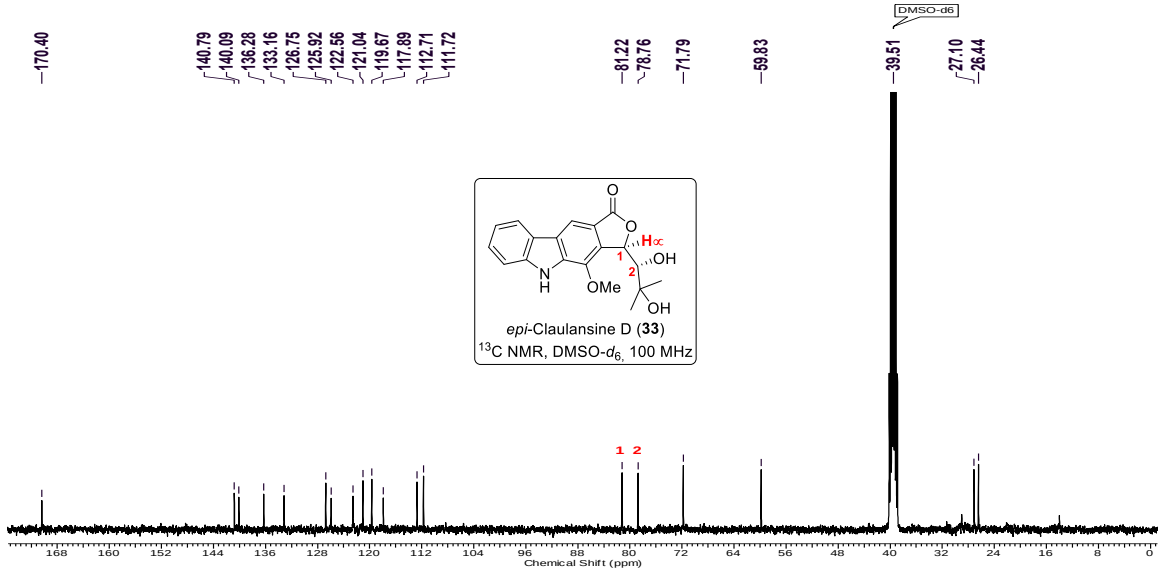
(+)-(3*S*,4*R*)-4-Hydroxy-3-(2-hydroxypropan-2-yl)-5-methoxy-4,6-dihydropyrano[4,3-*b*]carbazol-1(3*H*)-one (*epi*-Claulansine C, 42). To a stirred solution of compound **33**/**21** (20 mg, 0.05 mmol) in dry MeOH (5 mL) was added K_2CO_3 (16 mg, 0.11 mmol) at 25 °C and the reaction mixture was refluxed for 10 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (10 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel (230–400 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (7:3) as eluent yielded pure product (+)-*epi*-claulansine C (**42**) as gummy solid (14.2 mg, 71%). $[\alpha]^{25}_{D}$ +8.13 (*c* 0.15 MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.37 (s, 6H), 4.05 (s, 3H), 4.16 (s, 1H), 5.11 (s, 1H), 5.37 (d, *J* = 8 Hz, 1H), 5.67 (d, *J* = 8 Hz, 1H), 7.26 (t, *J* = 8 Hz, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.57 (d, *J* = 8 Hz, 1H), 8.28 (d, *J* = 8 Hz, 1H), 8.61 (s, 1H), 11.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz); δ 25.9, 27.3, 59.0, 62.1, 71.2, 84.7, 111.7, 115.8, 118.8, 119.9, 121.0, 122.7, 124.5, 126.8, 130.2, 135.9, 140.6, 140.7, 165.7; ESIMS (*m*/*z*) 364 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_5NNa$ 364.1155, found 364.1152; IR (Nujol) ν_{max} 3356, 1711, 1604 cm^{-1}.

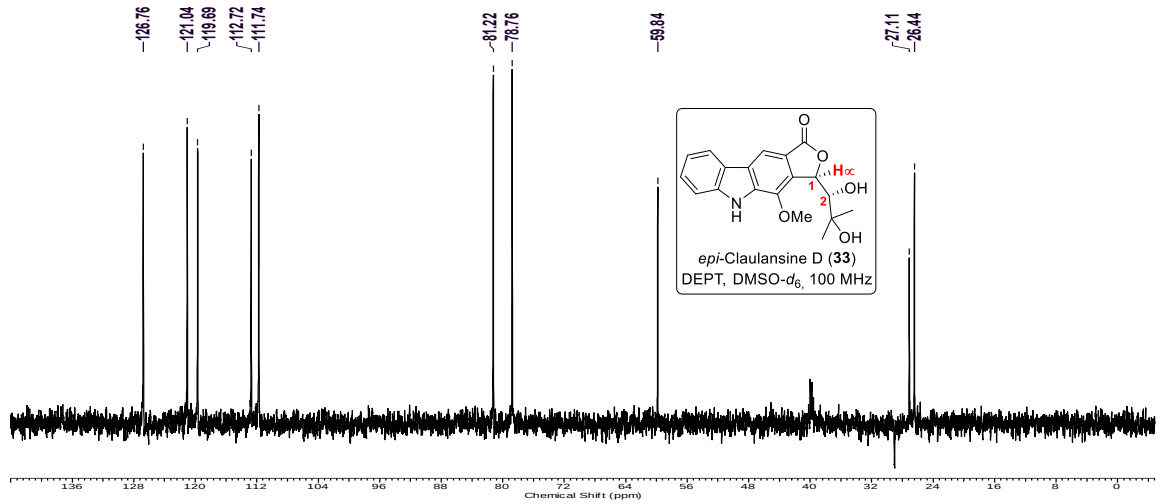


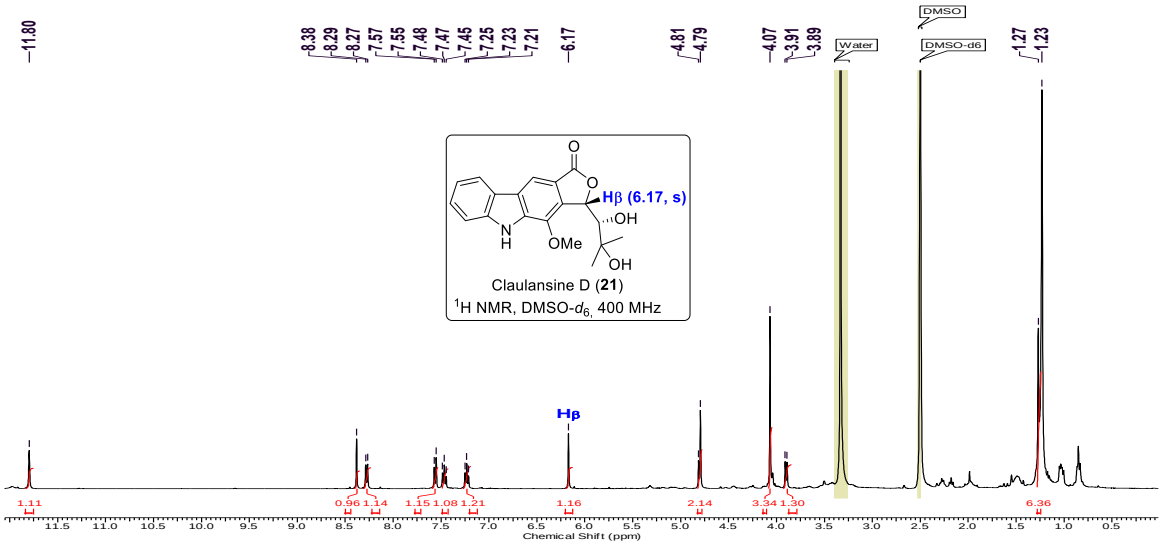
(+)-*epi*-Claulansine C (**42**, 97% *ee*)

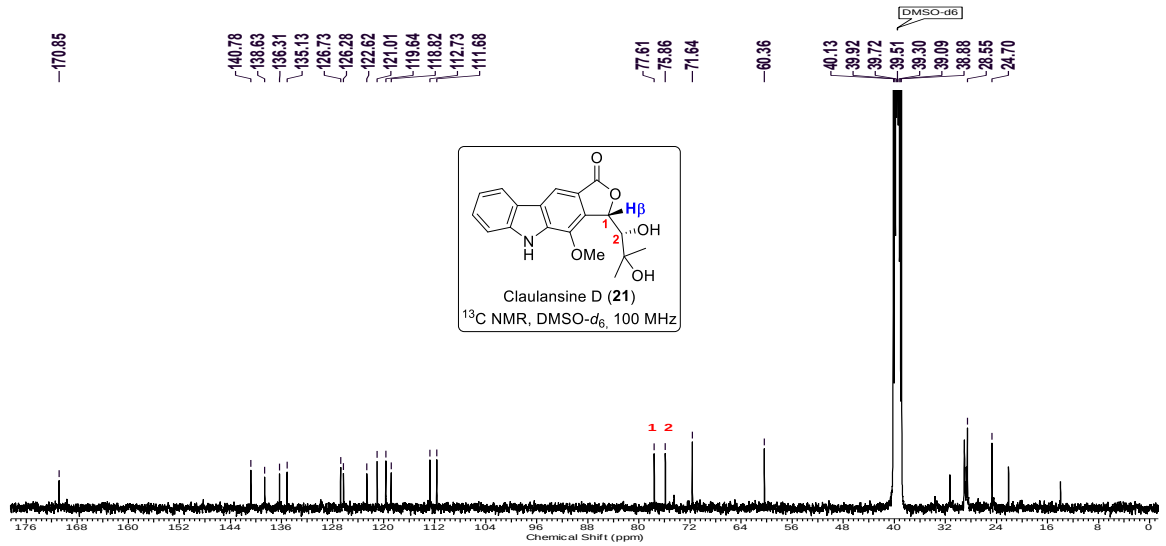
3.6 Selected Spectra

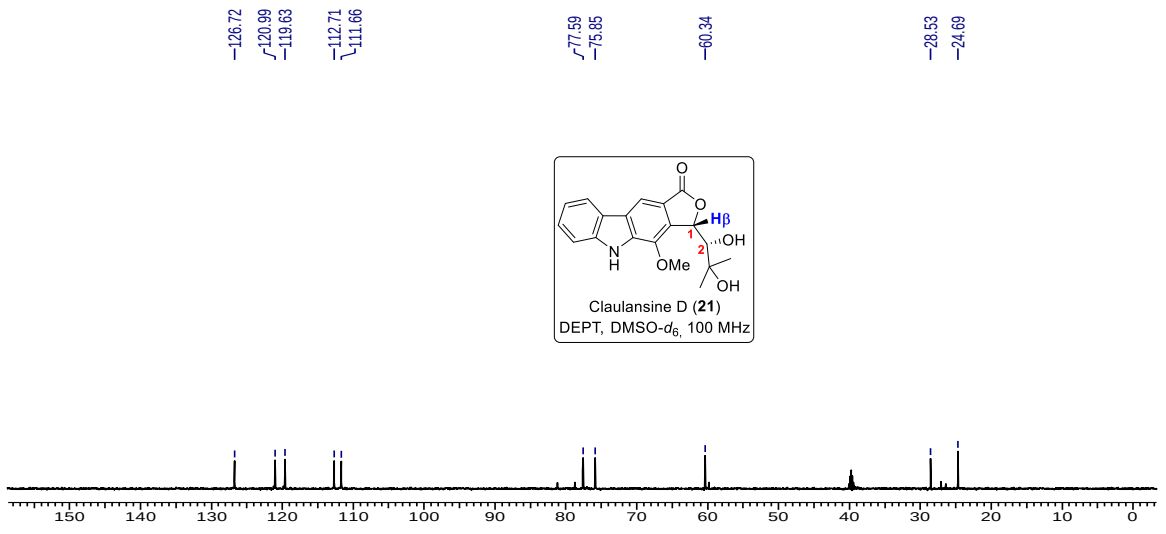

11.77
8.38
8.28
8.26
7.57
7.55
7.48
7.46
7.45
7.25
7.23
7.21
5.99
5.98
5.32
5.31
4.32
4.11
3.61
3.60
3.58
1.19
1.05
Water
DMSO
DMSO-d6
Hα (5.99, d)
OH
OMe
OH
epi-Claulansine D (33)
1H NMR, DMSO-d6, 400 MHz
Hα
1.01
0.98
1.02
1.09
1.06
1.14
1.00
1.05
1.09
3.07
1.07
3.47
3.39
Chemical Shift (ppm)

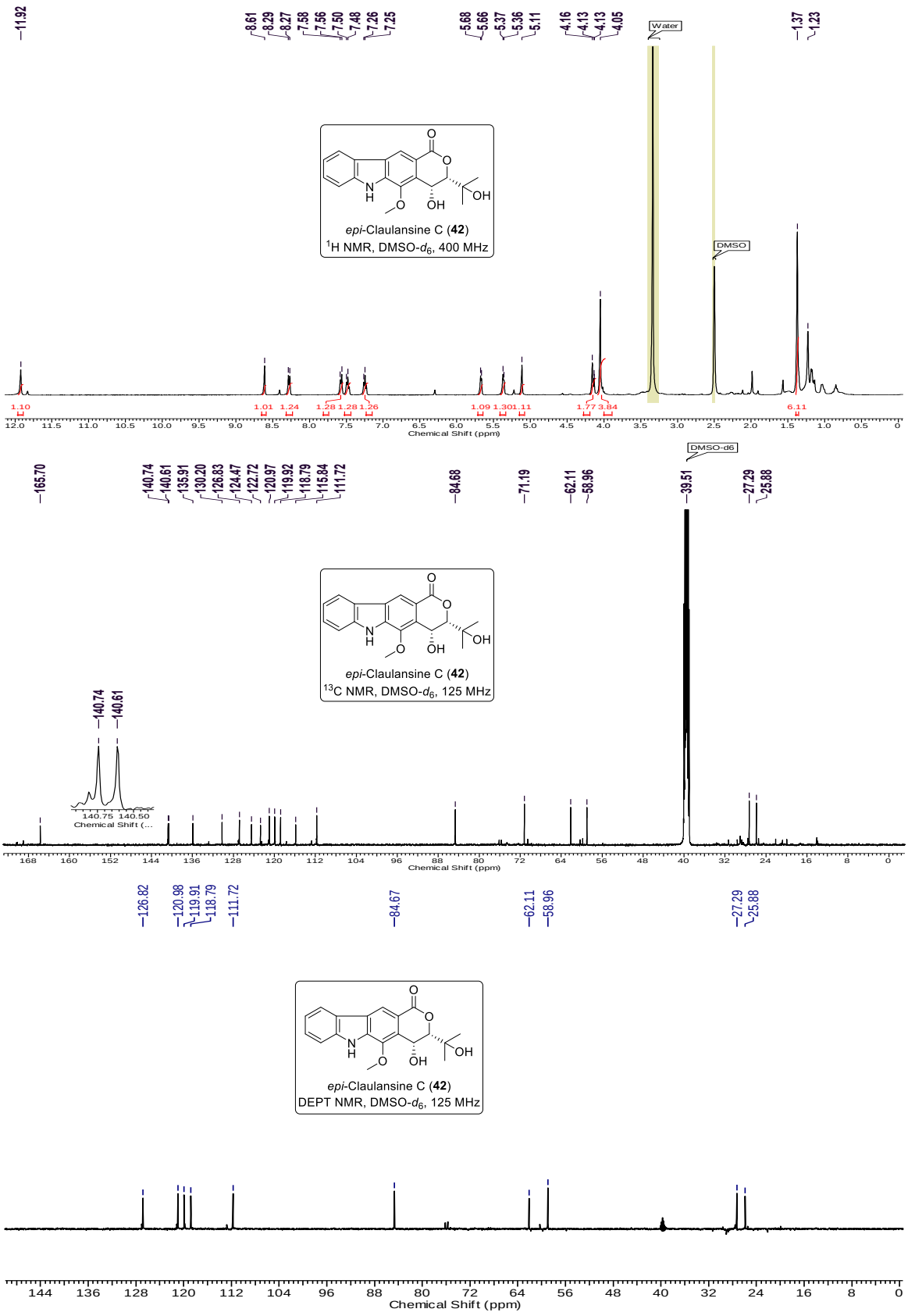

DMSO-d6
170.40
140.79
140.09
136.28
133.16
126.75
125.92
122.56
121.04
119.67
117.89
112.71
111.72
81.22
78.76
71.79
59.83
39.51
27.10
26.44
Hα
OH
OMe
OH
epi-Claulansine D (33)
13C NMR, DMSO-d6, 100 MHz
1 2
Chemical Shift (ppm)


126.76
121.04
119.69
112.72
111.74
81.22
78.76
59.84
27.11
26.44
Hα
OH
OMe
OH
epi-Claulansine D (33)
DEPT, DMSO-d6, 100 MHz
Chemical Shift (ppm)

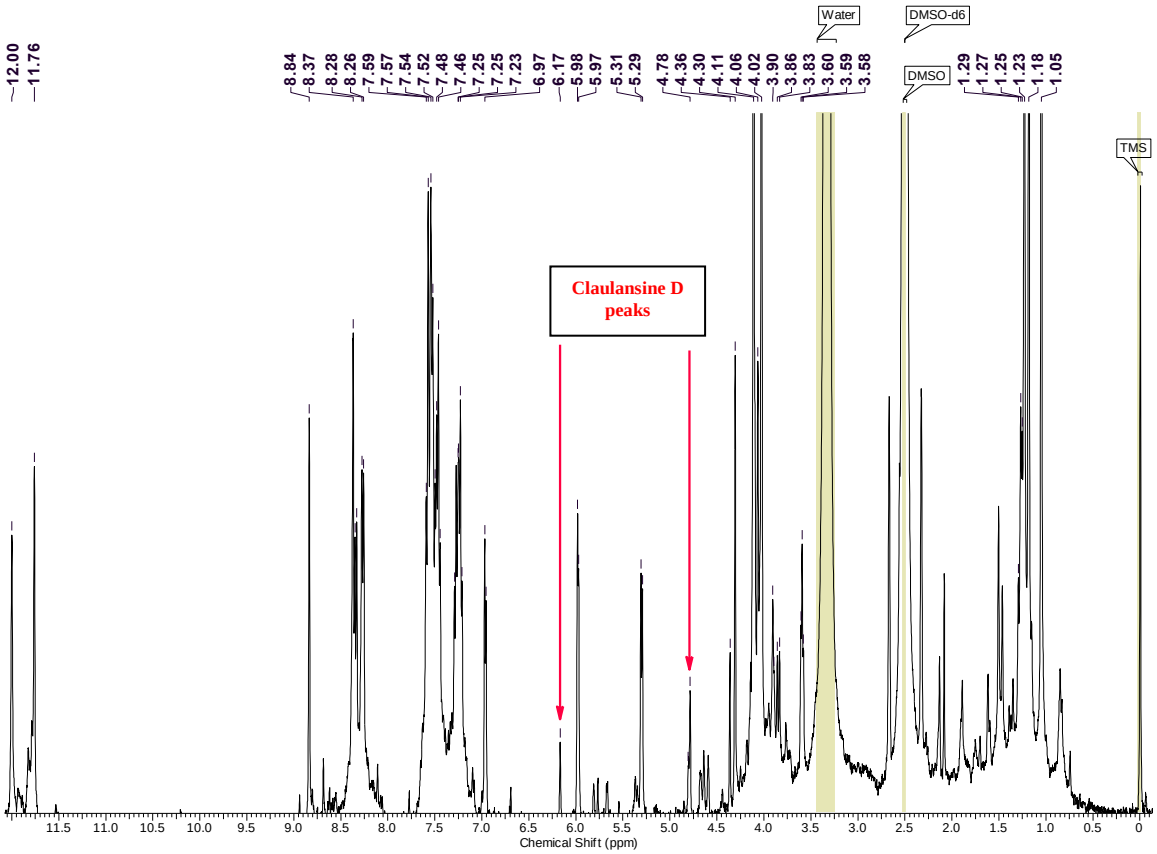

11.80
8.38
8.29
8.27
7.57
7.55
7.48
7.47
7.45
7.25
7.23
7.21
6.17
4.81
4.79
4.07
3.91
3.89
Water
DMSO
DMSO-d6
1.27
1.23
Hβ (6.17, s)
OH
OMe
OH
Claulansine D (21)
1H NMR, DMSO-d6, 400 MHz
Hβ
1.11
0.96
1.14
1.15
1.08
1.21
1.16
2.14
3.34
1.30
6.36
Chemical Shift (ppm)


170.85
140.78
138.63
136.31
135.13
126.73
126.28
122.62
121.01
119.64
118.82
112.73
111.68
77.61
75.86
71.64
60.36
40.13
39.92
39.72
39.51
39.30
39.09
38.88
28.55
24.70
DMSO-d6
Hβ
OH
OMe
OH
Claulansine D (21)
13C NMR, DMSO-d6, 100 MHz
1 2
Chemical Shift (ppm)


126.72
120.99
119.63
112.71
111.66
77.59
75.85
60.34
28.53
24.69
Hβ
OH
OMe
OH
Claulansine D (21)
DEPT, DMSO-d6, 100 MHz


11.92
8.61
8.29
8.27
7.58
7.56
7.50
7.48
7.26
7.25
5.68
5.66
5.37
5.36
5.11
4.16
4.13
4.13
4.05
Water
1.37
1.23
DMSO
epi-Claulansine C (42)
1H NMR, DMSO-d6, 400 MHz
Chemical Shift (ppm)
165.70
140.74
140.61
135.91
130.20
126.83
124.47
122.72
120.97
119.92
118.79
115.84
111.72
84.68
71.19
62.11
58.96
DMSO-d6
39.51
27.29
25.88
epi-Claulansine C (42)
13C NMR, DMSO-d6, 125 MHz
Chemical Shift (...
Chemical Shift (ppm)
126.82
120.98
119.91
118.79
111.72
84.67
62.11
58.96
27.29
25.88
epi-Claulansine C (42)
DEPT NMR, DMSO-d6, 125 MHz
Chemical Shift (ppm)

NMR spectra of mixture of compounds **21**, **33** and decomposed material (heating of compound **33** at 190 °C for 8 h)



3.7 Selected HPLC plots

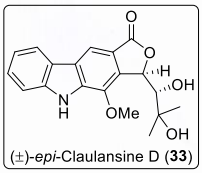
Analyzed: 04/05/17 12:36 PM

Reported: 04/05/17 01:29 PM
Processed: 04/05/17 01:29 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9339\
Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: SM-(Rac)
Injection from this vial: 1 of 1
Sample Description: EtOH:n-Hexane(30:70)

Series:9339
Volume: 10.0 ul



(±)-*epi*-Claulansine D (**33**)

Chrom Type: HPLC Channel : 1

No.	RT	Area	Conc 1
1	7.65	2249720	49.934
2	9.91	2255653	50.066
		4505373	100.000

Analyzed: 04/05/17 12:15 PM

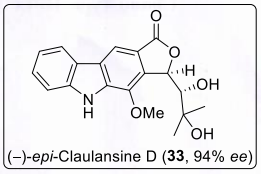
Reported: 04/05/17 01:28 PM
Processed: 04/05/17 01:27 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9338\
Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: SM-(Chiral)
Injection from this vial: 1 of 1
Sample Description: EtOH:n-Hexane(30:70)

Series:9338
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



(–)-*epi*-Claulansine D (**33**, 94% *ee*)

No.	RT	Area	Conc 1
1	7.66	121001	2.649
2	9.91	4447626	97.351
		4568627	100.000

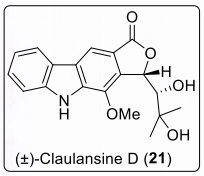
Project Leader: Dr. N. P. Argade
Column : Chiralcel OJ-H (250 x 4.6 mm)
Mobile Phase: EtOH: *n*-Hexane (30:70)
Wavelength : 254 nm
Flow Rate : 1 ml/min
Inj. Vol. : 2 μl

Analyzed: 04/07/17 11:23 AM

Reported: 04/07/17 11:53 AM
Processed: 04/07/17 11:53 AM

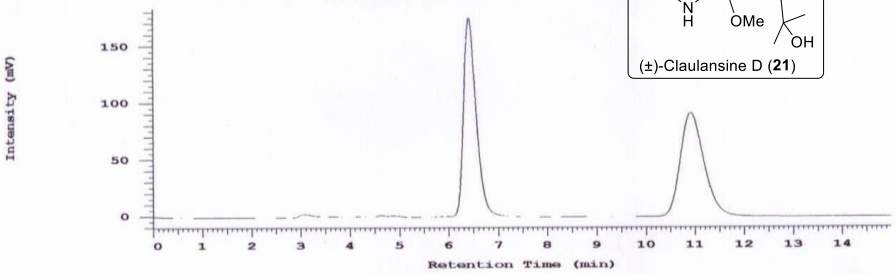
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9347\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: SM-NP (Rac)
Injection from this vial: 1 of 1
Sample Description: EtOH:n-Hexane(30:70)

Series:9347
Volume: 10.0 ul



(±)-Claulansine D (**21**)

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1
1	6.41	3010676	50.679
2	10.91	2930044	49.321
		5940720	100.000

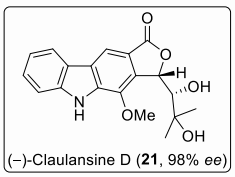
Analyzed: 04/28/17 02:43 PM

Reported: 04/28/17 03:07 PM
Processed: 04/28/17 03:05 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9371\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: SM-Chiral
Injection from this vial: 1 of 1
Sample Description: ETOH:n-Hexane(30:70)

Series:9371
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



(–)-Claulansine D (**21**, 98% *ee*)

No.	RT	Area	Conc 1
1	6.39	8391056	99.098
2	10.82	76411	0.902
		8467467	100.000

Project Leader: Dr. N. P. Argade
Column : Chiralcel OJ-H (250 x 4.6 mm)
Mobile Phase: EtOH : *n*-Hexane (30:70)
Wavelength : 254 nm
Flow Rate : 1 ml/min
Inj. Vol. : 5 μl

Analyzed: 04/19/17 11:07 AM

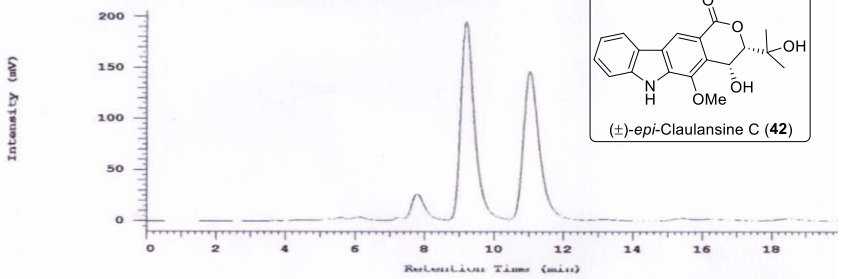
Reported: 04/19/17 11:41 AM
Processed: 04/19/17 11:41 AM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9358\
Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: SM-epi NP (Rac)
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O:TFA(75:25:0.1)

Series:9358
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



(±)-*epi*-Claulansine C (**42**)

No.	RT	Area	Conc 1
1	9.19	5062482	52.734
2	11.03	4537599	47.266
		9600081	100.000

Analyzed: 04/19/17 11:47 AM

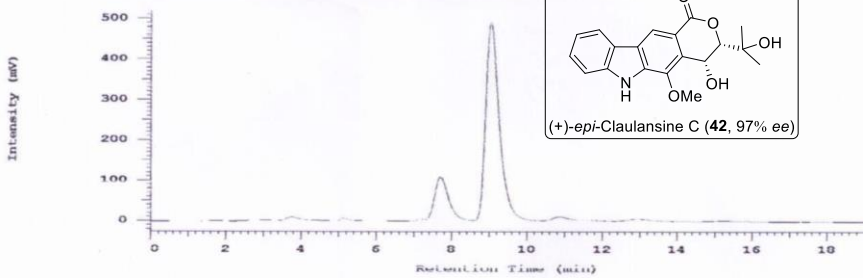
Reported: 04/19/17 12:10 PM
Processed: 04/19/17 12:10 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9360\
Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: SM-epi NP(Chiral)
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O:TFA(75:25:0.1)

Series:9360
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



(+)-*epi*-Claulansine C (**42**, 97% *ee*)

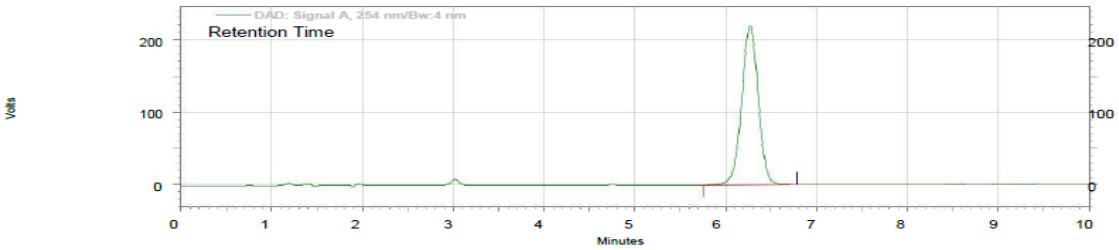
No.	RT	Area	Conc 1
1	9.04	12229204	98.749
2	10.87	154964	1.251
		12384168	100.000

Project Leader: Dr. N. P. Argade
Column : Chiralcel OJ-RH (150 x 4.6 mm)
Mobile Phase: MeOH: H_2O: TFA (75:25:0.1)
Wavelength : 254 nm
Flow Rate : 0.5 ml/min
Inj. Vol. : 2 μl

HPLC plot of *epi*-Claulansine D

Area % Report

Data File: C:\Documents and Settings\Administrator\Desktop\Dr. Argade\Sm11.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Dr Argade\shivaji OCT 11.met
Acquired: 6/3/2017 2:16:59 PM
Printed: 10/12/2017 6:17:36 PM



DAD: Signal A,

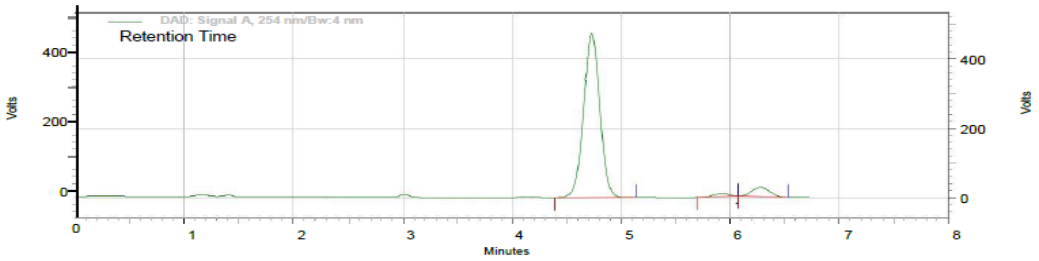
254 nm/Bw:4 nm

Results

Retention Time	Area	Area %	Height	Height %
6.267	5836304	100.00	458995	100.00
Totals	5836304	100.00	458995	100.00

HPLC plot of Claulansine D

Data File: C:\Documents and Settings\Administrator\Desktop\Dr. Argade\Sm14.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Dr Argade\shivaji OCT 11.met
Acquired: 6/3/2017 2:48:49 PM
Printed: 10/12/2017 6:21:31 PM



DAD: Signal A,

254 nm/Bw:4 nm

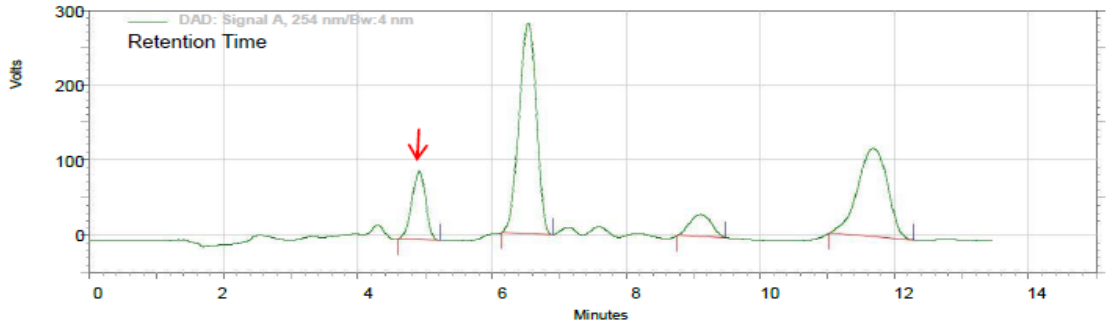
Results

Retention Time	Area	Area %	Height	Height %
4.727	10402157	92.75	990974	93.14
5.927	177109	1.58	17528	1.65
6.280	635973	5.67	55455	5.21
Totals	11215239	100.00	1063957	100.00

HPLC plot of Claulansine D (heating of *epi*-Claulansine D at 190 ºC for 8 h)

Area % Report

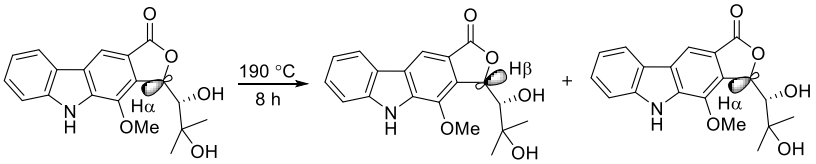
Data File: D:\Dr.Argade\SM 190 C 8 h.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Dr Argade\shivaji OCT 11.met
Acquired: 10/23/2017 5:30:59 PM
Printed: 10/23/2017 5:48:01 PM



DAD: Signal A, 254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
(Compound 10) 4.913	2678010	12.13	187405	17.33
(Compound 8) 6.533	10448219	47.33	587786	54.35
9.107	1417874	6.42	62792	5.81
11.680	7531035	34.12	243497	22.52
Totals	22075138	100.00	1081480	100.00

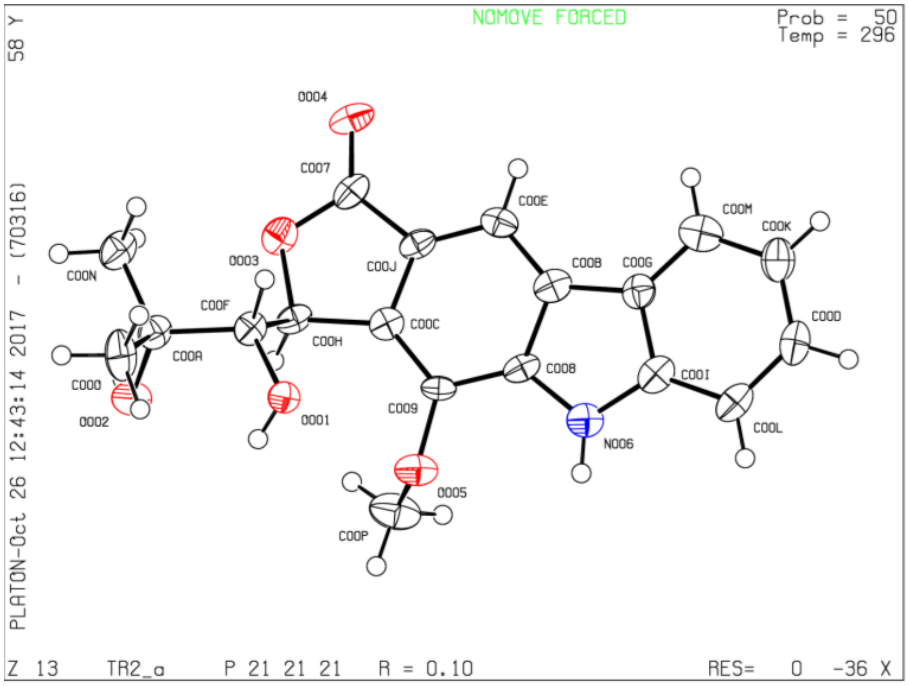
Project Leader: Dr. N. P. Argade
Column : Kromasil-C18 (150 x 4.6 mm)
Mobile Phase: MeOH: H_2O (60:40)
Wavelength : 254 nm
Flow Rate : 1 ml/min
Inj. Vol. : 5 μl

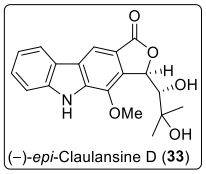


epi-Claulansine D (**33**) → Claulansine D (**21**) + *epi*-Claulansine D (**33**)

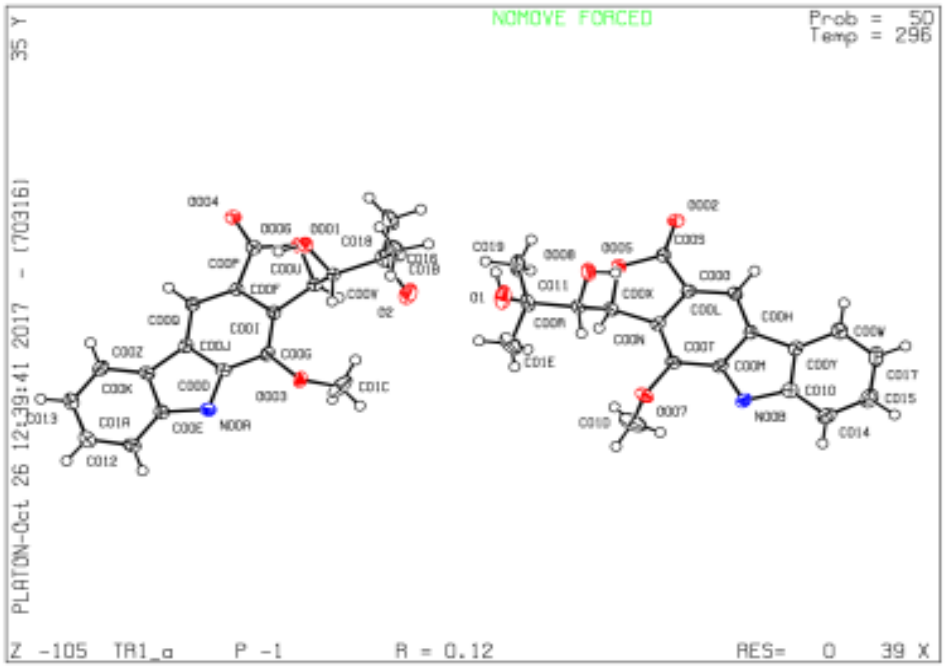
3.8 X-ray Data

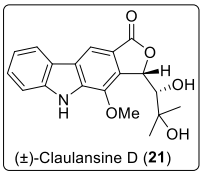
Crystallographic data for compound (–)-33:





Crystallographic data for compound (±)-21:





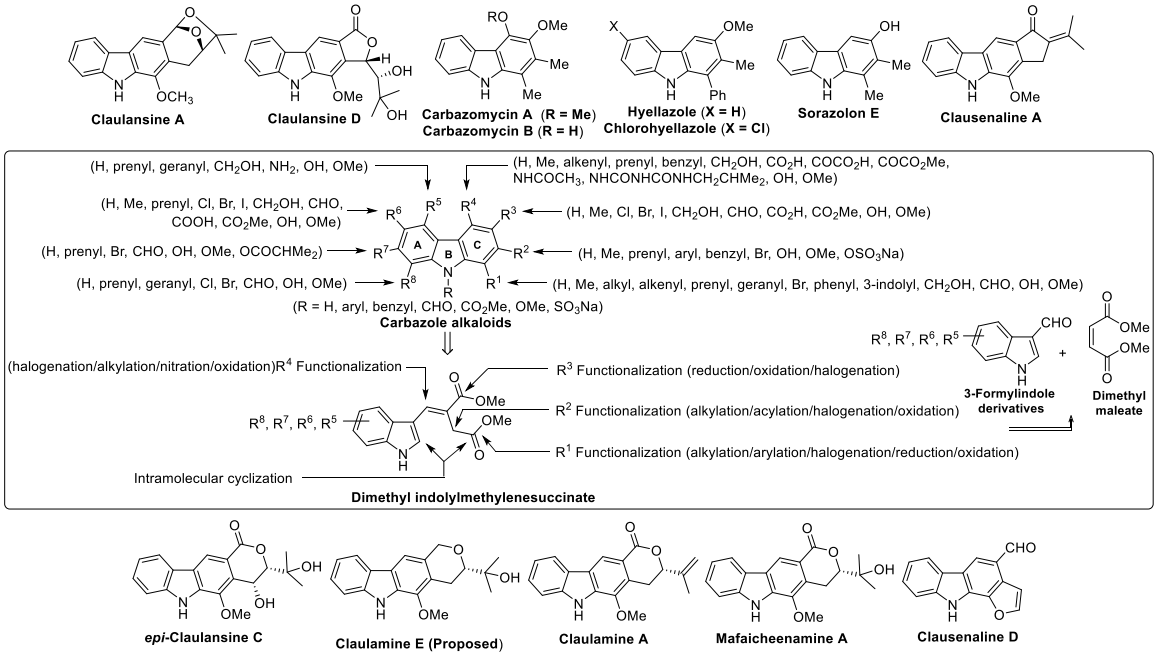
3.9 References

1. Toda, F. *Acc. Chem. Res*. **1995**, *28*, 480.
2. Toda, F. *Synlett* **1993**, 303.
3. Toda, F. *Aust. J. Chem*. **2001**, *54*, 573.
4. Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res*. **1979**, *12*, 191.
5. Sakamoto, M.; Iwamoto, T.; Nono, N.; Ando, M.; Arai, W.; Mino, T.; Fujita, T. *J. Org. Chem*. **2003**, *68*, 942.
6. Sakamoto, M. *Chem. Eur. J*. **1997**, *3*, 684.
7. Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res*. **1996**, *29*, 203.
8. Anderson, N. G. *Org. Process Res. Dev*. **2005**, *9*, 800.
9. Wilson, K. R.; Pincock, R. E. *J. Am. Chem. Soc*. **1975**, *97*, 1474.
10. Einhorn, C.; Durif, A.; Averbuch, M.-T.; Einhorn, J. *Angew. Chem., Int. Ed*. **2001**, *40*, 1926.
11. Reddy, L. R.; Bhanumathi, N.; Rao, K. R. *Chem. Commun*. **2000**, 2321.
12. Boesten, W. H. J.; Seerden, J.-P. G.; de Lange, B.; Dielemans, H. J. A.; Elsenberg, H. L. M.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett*. **2001**, *3*, 1121.
13. Sakurai, R.; Suzuki, S.; Hashimoto, J.; Baba, M.; Itoh, O.; Uchida, A.; Hattori, T.; Miyano, S.; Yamaura, M. *Org. Lett*. **2004**, *6*, 2241.
14. Osano, Y. T.; Uchida, A.; Ohashi, Y. *Nature* **1991**, *352*, 510.
15. Hashizume, D.; Ohashi, Y. *J. Phys. Org. Chem*. **2000**, *13*, 415.
16. (a) Rozovsky, A.; Regozin, E.; Herman, M. O.; Albeck, A.; Gellerman, G. *Eur. J. Org. Chem*. **2015**, 1811. (b) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099.
17. (a) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev*. **2012**, *112*, 3193. (b) Knölker, H.-J.; Reddy, K. R. *Chem. Rev*. **2002**, *102*, 4303.
18. Mal, D.; Roy, J. *Org. Biomol. Chem*. **2015**, *13*, 6344.
19. Levick, M. T.; Grace, I.; Dai, S.-Y.; Kasch, N.; Muryn, C.; Lambert, C.; Turner, M. L.; Procter, D. J. *Org. Lett*. **2014**, *16*, 2292.

20. Yang, W.; Zhang, Z.; Han, C.; Zhang, Z.; Xu, H.; Yan, P.; Zhao, Y.; Liu, S. *Chem*. *Commun*. **2013**, *49*, 2822.
21. Tsvelikhovsky, D.; Buchwald, S. L. *J*. *Am*. *Chem*. *Soc*. **2011**, *133*, 14228.
22. Liu, H.; Li, C.-J.; Yang, J.-Z.; Ning, N.; Si, Y.-K.; Li, L.; Chen, N.-H.; Zhao, Q.; Zhang, D.-M. *J*. *Nat*. *Prod*. **2012**, *75*, 677.
23. Shen, D.-Y.; Chan, Y.-Y.; Hwang, T.-L.; Juang, S.-H.; Huang, S.-C.; Kuo, P.-C.; Thang, T.-D.; Lee, E.-J.; Damu, A.-G.; Wu, T.-S. *J*. *Nat*. *Prod*. **2014**, *77*, 1215.
24. Zhang, H.; Zhang, S.; Liu, L.; Luo, G.; Duan, W.; Wang, W. *J*. *Org*. *Chem*. **2010**, *75*, 368.
25. Karmakar, R.; Pahari, P.; Mal, D. *Chem*. *Rev*. **2014**, *114*, 6213 and references cited therein.
26. Kalshetti, M. G.; Argade, N. P. *J*. *Org*. *Chem*. **2017**, *82*, 11126.
27. Markad, S. B.; Argade, N. P. *Org. Lett.* **2014**, *16*, 5470.
28. Markad, S. B.; Argade, N. P. *J*. *Org*. *Chem*. **2016**, *81*, 5222.
29. Miyawaki, A.; Osaka, M.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Tetrahedron* **2011**, *67*, 6753.
30. The seasonal dynamics point of view; please note that the fastest auto inversion of configuration in solid state took place under the normal atmospheric conditions in five weeks during April/May 2017 at the Pune city from India.
31. Babu, D. C.; Rao, C. B.; Ramesh, D.; Swamy, S. R.; Venkateswarlu, Y. *Tetrahedron Lett*. **2012**, *53*, 3633.

The carbazole alkaloids are an important class of compounds from their fascinating structural topographies and remarkable bioactivities points of view. On the basis of these points large amount of efforts towards the total synthesis and bioactivity studies of carbazoles have been devoted by chemist's community worldwide. An elegant review authoritatively summarizing the carbazole chemistry has been published by Schmidt, Reddy and Knölker in 2012. The part one of present dissertation describes concise account on carbazole chemistry from contemporary literature comprising new efficient approaches for the synthesis of various natural and unnatural carbazoles employing novel synthetic strategies. The part two and three of present dissertation provide complete literature summary on targeted carbazole alkaloids along with our contribution on collective total synthesis of them implementing conceptually new synthetic approaches.

We have presented a brief literature account on the isolation, bioactivity and synthesis of our target carbazole alkaloids sorazolon E, carbazomycin A, carbazomycin B, hyellazole, chlorohyellazole, clausenaline D, indizoline, mafaicheenamine A, claulamine A, claulansine A, proposed Claulamine E, (–)-claulansine D and (+)-epi-claulansine C. We have demonstrated a diversity oriented convergent access for collective synthesis of all above specified carbazole alkaloids with very good overall yields. In the present approach, generation of suitably substituted basic carbazole skeleton in just 4/5-steps utilizing three carbon fragments from each 3-formylindole and dimethyl maleate is imperative. Furthermore, the generation of biaryl systems without the aryl–aryl coupling is also noteworthy. An appropriate functionalization of aromatic ring A can be performed in two different ways, the synthesis itself can begin with suitably substituted indole derivatives; otherwise the functionalization of aromatic ring A towards the end part of total synthesis would also be feasible. The involved different types of intramolecular cyclizations with the generation of new carbon–oxygen bonds selectively leading to those natural products are notable from both basic chemistry and applications point of view. The significant cascade reaction has been demonstrated in the synthesis of claulansine A by taking the advantage of reactivity difference in three different types of alcohol units. We have accomplished an efficient total synthesis of the proposed structure of claulamine E and regioisomeric revision in structural assignment of natural product is necessary.



Enantioselective total synthesis of (–)-claulansine D has been demonstrated via remarkable solid state auto epimerization of (–)-epi-claulansine D and it represents first example of crystal engineering driven inversion of C-centrochirality. The present synthesis demonstrates diastereomeric enrichment of phthalide moiety in the crystal lattice to a single isomer and we feel that it will be conceptually highly useful in future from applications point of view. Moreover further elaboration of solid state dynamic resolutions will provide the environment friendly and cost effective approaches to some of the enantiomerically pure essential chemical products.

More specifically, the first total synthesis of clausenaline D, mafaicheenamine A, claulamine A, claulansine A, (–)-claulansine D, (+)-epi-claulansine C and proposed claulamine E have been accomplished with good overall yields. Overall the total synthesis of above depicted all carbazole alkaloids were successfully accomplished by using base induced generation of an allylic carbanion on our potential common precursor and its alkylations, allylations and condensation with aldehydes. Furthermore the generation of an allylic carbanion on our potential common precursor followed its reactions with α-haloestesrs, suitable Michael acceptors and the Davis reagent will pave elegant routes to several other carbazole alkaloids and efforts in this direction are in active progress in our laboratory.

All these studies provided us a nice opportunity for learning a lot of new basic and applied chemistry not just from our work but also from the vast literature in this field. We also feel that the approaches which we have developed are quite general and biogenetic

in nature and would be useful in designing several important complex natural products and natural product hybrids for structure activity relationship studies. A look at the recent literature also revealed that the histogram of the carbazole chemistry is in escalating slope and increasing medicinal and pharmaceutical demands for natural and designed carbazoles would maintain the high positive slope in the present day world of medicinal and synthetic chemistry. In our opinion, a combination of natural and hybrid carbazoles would serve as a launching pad to fight against new generation diseases. In a broader prospective one can state with a positive feel that lot of carbazole based new drugs, agrochemicals and electroluminescent materials will capture highly demanding place in providing services to plant kingdom, animal kingdom and also for the welfare of human beings. Finally, on the basis of exposure to the literature of carbazole chemistry and our contribution to the same, it can be said with assurance that this interesting discipline will spread the wings still wider in the field of organic and pharmaceutical chemistry in future.

List of Publications

1. Diversity Oriented Convergent Access for Collective Total Synthesis of Bioactive Multifunctional Carbazole Alkaloids: Synthesis of Carbazomycin A, Carbazomycin B, Hyellazole, Chlorohyellazole and Clausenaline D
   Markad, S. B; Argade, N. P. *Org. Lett.* **2014**, *16*, 5470.

2. A Biomimetic Collective Total Synthesis of Bioactive Carbazole Alkaloids Indizoline, Mafaicheenamine A, Claulamine A, Claulansine A and the Proposed Claulamine E
   Markad, S. B; Argade, N. P. *J. Org. Chem.* **2016**, *81*, 5222.

3. Solid State Auto Inversion of *C*-Centrochirality: Enantioselective Total Synthesis of Furocarbazolones (–)-*epi*-Claulansine D and (–)-Claulansine D and Pyranocarbazolone (+)-*epi*-Claulansine C
   Markad, S. B; Argade, N. P. *J. Org. Chem.* **2017**~~, *revision submitted*~~.

4. Collective Synthesis of Basic Carbazole Alkaloids
   Markad, S. B; Argade, N. P. *Manuscript under preparation.*