Homophthalic Anhydride Derivatives to Bioactive Natural Products

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In

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BY

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Dedicated to

My Family and Teachers

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Homophthalic anhydride derivatives to bioactive natural products**" submitted by **Mr. Ravi Jangir** 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.

Ravi Jangir
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Dr. N. P. Argade
(Research Supervisor)

CSIR-NATIONAL CHEMICAL LABORATORY

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Homophthalic anhydride derivatives to bioactive natural products''** 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 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.

Ravi Jangir

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CONTENTS

CONTENTS

Research is a never ending process involving a team of persons striving to attain newer horizons in the field of sciences. This thesis would not have been completed without the encouragement and co-operation of my teachers, parents, friends, well-wishers and relatives. I take this opportunity to express my deep gratitude to one and all.

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Finally, my acknowledgement would not be completed without thanking the God, for giving me the strength and the determination to overcome the hardship faced in my life.

…Ravi

ABBREVIATIONS

Ac	Acetyl
AIBN	Azobisisobutyronitrile
o-ATP	2-Aminothiophenol
Bn	Benzyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
CSA	Camphor sulfonic acid
DCC	*N,N'*-Dicyclohexylcarbodiimide
DIAD	Diisopropyl azodicarboxylate
DMF	Dimethyl formamide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-enzoquinone
DMSO	Dimethyl sulphoxide
DIBAL-H	Diisobutylaluminium hydride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
ee	Enantiomeric excess
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	Ethyl acetate
g	Grams
GABA	Gamma Amino-Butyric Acid
h	Hours
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectroscopy
HWE	Horner-Wadsworth-Emmons
IR	Infra-red
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
LiTMP	Lithium tetramethylpiperidide
M+	Molecular ion
Me	Methyl
min	Minute
mg	Miligram
mL	Milliliter
MOM	Methoxymethyl
MS	Mass spectrum
Ms	Mesyl
NMR	Nuclear Magnetic Resonance
Pd/C	Palladium on activated charcoal
Ph	Phenyl
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
Py	Pyridine
TEPA	Tetraethylenepentamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid

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) and neutral alumina.
5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}CNMR spectra were recorded on Brucker FT AC-200 MHz, Brucker Avance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and app = apparent.
8. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.
9. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
10. Elemental analysis was done on Carlo ERBA EA 110B instrument.
11. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter 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. Ravi Jangir
Degree Enrolment No. & Date	Ph. D. in Chemical Sciences (10CC11J26061); January 2011
Title of the Thesis	Homophthalic Anhydride Derivatives to Bioactive Natural Products
Research Supervisor	Dr. Narshinha P. Argade (AcSIR, CSIR-NCL, Pune)

Introduction

Homophthalic acids/anhydrides are versatile synthons in organic synthesis. After first report[1] in 1890, interest in their chemistry has grown consistently, particularly in the natural products synthesis. This small molecule with multiple functionalities has proven its efficacy through building the backbones of many structurally complex and medicinally important molecules in a convergent manner. Syntheses of these creatures would have become difficult otherwise. This has been exemplified by the laboratory access to large number of protoberberine, benzophenanthridine and anthracycline class of natural and synthetic products from the homophthalic anhydrides. Many bioactive indenoisoquinolines as well as anthracyclines have been synthesized by using homophthalic anhydrides, few of them are in clinical practice and some are in development stages. This ascertains the utility of homophthalic anhydrides and their derivatives in the organic synthesis and medicinal chemistry.

Statement of Problem

Concise and efficient total synthesis of various bioactive natural and unnatural products starting from the homophthalic anhydride derivatives is a challenging task of current interest.

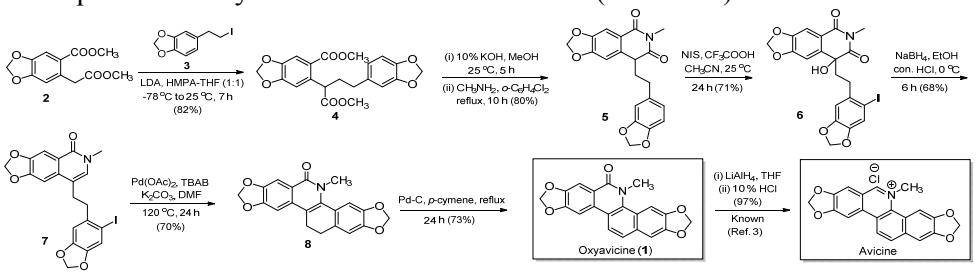
Methodology Used

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.

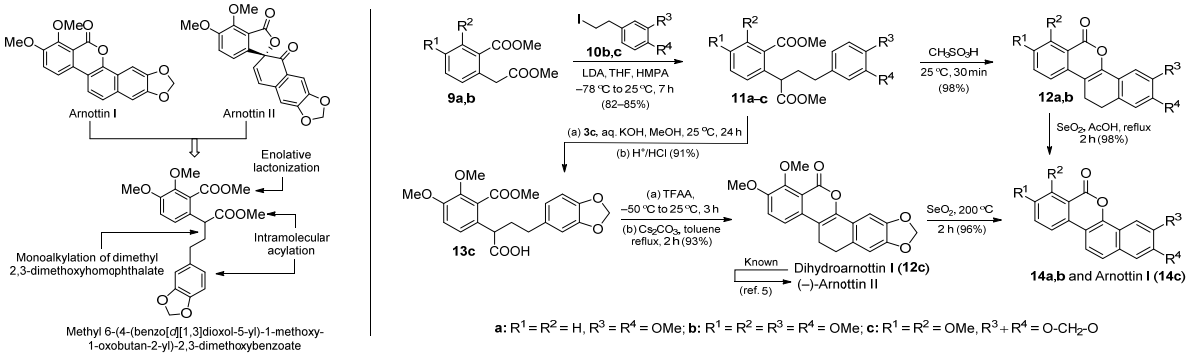
Sample Results

1.1. Starting from dimethyl 3,4-methylenedioxyhomophthalate, a concise total synthesis of oxyavicine has been described via the base catalyzed monoalkylation, homophthalimide formation, oxidative selective iodination, regioselective reductive dehydration and an intramolecular Heck coupling reaction followed by the oxidation pathway with 16% overall yield in six steps.[2] Formal synthesis of avicine is known[3] (Scheme 1).



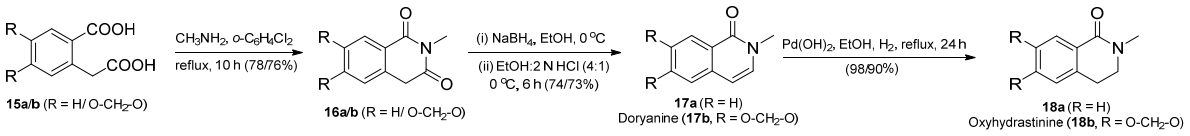
Scheme 1. Convergent Access to Oxyavicine via an Intramolecular Heck Coupling Reaction

A simple and efficient 3-step synthetic protocol has been developed for dimethyl homophthalates to naphthopyrans. Starting from dimethyl 2,3-dimethoxyhomophthalate, a practical synthesis of arnottin I has been described via base catalyzed mono-alkylation, selective hydrolysis of an aliphatic ester moiety, two conjugative intramolecular cyclizations and oxidative aromatization pathway with very good overall yield. The involved intramolecular acylation followed by an in situ enolative lactonization was the decisive step.[4] Synthesis of final step intermediate of arnottin I also completes the formal synthesis of (–)-arnottin II[5] (Scheme 2).



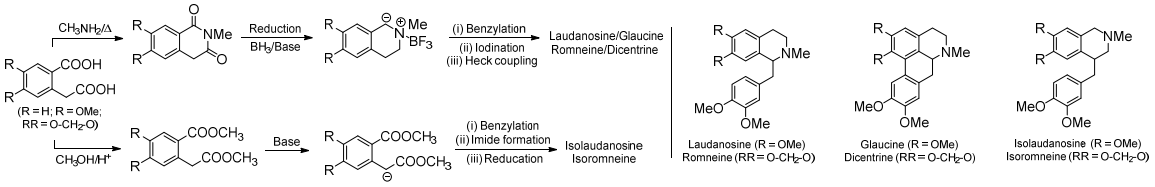
Scheme 2. General Approach to Naphthopyrans and Total Synthesis of Arnottin I

1.3 Isoquinoline alkaloids are imperative from their structural architectures and wide range of bioactivities point of view. The homophthalic acid and derivatives bear an appropriate carbon skeleton and functional groups to serve as a central precursor for the synthesis of isoquinoline alkaloids. Starting from 4,5-methylenedioxy homophthalic acid, concise and efficient synthesis of isoquinoline alkaloids doryanine and oxyhydrastinine have been described via corresponding homophthalimide utilizing one-pot regioselective reductive dehydration and catalytic hydrogenation pathway in the initial part (Scheme 3).[6]

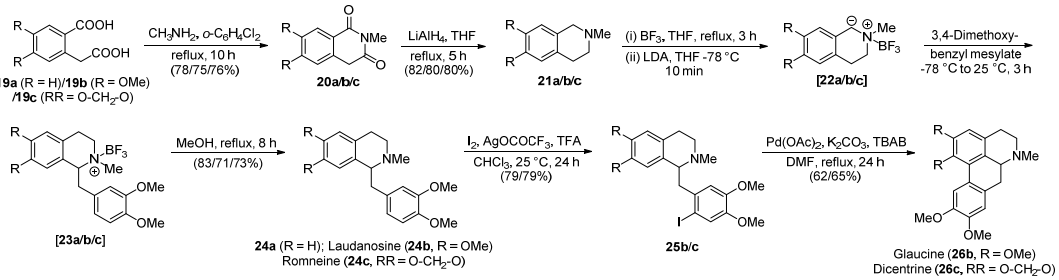


Scheme 3. Synthesis of Isoquinoline Alkaloids Doryanine and Oxyhydrastinine

Starting from suitably substituted homophthalic acids total synthesis of laudanosine, romneine, isolaudanosine and isoromneine have been demonstrated in very good yields. The obtained natural products laudanosine and romneine were further utilized to respectively accomplish the synthesis of another two isoquinoline based alkaloids glaucine and dicentrine. The base catalyzed selective generation of two different benzylic carbanions, their condensatuions with the 3,4-dimethoxybenzyl mesylate and regioselective iodination followed by intramolecular Heck coupling reactions to form biaryl systems as the key steps.[7] The isolaudanosine and isoromneine were synthesized via alternative reaction pathways (Schemes 4 and 5).

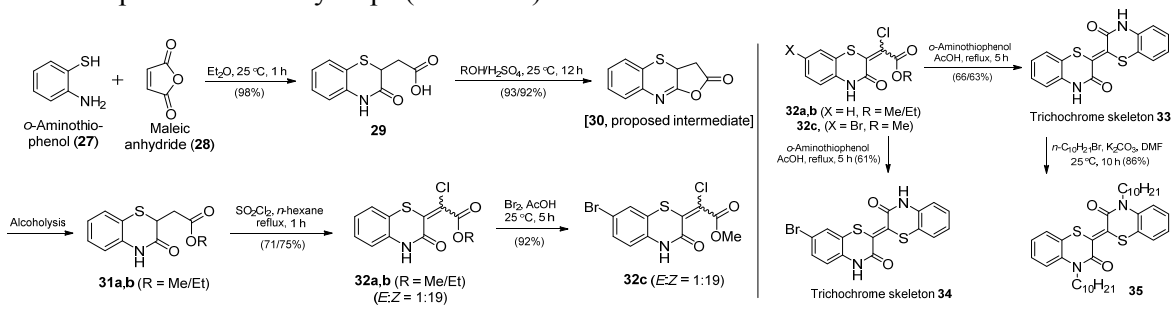


Scheme 4. Synthesis of Isoquinoline Based Alkaloids and their Regioisomers



Scheme 5. Homophthalimides Leading to Isoquinoline Based Alkaloids via Intramolecular Heck Reactions

2. Chemo- and stereoselective total synthesis of trichochromes basic skeleton has been described starting from *o*-aminothiophenol and maleic anhydride in very good overall yield. The process involves synthesis of corresponding benzothiazinyl-acetates followed by their sulfuryl chloride induced dihalogenation-dehydrohalogenation and the second condensation with *o*-aminothiophenol as the key steps (Scheme 6).[8]



Scheme 6. Synthesis of Symmetrical and Unsymmetrical Trichochrome Pigments' Skeleton

Summary

Total synthesis of various bioactive natural and unnatural products have been described by an appropriately activating the methylenic position of homophthalic anhydride and derivatives. Flexible stepwise synthesis of human red hair containing trichrome pigments skeleton has been described.

References

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2. Jangir, R.; Argade, N. P. *RSC Adv.* **2012**, *2*, 7087.
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4. Jangir, R.; Argade, N. P. *RSC Adv.* **2014**, *4*, 5531.
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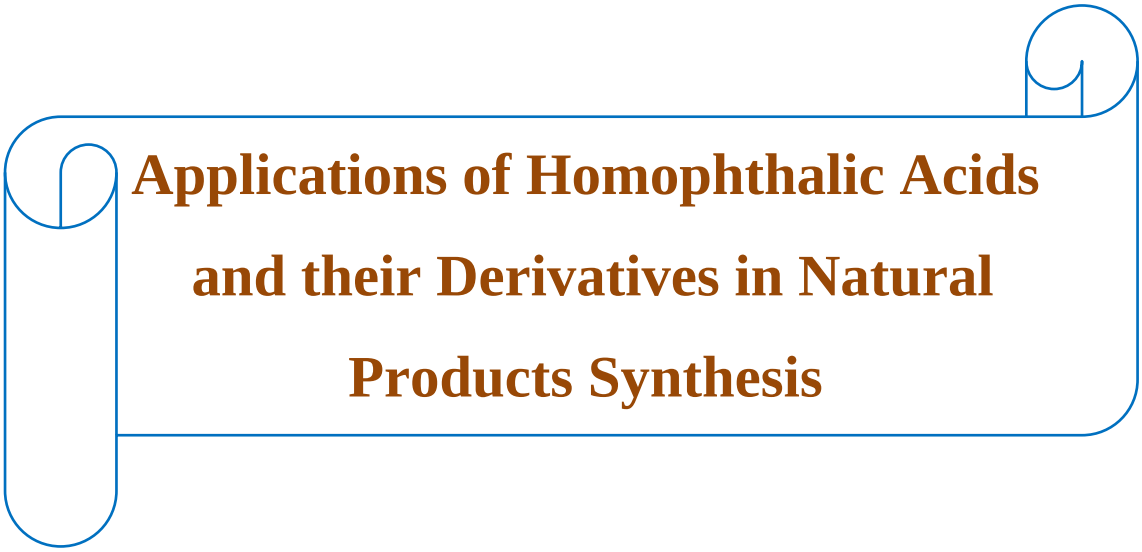
7. Jangir, R.; Argade, N. P. Manuscript under preparation.
8. Jangir, R.; Gadre, S. R.; Argade, N. P. *Synthesis* **2015**, *47*, 2631.

Chapter 1



Applications of Homophthalic Acids and their Derivatives in Natural Products Synthesis

1.1 Introduction

Homophthalic anhydride has been known for more than a century and is widely used as a building block for the synthesis of alkaloids, dyes and a variety of medicinally important compounds. According to IUPAC nomenclature, the homophthalic anhydrides **1** are named as 1*H*-2-benzopyran-1,3(4*H*)-diones. Positions of substitution in the benzene nucleus are usually indicated by the numbering system for the respective 2-carboxy phenylacetic acids **2** and substitution at the methylene position is called α-substitution. Homophthalimides **3**, an important derivative of homophthalic anhydrides/acids are also known for more than a century and have wide applications in organic synthesis (Figure 1). Homophthalates **4** are also obtained from corresponding acids and anhydrides and are building block of various natural and unnatural products.

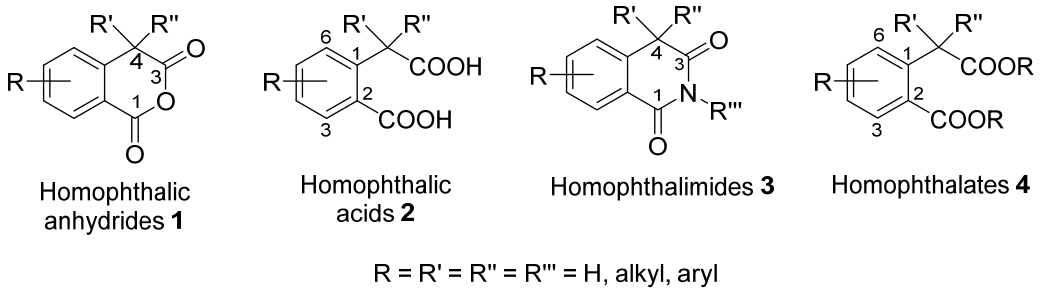
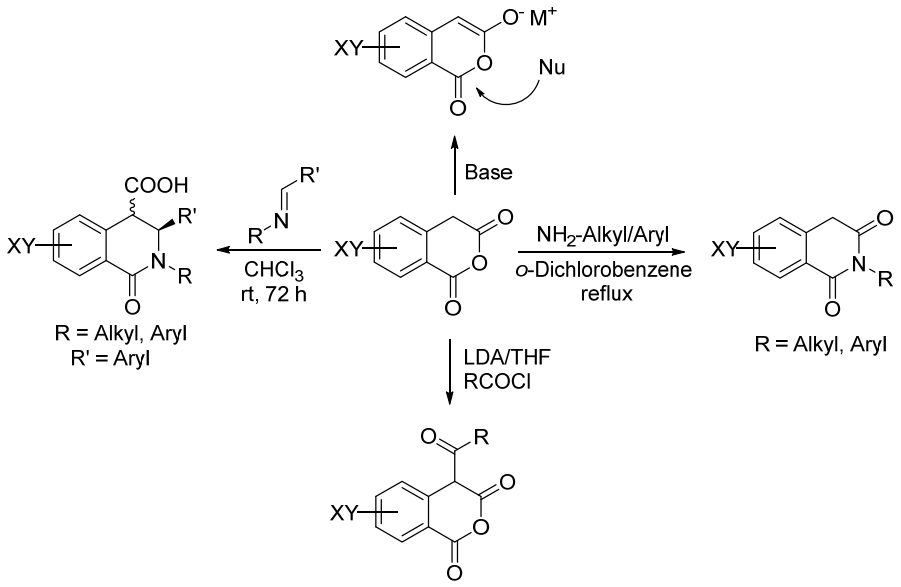


Figure 1. Homophthalic Acids and Derivatives

Homophthalic anhydrides/acids are frequently being used in the organic synthesis, interest in their chemistry has grown after sixties, mainly due to their successful applications in the form of Diels-Alder-type cycloaddition reaction in the synthesis of a variety of natural and synthetic compounds. Comprehensive reviews on homophthalic anhydrides and their applications in organic synthesis are published by Stanoeva et al. in 1984[1] and by Gonzalez-Lopez et al. in 2009.[2] This chapter summarizes various reports on syntheses and applications of homophthalic anhydrides/acids/esters and homophthalimides in synthetic organic chemistry. Total synthesis of natural products occupies a keystone position in organic chemistry and hence an attempt has been made to focus more on natural product synthesis reports involving homophthalic anhydrides/acids/esters and homophthalimides in the synthetic scheme. A short overview of synthesis of homophthalic anhydrides/acids/esters and homophthalimides has been presented prior to their applications in organic synthesis; however, no pretension of completeness has been claimed.

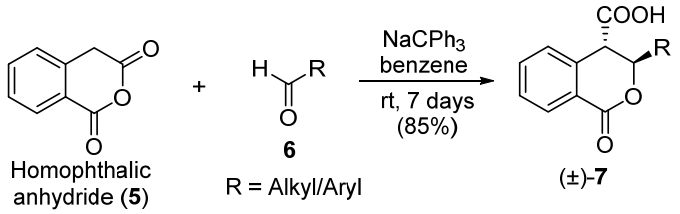
1.2 Background

Prior to discussion on the synthesis and applications, we wish to reason why homophthalic anhydrides are such useful synthons in organic chemistry. Few properties which attribute to this versatile molecule have been discussed in brief. The α-methylene protons of homophthalic anhydrides are highly acidic and exchangeable with deuterated methanol. Hence, number of α-substituted derivatives of homophthalic anhydrides and homophthalimides are reported in literature. Also, both the carbonyl groups present are in different chemical environment with respect to the benzene ring. This results in a highly regioselective anhydride ring opening by nucleophiles attacking the non-conjugated carbonyl group. In homophthalides also the presence of unconjugated carbonyl with respect to benzene ring makes it more reactive for reduction. Apart from these general properties, the following reactions have made homophthalic anhydrides truly useful synthons in organic synthesis (Scheme 1).



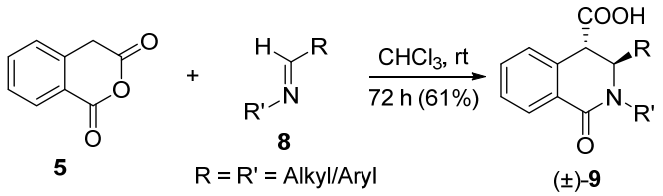
Scheme 1. General Reactions of Homophthalic Anhydrides

The reaction of homophthalic anhydride (**5**) with an aldehyde **6** using strong base to form annulation product **7** was observed for the first time by Muller in 1931 and later it was studied in details by Pinder & co-workers in 1958 (Scheme 2).[3,4] The reaction involves nucleophilic attack on the aldehyde carbonyl by an anhydride-derived enolate. More importantly, for the first time this demonstrated the ability of homophthalic anhydride to undergo annulation reaction.



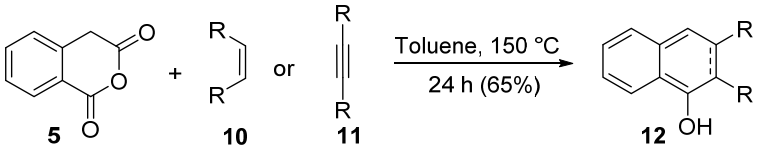
Scheme 2. Muller/Pinder Cycloaddition Reaction

Cushman et al. and Haimova et al. in 1977 observed the similar annulation reaction of homophthalic anhydride with substituted imine **8** to form isoquinoline moiety **9** (Scheme 3).[5,6] This reaction laid the foundation for much of the subsequent work on isoquinoline chemistry and synthesis of many useful protoberberine alkaloids.



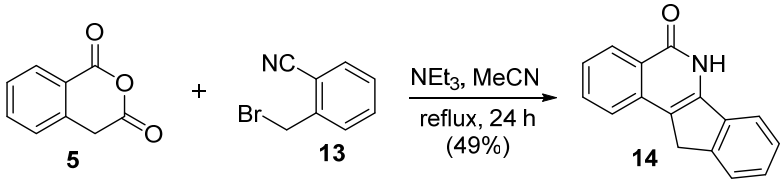
Scheme 3. Cushman/Haimova Isoquinoline Synthesis

Tamura et al. in 1981 reported a Diels-Alder-type cycloaddition of homophthalic anhydride with alkenes **10** or alkynes **11** to produce fused products **12** (Scheme 4).[7]



Scheme 4. Tamura Cycloaddition Reaction

Jagtap et al. reported the synthesis of indeno[1,2-*c*] isoquinoline alkaloids from homophthalic anhydride. This reaction is initiated by the alkylation of homphthalic anhydride with benzylbromonirtile **13** (Scheme 5).[8]



Scheme 5. Synthesis of Indeno[1,2-*c*]isoquinolines

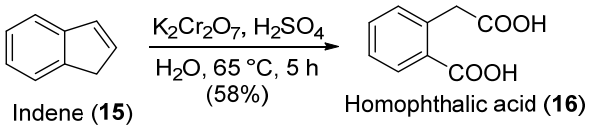
Much of the synthetic chemistry evolved subsequent to discovery of these above specified reactions, which made homophthalic anhydrides the versatile synthons. This resulted in the development of large numbers of methods for the synthesis of various substituted

homophthalic anhydrides/acids as they needed; by known, modified or new methods. A few general methods have been discussed in the following section.

1.3 Synthesis of Homophthalic Acids/Anhydrides

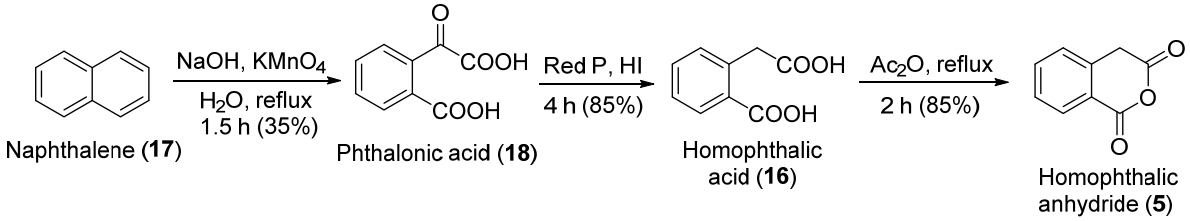
1.3.1 General Methods for the Synthesis of Homophthalic Acids/Anhydrides

Homophthalic anhydrides are generally synthesized from the corresponding homophthalic acids by using dehydrating agents like acetyl chloride, thionyl chloride, DCC, acetic anhydride and trimethylsilylethoxyacetylene. Miller et al. in 1890, first synthesized homophthalic acid (**16**) from the fraction of coal-tar oil which is rich in indene. Oxidation of indene (**15**) with chromate or permanganate resulted into the formation of homophthalic acid (**16**) (Scheme 6).[9,10]



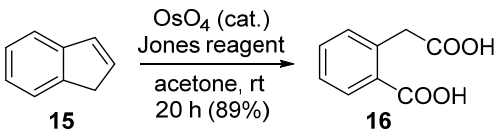
Scheme 6. First Report on Synthesis of Homophthalic Acid

Homophthalic anhydride (**5**) was synthesized for the first time by Graebe and Trumpy in 1898 (Scheme 7).[11] Oxidation of naphthalene (**17**) by permanganate formed the phthalonic acid (**18**). Phthalonic acid (**18**) was reduced to homophthalic acid (**16**) by using the red phosphorus and hydroiodic acid. Further heating of homophthalic acid in acetic anhydride furnished homophthalic anhydride (**5**).



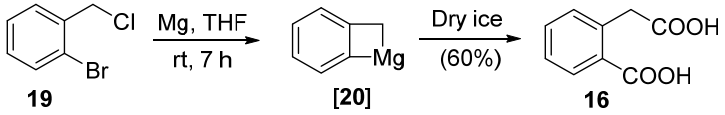
Scheme 7. First Report on Synthesis of Homophthalic Anhydride

Weinreb et al. in 1993 reported that a combination of catalytic amount of OsO_4 and stoichiometric Jones reagent in acetone at room temperature oxidize various types of alkenes into acids and/or ketones.[12] They have synthesized homophthalic acid (**16**) by the oxidation of indene (**15**) in 89% yield (Scheme 8).



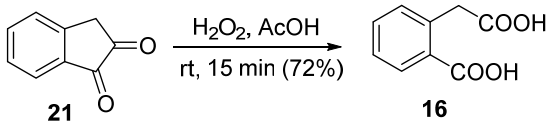
Scheme 8. Synthesis of Homophthalic Acid from Indene via Oxidation

De Boer et al. in 1987 reported the synthesis of homophthalic acid (**16**) by using 1,3-divalent organomagnesium reagent **20** (Scheme 9).[13] The reaction involves slow addition of a dilute solution of *o*-bromobenzyl chloride (**19**) in THF to activated magnesium metal. The activated complex is further treated with dry ice to obtain homophthalic acid (**16**) in 60% yield.



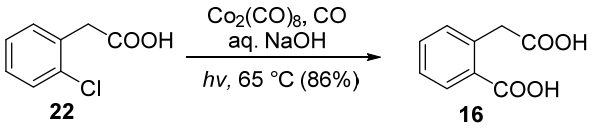
Scheme 9. Synthesis of Homophthalic Acid via Organomagnesium Complex

Qadeer et al. and Sengupta et al. synthesized homophthalic acid (**16**) by hydrogen peroxide oxidation of 1,2-indanedione (**21**) (Scheme 10).[14,15]



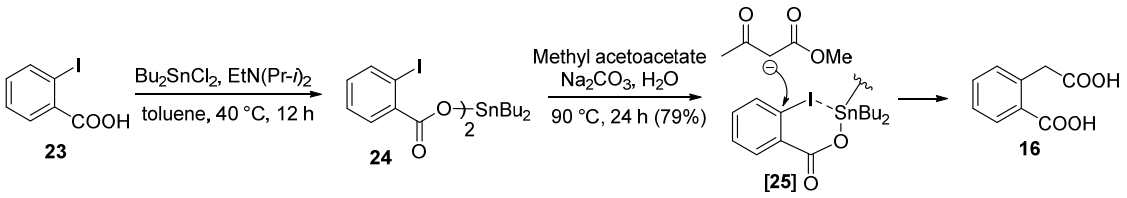
Scheme 10. Synthesis of Homophthalic Acid by H_2O_2 Oxidation

Kashimura et al. reported the synthesis of homophthalic acid (**16**) by cobalt carbonyl catalyzed carbonylation of *o*-chlorophenylacetic acid (**22**) under photostimulation in aqueous sodium hydroxide (Scheme 11).[16]



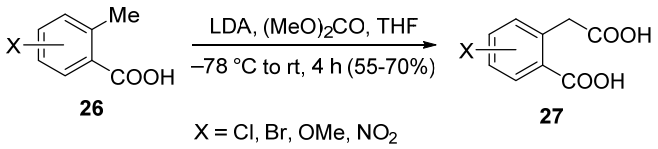
Scheme 11. Synthesis of Homophthalic Acid via Carbonylation

Maitra and co-workers reported di-*n*-butyltin dichloride (DBTDC) induced nucleophilic substitution of 2-iodobenzoates with methyl acetoacetate in water to provide homophthalic acid (**16**) in good yield (Scheme 12).[17] Toxic organo-tin compound used was only 0.75 equivalent. This is the advantage over their previous method in which 1 to 3 equivalents of organo-tin reagent was required.[18]



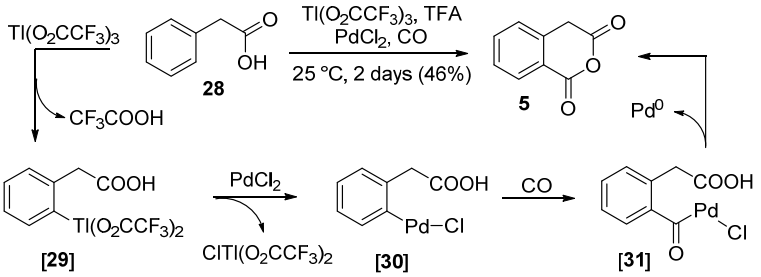
Scheme 12. Synthesis of Homophthalic Acid via Nucleophilic Substitution

Tsou et al. reported the synthesis of substituted homophthalic acids **27** via the deprotonation of the methyl group of *o*-toluic acids **26** and carboxylation of the resulting dianion (Scheme 13).[19]



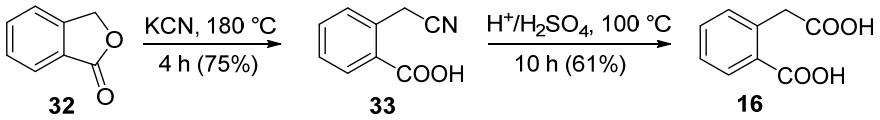
Scheme 13. Synthesis of Homophthalic Acid via Carboxylation

Larock et al. synthesized homophthalic anhydride (**5**) by metallization of the aromatic nucleus with thallium(III) trifluoroacetate followed by carbonylation reaction (Scheme 14).[20]



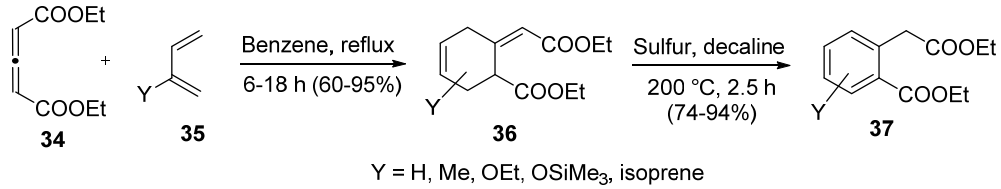
Scheme 14. Synthesis of Homophthalic Acid via Carbonylation

Homophthalic acid (**16**) can also be synthesized from corresponding phthalide (**32**) by nucleophilic attack of cyanide (Scheme 15).[21] Phthalide (**32**) is treated with potassium cyanide to obtain the ring-opened 2-carboxybenzyl nitrile (**33**) and hydrolyzed using sulfuric acid to obtain homophthalic acid (**16**).



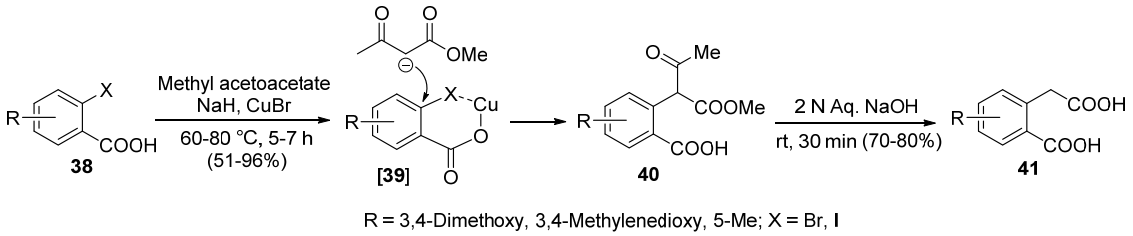
Scheme 15. Synthesis of Homophthalic Acid from Phthalide

Kozikowski et al. accomplished an elegant preparation of homophthalates **37** from nonaromatic compounds by employing a Diels-Alder reaction (Scheme 16).[22] The Diels-Alder reaction of allene **34** with various substituted butadienes **35** yielded the cycloadducts **36** in high yields, which were easily transformed to the desired compounds by a sulfur-mediated dehydrogenation. If the dienes bearing functional groups have weak electronic effects (e.g. methyl, isoprene), the mixtures of regioisomeric homophthalates were obtained after dehydrogenation.



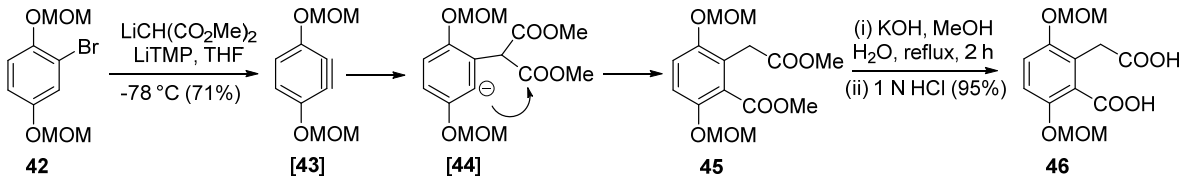
Scheme 16. Synthesis of Homophthalic Acid via Diels-Alder Reaction

Mckillop and co-workers synthesized homophthalic acids by direct arylation of *β*-dicarbonyl compound with *o*-halobenzoic acids **38** (Scheme 17).[23] The nucleophilic attack of *β*-dicarbonyl compound on *o*-halobenzoic acids in presence of a strong base and a copper (I) halide gave the coupled compound **40**. The retro-Claisen condensation of the intermediate *α*-aryl-*β*-dicarbonyl compounds **40** furnished homophthalic acids. This method has wide applicability as various substituted homophthalic acids **41** have been synthesized by using this protocol.



Scheme 17. Synthesis of Homophthalic Acid via Coupling Reaction

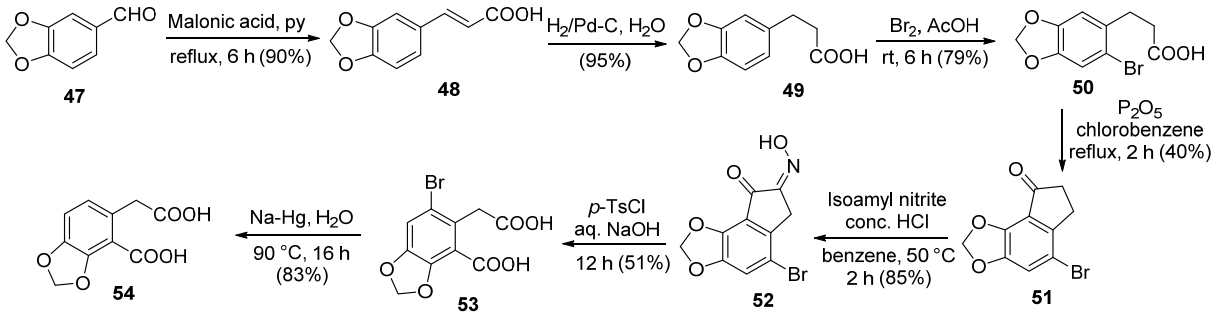
Guyot et al. reported the arylation of malonic ester with aryne in the presence of a strong base to provide homophthalic acids (Scheme 18).[24] Further Danishefsky et al. optimized the reaction condition to obtain the various substituted homophthalic acids in good yields and utilized the same for synthesis of various natural products.[25] One representative example has been depicted in scheme 18.



Scheme 18. Synthesis of Homophthalic Acid via Aryne Intermediate

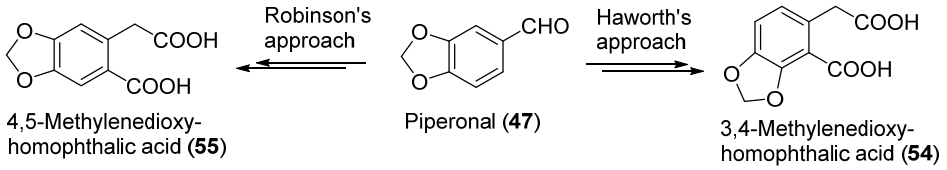
Shamma et al. developed an eight step sequence for the synthesis of 3,4-methylenedioxyhomophthalic acid (**54**) (Scheme 19).[26] The condensation reaction between piperonal (**47**) and malonic acid formed cinnamic acid **48** which upon catalytic hydrogenation furnished the acid **49** in 95% yield. The reactive position of aromatic ring in acid **49** was blocked by bromination, which permitted the regioselective hydrindone **51**

formation from acid **50**. Second order Beckmann rearrangement of oxime **52** yielded bromo-homophthalic acid **53** in 51% yield. The bromo acid **53** was then debrominated to form 3,4-methylenedioxyhomophthalic acid (**54**) in 83% yield.



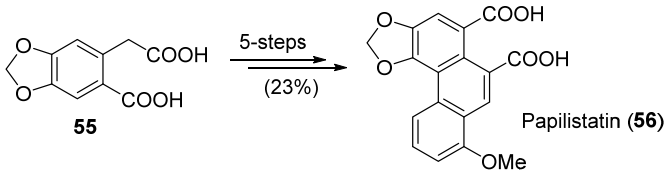
Scheme 19. Synthesis of Homophthalic Acid via Beckmann Rearrangement

The above discussed strategy was originally developed by Sir Robert Robinson[27] in 1907 for the synthesis of 4,5-methylenedioxyhomophthalic acid (**55**) during their studies towards natural product brazilin and haematoxylin. Later, in 1926 Haworth et al.[28] modified this strategy and used for the synthesis of 3,4-methylenedioxyhomophthalic acid (**54**) (Scheme 20).



Scheme 20. Synthesis of 3,4-Methylenedioxyhomophthalic Acid (**55**) and 4,5-Methylenedioxyhomophthalic Acid (**54**)

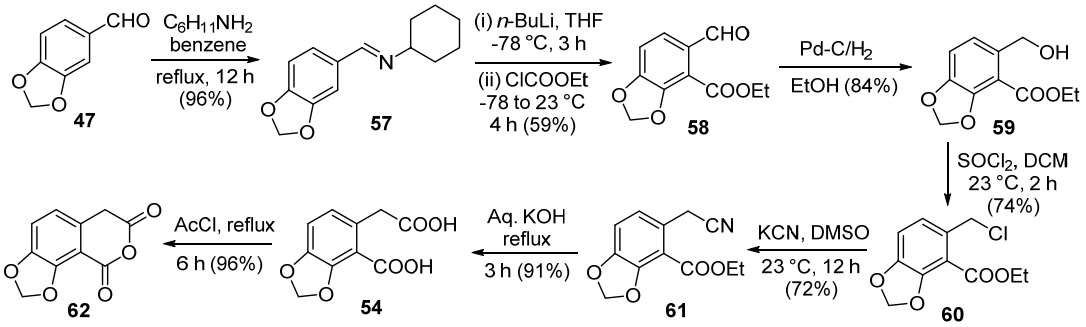
All the three routes utilize piperonal (**47**) as the precursor for hydrindone synthesis followed by Beckmann rearrangement. Shamma et al. claimed some advantage with respect to yield and work-up procedures over the Robinson's and Haworth's approaches. Very recently, Wu et al.[29] completed the first total synthesis of papilistatin (**56**) by synthesizing required 4,5-methylenedioxyhomophthalic acid (**55**) with further refinements in the process (Scheme 21).



Scheme 21. Total Synthesis of Papilistatin

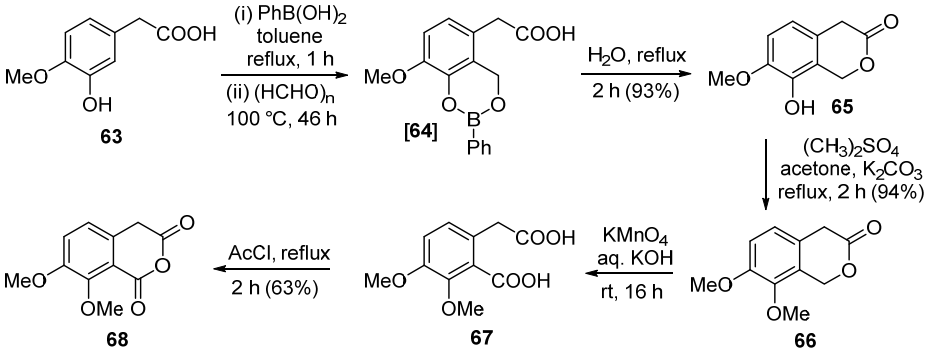
Cushman et al reported the synthesis of 3,4-methylenedioxyhomophthalic anhydride (**62**) in 7 steps (Scheme 22).[30] Piperonal (**47**) was condensed with cyclohexylamine to obtain

piperonylidenecyclohexylimine (**57**). Imine **57** upon *ortho*-lithiation and reaction with ethyl chloroformate followed by acidic work-up provided product **58** in 59% yield. The catalytic hydrogenation of the aldehyde **58** to the benzyl alcohol **59** proceeded with 84% yield. The conversion of the benzyl alcohol **59** to the benzyl chloride **60** was achieved by treatment with thionyl chloride. The displacement of the chloride from **60** with cyanide gave desired cyano compound **61**, which on basic hydrolysis provided the corresponding homophthalic acid in 91% yield. The cyclodehydration of the diacid **54** in acetyl chloride furnished the homophthalic anhydride **62** in 96% yield.



Scheme 22. Synthesis of Homophthalic Acid via *ortho*-Lithiation

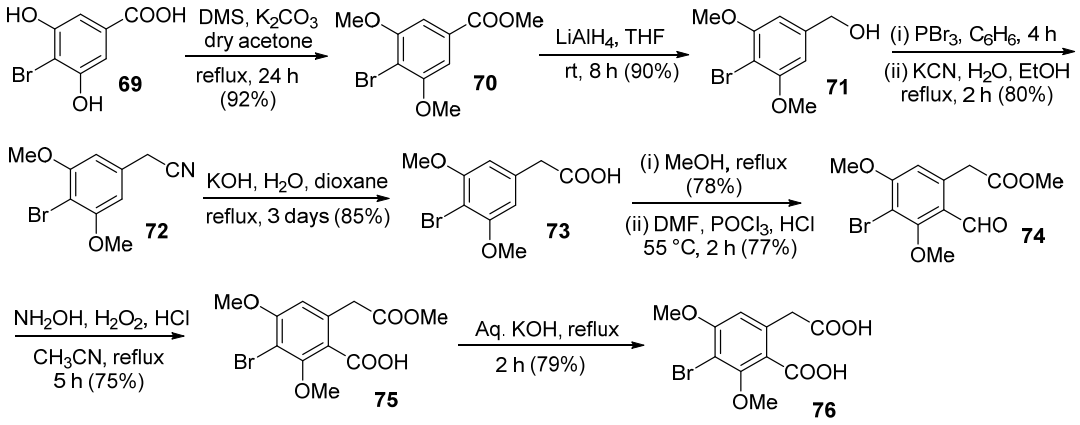
Cushman et al. synthesized 3,4-dimethoxyhomophthalic anhydride (**68**) by using anchimerically assisted hydroxymethylation of the homoisovanillic acid (**63**) (Scheme 23).[31] The obtained intermediate **64** was hydrolyzed without isolation to the lactone **65** with 93% yield. The phenolic group was *O*-methylated to **66** by using dimethyl sulfate in 94% yield. Corresponding methyl ether **66** upon oxidation with potassium permanganate provided the crude 3,4-dimethoxyhomophthalic acid (**67**), which was further dehydrated to the desired anhydride **68** in 63% yield.



Scheme 23. Synthesis of Homophthalic Acid via Hydroxymethylation

Saeed et al. reported the synthesis of 4-bromo-3,5-dimethoxyhomophthalic acid (**76**) in 7 steps (Scheme 24).[32] 4-Bromo-3,5-dihydroxybenzoic acid (**69**) was methylated with dimethyl sulfate (DMS) in the presence of K_2CO_3 to afford the ester **70** in 92% yield.

Ester **70** was reduced with $LiAlH_4$ to obtain benzyl alcohol **71** in 90% yield. The primary alcoholic function was converted to benzyl nitrile **72** by two successive nucleophilic substitutions using PBr_3 and KCN with 80% yield. Hydrolysis of nitrile under basic conditions lead to the formation of corresponding phenylacetic acid **73** in 85% yield. The methyl ester of phenylacetic acid **73** was subjected to the Vilsmeier-Haak formylation to furnish the formyl ester **74**. Formylated ester **74** was oxidized to the acid **75** using hydroxylamine hydrochloride, H_2O_2 and HCl in acetonitrile. The saponification of ester **75** furnished the desired homophthalic acid **76** in 79% yield.



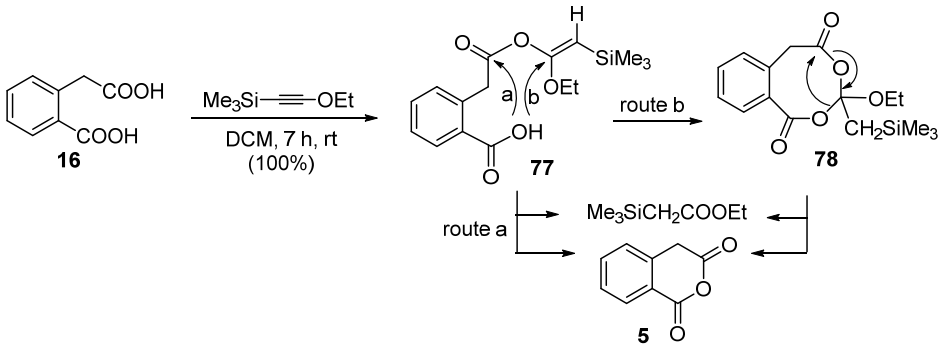
Scheme 24. Synthesis of 4-Bromo-3,5-dimethoxyhomophthalic Acid

1.3.2 Synthesis of Homophthalic Anhydrides from Homophthalic Acids

Homophthalic anhydrides are generally synthesized by dehydration of respective homophthalic acids by using dehydrating agents such as acetyl chloride and acetic anhydride.[33] Other reagents used are thionyl chloride, trifloroacetic acid, isopropenyl acetate, DCC, ethoxyacetylene and trimethylsilylethoxyacetylene.[34-38] Acetic anhydride in some cases causes acylation of active methylene group of homophthalic acid and requires aqueous work-up. Initially acetylene based reagent, ethoxyacetylene was used for this purpose.[37] However, it is unstable and highly volatile. Analogous to ethoxyacetylene, Kita et al.[38] discovered trimethylsilylethoxyacetylene to circumvent those disadvantages. It can be readily prepared by the trimethylsilylation of the commercially available ethoxyacetylene. This is the most powerful dehydrating agent for the formation of wide range of anhydrides in almost quantitative yields.

The plausible mechanism involves addition of carboxylic acid across the triple bond to form acetal intermediate **77**, which directly transforms to the anhydride (route a) (Scheme 25). Second possibility involves the formation of orthoester intermediate **78** followed by

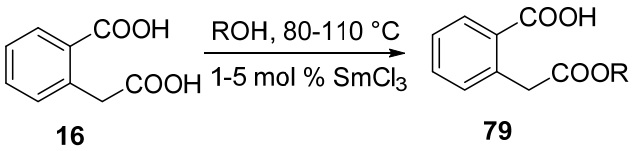
rapid ring contraction to yield the anhydride with elimination of ethyl trimethylsilyl acetate (route b).



Scheme 25. Dehydrative Cyclization of Homophthalic Acid

1.3.3 Synthesis of Homophthalates from Homophthalic Acids

Esterification, one of the most simple but most sought after reactions in organic chemistry, can be carried out under acid catalysis or in the presence of bases.[39,40] Homophthalates are generally synthesized by esterification in acidic media like HCl, H_2SO_4 and $SOCl_2$. Direct methyl ester formation using diazomethane or base-mediated esterification employing dimethyl sulfate or alkyl halides are other options; these reagents, however, pose toxicity, safety and handling problems. It is difficult to selectively esterify one group of homophthalic acids. Muraleedharan et al. reported selective esterification by using $SmCl_3$ (Scheme 26).[41] Homophthalic acid underwent efficient esterifications and the results show high catalytic potential of Sm(III) in chemoselective catalytic esterifications.

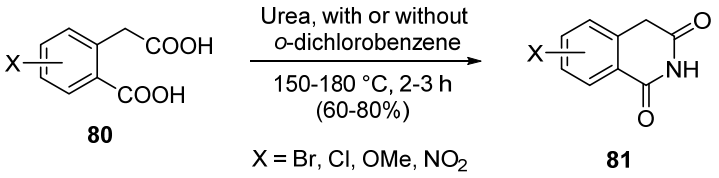


Scheme 26. Selective Esterification by Using $SmCl_3$

1.3.4 Synthesis of Homophthalimide

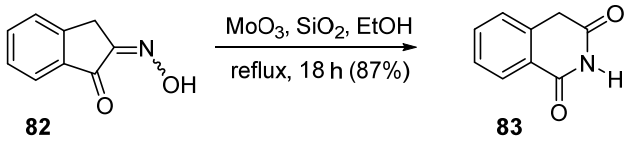
Homophthalimides are generally synthesized by the condensation of homophthalic anhydrides/acids and various substituted amines. We have made considerable efforts for the synthesis of various natural and synthetic products by using homophthalimides and will be discussed in the subsequent part. Few other methods of homophthalimides synthesis have been briefly summarized in this part.

Crockett et al.[42] and Tsou et al.[19] have reported the synthesis of homophthalimide by condensation of urea and homophthalic anhydrides/acids **80** (Scheme 27).



Scheme 27. Synthesis of Homophthalimide by Using Urea

Dongare and co-workers[43] developed silica supported molybdenum oxide catalyst for Beckmann rearrangement of various oximes (Scheme 28). The reaction condition is tolerable for various acid sensitive protecting groups which is the advantage of this methodology.



Scheme 28. Synthesis of Homophthalimide via Beckmann Rearrangement

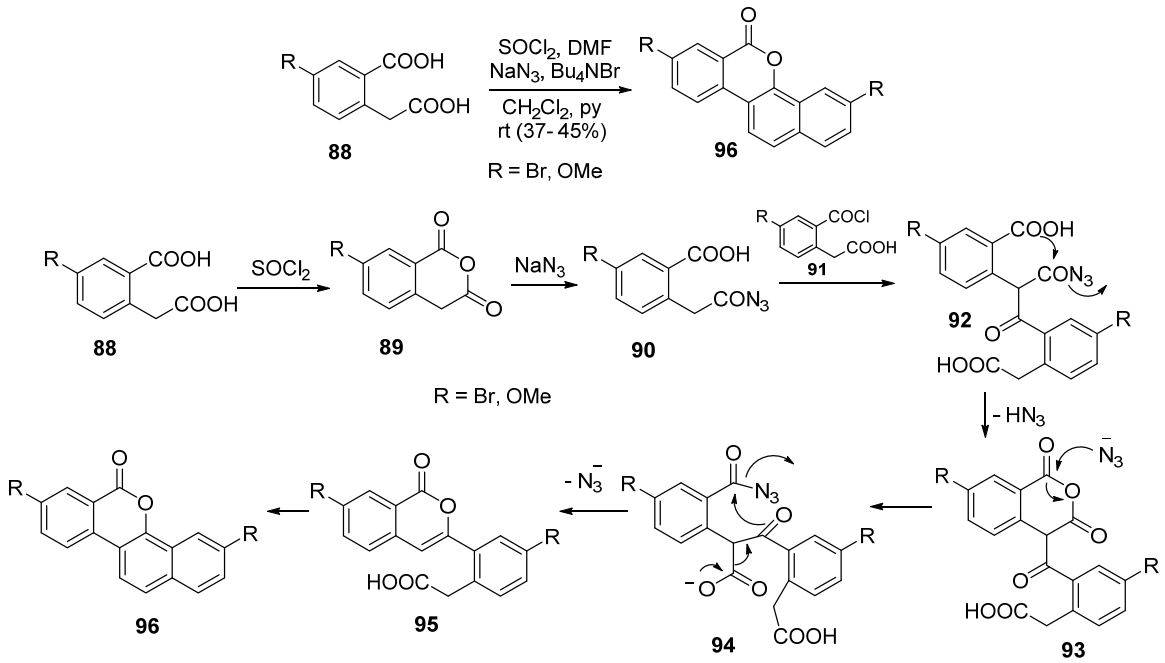
Zard & co-workers reported the synthesis of homophthalimides based on a radical cyclization of xanthates **86** to homophthalimides **87** (Scheme 29).[44] Heating xanthates **86** in refluxing *o*-dichlorobenzene with slow addition of stoichiometric amount of di-*tert*-butyl peroxide yielded the desired homophthalimides **87**. The products very often precipitated upon cooling of the reaction mixture or after partial evaporation of the solvent under vacuum and could be isolated by filtration. The formation of regioisomers with unsymmetrical substrates is the limitation of this methodology.

Scheme 29. Synthesis of Homophthalimide via Xanthates

1.4 Applications of Homophthalic Anhydrides

Large number of bioactive natural products has been synthesized by using homophthalic anhydrides as the convergent building blocks. Cycloaddition of homophthalic anhydride and imine provided an easy access to protoberberine as well as benzo[*c*]phenanthridine family alkaloids. Cycloaddition with quinones also proved efficient access to many complex anthracycline antibiotics. Uses of homophthalic acid and derivatives for the synthesis of various natural products have been described in this section.

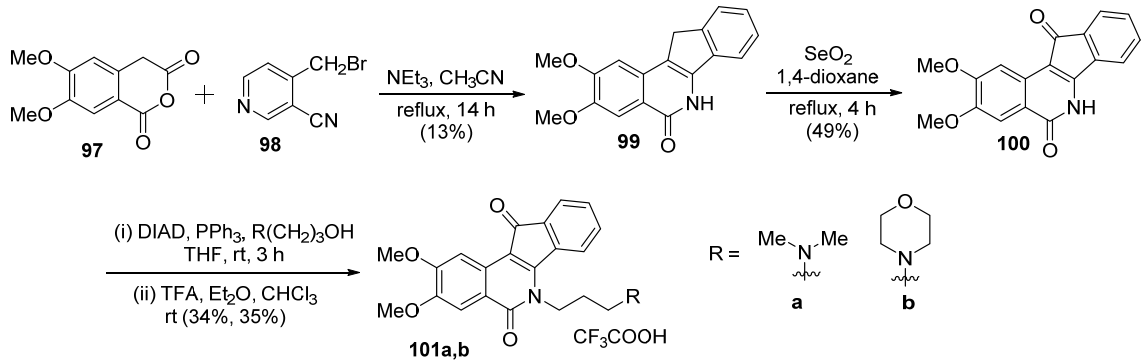
Balci et al. reported the synthesis of dibenzo[*c,h*]chromen-6-one skeleton from homophthalic acid (Scheme 30).[45] *N,N*-Dimethyl(chlorosulfinyloxy)methaniminium chloride formed from thionyl chloride and dimethyl formamide is an efficient reagent for the synthesis of acyl azides from carboxylic acids.[46] Homophthalic acid **88** was reacted with thionyl chloride, DMF and sodium azide in the presence of tetrabutylammonium bromide as a catalyst in methylene chloride anticipating formation of the diazide. However, the desired diazide was not formed and the major product 6*H*-dibenzo[*c,h*]chromen-6-one **96** was obtained (Scheme 30).[47,48] The plausible mechanism involves formation of the anhydride **89**, which could then be regiospecifically opened up by the azide anion to the corresponding monoazide **90**. Formation of an acyl azide activates the methylenic protons for further reaction. Intermolecular acylation of **90** with acyl chloride **91** followed by ring-closure would result in the formation of **93**. This anhydride might undergo again ring-opening by azide anion attack to form *β*-keto-acid carboxylate **94**. Decarboxylation of **94** would led to cyclization to form the key intermediate **95**, which could easily be converted in the dibenzochromenone derivatives **96**. Recently, Threadgill et al.[49] obtained relevant information about the mechanism of the acylation of isocoumarin derivatives which strongly support this suggestion.



Scheme 30. Synthesis and Mechanism of Dibenzo[*c,h*]chromen-6-one Skeleton

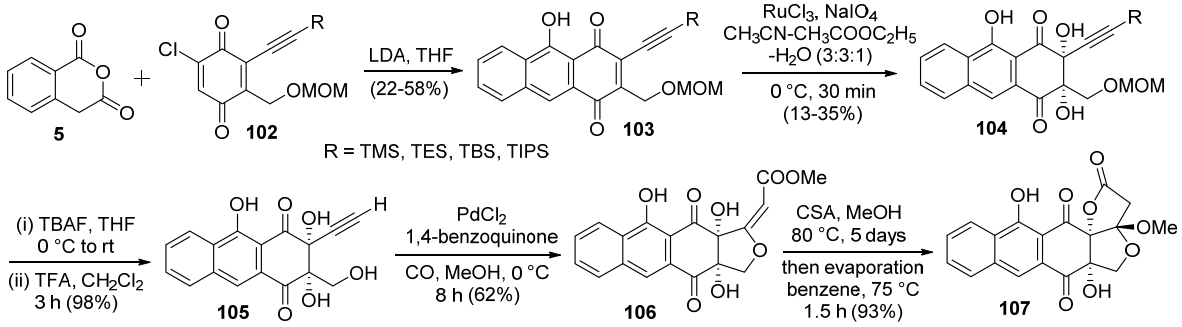
Cushman et al. synthesized 8-azaindenoisoquinolines **101a**,**b** by preparation of starting material 4-methylnicotinonitrile (Scheme 31).[50] Intermediate bromide **98** was obtained by

bromination of 4-methylnicotinonitrile with NBS, which was reacted with 4,5-dimethoxyhomophthalic anhydride (**97**)[51] to produce **99** in 13% yield. Oxidation of compound **99** with SeO_2 afforded the key intermediate dioxoindenoisoquinoline **100** in 49% yield. The synthesis of 8-azaindenoisoquinoline analogues was completed with alkylation of **100** by means of Mitsunobu reaction to prepare the dimethylaminopropyl and morpholinopropyl products **101a** and **101b** in 34% and 35% yield respectively.



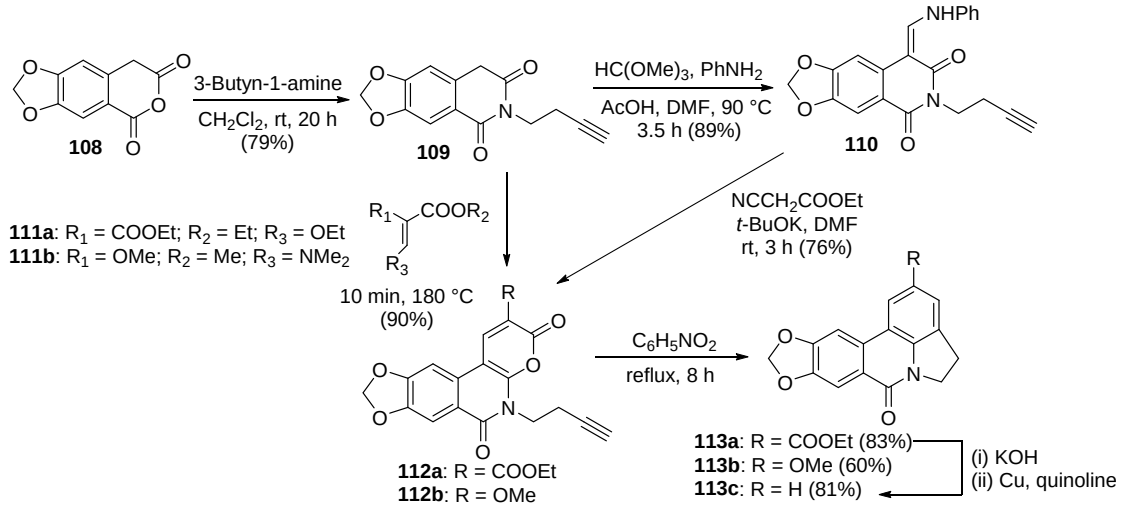
Scheme 31. Synthesis of 8-Azaindenoisoquinolines

Nakata et al. reported the model synthetic study of lactonamycin using homophthalic anhydride (Scheme 32).[52] Homophthalic anhydride (**5**) was used as the diene precursor with which silylethynylchloroquinones **102** were reacted under Tamura's condition[53] to afford the expected cycloaddition products **103** in good yields. When **103** were treated with a catalytic amount of $RuCl_3$ and 1.50 molar amounts of $NaIO_4$ in 3:3:1 acetonitrile-ethyl acetate-water, the desired dihydroxylated products **104** were obtained in low to good yields. All of the obtained **104** were converted to the desilylated product by treatment with TBAF in THF and further subjected to TFA in CH_2Cl_2 to afford ethynyltetraol **105** in 98% yield. Ethynyltetraol **105** was treated with a catalytic amount of $PdCl_2$ and 1,4-benzoquinone in the presence of an atmospheric pressure of CO (balloon) at rt to afford the D-ring compound **106** in 62% yield as a single stereoisomer. Compound **106** was treated in methanol with 1 molar amount of CSA to afford the model aglycon **107**. Dissolution of the residue in benzene and heating provided the model lactonamycin aglycon **107** in 93% yield .



Scheme 32. Synthetic Study of Model Lactonamycin

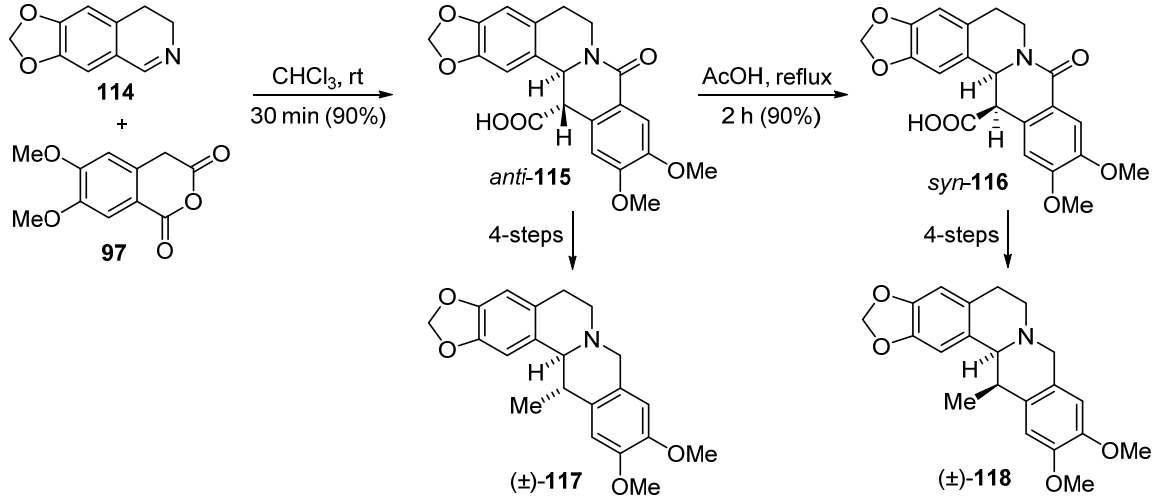
Castedo et al. proposed synthesis of lycorine by intramolecular Diels Alder reaction (Scheme 33).[54] Treatment of 4,5-(methylenedioxy)homophthalic anhydride (**108**) with a solution of 3-butyn-1-amine followed by heating of the resulting salt afforded imide **109** in 78% yield. Transformation of imide **109** into pyrone **112a** was accomplished by two routes: treatment with methyl orthoformate, aniline and AcOH furnished enamine **110**, which reacted with ethyl cyanoacetate and *t*-BuOK to give pyrone **112a** in 68% overall yield; while simply heating **109** with the malonyl derivative **111a** achieved the same transformation in one pot with 60% yield. Heating solution of **112a** in nitrobenzene at 210 °C brought about both intramolecular cycloaddition between pyrone and alkyne, and subsequent loss of CO_2 through a retro-Diels-Alder reaction to afford **113a** in 83% yield. Synthesis of the naturally occurring alkaloid anhydrolycorin-7-one (**113c**)[55,56] was completed in 81% yield via basic hydrolysis of the ethyl ester followed by decarboxylation in presence of copper and quinoline.



Scheme 33. Synthesis of Lycorine

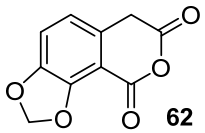
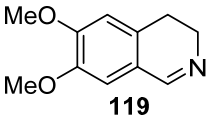
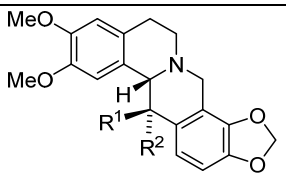
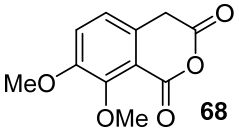
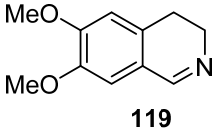
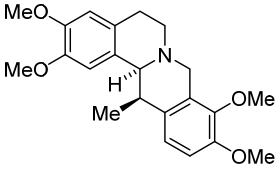
Cushman et al.[5] and Haimova et al.[6] independently carried out the cycloaddition reaction of dihydroisoquinoline **114** with 4,5-dimethoxyhomophtalic anhydride (**97**) to from

protoberberine alkaloids (Scheme 34). Mixture of both *anti*-**115** and *syn*-**116** diastereomers was obtained from cycloaddition reaction out of which *anti*-**115** precipitated as the major product (90% yield). The thermodynamically more stable *syn*-diastereomer **116** was also accessed via epimerization in >95:5 diastereoselectivity by refluxing the *anti*-diastereomer **115** in acetic acid. Thus obtained both the *anti*-**115** and *syn*-**116** were converted into *anti*- and *syn*-13-methyltetrahydroprotoberberine alkaloids **117** and **118** respectively by converting the carboxylic acid unit to a methyl group in four steps.



Scheme 34. Synthesis of Protoberberine Alkaloids

This approach was proved to be a general method for the synthesis of 13-methyltetrahydroprotoberberine family alkaloids. Synthesis of few members of this family have been summarised in Table 1.

 **62** Cushman et al. (1981)[57]	 **119**	 **120a**: (±)-Thalictrifoline (R^1 = Me, R^2 = H) **120b**: (±)-Cavidine (R^1 = H, R^2 = Me)
 **68** Cushman et al. (1978)[58]	 **119**	 (±)-Corydaline (**121**)

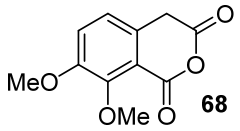
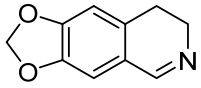
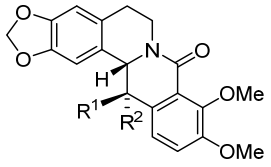
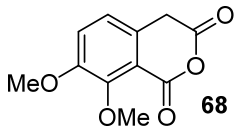
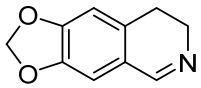
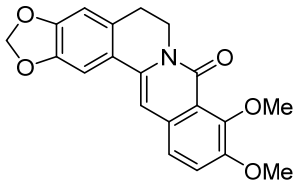
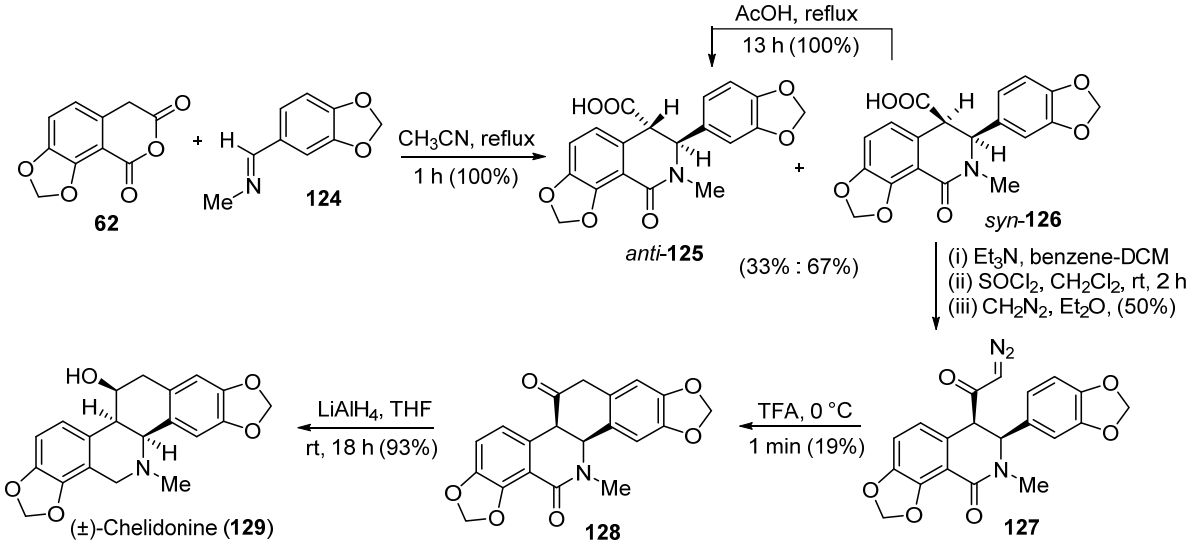
 Cushman et al. (1978)[31]	 **114**	 **122a**: (±)-Canadine ($R^1 = R^2 = H$) **122b**: (±)-Thalictricavine (R^1 = Me, R^2 = H)
 Cushman et al. (1978)[31]	 **114**	 Berlambine (**123**)

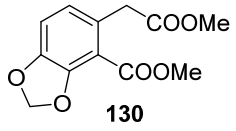
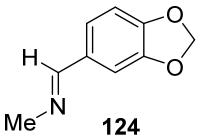
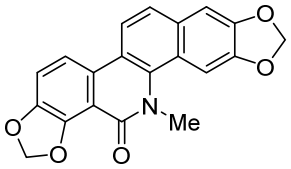
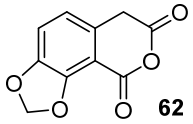
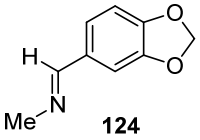
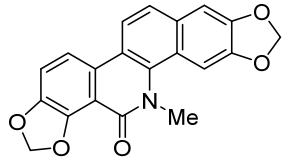
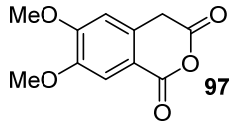
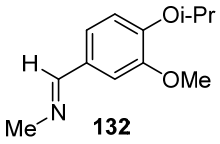
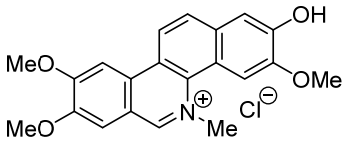
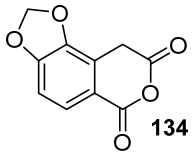
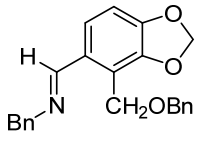
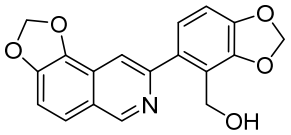
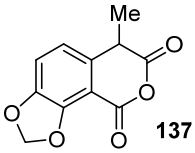
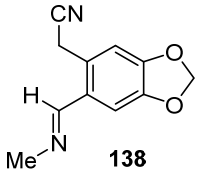
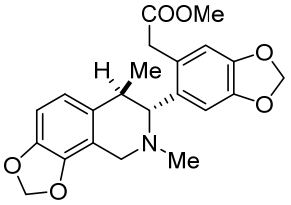
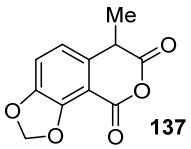
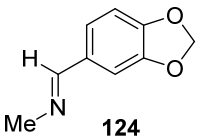
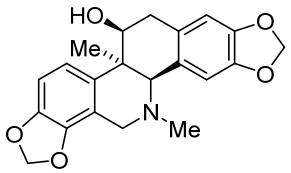
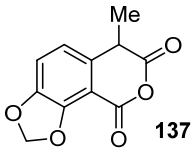
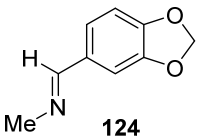
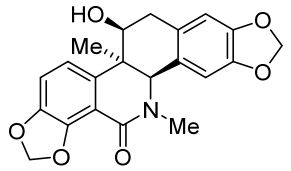
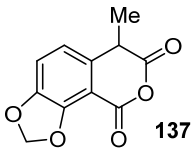
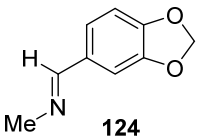
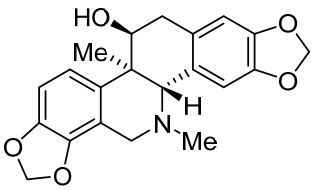
Table 1. Synthesis of Protoberberine Alkaloids by Using Imine Cycloaddition

Cushman and co-workers[36] synthesized (±)-chelidonine (**129**) by condensation of 3,4-methylenedioxyhomophthalic anhydride (**62**) and Schiff base **124** (Scheme 35).[30] This results into the formation of 33% *anti*-**125** and 67% *syn*-**126**. *Syn*-diastereomer **126** could be converted to *anti*-product **125** by refluxing in acetic acid. Acid chloride of *syn*-diastereomer **126** was converted to diazoketone **127**, which upon brief exposure to strong acid resulted in the formation of cyclic ketone **128** in 19% yield. Finally $LiAlH_4$ reduction of **128** furnished (±)-chelidonine (**129**) in 93% yield.



Scheme 35. Synthesis of (±)-Chelidonine

A few more alkaloids of benzophenanthridine and isoquinoline class were synthesized by cycloaddition of various substituted homophthalic anhydrides and imine, and are listed in Table 2.

 **130** Shamma et al. (1978)[26]	 **124**	 Oxysanguinarine (**131**)
 **62** Smidrkal et al. (1984)[59]	 **124**	 Oxysanguinarine (**131**)
 **97** Cushman et al. (1985)[60]	 **132**	 Fagaronine chloride (**133**)
 **134** Xu & co-workers (1998)[61]	 **135**	 Decumbenine B (**136**)
 **137** Cushman & co-workers (1984)[62]	 **138**	 Corydalic acid methyl ester (**139**)
 **137** Cushman & co-workers (1984)[63]	 **124**	 (±)-Corynoline (**140**)
 **137** Cushman & co-workers (1984)[63]	 **124**	 (±)-6-Oxocorynoline (**141**)
 **137** Cushman & co-workers (1984)[63]	 **124**	 (±)-Isocorynoline (**142**)

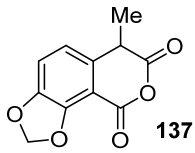
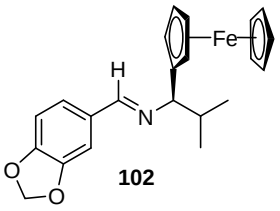
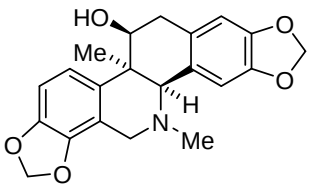
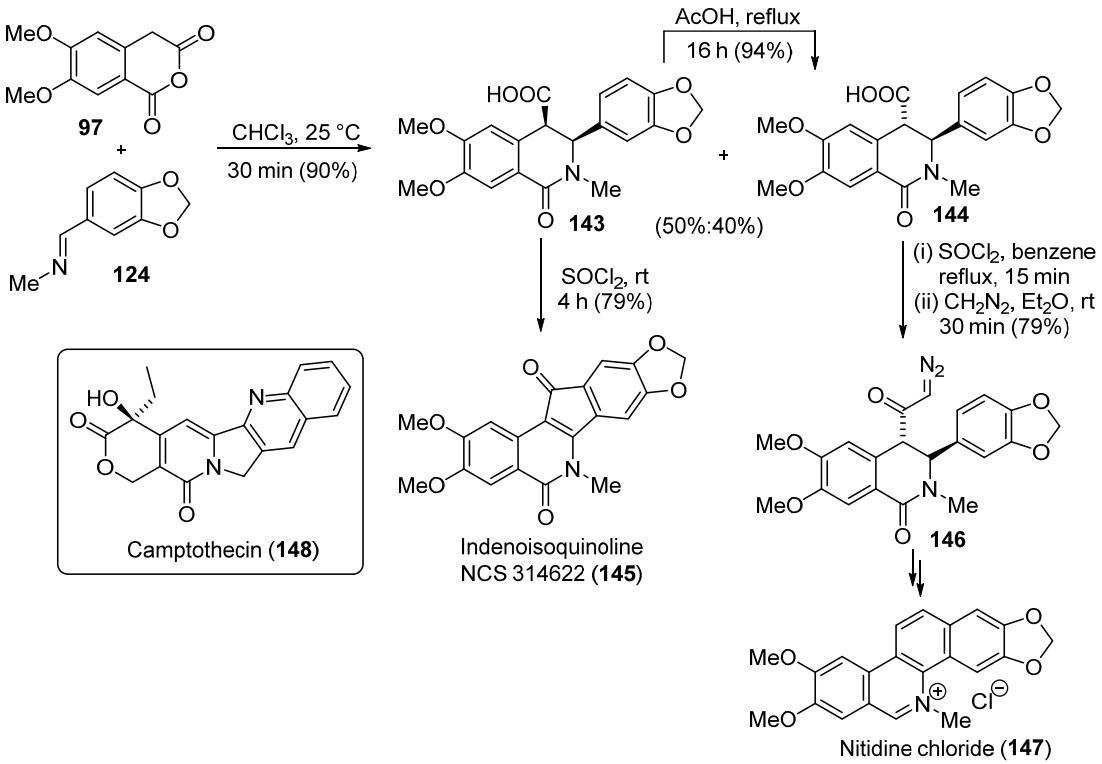
 **137**	 **102**	
Cushman & co-workers (1984)[64]		(+)-Corynoline (**140**)

Table 2. Synthesis of Benzo[*c*]phenanthridine Alkaloids by Using Imine Cycloaddition

Cushman & co-workers in 1978 reported the formation of indenoisoquinoline **145** from the *cis*-cycloadduct **143** (Scheme 35).[65] At the same time *trans*-cycloadduct **144** was transformed via diazo-compound **146** to nitidine chloride (**147**),[66] a potent hepatitis B virus inhibitor.[67] Twenty years later in 1998 during *in vitro* screening, author reported moderate cytotoxicity for indenoisoquinoline **145** parallel to camptothecin (**148**).[68] As camptothecins are the only class of topoisomerase I inhibitors approved for cancer treatment, indenoisoquinoline **145** showed certain advantages over camptothecin (**148**).[69]



Scheme 35. Synthesis of Indenoisoquinoline and Nitidine

Anthracycline antibiotics are a class of drugs used in cancer chemotherapy and are the most effective anticancer agents ever developed.[70] They are effective against different types of cancer than any other class of chemotherapy agents with proven clinical effectiveness against leukemias, lymphomas, breast carcinomas and sarcomas.[71] Still,

usefulness of these drugs was considerably limited due to their cardiotoxicity, acquired resistance and vomiting.

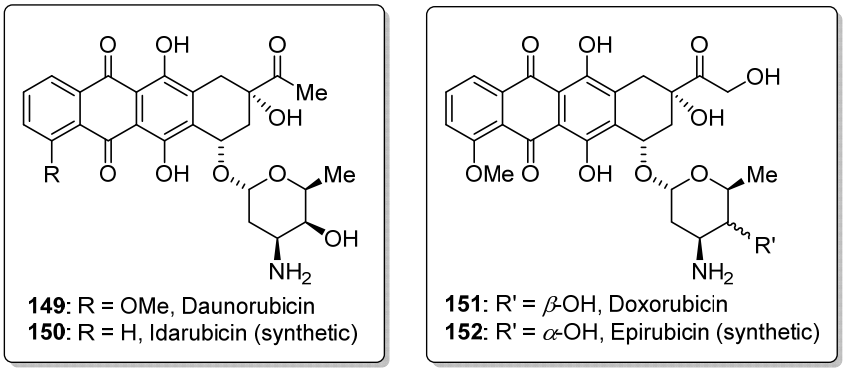
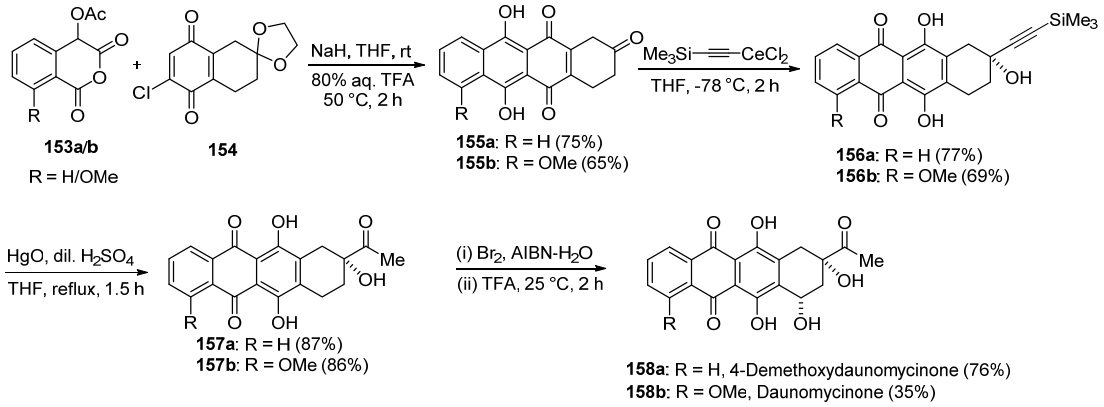


Figure 2. Anthracycline Antibiotic Drugs Currently in Clinical Practice

Tamura et al. completed the total synthesis of anthracycline antibiotics daunomycinone (**158b**) and 4-demethoxydaunomycinone (**158a**) via 'anionically mediated' Diels-Alder cycloaddition (Scheme 36).[72] The presence of a chlorine atom in quinone **154** controls the regiochemistry of the cycloaddition and facilitates aromatization of the formed cycloadducts via elimination of HCl. The Diels-Alder cycloaddition between enolate generated from homophthalic anhydride **153a/b** and chloroquinone **154** afforded the cycloadducts which were hydrolyzed with CF_3COOH to obtain cyclic ketone **155a/b** in 75 and 65% yields. Trimethylsilylethynylation of the tetracyclic ketones **155a/b** gave the trimethylsilylethynyl alcohols **156a/b** in 77 and 69% yields. The trimethylsilylethynyl group was transformed to methyl ketone using HgO in dil. H_2SO_4 to obtain hydroxyacetone compounds **157a/b** in 87 and 86% yields. The compounds **157a/b** were then converted to daunomycinone (**158b**) and 4-demethoxydaunomycinone (**158a**) in 76 and 35% yields.[73,74]



Scheme 36. Synthesis of Anthracycline Antibiotics

Quite a few anthracyclines and related natural and synthetic products have been synthesized by cycloaddition of homophthalic anhydrides and quinones. They are listed along with their respective anhydride and quinone precursors in Table 3.

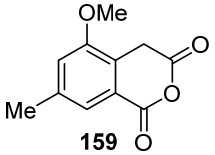
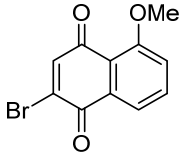
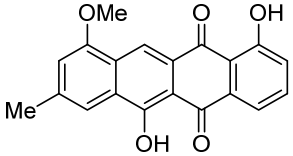
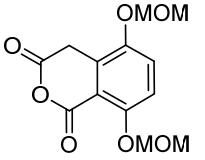
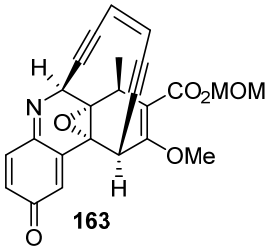
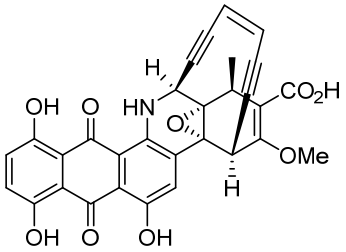
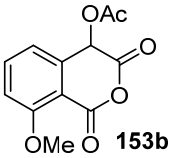
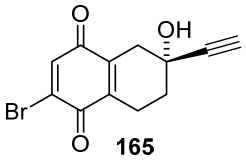
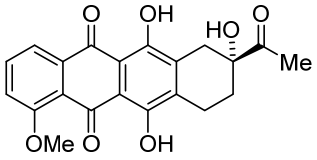
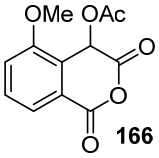
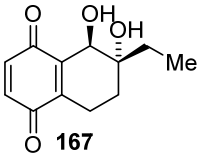
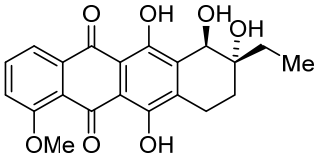
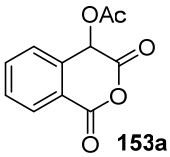
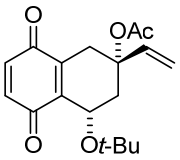
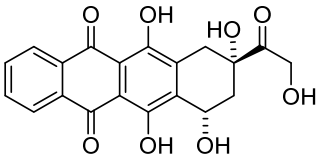
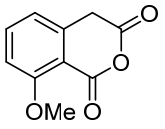
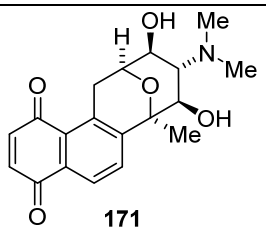
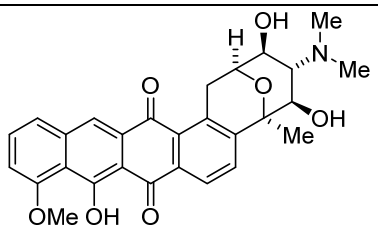
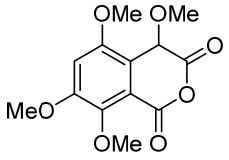
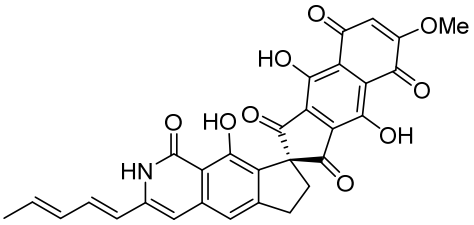
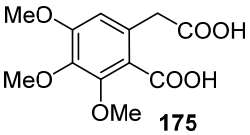
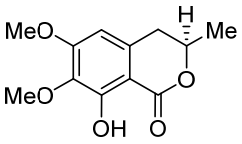
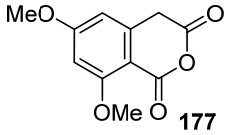
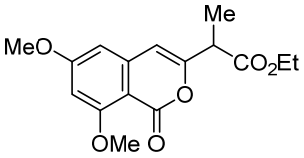
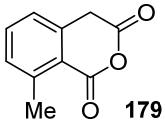
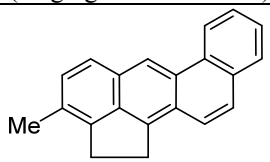
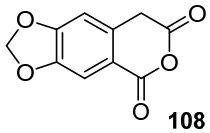
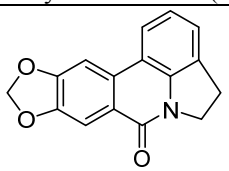
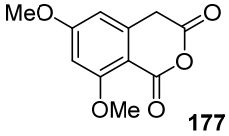
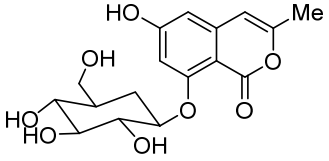
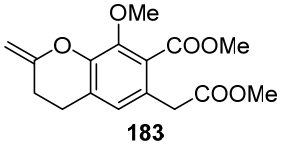
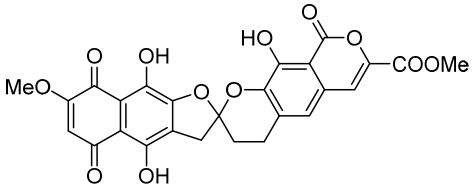
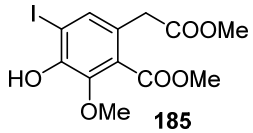
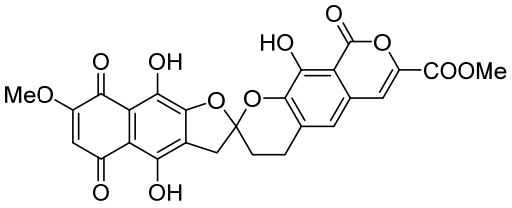
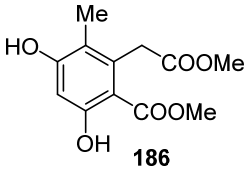
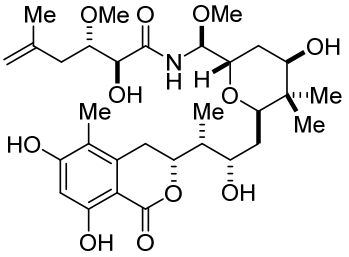
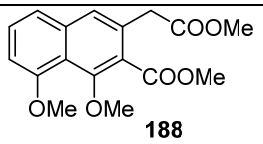
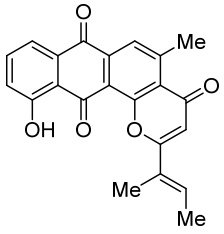
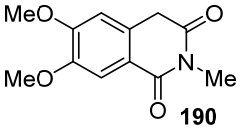
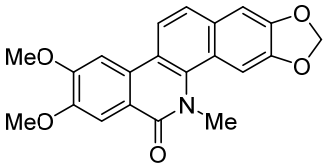
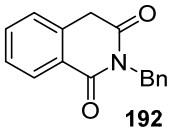
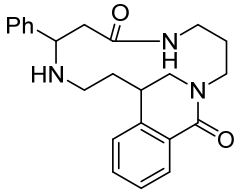
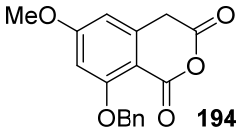
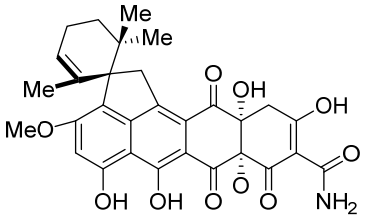
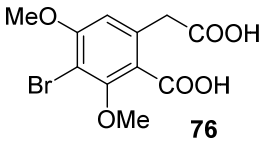
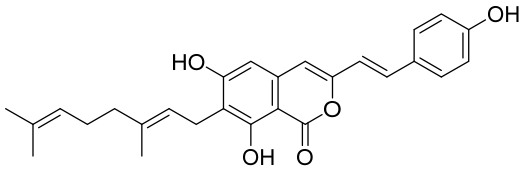
 **159** Tamura et al. (1986)[75]	 **160**	 SS-228R (**161**)
 **162** Danishefsky & co-workers (1996)[25]	 **163**	 Dynemicin A (**164**)
 **153b** Kita & co-workers (1985)[76]	 **165**	 (–)-7-Deoxydaunomycinone (**157b**)
 **166** Kita & co-workers (1989)[77]	 **167**	 (–)-γ-Rhodomycinone (**168**)
 **153a** Hottop et al. (2001)[78]	 **169**	 4-Demethoxyadriamycinone (**158a**)
 **170** Kawasaki et al. (1985)[79]	 **171**	 (+)-7-Methoxynogarene (**172**)

Table 3. Synthesis of Anthracycline Antibiotics and Related Natural Products

Few other natural products of different types have also been synthesized by using homophthalic anhydrides as the precursors (Table 4). Various novel strategies were used to synthesize these natural products as well as differently substituted homophthalic acids/anhydrides. This has not just provided the access to the complex natural products but the efforts towards these targets also served as the principle driving force for the

discovery of new chemistry. Fredericamycin A (**174**), γ-rubromycin (**184**) are the two complex spiro-cycles synthesized by using diester of homophthalic acid as the key precursors. Three different syntheses appeared recently for (+)-psymberin (**187**) starting from same precursor dimethyl homophthalate **186**. In few cases homophthalimides were used for the synthesis of natural products like oxynitidine (**191**) and isocyclocelabenzine (**193**) in which isocyclocelabenzine (**193**) is the 13-membered macrocycle. These natural products have been listed in table 4. along with the precursor homophthalic anhydrides.

 **173** Kita et al. (2001)[80]	 Fredericamycin A (**174**)
 **175** Saeed et al. (2005)[81]	 Kigelin (**176**)
 **177** Bauta et al. (2003)[82]	 NM-3 (**178**) (Angiogenesis inhibitor)
 **179** Koreeda & co-workers (1993)[83]	 3-Methylcholanthrene (**180**)
 **108** Castedo & co-workers (1996)[84]	 Lycorines (**181**)
 **177** Saeed et al. (2005)[85]	 Delphoside (**182**)
 **183** Kita & co-workers (2007)[86]	 γ-Rubromycin (**184**)

 **185** Brimble & co-workers (2009)[87]	 γ-Rubromycin (**184**)
 **186** Crimmins et al. (2009)[88] Smith & co-worker (2008)[89] Floreancig & co-worker (2005)[90]	 (+)-Psymberin (**187**)
 **188** McDonald & co-worker (2005)[91]	 Kidamycinone (**189**)
 **190** Parez et al. (1992)[92]	 Oxynitidine (**191**)
 **192** Iida et al. (1986)[93]	 Isocyclocelabenzine (**193**)
 **194** K. C. Nicolaou et al. (2014)[94]	 Viridicatumtoxin B (**195**)
 **76** Saeed et al. (2014)[32]	 Achlisocoumarins II (**196**)

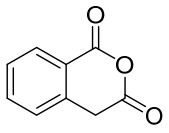
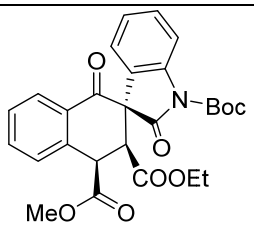
 **5** Connon et al. (2014)[95]	 Spirocompound (**197**)

Table 4. Different Types of Natural Products Synthesized from Homophthalic Anhydrides and Their Derivatives

Since many years, our research group is making considerable attempts for the synthesis of natural and synthetic products by using homophthalic anhydrides. To avoid repetition a brief summary has been provided in figure 3. The synthesis of isogusanlung D (**198**) and dehydroisogusanlung D (**199**) were completed earlier by taking the advantage of intramolecular radical induced cyclizations and Heck-coupling reaction, respectively.[96] Our group also achieved a noteworthy total synthesis of nuevamine (**200**) and Isonuevamine (**201**) by using the facile air-oxidation of homophthalimide.[97] The second application of air-oxidation propensity of homophthalimide was the stereoselective synthesis of (+)-isoindolo-*β*-carboline (**202**) with high enantiomeric excess.[98] Third application of the air-oxidation propensity was the five steps total synthesis of berberis natural products chilenine (**203**), deoxychilenine (**204**) and lennoxamine (**205**) in decent overall yields.[99]

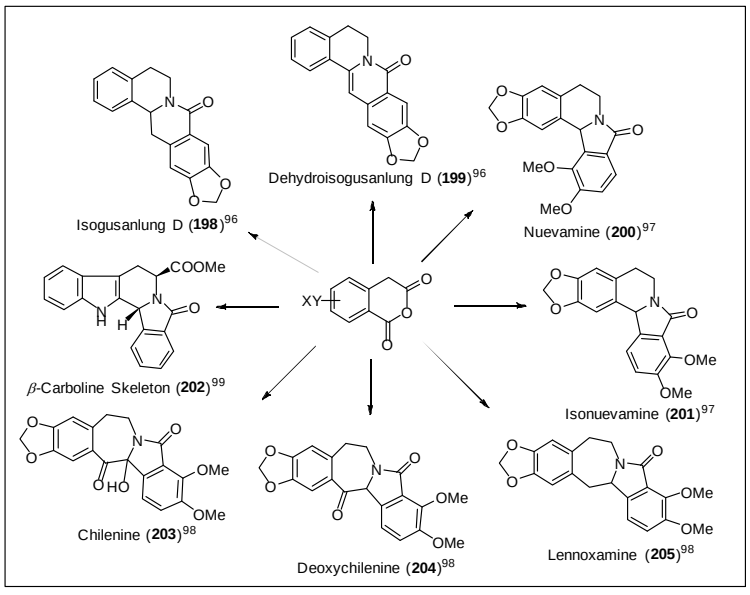


Figure 3. Natural Products Synthesized in our Group Using Homophthalic Anhydride

1.5 Summary

The above discussion reveals that homophthalic acid and its derivatives are a versatile synthons in organic synthesis. After first report in 1890, interest in their chemistry has grown consistently, particularly in the natural products synthesis. Due to the various reactive sites, this molecule has proven its efficacy through building the backbones of many structurally complex and medicinally important molecules in a convergent manner. Many bioactive indenoisoquinolines, anthracyclines and various members of isoquinoline family have been synthesized by the use of homophthalic anhydrides, few of them are in clinical practice and few are in development stages. This ascertains the utility of homophthalic anhydrides and their derivatives in the organic synthesis and medicinal chemistry.

Our research group is using cyclic anhydrides as the starting materials for the natural product synthesis from many years. This research work is mainly in context with the synthesis of various natural products using the homophthalic acid and its derivatives as the starting material. Further in next chapter, our synthetic studies towards isoquinoline alkaloids starting from homophthalic acid and derivatives have been presented. We have been successful in the total synthesis of oxyavcine, arnottin I, doryanine, oxyhydrastinine, laudanosine, romneine, dicentrine, glaucine, isolaudanosine and isoromneine by alkylation of homophthalates. We have also successfully completed the formal synthesis of avicine, (-)-arnottin-II. These studies have been discussed in details in chapter 2.

1.6 References

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Chapter 2

Section A

Total Synthesis of Oxyavicine and the Formal Synthesis of Avicine

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

2A.1 Background

Among the isoquinoline alkaloids, benzo[*c*]phenanthridine alkaloids contain a tetracyclic core with different substitution patterns in rings A and D (Figure 1).[1] Benzo[*c*]phenanthridine alkaloids have been considered to be biosynthesized from the corresponding protoberberine alkaloids presumably via a 3-arylisoquinoline intermediates.[2] The first reported isolation of benzophenanthridine alkaloids, albeit in impure form, date back to the first half of the 19th century.[3] Since then several other benzophenanthridine alkaloids have been isolated from plants and today large number of naturally occurring compounds of this type are known in the literature.[1] It should be pointed out that most of the benzophenanthridine alkaloids are found within three plant families only, namely the *Papaveraceae*, *Fumariaceae* and *Rutaceae*.

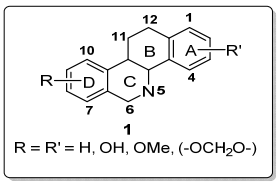
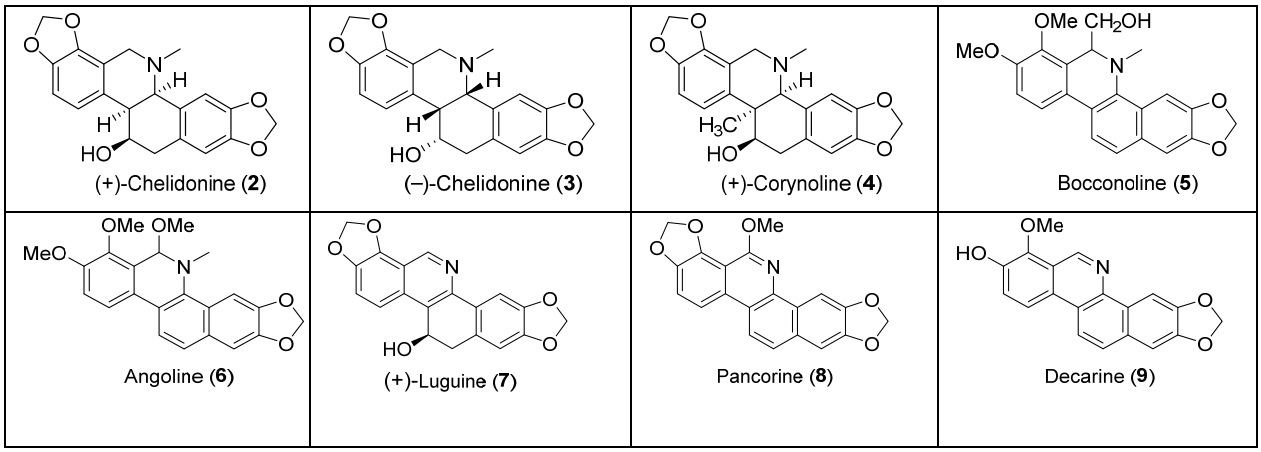


Figure 1. Benzo[*c*]phenanthridine skeleton

Some members of the benzophenanthridines and their derivatives have been studied extensively for their nematocidal, antitumor and cytotoxic activities (Table 1).[4-6] Oxynitidine (**24**) and fagaronine (**26**) exhibit antileukemic activity.[6] Sanguinarine (**15**) as a contaminant in cooking oil, has been implicated in outbreaks of heart disease, glaucoma, cancer and other illnesses in the Indian population.[7,8] One of the important traditional drug in both China and Japan was from rhizomes of *Coptis spp*.; oxysanguinarine was one of the constituents in the drug. Oxyavicne (**25**) is also used to treat ophthalmic disorders.[9] In addition, it exhibits analgesic and anti-inflammatory effects.[10] Oxynitidine (**24**) exhibits potent inhibitory activity towards the hepatitis B virus.[11]



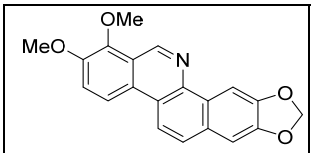
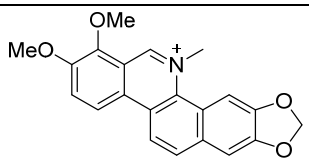
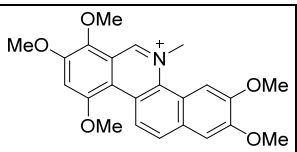
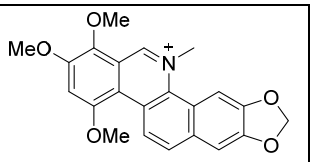
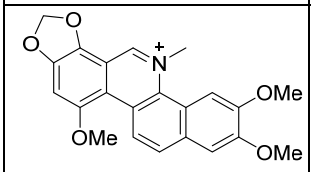
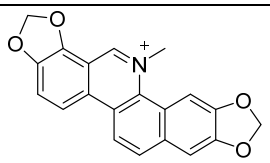
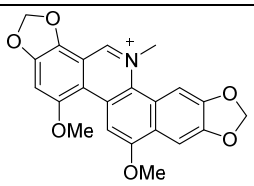
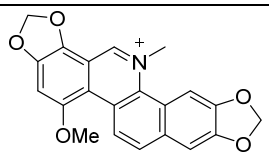
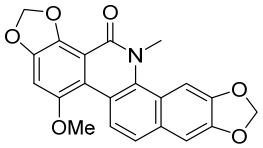
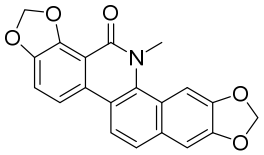
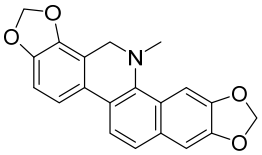
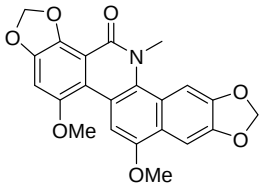
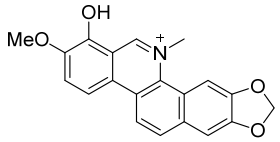
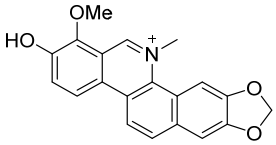
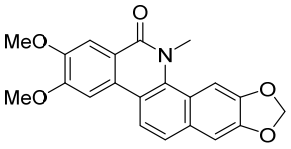
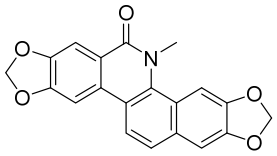
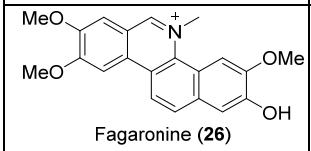
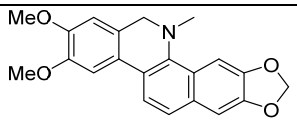
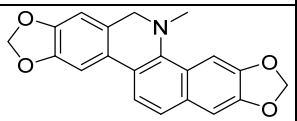
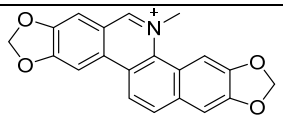
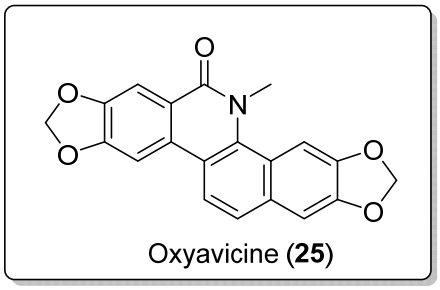
 Norchelerythrine (**10**)	 Chelerythrine (**11**)	 Sanguilutine (**12**)	 Chelilutine (**13**)
 Sanguirubine (**14**)	 Sanguinarine (**15**)	 Macarpine (**16**)	 Chelirubine (**17**)
 Oxychelirubine (**18**)	 Oxysanguinarine (**19**)	 Dihydrosanguinarine (**20**)	 Oxymacarpine (**21**)
 Fagaridine (**22**)	 *N*-Methyldecarine (**23**)	 Oxynitidine (**24**)	 Oxyavicine (**25**)
 Fagaronine (**26**)	 Dihydronitidine (**27**)	 Dihydroxyavicine (**28**)	 Avicine (**29**)

Table 1. Some of the Selected Benzo[*c*]phenethridine Alkaloids

Till date there are numerous reports on synthesis of benzo[*c*]phenanthridine alkaloids in literature and development of new synthetic approach to these alkaloids is a challenging task. Robinson–Bailey synthesis[12] and enamide photocyclization[13] methods as key steps were reported for the total synthesis of benzo[*c*]phenanthridine alkaloids by Bailey et al. and Ninomiya et al. Diels–Alder cycloaddition reactions with arynes by using pyrrolinediones and α-pyrones as aza diene equivalents are known for the same.[14] Condensation of the homophthalic ester[15] with Schiff base and 3,4-(methylenedioxy)homophthalic anhydride[16] reaction with Schiff base in benzene solution followed by diazo ketone cyclization were devised for the total synthesis of benzophenanthridines, but most of these syntheses require crucial starting materials.[17] Clark described the synthesis of oxynitidine by a cycloaddition reaction of lithiated

toluamide with imine.[18] Cho et al. reported syntheses[19-20] of oxyavicine, oxynitidine and oxysanguinarine from benzonitriles derived from *o*-bromobenzaldehyde. Cheng et al. reported protecting group free synthesis of these alkaloids by nickel catalyzed annulations of *o*-halobenzaldimine and alkyene.[2]

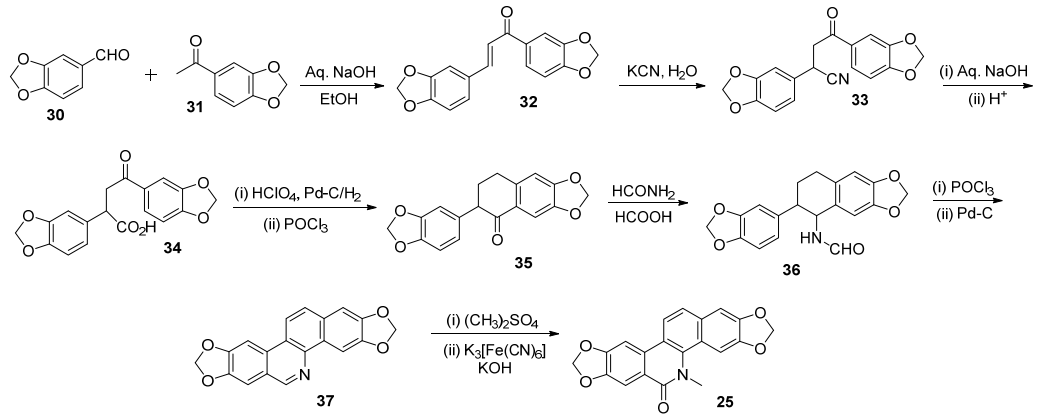


Oxyavicine (**25**)

Out of these very large number of bioactive benzo[*c*]phenanthridine alkaloids, we choose oxyavicine as our target molecule because of its potent biological activities. Oxyavicine is known to exhibit analgesic and anti-inflammatory activity,[9] and it is also useful for the treatment of ophthalmic disorders.[10] Oxyavicine has been isolated from *Zanthoxylum avicennae*, *Broussonetia papyrifera* and *Zanthoxylum nitidum* plant species.[9,10,21] Oxyavicine has been synthesized by several research groups utilizing an array of elegant synthetic methodologies, till now total eleven syntheses are known in the literature.

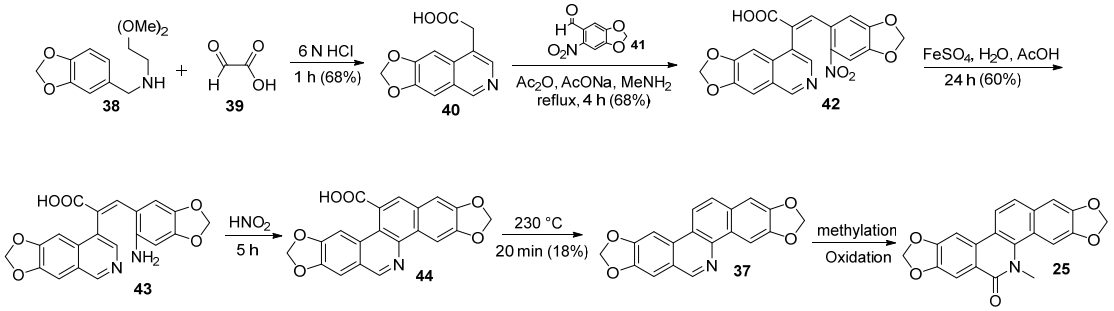
2A.2 Reported Synthetic Approaches Towards Oxyavicine

First synthesis of oxyavicine was reported by Gopinath et al.[22] in 1961 (Scheme 1), they not only synthesized oxyavicine but also corrected the earlier structure as proposed by Arthur et al.[21] They have condensed piperonal (**30**) with acetopiperone (**31**) to obtain *bis*-methylenedioxychalkone **32**. Addition of hydrogen cyanide gave the nitrile **33** which was hydrolyzed to the corresponding keto-acid **34**. Reduction with hydrogen and palladium-charcoal in the presence of perchloric acid formed the substituted *n*-butyric acid which was cyclized with phosphorus oxychloride to obtain tetralone **35**. Leuckart reaction on this afforded the formamido derivative **36**, this formamide was cyclized with phosphorus oxychloride in toluene and then dehydrogenated to the benzophenanthridine **37**. The methosulphate of this base, on oxidation with alkaline potassium ferricyanide provided oxyavicine (**25**).



Scheme 1. First Synthesis of Oxyavicine (yields not mentioned)

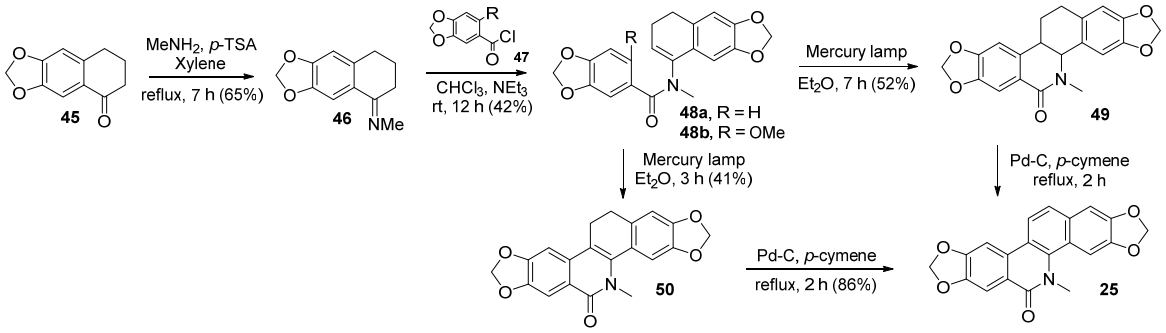
Moon et al. in 1967 reported the following synthesis of oxyavicine (Scheme 2).[23] The reaction of the aminoacetal **38** with glyoxylic acid (**39**) in HCl solution gave the 4-isoquinolylacetic acid **40** in 68% yield. Condensation of compound **40** with 6-nitropiperonal (**41**) furnished the styrene **42**, which was reduced with ammoniacal ferrous sulphate to amine **43** in 60% yield. Ring-closure of amine **43** essentially as described by Abramovitch and Tertzakian[24] gave cyclized product **44**, which was directly decarboxylated at 230 °C to 2,3,8,9-*bis*-methylenedioxybenzo[*c*]phenanthridine (**37**). The overall yield of **37** from piperonal was only 5%. Finally *N*-methylation of **37**, followed by oxidation yielded oxyavicine (**25**).



Scheme 2. Synthesis of Oxyavicine by Using Aminoacetal

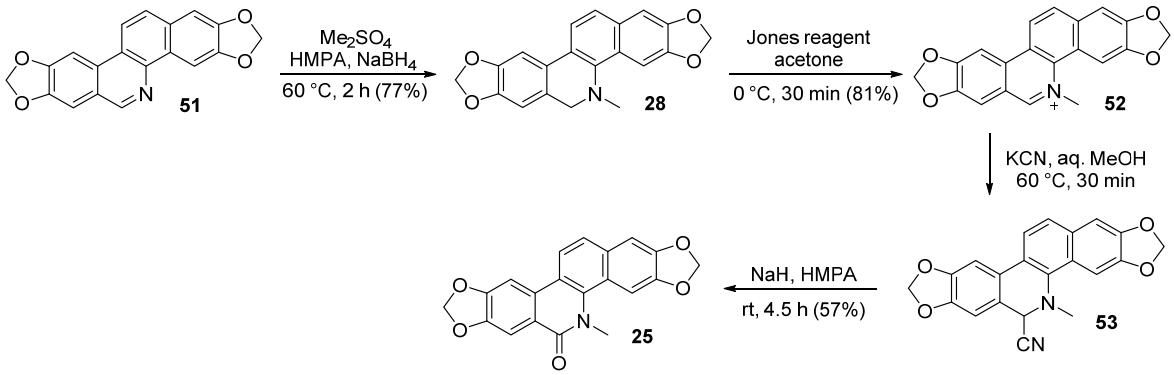
Ninomiya et al. in 1975 reported the synthesis of oxyavicine (Scheme 3),[13] starting from the imine **46**, which was obtained from the tetralone **45** and methylamine in 65% yield. The imine **46** was readily acylated with 3,4-methylenedioxybenzoyl chloride and 2-methoxy-4,5-methylenedioxybenzoyl chloride to afford the enamides **48a** and **48b** in good yields. Irradiation of methanolic solution of the enamide **48a** with a low pressure mercury lamp for 7 h afforded the lactam **49** in 52% yield. This photoproduct was dehydrogenated by heating with 30% palladium-charcoal in *p*-cymene. However the yield was too low for preparative purposes. Then the regiospecific photocyclization to the

didehydrolactam **50** by employing the enamide **48b** was performed,[25] which has an additional *ortho*-methoxy group to afford the didehydro-lactam **50** in 41% yield. Dehydrogenation of lactam **50** proceeded smoothly to afford oxyavicine (**25**) in 86% yield.



Scheme 3. Synthesis of Oxyavicine by Enamide Photocyclization

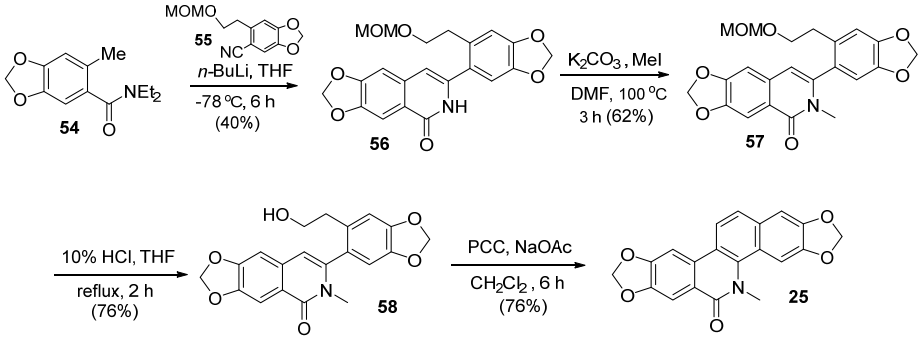
Ishii et al. in 1984 reported the synthesis of oxyavicine from its norbase **51** (Scheme 4).[26] Treatment of a mixture of noroxyavicine (**51**) and dimethyl sulphate in HMPA with sodium borohydride afforded dihydroxyavicine (**28**) in 77% yield. The formed dihydroxyavicine (**28**) was readily converted to its corresponding quaternary benzo[*c*]phenanthridine alkaloid **52** by oxidation with Jones reagent in 81% yield. This quaternary alkaloid **52** was converted to its corresponding cyanide **53** by reacting with KCN in aqueous methanol. In the course of their studies they aimed the preparation of a carbanion on cyano compound **53**, they found that the carbanion readily underwent air-oxidation to deliver oxyavicine (**25**) in 57% yield.



Scheme 4. Synthesis of Oxyavicine by Using Norbase

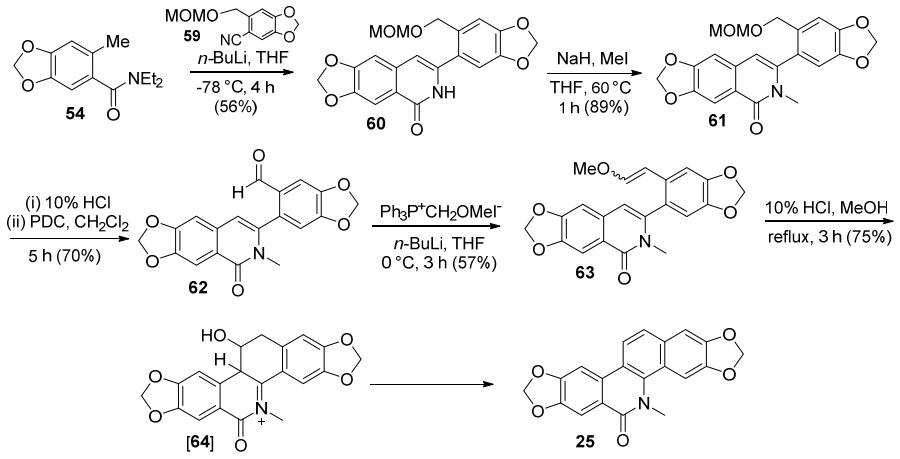
Won-Jea Cho et al. in 2004 reported the synthesis of oxyavicine (Scheme 5).[19] The strategy used by them was based on the synthesis of 3-arylisoquinolinone, which is a crucial intermediate in the formation of C ring of benzo[*c*]phenanthridines. *N,N*-Diethyl-*o*-toluamide **54** was deprotonated with *n*-butyllithium to form the anion, which was treated with benzonitrile **55** at –78 °C in THF to afford the 3-arylisoquinoline-1(2*H*)-one

56 in 40% yield. MOM-protected alcohol **56** was treated with MeI/K_2CO_3 to provide the *N*-methylated product **57** with 62% yield. The deprotection of MOM-group with 10% HCl gave the alcohol **58** in 76% yield. The alcohol was then oxidized with PCC/NaOAc[27] to provide the desired benzo[*c*]-phenanthridine alkaloid oxyavicine (**25**) in 76% yield as portrayed in Scheme 5.



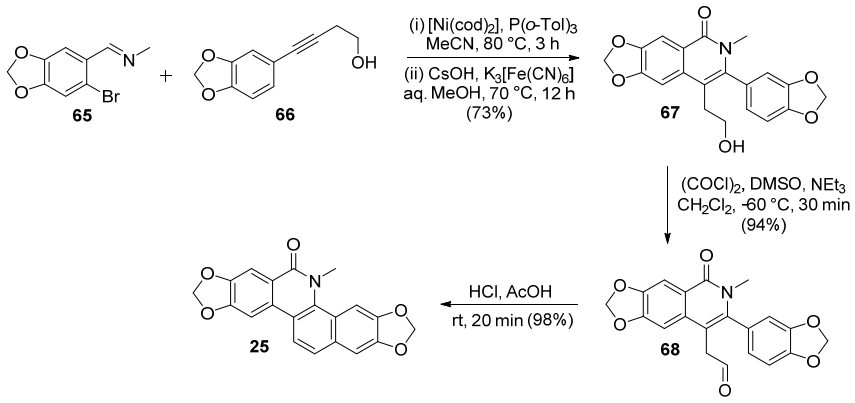
Scheme 5. Synthesis of Oxyavicine by Using Oxidative Cyclization

Won-Jea Cho et al. in 2006 reported one more synthesis of oxyavicine (Scheme 6).[28] For the synthesis of oxyavicine, the substituted *N*,*N*-diethyl *o*-toluamide **54**[19] was deprotonated with *n*-BuLi and then treated with benzonitrile **59**. The cycloaddition reaction between *N*,*N*-diethyl toluamides **54** and MOM-protected benzonitrile **59** produced 3-arylisoquinolinones **60** in 56% yield, which was then treated with MeI in the presence of 60% NaH to form *N*-methylated compound **61**. The MOM group was removed by refluxing in 10% HCl and the obtained alcohol was oxidized with PDC to afford aldehyde **62** in 70% yield. Wittig reaction was carried out with the aldehyde **62** to yield mixture of *cis*/*trans* isomers. Without separating the *cis/trans* mixture of **63**, it was hydrolyzed with 10% HCl to give natural benzo[*c*]phenanthridine alkaloid oxyavicine (**25**) in 75% yield.



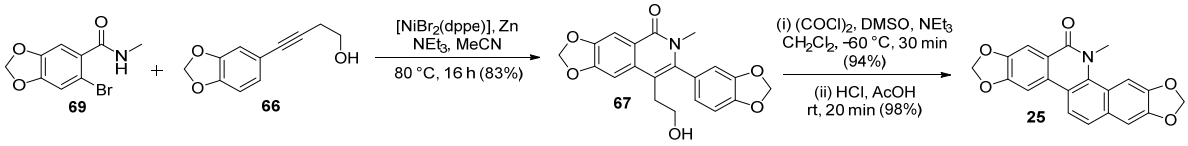
Scheme 6. Synthesis of Oxyavicine by Using Wittig Reaction

Chien-Hong Cheng in 2010 reported the total synthesis of oxyavicine by using the nickel-catalysis methodology (Scheme 7).[2] The required imine **65** was synthesized from commercially available 2-bromopiperonal and methylamine. The $[Ni(cod)_2]/P(o\text{-}Tol)_3$ catalyzed annulation of imine **65** with alkyne **66** and subsequent nucleophilic addition and oxidation procedure gave amide **67** in 73% yield. Then this intermediate was converted to the corresponding aldehyde **68** by Swern oxidation in 94% yield. After a successful acid-catalyzed ring-closing and dehydration reaction the oxyavicine (**25**) was obtained in 98% yield.



Scheme 7. Synthesis of Oxyavicine by Using Nickel Catalyst

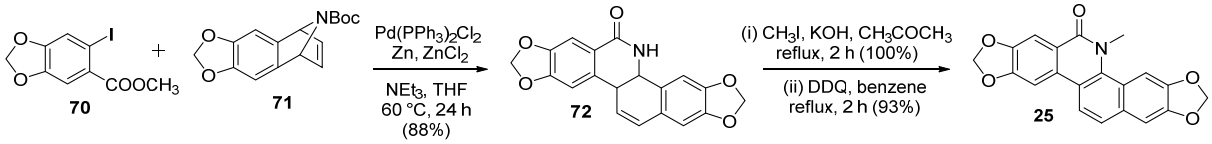
Chien-Hong Cheng in 2010 reported one more total synthesis of oxyavicine by using the same nickel-catalysis methodology (Scheme 8).[29] The reaction of benzamide **69** with alkyne **66** in the presence of $[Ni(dppe)Br_2]$, zinc and Et_3N in acetonitrile at 80 °C for 16 h provided the same isoquinolone derivative **67** in 83% yield in a highly regioselective manner. Other steps used for the synthesis of oxyavicine (**25**) were same as described in earlier Scheme 7.



Scheme 8. Synthesis of Oxyavicine via Intramolecular Cyclization

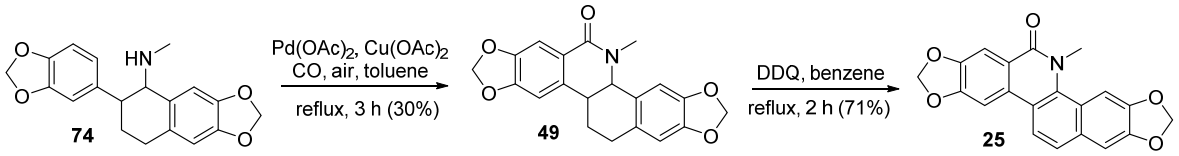
Xiaohua Xu et al. in 2011 reported the total synthesis of oxyavicine by using palladium-catalyzed cyclization (Scheme 9).[30] Under the optimized conditions, the palladium-catalyzed tandem coupling–cyclization of functionalized *o*-iodobenzoate **70** with azabicycle **71** was done to achieve dihydro benzo[*c*]phenanthridinone **72** in 88% yield. For *N*-methylation, treatment of dihydrobenzo[*c*]phenanthridinone **72** with iodomethane and potassium hydroxide in acetone was used to afford the corresponding *N*-methylated

product **73** in quantitative yield. Oxidation of *N*-methylated product with DDQ in benzene was successfully carried out to form oxyavicine (**25**) in 93% yield.



Scheme 9. Synthesis of Oxyavicine by Using Palladium Induced Coupling

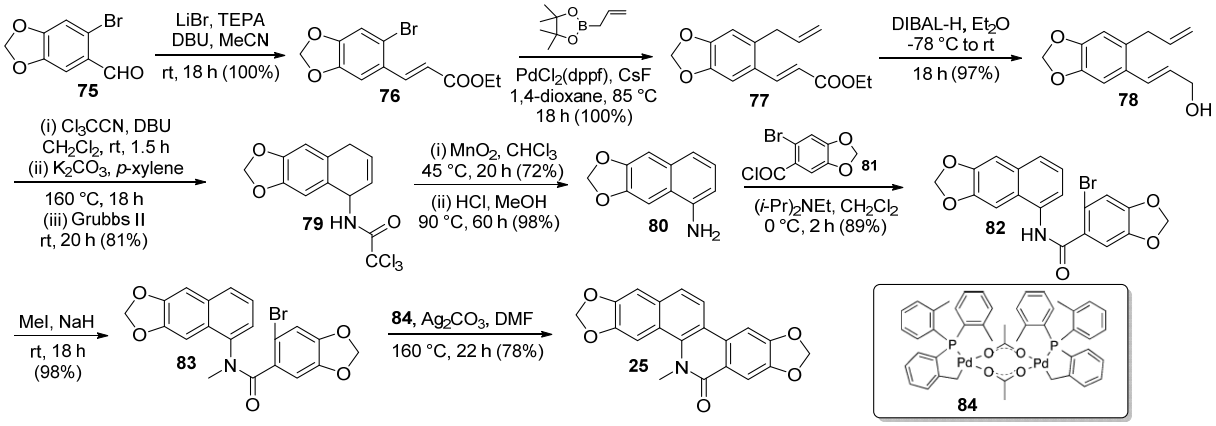
Kazuhiko Orito et al. reported the $Pd(OAc)_2$-induced carbonylation of alkoxy-substituted 1-amino-2-aryltetraline **74** to provide the benzo[*c*]phenanthridine ring system (Scheme 10).[31] Tetrahydronaphthyl amine **74** was prepared following the procedure developed by Ishii and Ishikawa.[32] The direct carbonylation of **74** with a stoichiometric amount of $Pd(OAc)_2$ and $Cu(OAc)_2$ was carried out under CO atmosphere in refluxing toluene to produce lactam **49** in 30% yield. Dehydrogenation of lactam **49** with DDQ (in refluxing benzene) gave oxyavicine (**25**) in 71% yield.



Scheme 10. Synthesis of Oxyavicine by Using Carbonylation

Recently, Andrew Sutherland et al. reported the total synthesis of oxyavicine by using the intramolecular biaryl Heck coupling reaction (Scheme 11).[33] The aldehyde moiety in compound **75** was initially converted to the more stable (*E*)-*α*,*β*-unsaturated ester **76** using HWE reaction with triethylphosphonoacetate (TEPA) in ~100% yield. The use of a Suzuki−Miyaura reaction with allylboronic acid pinacol ester and $PdCl_2$(dppf) as a catalyst gave allylated product **77** in quantitative yield.[34] DIBAL-H reduction of ester **77** afforded the (*E*)-(2-allyl)-cinnamyl alcohol **78** in 97% yield. Cinnamyl alcohol **78** was converted to the corresponding allylic trichloroacetimidate using trichloroacetonitrile and catalytic amount of DBU and without purification it was subjected to a thermally mediated Overman rearrangement at 160 °C.[35] Grubbs first generation catalyst was initially used for the RCM step.[36] However for the complete conversion, Grubbs second generation catalyst was used for one-pot process to yield 1,4-dihydronaphthalene **79** with overall 81% yield in 3 steps. For conversion of **79** to the corresponding naphthalene, manganese dioxide was used, which on acid catalyzed hydrolysis of trichloroacetamide gave the corresponding amine **80** in 98% yield. The coupling of resulting amine **80** with

2-bromobenzoyl chloride **81** under standard conditions gave the bromo-amide **82** with 89% yield. Methylation with iodomethane and sodium hydride gave the penultimate compound **83** in excellent (98%) yield.



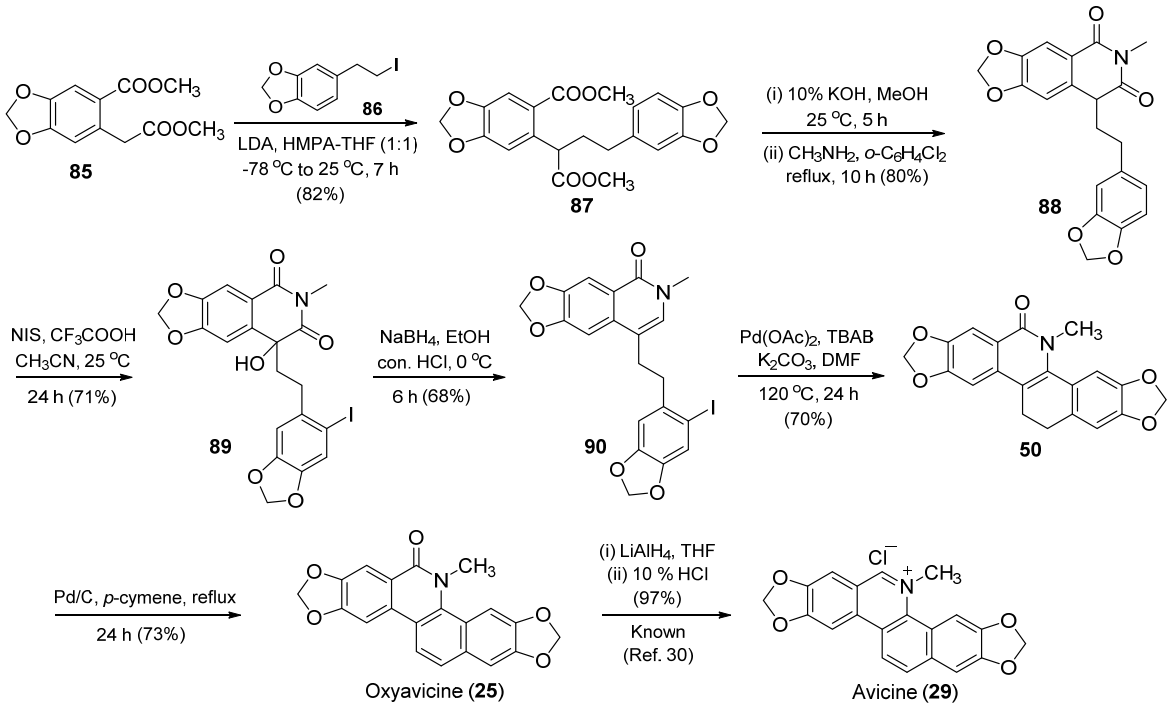
Scheme 11. Synthesis of Oxyavicine by Heck Coupling

To develop a more general and efficient intramolecular biaryl Heck reaction for the synthesis of the oxybenzo[*c*]phenanthridine alkaloids using aryl bromide precursor, the high temperature and more stable palladium catalyst was required. The Hermann−Beller palladacycle **84** is well-known for its reactivity at high temperatures.[37,38] This was essential for the slow release of active Pd(0) during the course of reaction, which prevents deactivation processes.[39] Palladacycle **84** was used for intramolecular Heck coupling of aryl bromide **83**. Using 10 mol % loading of catalyst in the presence of silver carbonate at 160 °C, conversion was complete after 22 h to give oxyavicine (**25**) in 78% yield.

2A.3 Rationale for Present Work

As discussed above oxyavicine has been synthesized by several research groups utilizing an array of elegant synthetic methodologies. In continuance with our cyclic anhydrides/imides to bioactive natural products aspire; we reasoned that the homophthalimides would be the potential building block for the synthesis of benzophenanthridine class of alkaloids.[40] In this context we described our results on the synthesis of oxyavicine (Scheme 12). The methyl 6-(2-methoxy-2-oxoethyl)benzo[*d*][1,3]dioxole-5-carboxylate (**85**)[41] on base catalyzed alkylation with 5-(2-iodoethyl)benzo[*d*][1,3]dioxole (**86**)[42] exclusively furnished the desired mono-alkylated coupling product **87** in 82% yield.[43] The potassium hydroxide induced hydrolysis of diester **87** to the corresponding dicarboxylic acid followed by the formation

of corresponding salt with methylamine and the thermal intramolecular dehydrative cyclization in refluxing *o*-dichlorobenzene provided the *N*-methylhomophthalimide **88** in 80% yield. At this stage we planned to introduce the iodine at an appropriate position in an aryl part of an alkyl unit in imide **88** for the Heck coupling reaction.[44] We avoided the direct coupling of diester **85** with the corresponding *o*-iododerivative of compound **86**, foreseeing the plausibility of formation of an undesired aryne intermediate. The selective electrophilic iodination of the activated aryl moiety in compound **88** using *N*-iodosuccinimide (NIS, 1.10 equiv) in the presence of catalytic amount of trifluoroacetic acid yielded the required iodo-compound **89** in 71% yield along with an in situ introduction of tertiary hydroxyl group at the activated methine position of the homophthalimide unit.



Scheme 12. Convergent Access to Oxyavicine via an Intramolecular Heck Coupling

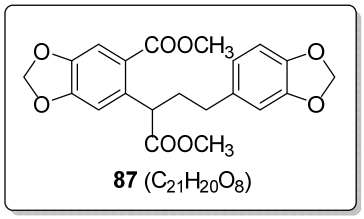
The activated methine/methylene positions of the homophthalimides are known to be prone for the facile air-oxidations and respectively form the corresponding tertiary alcohols/ketones.[45] In the above specified iodination of compound **88** to imide **89**, an air-oxidation of the methine carbon also took place simultaneously to yield the hydroxylated iodo-compound. The presence of tertiary hydroxyl unit in compound **89** was confirmed on the basis of IR (stretching frequency at 3460 cm^{-1}), ^1H NMR (broad singlet at δ 3.92), ^{13}C NMR (quaternary carbon at 74.6 ppm) and mass spectral data ($M+Na^+$ peak at 532). At this stage the $NaBH_4$ reduction of compound **89** was studied in detail to obtain the desired lactam **90**. The regioselective $NaBH_4$ reduction of the more reactive unconjugated

carbonyl group of the homophthlimide **89** followed by the acid-catalyzed dehydration took place in one-pot to provide the desired pivotal building block **90** in 68% yield. An intramolecular palladium-catalyzed Heck coupling reaction of the thus formed unsaturated lactam **90** under the standard set of reaction conditions delivered the desired oxyavicine architecture **50** in 70% yield. Finally, the palladium on charcoal induced dehydrogenation of compound **50** in refluxing *p*-cymene furnished the natural product oxyavicine (**25**) in 73% yield.[13] The oxyavicine was obtained in six steps with 16% overall yield and the analytical and spectral data obtained for the synthesized natural product were in complete agreement with the reported data. The conversion of oxyavicine (**25**) to the avicine (**29**) with 97% efficiency is known in the literature.[30]

2A.4 Summary

Highly potent biological activities of benzophenanthridine alkaloids make them a imperative class of drugs. In benzo[*c*]phenanthridine alkaloids oxyavicine has its own significance due to its potent bioactivities along with its simple configuration. As seen various research groups have synthesized oxyavicine by different strategies. In summary, we have accomplished the convergent synthesis of oxyavicine from the economically available homophthalate and utilizing the regiospecific makeup of homophthalimide. The construction of ring B and C utilizing an intramolecular Heck-coupling reaction was the key step. We feel that our present approach is general in nature and will be useful to design several naturally occurring benzophenanthridine alkaloids, their unnatural derivatives and congeners for SAR studies.

2A.5 Experimental Section

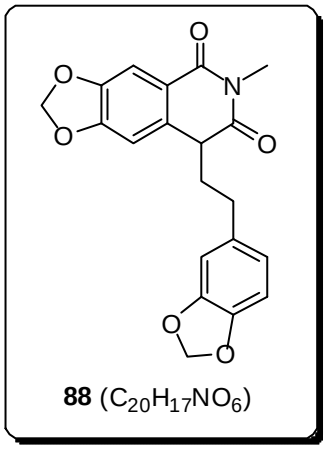


87 ($C_{21}H_{20}O_8$)

Methyl 6-(4-(benzo[*d*][1,3]dioxol-5-yl]-1-methoxy-1-oxobutan-2-yl)benzo[*d*][1,3]dioxole-5-carboxylate (87). A freshly prepared solution of LDA from diisopropylamine (1.67 mL, 12.00 mmol) and *n*-BuLi (1.60 M in hexane, 8.12 mL, 13.00 mmol) in THF (5 mL) under argon atmosphere at 0 °C was added to solution of compound **85** (2.52 g, 10.00 mmol) in THF (15 mL) plus HMPA (15 mL) mixture at –78 °C under argon atmosphere and the reaction mixture was further stirred at same temperature for 30 min. To the above reaction mixture was added solution of compound **86** (3.04 g, 11.00 mmol) in THF (5

mL) in a dropwise fashion. The reaction mixture was allowed to gradually attain the room temperature in 7 h. The reaction was quenched with saturated NH_4Cl solution. The solvent was removed in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL), washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 25% ethyl acetate/petroleum ether as an eluent gave pure product **87** as a thick oil (3.28 g, 82%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.90–2.10 (m, 1H), 2.25–2.60 (m, 3H), 3.66 (s, 3H), 3.84 (s, 3H), 4.75 (t, J = 8 Hz, 1H), 5.91 (s, 2H), 6.02 (d, J = 2 Hz, 2H), 6.53–6.75 (m, 3H), 6.91 (s, 1H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.4, 35.5, 45.9, 52.0 (2 carbons), 100.7, 101.9, 108.0, 108.4, 108.8, 110.4, 121.1, 123.0, 135.3, 136.6, 145.6, 146.4, 147.5, 150.9, 167.0, 174.4; ESIMS (*m*/*z*) 423 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{20}O_8$ $[M]^+$ 368.1134, found 368.1125; IR ($CHCl_3$) ν_{max} 1716, 1666, 1620 cm^{-1}. Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.03. Found: C, 62.82; H, 4.77.

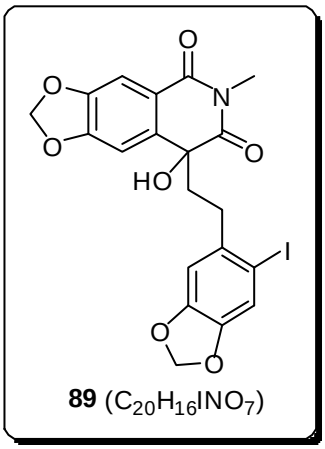
8-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-6-methyl-[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione (88). The compound **87** (2.80 g, 7.00 mmol) was added to a stirred solution of 10% KOH (25 mL) plus MeOH (25 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and further stirred for 12 h and then it was acidified with 2 N HCl. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL), washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and to the obtained residue was added 40% aqueous solution of methyl amine (3 mL) and it was stirred for 5 min. The above reaction mixture was again concentrated in vacuo and dried. To the obtained salt was added *o*-dichlorobenzene (20 mL) and it was refluxed for 10 h. The mixture was allowed to cool to room temperature. The direct silica gel column chromatographic purification of the resulting solution using 25% ethyl acetate/petroleum ether as an eluent gave pure product **88** as a yellow thick oil (2.05 g, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13–2.25 (m, 1H), 2.31–2.43 (m, 2H), 2.43–2.53 (m, 1H), 3.29 (s, 3H), 3.87 (t, J = 8 Hz, 1H), 5.90 (s, 2H), 6.09 (d, J = 4 Hz, 2H), 6.51 (d, J = 8 Hz, 1H), 6.57 (s, 1H), 6.67 (d, J = 8 Hz, 1H), 6.68 (s, 1H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8, 30.9, 38.3, 45.3, 100.8, 102.1, 106.0, 107.7, 108.1, 108.8, 119.8, 121.3, 134.0, 135.0, 145.8, 147.55, 147.61, 152.6,



88 ($C_{20}H_{17}NO_6$)

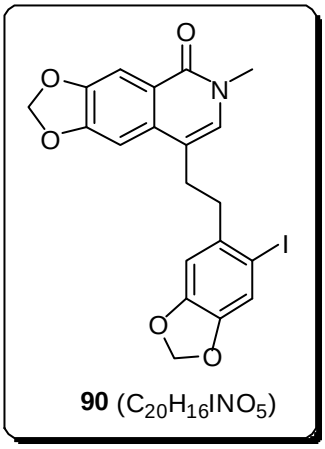
164.1, 173.5; ESIMS (*m*/*z*) 389 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{17}NO_6$ $[M]^+$ 401.1236, found 401.1240; IR ($CHCl_3$) ν_{max} 1709, 1663, 1623 cm^{-1}.

8-Hydroxy-8-(2-(6-iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)-6-methyl-[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione (89). To a stirred solution of compound **88** (1.50 g, 4.08 mmol) in acetonitrile (30 mL) plus CF_3COOH (0.50 mL) was added *N*-iodosuccinimide (1.01 g, 4.50 mmol). The reaction mixture was stirred at room temperature for 24 h and then it was concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (30 mL), washed with 5% aq. $Na_2S_2O_3$, water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 25% ethyl acetate/petroleum ether as an eluent gave pure product **89** as yellow crystalline solid (1.47 g, 71%); Mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.83–2.10 (m, 2H), 2.35–2.63 (m, 2H), 3.38 (s, 3H), 3.92 (br s, 1H), 5.90 (s, 2H), 6.09 (s, 2H), 6.58 (s, 1H), 7.12 (s, 1H), 7.16 (s, 1H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.6, 35.0, 47.2, 74.6, 87.4, 101.5, 102.2, 105.2, 107.6, 109.0, 118.46, 118.53, 135.6, 137.3, 146.9, 148.2, 148.5, 152.8, 163.3, 176.9; ESIMS (*m*/*z*) 532 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{16}NO_7I$ $[M+Na]^+$ 531.9871, found 531.9865; IR ($CHCl_3$) ν_{max} 3460, 1715, 1668, 1621 cm^{-1}.



89 ($C_{20}H_{16}INO_7$)

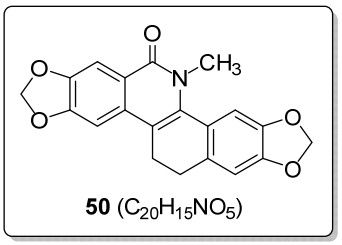
8-(2-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)-6-methyl-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (90). To a stirred solution of compound **89** (1.20 g, 2.35 mmol) in EtOH (20 mL) was portion wise added $NaBH_4$ (717 mg, 18.86 mmol) at 0 °C. The reaction mixture was stirred under argon atmosphere at 0 °C with periodic addition of 2 drops solution of EtOH (8 mL) plus 2 N HCl (2 mL) at the interval of 15 min. At the end of 6 h, excess of $NaBH_4$ was quenched at 0 °C by the addition of 2 N HCl in EtOH until the reaction mixture became acidic. The EtOH was removed in vacuo and the reaction mixture was extracted with ethyl acetate (25 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by



90 ($C_{20}H_{16}INO_5$)

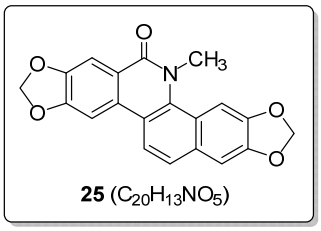
silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent gave pure product **90** as crystalline solid (764 mg, 68%); Mp 189–192 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.70–3.00 (m, 4H), 3.55 (s, 3H), 5.95 (s, 2H), 6.09 (s, 2H), 6.67 (s, 1H), 6.78 (s, 1H), 7.14 (s, 1H), 7.24 (s, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 30.7, 36.9, 40.8, 87.5, 101.0, 101.6, 101.8, 106.2, 109.4, 114.8, 118.6, 121.8, 129.5, 133.9, 137.0, 147.0, 147.5, 148.5, 151.9, 161.4; ESIMS (*m*/*z*) 500 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{16}NO_5$ $[M+Na]^+$ 499.9973, found 499.9955; IR ($CHCl_3$) ν_{max} 1655, 1611 cm^{-1}.

5-Methyl-12,13-dihydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-*c*][1,3]dioxolo[4,5-*j*]phenanthridin-6(5*H*)-one (50). To a stirred solution of compound **90** (600 mg, 1.26 mmol) in DMF (15 mL) was added K_2CO_3 (1.04 g, 7.56 mmol), TBAB (812 mg, 2.52 mmol) and $Pd(OAc)_2$ (30 mg, 10 mol%) at 25 °C under argon atmosphere and the reaction mixture was heated at 120 °C for 24 h. The reaction mixture was allowed to gradually attain the room temperature and then it was diluted with ethyl acetate (50 mL), washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent gave pure product **50** as crystalline solid (307 mg, 70%); Mp 230–232 °C (lit.[13] 237–241 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.60–2.85 (m, 4H), 3.72 (s, 3H), 5.99 (s, 2H), 6.07 (s, 2H), 6.80 (s, 1H), 6.93 (s, 1H), 7.06 (s, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.2, 29.1, 37.9, 100.3, 101.2, 101.7, 106.2, 106.7, 108.4, 115.4, 120.4, 124.0, 132.9 (2 carbons), 136.9, 146.1, 146.7, 147.4, 152.1, 163.4; ESIMS (*m*/*z*) 372 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1650, 1615 cm^{-1}.



50 ($C_{20}H_{15}NO_5$)

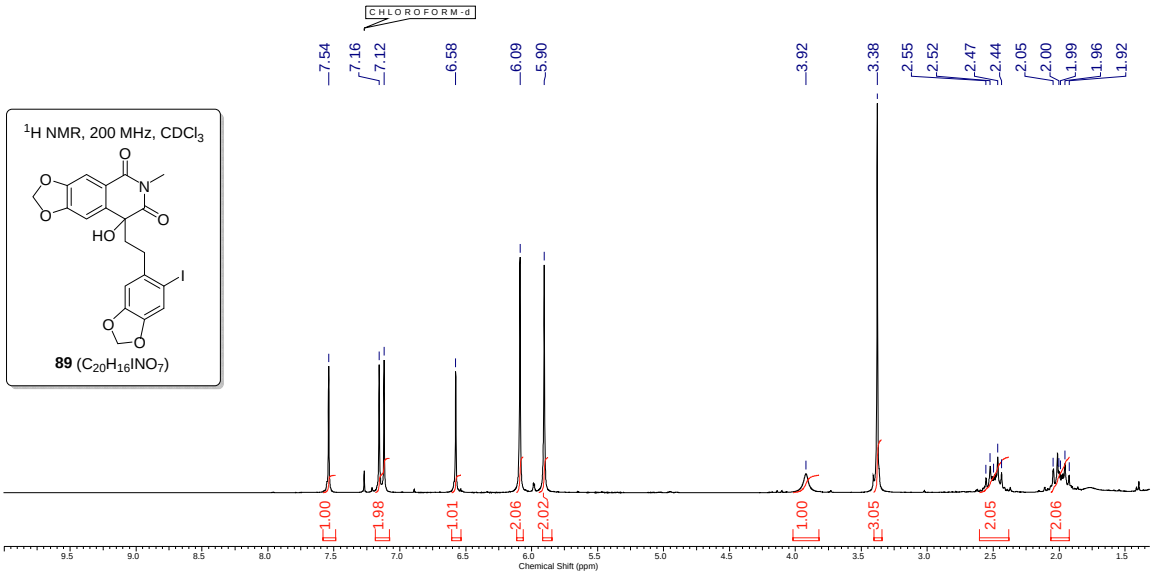
5- Methyl-[1,3]dioxolo[4',5':4,5]benzo[1,2-*c*][1,3]dioxolo[4,5-*j*]phenanthridin-6(5*H*)-one (Oxyavicine, 25). A mixture of compound **50** (200 mg, 0.57 mmol) and 10% Pd-charcoal (180 mg) in *p*-cymene (5 mL) in a sealed tube was heated at 200 °C under argon atmosphere for 24 h. The reaction mixture was allowed to attain room temperature, diluted with $CHCl_3$ (25 mL) and the catalyst was filtered off. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 30% ethyl acetate/petroleum ether as an eluent gave pure oxyavicine (**25**) as a crystalline solid (145



25 ($C_{20}H_{13}NO_5$)

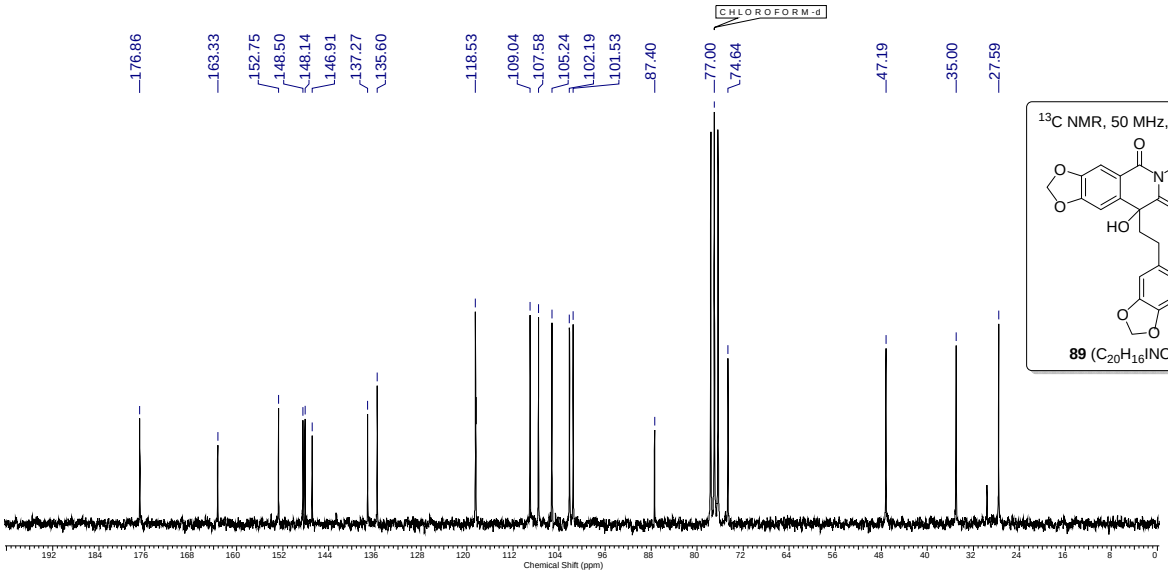
mg, 73%); Mp 278–279 °C (lit.[13] 278–283 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 3H), 6.11 (s, 2H), 6.14 (s, 2H), 7.19 (s, 1H), 7.57 (d, J = 8 Hz, 1H), 7.63 (s, 1H), 7.64 (s, 1H), 7.91 (s, 1H), 7.94 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.2, 100.7, 101.5, 101.9, 102.7, 104.8, 106.6, 116.8, 118.5, 120.7, 120.9, 123.3, 131.0, 131.9, 135.8, 147.0, 147.6, 148.2, 152.4, 164.1; ESIMS (m/z) 370 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1646 cm^{-1}.

2A.6 Selected Spectra:



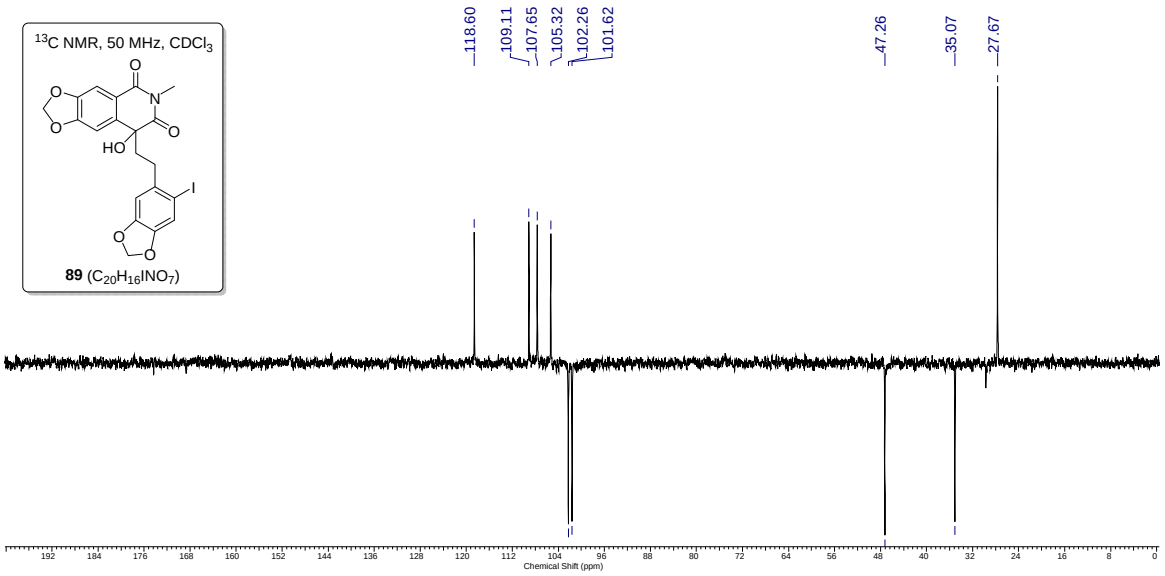
^{1}H NMR, 200 MHz, $CDCl_3$

89 ($C_{20}H_{16}INO_7$)



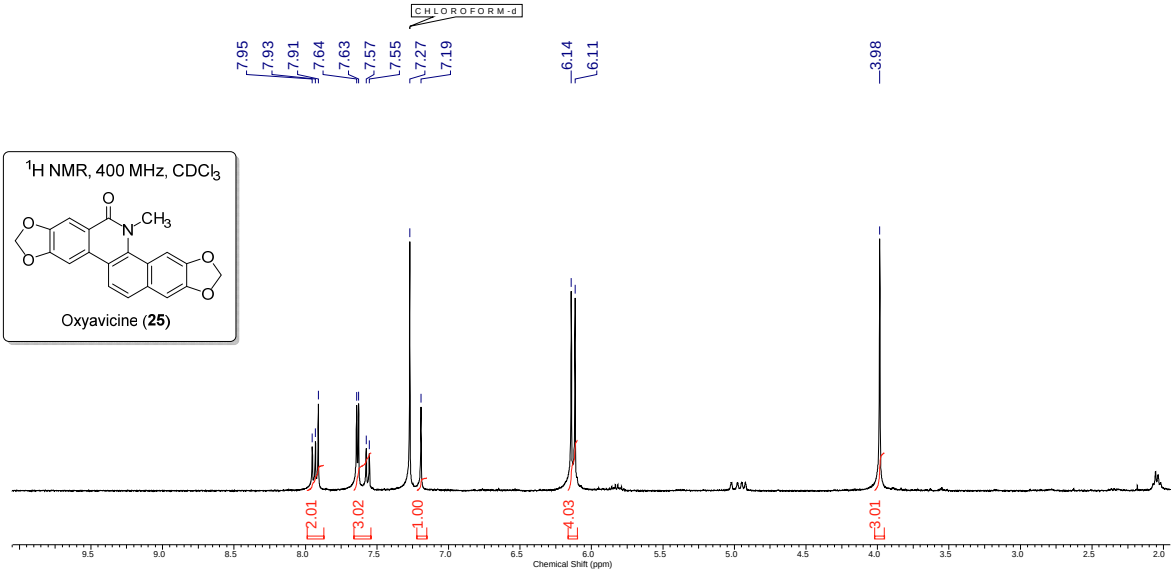
^{13}C NMR, 50 MHz, $CDCl_3$

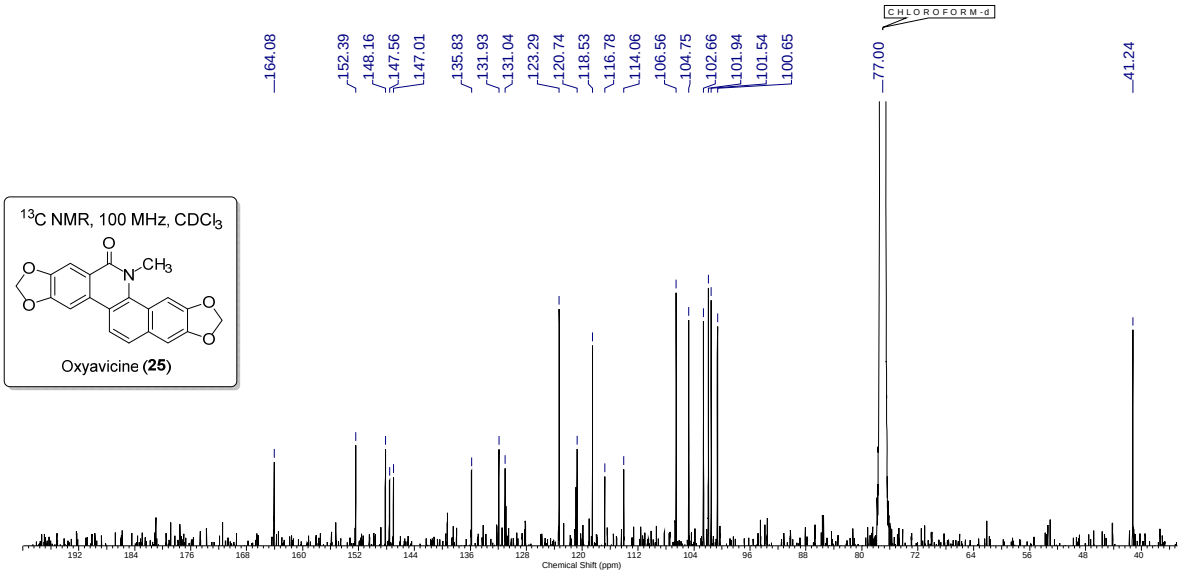
89 ($C_{20}H_{16}INO_7$)

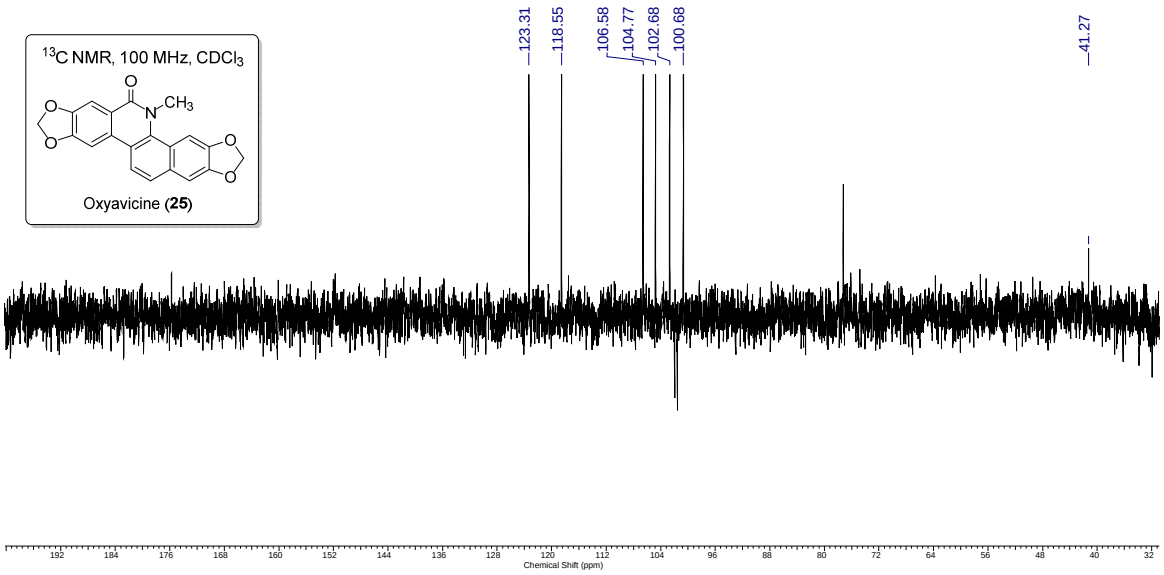


^{13}C NMR, 50 MHz, $CDCl_3$

89 ($C_{20}H_{16}INO_7$)


CHLOROFORM-d
7.95
7.93
7.91
7.64
7.63
7.57
7.55
7.27
7.19
6.14
6.11
3.98
^{1}H NMR, 400 MHz, $CDCl_3$
Oxyavicine (**25**)
2.01
3.02
1.00
4.03
3.01
Chemical Shift (ppm)


CHLOROFORM-d
164.08
152.39
148.16
147.56
147.01
135.83
131.93
131.04
123.29
120.74
118.53
116.78
114.06
106.56
104.75
102.66
101.94
101.54
100.65
77.00
41.24
^{13}C NMR, 100 MHz, $CDCl_3$
Oxyavicine (**25**)
Chemical Shift (ppm)


123.31
118.55
106.58
104.77
102.68
100.68
41.27
^{13}C NMR, 100 MHz, $CDCl_3$
Oxyavicine (**25**)
Chemical Shift (ppm)

2A.7 References

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Chapter 2

Section B

Total Synthesis of Arnottin I and the Formal Synthesis of Arnottin II

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

2B.1 Background

Aryl *C*-glycoside antibiotics constitute an emerging class of bioactive natural products and possess a characteristic aromatic-carbohydrate hybrid structure as shown in compounds **1-3** (Figure 1). They exhibit a wide range of biological activities such as antibacterial, antitumor and enzyme inhibitory effects and are currently attracting considerable synthetic interests.[1] The gilvocarcins belong to such a class of natural products and contain *C*-glycosylated benzonaphthopyranone skeleton. Among these, gilvocarcin V (**3b**) has been attracting considerable attention due to the high antitumor and antiviral activities with exceptionally low toxicity.[2,3]

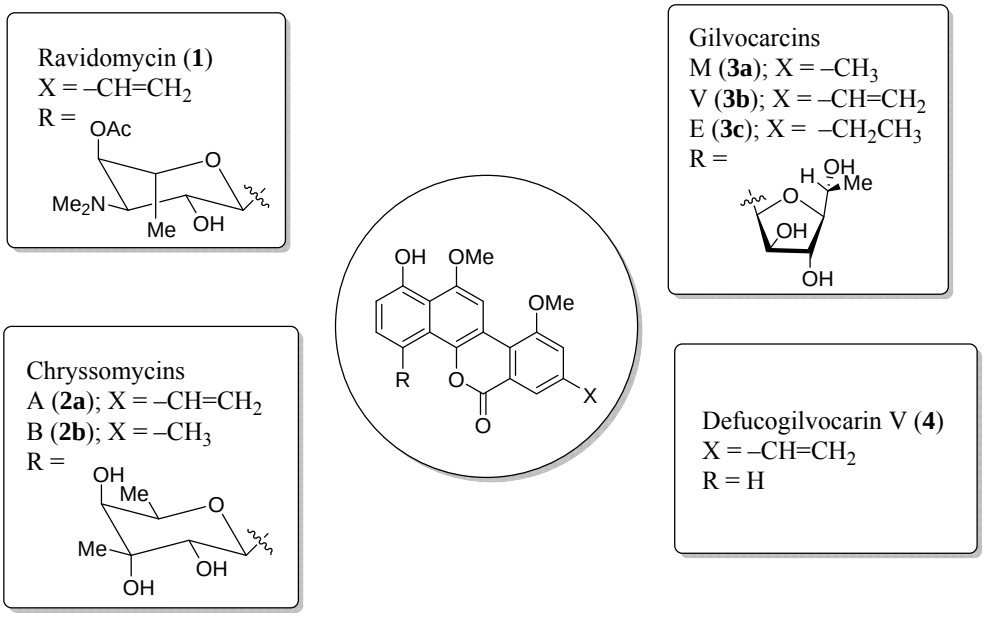


Figure 1. Some Selected Members of Gilvocarcin Class of Antibiotics

The core structure of Arnottin I is same as that of gilvocarcin class of antibiotics. In comparison to the gilvocarcins, arnottin I is a sugarless naphtho[*b*,*d*]benzopyranone with a different oxygen substituents pattern. It was isolated in 1977 by Ishikawa and co-workers as a minor constituent from the bark of *Xanthoxylum arnottianum* together with arnottin II (a spirolactone).[4] The structural elucidation of arnottin I was not achieved until 1993 due to the fact that the plant produced only small quantities of the material.[5] Arnottin I was obtained as colourless prisms, the elemental analysis and mass spectrum of which were in accordance with the molecular formula $C_{20}H_{14}0_6$. The presence of lactone carbonyl group in the molecule was suggested by absorption at 1740 cm^{-1} in its IR spectrum. The ^1H NMR spectrum showed a simple pattern of signals similar to that of chelerythrine (**5**), a benzo[*c*]phenanthridine alkaloid co-existing in the same plant as a

main component.[4] The spectral data confirmed a 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton as the structure of arnottin I (**6**), in which the *N*-methyl group in **5** was formally replaced by oxygen. The co-isolation of the benzophenanthridine alkaloid chelerythrine was a biogenetic hint for the relationship of these three natural products **5** to **7** (Figure 2).[6] In fact, Ishikawa has suggested that arnottin I was a potential biosynthetic intermediate of chelerythrine. [4] Although the biological activity of the arnottins has not been established, compounds related to chelerythrine have shown significant antileukemic properties.[7,8]

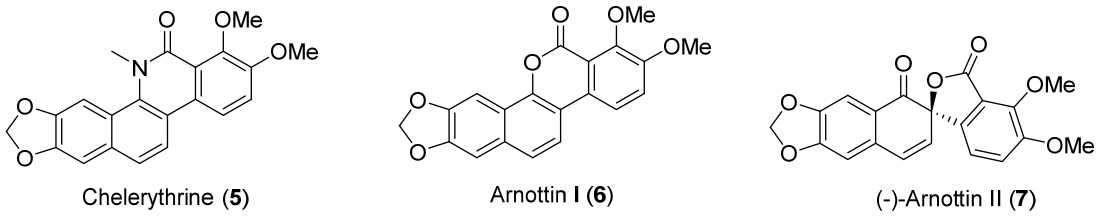
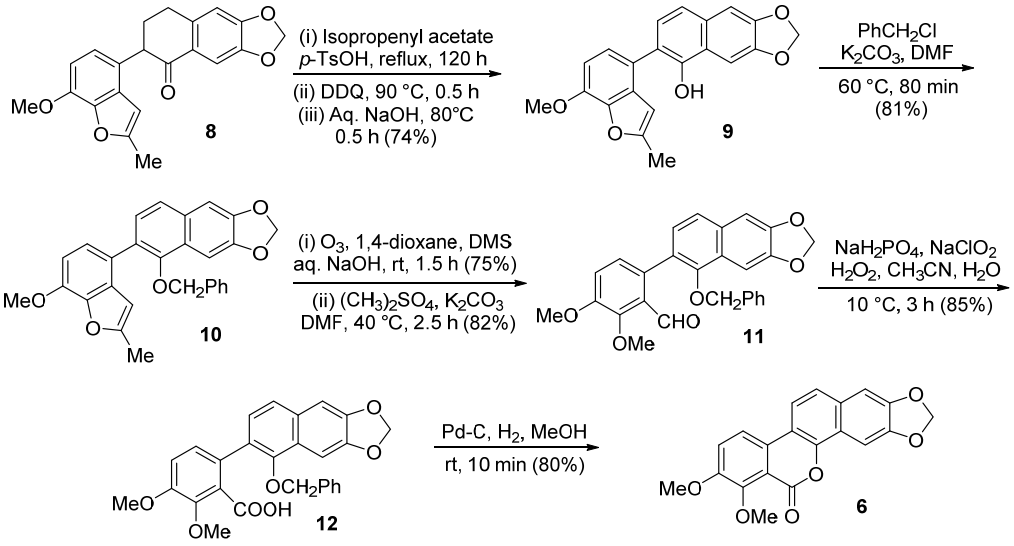


Figure 2. Structure of Chelerythrine and Arnottins I and II

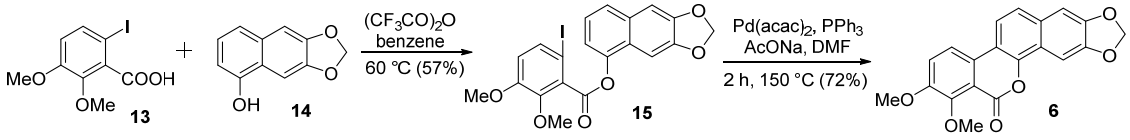
2B.2 Earlier Reported Synthesis of Arnottin I

Ishii et al. in 1993 reported the structural elucidation and first synthesis of arnottin I (Scheme 1).[5] Treatment of tetralone **8**[9] with isopropenyl acetate in the presence of a catalytic amount of *p*-toluenesulfonic acid followed by DDQ dehydrogenation and alkaline hydrolysis afforded the desired phenol **9** in 74% yield. After protection of the phenolic group as benzyl ether **10**, the furan ring was cleaved by reductive ozonolysis to obtain the salicylaldehyde derivative. Then it was smoothly methylated to obtain the methyl ether **11**. Oxidation of compound **11** by sodiumchlorite hydrogen-peroxide[10] gave the desired acid **12** in 85% yield. Catalytic debenzylation smoothly gave colourless prisms of arnotiin I (**6**) in 80% yield, which was identical with natural arnottin I. Thus the structure of arnottin I (**6**) was unequivocally confirmed by its first synthesis.



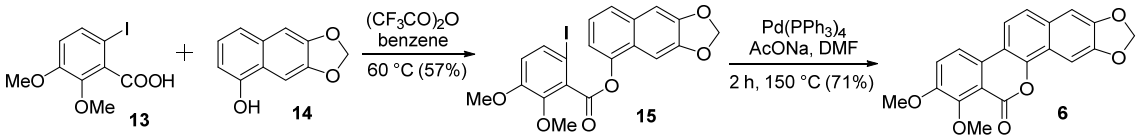
Scheme 1. First Synthesis of Arnottin I via Reductive Ozonolysis

Harayama et al. in 1997 reported the synthesis of arnottin I using internal biaryl coupling by Palladium as the key step (Scheme 2).[11] The compound **14** was prepared by demethylation of 6,7-dimethoxy-1-tetralone using BBr_3 followed by methynelation; which was further subjected to enol acetate formation, dehydrogenation and hydrolysis. The ester **15** was prepared from acid **13**[12] and naphthol **14** in 57 % yield by using Parish's method.[13] Finally the palladium mediated internal biaryl coupling reaction of ester **15** provided them the desired cyclized product arnottin I (**6**) in 72% yield.



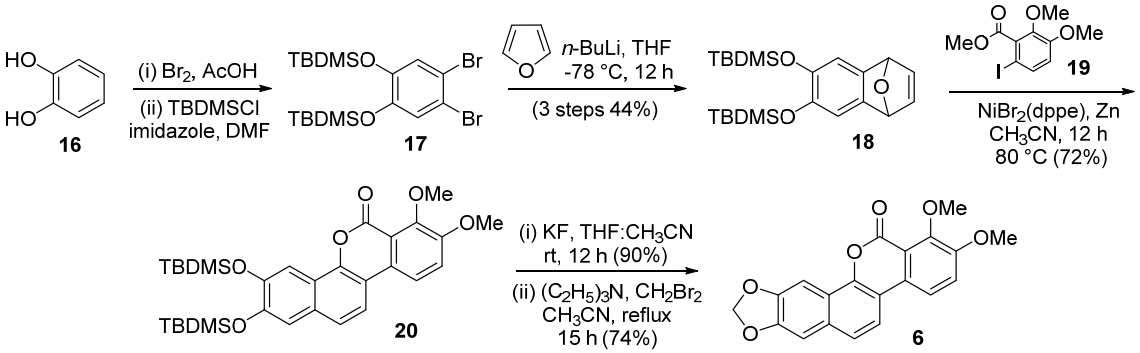
Scheme 2. Synthesis of Arnottin I via Intramolecular Biaryl Coupling

Harayama et al. in 2000 reported one more total synthesis of arnottin I by using the same palladium catalyzed cyclization (Scheme 3).[14] The esterification of acid **13**[12] with naphthol **14** in trifloroacetic acid afforded the condensed product **15** in 57% yield. Then the intramolecular biaryl coupling of **15** in presence of palladium catalyst was tried in presence of different catalysts and at different temperatures to obtain the natural product arnottin I (**6**). This reaction at 130 °C gave moderate yield (58%), which improved to 71% at 150 °C.



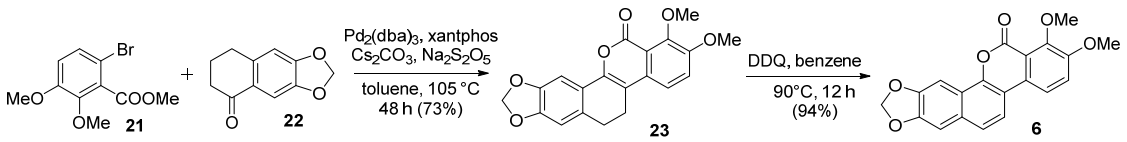
Scheme 3. Synthesis of Arnottin I using Palladium Catalysis

Cheng et al. in 2006 reported the synthesis of arnottin I via cyclization in the presence of $NiBr_2$(dppe) and Zn metal powder (Scheme 4).[15] Treatment of catechol (**16**) with bromine in acetic acid gave 4,5-dibromocatechol.[16] Protection using *tert*-butyldimethylsilyl chloride was done for the free hydroxyl groups in 4,5-dibromocatechol to obtain 1,2-bis(*tert*-butyldimethylsilyloxy)-4,5-dibromobenzene (**17**). Diels-Alder reaction of the corresponding benzyne generated from dibromo compound **17** and *n*-BuLi with furan afforded 1,2-bis(*tert*-butyldimethylsilyloxy)-7-oxabenzonorbornadiene (**18**) in 44% yield over three steps. Finally, TBDMS protected oxabenzonorbornadiene **18** was reacted with *o*-iodobenzoate **19** in the presence of $NiBr_2$(dppe) and Zn metal powder to form the corresponding coumarin derivative **20** in 72% yield. The silyl groups were successfully removed by KF in a mixture of THF and CH_3CN (1:1 by volume) to provide the corresponding dihydroxy derivative. Finally, the reaction with CH_2Br_2 in the presence of NEt_3 furnished the title compound arnottin I (**6**) in 74% yield.



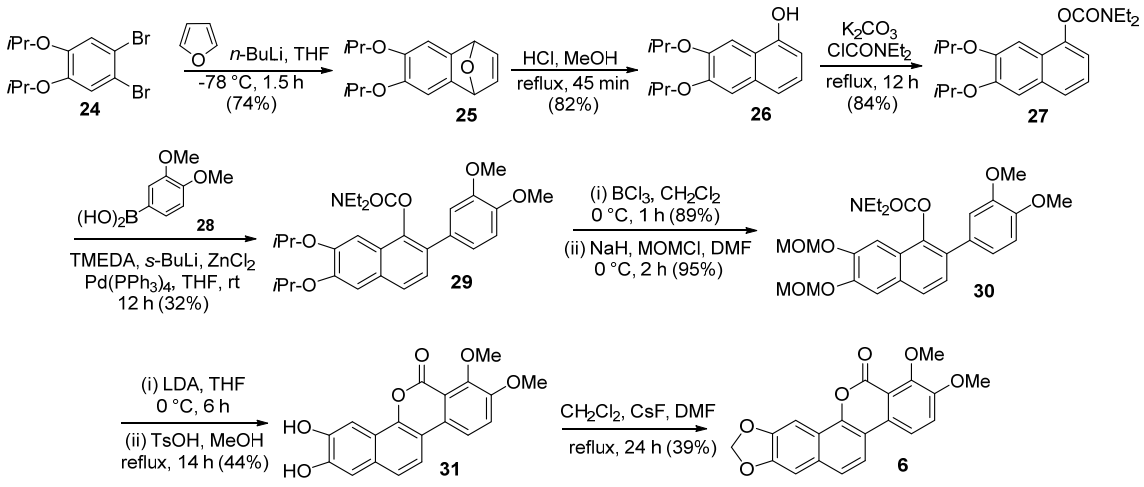
Scheme 4. Synthesis of Arnottin I by Using Nickel Catalyzed Cyclization

Ishikawa et al. in 2006 reported the synthesis of arnottin I via palladium catalyzed coupling reaction (Scheme 5).[17] Dihydroarnottin I (**23**) was directly prepared by palladium catalyzed coupling of *o*-bromobenzoate **21** and 6,7-methylenedioxy-1-tetralone (**22**) using Buchwald protocol in 73% yield.[18] The formed dihydroarnottin was aromatized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to obtain arnottin I (**6**) in 94% yield.



Scheme 5. Synthesis of Arnottin I via Palladium Catalyzed Coupling

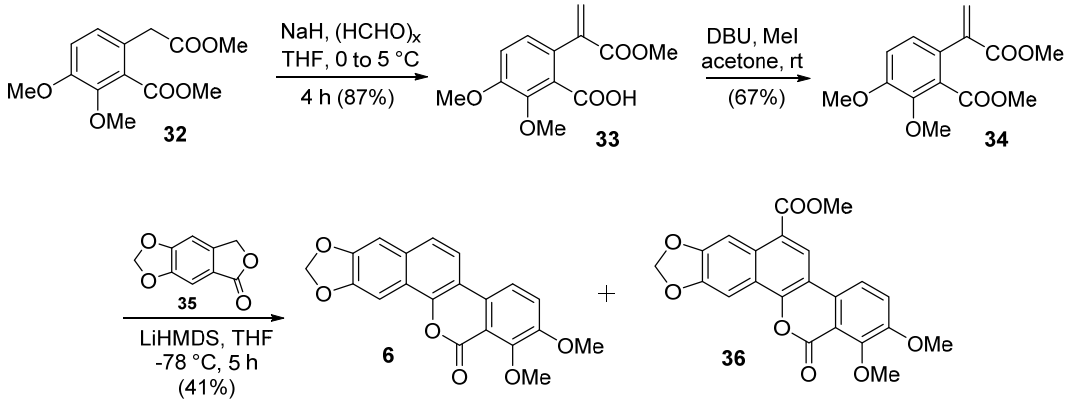
Snieckus et al. in 2009 reported the synthesis of arnottin I in 11 steps (Scheme 6).[19] The starting material **24** was prepared from readily available 6-bromosesamol.[20] Treatment of **24** with *n*-BuLi at –78 °C in the presence of a large excess of furan afforded the cycloadduct **25** in 74% yield, whose ring opening-aromatization was done by acid catalysis under refluxing conditions to furnish the naphthol **26**. The compound **26** was acylated to provide the key *o*-carbamate **27** in 84% yield. Subsequently, the Suzuki-Miyaura transmetalation cross coupling reaction of **27** with arylborane **28** afforded biaryl **29** in 32% yield. BCl_3 mediated isopropyl ether cleavage proceeded to give the corresponding catechol which, upon treatment with MOMCl furnished the requisite product **30** in 95% yield. Treatment of **30** with excess LDA formed the cyclized product, which on treatment with TsOH in MeOH lead to the desired catechol **31** in 44% yield. Of the available methods for catechol methylenation,[21,22] the conditions of Clark[23] were adapted to transform the insoluble **31** to desired arnottin I (**6**) with 2% overall yield in 11 steps.



Scheme 6. Synthesis of Arnottin I Employing Suzuki Miyaura Coupling

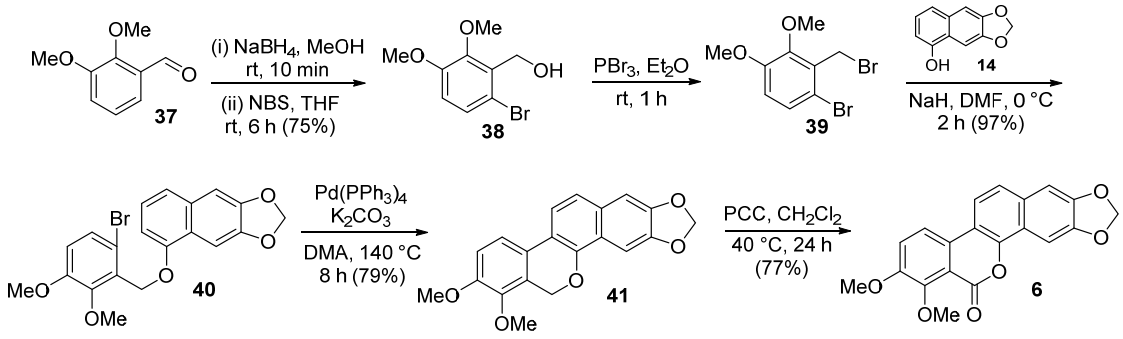
Deepakranjan Mal et al. in 2011 reported the synthesis of arnottin I by using the benzannulation reaction (Scheme 7).[24] The phthalide **35**[25] was prepared in one step from commercially available piperonylic acid by its reaction with CH_2Br_2 in the presence of

$Pd(OAc)_2$.[26] Homophthalate **32**[27] was methylenated with paraformaldehyde and NaH in THF at 0 °C to form half-ester **33** in 87% yield. The compound **33** was converted to diester **34** by using DBU and MeI in acetone with 67% yield.[28] The annulation between homophthalate **34** and phthalide **35** was performed in the presence of LiHMDS in THF, which provided an inseparable mixture of two compounds, arnottin I (**6**) and undesired product **36**. Repeated fractional recrystallizations of the above mixture in chloroform delivered arnottin I (**6**) in 41% yield.



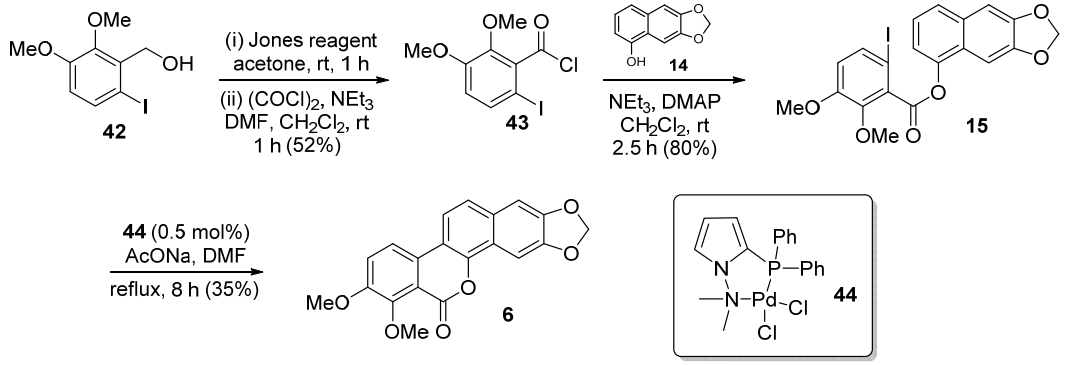
Scheme 7. Synthesis of Arnottin I via Benzannulation Reaction

Alakesh Bisai et al. recently reported the total synthesis of arnottin I using the palladium catalyzed direct arylation (Scheme 8).[29] The naphthol **14** was prepared in few steps using the known literature pathway.[30] On the other hand 2-bromobenzyl bromide **39** was prepared from the corresponding aldehyde **37** using three steps. $NaBH_4$ reduction of aldehyde **37** afforded benzyl alcohol, which was subjected to bromination using NBS to obtain bromobenzyl alcohol **38** in 75% yield. The bromobenzyl alcohol **38** was further treated with phosphorous tribromide to obtain 2-bromobenzyl bromide **39**. Which was condensed with naphthol **14** in presence of base to obtain naphthyl ether **40** in quantitative yield. The naphthyl ether **40** was subjected to direct intramolecular biaryl coupling using palladium catalyst to obtain the cyclized product **41** in 77% yield. The cyclized ether **41** was oxidized in the presence of PCC under refluxing dichloromethane[31] to obtain arnottin I (**6**) in 77% yield.



Scheme 8. Synthesis of Arnottin I by Palldium Catalyzed Direct Arylation Method

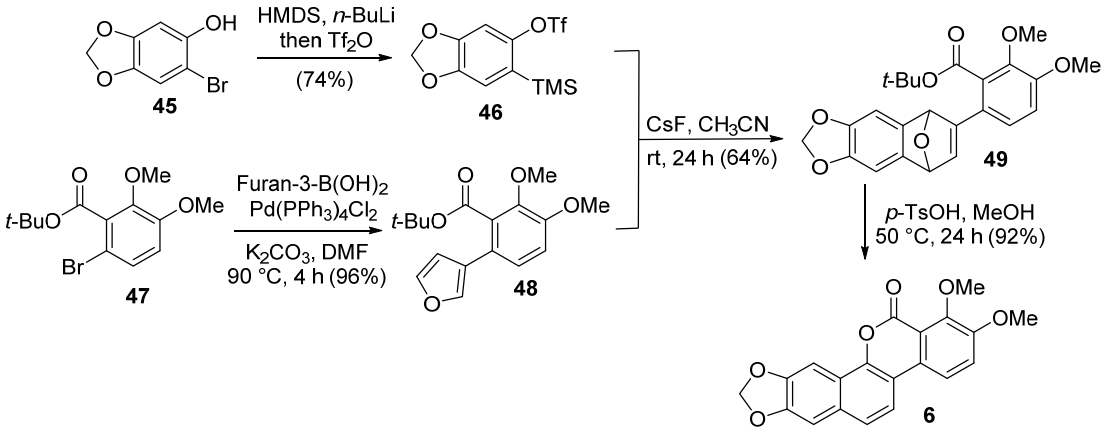
Lopez-Cortes et al. in 2014 reported the synthesis of arnottin I via cyclization pathway using the [N,P] ligand palladium complex **44** synthesized by them (Scheme 9).[32] The naphthol **14** was prepared by the aromatization of tetralone **22**. On the other hand, the required acid chloride **43** was prepared in 52% yield from known alcohol **42**[33] via Jones oxidation followed by treatment with oxalyl chloride. The acid chloride **43** was reacted with naphthol **14** under standard conditions to obtain coupled compound **15** in 80% yield. Finally, palladium complex **44** was used to complete the conversion of **15** into arnottin I (**6**) in 35% yield, recovering a small amount of the starting material.



Scheme 9. Synthesis of Arnottin I by Using *N*,*P*-Palldium Complex

Chad A. Lewis et al. recently reported the synthesis of arnottin I using a benzyne cycloaddition with 3-furyl benzoate followed by lactonization (Scheme 10).[34] Bis-lithiation of 6-bromosesamol **45**,[35] followed by trimethylsilyl chloride quench and triflation using Mori's procedure[36] afforded benzyne precursor **46** in 74% overall yield. The furyl coupling partner was prepared from readily available dimethoxybenzoic acid which was converted to *tert*-butyl bromoester **47** in 2 steps.[15] The bromoester **47** was cross-coupled under Suzuki conditions with the commercially available 3-furylboronic acid to obtain furyl-coupled ester **48** in 96% yield. The benzyne-mediated in situ

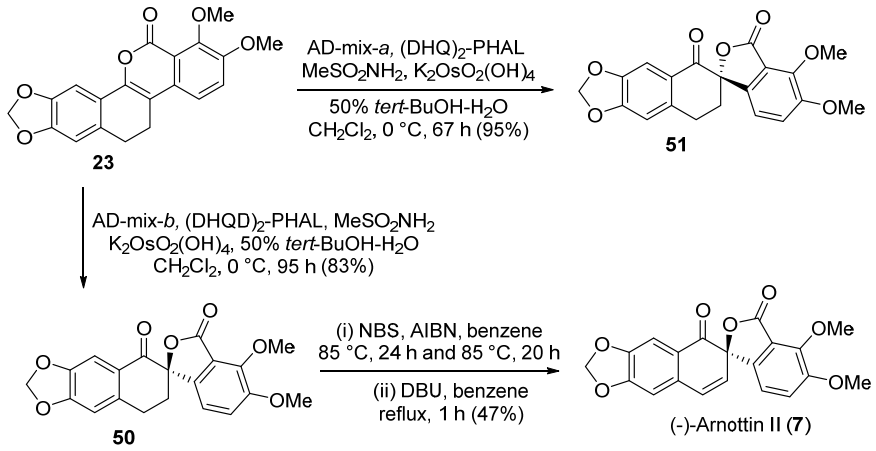
cycloaddition in presence of CsF produced the arnottin I progenitor (rac-**49**) in 64% yield. Bronsted acid *p*-TsOH was used for conversion of racemic *tert*-butyl ester **49** to arnottin I (**6**) in 92% yield.



Scheme 10. Synthesis of Arnottin I via Benzyne Intermediate

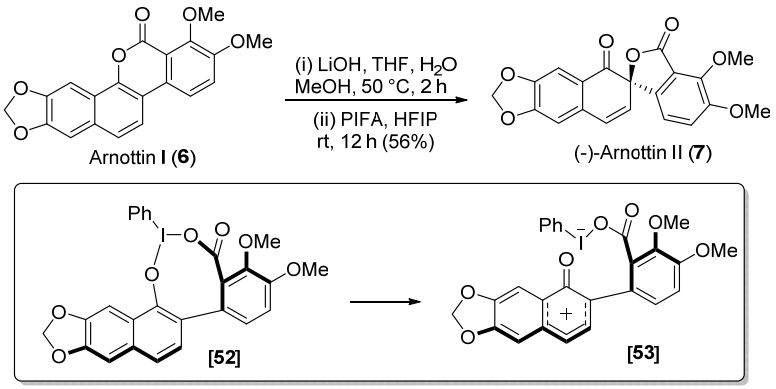
2B.3 Earlier Reported Synthesis of Arnottin II

Ishikawa et al. in 2006 reported the synthesis of arnottin II by using the asymmetric dihydroxylation (AD) of dihydroarnottin I (**23**) (Scheme 11).[17] The combination of AD-mix-*β* and $(DHQD)_2$-PHAL afforded (+)-dihydroarnottin II (+)-**50** in 83% yield and 88% *ee*, where as *ent*-(–)-dihydroarnottin II (–)-**51** was obtained in 95% yield and 88% *ee* when AD-mix-*α* and $(DHQ)_2$-PHAL were used. Introduction of a double bond into (+)-dihydroarnottin II (+)-**50** by application of the reported procedure (bromination-dehydrobromination)[37] gave (–)-arnottin II (**7**) in 47% yield.



Scheme 11. Synthesis of Arnottin II by Using Asymmetric Dihydroxylation

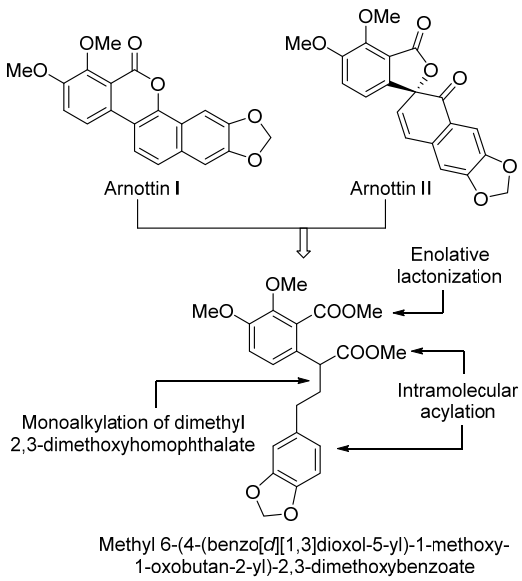
Recently, Chad A. Lewis et al. reported the synthesis of arnottin II by saponification of arnottin I (Scheme 12).[34] The Saponification of arnottin I (**6**) required immediate exposure to spirocyclization conditions due to competitive recyclization and recovery of corresponding acid. Careful hydrolysis of arnottin I was followed by acidification to pH 2-3, which reduced the conversion to arnottin I and retained solubility for the spirocyclization studies. The acid was immediately exposed to slow addition of PIFA over 1 h in hexafloroisopropanol (HFIP) to provide arnottin II (**7**) with 56% overall yield in two steps via intermediates **52** and **53**.



Scheme 12. Synthesis of Arnottin II by Using Hypervalent Iodine

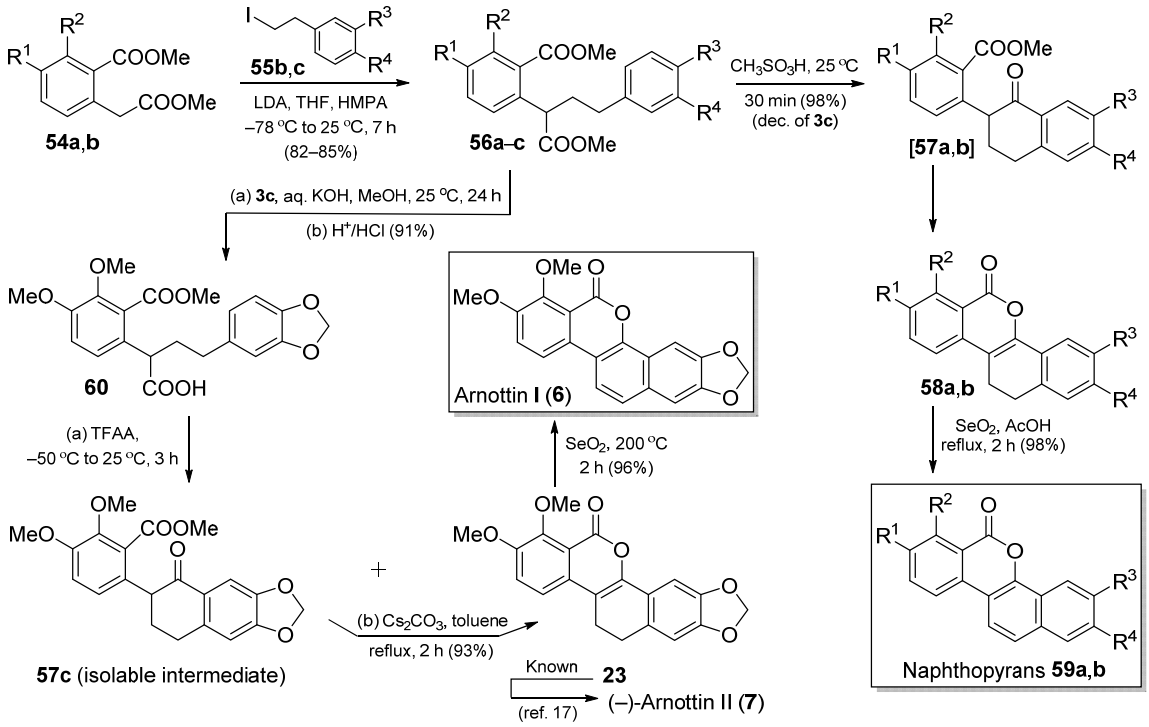
2B.4 Rationale for Present Work

A careful scrutiny of arnottins I and II structures and their retrosynthetic analysis revealed that the multifunctional methyl 6-(4-(benzo[d][1,3]dioxol-5-yl)-1-methoxy-1-oxobutan-2-yl)-2,3-dimethoxybenzoate would be a potential precursor to provide convergent access to both the target compounds (Scheme 13). More specifically, selective intramolecular acylation of the diester followed by a concomitant enolization-lactonization would be the strategic step in generating rings B and C to obtain the desired advanced common intermediate of arnottins I and II. In continuance of our efforts to synthesize structurally interesting and biologically important natural and unnatural products from cyclic anhydrides and their derivatives as the potential precursors,[38-42] we herein describe concise and efficient access to naphthopyrans, arnottin I and arnottin II (Scheme 14).



Scheme 13. Retrosynthetic Analysis of Arnottins I and II

Dimethyl homophthalates **54a**,**b** on base promoted alkylation with alkyl iodides **55b**,**c** exclusively furnished the requisite mono-alkylated coupling products **56a**–**c** in 82–85% yields.[43,44] Reaction of appropriate precursors **56a**,**b** with methanesulfonic acid at room temperature directly formed the desired double cyclized products **58a**,**b** in nearly quantitative yields (98%) via the corresponding unisolable tetralone intermediates **57a**,**b**. As per the planned strategy, acid-promoted regioselective intramolecular Friedel–Crafts acylation utilizing an aliphatic ester moiety, instantaneous enolization of the thus formed tetralone intermediates **57a**,**b** using an acidic α-methine proton and the concurrent δ-lactonization employing a less reactive aromatic ester unit took place in one-pot to deliver the aimed products **58a**,**b**. Compounds **58a**,**b** on treatment with SeO_2 in refluxing acetic acid provided the corresponding expected aromatized products **59a**,**b** in 2 h with quantitative yield (98%). The aromatization plausibly took place via a regioselective introduction of an acetate function at the relatively more reactive allylic site followed by it's in situ elimination by abstracting the adjacent benzylic proton.[45] Thus starting from dimethyl homophthalates we developed a new practical approach to naphthopyran systems and it has advantages in terms of number of steps involved and obtained yields.



a: $R^1 = R^2 = H$, $R^3 = R^4 = OMe$; **b:** $R^1 = R^2 = R^3 = R^4 = OMe$; **c:** $R^1 = R^2 = OMe$, $R^3 + R^4 = O\text{-}CH_2\text{-}O$

Scheme 14. General Approach to Naphthopyrans and Total Synthesis of Arnottin I

In the second part of our studies, we planned the synthesis of arnottin I and (–)-arnottin II by using above defined synthetic protocol. The pivotal arnottin's antecedent compound **56c** on similar treatment with methanesulfonic acid underwent unfortunate instantaneous decomposition under the several sets of reaction conditions. We also tried various conditions to effect the transformation of **56c** to **23** utilizing reagents such as acetic acid, trifluoroacetic acid and *p*-TSA, but always ended up with isolation of starting material and/or decomposition. The cause for such decomposition of compound **56c** under acidic conditions was the presence of a labile dioxymethylene bridge attached to ring D. To circumvent the above specified difficulty, we initially performed base catalyzed regioselective mono-hydrolysis of an aliphatic ester moiety in compound **56c** and obtained the product **60** in 91% yield, as the synthesis of corresponding dicarboxylic acid followed by treatment with dehydrating agents would form the cyclic anhydride and demand sequential synthetic steps to transform compound **56c** into the essential product **23**. The acid-ester **60** on treatment with trifluoroacetic anhydride at –50 °C to 25 °C formed a reactive mixed anhydride intermediate and delivered a mixture of corresponding simple acylation product; the known tetralone intermediate **57c** and desired double

cyclized advanced intermediate **23** in quantitative yield[17] (~7:3 ratio, by ^{1}H NMR). Herein the second cyclization step was relatively slow due to the mesomeric deactivation of an aromatic ester function by the corresponding *ortho*-methoxy group. An increase in reaction temperature and/or extending the reaction time again resulted in some decomposition. The above specified mixture of tetralone intermediate **57c** and compound **23** was silica gel column chromatographically inseparable. Thus to ensure a complete transformation into the essential compound **23**, the above mixture of products was further treated with Cs_2CO_3 in refluxing toluene (93% yield). Starting from the advanced common intermediate **23**, synthesis of arnottin I by employing DDQ-oxidation in benzene and synthesis of (–)-arnottin II via the Sharpless asymmetric dihydroxylative spiro-lactonization route have been known in the literature.[17] Similarly, we repeated the DDQ-oxidation of **23** in refluxing toluene and obtained the natural product arnottin I (**6**) in quantitative yield (98%). However, analogous to **58a**,**b** to **59a**,**b** transformation, the SeO_2 oxidation of compound **23** in refluxing acetic acid resulted in decomposition of reaction mixture. Alternatively performed SeO_2 oxidation of compound **23** in refluxing benzene, toluene and freshly distilled acetic anhydride were very slow and provided the silica gel column chromatographically inseparable mixture of starting material **23** and arnottin I (**6**) in 48 h. The ^{1}H NMR spectra of above specified mixtures indicated only 10 to 20% conversions into the desired product **6**. As anticipated, the neat SeO_2 (10.00 equiv) induced oxidative aromatization of dihydronaphthopyran **23** at 200 °C took place in 2 h without any decomposition and provided the desired natural naphthopyran **6** in 96% yield. The analytical and spectral data obtained for arnottin I was in complete agreement with the reported data.[6,17] Arnottin I was obtained in four steps by using two different oxidizing agents at the ultimate step with 71% and 69% overall yields respectively.

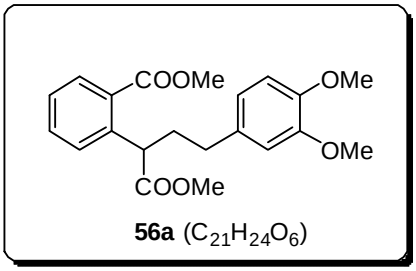
2B.5 Summary

In summary, we have demonstrated a bio-inspired protection-free concise and efficient total synthesis of arnottin I and the formal synthesis of (–)-arnottin II from the economically available homophthalate and utilizing the regiospecific makeup of these homophthalates. The construction of ring B and C utilizing an intramolecular Friedel–Crafts acylation, followed by enolative lactonization reaction was the key step. The present transition metal free and diversity oriented 3-step new approach to the imperative naphthopyran architectures is general in nature and will be useful to design

several focused mini-libraries of their natural and unnatural analogues and congeners for SAR studies. Our present approach also provides an efficient access to several corresponding isoquinoline alkaloids.[44,46]

2B.6 Experimental Section

Methyl 2-(4-(3,4-Dimethoxyphenyl)-1-methoxy-1-oxobutan-2-yl)benzoate (56a). A

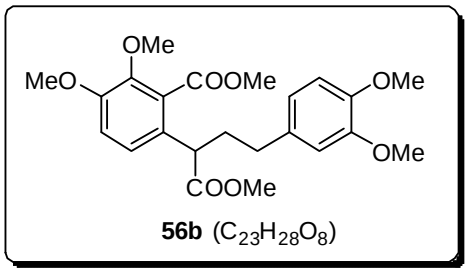


56a ($C_{21}H_{24}O_6$)

fresh solution of LDA was prepared from diisopropylamine (0.87 mL, 6.24 mmol) and *n*-BuLi (1.60 M in hexane, 4.20 mL, 6.72 mmol) in THF (5 mL) under argon atmosphere at 0 °C. It was added to a solution of compound **54a** (1.00 g, 4.80 mmol) in THF (10 mL) and HMPA (10 mL) mixture at –78 °C under argon atmosphere and the reaction mixture was further stirred at same temperature for 30 min. To the above reaction mixture was added solution of compound **55b** (1.54 g, 5.28 mmol) in THF (5 mL) in a dropwise fashion. The reaction mixture was allowed to gradually attain rt in 7 h. The reaction was quenched with saturated NH_4Cl solution and solvent was removed in vacuo. The obtained residue was dissolved in ethyl acetate and the organic layer was washed with water, brine and dried over Na_2SO_4. The 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 (1:3) as an eluent gave pure product **56a** as a thick oil (1.46 g, 82%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.95–2.25 (m, 1H), 2.35–2.70 (m, 3H), 3.68 (s, 3H), 3.87 (s, 6H), 3.88 (s, 3H), 4.64 (t, J = 8 Hz, 1H), 6.69 (s, 1H), 6.72 (t, J = 8 Hz, 1H), 6.78 (t, J = 8 Hz, 1H), 7.27–7.42 (m, 1H), 7.42–7.60 (m, 2H), 7.92 (dd, J = 8, 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.4, 35.2, 46.5, 52.0, 52.1, 55.7, 55.9, 111.1, 111.7, 120.2, 126.9, 128.7, 129.8, 130.7, 132.2, 134.0, 140.2, 147.2, 148.7, 167.8, 174.3; ESIMS (*m*/*z*) 395 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{25}O_6$ 373.1646, found 373.1639; IR ($CHCl_3$) ν_{max} 1732, 1721, 1602 cm^{-1}.

The products **56b** and **56c** were similarly obtained by using above specified procedure.

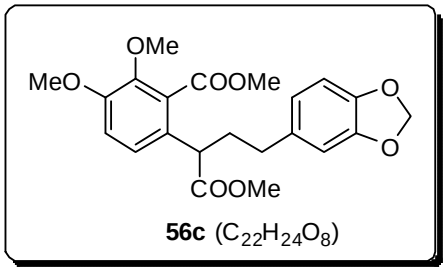
Methyl 6-(4-(3,4-Dimethoxyphenyl)-1-methoxy-1-oxobutan-2-yl)-2,3-dimethoxybenzoate (56b). Thick oil (1.33 g, 83%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.90–2.15 (m, 1H), 2.25–2.68 (m, 3H), 3.55 (t, J = 8 Hz, 1H), 3.67 (s, 3H), 3.82 (s, 3H),



56b ($C_{23}H_{28}O_8$)

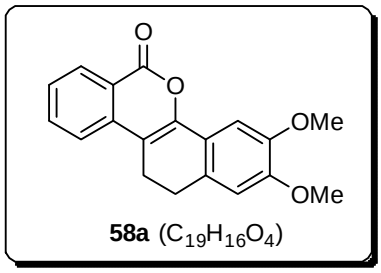
3.85 (s, 6H), 3.86 (s, 3H), 3.88 (s, 3H), 6.62–6.74 (m, 2H), 6.79 (d, J = 8 Hz, 1H), 6.94 (d, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.2, 35.3, 46.5, 52.0, 52.1, 55.7, 55.8 (2 C), 61.4, 111.1, 111.6, 113.7, 120.2, 123.1, 128.3, 129.4, 133.7, 145.8, 147.1, 148.7, 151.5, 167.5, 173.9; ESIMS (*m*/*z*) 455 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{29}O_8$ 433.1857, found 433.1851; IR ($CHCl_3$) ν_{max} 1735, 1610 cm^{-1}.

Methyl 6-(4-(Benzo[d][1,3]dioxol-5-yl)-1-methoxy-1-oxobutan-2-yl)-2,3-dimethoxybenzoate (56c). Thick oil (1.32 g, 85%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65–2.10 (m, 1H), 2.20–2.65 (m, 3H), 3.54 (t, J = 8 Hz, 1H), 3.65 (s, 3H), 3.85 (s, 9H), 5.89 (s, 2H), 6.58 (dd, J = 8, 2 Hz, 1H), 6.64 (d, J = 2 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 6.94 (d, J = 10 Hz, 1H), 7.13 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.3, 35.3, 46.5, 51.9, 52.1, 55.8, 61.4, 100.6, 108.0, 108.8, 113.8, 121.1, 123.1, 128.2, 129.4, 135.0, 145.6, 145.8, 147.4, 151.5, 167.5, 173.8; ESIMS (*m*/*z*) 439 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{25}O_8$ 417.1544, found 417.1537; IR ($CHCl_3$) ν_{max} 1733, 1604 cm^{-1}.



56c ($C_{22}H_{24}O_8$)

2,3-Dimethoxy-11,12-dihydro-6*H*-dibenzo[c,h]chromen-6-one (58a). To a compound **56a** (372 mg, 1.00 mmol) was added CH_3SO_3H (4 mL) at rt under argon atmosphere and the reaction mixture was stirred for 30 min. The reaction mixture was poured on crushed ice and the obtained precipitate was filtered, washed with water, 10% aqueous $NaHCO_3$ and dried to vacuum pump. The silica gel (60–120 mesh) column chromatographic purification of the resulting compound using ethyl acetate–petroleum ether (3:7) as an eluent gave pure product **58a** as yellow solid (302 mg, 98%). Mp 167–169 °C (lit.[47] 105 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.85–3.00 (m, 4H), 3.92 (s, 3H), 3.96 (s, 3H), 6.75 (s, 1H), 7.38 (s, 1H), 7.45 (t, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.75 (t, J = 8 Hz, 1H), 8.33 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 26.9, 56.0, 56.3, 106.1, 107.6, 110.9, 120.4, 121.3, 121.8, 127.1, 129.7, 130.2, 134.7, 137.6,

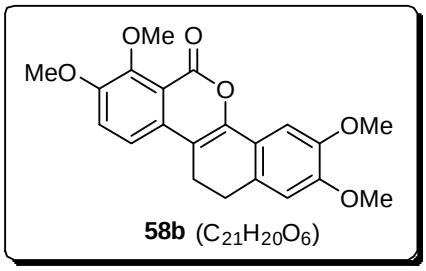


58a ($C_{19}H_{16}O_4$)

148.0, 148.3, 149.8, 162.3; ESIMS (*m*/*z*) 331 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1733, 1722, 1631, 1603 cm^{-1}.

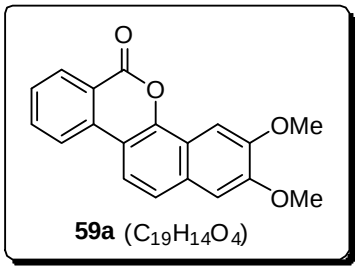
The product **58b** was similarly obtained by using above specified procedure.

2,3,7,8-Tetramethoxy-11,12-dihydro-6*H*-dibenzo[c,h]chromen-6-one (58b). Yellow solid (360 mg, 98%); mp 172–174 °C (lit.[48] 171–172 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.80–3.02 (m, 4H), 3.93 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 6.75 (s, 1H), 7.30 (d, J = 10 Hz, 1H), 7.38 (s, 1H), 7.39 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.6, 27.0, 56.0, 56.3, 56.6, 61.5, 105.8, 106.9, 110.9, 115.0, 117.7, 119.9, 121.3, 129.1, 132.2, 146.6, 147.9, 149.3, 151.5, 152.1, 158.7; ESIMS (*m*/*z*) 391 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1730 cm^{-1}.



58b ($C_{21}H_{20}O_6$)

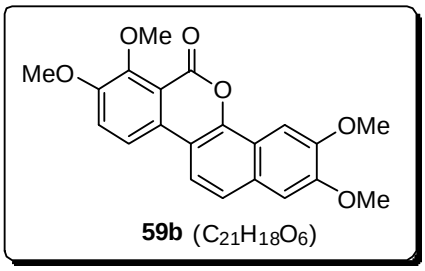
2,3-Dimethoxy-6*H*-dibenzo[c,h]chromen-6-one (59a). To a stirred solution of compound **58a** (154 mg, 0.50 mmol) in AcOH (5 mL) was added SeO_2 (165 mg, 1.50 mmol) and the reaction mixture was refluxed for 2 h under argon atmosphere. It was allowed to reach rt and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (20 mL) and the organic layer was washed with water, saturated solution of $NaHCO_3$, brine and dried over Na_2SO_4. The 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 (3:7) as an eluent gave pure product **59a** as faint yellow solid (150 mg, 98%). Mp 217–220 °C (lit.[47] 213 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 4.02 (s, 3H), 4.09 (s, 3H), 7.10 (s, 1H), 7.54 (t, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.74 (s, 1H), 7.82 (dt, J = 8, 2 Hz, 2H), 7.87 (d, J = 10 Hz, 1H), 8.11 (d, J = 10 Hz, 1H), 8.41 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.8, 56.2, 100.7, 106.1, 111.5, 117.2, 118.6, 120.3, 121.5, 122.6, 127.8, 130.1, 130.2, 134.6, 135.4, 146.0, 149.9, 150.5, 161.2; ESIMS (*m*/*z*) 306 $[M]^+$; IR ($CHCl_3$) ν_{max} 1732, 1629, 1607 cm^{-1}.



59a ($C_{19}H_{14}O_4$)

The product **59b** was similarly obtained by using above specified procedure.

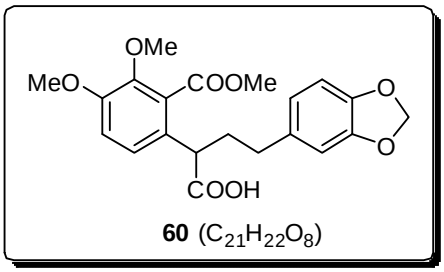
2,3,7,8-Tetramethoxy-6*H*-dibenzo[c,h]chromen-6-one (59b). Faint yellow solid (179 mg, 98%); mp 230–232 °C (lit.[49] 218–220 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 4.00 (s,



59b ($C_{21}H_{18}O_6$)

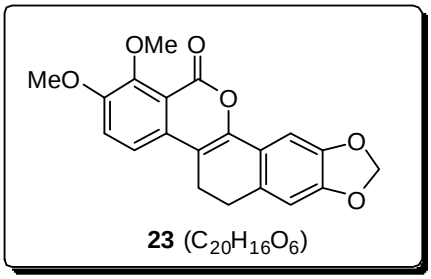
3H), 4.05 (s, 6H), 4.12 (s, 3H), 7.15 (s, 1H), 7.46 (d, J = 8 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 7.80 (s, 1H), 7.86 (d, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.9, 56.3, 56.4, 61.5, 100.9, 106.3, 111.5, 115.1, 117.4, 117.7, 118.6, 119.5, 122.5, 129.70, 129.74, 145.4, 150.0, 150.4, 151.5, 152.8, 157.9; ESIMS (*m*/*z*) 389 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1735, 1633 cm^{-1}.

4-(Benzo[d][1,3]dioxol-5-yl)-2-(3,4-dimethoxy-2-(methoxycarbonyl)phenyl)butanoic Acid (60). To a stirred solution of compound **56c** (1.25 g, 3.00 mmol) in MeOH (25 mL) was added 2% aqueous KOH (25 mL) at 0 °C. The reaction mixture was allowed to gradually attain rt and further stirred for 24 h. It was acidified with 2 N HCl and the formed product was extracted in ethyl acetate (25 mL × 2). The organic layer was washed with water, brine and dried over Na_2SO_4. The 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 (4:6) as an eluent gave pure product **60** as a thick oil (1.10 g, 91%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.90–2.15 (m, 1H), 2.20–2.60 (m, 3H), 3.52 (t, J = 8 Hz, 1H), 3.86 (s, 9H), 5.89 (s, 2H), 6.57 (dd, J = 8, 2 Hz, 1H), 6.62 (d, J = 2 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 6.96 (d, J = 10 Hz, 1H), 7.14 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.1, 34.5, 46.4, 52.4, 55.9, 61.4, 100.7, 108.1, 108.9, 114.2, 121.2, 123.2, 127.7, 129.3, 134.8, 145.7, 146.1, 147.5, 151.8, 168.2, 177.9; ESIMS (*m*/*z*) 425 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{22}O_8Na$ 425.1207, found 425.1204; IR ($CHCl_3$) ν_{max} 2700–2500, 1731, 1709, 1606 cm^{-1}.



60 ($C_{21}H_{22}O_8$)

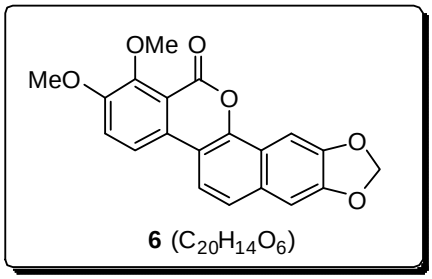
1,2-Dimethoxy-13*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-h]benzo[c]chromen-13-one (23). To a compound **60** (200 mg, 0.49 mmol) was added TFAA (2 mL) at –50 °C and the reaction mixture was stirred under argon atmosphere at –50 °C to 25°C for 3 h. The reaction mixture was concentrated in vacuo and the obtained residue was dried to vacuum pump. To the residue was added toluene (5 mL) and Cs_2CO_3 (326 mg, 1.00 mmol), and the stirred reaction mixture was



23 ($C_{20}H_{16}O_6$)

refluxed for 2 h. It was allowed to reach rt and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (30 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column (60–120 mesh) chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent gave pure product **23** as yellow solid (162 mg, 93%). Mp 245–248 °C (lit.[17] 250–251 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.81 (dd, J = 10, 2 Hz, 1H), 2.82 (d, J = 10 Hz, 1H), 2.91 (d, J = 10 Hz, 1H), 2.92 (dd, J = 10, 2 Hz, 1H), 3.95 (s, 3H), 3.99 (s, 3H), 5.97 (s, 2H), 6.70 (s, 1H), 7.28 (d, J = 10 Hz, 1H), 7.35 (s, 1H), 7.36 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 27.6, 56.6, 61.5, 101.2, 103.5, 107.1, 108.3, 115.2, 117.8, 119.9, 122.7, 130.8, 132.1, 146.6, 146.7, 147.9, 151.6, 152.2, 158.5; ESIMS (m/z) 375 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1734, 1700, 1670 cm^{-1}.

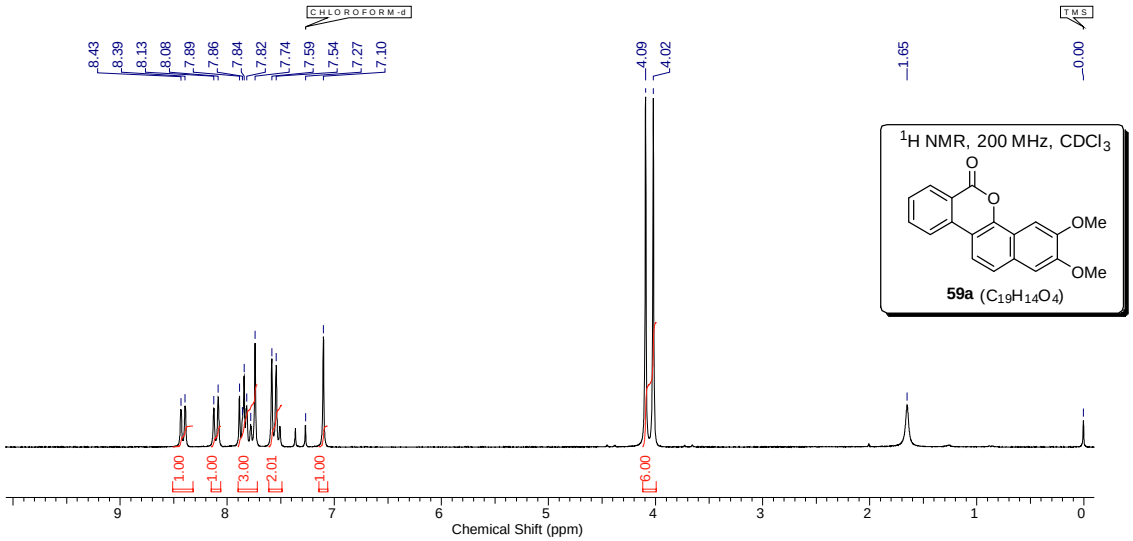
1,2-Dimethoxy-13*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-h]benzo[c]chromen-13-one

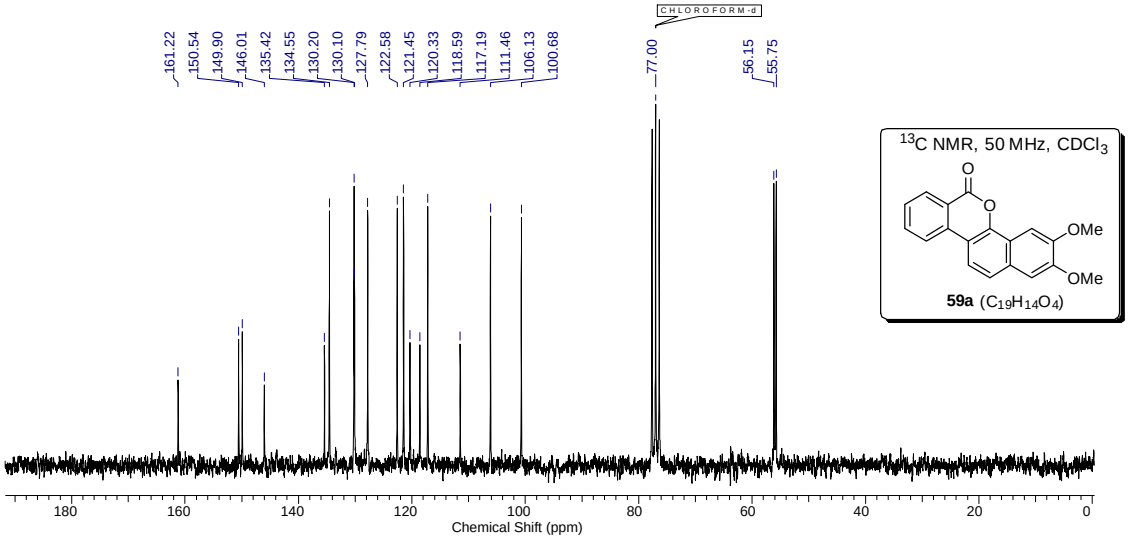


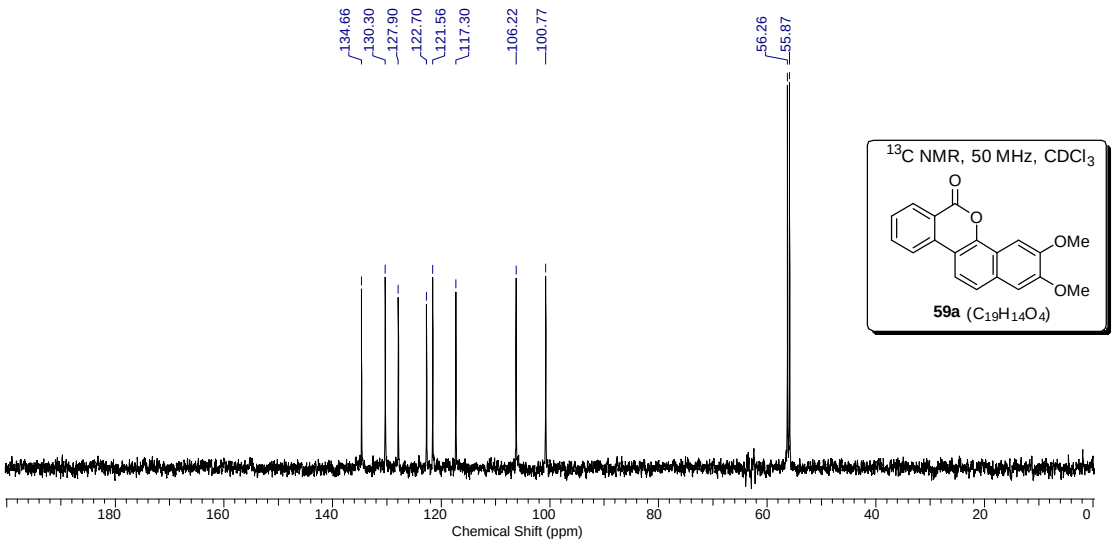
6 ($C_{20}H_{14}O_6$)

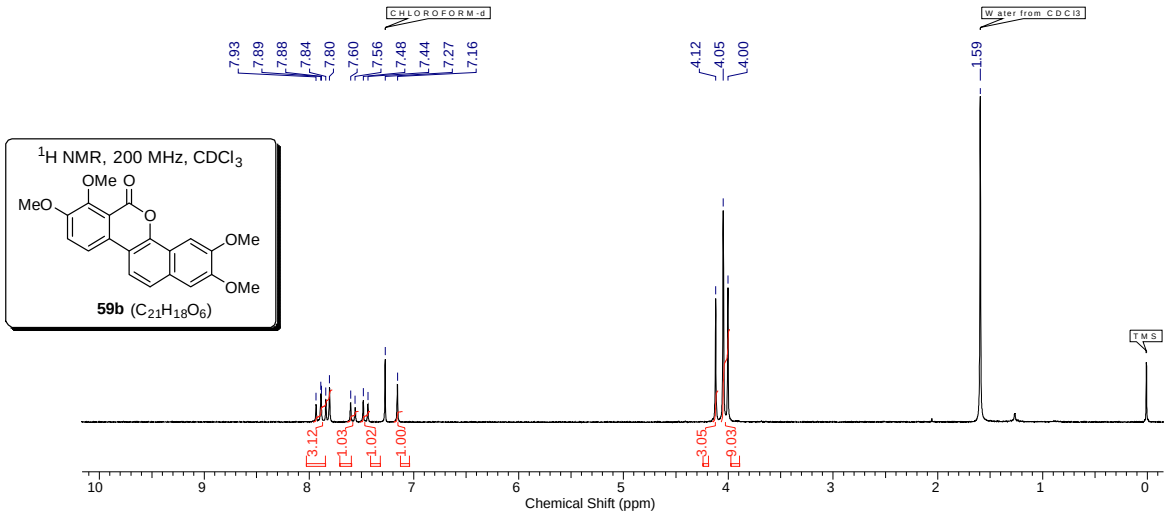
(Arnottin I, 6). A neat mixture of compound **23** (70 mg, 0.20 mmol) and SeO_2 (220 mg, 2.00 mmol) was heated in the sealed tube at 200 °C for 2 h. It was allowed to reach rt and the obtained residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with water, saturated solution of $NaHCO_3$, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo provided the pure product **6** as yellow solid (67 mg, 96%). The analytically pure sample of **6** was obtained by recrystalization from chloroform. Mp 296–298 °C (lit.[5] 293–297 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.00 (s, 3H), 4.04 (s, 3H), 6.11 (s, 2H), 7.15 (s, 1H), 7.46 (d, J = 10 Hz, 1H), 7.55 (d, J = 10 Hz, 1H), 7.86 (d, J = 10 Hz, 1H), 7.86 (s, 1H), 7.90 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.6, 61.6, 99.1, 101.5, 104.0, 112.1, 115.5, 117.7, 117.8, 119.7, 120.2, 123.2, 129.8, 131.2, 146.1, 148.5, 148.9, 151.7, 153.1, 157.7; ESIMS (m/z) 373 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1734,1651 cm^{-1}.

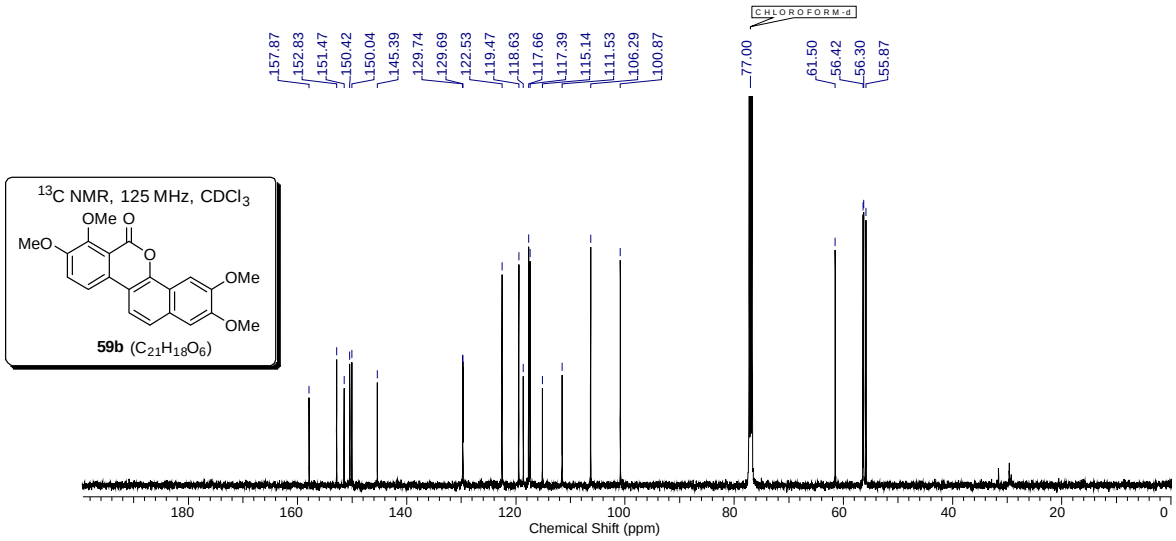
2B.7 Selected Spectra:

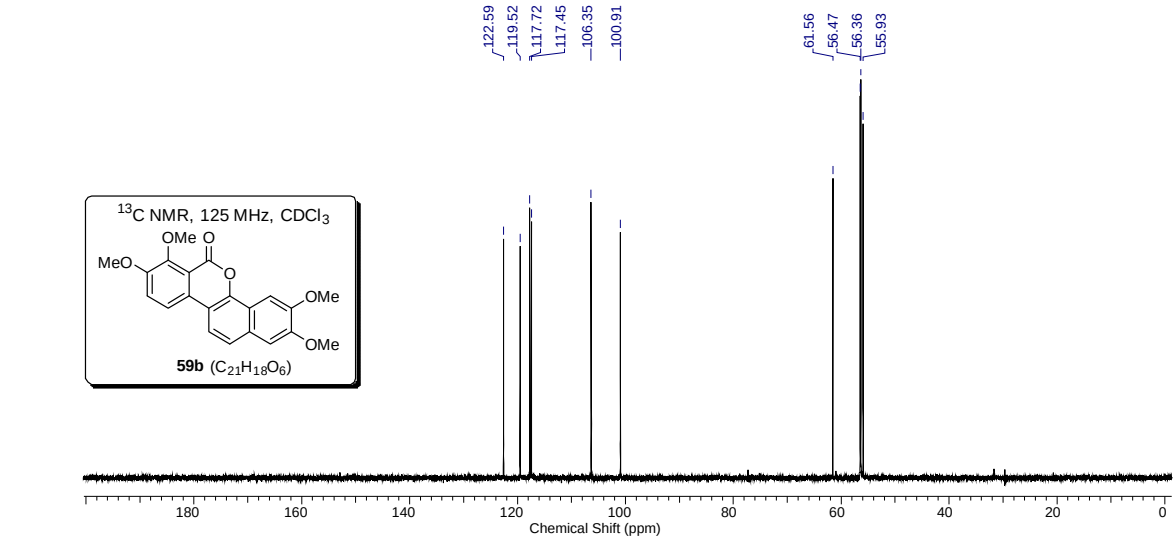

CHLOROFORM-d
TMS
8.43
8.39
8.13
8.08
7.89
7.86
7.84
7.82
7.74
7.59
7.54
7.27
7.10
4.09
4.02
1.65
0.00
1.00
1.00
3.00
2.01
1.00
6.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
^{1}H NMR, 200 MHz, CDCl$_3$
OMe
OMe
59a ($C_{19}H_{14}O_4$)

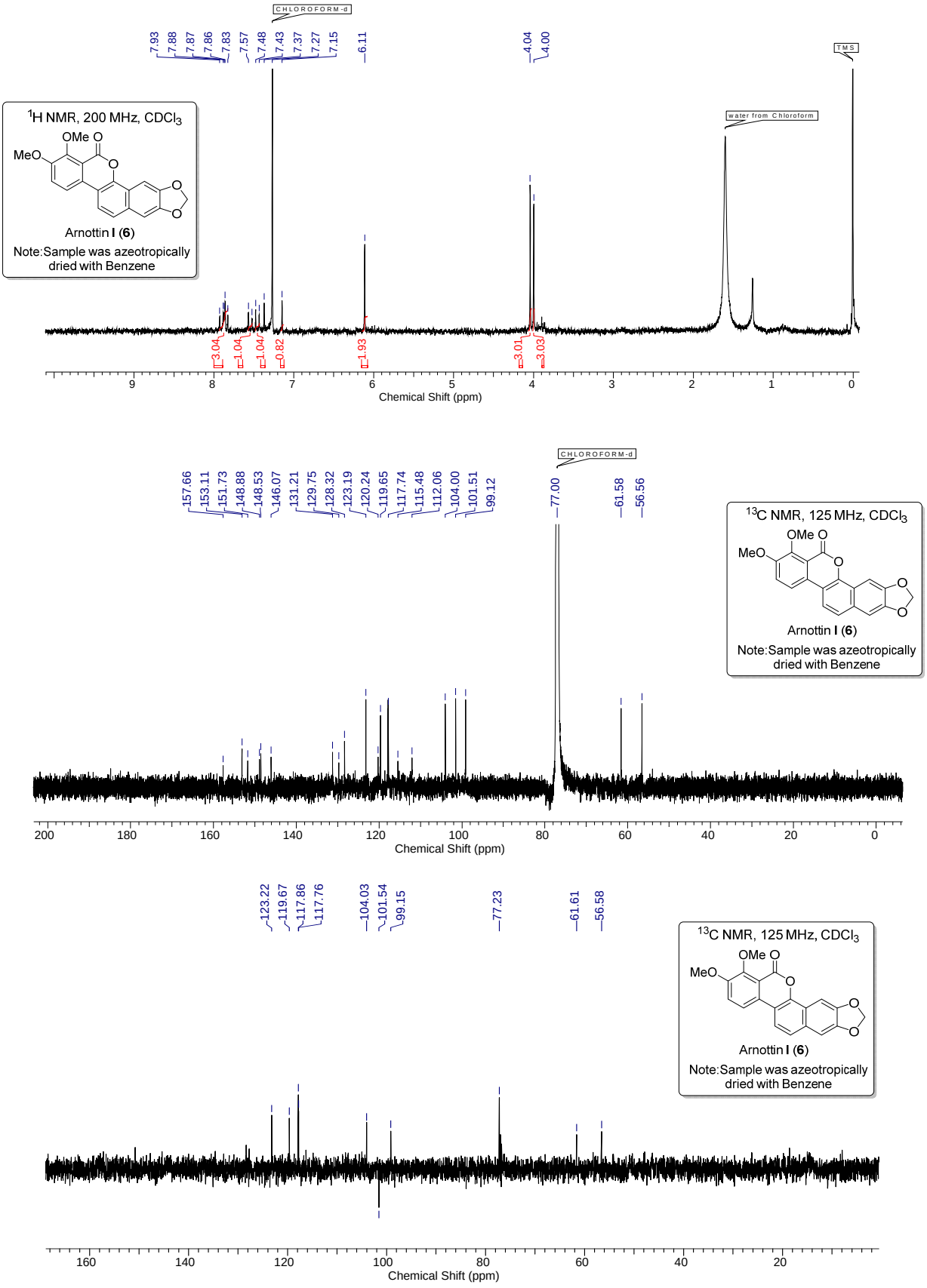

CHLOROFORM-d
161.22
150.54
149.90
146.01
135.42
134.55
130.20
130.10
127.79
122.58
121.45
120.33
118.59
117.19
111.46
106.13
100.68
77.00
56.15
55.75
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
^{13}C NMR, 50 MHz, CDCl$_3$
OMe
OMe
59a ($C_{19}H_{14}O_4$)


134.66
130.30
127.90
122.70
121.56
117.30
106.22
100.77
56.26
55.87
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
^{13}C NMR, 50 MHz, CDCl$_3$
OMe
OMe
59a ($C_{19}H_{14}O_4$)


CHLOROFORM-d
Water from CDCl3
7.93
7.89
7.88
7.84
7.80
7.60
7.56
7.48
7.44
7.27
7.16
4.12
4.05
4.00
1.59
TMS
3.12
1.03
1.02
1.00
3.05
9.03
Chemical Shift (ppm)
^{1}H NMR, 200 MHz, CDCl$_3$
OMe O
MeO
O
OMe
OMe
59b ($C_{21}H_{18}O_6$)


CHLOROFORM-d
157.87
152.83
151.47
150.42
150.04
145.39
129.74
129.69
122.53
119.47
118.63
117.66
117.39
115.14
111.53
106.29
100.87
77.00
61.50
56.42
56.30
55.87
Chemical Shift (ppm)
^{13}C NMR, 125 MHz, CDCl$_3$
OMe O
MeO
O
OMe
OMe
59b ($C_{21}H_{18}O_6$)


122.59
119.52
117.72
117.45
106.35
100.91
61.56
56.47
56.36
55.93
Chemical Shift (ppm)
^{13}C NMR, 125 MHz, CDCl$_3$
OMe O
MeO
O
OMe
OMe
59b ($C_{21}H_{18}O_6$)


CHLOROFORM-d
7.93
7.88
7.87
7.86
7.83
7.57
7.48
7.43
7.37
7.27
7.15
6.11
4.04
4.00
TMS
water from Chloroform
^{1}H NMR, 200 MHz, CDCl$_3$
OMe O
MeO
O
O
O
Arnottin I (6)
Note:Sample was azeotropically dried with Benzene
3.04
1.04
1.04
0.82
1.93
3.01
3.03
Chemical Shift (ppm)
CHLOROFORM-d
157.66
153.11
151.73
148.88
148.53
146.07
131.21
129.75
128.32
123.19
120.24
119.65
117.74
115.48
112.06
104.00
101.51
99.12
77.00
61.58
56.56
^{13}C NMR, 125 MHz, CDCl$_3$
OMe O
MeO
O
O
O
Arnottin I (6)
Note:Sample was azeotropically dried with Benzene
Chemical Shift (ppm)
123.22
119.67
117.86
117.76
104.03
101.54
99.15
77.23
61.61
56.58
^{13}C NMR, 125 MHz, CDCl$_3$
OMe O
MeO
O
O
O
Arnottin I (6)
Note:Sample was azeotropically dried with Benzene
Chemical Shift (ppm)

2B.8 References

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Chapter 2

Section C

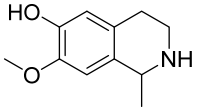
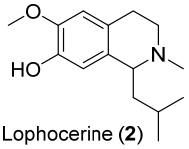
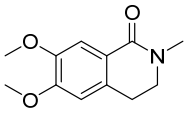
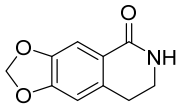
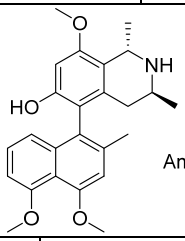
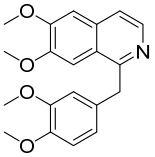
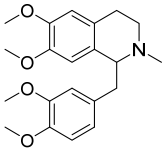
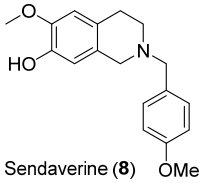
Total Synthesis of Laudanosine, Romneine, Glaucine, Dicentrine, Isolaudanosine and Isoromneine

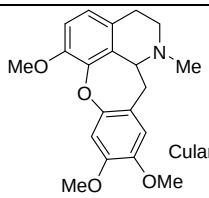
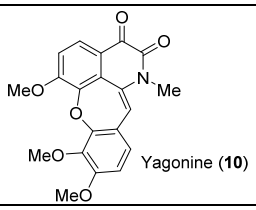
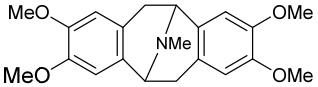
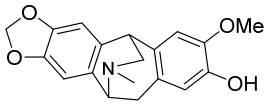
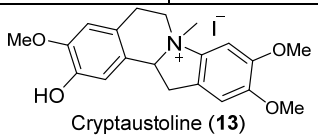
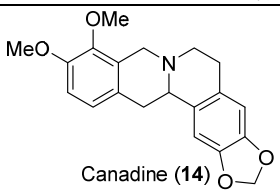
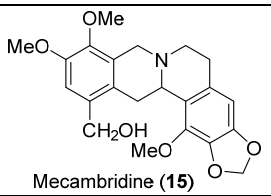
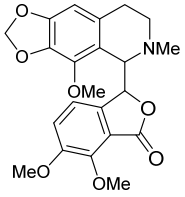
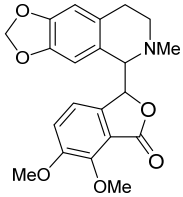
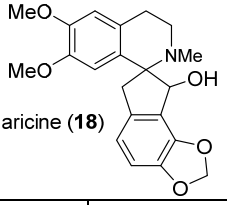
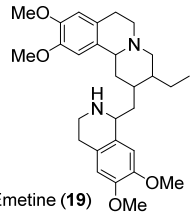
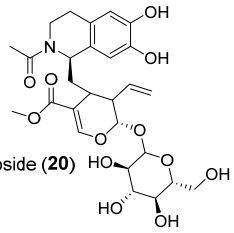
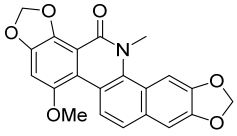
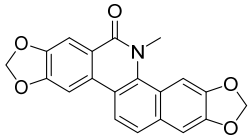
Note: An independent figure, table, scheme, structure and reference numbers have been used for the each section.

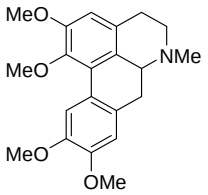
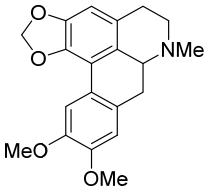
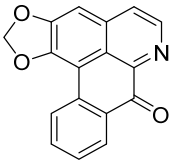
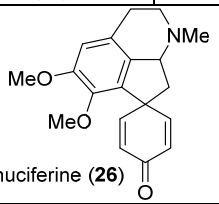
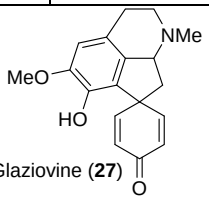
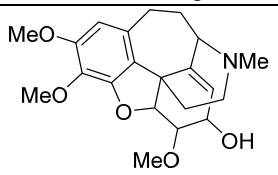
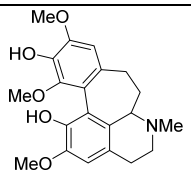
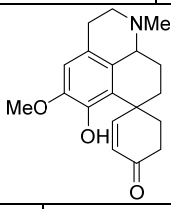
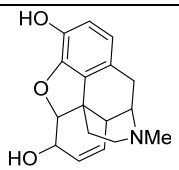
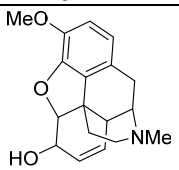
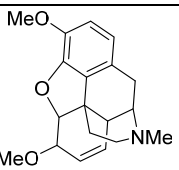
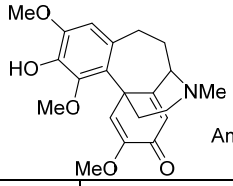
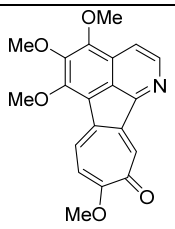
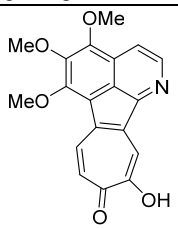
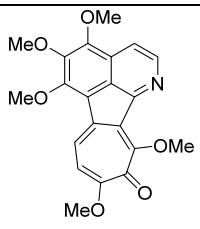
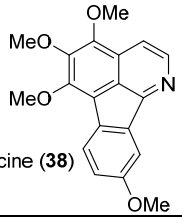
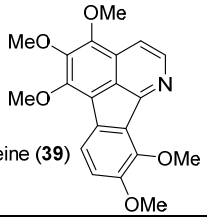
2C.1 Background

Isoquinoline was first isolated from coal tar in 1885 by Hoogewerf and Van Dorp.[1] They isolated it by fractional crystallization of the acid sulfate. Isoquinoline alkaloids constitute a large family which has over 400 members.[2] Isoquinolines and derivatives are used in the manufacture of dyes, paints, insecticides and antifungals. Isoquinoline alkaloids are widely distributed in nature. They exhibit broad range of biological activities owing to their various structures, including antibacterial, antitumor, analgesic, antiarrhythmic, anti-platelet aggregation, antihypertensive and immunoregulation activities. Structure-activity relationships of isoquinoline alkaloids are paid attention all the while.[3]

The active neurotoxins destroy dopaminergic neurons leading to parkinsonism and Parkinson's disease. Several tetrahydroisoquinoline derivatives have been found to have neurochemical properties. These derivatives act as neurotoxin precursors for active neurotoxins.[4] Isoquinoline alkaloids is a large family and has been divided in various groups of natural products. Some of the major groups of isoquinoline alkaloid family along with some of selected members are presented in Table 1.

S. No.	**Name of the Group**	**Members of the Group**	
1.	Simple derivatives of isoquinoline[5]	 Salsoline (**1**)	 Lophocerine (**2**)
2.	Derivatives of 1-isoquinolines[6]	 Methylcoridaldine (**3**)	 Noroxyhydrastinine (**4**)
3.	Derivative of 5-naftil-isoquinoline[7]	 Ancistrocladine (**5**)	
4.	Derivative of 1- and 2-benzyl isoquinolines[8,9,10]	 Papaverine (**6**)	 Laudanosine (**7**)  Sendaverine (**8**)

5.	Cularine group[11]	 Cularine (**9**)	 Yagonine (**10**)
6.	Pavines and isopavines[12]	 Argemonine (**11**)	 Amurensine (**12**)
7.	Benzopyrrocolines[13]	 Cryptaustoline (**13**)	
8.	Protoberberines[14,15]	 Canadine (**14**)	 Mecambridine (**15**)
9.	Phthalidisoquinolines[16]	 Noscapine (**16**)	 Hydrastine (**17**)
10.	Spirobenzylisoquinolines[17]	 Fumaricine (**18**)	
11.	Ipecacuanha alkaloids[18]	 Emetine (**19**)	 Ipecoside (**20**)
12.	Benzophenanthridines[19,20]	 Oxychelirubine (**21**)	 Oxyavicine (**22**)

13.	Aporphines[21]	 Glaucine (**23**)	 Dicentrine (**24**)	 Liriodenine (**25**)
14.	Proaporphines[22]	 Pronuciferine (**26**)	 Glaziovine (**27**)	
15.	Homoaporphines[23]	 Kreysiginine (**28**)	 Multifloramine (**29**)	
16.	Homoproaporphines[24]	 Bulbocodine (**30**)		
17.	Morphines[25]	 Morphine (**31**)	 Codeine (**32**)	 Thebaine (**33**)
18.	Homomorphines[23]	 Androcymbine (**34**)		
19.	Tropoloisoquinolines[26]	 Imerubine (**35**)	 Grandirubine (**36**)	 Pareirubine A (**37**)
20.	Azofluoranthenes[26]	 Rufescine (**38**)	 Imeluteine (**39**)	

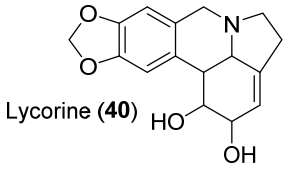
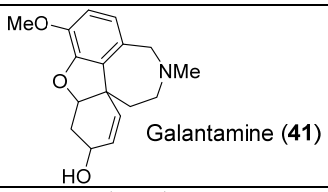
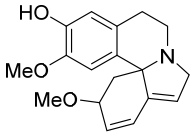
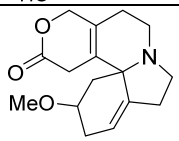
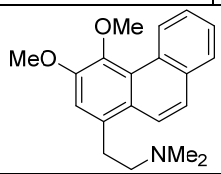
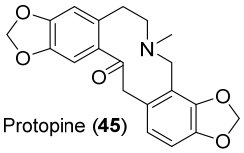
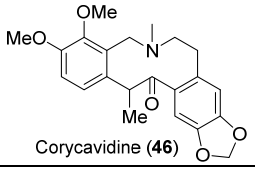
21.	Amaryllis alkaloids[27]	 Lycorine (**40**)	 Galantamine (**41**)
22.	Erythrina alkaloids[28]	 Erysodine (**42**)	 Beta-Erythroidine (**43**)
23.	Phenanthrene derivatives[29]	 Atherosperminine (**44**)	
24.	Protopines[30]	 Protopine (**45**)	 Corycavidine (**46**)

Table 1. Some Selected Members of Isoquinoline Family

Isoquinoline alkloids have been synthesized by various methods. There are certain methods and reactions which are used to form a particular bond in the isoquinoline. A brief account is shown in the Table 2.

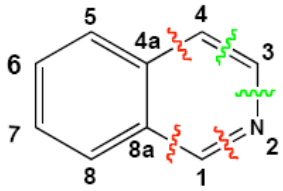
Synthesis of core 	**Classic:** C8a-C1: Bischler-Napieralski reaction Pictet-Gams reaction C1-N2: Pictet-Spengler reaction C4-C4a: Pomeranz-Fritsch reation
	Novel: Formation of C3-C4 and N2-C3 Ring expansion of other ring system

Table 2. Synthetic Approaches Towards Isoquinoline Alkaloids

Out of very large number of bioactive isoquinoline alkaloids, firstly we synthesized simple isoquinolines doryanine (**47**) and oxyhydrastinine (**48**). After synthesis of these isoquinoline alkaloids we moved forward for the synthesis of benzyl isoquinolines laudanosine (**7**) and romneine (**49**) which further lead to the synthesis of aporphine class of isoquinoline alkaloids glaucine (**23**) and dicentrine (**24**) via intramolecular cyclization pathaway. We have also synthesized the regioisomers of the corresponding benzyl isoquinoline alkaloids isolaudanosine (**50**) and Isoromneine (**51**).

The alkaloid doryanine was isolated from *Cryptocarya chinensis*, *Doryphora sassafras* and *Mitragyna speciosa* species.[31] The alkaloid oxyhydrastinine has been widely spread in nature and it was isolated from *Argemone mexicana*, *Hunnemania fumariaefolia*, *Hydrastis canadensis*, *Hypecoum erectum*, *Hypecoum leptocarpum*, *Fumaria agraria*, *Fumaria bastardii*, *Fumaria indica*, *Fumaria sepium* and *Papaveraceae* species. It is known to possess antibacterial, antitubercular and immunostimulant activities.[32]

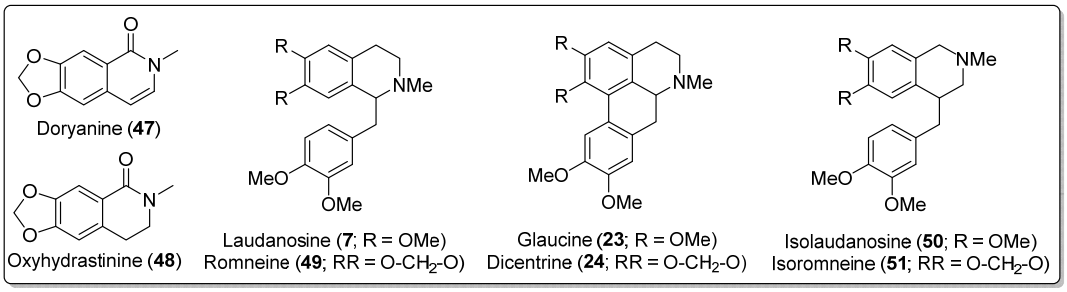


Figure 1. Tetrahydroisoquinoline based bioactive alkaloids

Laudanosine (from the roots of *Polyalthia cerasoides*),[33] romneine (from the leaves of *Ctyptrxarya chinensis*),[34] glaucine (from the bark of *Artabotrys lastouwillmsis*)[35] and dicentrine (from parts of *Ocotea leucoxylon*)[36] have been isolated from various plant species and they exhibit potential anti-cancer, anti-neuropsychiatric, vasorelaxing, GABA receptor and an anticough activities.[37-40] Homophthalic acids bear an appropriate carbon skeleton and functional groups and serve as central precursors for the synthesis of isoquinoline alkaloids.[41-45]

2C.2.1 Reported Synthetic Approaches Towards Doryanine and Oxyhydrastinine

Several synthesis of these two simple natural products are known in the literature.[4,5] They have been designed by employing new C–C and C–N bond forming reactions.[46-61] A brief account of literature is represented in the Table 3.

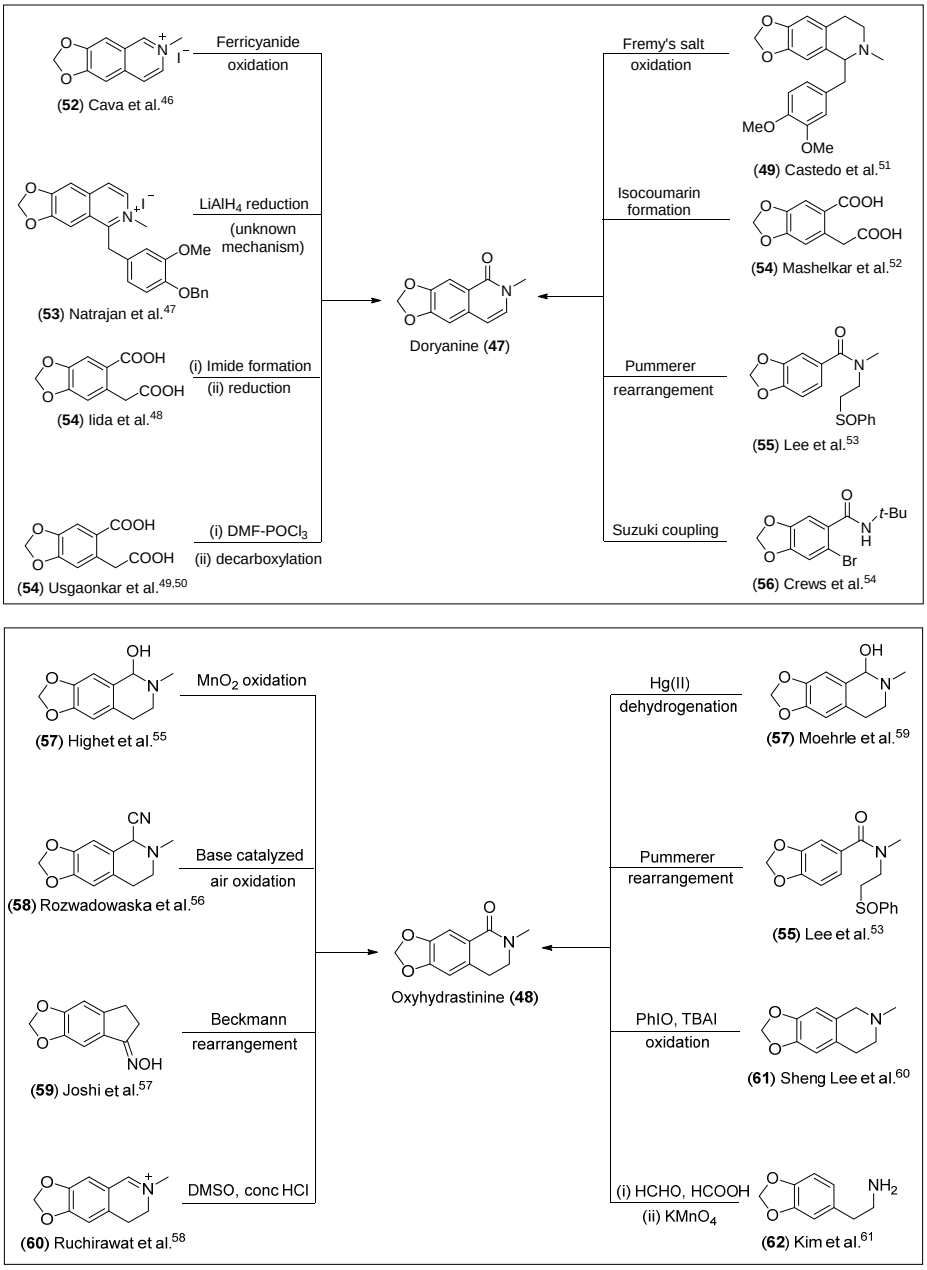
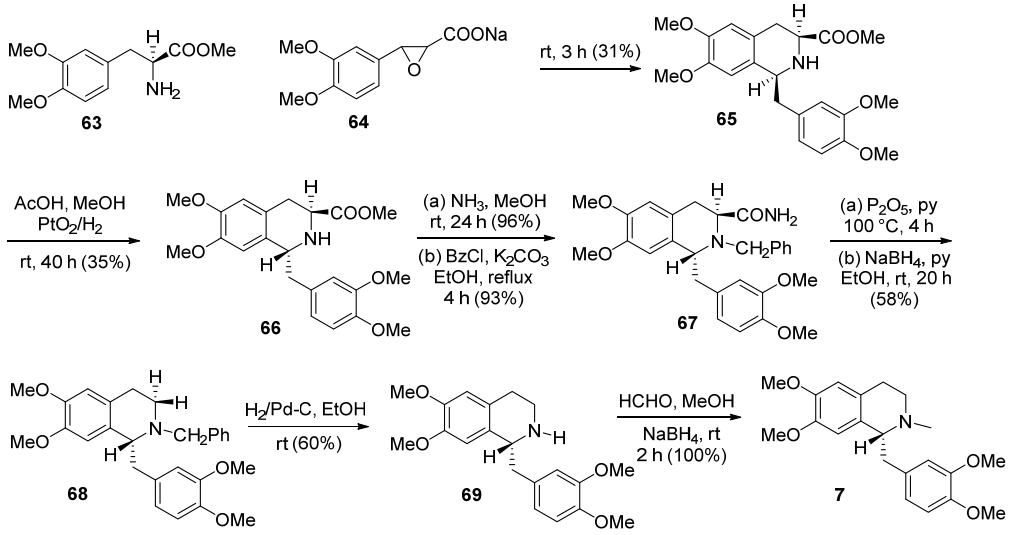


Table 3. Consice Summary of Known Doryanine and Oxyhydrastinine Synthesis

2C.2.2 Reported Synthetic Approaches Towards Romneine and laudanosine

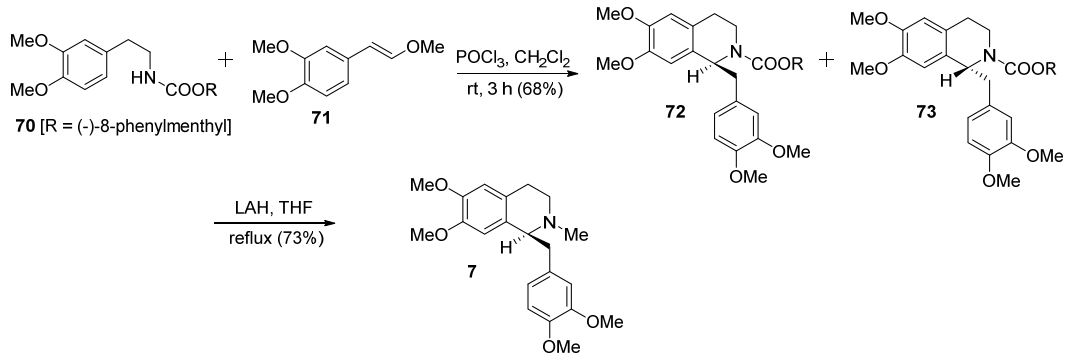
Yamada et al. in 1977 synthesized (-)-laudanosine (**7**) via Pictet-Spengler reaction (Scheme 1).[62] The desired isomer *cis*-ester **65** was synthesized by the Pictet-Spengler reaction of chiral amine **63** and (±)-epoxide **64** in 31% yield. The compound **65** was stirred with PtO_2/H_2 in AcOH and MeOH; which gave *cis*-ester **65** and *trans*-ester **66** in 1:3.8 ratio and *trans*-ester **66** was isolated in 35% yield. Amide **67** was synthesized by using methanolic ammonia followed by *N*-benzylation in 93% yield. Dehydration of **67** to

nitrile was effected by heating at 100 °C with P_2O_5 in pyridine, which was immediately subjected to decyanization with $NaBH_4$ to obtain compound **68** in 58% yield. Debenzylation of **68** with H_2/Pd-C gave (-)-nor-laudanosine (**69**) in 60% yield. Finally (-)-laudanosine (**7**) was obtained by methylation with formaldehyde and $NaBH_4$ in quantitative yield.



Scheme 1. Synthesis of Laudanosine via Pictet-Spengler Reaction

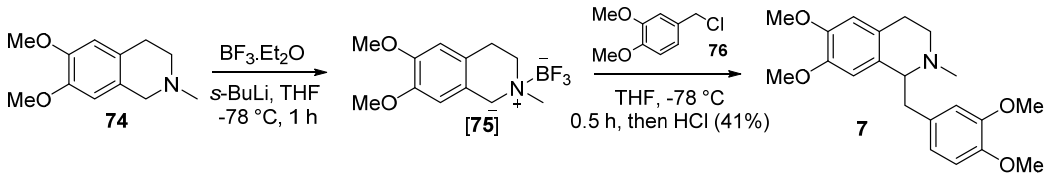
Comins et al. in 1991 completed the enantioselective synthesis of (-)-laudanosine by using chiral auxillary mediated Pictet-Spengler reaction (Scheme 2).[63] The enantiopure carbamate **70** was prepared from 3,4-dimethoxyphenethylamine and (-)-8-phenylmenthyl chloroformate.[64] Condensation of **70** and vinyl ether **71** gave a mixture of diastereomers **72** and **73** in 68% yield with 83:17 ratio. The mixture of **72** and **73** was heated with lithium aluminum hydride to give (-)-laudanosine (**7**) in 73% yield with 63% *ee*.



Scheme 2. Synthesis of Laudanosine by Using Chiral Auxillary Approach

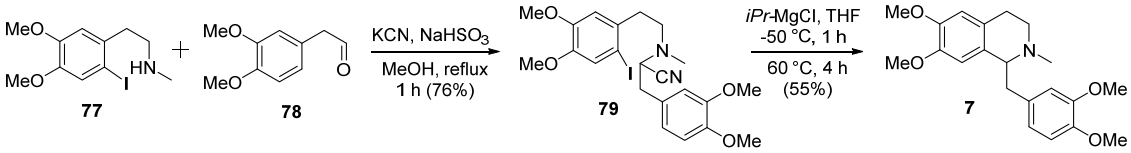
Kessar et al. in 1991 reported the synthesis of laudanosine via α-metallation of tertiary amine (Scheme 3).[65] Amine **74** was treated with Lewis acid $BF_3.Et_2O$ to form borone

complex which was further treated with *s*-BuLi to obtain the intermediate carbanion **75**. Carbanion **75** on reaction with electrophile **76** furnished laudanosine (**7**) in 41% yield.



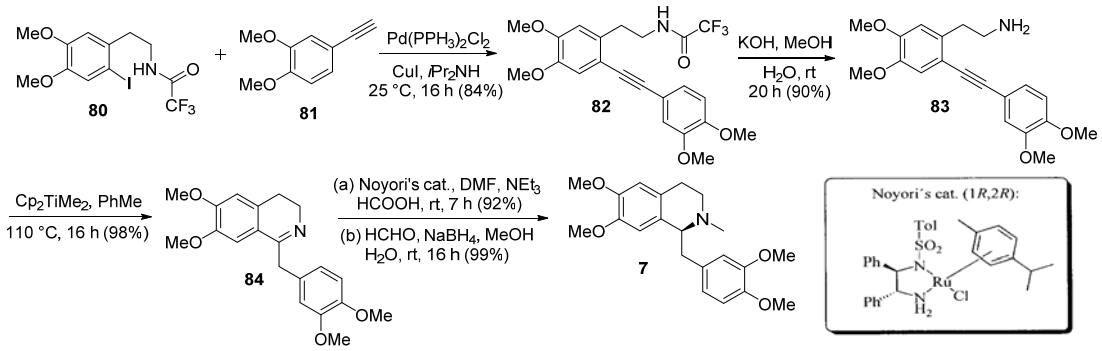
Scheme 3. Synthesis of Laudanosine by Metallation Reaction

Reimann et al. in 2004 reported the synthesis of laudanosine using the Strecker-Bruylant reaction (Scheme 4).[66] The iodophenethylamine **77** was reacted with the phenylacetaldehyde **78** in the presence of KCN affording the aminonitrile **79** (Strecker reaction) in 76% yield. The nitrile **79** was treated with *iso*-propyl magnesium chloride in THF which underwent iodine-magnesium exchange and furnished the laudanosine (**7**) via Bruylant reaction in 55% yield.



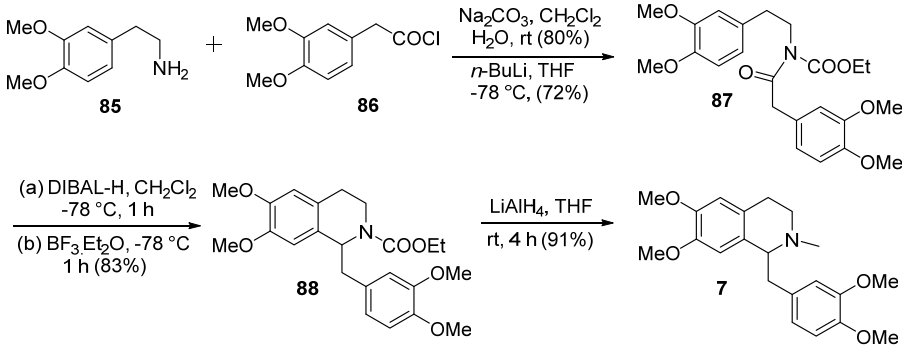
Scheme 4. Synthesis of Laudanosine by Using Strecker-Bruylant Reaction

Doye et al. in 2005 reported the enantioselective synthesis of (+)-laudanosine using Sonogashira coupling and Noyori's catalyst (Scheme 5).[67] Aryl iodide **80** and alkyne **81** were subjected to standard Sonogashira coupling condition to give trifluoroacyl-protected alkyne **82** in 84% yield. Liberation of the NH_2 group under basic condition delivered aminoalkyne **83** in 90% yield. This key intermediate was then subjected to an intramolecular hydroamination reaction at 110 °C in toluene by employing 10 mol% Cp_2TiMe_2 to produce imine **84** in 98% yield. Imine **84** was enantioselectively reduced by Noyori's protocol[68] to the corresponding secondary amine in 92% yield with 93% *ee*, which was subjected to reductive amination to obtain (+)-laudanosine (**7**) in 99% yield.



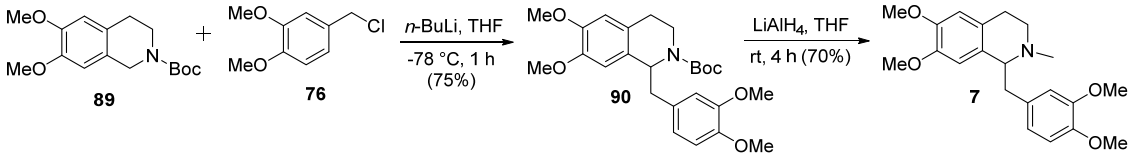
Scheme 5. Synthesis of Laudanosine by Using Sonogashira Coupling

Ruchirawat et al. in 2007 reported the synthesis of laudanosine via Pictet-Spengler reaction (Scheme 6).[69] The phenylethylamine **85** was treated with acid chloride **86** under biphasic conditions to obtain amide in 80% yield. The resulting amide was lithiated with *n*-BuLi followed by trapping with ethyl chloroformate to yield *N*-acylcarbamate **87** with 72% yield. Treatment of *N*-acylcarbamate **87** with 1.50 equiv of DIBAL-H in hexane followed by sequential addition of $BF_3.Et_2O$ gave tetrahydroisoquinoline derivative **88** in 83% yield. Reduction of **88** by $LiAlH_4$ afforded laudanosine (**7**) in 91% yield.



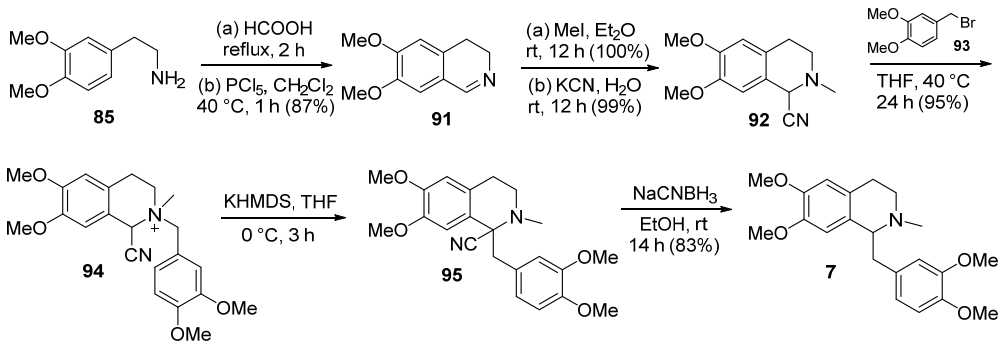
Scheme 6. Synthesis of Laudanosine via Reductive Intramolecular Cyclization

Coldham et al. in 2013 reported the synthesis of laudanosine by lithiation and electrophilic quenching (Scheme 7).[70] Treatment of tetrahydroisoquinoline **89** with *n*-BuLi in THF for 4 min, followed by addition of 3,4-dimethoxybenzyl chloride (**76**) gave product **90**, which was reduced with $LiAlH_4$ to obtain the laudanosine (**7**) in 70% yield.



Scheme 7. Synthesis of Laudanosine via Electrophilic Quenching

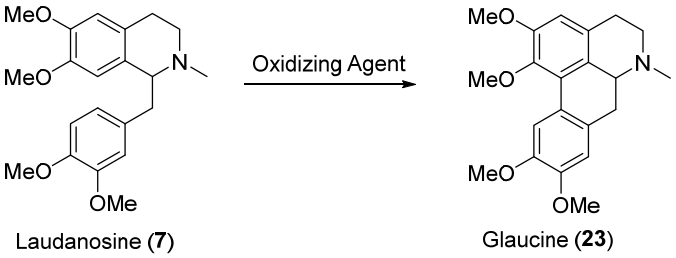
Opatz et al. in 2013 reported the synthesis of laudanosine via Steven's rearrangement (Scheme 8).[71] Condensation of homoveratrylamine (**85**) with formic acid followed by Bischler−Napieralski cyclization provided 6,7-dimethoxy-3,4-dihydroisoquinoline (**91**) in 87% yield. *N*-Methylation with methyl iodide was done in quantitative yield, which was followed by treatment with aqueous KCN to obtain *α*-aminonitrile **92** in 99% yield. *N*-Benzylation of **92** with benzyl bromide **93** led to the corresponding tetrahydroisoquinolinium salt **94** in 95% yield. The formed salt was treated with KHMDS in THF to generate the nitrile-stabilized ammonium ylide, which readily underwent a Steven's rearrangement to lead to *C*-alkylated *α*-aminonitrile **95**.[72] In situ reduction of the rearrangement product **95** with $NaCNBH_3$ gave laudanosine (**7**) in 83% yield.



Scheme 8. Synthesis of Laudanosine via Steven's Rearrangement

2C.2.3 Reported Synthetic Approaches Towards Glaucine and Dicentine

Glaucine is an aporphine alkaloid which has been synthesized from oxidation of laudanosine by many research groups, details of which are summarized below (Table 4).

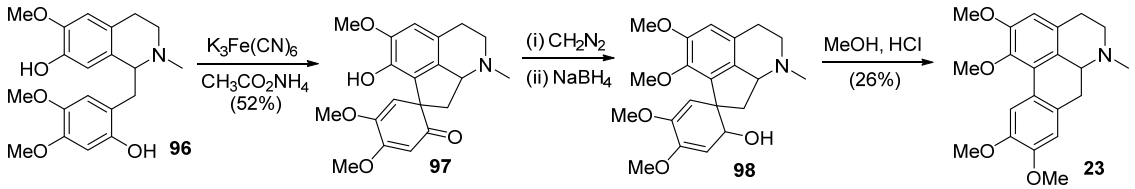


Research Group	Oxidizing Agent	Reaction Condition	% Yield
Szarek et al.[73]	$Tl(CF_3COO)_3$, CF_3COOH, $BF_3.Et_2O$	0 °C, 3 h	47
Robin et al.[74]	$Ru(CF_3COO)_4$	20 °C, 24 h	76
Meyers et al.[75]	VOF_3, TFA, TFAA, CH_2C1_2	–10 °C, 40 min	40
Robin et al.[76]	$RuO_2.2H_2O$, CH_2C1_2, TFA, TFAA, $BF_3.Et_2O$	20 °C, 12 h	66
Robin et al.[77]	$Ce(OH)_4$, CH_2C1_2, TFA, TFAA, $BF_3.Et_2O$	0 °C, 6 h	80
Badia et al.[78]	PIFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2	–20 °C, 30 min	75
Lee et al.[79]	PIFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2	–40 °C, 3 h	33
Ruchirawat et al.[80]	PIFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2	–40 °C, 1 h	36

Table 4. Oxidative Transformation of Laudanosine to Glaucine

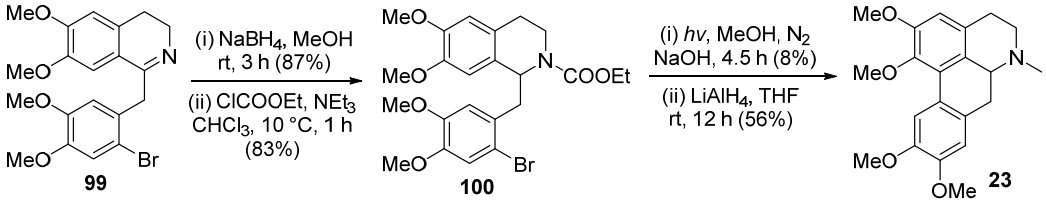
Shamma et al. in 1965 reported the synthesis of glaucine by using acid catalyzed intramolecular coupling reaction (Scheme 9).[81] The benzyltetrahydroisoquinoline **96** was

was oxidized with aqueous potassium ferricyanide and ammonium acetate to give the spirocompound **97** in 52% yield. Treatment of **97** with diazomethane afforded the amorphous tetramethoxy-base, which was reduced by sodium borohydride to obtain 2,4-dienol **98**. Rearrangement of the dienol **98** using anhydrous methanolic HCl delievered the glaucine (**23**) in 26% yield.



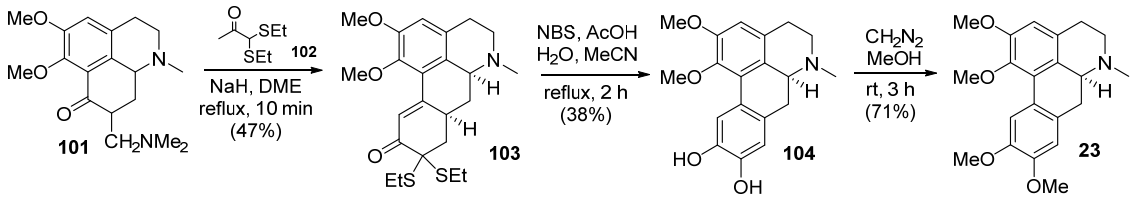
Scheme 9. Synthesis of Glaucine via Acid Catalyzed Ring Expansion

Gupta et al. in 1989 reported the photochemical synthesis of Glaucine (Scheme 10).[82] The compound **99**[83] was reduced with $NaBH_4$, which on subsequent treatment with ethyl chloroformate furnished the bromourethane **100** in 83% yield. Irradiation of **100** under a current of nitrogen for 4.5 h in aqueous methanol in the presence of sodium hydroxide afforded the corresponding cyclized product in only 8% yield. Subsequent reduction with LAH in THF afforded glaucine (**23**) in 56% yield.



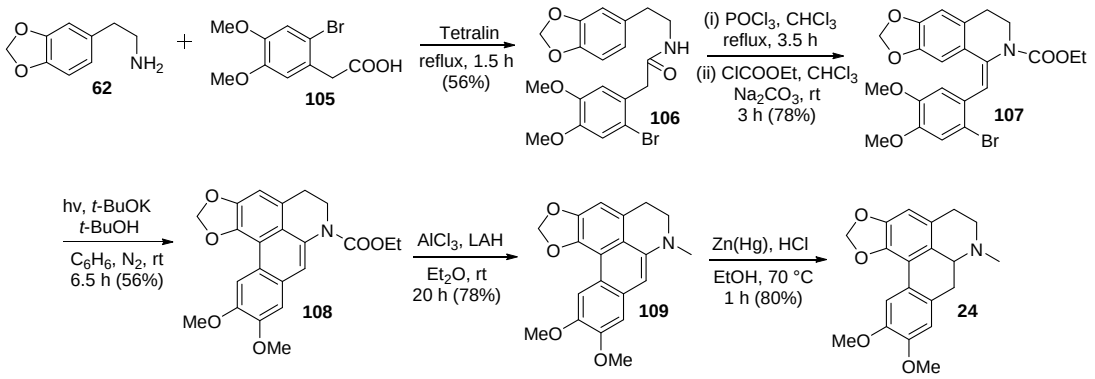
Scheme 10. Synthesis of Glaucine via Photochemical Pathway

Kim et al. in 1993 reported the synthesis of (+)-glaucine by using [3C + 3C] annulation reaction (Scheme 11).[84] The base **101** was condensed with **102** to obtain the tetracyclic compound **103** in 47 % and its isomer in 11% yield respectively. The cyclohexanone **103** was dethioacetalized by NBS in AcOH, H_2O and MeCN; which on treatment with boiling AcOH furnished the diol **104** in 38% yield. The phenolic compound **104** was treated with diazomethane to obtain (+)-galucine (**23**) in 71% yield.



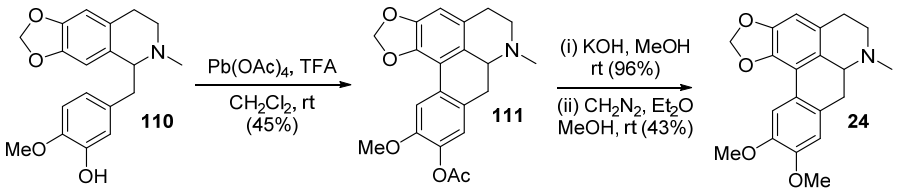
Scheme 11. Synthesis of Glaucine by Using [3C + 3C] Annulation

Cava et al. in 1973 reported photochemical synthesis of dicentrine (Scheme 12).[85] The amide **106** was prepared from homopiperonylamine (**62**) and 6-bromohomoveratric acid (**105**) in 56% yield. Amide **106** was cyclized by Bischelr-Napieralski reaction and treated with ClCOOEt to obtain **107** in 78% yield. Bromide **107** was irradiated in 20% *t*-BuOH-C_6H_6 in the presence of *t*-BuOK as the base to obtain tetracyclic core structure **108** in 56% yield. Alane reduction of urethane **108** with $LiAlH_4$ in the presence of $AlCl_3$ gave dehydrodicentrine **109** in 78% yield. Reduction of **109** with zinc amalgam and HCl afforded dicentrine (**24**) in 80% yield.



Scheme 12. Synthesis of Dicentrine via Photchemical Pathway

Umezawa et al. in 1986 reported the synthesis of dicentrine employing leadtetracetate oxidation (Scheme 13).[86] The benzylisoquinoline **110** was oxidized with $Pb(OAc)_4$ in presence of TFA to afford aceylated dicentrine **111** in 45% yield. Compound **111** was hydrolyzed and methylated to obtain dicentrine (**24**) in 43% yield.



Scheme 13. Synthesis of Dicentrine by Using Leadtetracetate Induced Coupling

2C.3 Rationale for the Present Work

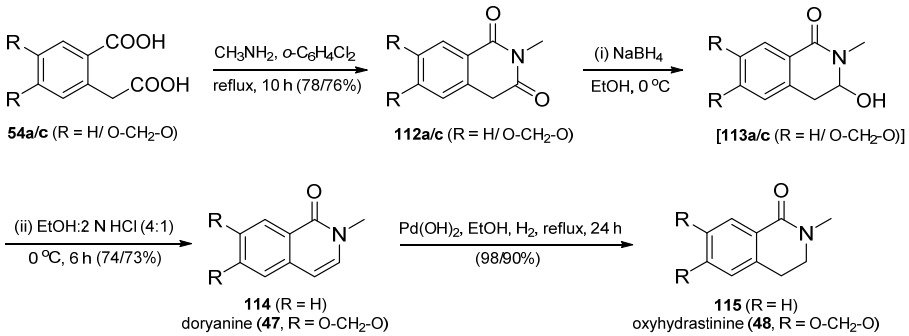
2C.3.1 Synthesis of Doryanine and Oxyhydrastanine

Several synthesis of these two simple natural products are known in the literature.[46-61] They have been designed by employing new carbon–carbon and carbon–nitrogen bond forming reactions. In continuance with our past two decades studies on cyclic anhydrides and their derivatives to bioactive natural products, we reasoned that 4,5-

methylenedioxyhomophthalic anhydride[87] would be a potential precursor for the synthesis of doryanine and oxyhydrastinine. In this context, now we herein present the practical synthesis of the target compounds (Scheme 14).

The homophthalic acids **54a** and **54c** were initially stirred with excess of 40% aqueous solution of methyl amine at 25 °C for few minutes to form their salts. The obtained dry salts on vigorous refluxing in *o*-dichlorobenzene for 10 hours provided the corresponding precursor homophthalimides **112a** and **112c** in very good yields via the amide formation followed by intramolecular dehydrative cyclization route.[88] The regioselective sodium borohydride reduction of more reactive unconjugated imide carbonyl group in imides **112a** and **112c** formed the corresponding geminal aminohydrin intermediates **113a** and **113c**. Herein the boron atom selectively complexes with an oxygen atom from more electron rich unconjugated imide carbonyl group resulting in complete regioselectivity. These aminohydrin intermediates exhibit ring-chain tautomerism and were prone for decomposition. During the course of reduction we also noticed the formation of undesired acyclic over reduced product, which is in accordance with Cheng et al observation.[8b] Therefore an in situ dehydration with the periodic addition of controlled amount of hydrochloric acid was performed to directly obtain the desired model compound **114** and the natural product doryanine (**47**) in nearly 75% yields. Similar protocol has been earlier employed by Iida et al. to design the doryanine (**47**), however the complete experimental details are not avilable.[48] On completion of sodium borohydride reduction reaction they have acidified the reaction mixture with 10% hydrochloric acid. As per our studies a periodic addition of hydrochloric acid to the reaction mixture is essential for the completion of reaction and yield issues. It also helps in avoiding the decomposition and formation of undesired over reduction products. In the next part, we performed the reduction of carbon–carbon double bond in heterocyclic ring B in compound **114** by using palladium on carbon in ethyl acetate and obtained the desired second prototypical compound **115** in quantitative yield. The above specified hydrogenation reaction at room temperature under 30 psi of hydrogen pressure was very slow and it took almost three days for the completion (monitored by ^{1}H NMR). In our hands repetition of the same reduction reaction with substrate **47** was not feasible and the starting material remained completely unreacted. We also tried the palladium on carbon catalyzed reduction of compound **47** at room temperature in other solvents such as methanol, ethanol and petroleum ether using hydrogenation Parr shaker under 65 psi of hydrogen pressure. The

results were not encouraging and we always ended up with isolation of starting material. We feel that the cause for failure could be the relatively lower reactivity of substrate **47** bearing the oxymethylene bridge. Finally, the palladium hydroxide induced hydrogenation of both compounds **114** and **47** under the balloon pressure hydrogen atmosphere in refluxing ethanol delivered the desired compound **115** and natural product oxyhydrastinine (**48**) in nearly quantitative yields. The analytical and spectral data obtained for synthetic **47** and **48** were in complete agreement with the reported data.[31,32] Thus starting from 4,5-methylenedioxyhomophthalic acid, we completed the two-step synthesis of doryanine and three-step synthesis of oxyhydrastinine in decent overall yields.



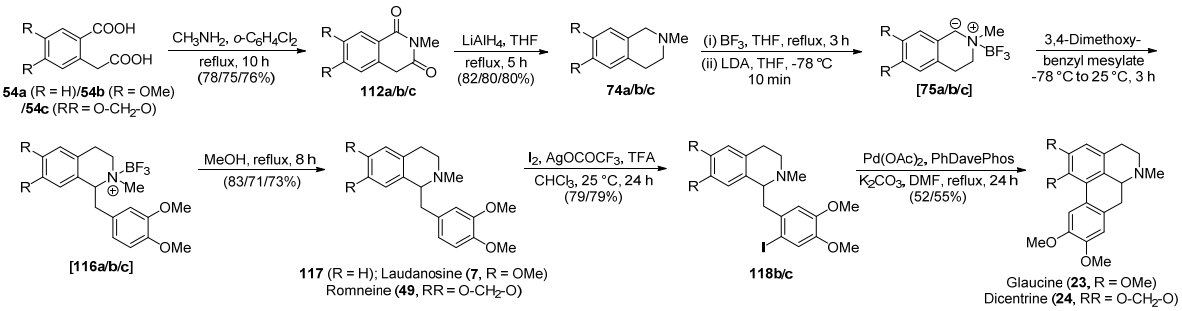
Scheme 14. Synthesis of Isoquinoline Alkaloids Doryanine and Oxyhydrastinine

2C.3.2 Synthesis of Benzyl Isoquinoline and Aporphine Alkaloids

Isoquinoline alkaloids are imperious from their structural architectures and a wide range of biological activities point of view. Homophthalic acids bear an appropriate carbon skeleton and functional groups and serve as a central precursors for the synthesis of isoquinoline alkaloids.[41–45] Large number of synthetic approaches to achieve total synthesis of these alkaloids has been reported in the earlier and contemporary literature by means of activation of benzylic positions and oxidative intramolecular cyclizations. We have been using cyclic anhydrides and their derivatives for total synthesis of bioactive natural products for more than past two decades.[89–94] Our present synthetic proposal towards the selected target compounds is mainly based on (i) generation of two different benzylic carbanionic species by altering a sequence of reduction in homophthalic imides/esters, (ii) their coupling reactions with benzyl mesylate instead of lachrymator benzyl halides and (iii) regioselective mono-iodination followed by intramolecular aryl−aryl coupling reactions leading to the fused biaryl compounds. In this

context we herein report total synthesis of designated bioactive alkaloids starting from the corresponding requisite homophthalic acids (Schemes 15 and 16).

Reactions of homophthalic acids **54a-c** with methylamine in refluxing *o*-dichlorobenzene directly furnished the corresponding known homophthalimides **112a**/**c** and an unknown homophthalimide **112b** in very good yields via the formation of corresponding homophthalamic acids followed by intramolecular dehydrative cyclizations[95] (Scheme 15). Imides **112a-c** on LAH-reduction delivered the desired tetrahydroisoquinolines **74a-c** in 80–82% yields. Tetrahydroisoquinolines **74a-c** on reaction with $BF_3.Et_2O$ in refluxing THF formed the corresponding boron complexes containing a quaternary nitrogen atom; which on treatment with LDA formed the required carbanionic species **75a-c**.[65] The carbanionic species **75a-c** on reactions with relatively less reactive 3,4-dimethoxybenzyl acetate failed to deliver the desired products **117**, **7**, **49**.

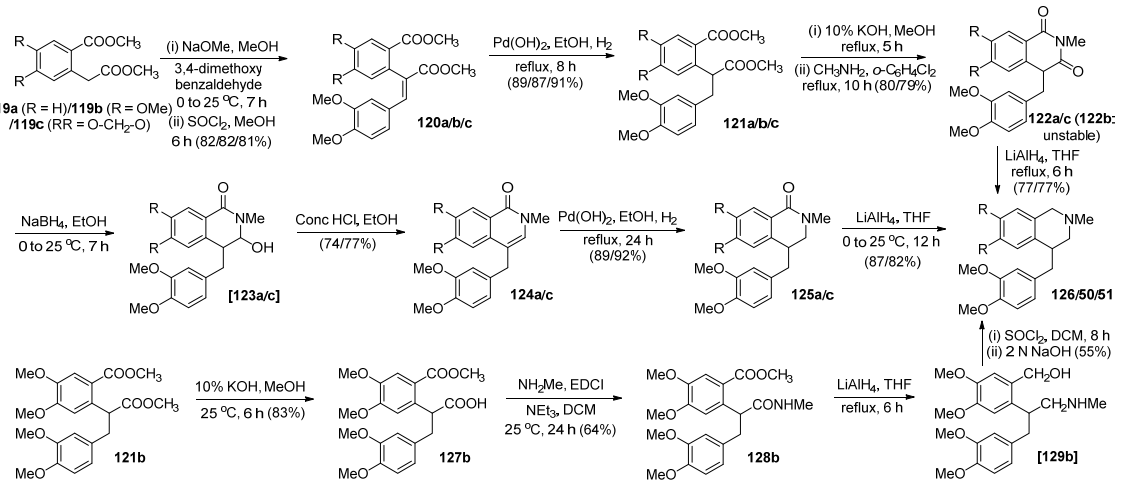


Scheme 15. Homophthalimides Reduction, Alkylation, Iodination and Intramolecular Aryl−Aryl Coupling Reactions Leading to Isoquinoline Based Alkaloids

However, the carbanionic species **75a-c** smoothly reacted with the freshly prepared 3,4-dimethoxybenzyl mesylate to form intermediates **116a-c**. Compounds **116a-c** on refluxing in methanol underwent the expected deboronation and furnished the desired products **117** (83%), laudanosine (**7**, 71%) and romneine (**49**, 73%). Above mentioned transformations of tetrahydroisoquinolines **74a-c** to the products **117**, **7**, **49** were carried out in one-pot without isolation of formed intermediates **116a-c**. Attempted *N*-iodosuccinimide induced iodinations of laudanosine (**7**) and romneine (**49**) were selective, but those reactions were not reaching to completion (~50 to 55% conversions; by ^{1}H NMR). Unfortunately the starting materials and products were having almost same R_f values and all our attempts to separate them met with failure. However, the silver trifluoroacetate/TFA mediated regioselective iodination of laudanosine (**7**) and romneine (**49**) exclusively provided the corresponding requisite pure products **118b**/**c** both in 79% yield. Base-induced generation of the corresponding internal aryne intermediate from

compound **118b** is known to provide a mixture of undesired products instead of an aimed glaucine (**8b**).[96] Initially performed aryl−aryl coupling reactions of compounds **118b**/**c** by using the well-known $Pd(OAc)_2$/TBAB catalytic system, respectively delivered the desired alkaloids glaucine (**23**) and dicentrine (**24**), but only in ~20% yields. Finally, an efficient catalytic pathway developed by Fagnou et al. by employing the 2-(diphenylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl (PhDavePhos) as a suitable ligand for such type of intramolecular aryl−aryl coupling reactions was used to improve the yields.[97] Palladium catalyzed intramolecular coupling reactions of compounds **118b**/**c** under Fagnou et al conditions successfully delivered the desired glaucine (**23**) and dicentrine (**24**) in 52/55% yields. Though several syntheses of glaucine (**23**) and dicentrine (**24**) have been known; it is remarkable approach involving an intramolecular aryl−aryl coupling reaction which is difficult from the geometry point of view.[97,98] The unnatural product **117** and all other four alkaloids **7**, **49** and **23**, **24** were highly prone for air-oxidations and they were also sensitive to the silica gel column chromatographic purifications. Hence all of them were essentially purified by quick neutral alumina column chromatography. The obtained analytical and spectral data for natural products **7**, **49** and **23**, **24** were in complete agreement with reported data.[34,36,71,78]

In the next part of our studies, we chose a pathway encompassing simple base-mediated benzylation of active benzylic methylene position in dimethylhomophthalates **119a-c** and the sequential reductions of formed compounds to design isomeric unnatural products **50**, **51**, **126** (Scheme 16). Dimethyl homophthalates **119a-c** on LDA-induced coupling reactions with 3,4-dimethoxybenzyl mesylate exclusively delivered the corresponding benzylated products **121a-c** in 65–70% yields. As shown in scheme 16, the products **121a-c** were also alternatively synthesized via base-induced condensations of dimethylhomophthalates **119a-c** with 3,4-dimethoxybenzaldehyde followed by esterification of the formed intermediate mono carboxylic acids using $SOCl_2/CH_3OH$ to solely deliver *trans* products **120a-c** in 82/82/81% yield. Esterification of intermediate mono carboxylic acids were essential for purification and the subsequent smooth carbon–carbon double bond reduction. Finally, the obtained cinnamates **120a-c** on catalytic hydrogenation also delivered the same products **121a-c** in 87–91% yields. Products **121a-c** on base induced mono-hydrolysis of more reactive unconjugated ester moiety furnished the corresponding intermediate carboxylic acids. Above specified acids



Scheme 16. Dimethyl Homophthalates Alkylation, Imide Formation and Reductions Constituting the Isomeric Isolaudanosine and Isoromneine

on treatment with methyl amine generated the corresponding ammonium salts, which on refluxing in *o*-dichlorobenzene formed imides **122a-c**. Imides **122a**/**c** were fairly stable and were obtained in 80/79% yields; however all our attempts to isolate the formed imide **122b** (checked by TLC) met with failure. Plausibly, an instantaneous oxidative hydrolytic cleavage could be the cause for inherent instability of imide **122b**.[94] Imides **122a**/**c** on LAH-reduction furnished the desired target compounds **126** and isoromneine (**51**) both in 77% yield. As portrayed in scheme 16, the products **126**, **51** were also obtained from the corresponding imides **122a**/**c** in a stepwise fashion via $NaBH_4$ reduction, acid-induced dehydration, catalytic hydrogenation and final LAH-reduction route in very good overall yields. Selective mono-hydrolysis of diester **121b** provided an acid **127b**, which on EDCI induced coupling with methyl amine formed the ester-amide **128b** in very good yield. Finally, LAH-reduction of ester **128b** to the corresponding intermediate alcohol **129b** followed by reaction with $SOCl_2$/base furnished the cyclized yet another isomeric product isolaudanosine (**50**) in 55% yield over two steps.The products **50**, **51**, **126** were also immediately purified by using neutral alumina column chromatography for stability issues.

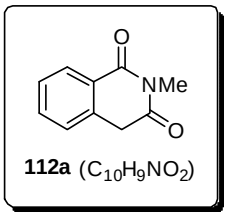
2C.4 Summary

In summary, we have described the well-organized synthesis of doryanine and oxyhydrastinine from homophthallic acids. Total synthesis of tetrahydroisoquinoline based bioactive alkaloids have been completed from the respective homophthalic acids

via generation of two different types of benzylic carbanions and uncommon intramolecular aryl−aryl coupling reactions. Application of benzyl mesylate instead of benzyl bromide as a coupling partner is significant from both its non-lachrymatory nature and yields point of view. The demonstrated generation of fused biaryl systems via intramolecular coupling reactions is noteworthy from basic chemistry and application point of view. The present approach to natural and unnatural tetrahydroisoquinoline based products is general in nature and will be useful for rational design of focused mini-libraries of their analogues and congeners for SAR-studies.

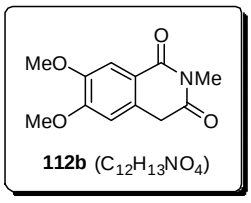
2C.5. Experimental Section

2-Methylisoquinoline-1,3(2*H*,4*H*)-dione (112a). To the homophthalic acid (**54a**, 1.80 g, 10.00 mmol) was added 40% aq. solution of methyl amine (5 mL) at room temperature and the reaction mixture was stirred for 5 min. It was then concentrated in vacuo and dried to the vacuum pump. To the obtained salt was added *o*-dichlorobenzene (20 mL) and it was vigorously refluxed for 10 h. The reaction mixture was allowed to cool to room temperature. The direct silica gel column chromatographic purification of the resulting reaction mixture using ethyl acetate–petroleum ether (1:3) as an eluent gave pure product **112a** as a white solid (1.36 g, 78%). Mp 119–121 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.38 (s, 3H), 4.06 (s, 2H), 7.28 (d, J = 8 Hz, 1H), 7.45 (t, J = 8 Hz, 1H), 7.60 (dt, J = 8 and 2 Hz, 1H), 8.23 (dd, J = 8 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.8, 36.3, 125.3, 127.1, 127.7, 129.1, 133.6, 134.0, 165.1, 170.2; ESIMS (*m*/*z*) 176 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 1710, 1664 cm^{-1}.



112a ($C_{10}H_9NO_2$)

6,7-Dimethoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (112b). It was similarly obtained from acid **54b** by using the above specified procedure as a faint yellow solid (1.32 g, 75%). Mp 198–200 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.36 (s, 3H), 3.96 (s, 6H), 3.98 (s, 2H), 6.67 (s, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.7, 36.1, 56.18, 56.24, 108.6, 110.1, 117.9, 128.2, 148.8, 153.8, 164.9, 170.5; ESIMS (*m*/*z*) 236 $[M + H]^+$; HRMS (ESI) calcd for $C_{12}H_{14}O_4N$ 236.0917, found 236.0917; IR ($CHCl_3$) ν_{max} 1748, 1709, 1659, 1603 cm^{-1}.



112b ($C_{12}H_{13}NO_4$)

6-Methyl-[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione (112c). It was similarly obtained from acid **54c** by using the above specified procedure as a faint yellow solid (1.33 g, 76%). Mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.34 (s, 3H), 3.94 (s, 2H), 6.06 (s, 2H), 6.66 (s, 1H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7, 36.4, 102.1, 106.4, 107.9, 119.4, 130.2, 147.8, 152.5, 164.5, 170.2; ESIMS (*m*/*z*) 220 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 1708, 1665 cm^{-1}.

112c ($C_{11}H_9NO_4$)

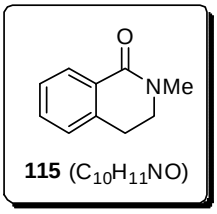
2-Methylisoquinolin-1(2*H*)-one (114). To a stirred solution of imide **112a** (1.20 g, 6.85 mmol) in EtOH (20 mL) was portion wise added $NaBH_4$ (2.08 g, 54.80 mmol) at 0 °C. The reaction mixture was stirred under argon atmosphere at 0 °C with periodic addition of 2 drops solution of EtOH (8 mL) plus 2 N HCl (2 mL) at the interval of 15 min. At the end of 6 h, excess of $NaBH_4$ was quenched at 0 °C by the addition of 2 N HCl in EtOH until the reaction mixture became acidic. The solvent was removed in vacuo and the obtained residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent gave pure product **114** as thick oil (806 mg, 74%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.60 (s, 3H), 6.47 (d, J = 8 Hz, 1H), 7.06 (d, J = 8 Hz, 1H), 7.40–7.67 (m, 3H), 8.43 (d, J = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.9, 105.9, 125.8, 126.0, 126.7, 127.6, 131.9, 132.3, 137.1, 162.6; ESIMS (*m*/*z*) 160 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 1646, 1595 cm^{-1}.

114 ($C_{10}H_9NO$)

6-Methyl-[1,3]dioxolo[4,5-g]isoquinolin-5(6*H*)-one (Doryanine, 47). It was similarly obtained from imide **112c** by using the above specified procedure as a faint yellow solid (812 mg, 73%). Mp 158–160 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.59 (s, 3H), 6.07 (s, 2H), 6.37 (d, J = 8 Hz, 1H), 6.85 (s, 1H), 6.99 (d, J = 8 Hz, 1H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.0, 101.6, 103.6, 105.5, 105.8, 121.6, 131.2, 134.3, 147.8, 151.6, 161.8; ESIMS (*m*/*z*) 226 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 1653, 1581 cm^{-1}.

47 ($C_{11}H_9NO_3$)

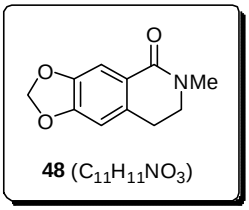
2-Methyl-3,4-dihydroisoquinolin-1(2*H*)-one (115). To a stirred solution of lactam **114** (636 mg, 4.00 mmol) in EtOH (20 mL) was added catalytic amount of $Pd(OH)_2$ (25 mg, 0.20 mmol) and the reaction mixture was refluxed under the balloon pressure hydrogen



115 ($C_{10}H_{11}NO$)

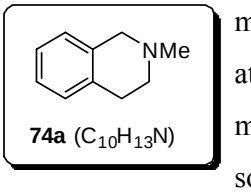
atmosphere for 24 h. The reaction mixture was allowed to cool to room temperature and it was filtered through a pad of Celite to remove the catalyst and concentrated in vacuo. The obtained crude product was directly purified by silica gel column chromatographic purification using 40% ethyl acetate/petroleum ether as an eluent to provide product **115** as thick oil (631 mg, 98%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.99 (t, J = 8 Hz, 2H), 3.15 (s, 3H), 3.56 (t, J = 8 Hz, 2H), 7.16 (d, J = 8 Hz, 1H), 7.25–7.45 (m, 2H), 8.08 (dd, J = 8 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.7, 35.0, 48.0, 126.7, 126.8, 127.9, 129.2, 131.4, 137.8, 164.6; ESIMS (m/z) 162 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 1643, 1606 cm^{-1}.

6-Methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5(6*H*)-one (Oxyhydrastinine, 48). It was similarly obtained from compound **47** by using the above specified procedure as a crystalline solid (629 mg, 90%). Mp 95–97 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.91 (t, J = 8 Hz, 2H), 3.13 (s, 3H), 3.52 (t, J = 8 Hz, 2H), 5.99 (s, 2H), 6.61 (s, 1H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 35.1, 48.2, 101.4, 106.8, 108.1, 123.5, 133.4, 146.8, 150.2, 164.5; ESIMS (m/z) 228 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 1641, 1605 cm^{-1}.

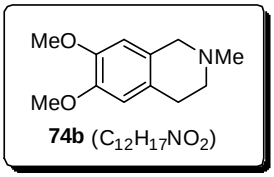


48 ($C_{11}H_{11}NO_3$)

2-Methyl-1,2,3,4-tetrahydroisoquinoline (74a). A solution of imide **112a** (1.20 g, 6.81 mmol) in THF (10 mL) was added dropwise to LAH in THF (10 mL) at 0 °C and the reaction mixture was refluxed for 5 h. The reaction mixture was cooled in ice bath and quenched with aq. saturated solution of Na_2SO_4 (5 mL). It was filtered and the filtrate was concentrated in vacuo. Neutral alumina column chromatographic purification of the obtained residue using dichloromethane–methanol (19:1) as an eluent afforded amine **74a** as a yellow solid (827 mg, 82%). Mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.47 (s, 3H), 2.70 (t, J = 6 Hz, 2H), 2.95 (t, J = 6 Hz, 2H), 3.60 (s, 2H), 6.97–7.07 (m, 1H), 7.07–7.17 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.1, 46.0, 52.8, 57.9, 125.5, 126.0, 126.3, 128.5, 133.7, 134.6; ESIMS (m/z) 148 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 1661, 1609 cm^{-1}.



74a ($C_{10}H_{13}N$)

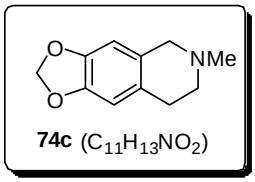


74b ($C_{12}H_{17}NO_2$)

6-Methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (74b). It was similarly obtained from imide **112b** by using the above specified procedure as a yellow solid (850 mg, 80%). Mp

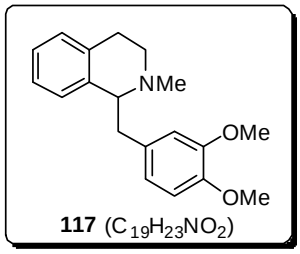
83–84 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 2.65 (t, J = 6 Hz, 2H), 2.83 (t, J = 6 Hz, 2H), 3.49 (s, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 6.50 (s, 1H), 6.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.6, 45.9, 52.8, 55.78, 55.82, 57.4, 109.2, 111.3, 125.6, 126.4, 147.1, 147.4; ESIMS (m/z) 208 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 1662, 1610 cm^{-1}.

6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (74c). It was similarly obtained from imide **112c** by using the above specified procedure as a yellow solid (838 mg, 80%). Mp 67–68 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.44 (s, 3H), 2.65 (t, J = 6 Hz, 2H), 2.83 (t, J = 6 Hz, 2H), 3.48 (s, 2H), 5.89 (s, 2H), 6.49 (s, 1H), 6.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.2, 45.9, 52.8, 57.9, 100.6, 106.3, 108.4, 126.7, 127.4, 145.6, 146.0; ESIMS (m/z) 192 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 1662, 1608 cm^{-1}.



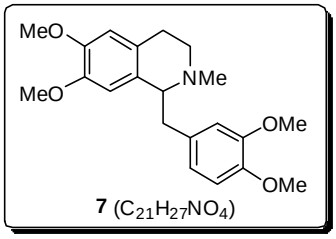
74c ($C_{11}H_{13}NO_2$)

1-(3,4-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (117). To a stirred solution of amine **74a** (750 mg, 5.06 mmol) in THF (10 mL) was added $BF_3.Et_2O$ solution (1.40 mL, 5.56 mmol) and it was refluxed for 3 h. The above reaction mixture was then cooled and LDA (2 M, 3.03 mL) was added dropwise at –78 °C to form the corresponding carbanions **75a**. A solution of 3,4-dimethoxybenzyl mesylate (1.37 g, 5.56 mmol) in THF (5 mL) was added to the above specified reaction mixture and it was further stirred for 3 h to form the alkylated borane complex **116a**. The reaction mixture was then concentrated in vacuo, MeOH (15 mL) was added to the obtained residue and the reaction mixture was refluxed for 8 h. It was allowed to cool to room temperature and concentrated in vacuo. The obtained residue was basified with aq. ammonia solution (10 mL) and extracted with dichloromethane (25 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo and neutral alumina column chromatographic purification of the resulting residue using dichloromethane–methanol (19:1) as an eluent gave pure product **117** as thick gum (1.25 g, 83%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.53 (s, 3H), 2.70–2.95 (m, 4H), 3.05–3.23 (m, 2H), 3.74 (s, 3H), 3.86 (s, 3H), 3.70–3.90 (m, 1H), 6.52 (d, J = 2 Hz, 1H), 6.65–6.85 (m, 3H), 7.00–7.15 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.2, 40.8, 42.9, 47.3, 55.6, 55.7, 65.0, 110.7, 112.8, 121.5, 125.1, 125.8, 127.9, 128.6, 132.2, 134.5, 137.6, 147.1, 148.2; ESIMS (m/z) 298 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{24}O_2N$ 298.1802, found 298.1803; IR ($CHCl_3$) ν_{max} 1665, 1608 cm^{-1}.



117 ($C_{19}H_{23}NO_2$)

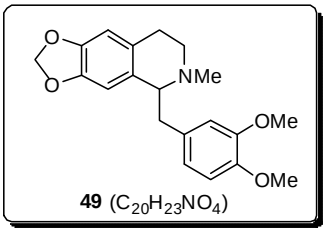
1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline



7 ($C_{21}H_{27}NO_4$)

(Laudanosine, 7).[34] It was similarly obtained from amine **74b** by using the above specified procedure as a yellow solid (918 mg, 71%). Mp 112–114 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.55 (s, 3H), 2.60–2.93 (m, 4H), 3.05–3.22 (m, 2H), 3.58 (s, 3H), 3.63–3.75 (m, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 6.06 (s, 1H), 6.56 (s, 1H), 6.61 (s, 1H), 6.63 (d, J = 8 Hz, 1H), 6.77 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.2, 40.7, 42.4, 46.7, 55.4, 55.66, 55.71, 55.8, 64.7, 110.9, 111.0, 111.1, 112.9, 121.8, 125.7, 128.8, 132.2, 146.2, 147.2 (2C), 148.5; ESIMS (*m*/*z*) 358 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{28}O_4N$ 358.2013, found 358.2011; IR ($CHCl_3$) ν_{max} 1666, 1601 cm^{-1}.

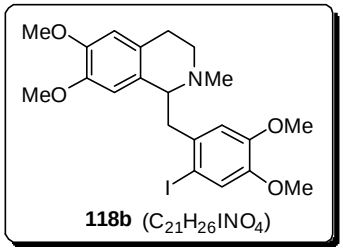
5-(3,4-Dimethoxybenzyl)-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline



49 ($C_{20}H_{23}NO_4$)

(Romneine, 49).[36] It was similarly obtained from amine **74c** by using the above specified procedure as thick gum (977 mg, 73%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.49 (s, 3H), 2.40–2.62 (m, 1H), 2.65–2.90 (m, 3H), 3.00–3.20 (m, 2H), 3.70 (t, J = 6 Hz, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 5.86 (d, J = 2 Hz, 2H), 6.24 (s, 1H), 6.54 (s, 1H), 6.62 (d, J = 2 Hz, 1H), 6.68 (dd, J = 6 and 2 Hz, 1H), 6.78 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.6, 41.0, 42.4, 46.6, 55.8 (2C), 65.0, 100.5, 107.9, 108.3, 110.8, 112.7, 121.5, 127.2, 130.3, 132.1, 145.2, 145.8, 147.2, 148.4; ESIMS (*m*/*z*) 342 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{24}O_4N$ 342.1700, found 342.1698; IR ($CHCl_3$) ν_{max} 1662, 1607 cm^{-1}.

1-(2-Iodo-4,5-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-

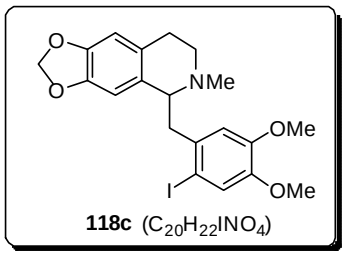


118b ($C_{21}H_{26}INO_4$)

tetrahydroisoquinoline (118b). To a stirred solution of compound **7** (500 mg, 1.40 mmol) and CF_3COOH (0.50 mL) in chloroform (20 mL) was added $AgOCOCF_3$ (310 mg, 1.40 mmol) and I_2 (353 mg, 1.40 mmol) and it was further stirred for 24 h at room temperature. It was concentrated in vacuo and the reaction mixture was basified with aq. ammonia solution (10 mL) and further extracted with dichloromethane (25 mL × 3). The combined organic layer was washed with 5% aq. $Na_2S_2O_3$, water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo and neutral alumina column chromatographic

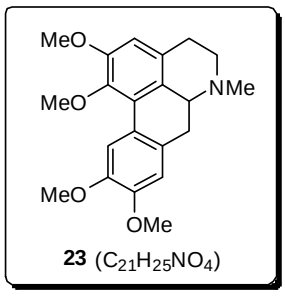
purification of the resulting residue using dichloromethane–methanol (19:1) as an eluent gave pure product **118b** as a yellow crystalline solid (534 mg, 79%). Mp 106–107 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.57 (s, 3H), 2.60–2.75 (m, 2H), 2.80–3.05 (m, 2H), 3.15–3.40 (m, 2H), 3.55 (s, 3H), 3.73 (s, 3H), 3.84 (s, 6H), 3.75–3.95 (m, 1H), 5.97 (s, 1H), 6.56 (s, 1H), 6.59 (s, 1H), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.6, 42.2, 44.6, 46.1, 55.4, 55.7, 55.8, 56.1, 62.8, 89.3, 111.2, 111.3, 114.4, 121.3, 125.4, 127.5, 134.2, 146.3, 147.5, 147.9, 148.8; ESIMS (*m*/*z*) 484 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{27}IO_4N$ 484.0979, found 484.0972; IR ($CHCl_3$) ν_{max} 1669, 1602 cm^{-1}.

5-(2-Iodo-4,5-dimethoxybenzyl)-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (118c). It was similarly obtained from amine **49** by using the above specified procedure as a yellow crystalline solid (540 mg, 79%). Mp 115–117 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.47 (s, 3H), 2.40–2.65 (m, 1H), 2.70–3.00 (m, 3H), 3.00–3.35 (m, 2H), 3.74 (s, 3H), 3.65–3.80 (m, 1H), 3.85 (s, 3H), 5.85 (s, 2H), 6.18 (s, 1H), 6.56 (s, 2H), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.2, 42.6, 45.2, 46.1, 55.8, 56.0, 63.2, 89.0, 100.4, 108.27, 108.34, 114.3, 121.3, 127.3, 130.0, 134.5, 145.1, 145.9, 147.9, 148.7; ESIMS (*m*/*z*) 468 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}IO_4N$ 468.0666, found 468.0660; IR ($CHCl_3$) ν_{max} 1650, 1599 cm^{-1}.



118c ($C_{20}H_{22}INO_4$)

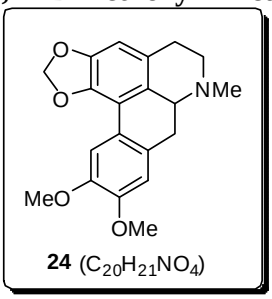
1,2,9,10-Tetramethoxy-6-methyl-5,6,6*a*,7-tetrahydro-4*H* dibenzo[*de*,*g*]quinoline (Glaucine, 23).[71] *Method A*: To a stirred solution of compound **118b** (200 mg, 0.42 mmol) in DMF (15 mL) was added K_2CO_3 (343 mg, 2.48 mmol), TBAB (266 mg, 0.82 mmol) and $Pd(OAc)_2$ (10 mg, 10 mol%) at 25 °C under argon atmosphere, the mixture was heated at 120 °C for 24 h. It was allowed to cool to room temperature and the reaction mixture was basified with aq. ammonia solution (10 mL) and extracted with dichloromethane (25 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo and neutral alumina column chromatographic purification of the resulting residue using dichloromethane–methanol (19:1) as an eluent gave pure product **23** as a brown solid (29 mg, 20%). *Method B*: To the mixture of compound **118b** (100 mg, 0.21 mmol), K_2CO_3 (57.14 mg, 0.41 mmol), $Pd(OAc)_2$ (21 mg, 20 mol%) and



23 ($C_{21}H_{25}NO_4$)

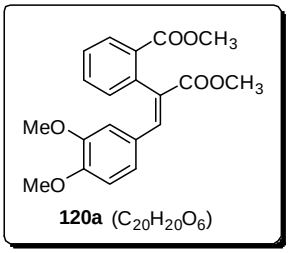
the ligand PhDave-Phos (105 mg) was added DMF (3 mL) at 25 °C under argon atmosphere [the ratio of $Pd(OAc)_2$ and ligand is 7 mg/mL of $Pd(OAc)_2$ with 35 mg/mL of the ligand]. The reaction mixture was heated at 120 °C for 24 h. It was allowed to cool to room temperature and the reaction mixture was basified with aq. ammonia solution (5 mL) and extracted with dichloromethane (25 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo and neutral alumina column chromatographic purification of the resulting residue using dichloromethane–methanol (19:1) as an eluent provided pure product **23** as a brown solid (38 mg, 52%). Mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.58 (s, 3H), 2.45–2.75 (m, 3H), 2.98–3.12 (m, 3H), 3.12–3.25 (m, 1H), 3.66 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 6.60 (s, 1H), 6.79 (s, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.1, 34.5, 44.0, 53.3, 55.8 (2C), 55.9, 60.2, 62.5, 110.3, 110.8, 111.6, 124.4, 126.9 (2C), 128.8, 129.2, 144.3, 147.5, 148.0, 152.0; ESIMS (*m*/*z*) 356 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{26}O_4N$ 356.1856, found 356.1856; IR ($CHCl_3$) ν_{max} 1604 cm^{-1}.

10,11-Dimethoxy-7-methyl-6,7,7*a*,8-tetrahydro-5*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-*de*]benzo[*g*]quinoline (Dicentrine, 24).[78] It was similarly obtained from iodo compound **118c** by using the above specified method A procedure as a brown crystalline solid (29 mg, 20%). It was also similarly obtained from iodo compound **118c** by using the above specified method B procedure as a brown crystalline solid (40 mg, 55%). Mp 179–180 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.57 (s, 3H), 2.40–2.79 (m, 3H), 2.99–3.25 (m, 4H), 3.93 (s, 6H), 5.94 (d, J = 2 Hz, 1H), 6.09 (d, J = 2 Hz, 1H), 6.53 (s, 1H), 6.79 (s, 1H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.1, 34.2, 43.9, 53.5, 55.9, 56.1, 62.4, 100.6, 106.8, 110.5, 111.2, 116.6, 123.5, 126.3, 126.6, 128.3, 141.8, 146.6, 147.7, 148.2; ESIMS (*m*/*z*) 340 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{22}O_4N$ 340.1543, found 340.1543; IR ($CHCl_3$) ν_{max} 1598 cm^{-1}.



24 ($C_{20}H_{21}NO_4$)

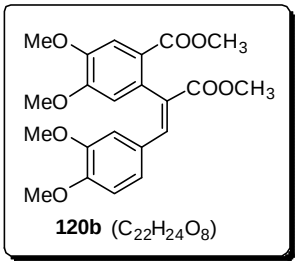
Methyl (*E*)-2-(1-(3,4-Dimethoxyphenyl)-3-methoxy-3-oxoprop-1-en-2-yl)benzoate (120a). Fresh solution of sodium methoxide in methanol was prepared by addition of sodium (486 mg, 21.15 mmol) in stirred methanol (30 mL) at 0 °C. To the above solution was added homophthalate **119a** (2.00 g, 9.61 mmol) and then



120a ($C_{20}H_{20}O_6$)

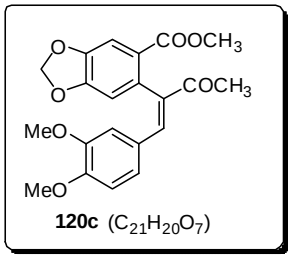
solution of 3,4-dimethoxybenzaldehyde (1.75 g, 10.58 mmol) in methanol (10 mL) was added dropwise. The mixture was stirred for 7 h, it was allowed to cool to room temperature and concentrated in vacuo. The resulting residue was acidified with 2 N HCl (10 mL), filtered, washed with water (10 mL) and dried. To the solution of above residue in MeOH (25 mL) was dropwise added $SOCl_2$ (14 mL) at 0 °C and the reaction mixture was refluxed for 6 h. It was allowed to cool to room temperature and concentrated in vacuo. The resulting residue was dissolved in ethyl acetate (25 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent gave pure product **120a** as a white crystalline solid (2.80 g, 82%). Mp 110–112 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.39 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 6.29 (d, J = 2 Hz, 1H), 6.65–6.80 (m, 2H), 7.26 (dd, J = 8 and 2 Hz, 1H), 7.40–7.55 (m, 2H), 7.75 (s, 1H), 8.13 (dd, J = 8 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.0, 52.1, 55.1, 55.7, 110.5, 112.1, 125.0, 127.3, 127.9, 130.5, 130.6, 130.8, 131.7, 132.7, 138.0, 138.3, 148.2, 149.7, 166.8, 167.9; ESIMS (*m*/*z*) 379 $[M + Na]^+$; HRMS (ESI) calcd for $C_{20}H_{20}O_6Na$ 379.1152, found 379.1142; IR ($CHCl_3$) ν_{max} 1718, 1598 cm^{-1}.

Methyl (*E*)-2-(1-(3,4-Dimethoxyphenyl)-3-methoxy-3-oxoprop-1-en-2-yl)-4,5-dimethoxybenzoate (120b). It was similarly obtained from homophthalate **119b** and 3,4-dimethoxybenzaldehyde by using the above specified procedure as a white crystalline solid (2.54 g, 82%). Mp 106–108 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.51 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 3.97 (s, 3H), 6.43 (s, 1H), 6.65 (s, 1H) , 6.70 (s, 2H), 7.66 (s, 1H) 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 51.9, 52.2, 55.3, 55.7, 56.1 (2C), 110.6, 112.5, 113.3, 113.7, 122.2, 124.7, 127.4, 130.7, 132.3, 137.7, 148.19, 148.22, 149.7, 152.6, 166.4, 168.2; ESIMS (*m*/*z*) 439 $[M + Na]^+$; HRMS (ESI) calcd for $C_{22}H_{24}O_8Na$ 439.1363, found 439.1363; IR ($CHCl_3$) ν_{max} 1711, 1602 cm^{-1}.



120b ($C_{22}H_{24}O_8$)

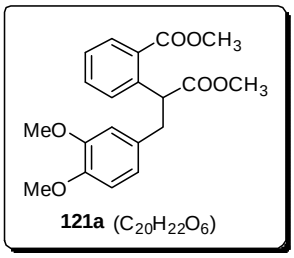
Methyl (*E*)-6-(1-(3,4-Dimethoxyphenyl)-3-methoxy-3-oxoprop-1-en-2-yl)benzo[*d*][1,3] dioxole-5-carboxylate (120c). It was similarly obtained from homophthalate **119c** and 3,4-dimethoxybenzaldehyde by using the above specified procedure as a white crystalline solid (2.57 g, 81%). Mp 89–91 °C; ^{1}H NMR ($CDCl_3$, 200



120c ($C_{21}H_{20}O_7$)

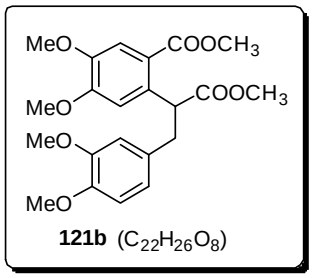
MHz) δ 3.54 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 6.03 (d, J = 2 Hz, 2H), 6.44 (d, J = 2 Hz, 1H), 6.60 (s, 1H), 6.73 (s, 2H) , 7.59 (s, 1H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.0, 52.2, 55.3, 55.8, 102.1, 110.6, 110.7, 111.4, 112.5, 123.9, 124.7, 127.3, 130.7, 134.3, 137.8, 147.4, 148.3, 149.7, 151.3, 166.0, 168.0; ESIMS (*m*/*z*) 423 $[M + Na]^+$; HRMS (ESI) calcd for $C_{21}H_{20}O_8Na$ 423.1050, found 423.1048; IR ($CHCl_3$) ν_{max} 1714, 1610 cm^{-1}.

Methyl 2-(3-(3,4-Dimethoxyphenyl)-1-methoxy-1-oxopropan-2-yl)benzoate (121a).



121a ($C_{20}H_{22}O_6$)

To a stirred solution of unsaturated diester **120a** (1.42 g, 4.00 mmol) in EtOH (20 mL) was added catalytic amount of $Pd(OH)_2$ (25 mg, 0.20 mmol) and the reaction mixture was refluxed under the balloon pressure hydrogen atmosphere for 8 h. The reaction mixture was allowed to cool to room temperature and it was filtered through a pad of Celite and concentrated in vacuo. The obtained crude product was directly purified by silica gel column chromatography by using ethyl acetate–petroleum ether (2:3) as an eluent to provide product **121a** as thick oil (1.27g, 89%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.98 (dd, J = 14 and 6 Hz, 1H), 3.36 (dd, J = 14 and 8 Hz, 1H), 3.61 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.96 (t, J = 8 Hz, 1H), 6.60–6.78 (m, 3H), 7.32 (dd, J = 8 and 2 Hz, 1H), 7.37–7.52 (m, 2H), 7.86 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.4, 49.1, 51.9, 52.0, 55.6, 55.8, 110.9, 112.4, 121.1, 126.9, 128.8, 129.6, 130.6, 131.7, 132.1, 140.0, 147.4, 148.4, 167.7, 173.9; ESIMS (*m*/*z*) 381 $[M + Na]^+$; HRMS (ESI) calcd for $C_{20}H_{22}O_6Na$ 381.1309, found 381.1299; IR ($CHCl_3$) ν_{max} 1721, 1595 cm^{-1}.

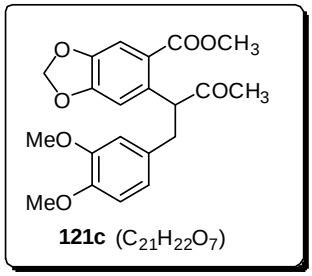


121b ($C_{22}H_{26}O_8$)

Methyl 2-(3-(3,4-Dimethoxyphenyl)-1-methoxy-1-oxopropan-2-yl)-4,5-dimethoxybenzoate (121b). It was similarly obtained from **120b** by using the above specified procedure as a white crystalline solid (1.24 g, 87%). Mp 101–102 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.98 (dd, J = 14 and 6 Hz, 1H), 3.33 (dd, J = 14 and 8 Hz, 1H), 3.61 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 5.09 (t, J = 8 Hz, 1H), 6.72 (s, 3H), 6.90 (s, 1H) , 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.6, 48.6, 51.9, 52.0, 55.7, 55.8, 56.0 (2C), 110.9, 111.1, 112.3, 113.2, 121.08, 121.13, 131.8, 134.5,

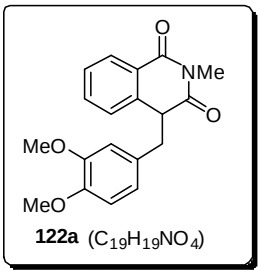
147.2, 147.3, 148.6, 151.9, 167.1, 174.3; ESIMS (*m*/*z*) 441 $[M + Na]^+$; HRMS (ESI) calcd for $C_{22}H_{26}O_8Na$ 441.1520, found 441.1520; IR ($CHCl_3$) ν_{max} 1721, 1597 cm^{-1}.

Methyl 6-(3-(3,4-Dimethoxyphenyl)-1-methoxy-1-oxopropan-2-yl)benzo[*d*][1,3]dioxole-5-carboxylate (121c). It was similarly obtained from **120c** by using the above specified procedure as a white crystalline solid (1.30 g, 91%). Mp 83–84 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.93 (dd, *J* = 14 and 6 Hz, 1H), 3.29 (dd, *J* = 12 and 8 Hz, 1H), 3.61 (s, 3H), 3.82 (s, 3H), 3.83 (s, 6H), 5.11 (dd, *J* = 10 and 8 Hz, 1H), 6.01 (d, *J* = 2 Hz, 2H), 6.73 (s, 3H), 6.94 (s, 1H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.5, 48.5, 51.9 (2C), 55.6, 55.7, 101.9, 108.5, 110.3, 110.9, 112.3, 121.1, 122.7, 131.6, 136.4, 146.3, 147.3, 148.4, 150.8, 166.8, 174.0; ESIMS (*m*/*z*) 425 $[M + Na]^+$; HRMS (ESI) calcd for $C_{21}H_{22}O_8Na$ 425.1207, found 425.1205; IR ($CHCl_3$) ν_{max} 1722, 1612 cm^{-1}.



121c ($C_{21}H_{22}O_7$)

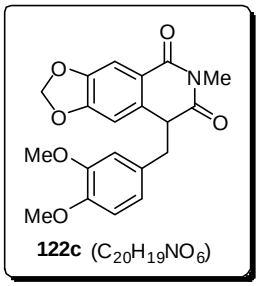
4-(3,4-Dimethoxybenzyl)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (122a). Compound **121a** (905 mg, 2.53 mmol) was added to a stirred 10% aq. solution of KOH (15 mL) and MeOH (15 mL) mixture at 0 °C. The reaction mixture was refluxed for 5 h, allowed to cool to room temperature and acidified with 2 N HCl (25 mL). The filtered residue was dissolved in ethyl acetate (25 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The dried organic layer was concentrated in vacuo. To the resulting residue was added 40% aq. solution of methyl amine (1.20 mL) and stirred for 5 min. Then toluene (10 mL) was added to the above reaction mixture and again stirred for 5 min. and concentrated in vacuo. To the obtained residue was added *o*-dichlorobenzene (20 mL) and the reaction mixture was refluxed for 10 h. The reaction mixture was allowed to cool to room temperature. Direct silica gel column chromatographic purification of the resulting solution using ethyl acetate–petroleum ether (1:3) as an eluent gave pure product **122a** as thick yellow oil (657 mg, 80%). ^1H NMR ($CDCl_3$, 200 MHz) δ 3.18 (s, 3H), 3.22 (dd, *J* = 12 and 8 Hz, 1H), 3.38 (dd, *J* = 12 and 8 Hz, 1H), 3.57 (s, 3H), 3.78 (s, 3H), 4.20 (t, *J* = 8 Hz, 1H), 6.05 (s, 1H), 6.23 (dd, *J* = 8 and 2 Hz, 1H), 6.59 (d, *J* = 8 Hz, 1H), 7.21 (d, *J* = 8 Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.59 (dt, *J* = 8 and 2 Hz, 1H), 8.06 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.4, 43.1, 48.1, 55.5, 55.6, 110.6, 112.2, 121.2, 125.8, 127.2, 127.46, 127.54,



122a ($C_{19}H_{19}NO_4$)

128.5, 133.1, 138.0, 148.1, 148.3, 164.2, 173.3; ESIMS (*m*/*z*) 348 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_4NNa$ 348.1206, found 348.1197; IR ($CHCl_3$) ν_{max} 1713, 1664, 1601 cm^{-1}.

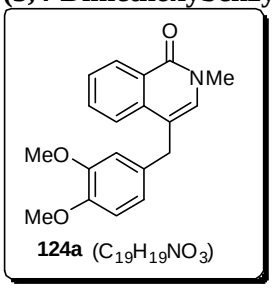
8-(3,4-Dimethoxybenzyl)-6-methyl-[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione



122c ($C_{20}H_{19}NO_6$)

(122c). It was similarly obtained from **121c** by using the above specified procedure as thick oil (656 mg, 79%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.15 (s, 3H), 3.17 (dd, J = 12 and 4 Hz, 1H), 3.55 (dd, J = 12 and 6 Hz, 1H), 3.68 (s, 3H), 3.79 (s, 3H), 4.08 (t, J = 8 Hz, 1H), 6.00–6.10 (m, 2H), 6.23 (s, 1H), 6.24 (dd, J = 8 and 2 Hz, 1H), 6.60 (s, 1H), 6.61 (d, J = 8 Hz, 1H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.5, 43.1, 48.2, 55.7 (2C), 102.0, 106.5, 107.5, 110.7, 112.2, 120.2, 121.4, 127.6, 134.4, 147.5, 148.1, 148.4, 152.1, 163.7, 173.4; ESIMS (*m*/*z*) 392 $[M + Na]^+$; HRMS (ESI) calcd for $C_{20}H_{20}O_6N$ 370.1285, found 370.1284; IR ($CHCl_3$) ν_{max} 1712, 1663, 1600 cm^{-1}.

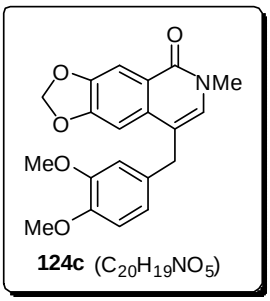
4-(3,4-Dimethoxybenzyl)-2-methylisoquinolin-1(2*H*)-one (124a). To a stirred solution



124a ($C_{19}H_{19}NO_3$)

of compound **122a** (488 mg, 1.50 mmol) in EtOH (20 mL) was added $NaBH_4$ (456 mg, 12.00 mmol) at 0 °C. The mixture was stirred under argon atmosphere for 7 h at 0 °C; while 2 drops of solution of 2 N HCl (2 mL) and EtOH (8 mL) were added at intervals of 15 min. The excess of $NaBH_4$ was quenched at 0 °C by the addition of 2 N HCl in EtOH (10 mL) until the mixture was acidic. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the dried organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:3) as an eluent gave pure product **124a** as a light yellow crystalline solid (344 mg, 74%). Mp 176–178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.57 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.98 (s, 2H), 6.70–6.82 (m, 4H), 7.43–7.50 (m, 1H), 7.55–7.63 (m, 2H), 8.48 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.1, 36.9, 55.8 (2C), 111.3, 111.8, 115.1, 120.6, 123.1, 126.1, 126.6, 128.1, 131.4, 131.5, 131.9, 136.7, 147.6, 149.0, 162.3; ESIMS (*m*/*z*) 332 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{20}O_3N$ 310.1438, found 310.1432; IR ($CHCl_3$) ν_{max} 1652, 1599 cm^{-1}.

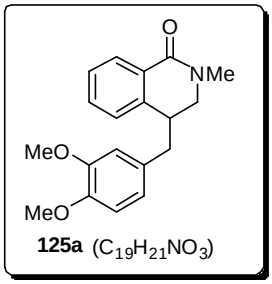
8-(3,4-Dimethoxybenzyl)-6-methyl-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (124c). It



124c ($C_{20}H_{19}NO_5$)

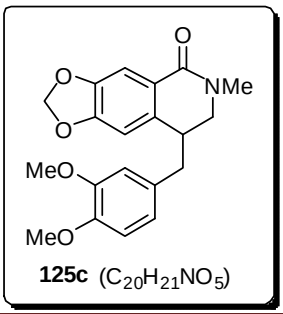
was similarly obtained from **122c** by using the above specified procedure as a yellow solid (360 mg, 77%). Mp 195–197 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.90 (s, 2H), 6.04 (s, 2H), 6.67–6.77 (m, 3H), 6.81 (d, J = 8 Hz, 1H), 6.90 (s, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.6, 37.0, 55.9 (2C), 101.6, 101.7, 106.0, 111.3, 111.7, 114.8, 120.5, 121.8, 130.5, 131.3, 134.1, 147.5, 147.7, 149.1, 151.7, 161.5; ESIMS (*m*/*z*) 376 [M + Na]$^+$; HRMS (ESI) calcd for $C_{20}H_{20}O_5N$ 354.1336, found 354.1334; IR ($CHCl_3$) ν_{max} 1657, 1607 cm^{-1}.

4-(3,4-Dimethoxybenzyl)-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (125a). To a



125a ($C_{19}H_{21}NO_3$)

stirred solution of unsaturated lactam **124a** (250 mg, 0.81 mmol) in EtOH (15 mL) was added catalytic amount of $Pd(OH)_2$ (28 mg, 0.20 mmol) and the reaction mixture was refluxed under the balloon pressure hydrogen atmosphere for 24 h. The reaction mixture was allowed to cool to room temperature, it was filtered through a pad of Celite and concentrated in vacuo. The obtained crude product was directly purified by silica gel column chromatographic purification using ethyl acetate–petroleum ether (2:3) as an eluent to provide product **125a** as a yellow crystalline solid (224 mg, 89%). Mp 108–109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.78 (dd, J = 12 and 12 Hz, 1H), 2.91 (dd, J = 12 and 8 Hz, 1H), 3.00–3.10 (m, 1H), 3.14 (s, 3H), 3.21 (dd, J = 12 and 4 Hz, 1H), 3.68 (dd, J = 12 and 4 Hz, 1H), 3.82 (s, 3H), 3.88 (s, 3H), 6.55 (d, J = 4 Hz, 1H), 6.68 (dd, J = 8 and 4 Hz, 1H), 6.82 (d, J = 8 Hz, 1H), 7.03 (dd, J = 8 and 4 Hz, 1H), 7.32–7.41 (m, 2H), 8.12 (dd, J = 8 and 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.3, 39.89, 39.94, 50.8, 55.7, 55.8, 111.1, 112.2, 121.0, 126.8, 127.1, 128.3, 128.4, 131.4 (2C), 141.5, 147.6, 148.8, 164.5; ESIMS (*m*/*z*) 334 [M + Na]$^+$; HRMS (ESI) calcd for $C_{19}H_{22}O_3N$ 312.1594, found 312.1589; IR ($CHCl_3$) ν_{max} 1646, 1600 cm^{-1}.

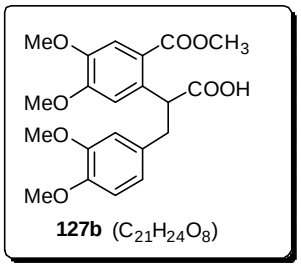


125c ($C_{20}H_{21}NO_5$)

8-(3,4-Dimethoxybenzyl)-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (125c). It was similarly obtained from **124c** by using the above specified procedure as thick gum (231 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.74 (dd, J = 12 and 8 Hz, 1H), 2.87 (dd, J = 12 and 4

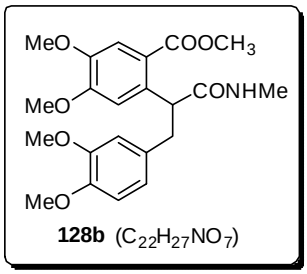
Hz, 1H), 2.90–2.97 (m, 1H), 3.11 (s, 3H), 3.15 (d, J = 12 Hz, 1H), 3.62 (dd, J = 12 and 4 Hz, 1H), 3.85 (s, 3H), 3.88 (s, 3H), 5.99 (s, 2H), 6.51 (s, 1H), 6.59 (s, 1H), 6.68 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 1H), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.3, 40.0, 40.1, 50.8, 55.8, 55.9, 101.4, 106.7, 108.3, 111.3, 112.2, 121.1, 122.8, 131.5, 137.4, 146.9, 147.7, 148.9, 150.2, 164.2; ESIMS (m/z) 355 $[M]^+$; HRMS (ESI) calcd for $C_{20}H_{22}O_5N$ 356.1492, found 356.1491; IR ($CHCl_3$) ν_{max} 1645, 1605 cm^{-1}.

2-(4,5-Dimethoxy-2-(methoxycarbonyl)phenyl)-3-(3,4-dimethoxyphenyl)propanoic Acid (127b). The compound **121b** (180 mg, 0.43 mmol) was added to mixture of 10% aq. solution of KOH (20 mL) and MeOH (20 mL) at 0 °C. The reaction mixture was stirred for 6 h and acidified with 2 N HCl (25 mL). The reaction mixture was filtered and the obtained residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the dried organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent gave pure product **127b** as thick gum (145 mg, 83%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.01 (dd, J = 14 and 6 Hz, 1H), 3.32 (dd, J = 12 and 8 Hz, 1H), 3.62 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 5.20 (dd, J = 10 and 6 Hz, 1H), 6.73 (s, 2H), 6.79 (s, 1H), 6.95 (s, 1H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.7, 48.8, 52.0, 55.6, 55.8, 55.95, 56.03, 110.9, 111.2, 112.2, 114.0, 119.4, 121.2, 131.7, 136.1, 147.3, 147.4, 148.6, 152.9, 172.2, 174.2; ESIMS (m/z) 427 $[M + Na]^+$; HRMS (ESI) calcd for $C_{21}H_{24}O_8Na$ 427.1363, found 427.1356; IR ($CHCl_3$) ν_{max} 2700–2500, 1735, 1678 cm^{-1}.



127b ($C_{21}H_{24}O_8$)

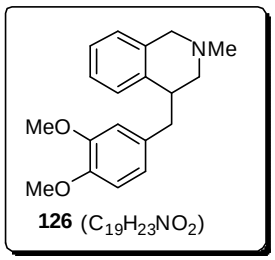
Methyl 2-(3-(3,4-Dimethoxyphenyl)-1-(methylamino)-1-oxopropan-2-yl)-4,5-dimethoxybenzoate (128b). To a stirred solution of acid **127b** (118 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) were added $NH_2Me.HCl$ (24 mg, 0.35 mmol), EDCI (140 mg, 0.73 mmol), triethylamine (0.13 mL, 0.88 mmol) and a catalytic amount of DMAP at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C and stirred for 24 h. The reaction was quenched with water (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by neutral alumina column



128b ($C_{22}H_{27}NO_7$)

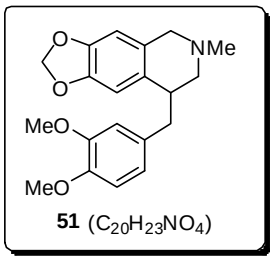
chromatographic purification of the resulting residue using dichloromethane–methanol (19:1) as an eluent afforded pure product **128b** as thick gum (78 mg, 64%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.71 (d, J = 6 Hz, 3H), 2.88 (dd, J = 14 and 6 Hz, 1H), 3.51 (dd, J = 12 and 8 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 3.98 (s, 3H), 4.77 (dd, J = 8 and 6 Hz, 1H), 6.60–6.75 (m, 4H), 7.21 (s, 1H), 7.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.2, 38.4, 48.0, 52.2, 55.7, 55.8, 56.0, 56.1, 110.7, 111.0, 112.0, 112.6 120.78, 120.82, 132.4, 136.6, 147.0, 147.2, 148.5, 152.4, 168.3, 173.4; ESIMS (m/z) 418 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{28}O_7N$ 418.1860, found 418.1859; IR ($CHCl_3$) ν_{max} 3382, 1707, 1665, 1596 cm^{-1}.

4-(3,4-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (126). *Method A*. A solution of lactam **125a** (180 mg, 0.58 mmol) in THF (5 mL) was dropwise added to LAH (24.2 mg, 0.64 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 12 h and the reaction was quenched with aq. saturated solution of Na_2SO_4 (5 mL). The reaction mixture was filtered and the filtrate was concentrated in vacuo. Neutral alumina column chromatographic purification of the residue using dichloromethane–methanol (19:1) as an eluent afforded amine **126** as thick oil (150 mg, 87%). *Method B*. A solution of imide **122a** (162 mg, 0.50 mmol) in THF (2 mL) was dropwise added to LAH (56.8 mg, 1.50 mmol) in THF (2 mL) at 0 °C. The reaction mixture was refluxed for 6 h and the reaction was quenched with aq. saturated solution of Na_2SO_4 (5 mL). The reaction mixture was filtered and the filtrate was concentrated in vacuo. Neutral alumina column chromatographic purification of the residue using dichloromethane–methanol (19:1) as an eluent afforded amine **126** as thick oil (114 mg, 77%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (dd, J = 12 and 4 Hz, 1H), 2.40 (s, 3H), 2.58 (dd, J = 12 and 2 Hz, 1H), 2.87 (dd, J = 14 and 12 Hz, 1H), 2.98–3.12 (m, 2H), 3.41 (d, J = 14 Hz, 1H), 3.76 (d, J = 16 Hz, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 6.75–6.88 (m, 3H), 7.00–7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.7, 42.0, 46.3, 55.77, 55.84, 56.1, 58.6, 111.1, 112.5, 121.1, 125.8, 126.1, 126.3, 128.3, 133.3, 134.8, 137.8, 147.2, 148.7; ESIMS (m/z) 320 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{24}O_2N$ 298.1802, found 298.1798; IR ($CHCl_3$) ν_{max} 1651, 1594 cm^{-1}.



126 ($C_{19}H_{23}NO_2$)

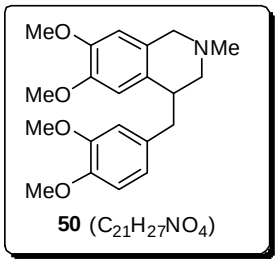
8-(3,4-Dimethoxybenzyl)-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline



51 ($C_{20}H_{23}NO_4$)

(Isoromneine, 51). It was similarly obtained from **125c** by using the above specified method A procedure as a brown solid (142 mg, 82%). It was also obtained from **122c** by using the above specified method B procedure as a brown solid (115 mg, 77%). Mp 59–60 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 2.41 (dd, J = 20 and 4 Hz, 1H), 2.56 (dd, J = 12 and 4 Hz, 1H), 2.84 (dd, J = 12 and 12 Hz, 1H), 2.95–3.05 (m, 2H), 3.37 (d, J = 16 Hz, 1H), 3.70 (d, J = 16 Hz, 1H), 3.88 (s, 6H), 5.90 (s, 2H), 6.51 (s, 1H), 6.69 (s, 1H), 6.76 (s, 1H), 6.77 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.3, 41.8, 45.8, 55.8, 55.9 (2C), 58.2, 100.7, 106.1, 108.0, 111.1, 112.4, 121.1, 126.9, 130.6, 132.8, 145.9, 146.2, 147.3, 148.8; ESIMS (*m*/*z*) 342 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{24}O_4N$ 342.1700, found 342.1700; IR ($CHCl_3$) ν_{max} 1648, 1603 cm^{-1}.

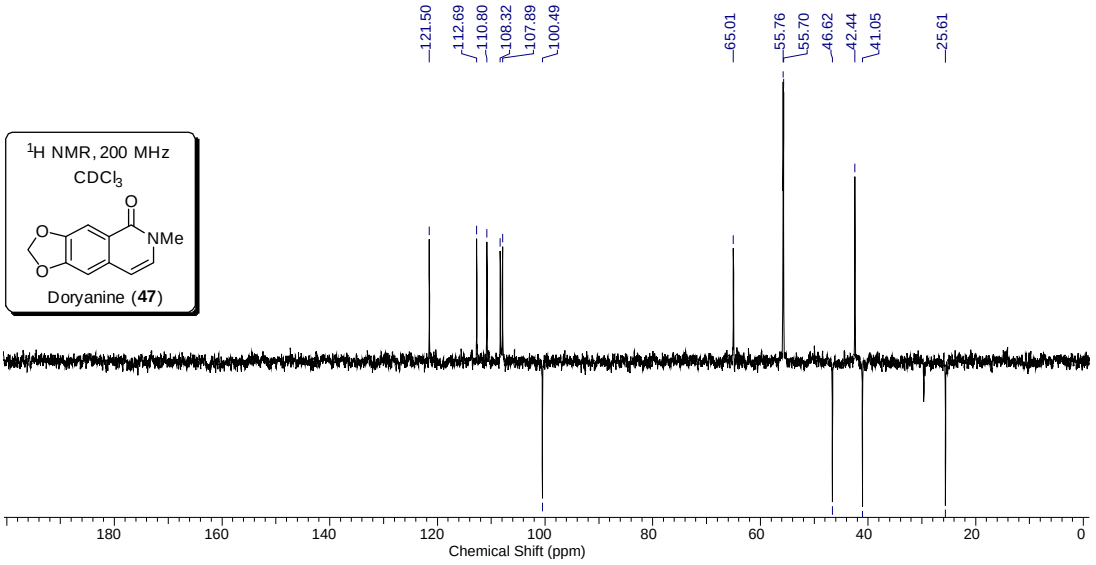
4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

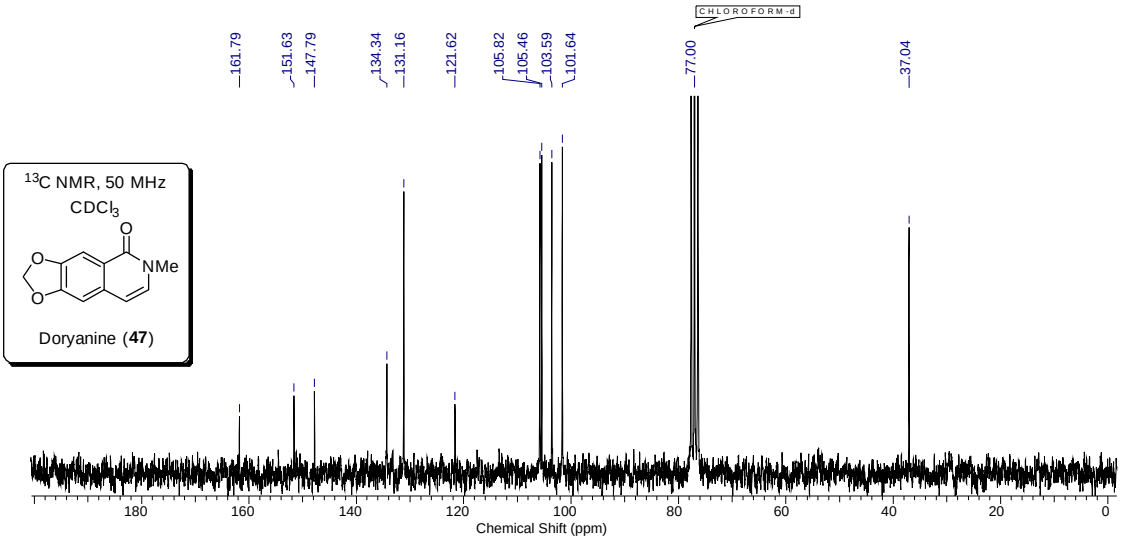


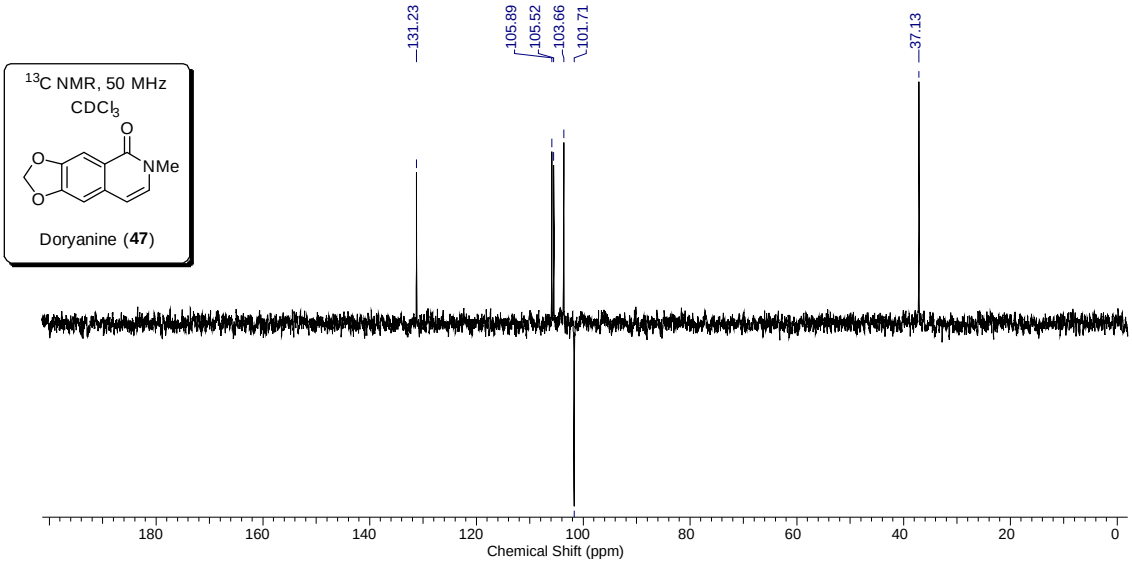
50 ($C_{21}H_{27}NO_4$)

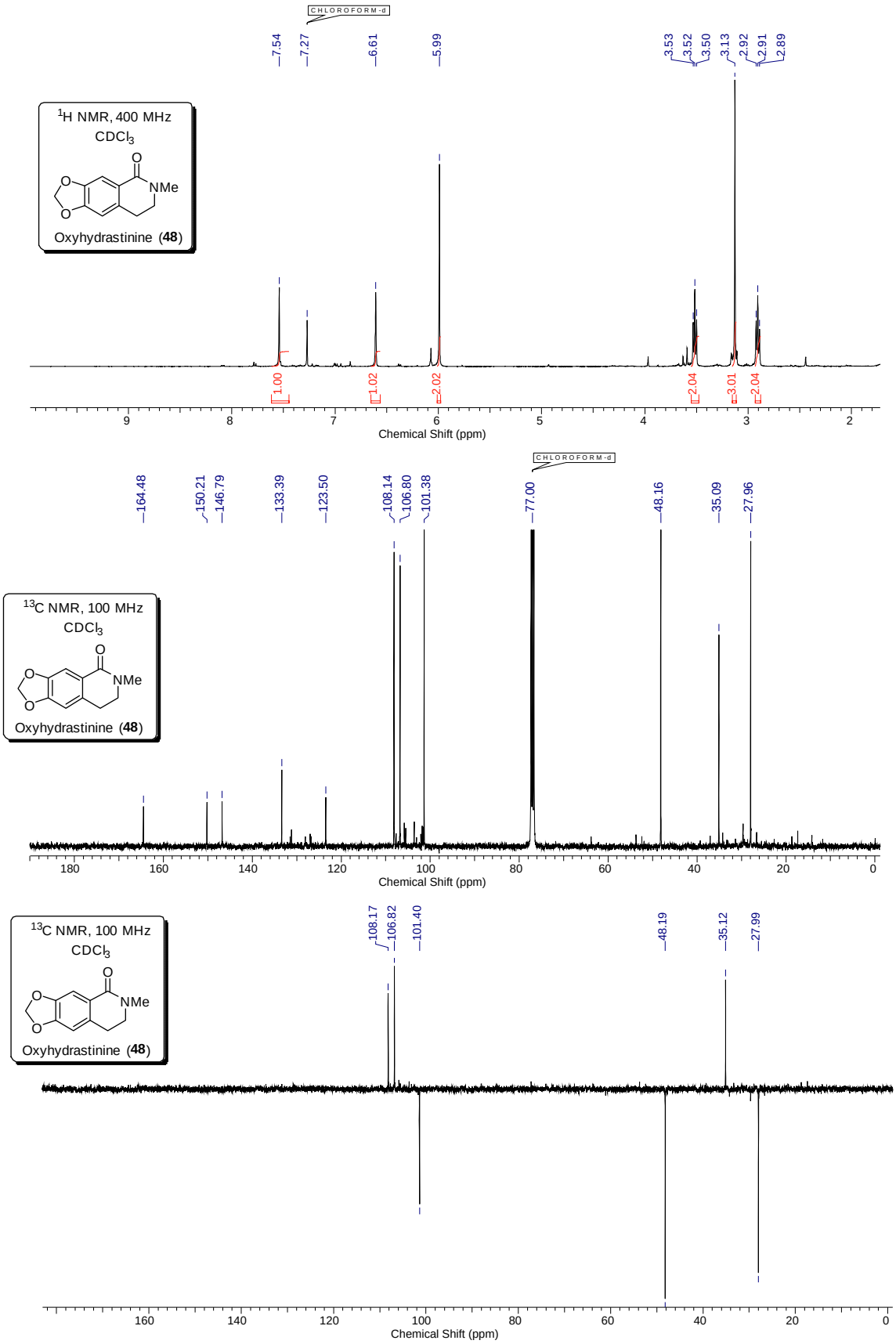
(Isolaudanosine, 50). A solution of amide-ester **128b** (58 mg, 0.14 mmol) in THF (8 mL) was dropwise added to LAH in THF (8 mL) at 0 °C and the mixture was refluxed for 6 h. The reaction was quenched with aq. saturated solution of Na_2SO_4 (5 mL) and filtered. Concentration of the filtrate in vacuo resulted in the crude amine-alcohol **129b**. To a solution of $SOCl_2$ (0.03 mL, 0.42 mmol) in CH_2Cl_2 (5 mL) was added the solution of amino alcohol **129b** in the same solvent in a dropwise fashion. The reaction mixture was allowed to stir for 8 h and the reaction was quenched with 2 N aq. NaOH (10 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL × 2) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by neutral alumina column chromatographic purification of the resulting residue using dichloromethane–methanol (19:1) as an eluent afforded pure product **50** as thick gum (28 mg, 55%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.32–2.45 (m, 1H), 2.40 (s, 3H), 2.57 (dd, J = 12 and 4 Hz, 1H), 2.75–3.10 (m, 3H), 3.34 (d, J = 14 Hz, 1H), 3.69 (d, J = 14 Hz, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 3.88 (s, 6H), 6.54 (s, 2H), 6.70–6.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.4, 42.1, 46.3, 55.8, 55.85 (2C), 55.91, 56.7, 58.2, 109.0, 111.1, 111.2, 112.6, 121.3, 126.7, 129.5, 133.3, 147.2, 147.27, 147.29, 148.8; ESIMS (*m*/*z*) 358 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{28}O_4N$ 358.2013, found 358.2003; IR ($CHCl_3$) ν_{max} 1652, 1601 cm^{-1}.

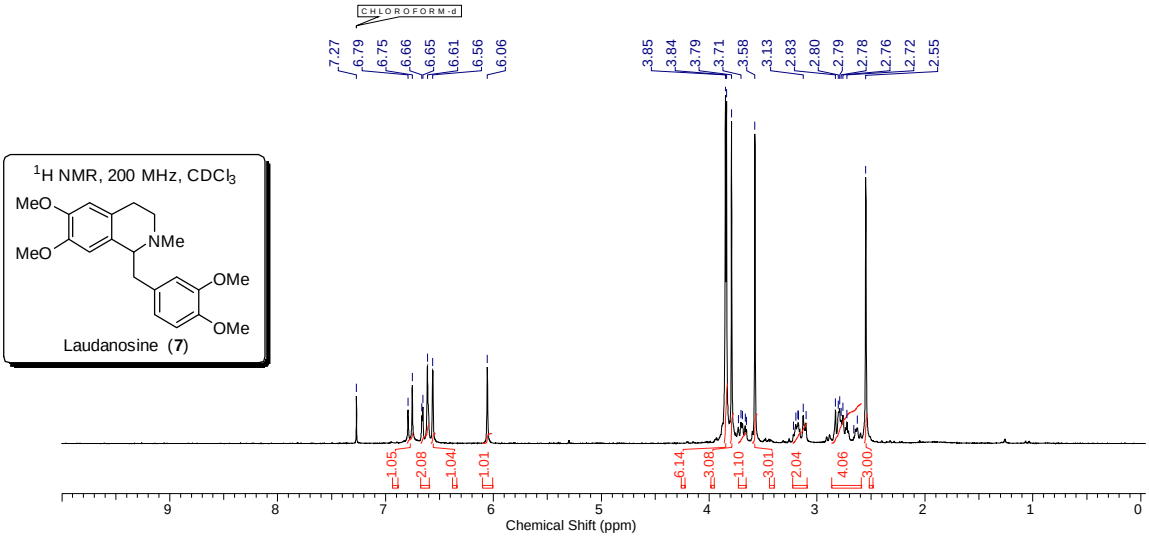
2C.5 Selected Spectra:

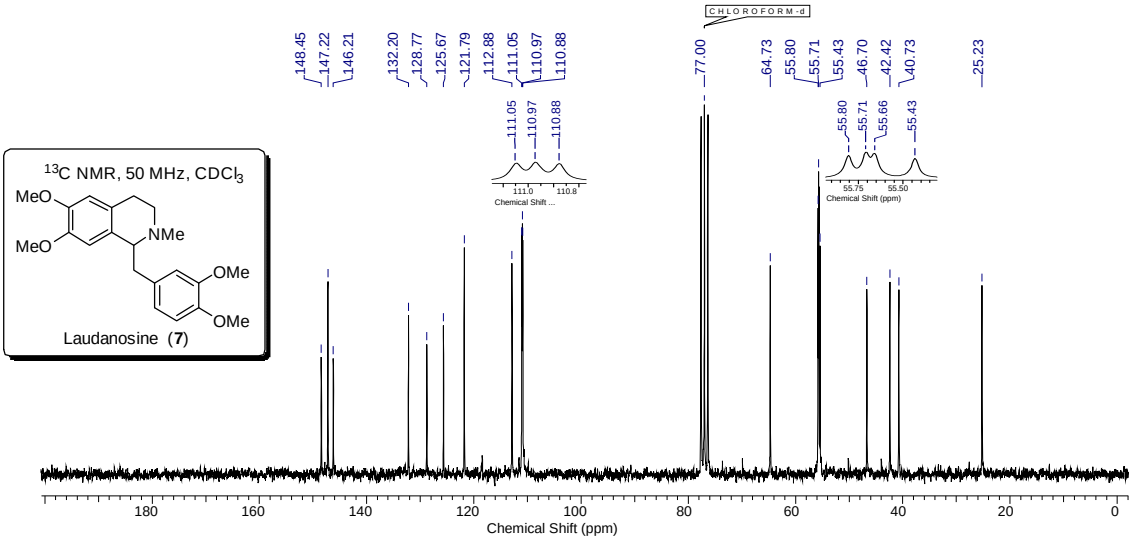

121.50
112.69
110.80
108.32
107.89
100.49
65.01
55.76
55.70
46.62
42.44
41.05
25.61
^{1}H NMR, 200 MHz
$CDCl_3$
NMe
Doryanine (**47**)
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

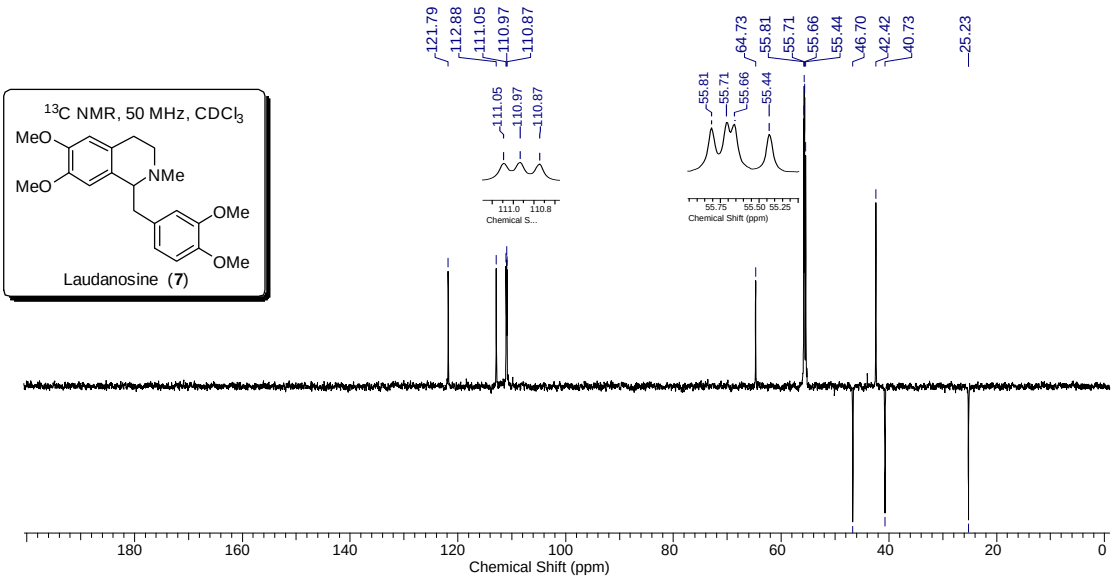

161.79
151.63
147.79
134.34
131.16
121.62
105.82
105.46
103.59
101.64
CHLOROFORM-d
77.00
37.04
^{13}C NMR, 50 MHz
$CDCl_3$
NMe
Doryanine (**47**)
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

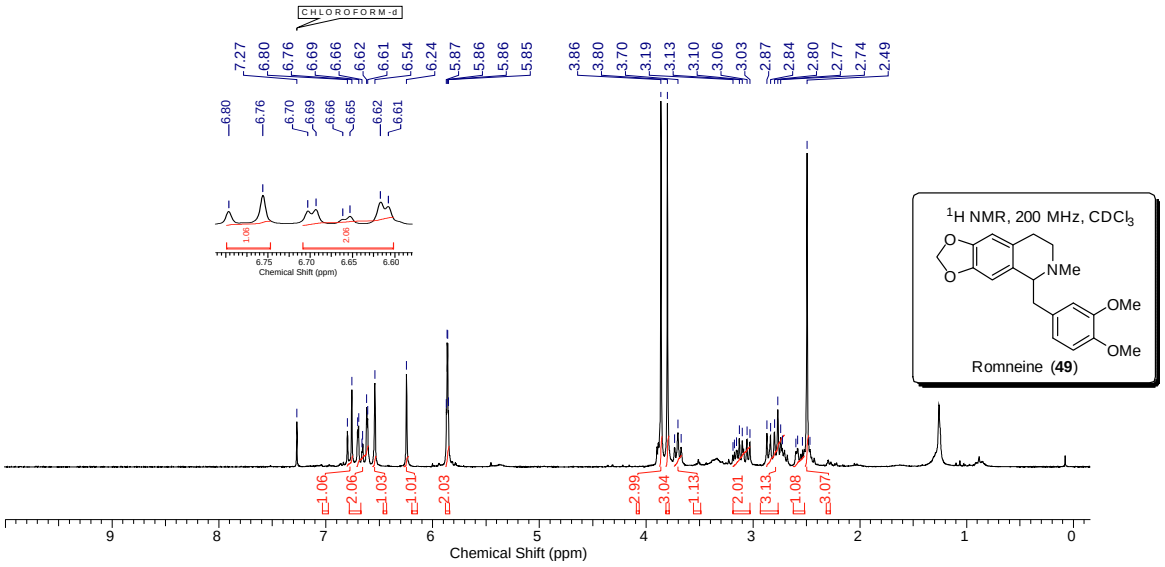

131.23
105.89
105.52
103.66
101.71
37.13
^{13}C NMR, 50 MHz
$CDCl_3$
NMe
Doryanine (**47**)
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

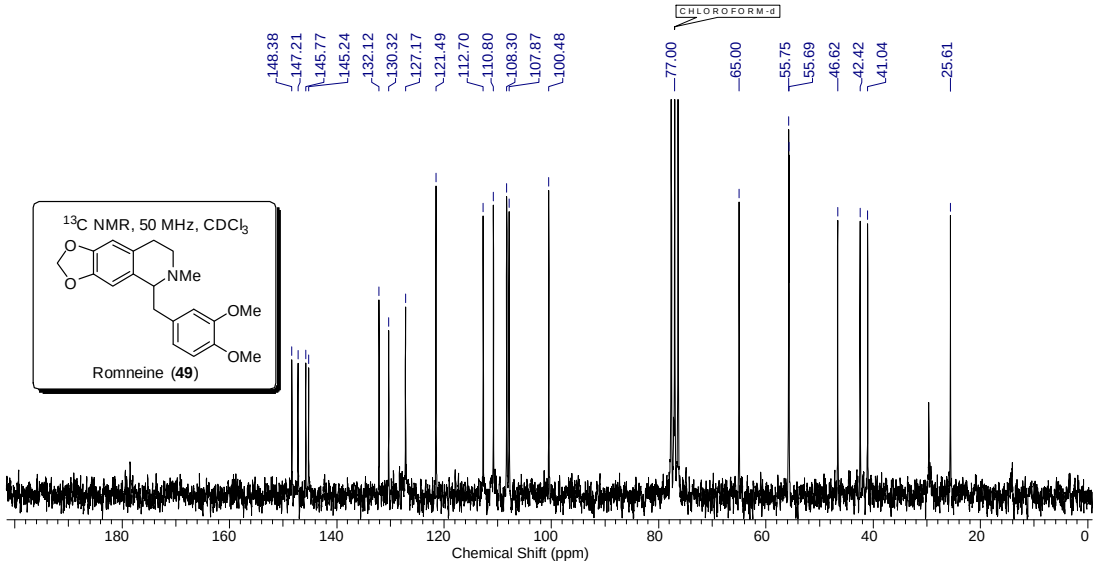

^{1}H NMR, 400 MHz
$CDCl_3$
Oxyhydrastinine (**48**)
CHLOROFORM-d
7.54
7.27
6.61
5.99
3.53
3.52
3.50
3.13
2.92
2.91
2.89
1.00
1.02
2.02
2.04
3.01
2.04
Chemical Shift (ppm)
^{13}C NMR, 100 MHz
$CDCl_3$
Oxyhydrastinine (**48**)
164.48
150.21
146.79
133.39
123.50
108.14
106.80
101.38
77.00
48.16
35.09
27.96
Chemical Shift (ppm)
^{13}C NMR, 100 MHz
$CDCl_3$
Oxyhydrastinine (**48**)
108.17
106.82
101.40
48.19
35.12
27.99
Chemical Shift (ppm)

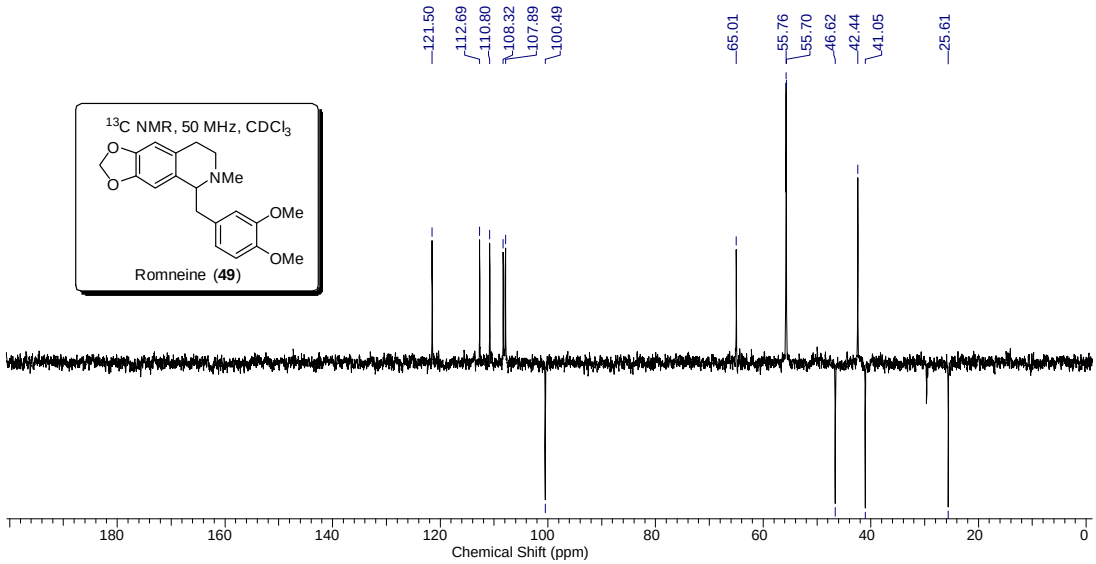

^{1}H NMR, 200 MHz, CDCl$_3$
MeO
MeO
NMe
OMe
OMe
Laudanosine (7)
CHLOROFORM-d
7.27
6.79
6.75
6.66
6.65
6.61
6.56
6.06
3.85
3.84
3.79
3.71
3.58
3.13
2.83
2.80
2.79
2.78
2.76
2.72
2.55
1.05
2.08
1.04
1.01
6.14
3.08
1.10
3.01
2.04
4.06
3.00
Chemical Shift (ppm)

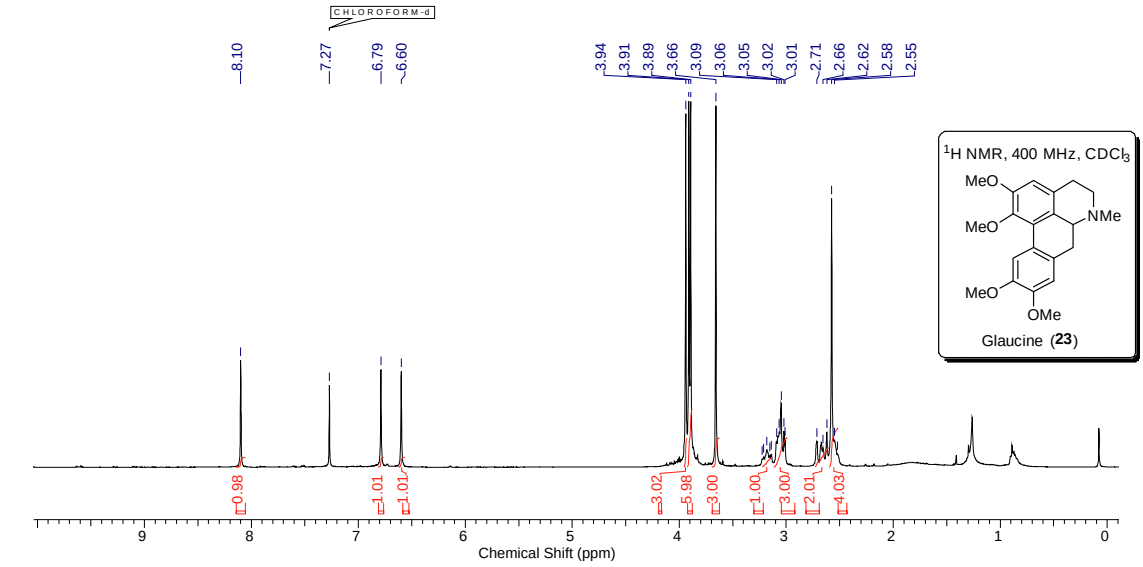

^{13}C NMR, 50 MHz, CDCl$_3$
MeO
MeO
NMe
OMe
OMe
Laudanosine (7)
CHLOROFORM-d
148.45
147.22
146.21
132.20
128.77
125.67
121.79
112.88
111.05
110.97
110.88
77.00
64.73
55.80
55.71
55.43
46.70
42.42
40.73
25.23
Chemical Shift (ppm)

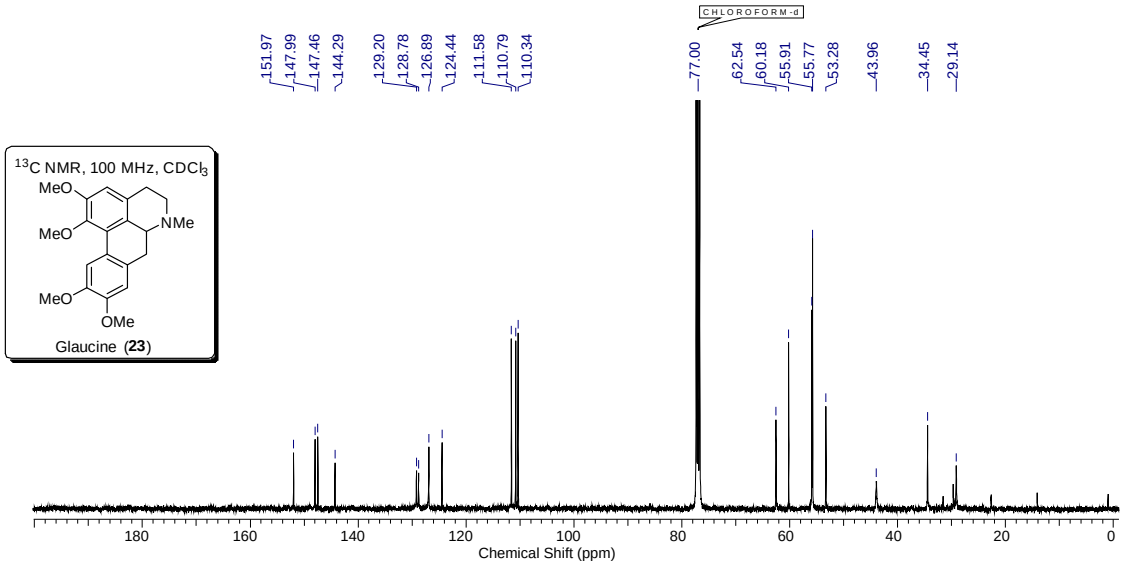

^{13}C NMR, 50 MHz, CDCl$_3$
MeO
MeO
NMe
OMe
OMe
Laudanosine (7)
121.79
112.88
111.05
110.97
110.87
64.73
55.81
55.71
55.66
55.44
46.70
42.42
40.73
25.23
Chemical Shift (ppm)

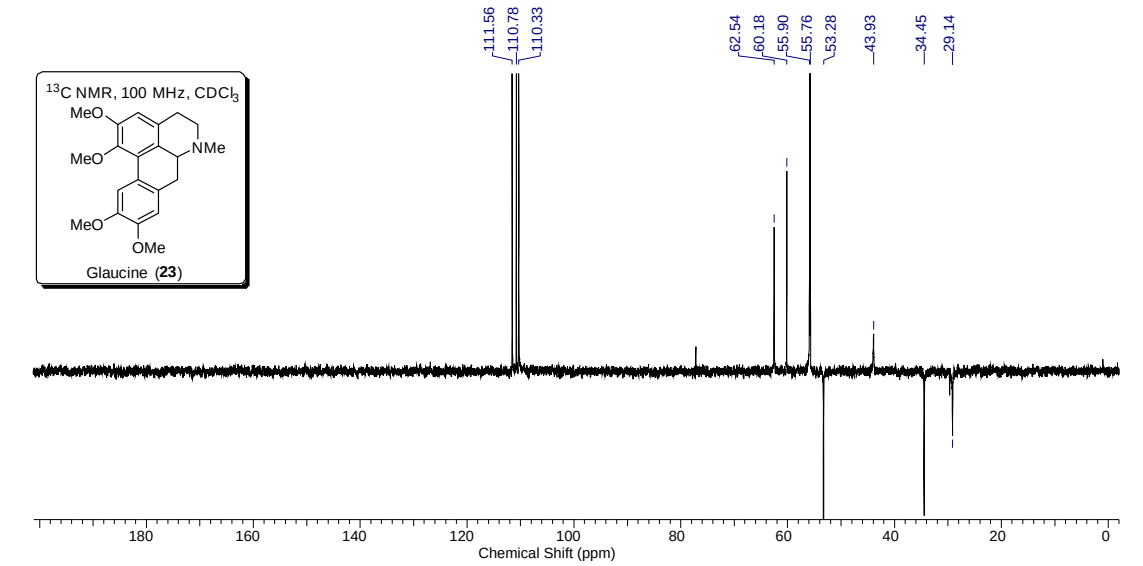

CHLOROFORM-d
7.27 6.80 6.76 6.69 6.66 6.62 6.61 6.54 6.24 5.87 5.86 5.86 5.85 3.86 3.80 3.70 3.19 3.13 3.10 3.06 3.03 2.87 2.84 2.80 2.77 2.74 2.49
6.80 6.76 6.70 6.69 6.66 6.65 6.62 6.61
1.06 2.06
6.75 6.70 6.65 6.60
Chemical Shift (ppm)
1.06 2.06 1.03 1.01 2.03 2.99 3.04 1.13 2.01 3.13 1.08 3.07
9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)
^{1}H NMR, 200 MHz, CDCl$_3$
NMe
OMe
OMe
Romneine (**49**)

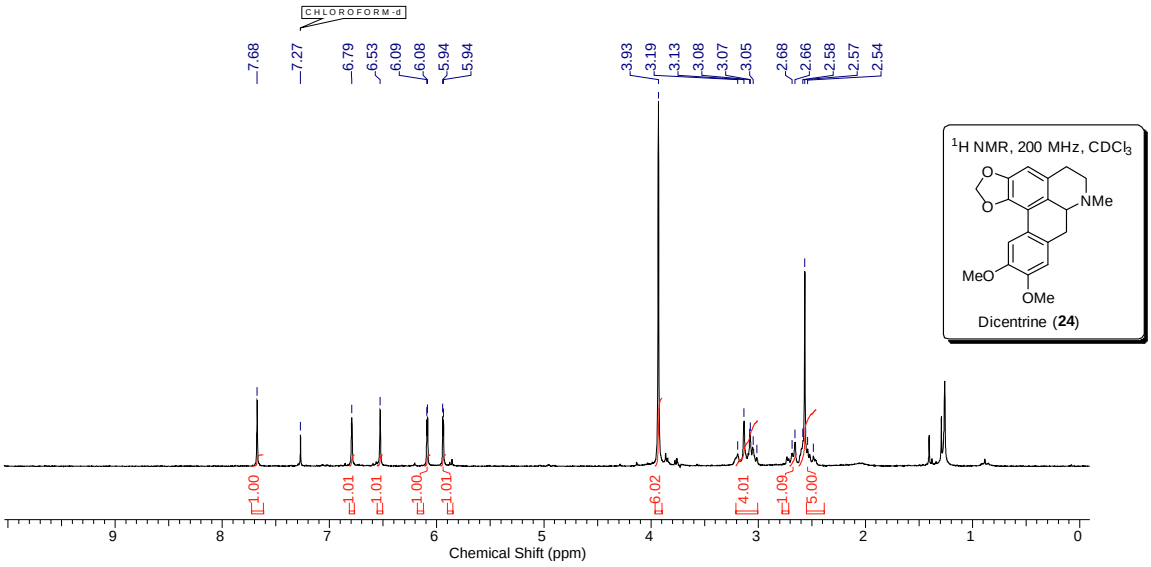

CHLOROFORM-d
148.38 147.21 145.77 145.24 132.12 130.32 127.17 121.49 112.70 110.80 108.30 107.87 100.48 77.00 65.00 55.75 55.69 46.62 42.42 41.04 25.61
180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)
^{13}C NMR, 50 MHz, CDCl$_3$
NMe
OMe
OMe
Romneine (**49**)

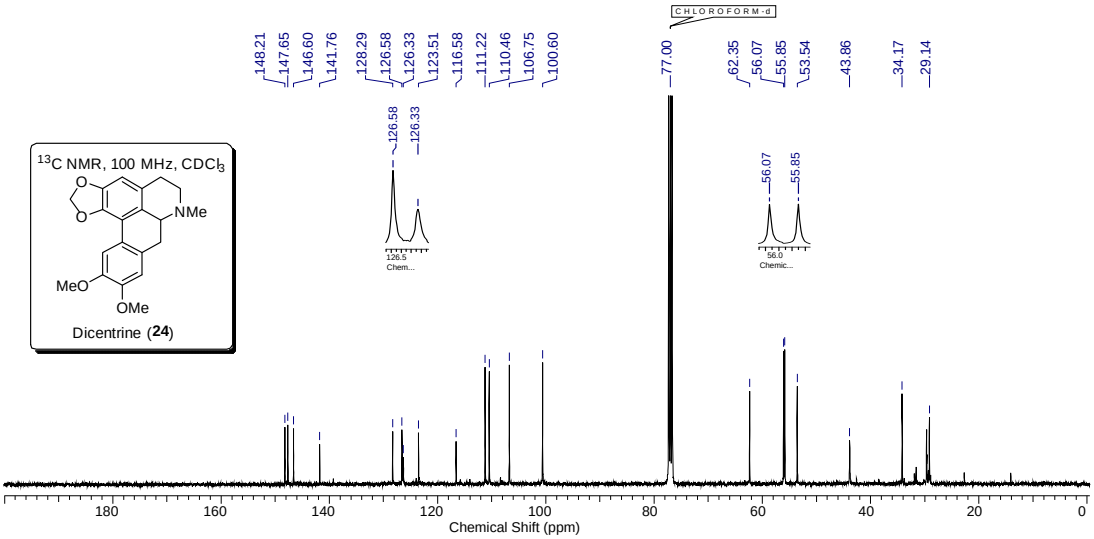

121.50 112.69 110.80 108.32 107.89 100.49 65.01 55.76 55.70 46.62 42.44 41.05 25.61
180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)
^{13}C NMR, 50 MHz, CDCl$_3$
NMe
OMe
OMe
Romneine (**49**)

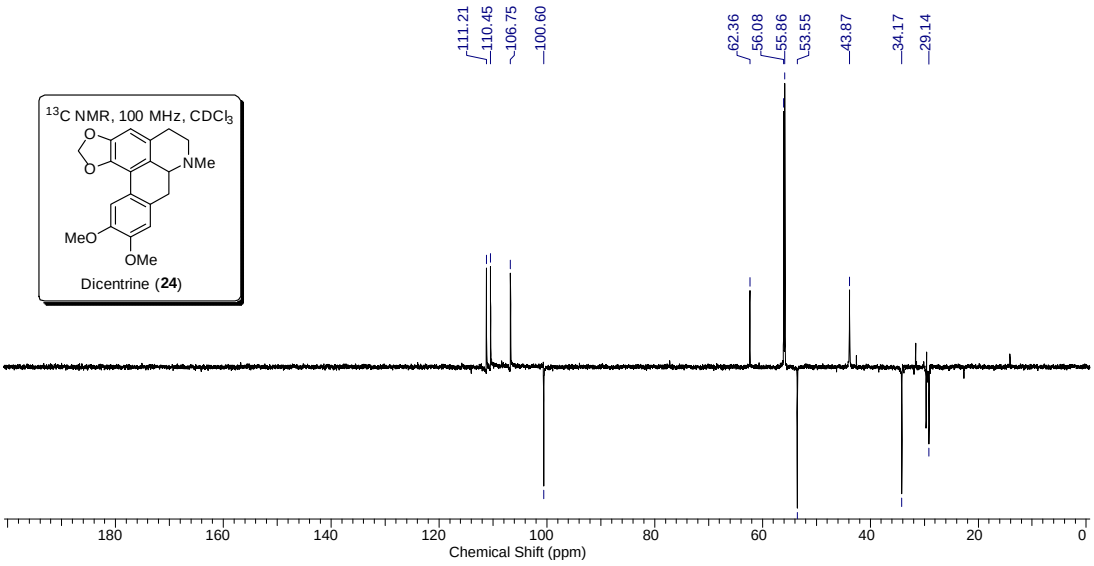

CHLOROFORM-d
8.10
7.27
6.79
6.60
3.94
3.91
3.89
3.66
3.09
3.06
3.05
3.02
3.01
2.71
2.66
2.62
2.58
2.55
0.98
1.01
1.01
3.02
5.98
3.00
1.00
3.00
2.01
4.03
Chemical Shift (ppm)
^{1}H NMR, 400 MHz, CDCl$_3$
MeO
MeO
MeO
NMe
OMe
Glaucine (**23**)

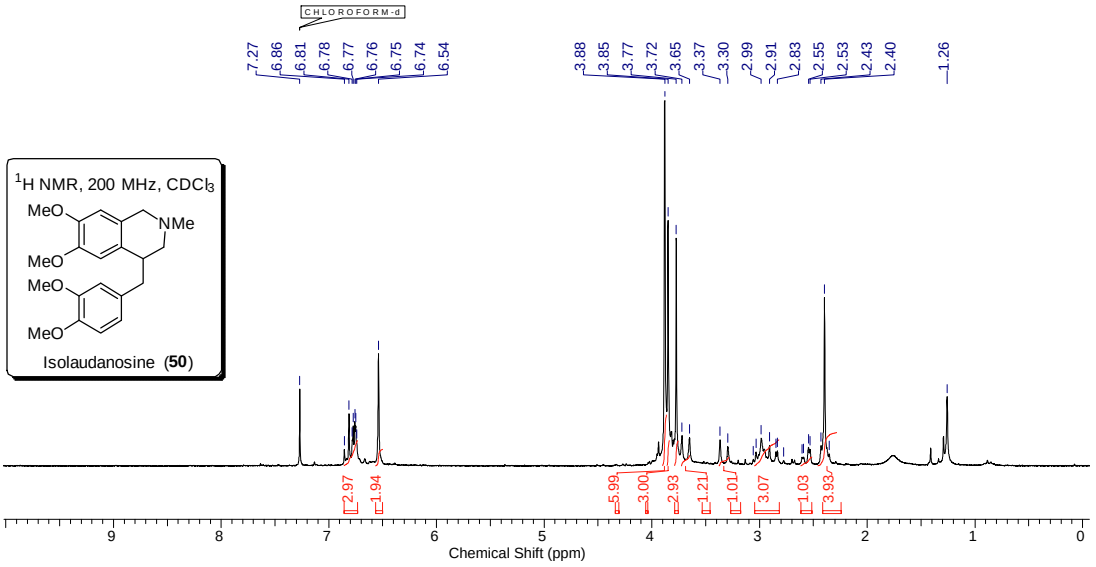

CHLOROFORM-d
151.97
147.99
147.46
144.29
129.20
128.78
126.89
124.44
111.58
110.79
110.34
77.00
62.54
60.18
55.91
55.77
53.28
43.96
34.45
29.14
Chemical Shift (ppm)
^{13}C NMR, 100 MHz, CDCl$_3$
MeO
MeO
MeO
NMe
OMe
Glaucine (**23**)

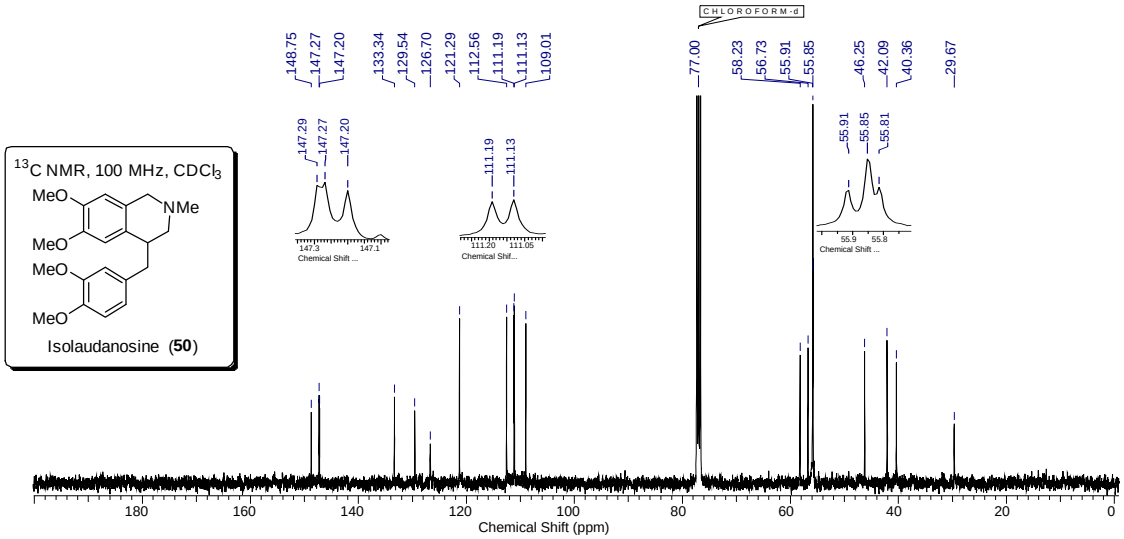

111.56
110.78
110.33
62.54
60.18
55.90
55.76
53.28
43.93
34.45
29.14
Chemical Shift (ppm)
^{13}C NMR, 100 MHz, CDCl$_3$
MeO
MeO
MeO
NMe
OMe
Glaucine (**23**)

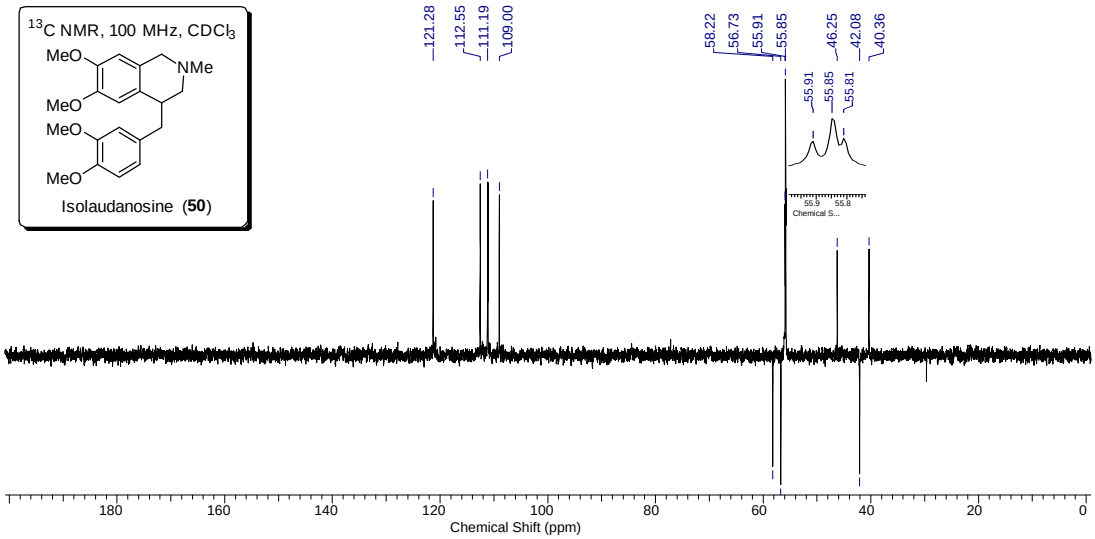

CHLOROFORM-d
7.68
7.27
6.79
6.53
6.09
6.08
5.94
5.94
3.93
3.19
3.13
3.08
3.07
3.05
2.68
2.66
2.58
2.57
2.54
1.00
1.01
1.01
1.00
1.01
6.02
4.01
1.09
5.00
Chemical Shift (ppm)
^{1}H NMR, 200 MHz, CDCl$_3$
NMe
MeO
OMe
Dicentrine (**24**)

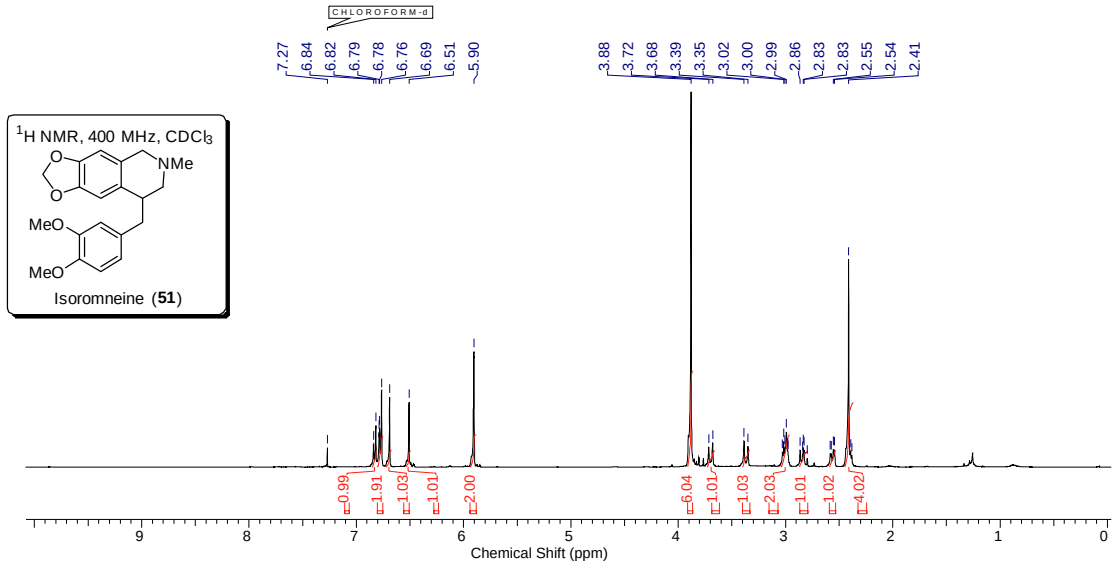

CHLOROFORM-d
148.21
147.65
146.60
141.76
128.29
126.58
126.33
123.51
116.58
111.22
110.46
106.75
100.60
77.00
62.35
56.07
55.85
53.54
43.86
34.17
29.14
126.58
126.33
56.07
55.85
Chemical Shift (ppm)
^{13}C NMR, 100 MHz, CDCl$_3$
NMe
MeO
OMe
Dicentrine (**24**)

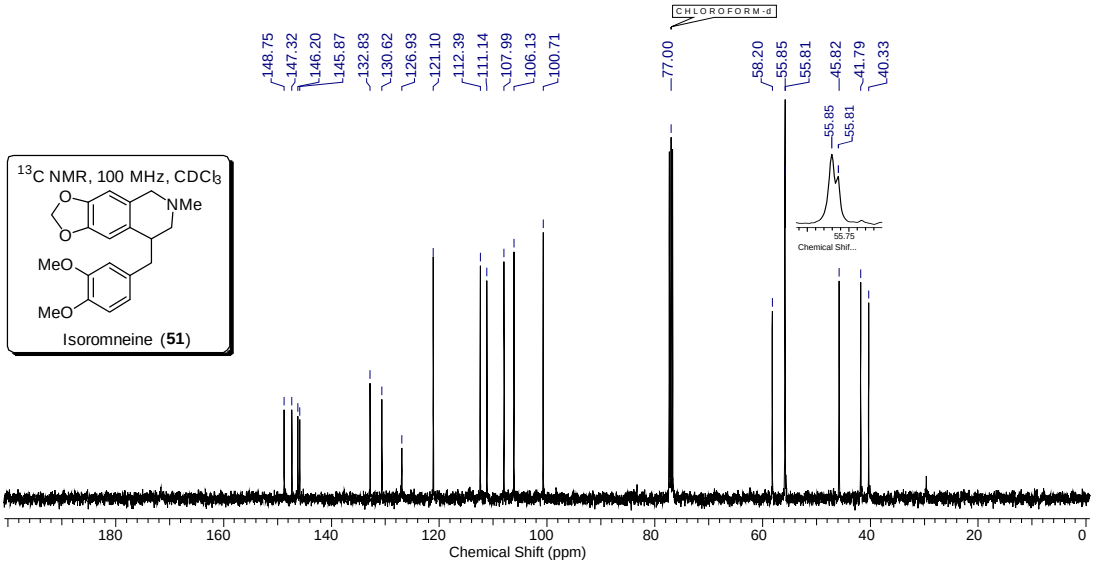

111.21
110.45
106.75
100.60
62.36
56.08
55.86
53.55
43.87
34.17
29.14
Chemical Shift (ppm)
^{13}C NMR, 100 MHz, CDCl$_3$
NMe
MeO
OMe
Dicentrine (**24**)

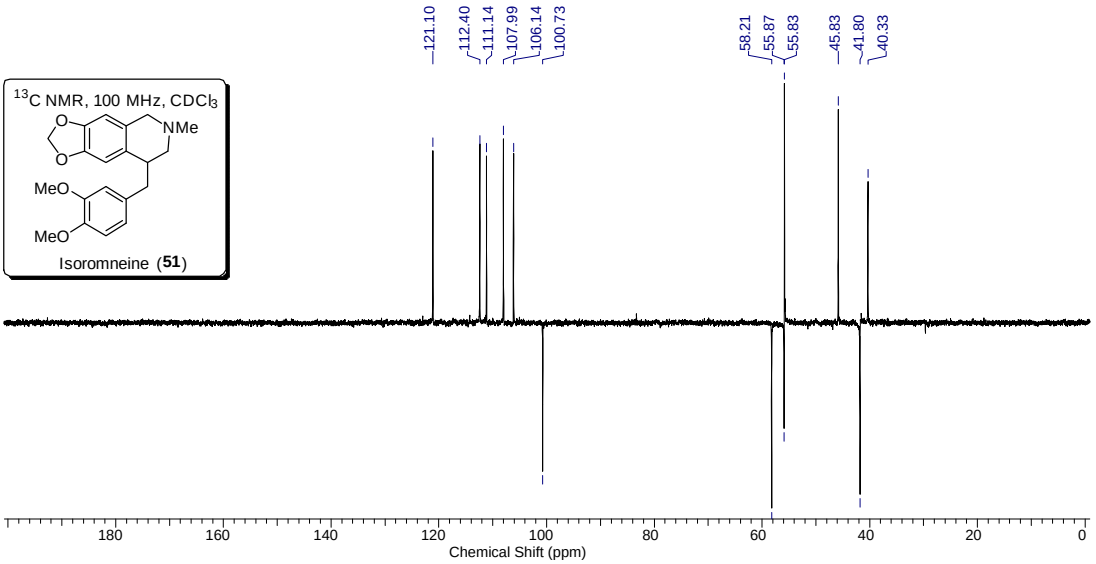

^{1}H NMR, 200 MHz, CDCl$_3$
MeO
MeO
MeO
MeO
NMe
Isolaudanosine (**50**)
CHLOROFORM-d
7.27
6.86
6.81
6.78
6.77
6.76
6.75
6.74
6.54
3.88
3.85
3.77
3.72
3.65
3.37
3.30
2.99
2.91
2.83
2.55
2.53
2.43
2.40
1.26
2.97
1.94
5.99
3.00
2.93
1.21
1.01
3.07
1.03
3.93
Chemical Shift (ppm)


^{13}C NMR, 100 MHz, CDCl$_3$
MeO
MeO
MeO
MeO
NMe
Isolaudanosine (**50**)
CHLOROFORM-d
148.75
147.27
147.20
133.34
129.54
126.70
121.29
112.56
111.19
111.13
109.01
77.00
58.23
56.73
55.91
55.85
46.25
42.09
40.36
29.67
Chemical Shift (ppm)


^{13}C NMR, 100 MHz, CDCl$_3$
MeO
MeO
MeO
MeO
NMe
Isolaudanosine (**50**)
121.28
112.55
111.19
109.00
58.22
56.73
55.91
55.85
46.25
42.08
40.36
55.91
55.85
55.81
Chemical Shift (ppm)


CHLOROFORM-d
7.27
6.84
6.82
6.79
6.78
6.76
6.69
6.51
5.90
3.88
3.72
3.68
3.39
3.35
3.02
3.00
2.99
2.86
2.83
2.83
2.55
2.54
2.41
^{1}H NMR, 400 MHz, CDCl$_3$
NMe
MeO
MeO
Isoromneine (**51**)
0.99
1.91
1.03
1.01
2.00
6.04
1.01
1.03
2.03
1.01
1.02
4.02
Chemical Shift (ppm)


CHLOROFORM-d
148.75
147.32
146.20
145.87
132.83
130.62
126.93
121.10
112.39
111.14
107.99
106.13
100.71
77.00
58.20
55.85
55.81
45.82
41.79
40.33
55.85
55.81
^{13}C NMR, 100 MHz, CDCl$_3$
NMe
MeO
MeO
Isoromneine (**51**)
Chemical Shift (ppm)


121.10
112.40
111.14
107.99
106.14
100.73
58.21
55.87
55.83
45.83
41.80
40.33
^{13}C NMR, 100 MHz, CDCl$_3$
NMe
MeO
MeO
Isoromneine (**51**)
Chemical Shift (ppm)

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Chapter 3

Synthesis of Human Red Hair Trichochrome Pigment's Skeleton

3.1.1 Introduction of Maleic Anhydrides

Maleic anhydride (2,5-furandione) was prepared for the first time two centuries ago and became commercially available a century later by the catalytic oxidation of benzene using vanadium pentoxide.[1] It is a versatile synthon wherein all the sites are amenable for a variety of reactions and possesses exceptional selectivity in reactions towards several nucleophiles. The vast array of nucleophilic reactions undergone by maleic anhydrides confer a high synthetic potential on them.[2] In the past century, several symmetrically and unsymmetrically substituted maleic anhydride derivatives have been prepared, the simplest of them being methylmaleic anhydride or citraconic anhydride (**1**) (Figure 1). Although the utilities of methylmaleic anhydride (**1**) have been well proven in laboratory as well as in industrial practice,[3] only three synthetic approaches towards methylmaleic anhydride are known in the literature: (i) starting from citric acid by double dehydrative decarboxylation and isomerization,[4] (ii) from ethyl acetoacetate via cyanohydrin formation followed by dehydrative cyclization[5] and (iii) by the gas phase oxidation of isoprene.[6] In the case of higher monoalkylmaleic anhydrides **2** only a few approaches are known for their synthesis. The first approach involves the conjugate addition of organocuprates to dimethyl acetylenedicarboxylate as a key reaction.[7] Recently, two synthetic approaches have been reported for compound **2** by palladium-catalyzed dicarbonylation of terminal acetylenes.[8,9]

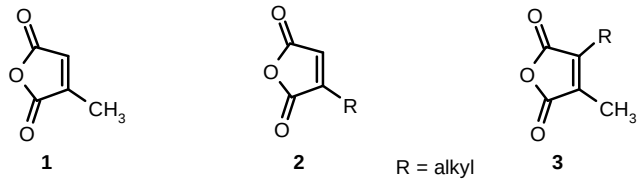
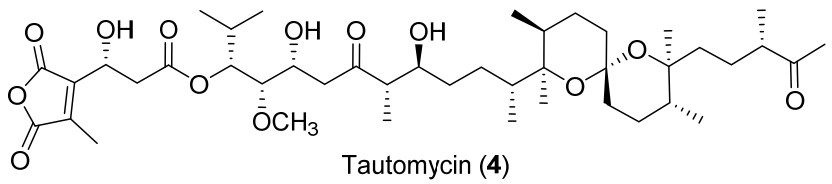


Figure 1. Monoalkyl Substituted and Methylalkylmaleic Anhydrides

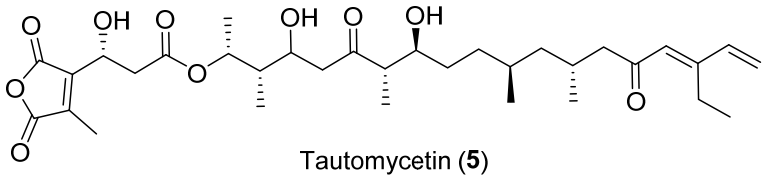
A simple and efficient access to monoalkyl and dialkylmaleimides was recently developed in our laboratory involving a novel contra thermodynamic rearrangement of alkylidene succinimides to alkyl maleimides via the corresponding isoimides.[10] Specifically there are a vast number of natural products containing maleic anhydride structure. Natural products with the maleic anhydride structure can be classified as nonadrides, tautomycin and tautomycetin, chaetomellic anhydrides, and other compounds according to whether the products contain the core structure of nonadrides, the presence of a nine-membered ring with an affixed maleic anhydride.

Research on the chemical modification and biological activity of tautomycin (**4**)[11,12] and tautomycetin (**5**),[13,14] which were isolated and identified by researchers from China and Japan in the 1980s at RIKEN, Japan, found that compounds with maleic anhydride structure have special biological activities, such as antibiotic activities and enzymatic inhibition. Later, many natural products with maleic anhydride structure, such as tyromycin A (**6**),[15] chaetomellic anhydride A (**7**), chaetomellic anhydride B (**8**),[16-18] phomoidride A (CP-225,917) (**9**), phomoidride B (CP-263,114) (**10**),[19-21] rubratoxin A (**11**),[22,23] rubratoxin B (**12**),[22,24-26] cornexistin (**13**),[27-30] hydroxycornexistin (**14**),[31,32] cordyanhydride A (**15**), cordyanhydride B (**16**),[33] zopfiellin (**17**),[34,35] heveadride (**18**),[36] dihydroepiheveadride (**19**),[37,38] glauconic acid (**20**), glaucanic acid (**21**),[39-42] scytalidin (**22**),[43-45] byssochlamic acid (**23**),[46,47] puberulonic acid (**24**),[48-50] stipitotanic acid (**25**),[51-53] itaconitin (**26**),[54,55] 2-carboxymethyl-3-hexyl-maleic acid anhydride (**27**),[56] telfairic anhydride (**28**),[57,58] (Table 1), and so on, also proved to have similar properties.

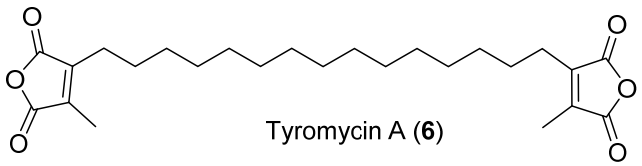
Table 1. Selected Natural Products with Maleic Anhydride Structure



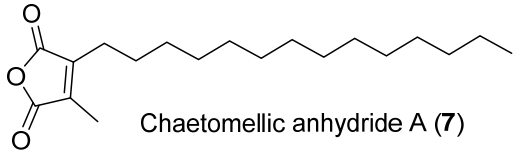
Tautomycin (**4**)



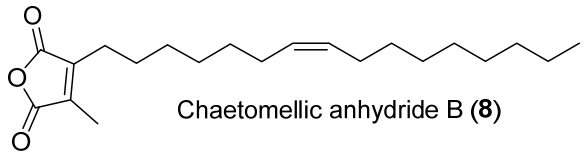
Tautomycetin (**5**)



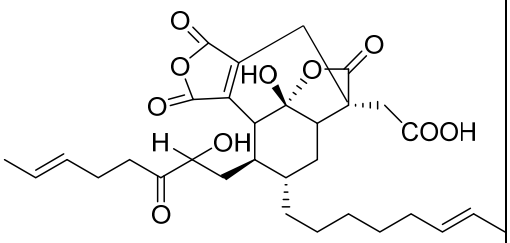
Tyromycin A (**6**)



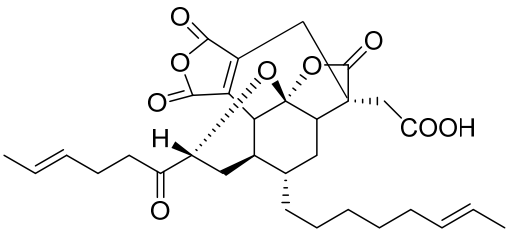
Chaetomellic anhydride A (**7**)



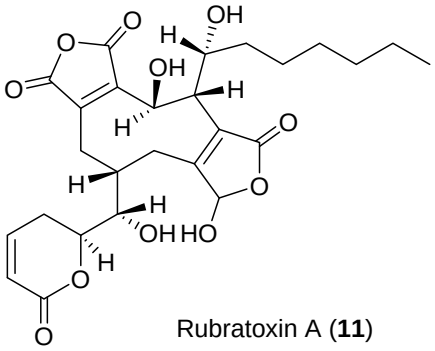
Chaetomellic anhydride B (**8**)



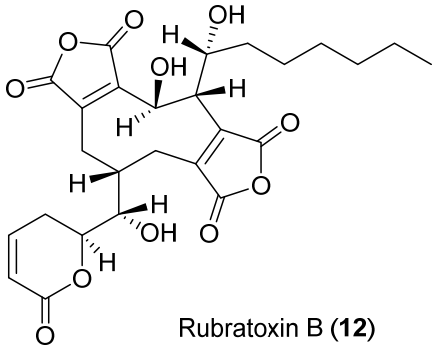
Phomoidride A (CP-225,917) (**9**)



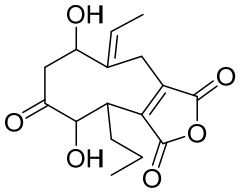
Phomoidride B (CP-263,114) (**10**)



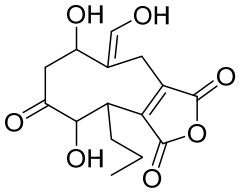
Rubratoxin A (**11**)



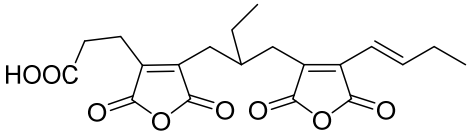
Rubratoxin B (**12**)



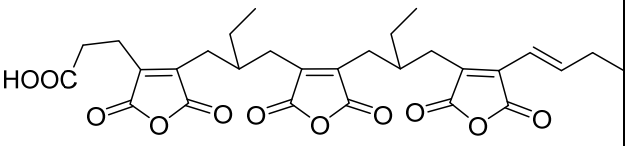
Cornexistin (**13**)



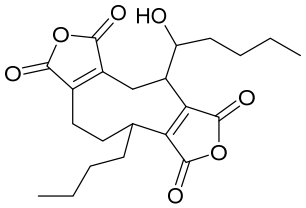
Hydroxycornexistin (**14**)

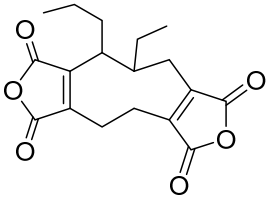


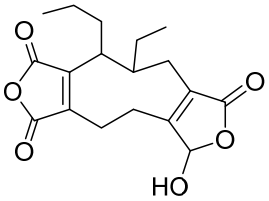
Cordyanhydride A (**15**)

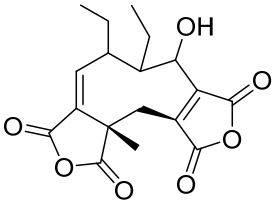


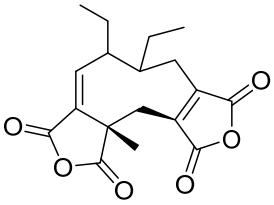
Cordyanhydride B (**16**)

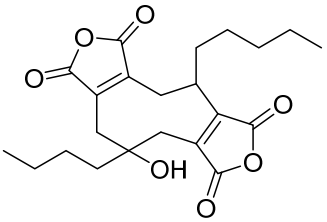

Zopfiellin (**17**)

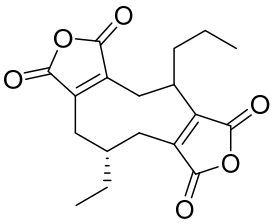

Heveadride (**18**)

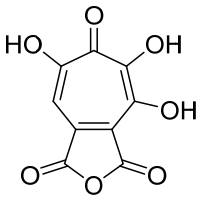

Dihydroepieveadride (**19**)

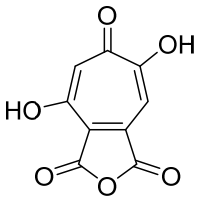

Glauconic acid (**20**)

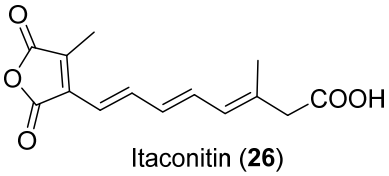

Glaucanic acid (**21**)

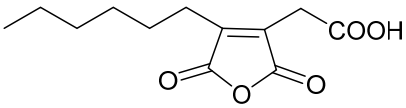

Scytalidin (**22**)

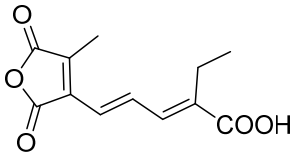

Byssochlamic acid (**23**)


Puberulonic acid (**24**)


Stipitatonic acid (**25**)


Itaconitin (**26**)


2-Carboxymethyl-3-hexyl-maleic acid anhydride (**27**)

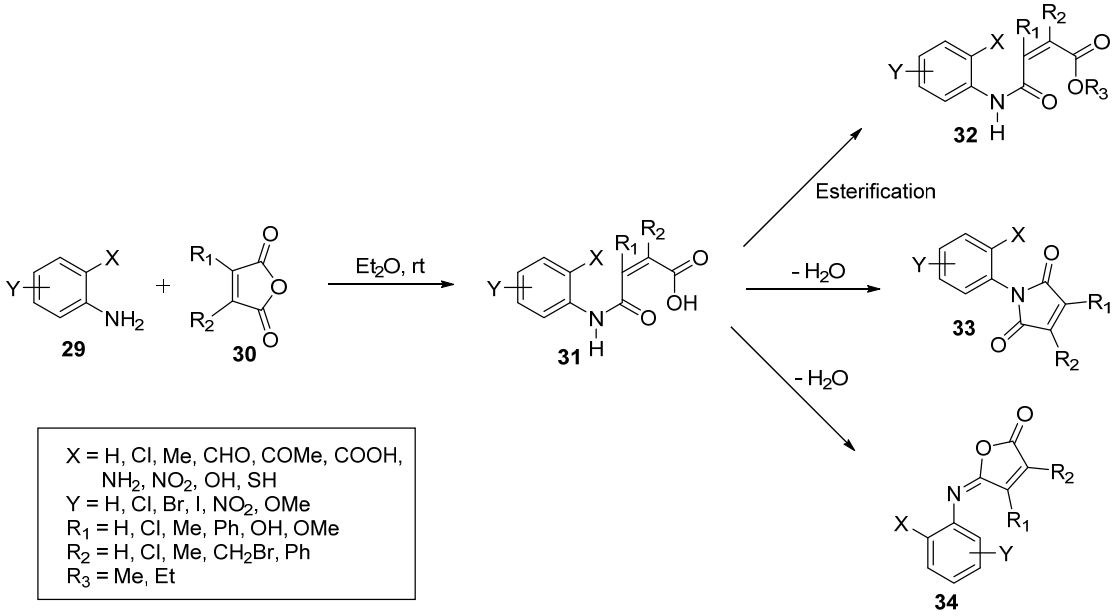

Telfairic anhydride (**28**)

3.1.2 Ring Closure Reactions of Suitably *ortho*-Substituted Maleanilic Acids

The vast array of nucleophilic reactions undergone by symmetrical and unsymmetrical maleic anhydrides confers on them a high synthetic potential. As such, maleic anhydrides and their derivatives have been extensively used to model a variety of (i) heterocyclic skeletons, (ii) natural products and their precursors, (iii) bioactive molecules, (iv)

compounds highlighting regiochemical dichotomy, and (v) a series of polymers with tailored material characteristics.[59]

The reactions of aniline derivatives **29** with maleic anhydrides **30** furnish[60] the corresponding maleanilic acids **31** in quantitative yield (Scheme 1). These acids on treatment with a variety of esterifying reagents provide corresponding alkyl maleanilates **32**,[61] while the maleanilic acids on dehydration yield the corresponding maleimides **33**[62] and isomaleimides **34**[63a,b] under thermodynamically controlled and kinetically controlled conditions respectively. The multifunctional maleanilic acids obtained from suitably *ortho*-substituted aniline derivatives (**29**: X = H, Cl, Me, CHO, COMe, COOH, NH_2, NO_2, OH and SH) and variety of maleic anhydrides have been employed to obtain a diverse menu of structurally interesting and biologically important heterocyclic systems *via* intramolecular Michael addition, condensation and dehydrative ring closure reactions.



Scheme 1. Reactions of Maleanilic Acids

3.1.3 Synthesis of Benzothiazoles, Benzothiazines and *bis*-Benzothiazines with Generation of Carbon–Sulphur Bond

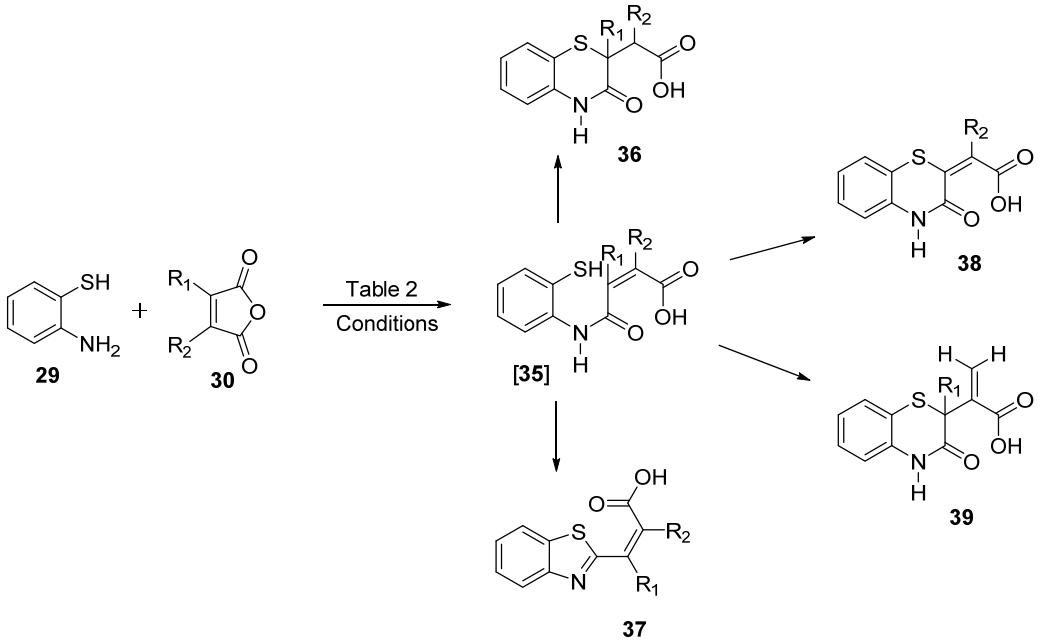
The reactions of symmetrical and unsymmetrical maleic anhydrides with *o*-aminothiophenol have been systematically studied earlier (Scheme 2). The reactions of alkyl and/or aryl substituted maleic anhydride with *o*-aminothiophenol (*o*-ATP) furnish benzothiazines (**36**)[64-69] in excellent yields (Table 2, entries 1-6). The formation of which can be visualized to proceed by initial aminolysis of the anhydrides with amino functional group of *o*-aminothiophenol, followed by intramolecular Michael type addition of thiol

function to the α,β-unsaturated carbonyl system in the intermediate maleanilic acid [**35**] to furnish benzothiazines **36** or vice versa. A scrutiny of the orientation of the addition of the thiol in the reaction of *o*-aminothiophenol with unsymmetrically substituted maleic anhydride reveals the competitive role of steric/electrical effects in these cases. Thus, in the unsymmetrical anhydrides, initial aminolysis is regioselectively favoured at a carbonyl, away from the bulkier substituent. The attenuation of carbonyl reactivity by hyperconjugative effect or mesomeric interaction does not seem to be strong enough to reverse the attack at apparently more hindered carbonyl. In the reaction of phenylmethylmaleic anhydride with *o*-aminothiophenol, formation of **36** (entry 6) as the exclusive product, again demonstrates the decreased electrical effect of the phenyl ring. The possible non planarity of phenyl group could justify such a view, also invoked earlier.[70] In contrast, hydroxyl and methoxy substituted maleic anhydride react with *o*-aminothiophenol to furnish benzothiazoles **37** (entries 7-9), apparently by a different pathway,[69] indicating that hydroxy and alkoxy substituents on carbon–carbon double bond can prevent such Michael type additions. As happens with *o*-aminophenol, the reactions of *o*-aminothiophenol with molar quantity of chloromaleic anhydride yields **38**[64] (entry 10). Interestingly, the reactions of dichloromaleic anhydride and dichloromaleimide with two equivalents of *o*-aminothiophenol provide the *bis*-benzothiazines **40** and **41** respectively *via* addition-elimination pathway (Figure 2).[71] The reaction of *o*-aminothiophenol with (bromomethyl)methylmaleic anhydride yields benzothiazine derivative **39**[72] (entry 11).

Table 2. Formation of Carbon–Sulphur Bond

Entry	In Compound **30**		Conditions	Product	Yield %	Refs.
	R_1	R_2				
1	H	H	Et_2O, rt	**36**	98	15, 25, 28-32
2	H	Me	Et_2O, rt	**36**	85	30
3	Me	H	$MeOH/H^+$, reflux	**36**	70	25
4	Me	Me	AcOH, reflux	**36**	90	33
5	H	Ph	Et_2O, rt	**36**	90	30
6	Me	Ph	PhCl, reflux	**36**	87	33
7	OMe	H	Acetone, rt	**37**	89	33
8	OH	Ph	Pyridine, reflux	**37**	75	33

9	OMe	Ph	Pyridine, reflux	**37**	75	33
10	Cl	H	Acetone, rt	**38**	60	28
11	Me	CH_2Br	$CHCl_3$, -15 °C	**39**	90	19



Scheme 2. Formation of Carbon–Sulphur Bond via Maleanilic Acids

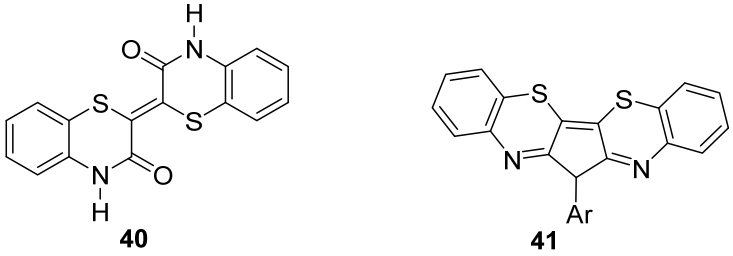
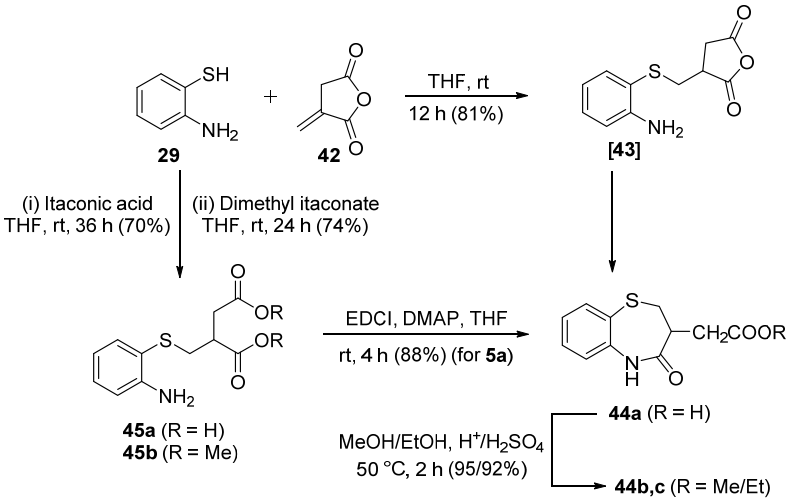


Figure 2. Structures of *bis*-Benzothiazine

3.1.4 Michael Adition of *ortho*-Aminothiophenol with Itaconic Anhydride

The Michael-type additions of aromatic thiols to activated carbon–carbon double bonds and nucleophilic ring opening of cyclic anhydrides with primary aromatic amines are well known in the litrature.[59,73] Earlier our group[74] has envisaged that in the reaction of itaconic anhydride (**42**) with *o*-ATP (**29**), the Michael type addition of thiol to a highly activated carbon–carbon double bond in itaconic anhydride (**42**) followed by an intramolecular nucleophilic ring opening of an adjacent anhydride carbonyl with an amine moiety would provide benzothiazepinylacetic acid **44a**. However, the first nucleophilic regioselective ring opening of anhydride **42** with *o*-ATP (**29**) at the

unconjugated carbonyl with primary amine moiety followed by intramolecular dehydrative condensation/Michael type addition of thiol unit could also provide an easy access to the benzothiazole/benzothioazocine system. The reaction of anhydride **42** with *o*-ATP (**29**) in tetrahydrofuran at room temperature provided a single product in 81% yield (Scheme 3). It was difficult to conclusively assign the structure **44a** or **50** to the formed product on the basis of NMR data. The reaction of itaconic acid with *o*-ATP (**29**) at room temperature form the Michael adduct **45a** in 70% yield. Similarly the reaction of dimethyl itaconate with *o*-ATP (**29**) also furnished the desired adduct **45b** in 74% yield. The water soluble carbodimide, *N*-ethyl-*N*'-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI), induced regioselective intramolecular dehydrative cyclization of diacid **45a** gave the same product in 88% yield, which was earlier obtained from the reaction of **29** and **42**. Since the formation of seven membered rings are preferred over the formation of 8-membered rings, the formation of benzothiazepinylacetic acid **44a** was proposed. The benzothiazepinylacetic acid **44a** was further characterized as its methyl and ethyl esters **44b** and **44c**. Finally, the formation of seven-membered benzothiazepine **44a** was confirmed by X-ray crystallographic data ruling out the possibility of formation of the eight-membered compound benzothioazocine **50**.

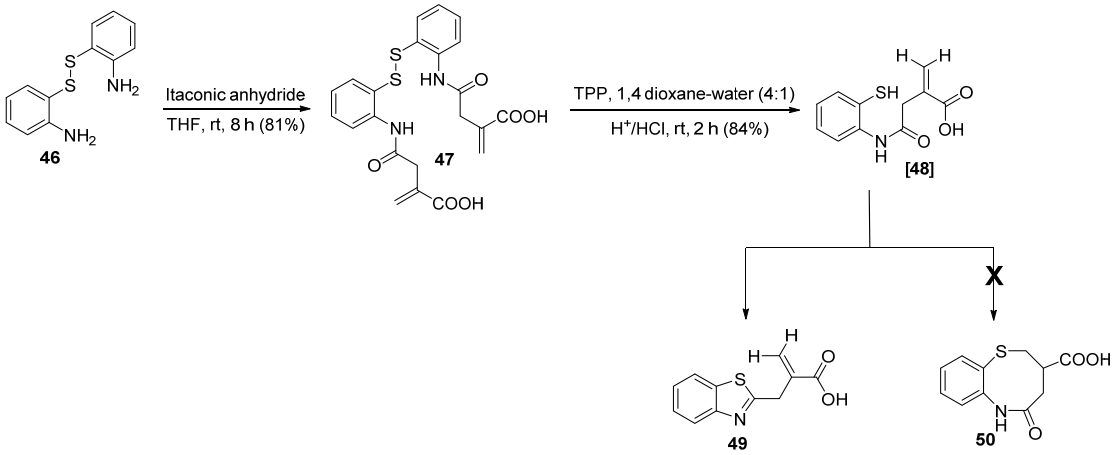


Scheme 3. Micahel Addition of *o*-Aminothiophenol with Itaconic Anhydride

From these observations it was proposed that in the reaction of itaconic anhydride (**42**) with *o*-ATP (**29**), chemoselective Michael type addition of thiol takes place first to form the unisolable intermediate **43**, the amine moiety of which condenses in an intramolecular fashion with the adjacent anhydride carbonyl to furnish the benzothiazepine **44a**. Herein, an addition of thiol to the carbon–carbon double bond on an anhydride system before the

anhydride ring opening with an amine moiety is shown as an example of delicately balanced selectivity.

The activation of *α,β*-unsaturated double bond by the carboxylic acid unit in itaconic acid is sufficient for Michael type addition of the thiol unit from *o*-ATP (Scheme 3, **29** → **45a**). The *o*-mercapto-*α*-methylene succinanilic acid (**48**) would be a potential precursor for the synthesis of benzothioazocine **50**. Hence the acid **47** was obtained from the reaction of 2-aminophenyl disulfide (**46**) with 2.20 equivalents of itaconic anhydride (**42**) in tetrahydrofuran at room temperature in 81% yield (Scheme 4). The triphenylphosphine-induced reductive cleavage of the sulfur–sulfur bond in diacid **47** formed the expected but unisolable intermediate acid **48**, which by an in situ intramolecular dehydrative cyclization furnished the 2-benzothiazo-2-ylmethylacrylic acid (**49**) in 84% yield. The expected benzothioazocine **50** was not obtained, indicating the reluctance for the intramolecular Michael type addition of thiol in intermediate **48** to form the eight-membered heterocycle.



Scheme 4. Formation of 2-Benzothiazo-2-ylmethylacrylic Acid

3.2.1 Background of Trichochromes

The distinctive color of "red" hair was at one time ascribed to melanin oxidation products.[75] In 1878 Sorby [76] traced a red pigment from "red" human hair, although the hair still retained its color. This pigment was eventually isolated in 1943 by Hensch and Rothmen[77] who suggested the tentative formula $(C_{15}H_{20}N_2O_9)_2Fe$ and proposed the name "trichosiderin". In 1956 Barnicot[78] showed that "trichosiderin" was an artefact, since extraction of "red" hair with cold dilute alkali yielded an orange-yellow pigment which was converted into the red "trichosiderin" by heating with acid. Later Boldt[79] found that the crude pigment obtained by acid extraction could be separated chromatographically

into nine components, yellow, orange, brown, and violet, some of which were interconvertible. Analysis of these pigments revealed the presence of sulfur but an iron was only detectable in traces the name "trichosiderin" was clearly inappropriate and these artefacts were named pyrrotricholes. Trichochromes bearing an indigoid chromophore have been isolated from human red hair and chicken feather. 'INDIGOID' nomenclature has been proposed for a group of colouring matters possessing the common chromophoric systems shown in Figure 3.

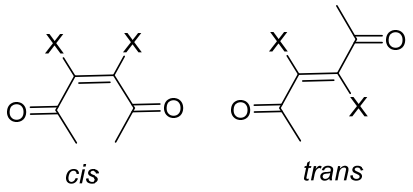


Figure 3. Indigoid Chromophores (X = NH/S)

Thiazine indigo a six membered analogue of thioindigo was described by Kaul. The presence of indigoid chromophore in these systems is responsible for the hair color even at very low concentrations.[80] Synthesis of such types of natural and unnatural safe coloring compounds would be useful to the flourishing dye-industries (Figure 4).

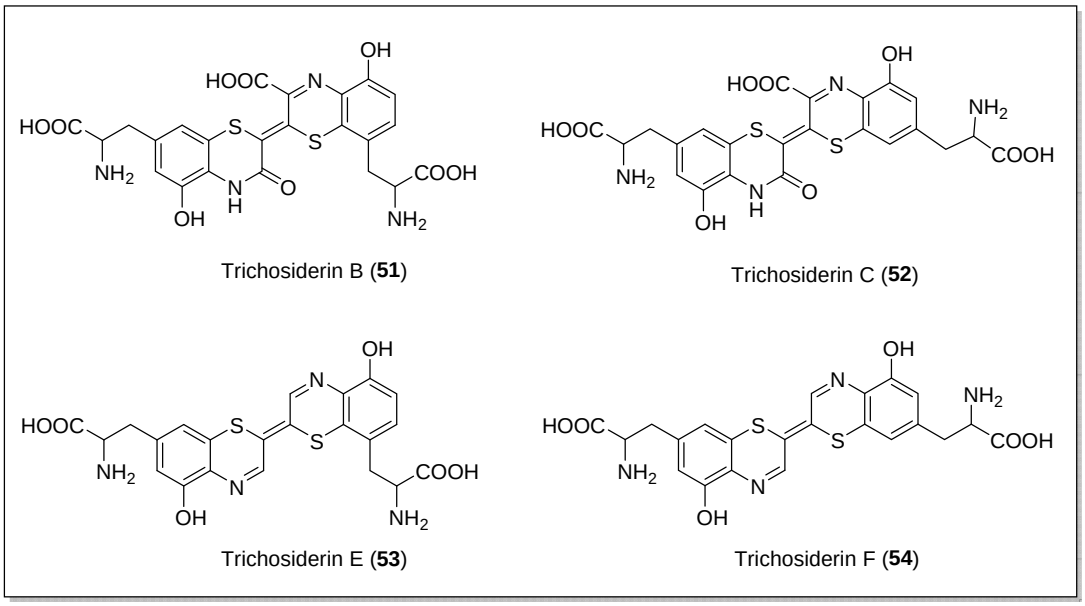
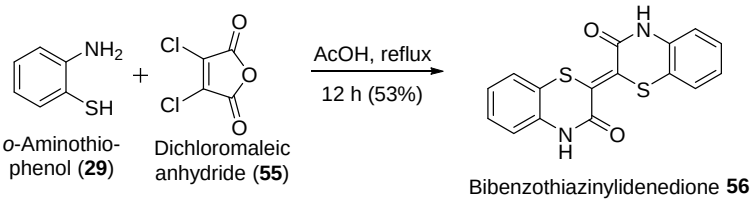


Figure 4. Naturally Occurring Unsymmetrical Trichochromes

3.2.2 Synthetic Approaches Towards Trichrome Skeleton

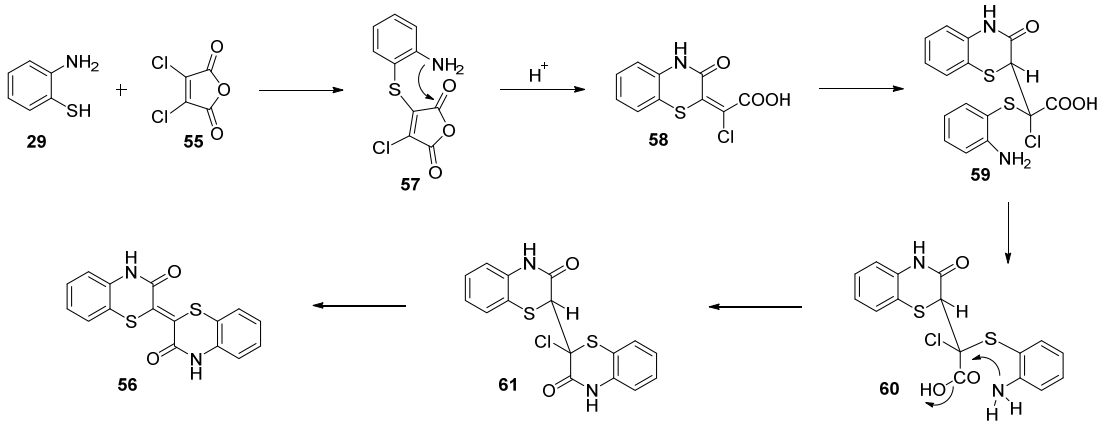
First of all Kaul[71] reported the one-pot synthesis of trichochrome skeleton starting from *o*-aminothiophenol and dichloromaleic anhydride. Treatment of 2,3-dichloromaleic anhydride **55** with 2-aminobenzenethiol **29** or its zinc salt in boiling acetic acid, resulted

in the formation of an extremely insoluble orange-red compound **56** (Scheme 5). This product was assigned the *trans*-2,2'-*bis*(4H-l,4-benzothiazine)-indigo structure **56** on the basis of elemental and spectral analysis.



Scheme 5. One Pot synthesis of Symmetrical Trichochrome Skeleton

The formation of **56** was assumed to occur by the *trans*-addition of **29** to the available activated double bonds in both steps but by the *cis*-elimination of hydrochloric acid in the first step and its *trans*-elimination in the second. Intramolecular lactamization processes, required for the derivation of benzothiazine rings, take place during the course of the reaction or in the last step. The cause of this dual mode of elimination is understandable. In the first step, only *cis*-elimination is both possible and favoured.[81] In the second, both modes of elimination are possible but the *trans* would be favoured[82] for stability reasons (Scheme 6).



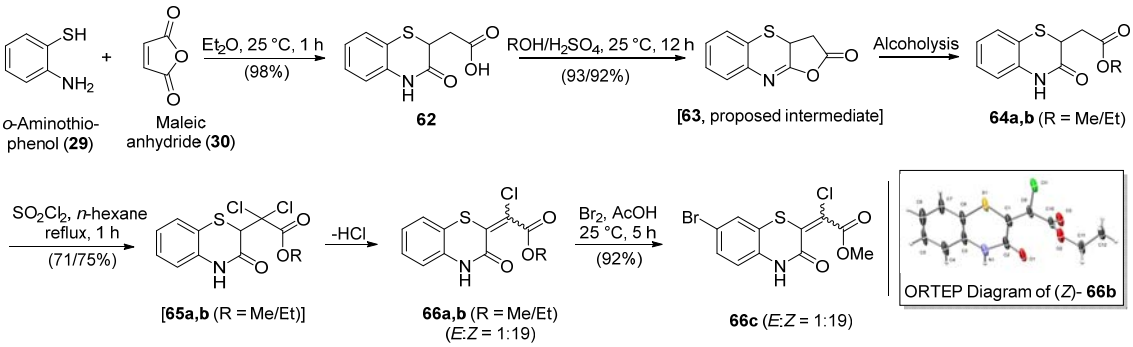
Scheme 6. Mechanism for Kaul's Synthesis of Trichochrome Skeleton

3.2.3 Rational for Present Work

In the introduction part we have described some of the exotic dialkyl substituted maleic anhydride based bioactive natural products and the reactions of *o*-ATP with various suitably substituted maleic anhydrides. As portrayed in Scheme 5, Kaul reported the one-pot synthesis of trichochrome skeleton starting from *o*-aminothiophenol and dichloromaleic anhydride. Above specified approach was limited for the synthesis of symmetrically substituted *bis*-benzothiazine derivatives. In continuation with our studies on cyclic anhydrides and derivatives,[83] we herein describe the flexible stepwise synthesis

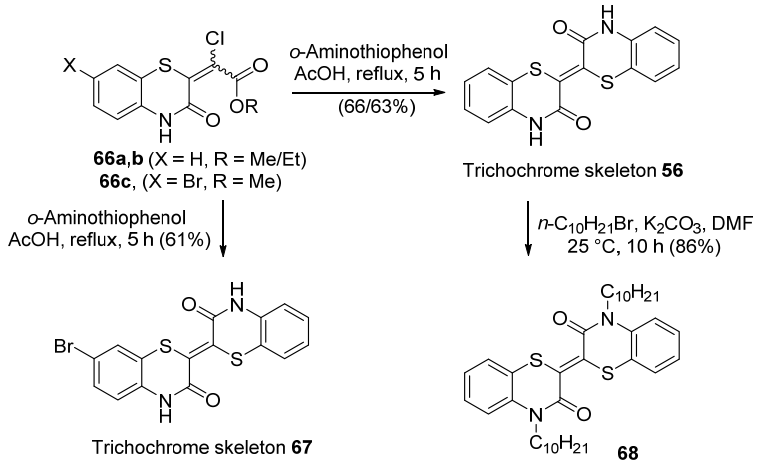
of trichochrome skeleton from the readily available maleic anhydride via a novel sulfuryl chloride attributed chlorination route.

As per the literature reports, reaction of *o*-aminothiophenol (**29**) with maleic anhydride (**30**) in diethyl ether at room temperature delivered the desired benzothiazinyl acetic acid **62** in 98% yield (Scheme 7).[59,84] Above specified reaction plausibly takes place via the Michael type addition of thiol unit from *o*-aminothiophenol (**29**) to the carbon–carbon double bond in maleic anhydride followed by a regioselective in situ intramolecular aminolysis pathway.[67] The acid-catalyzed esterifications of acid **62** with methanol and ethanol at room temperature smoothly delivered the corresponding desired methyl and ethyl esters **64a**,**b** in more than 90% yield. We presume that the above mentioned esterification reactions take place via a reactive isosuccinimide intermediate **63** and hence do not demand the reflux conditions. As per the literature reports, the sulfuryl chloride has been used earlier for both *gem*-dichlorination of active methylene compounds and also for desulfurization reactions.[85,86] The reactions of α-benzothiazinyl acetates **64a**,**b** with sulfuryl chloride under reflux conditions were highly chemo- and stereoselective and directly delivered the chloro-benzothiazinyl acrylates **66a**,**b** in more than 70% yields via the corresponding unisolable *gem*-dichloro intermediates **65a**,**b**. The mixtures of *E*- and *Z*-isomers were inseparable by silica gel column chromatography and they were formed in *E*:*Z* = 1:19 ratio (by ^{1}H NMR). The geometry of carbon–carbon double bond in the major isomers of **66a** and **66b** was confirmed on the basis of X-ray crystallographic data obtained for the ethyl ester **66b**. As expected the thermodynamically more stable *Z*-isomers were formed as a major product in both the transformations due to the effective conjugation of lone pairs on sulfur atom with the α,β-unsaturated ester moiety. Present observation is in concurrence with our earlier studies on NBS-induced isomerizations of carbon–carbon double bonds bearing the methoxy substituent.[87] In the SO_2Cl_2-prompted reactions of **64a**,**b** to **66a**,**b**; we did not notice any desulfurization taking place under the set of our reaction conditions. The reaction of bromine in acetic acid with the methyl ester **66a** at room temperature was regioselective and exclusively delivered the corresponding 3-bromoester **66c** in 92% yield.



Scheme 7. Synthesis of Trichochrome Intermediates from *o*-Aminothiophenol and Maleic Anhydride

As depicted in Scheme 8, the second coupling reactions of chlorobenzothiazinyl acrylates **66a**,**b** with *o*-aminothiophenol (**29**) in refluxing acetic acid furnished the desired dark red trichochrome product **56** in more than 60% yields. In the above mentioned reactions, the vinylic substitution of chloride anion by the relatively more reactive thiol function in *o*-aminothiophenol (**29**) plausibly takes place first via the addition-elimination pathway resulting in the isomerization of carbon–carbon double bond along with subsequent concomitant lactamization process. The trichochrome **56** was poorly soluble in most of the organic solvents and hence its hydrocarbon character was enhanced by the preparation of its didecyl derivative **68**. Finally the synthesis of unsymmetrical trichochrome skeleton was planned from the corresponding bromo-chlorobenzothiazinyl acrylate **66c**. The similar second coupling reaction of precursor **66c** with *o*-aminothiophenol (**29**) in



Scheme 8. Synthesis of Symmetrical and Unsymmetrical Trichochrome Skeletons

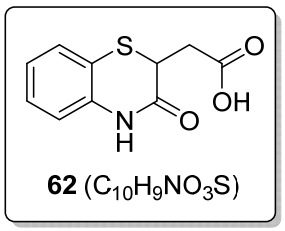
refluxing acetic acid furnished the desired unsymmetrical dark red trichochrome product **67** in 61% yield. The analytical and spectral data obtained for all three trichochrome systems **56**, **67** and **68** were in complete agreement with their assigned structures.

3.2.4 Summary

The advantages offered by cyclic anhydrides to the synthetic organic chemist are ample. Maleic anhydride and its derivatives especially have been useful in the synthesis of bioactive natural products, heterocycles, drug & drug intermediates and a variety of polymers with tailored material characteristics. Many natural products in this class have been synthesized, the most important being chaetomellic anhydride A, which is a promising anticancer agent. The fascinating structural features and remarkable activity of the nonadrides has spurred a lot of activity in the synthetic community towards their total synthesis that would pave the way for breakthroughs in medicinal chemistry. In summary, herein starting from cheap and readily available starting materials we have demonstrated a new efficient synthesis of trichochrome skeletons. The sulfuryl chloride mediated stereoselective halogenation of benzothiazinylacetates is noteworthy from basic chemistry point of view. The present approach to trichochrome is general in nature and it will be useful to design several symmetrical/unsymmetrical, natural/unnatural congeners of *bis*-benzothiazinylidenediones. We plan to synthesize the actual natural products from figure 4 in our next part of studies essentially employing our stepwise approach.

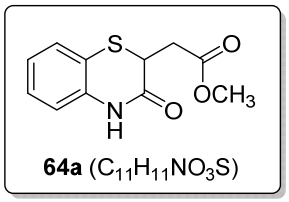
3.2.5 Experimental Section

2-(3-Oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-2-yl)acetic Acid (62). To a stirred solution of maleic anhydride (2.45 g, 25 mmol) in Et_2O (40 mL) was added *o*-aminothiophenol (3.13 g, 25 mmol) in a dropwise fashion at 25 °C under argon atmosphere. The reaction mixture was stirred for 1 h. The separated precipitate was filtered on Buckner funnel and washed with Et_2O (25 mL). The obtained product was dried under vacuum to get the pure acid **62** as a white solid (5.50 g, 98%). Mp181–182 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.43 (dd, J = 16 and 8 Hz, 1H), 2.85 (dd, J = 16 and 8 Hz, 1H), 3.79 (dd, J = 8 and 8 Hz, 1H), 6.99 (d, J = 8 Hz, 1H), 6.70 (t, J = 8 Hz, 1H), 7.21 (t, J = 8 Hz, 1H), 7.33 (d, J = 8 Hz, 1H), 10.67 (s, 1H), 12.54 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 33.7, 37.5, 117.1, 118.2, 123.1, 127.3, 127.6, 136.9, 165.7, 171.1; ESIMS (m/z) 246 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3204, 1699, 1662 cm^{-1}.



62 ($C_{10}H_9NO_3S$)

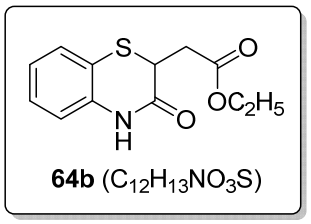
Methyl 2-(3-Oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-2-yl)acetate (64a). To a stirred solution of acid **62** (1.12 g, 5.00 mmol) in MeOH (25 mL) was added catalytic amount of



64a ($C_{11}H_{11}NO_3S$)

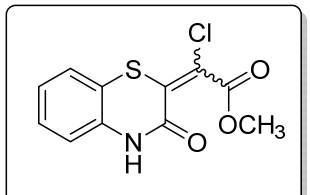
conc. H_2SO_4 at 25 °C. The reaction mixture was stirred for 12 h and concentrated in vacuo. The obtained residue was dissolved in EtOAc (50 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent afforded the methyl ester **64a** as a crystalline solid (1.10 g, 93%). Mp142–143 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.62 (dd, J = 16 and 8 Hz, 1H), 3.08 (dd, J = 16 and 8 Hz, 1H), 3.74 (s, 3H), 4.02 (dd, J = 8 and 6 Hz, 1H), 6.92 (dd, J = 8 and 2 Hz, 1H), 7.03 (dt, J = 8 and 2 Hz, 1H), 7.21 (dt, J = 8 and 2 Hz, 1H), 7.32 (dd, J = 8 and 2 Hz, 1H), 9.16 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.0, 38.0, 52.2, 117.3, 119.0, 124.0, 127.4, 128.1, 135.9, 167.2, 170.5; ESIMS (m/z) 260 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3200, 1745, 1668 cm^{-1}.

Ethyl 2-(3-Oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-2-yl)acetate (64b). It was similarly obtained from acid **62** and ethanol by using the above specified procedure as a crystalline solid (1.15 g, 92%). Mp122–123 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.29 (t, J = 8 Hz, 3H), 2.61 (dd, J = 18 and 8 Hz, 1H), 3.07 (dd, J = 16 and 6 Hz, 1H), 4.03 (dd, J = 16 and 6 Hz, 1H), 4.21 (q, J = 8 Hz, 2H), 6.91 (d, J = 8 Hz, 1H), 7.03 (t, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H), 7.32 (d, J = 8 Hz, 1H), 9.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 34.2, 38.0, 61.2, 117.2, 119.1, 124.2, 127.4, 128.1, 135.9, 167.2, 170.1; ESIMS (m/z) 274 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3206, 1739, 1670 cm^{-1}.



64b ($C_{12}H_{13}NO_3S$)

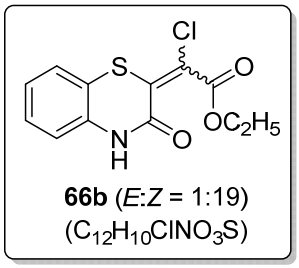
Methyl (*E*/*Z*)-2-Chloro-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-2-ylidene)acetate (66a). To a stirred slurry of methyl ester **64a** (118 mg, 0.50 mmol) in *n*-hexane (10 mL) was added SO_2Cl_2 (0.25 mL, 2.50 mmol) in dropwise fashionat 25 °C. The reaction mixture was refluxed for 1 h and allowed to reach room temperature. The reaction was slowly quenched with solid $NaHCO_3$ (250 mg) and it was further stirred for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (25 mL). The 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



66a (*E*:*Z* = 1:19)
($C_{11}H_8ClNO_3S$)

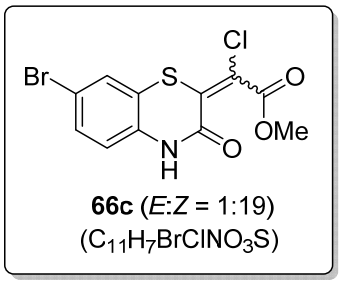
mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:8) as an eluent afforded the mixture of isomeric products (*E*:*Z* = 1:19) as a yellow crystalline solid (95 mg, 71%). Mp196–198 °C; (*Z*)-Isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (s, 3H), 6.93 (d, *J* = 8 Hz, 1H), 7.08 (t, *J* = 8 Hz, 1H), 7.20 (t, *J* = 8 Hz, 1H), 7.25 (d, *J* = 8 Hz, 1H), 9.98 (br s, 1H). (*Z*)-Isomer: ^{13}C NMR ($CDCl_3$, 100 MHz) δ53.4, 115.8, 117.3, 124.3, 124.4, 124.7, 125.4, 127.2, 132.6, 156.9, 164.4; ESIMS (*m*/*z*) 292/294 $[M + Na]^+$; HRMS (ESI) calcd for $C_{11}H_8O_3NClNaS$ 291.9806, found 291.9800; IR ($CHCl_3$) ν_{max} 3315, 1727, 1665 cm^{-1}.

Ethyl (*E*/*Z*)-2-Chloro-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-2-ylidene)acetate (66b). It was similarly obtained from ethyl ester **64b** by using the above specified procedure as a yellow crystalline solid (*E*:*Z* = 1:19; 105 mg, 75%). Mp151–153 °C; (*Z*)-Isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (t, *J* = 8 Hz, 3H), 4.38 (q, *J* = 8 Hz, 2H), 6.95 (dd, *J* = 8 and 2 Hz, 1H), 7.07 (dt, *J* = 8 and 2 Hz, 1H), 7.20 (dt, *J* = 8 and 2 Hz, 1H), 7.25 (dd, *J* = 8 and 2 Hz, 1H), 10.27 (br s, 1H); (*Z*)-Isomer: ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 62.7, 115.8, 117.3, 123.9, 124.3, 125.1, 125.3, 127.1, 132.7, 157.1, 163.9; ESIMS (*m*/*z*) 306/308 $[M + Na]^+$; HRMS (ESI) calcd for $C_{12}H_{10}O_3NClNaS$ 305.9962, found 305.9964; IR ($CHCl_3$) ν_{max} 3191, 1734, 1669 cm^{-1}.



66b (*E*:*Z* = 1:19)
($C_{12}H_{10}ClNO_3S$)

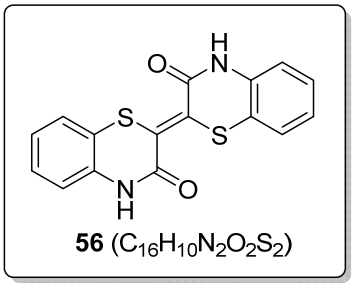
Methyl (*E*/*Z*)-2-(7-Bromo-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-2-ylidene)-2-chloroacetate (66c). To a stirred solution of methyl ester **66a** (50 mg, 0.185 mmol) in glacial AcOH (5 mL) was added bromine (148 mg, 0.92 mmol) at 25 °C and the reaction mixture was stirred for 5 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissoleved in ethyl acetate (20 mL). The organic layer was washed with 5% aqueous solution of sodium thiosulfate, 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 afforded the bromo ester **66c** as a yellow crystalline solid (60 mg, 92%). Mp 230–231 °C; (*Z*)-Isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.91 (s, 3H), 6.76 (d, *J* = 10 Hz, 1H), 7.31 (dd, *J* = 10 and 2 Hz, 1H), 7.41 (d, *J* = 2 Hz, 1H), 9.18 (br s, 1H); (*Z*)-Isomer: ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.5, 116.8, 117.9,



66c (*E*:*Z* = 1:19)
($C_{11}H_7BrClNO_3S$)

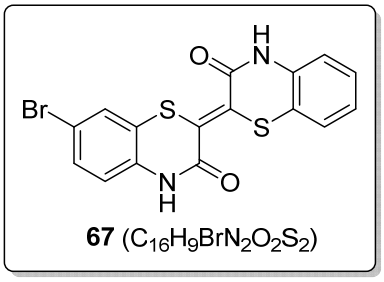
118.0, 118.3, 126.1, 127.9, 130.2, 131.8, 156.3, 164.0; HRMS (ESI) calcd for $C_{11}H_8O_3NBrClS$ 347.9091, found 347.9091; IR ($CHCl_3$) ν_{max} 3176, 1737, 1667 cm^{-1}.

(*E*)-[2,2'-Bibenzo[b][1,4]thiazinylidene]-3,3'(4H,4'H)-dione (56). To a stirred solution of methyl ester **66a** (81 mg, 0.30 mmol) in glacial AcOH (5 mL) was added *o*-aminothiophenol (75 mg, 0.45 mmol) at 25 °C under argon atmosphere. The reaction mixture was refluxed for 5 h. The separated solid product was filtered on buckner funnel and it was washed with AcOH (5 mL) and then EtOAc (10 mL). The obtained product was recrystallized from DMF to obtain the analytically pure product **56** as a dark red crystalline solid (65 mg, 66%). Mp >300 °C. It was also similarly obtained from the correspondine ethyl ester **66b (**62 mg, 63%); ^{1}H NMR (DMSO-d_6, 700 MHz) δ 6.99 (d, J = 7 Hz, 1H), 6.99 (t, J = 7 Hz, 1H), 7.14 (t, J = 7 Hz, 1H), 7.26 (d, J = 7 Hz, 1H), 11.16 (br s, 1H); ^{13}C NMR (DMSO-d_6, 175 MHz) δ 116.2, 118.9, 123.2, 123.9, 124.9, 126.7, 133.6, 158.3; ESIMS (m/z) 327 $[M + H]^+$; IR (Neat) ν_{max} 3393, 1638, 1582 cm^{-1}.



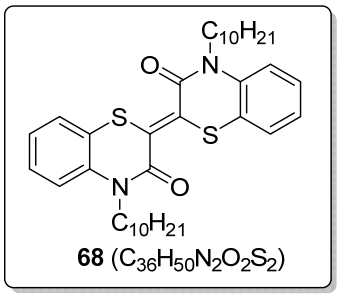
56 ($C_{16}H_{10}N_2O_2S_2$)

(*E*)-7-Bromo-[2,2'-bibenzo[b][1,4]thiazinylidene]-3,3'(4H,4'H)-dione (67). It was similarly obtained from bromo ester **66c** by using the above specified procedure as a dark red crystalline solid; yield: 31 mg (61%); mp>300 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 6.90 (d, J = 8 Hz, 1H), 6.94–7.04 (m, 2H), 7.15 (d, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 1H), 7.32 (dd, J = 8 and 2 Hz, 1H), 7.52 (d, J = 2 Hz, 1H), 11.23 (s, 1H), 11.26 (s, 1H); ^{13}C NMR(DMSO-d_6, 100 MHz) δ 114.7, 116.4, 118.0, 118.9, 121.7, 122.8, 123.3, 124.9, 125.0, 126.9, 127.0, 129.5, 133.2, 133.6, 158.28, 158.33; HRMS (ESI) calcd for $C_{16}H_9O_2N_2BrNaS_2$ 426.9181, found 426.9178; IR (Nujol) ν_{max} 3292, 3165, 1637, 1582 cm^{-1}.



67 ($C_{16}H_9BrN_2O_2S_2$)

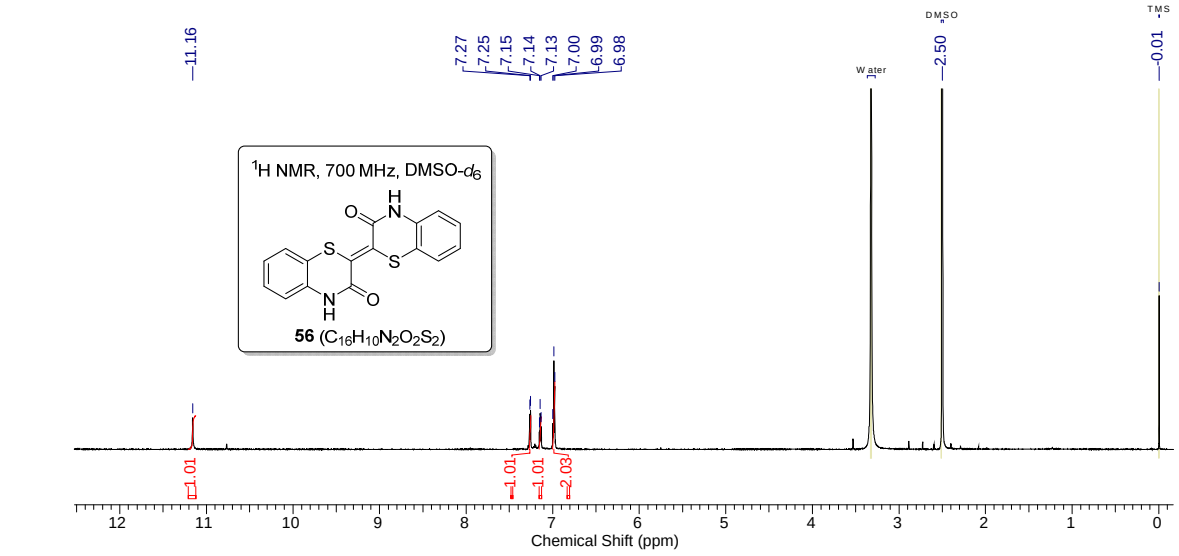
(*E*)-4,4'-Didecyl-[2,2'-bibenzo[b][1,4]thiazinylidene]-3,3'(4H,4'H)-dione (68). To a stirred solution of dione **56** (33 mg, 0.01 mmol) in dry DMF (5 mL) at 25 °C was added anhydrous K_2CO_3 (6.90 mg, 0.05 mmol). To the above reaction mixture was added *n*-decylbromide (0.10 mL, 0.05 mmol) after 15 minutes and it was further stirred for 24 h under argon atmosphere. The reaction mixture was diluted with EtOAc (20 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic



68 ($C_{36}H_{50}N_2O_2S_2$)

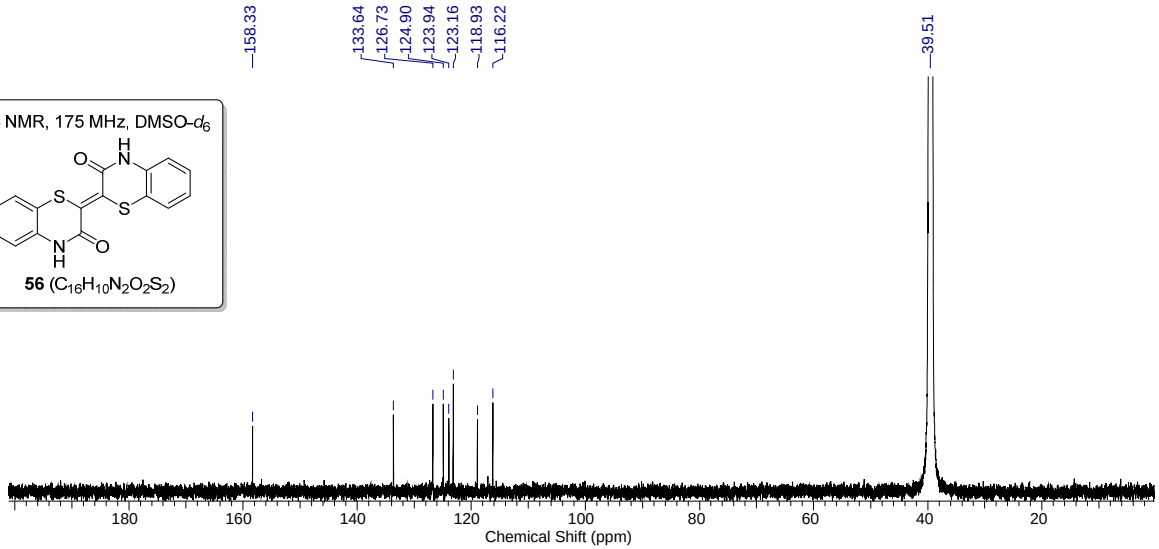
layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent afforded the pure product **68** as an orange crystalline solid (52 mg, 86%); Mp 82–83 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 6H), 1.27 (br s, 24H), 1.36 (br s, 4H), 1.74 (quintet, J = 8 Hz, 4H), 4.07 (t, J = 8 Hz, 4H), 6.90–7.10 (m, 4H), 7.10–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.7, 26.9, 27.3, 29.3 (2 carbon), 29.5, 29.6, 31.9, 45.3, 116.5, 122.5, 123.4, 126.5, 126.8, 126.9, 136.1, 159.2. ESIMS (*m*/*z*) 606 $[M]^+$; Anal calcd for $C_{36}H_{50}N_2O_2S_2$: C, 71.24; H, 8.30; N, 4.62. Found: C, 71.13; H, 8.54; N, 4.51; IR ($CHCl_3$) ν_{max} 3394, 1633, 1587 cm^{-1}.

3.2.6 Selected Spectra:



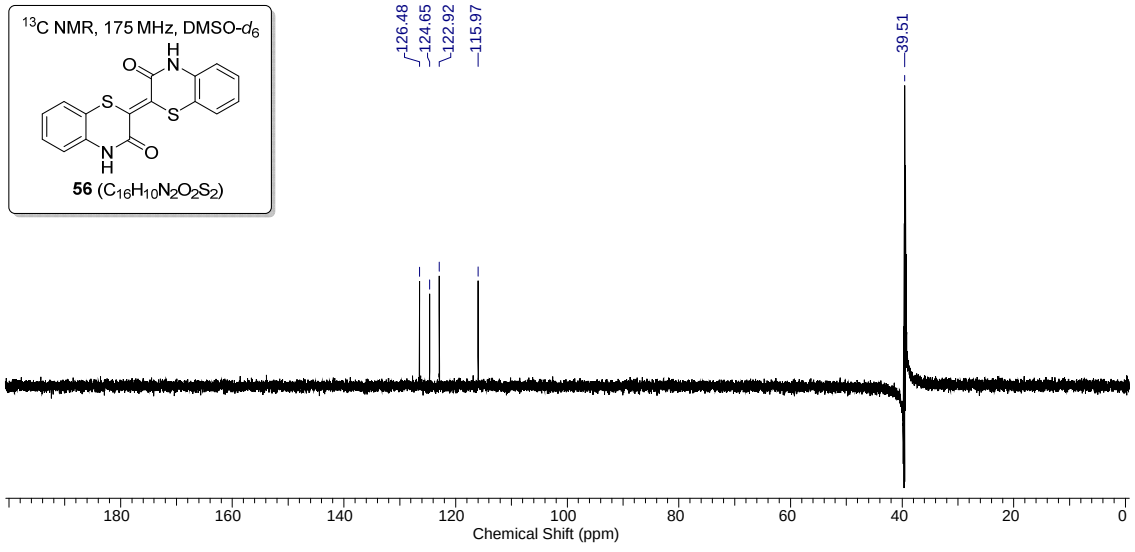
^{1}H NMR, 700 MHz, DMSO-d_6

56 ($C_{16}H_{10}N_2O_2S_2$)



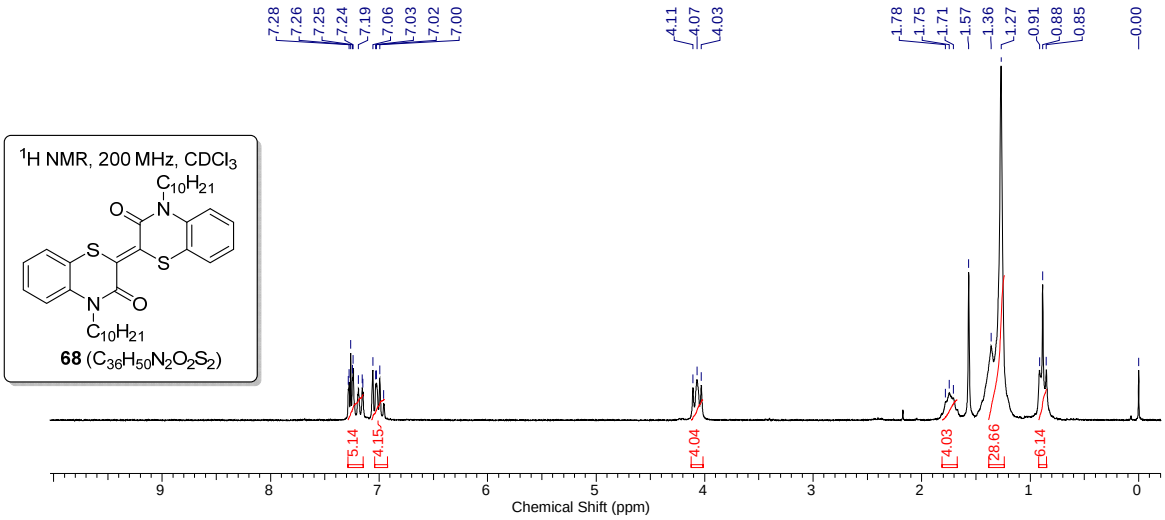
^{13}C NMR, 175 MHz, DMSO-d_6

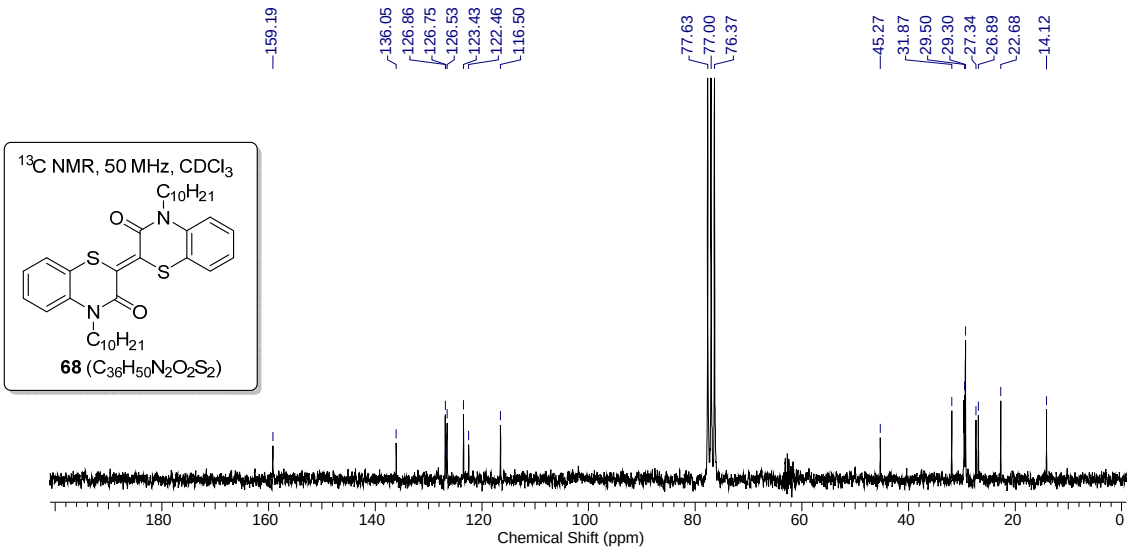
56 ($C_{16}H_{10}N_2O_2S_2$)



^{13}C NMR, 175 MHz, DMSO-d_6

56 ($C_{16}H_{10}N_2O_2S_2$)


7.28
7.26
7.25
7.24
7.19
7.06
7.03
7.02
7.00
4.11
4.07
4.03
1.78
1.75
1.71
1.57
1.36
1.27
0.91
0.88
0.85
0.00
^{1}H NMR, 200 MHz, CDCl$_3$
$C_{10}H_{21}$
$C_{10}H_{21}$
68 ($C_{36}H_{50}N_2O_2S_2$)
5.14
4.15
4.04
4.03
28.66
6.14
Chemical Shift (ppm)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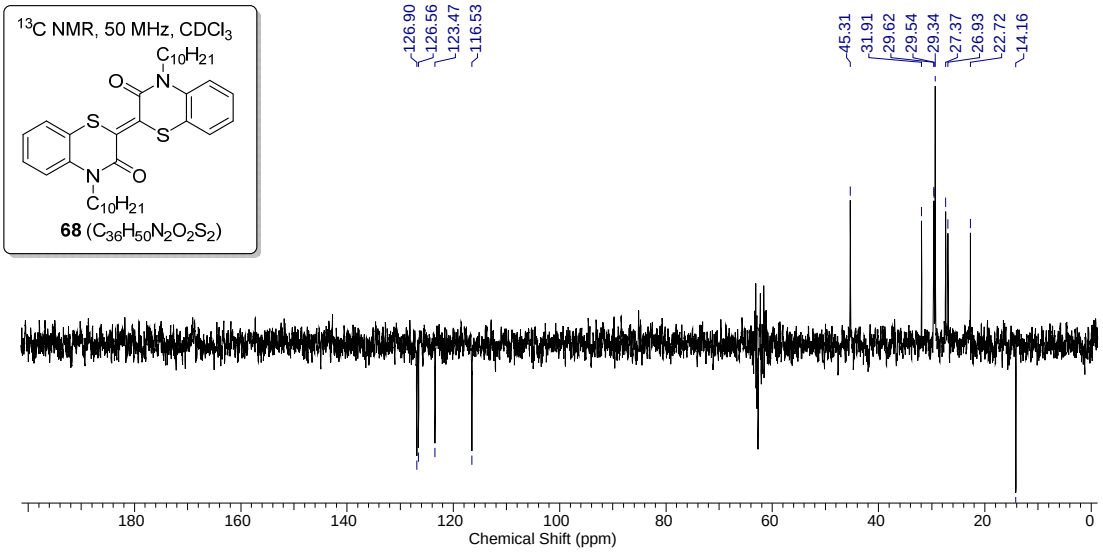
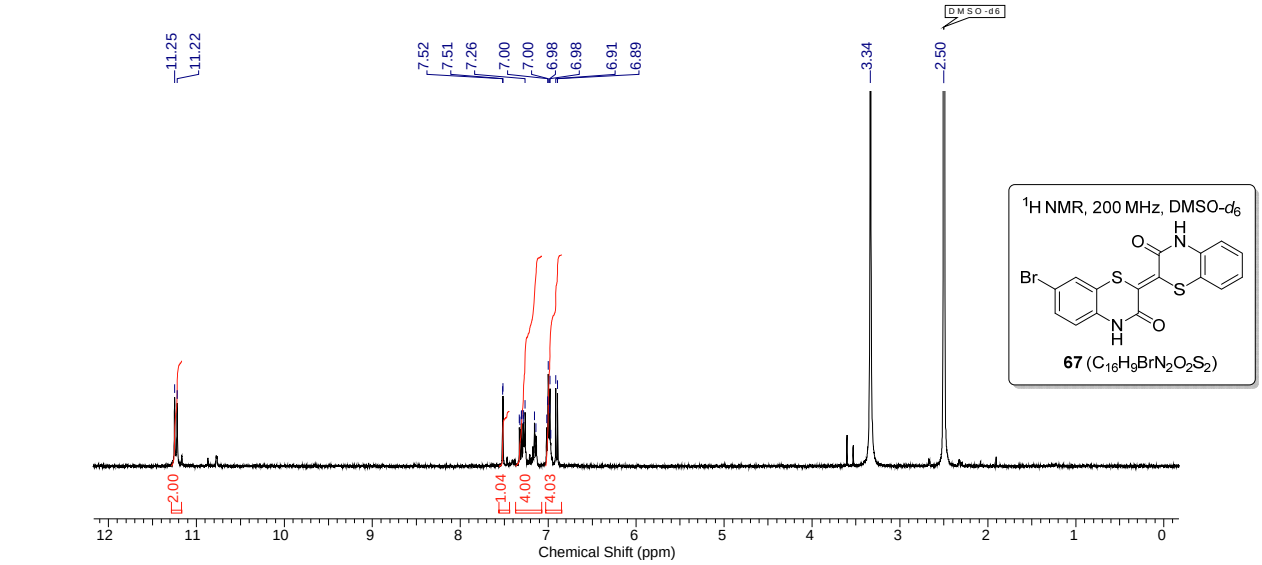
136.05
126.86
126.75
126.53
123.43
122.46
116.50
77.63
77.00
76.37
45.27
31.87
29.50
29.30
27.34
26.89
22.68
14.12
^{13}C NMR, 50 MHz, CDCl$_3$
$C_{10}H_{21}$
$C_{10}H_{21}$
68 ($C_{36}H_{50}N_2O_2S_2$)
Chemical Shift (ppm)


126.90
126.56
123.47
116.53
45.31
31.91
29.62
29.54
29.34
27.37
26.93
22.72
14.16
^{13}C NMR, 50 MHz, CDCl$_3$
$C_{10}H_{21}$
$C_{10}H_{21}$
68 ($C_{36}H_{50}N_2O_2S_2$)
Chemical Shift (ppm)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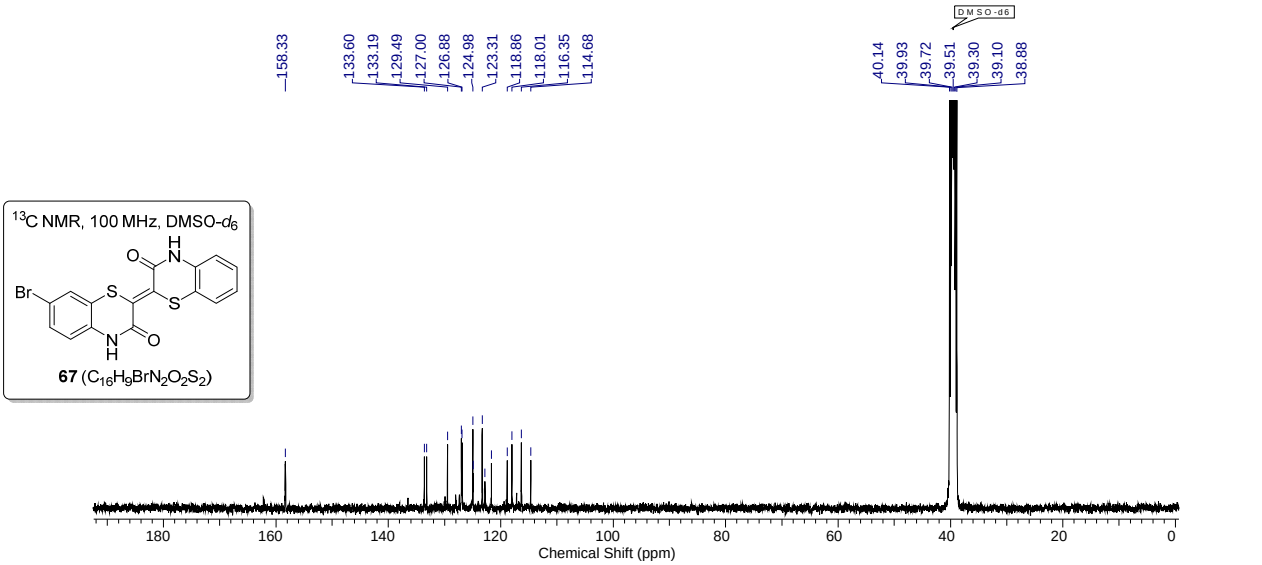
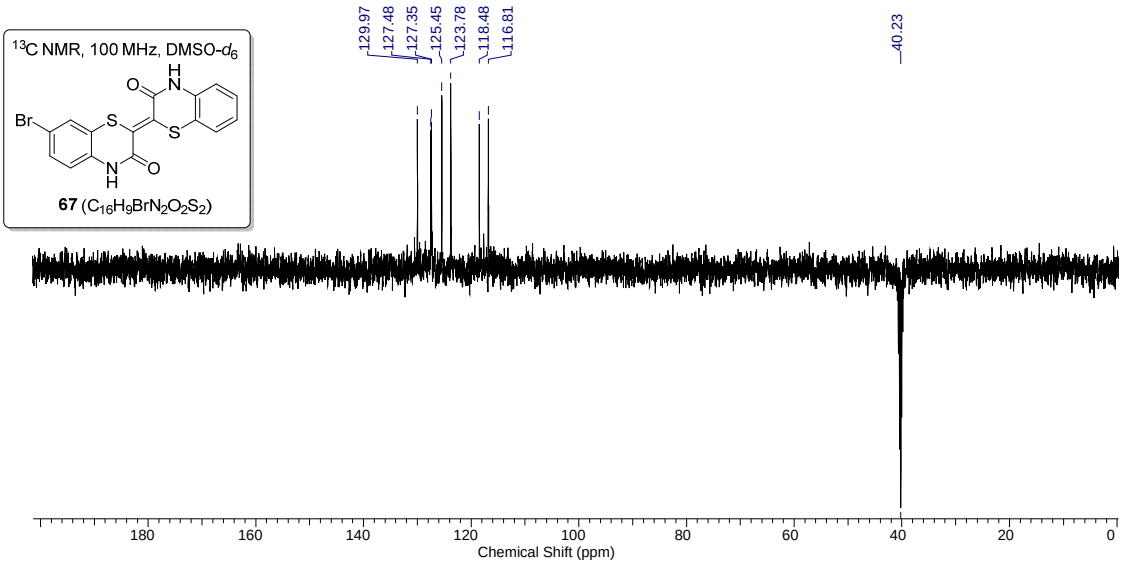
11.22
7.52
7.51
7.26
7.00
7.00
6.98
6.98
6.91
6.89
3.34
2.50
2.00
1.04
4.00
4.03
Chemical Shift (ppm)
^{1}H NMR, 200 MHz, DMSO-d_6
67 ($C_{16}H_9BrN_2O_2S_2$)


DMSO-d6
158.33
133.60
133.19
129.49
127.00
126.88
124.98
123.31
118.86
118.01
116.35
114.68
40.14
39.93
39.72
39.51
39.30
39.10
38.88
Chemical Shift (ppm)
^{13}C NMR, 100 MHz, DMSO-d_6
67 ($C_{16}H_9BrN_2O_2S_2$)


129.97
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118.48
116.81
40.23
Chemical Shift (ppm)
^{13}C NMR, 100 MHz, DMSO-d_6
67 ($C_{16}H_9BrN_2O_2S_2$)

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Overall Summary

Development of novel carbon–carbon and carbon–heteroatom bond forming reactions for the synthesis of complex bioactive natural and synthetic products has been foremost area of research in synthetic organic chemistry. Present dissertation describes our studies towards the development of carbon–carbon and carbon–heteroatom bond forming reactions with the cyclic anhydride derivatives and their applications for the facile synthesis of structurally interesting bioactive natural and synthetic products along with a concise account of the chemistry of homophthalic anhydrides and their derivatives. Homophthalic anhydrides/acids are versatile synthons in organic synthesis. This small molecule with multiple functionalities has been efficiently utilized for building the backbones of many structurally complex and medicinally important molecules in a convergent manner. Many bioactive indenoisoquinolines, anthracyclines and various members of isoquinoline family have been synthesized by the use of homophthalic anhydrides, few of them are in clinical practice and few are in development stages. This ascertains the utility of homophthalic anhydrides and their derivatives in the organic synthesis and medicinal chemistry.

Our research group is using cyclic anhydrides as the starting materials for the natural products synthesis from many years. Present research work is mainly in context with the synthesis of various natural products using the homophthalic acid and its derivatives as the starting materials. We have done alkylation of the benzylic position of homophthalic acid and derivatives for the synthesis of various natural products (Figure 1).

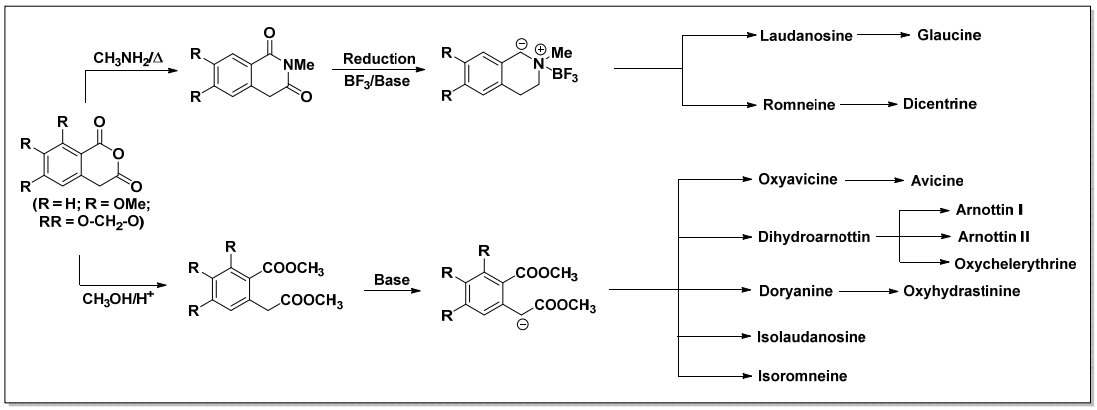

Figure 1. *Synthetic Strategy for Various Natural Products from Homophthalic Anhydrides*

We have accomplished the convergent synthesis of oxyavicine from the readily available homophthalate and utilizing the regiospecific utilization of homophthalimide. The

construction of ring B and C utilizing an intramolecular Heck-coupling reaction was the key step. We have demonstrated a bio-inspired protection-free concise and efficient total synthesis of arnottin I and the formal synthesis of (–)-arnottin II from the homophthalate. The construction of ring B and C utilizing an intramolecular Friedel–Crafts acylation, followed by enolative lactonization reaction was the key step. We have also described the well-organized synthesis of doryanine and oxyhydrastinine from homophthalic acids. Total synthesis of tetrahydroisoquinoline based bioactive alkaloids have been completed from the respective homophthalic acids via generation of two different types of benzylic carbanions and uncommon intramolecular aryl−aryl coupling reactions. Application of benzyl mesylate instead of benzyl bromide as a coupling partner is significant from both its non-lachrymatory nature and yields point of view. We have been successful in the total synthesis of oxyavcine, arnottin I, doryanine, oxyhydrastinine, laudanosine, romneine, dicentrine, glaucine, isolaudanosine and isoromneine by alkylation of homophthalates. We have also successfully completed the formal synthesis of avicine and (-)-arnottin-II.

The advantages offered by cyclic anhydrides to the synthetic organic chemist are ample. Maleic anhydride and its derivatives especially have been useful in the synthesis of bioactive natural products, heterocycles, drug & drug intermediates and a variety of polymers with tailored material characteristics. Herein starting from cheap and readily available starting materials we have demonstrated a new efficient synthesis of trichochrome skeletons. The sulfuryl chloride mediated stereoselective halogenation of benzothiazinylacetates is noteworthy from basic chemistry point of view.

Finally, on the basis of exposure to the literature of homophthalic anhydrides and their derivatives 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. A facile synthesis of oxyavicine.
   Jangir, R.; Argade, N. P. *RSC Adv*., **2012**, *2*, 7087**.**

2. Dimethyl Homophthalates to Naphthopyrans: Total Synthesis of Arnottin I and the Formal Synthesis of (–)-Arnottin II.
   Jangir, R.; Argade, N. P. *RSC Adv*., **2014**, *4*, 5531.

3. Facile Synthesis of Isoquinoline Alkaloids Doryanine and Oxyhydrastinine.
   Jangir, R.; Gadre, S. R.; Argade, N. P. *Synthesis* **2014**, *46*, 1954**.**

4. Sulfuryl Chloride Promoted *gem*-Dichlorination-Dehydrochlorinationin Alkyl Benzothiazinyl Acetates: Synthesis of Trichochrome Pigments Skeleton.
   Jangir, R.; Gadre, S. R.; Argade, N. P. *Synthesis* **2015**, *47*, 2631.

5. Total Synthesis of Tetrahydroisoquinoline Based Bioactive Natural Products Laudanosine, Romneine, Glaucine, Dicentrine and their Unnatural Analogues Isolaudanosine and Isoromneine.
   Jangir, R.; Argade, N. P. *Synthesis* **2016,** *48*, in press.