SYNTHETIC APPROACHES FOR SYNTHESIS OF LASUBINE I AND II

A M.Sc. Dissertation Report By:

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SYNTHESTIC APPROACHES FOR SYNTHESIS OF LASUBINE I AND II

A DISSERTATION REPORT

Submitted in Partial Fulfillment

Of

The Degree of M.Sc. (Organic Chemistry)

By

Mr. Vignesh R. Naidu

To The

School Of Chemical Sciences

Goa University

Goa 403206

MAY 2022

DECLARATION

I Declare that the literature Review Titled “Synthestic Approaches for Synthesis Of Lasubine I and II “ has been carried out by me in the Chemistry Department , School Of Chemical Sciences,Goa University. The Information Derived From The Literature has been duly acknowledged in the text and a list of References is Provided.

VIGNESH R NAIDU

CERTIFICATE

This is to certify that the literature review entitled : “Synthetic Approaches for Synthesis Of Lasubine I and II” submitted by the student is the record of research work carried out by the candidate during the Academic Year 2021-2022 Under My Supervision in partial Fulfilment Of The Requirement For The Master Of Science In Chemistry.

Dr. VINOD K. MANDREKAR (Project Guide)

PROF. Dr. VIDHYADATTA VERENKAR (Dean Of SCS, GOA UNIVERSITY)

ACKNOWLEDGEMENT

There is no good work done which comes without efforts; but those efforts cannot be obtained without proper guidance. So, in these few humble lines I take this opportunity to express my profound gratitude to the people who have made invaluable contribution during the course of completion of the literature review in time.

First of all I would like to thank my guide; **Dr. Vinod K. Mandrekar** for giving me an opportunity to work under his guidance; for his patience and invaluable help and assistance during the course of work on this literature review. I am also very much grateful to our respected Dean **Dr. Vidhyadatta Verenkar** for his support and for providing us the opportunity to work in the school of Chemical Sciences.

No acknowledgments would be complete without giving thanks to our Family and friends. Finally with silent words we thank God for the energy, health and life so far and in future.

INDEX

Abstract :

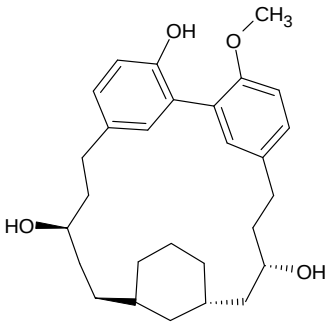
Lasubine I and II are Alkaloids Belonging to Lythraceae Family with Three Stereocenter and good biological activities. Lasubine I and II are isolated from the leaves of Lagerstroemia subcostata Koehne and featuring with 4-arylquinolizidine structure. This Report Mainly Consists of Literature Review on various research paper ,Including eleven research paper with six papers consisting of Racemic synthesis and five consisting of Enantioselective synthesis like kibayashi synthesis ,Takano Synthesis etc. and Their isolation, Total synthesis ,Biological and structural Activities.The information for the report is gathered from research articals reported from year 1962 till 2020 from reputed journals.

INTRODUCTION

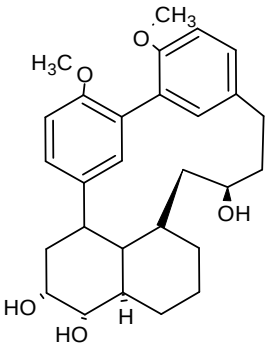
Heterocyclic compounds are very much interest in our daily life.Heterocyclic compouds have one or more heteroatoms in their structure.[17] They may be cyclic in nature.Heterocyclic compounds have a wide range of application. Medicinal and pharmaceutical chemistry are disciplines at the intersection of chemistry, especially synthetic organic chemistry, and pharmacology and various other biological specialties, leading to the design, chemical synthesis and development of bio-active molecules,for being approved as prescribed and market purchasable pharmaceutical agents.They also find application as Sanitizer,Antioxidant,as coplolymer,Dye stuff etc.[20] [21] Indolizidine, quinolizidine and piperidine alkaloids encompass a large group of natural products that display a broad range of biological activites.[20] Therefore intense research effort have been developed to the development of new approaches for their preparation. Lasubines I and II are two alkaloids isolated from plants of Lythraceae family which differ only at C-10.[1]

LYTHRACEOUS ALKALOIDS,

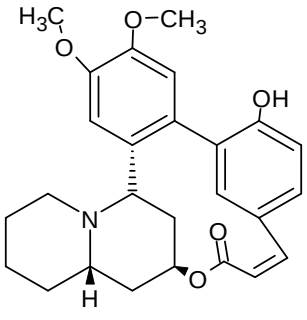
Plants from the family Lythraceae have been the source of over 40 alkaloids since the first one which were isolated from Decodon verticillatus by Ferris[1]. Lythraceae alkaloids are being extensively reviewed [18] and are divided into five classes on the basis of structure by Fujita et al. Example of each class are given below. [1]



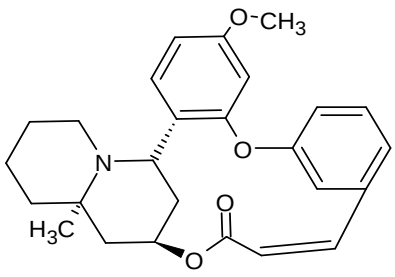
lythranidine
Type A



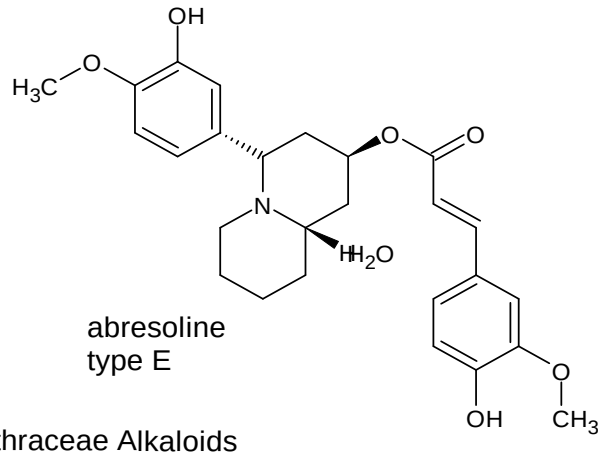
lythrancine-I
Type B



lythrine
Type C



lagerine
Type D

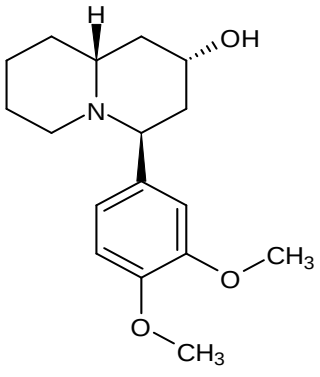


abresoline
type E

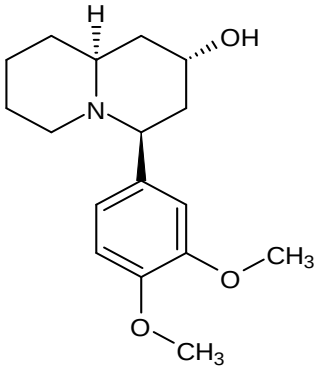
Classification of Lythraceae Alkaloids

The alkaloids of type A are distinct from the other classes in their lack of a 4-arylquinolizidine structure. Rather, they contain a 2,6-substituted piperidine ring along with a second ring containing a substituted biaryl group. The remaining types of Lythraceae alkaloids (B, C, D and E) all contain a 4-arylquinolizidine substructure. Type B is characterized by an alkyl linkage at the 6-position of the quinolizidine ring to a substituted biaryl group, forming a thirteen-member ring. Type C alkaloids contain a lactone linkage joining C-2 of the quinolizidine and the substituted biaryl moiety. Type D alkaloids are similar to type C in that they also posses a lactone linkage, but differ in the presence of a substituted diaryl ether. Type E alkaloids are the simplest; they contain only one aromatic substituent attached to the quinolizidine moiety and posses a hydroxyl group .[1 2]

Lasubine II was first isolated by Fujita et al from the leaves of Lagerstroemia subcostata Koehne (Japanese name: Shima-sarusuberi), along with three other closely related alkaloids, (-)-lasubine I (+)-subcosine I and (+)-subcosine II.[2]



lasubine I
1



lasubine II
2

SPECTRAL DATA

^{1}H NMR (200 MHz) :- δ 6.98 - 6.73 (m, 3 H, Ar), δ 3.90 (s, 3 H, OMe), δ 3.87 (s, 3 H, OMe), δ 3.84 - 3.65 (m, 1 H, H-2), δ 2.92 (dd, *J* = 11.4 and 2.4 Hz, 1 H, H-4), δ 2.67 (br d, *J*= 9.2 Hz, 1 H, H-6), δ 2.09 - 1.86 (m, 3 H), δ 1.84 - 1.15 (m, 10 H).

^{13}C NMR (200 MHz):- δ 147.7, δ 138.3, δ128.2, δ 119.5, δ 110.8, δ 110.4, δ 70.2, δ63.4, δ 55.9, δ 55.8, δ 53.6, δ 36.6, δ 33.9, δ 33.8, δ 26.3, δ 25.0, δ 24.

Mass Spectrum, *m/z* (relative intensity, %) 291 (M, 29), 248 (58), 232 (100),136(21), 96 (81).

Initial Spectroscopic data of ^{1}H NMR and ^{13}C NMR Suggest that a hydroxyl group and aromatic ring were present in **1** and **2** and also from above data supported 3,4-dimethoxybenzylamine being a key substructure. Mass Spectroscopy confirmed a quinolizidine structure by the prescence of a hexahydroquinolizine (m/z 136 ion) fragment.[7 19]

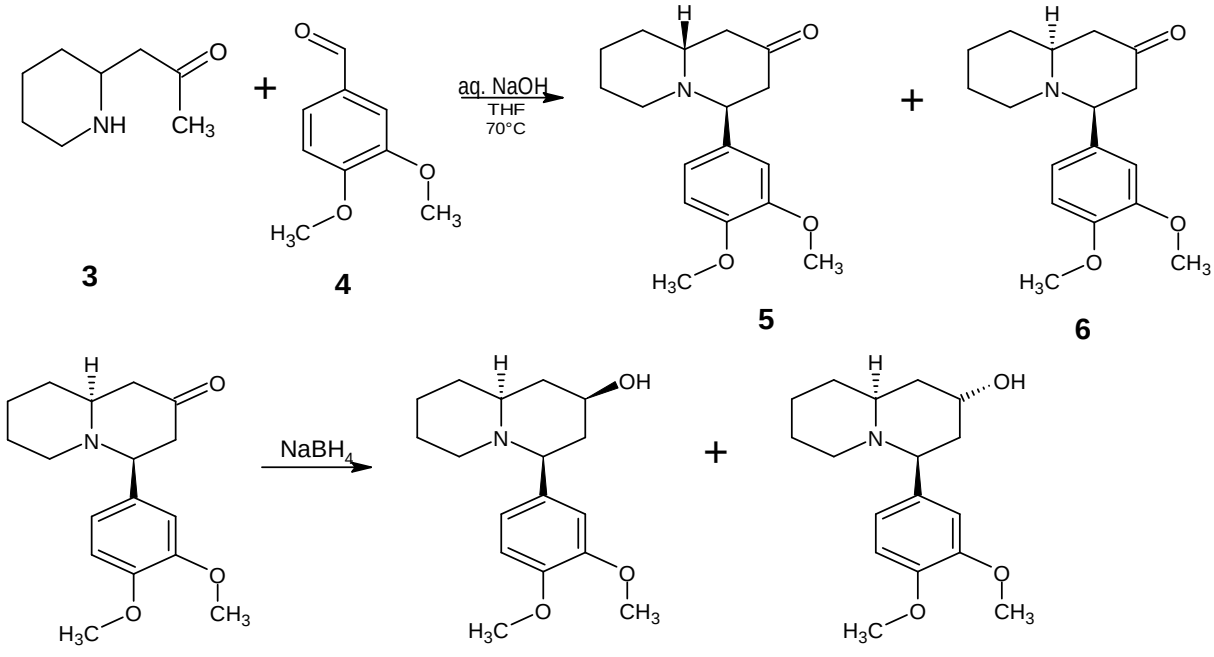
LITERATURE REVIEW

Lasubine I and II Has been target of Number of racemic and Enantionselective Synthesis.

Six Racemic Synthesis has been Discussed and Outlined in the Section From **1-6**

1.Kibayashi Synthesis.

The first total synthesis of racemic lasubine II was published in 1984 by Kibayashi , et. al. ,six years after the discovery of lasubine II in 1978.[3] The key steps of the synthetic sequence are described in Scheme 1 and were based on the normal biosynthetic pathway by which this compound is formed in nature.



Scheme 1 : Kibayashi Synthesis

The synthesis utilized the Mannich reaction of isopelletierine **(3)** with 3,4-dimethoxybenzaldehyde, which gave a mixture of cis and trans quinolizidinones (**5 and 6**, respectively). These diastereomers were separated and the trans quinolizidinone **6** was reduced

with sodium borohydride to produce two products, lasubine II and 2-epilasubine II. These were separated and obtained in overall yields of 4% and 15% respectively.

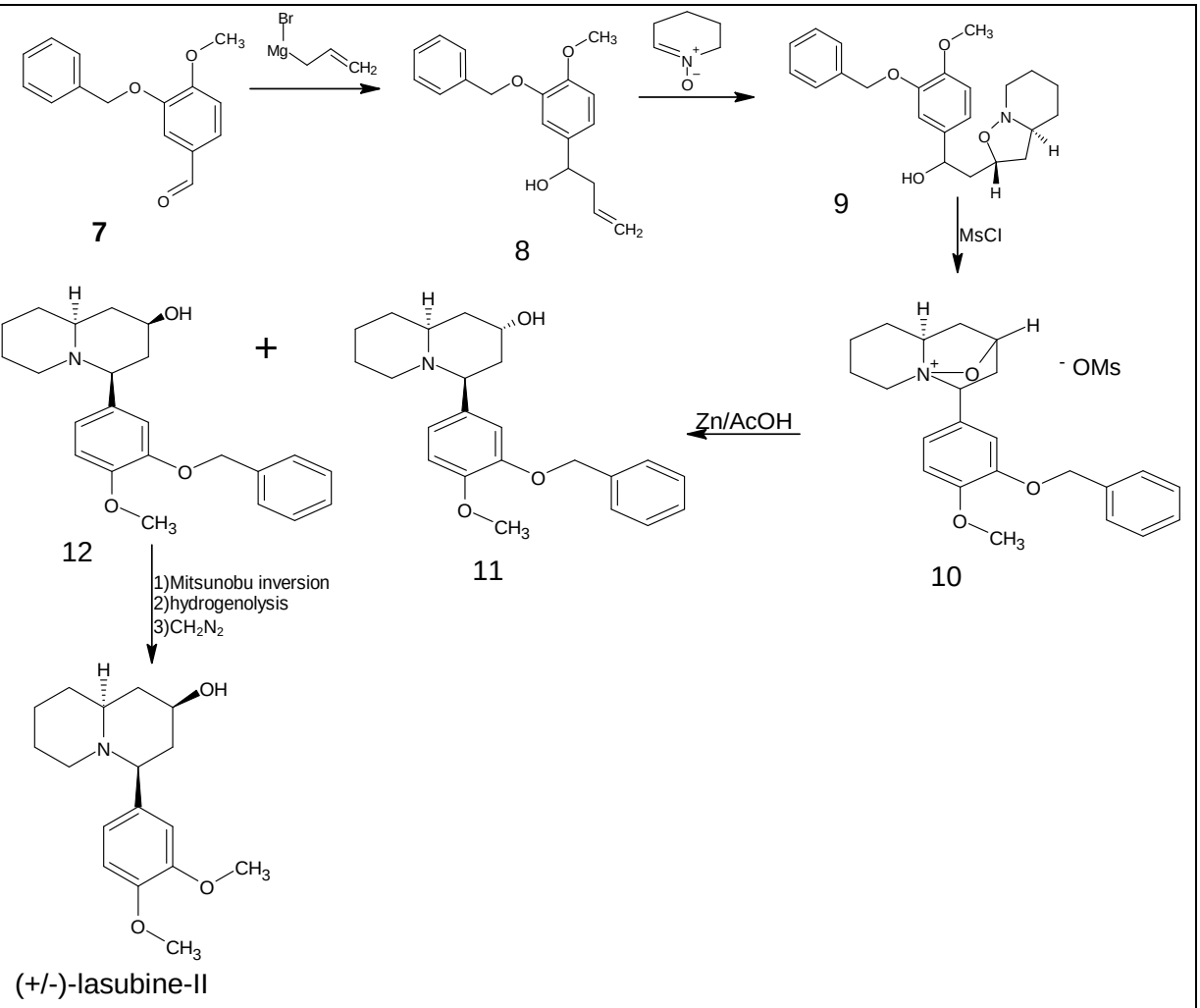
Although the synthesis is relatively concise, the overall yield of lasubine II is low and the reduction of the quinolizidinone is not stereoselective for lasubine II. [3]

2.Synthetic Studies On Lythraceae Alkaloids Via [3+2] Cycloaddition.

The synthesis reported by Takano , et. al. in 1984 involved a regio- and stereoselective [3+2]cycloaddition reaction and is outlined in Scheme 2.[4]

The synthesis began with O-benzyl vanillin (7), which was converted to the homoallylic alcohol 8 through its reaction with allylmagnesium bromide. The product was then heated in a mixture of refluxing toluene with 3,4,5,6-tetrahydropyridine-l-oxide to provide the adduct **9** as inseparable diastereomers. Treatment with methanesulfonyl chloride in pyridine, followed by reduction of the quartenary amine intermediate 10, using zinc and 50% aqueous acetic acid, gave two diastereomeric alcohols, **11** and **12** in a 1:1.5 ratio.

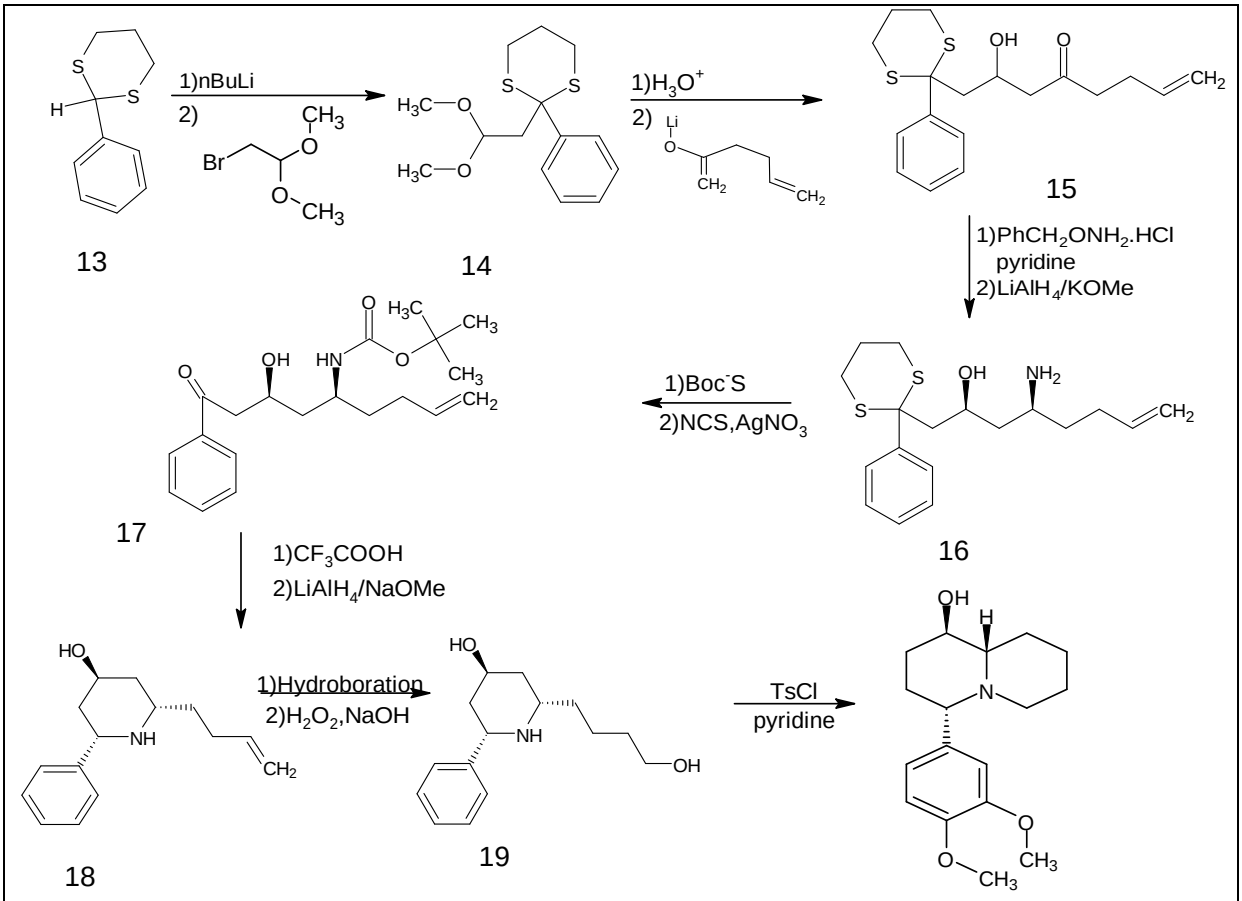
These two products were separated as the acetates. Conversion of the trans-acetate of **12** to lasubine II was carried out by inversion of the alcohol under Mitsunobu conditions, removal of the benzyl protecting group by hydrogenolysis and, finally, methylation of the resulting phenol using diazomethane. This provided (+/-)-lasubine II in a 17% yield over 6 steps. This synthesis provided an improvement in overall yield compared to Kibayashi's synthesis, but it too suffered from poor stereoselectivity, in this case during formation of the quinolizidine ring system, with poor selectivity for the desired quinolizidine **12**.



Scheme 2 :Synthetic Studies On Lythraceae Alkaloids Via [3+2] Cycloaddition

3. Synthesis of Lasubine II Via acyclic syn-1,3-amino alcohol which is derived stereo-selectively from a β-hydroxy ketone.

Ukaji ,et. al. published a racemic synthesis of this alkaloid in 1985.[5] The key step in the synthesis was the formation of a required syn-beta-amino alcohol via stereoselective reduction of a (Beta-O--benzyloxime alcohol. The synthesis is outlined in Scheme 3.

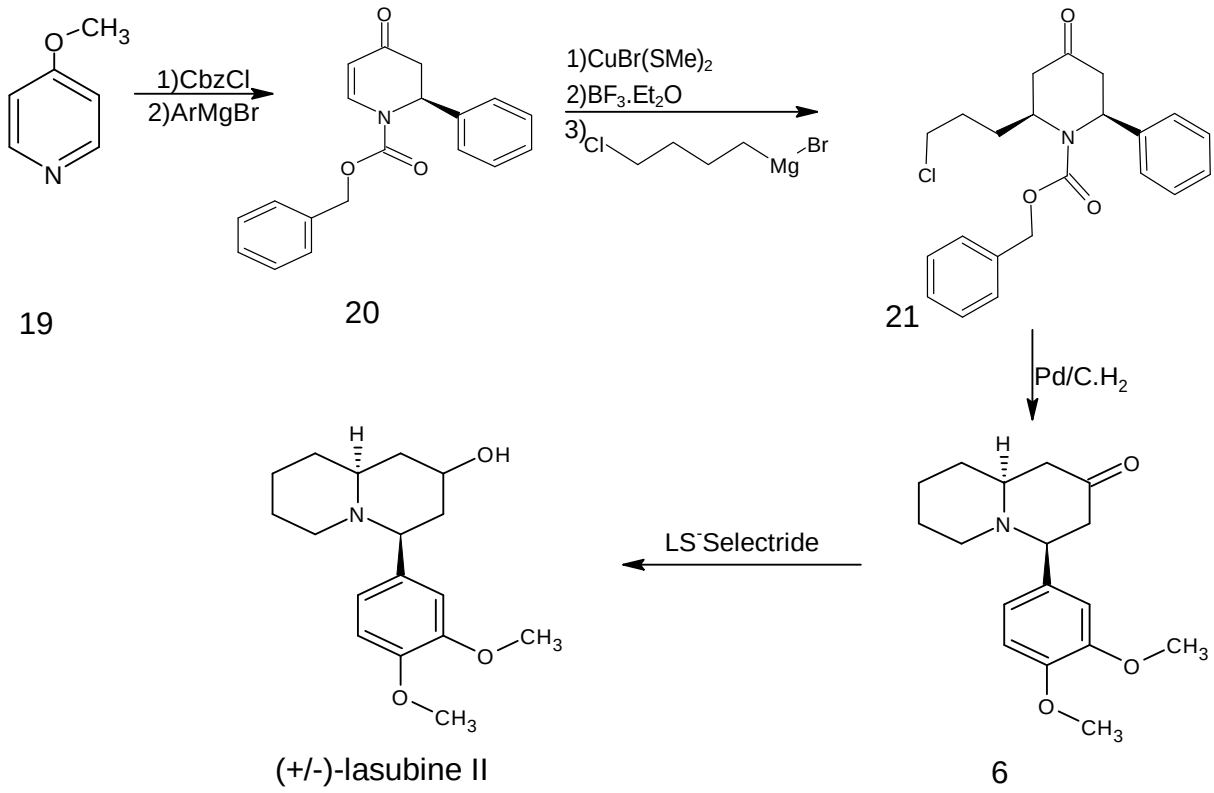


Scheme 3 : Synthesis of Lasubine II Via acyclic syn-1,3-amino alcohol which is derived stereo-selectively from a β-hydroxy ketone.

Dithiane **13** was deprotonated with n-butyllithium and was reacted with the dimethyl acetal of 2-bromoacetaldehyde to give **14**. Hydrolysis of **14** and aldol reaction of the resulting aldehyde gave the ketone **15**. A stereoselective reduction of the resulting O-benzyloxime of **15** using lithium aluminum hydride/potassium methoxide provided the 3-amino alcohol 16. Protection of the amine with a Boc group and removal of the dithiane protecting group gave the ketone **17** which, upon removal of the Boc protecting group with trifluoroacetic acid, resulted in cyclization to the piperidine imine, which was in turn reduced with lithium aluminum hydride/sodium methoxide to form **18**. Hydroboration and oxidation of **18** provided the alcohol **19**, which was cyclized to lasubine II by treatment with tosyl chloride/pyridine. This synthesis afforded (+/-)-lasubine II in 13 steps in an overall 7% yield. This synthesis is long in comparison to the others and results in a low yield. However, the diastereoselectivity of the synthesis is quite high, with little loss in yield due to the formation of unwanted isomers. [5]

4. A Highly Stereocontrolled, Four-Step Synthesis of (+/-)-Lasubine II.

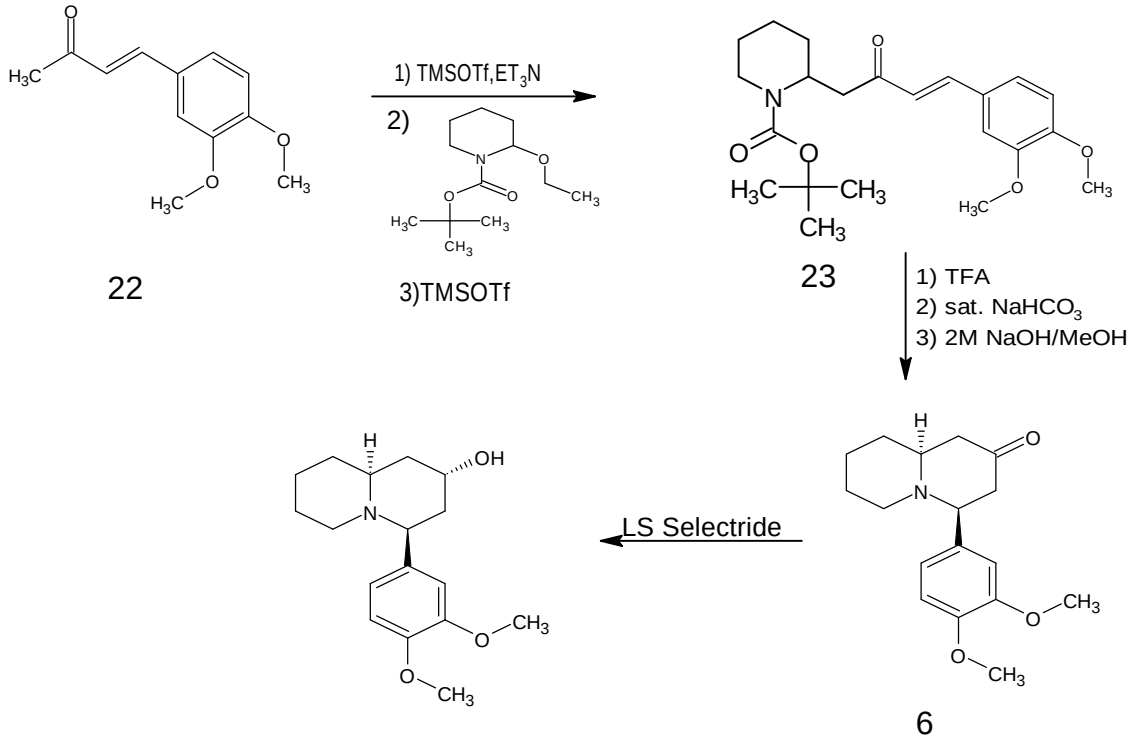
Comins , et. al. Synthesised of racemic lasubine II in 1988 via the synthetic pathway described in Scheme 4.[6] The conjugate addition of 3,4-dimethoxyphenylmagnesium bromide to 4-methoxypyridine **19** produced the enaminone **20.** The product was then further elaborated by a copper-catalyzed conjugate addition of 4-chlorobutylmagnesium bromide to give **21**. Hydrogenolysis removed the Cbz group, at which point the molecule underwent an intramolecular alkylation to afford the quinolizidinone 6. Reduction of the ketone using LS-Selectride provided racemic lasubine II in four steps and an overall 28% yield. Comins thus provided a very concise synthesis with excellent diastereoselectivity.[6]



Scheme 4:A Highly Stereocontrolled, Four-Step Synthesis of (+/-)-Lasubine II.

5. Tandem N-Acyliminium-Michael Addition Reaction. An Efficient Total Synthesis of the Quinolizidine Alkaloids (+/-)-Lasubine II.

Pilli ,et. al. utilized a tandem N-acyliminium coupling-Michael addition reaction in the synthesis of racemic lasubine II in 1993.[8] The reaction pathway is summarized in Scheme 5. The enone **31** was converted to the corresponding enol trillate, which added to the N-acyliminium ion generated from N-Boc-2-ethoxypiperidine and trimethylsilyl tritiate to afford compound **32**. The Boc group was removed under acidic conditions, and upon neutralization, an intramolecular conjugate addition occurred, which initially produced a mixture of cis and trans quinolizidinones. Since the conjugate addition is reversible, base-catalyzed equilibration was used to convert the mixture entirely to **6**. The latter quinolizidinone was subsequently converted to lasubine II via its reduction with LS-Selectride for an overall yield of 48%. Although the yield was excellent, this synthesis required an additional step in order to deal with the poor stereoselectivity in the initial formation of **6.** [8]



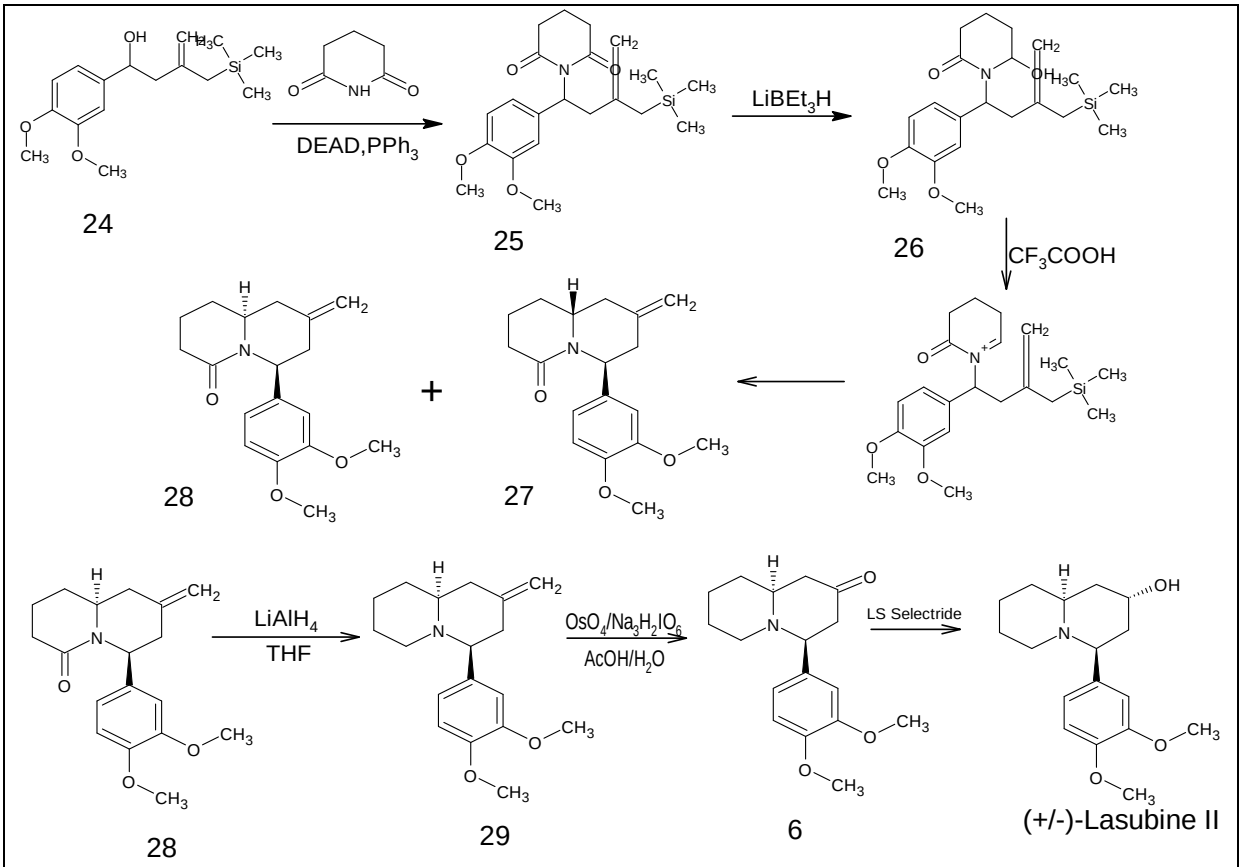
Scheme 5 :Tandem N-Acyliminium-Michael Addition Reaction. An Efficient Total Synthesis of the Quinolizidine Alkaloids (+/-)-Lasubine II.

6. A convenient allylsilane-*N*-acyliminium route toward indolizidine and quinolizidine alkaloids.

The most recent racemic synthesis of (-)-lasubine II was published by Chalard Remuson in 1996.The reaction pathway is summerised in scheme 6.[9] The first steps of synthesis was carried out as shown in Scheme 6. The starting material was 2-(2-hydroxyethyl) allylsilane **24** which was prepared in 86% yield by indium mediated allylsilylation of 3,4-dimethoxybenzaldehyde . The key step in their synthesis was an intramolecular cyclization of an acyliminium ion substituted by an allylsilyl side chain.

A Mitsunobu reaction was used to produce compound **25** from glutarimide and the previously reported homoallylic alcohol . Reduction of **25** using lithium triethylborohydride provided the carbinolamine **26**, which, upon treatment with trifluoroacetic acid, resulted in cyclization via the N-acyliminium ion, thus affording the methylenequinolizidines **27** and **28**. The appropriate diastereomer (**28**) for the synthesis of (+/-)-lasubine II was reduced using lithium aluminum hydride to give **29**. Compound **29** was oxidized by means of catalytic osmium tetroxide with periodate as the stoichiometric oxidant to give the quinolizidinone 6.

The final step was the stereoselective reduction of the ketone using LS- Selectride, , which gave (+/-)- lasubine II in an overall yield of 2% in 6 steps .The poor yield of this synthesis is due in part to the low stereoselectivity for the required *trans* methylenequinolizidine **28**.[9]



Scheme 6 :A convenient allylsilane-*N*-acyliminium route toward indolizidine and quinolizidine alkaloids.

ENANTIOSELECTIVE SYNTHESIS.

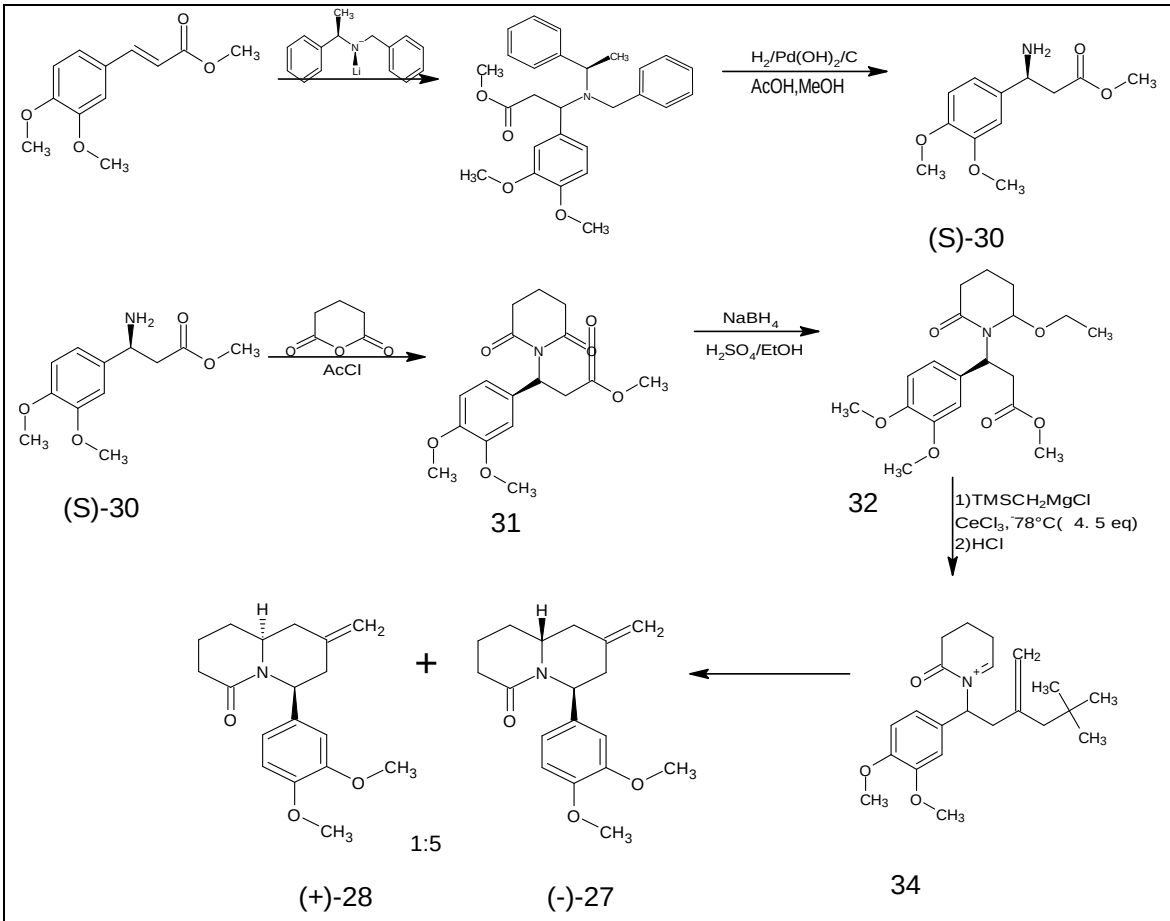
Four Enantioselective Synthesis has been Discussed and Outlined in Scetion from **7-10.**

7. Asymmetric Synthesis of Quinolizidine Alkaloids (−)-lasubine II .

The first enantioselective synthesis of (-)-lasubine II was reported by Remuson ,et. al. in 1998.[13] The approach was similar to the racemic synthesis by the same group with a different sequence used to obtain enantiopure methylenequinolidines **27** and **28**. The synthesis began with the required enantiomer of the β-amino ester **30**. The Reaction Pathway is Summerised in Scheme 7.

Formation of the quinolizidine skeleton was accomplished by the reaction of **30** with glutaric anhydride, followed by acetyl chloride . This produced the imide **31,** which was converted to the ethoxy lactam **32** through its reduction to the corresponding carbinolamine with sodium borohydride and treatment with a mixture of ethanol/sulfuric acid. Cyclization proceeded after treatment with the organocerium reagent (4.5 equivalents) produced from $CeCl_3$ and trimethysilylmethylmagnesium chloride, followed by hydrolysis with 1 N HC1. This gave methylenequinolizidines **(-)-27** and **(+)-28,** in a 1:5 mixture of diastereomers that was separated by flash chromatography.

Compound **(+)-28** was converted to (-)-lasubine II in a manner identical with the racemic synthesis for an overall yield of 14% in 8 steps. Although successful at synthesizing enantiopure (-)-lasubine **II,** the synthesis lacks selectivity for the required *trans* methylenequinolizidine **(+)-28,** resulting in poor overall efficiency of Product.[13]

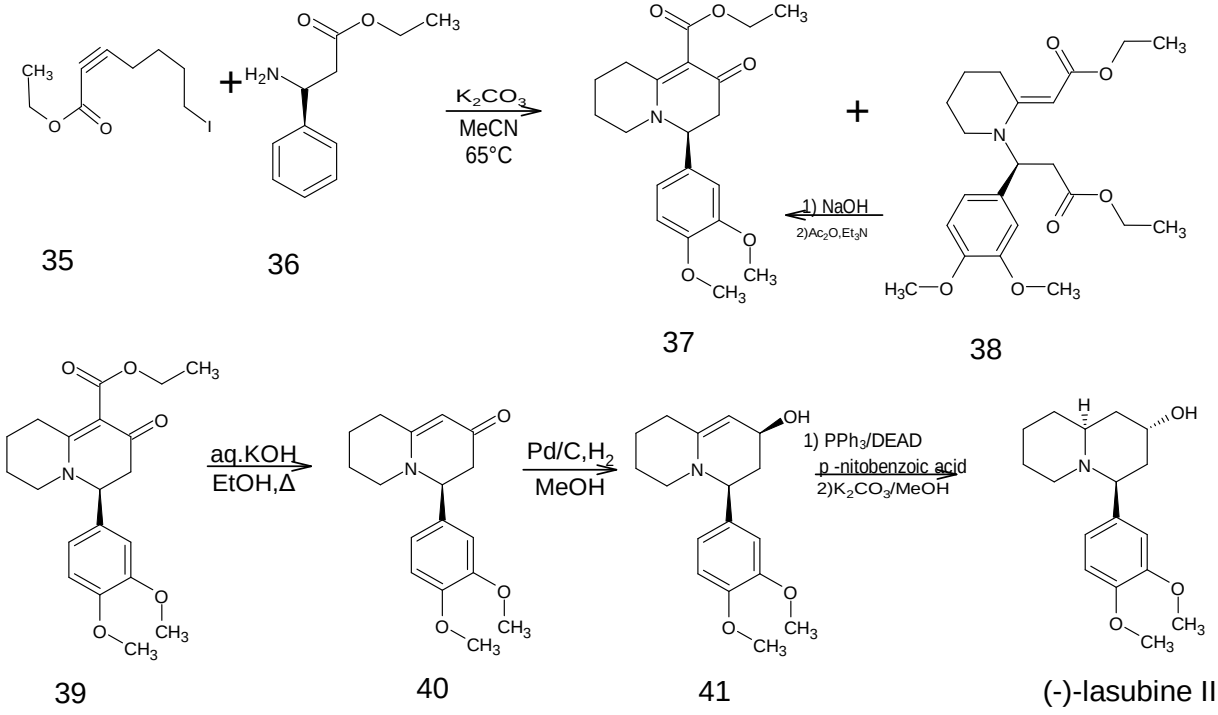


Scheme 7:Asymmetric synthesis of quinolizidine alkaloids (−)-lasubine II .

8. Two-Component Method to Enantiopure Quinolizidinones and Indolizidinones. Total Synthesis of (−)-Lasubine II .

The enantioselective synthesis of (-)-lasubine **II** was completed by Ma and Zhu in 2001.[10] The synthesis centered around a two-component method of producing quinolizidinones from the reaction of an iodoalkynoate and an enantiopure (3-amino ester. The synthesis is outlined in Scheme 1.12. Ethyl 7-iodohept-2-ynoate **(35)** and the (3- amino ester **36** were heated at 65 °C in the presence of potassium carbonate, using acetonitrile as the solvent. The result was a 1:1 mixture of products including the quinolizidinone **37** and the uncyclized diester **38.** This mixture of products was converted to **37** by hydrolysis of **38** using aqueous sodium hydroxide, followed by treatment with acetic anhydride/triethylamine. This procedure provided an overall 82% yield of **37** from **35.** Hydrolysis, followed by decarboxylation, was performed by refluxing a solution of **37** in ethanol/aqueous potassium hydroxide. This gave the enaminone **39** in 66% yield. Hydrogénation of **39** using a palladium catalyst provided the saturated alcohol **40** in 84% yield. The product had the correct stereochemistry at the ring junction; however, the carbinol

stereocenter had the opposite configuration of the desired product. Therefore, inversion of the alcohol was carried out under Mitsunobu conditions to give (-)-lasubine **II** in an 84% yield from **40.** The overall yield from **35** was 36% in 5 steps. Although this is the highest yielding synthesis of (-)-lasubine **II,** The starting materials **(35** and **36)** are not commercially available and need to be synthesized as well.[10]

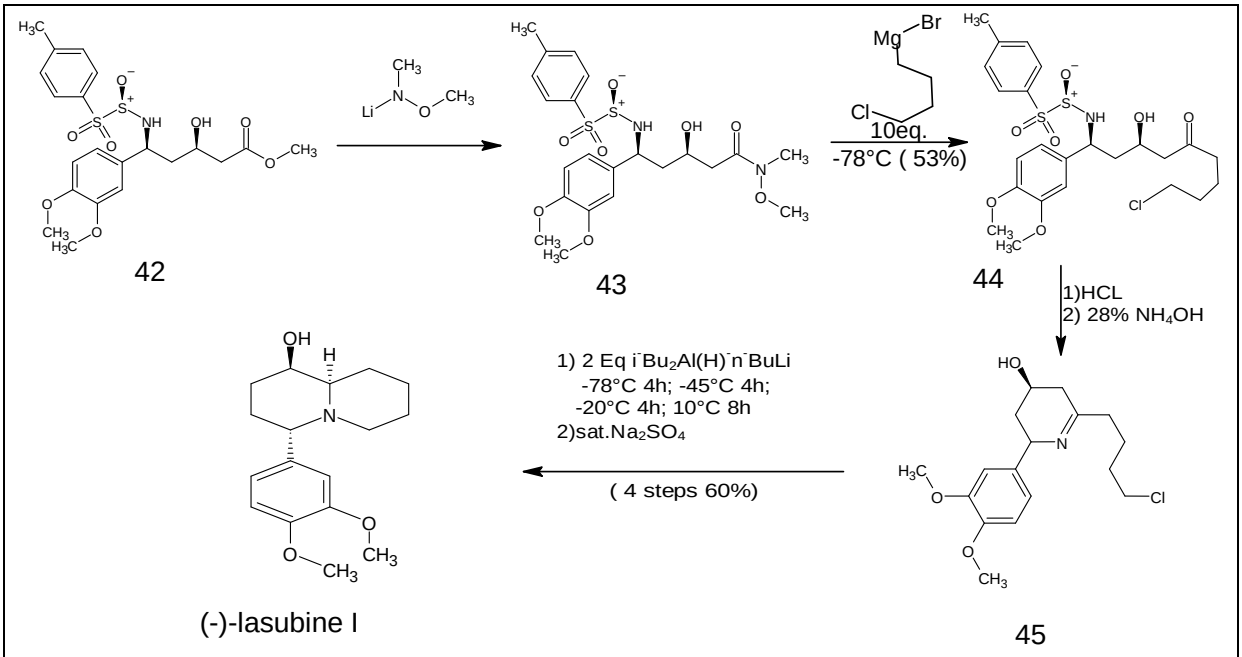


Scheme 8:Two-Component Method to Enantiopure Quinolizidinones and Indolizidinones. Total Synthesis of (−)-Lasubine II .

9. Asymmetric Synthesis of Functionalized trans-2,6-Disubstituted Piperidines with N-Sulfinyl *δ*-Amino *β* -Ketoesters. Synthesis of (−)-Lasubine I .

Davis, et. al. synthesis of (-)-lasubine **I** was reported in 2003.[7 11]It utilized a δ -amino β-hydroxy ketone as a polyfunctionalized chiral building block. The synthetic sequence is outlined in Scheme 2.The synthesis began with the Treatment of the *δ*-amino *β* -hydroxy esters with 10 equiv of lithium *N,O*-dimethylhydroxylamine afforded the corresponding Weinreb amide in 90-98% isolated yield . Then this Weinreb amide was treated with 10 equivalent of (4-chlorobutyl)magnesium bromide in ether-THF at -78 °C to give the chloro ketone (-)-**44** in

53% yield following isolation by preparative TLC. Removal of the sulfinyl group with 2 N HCl and neutralizing with 28% NH4OH gave 4-hydroxy 1,2-dehydropiperidine **45**, which was dried and immediately added to 2.0 equiv of the *i*-Bu2Al(H)-*n*-BuLi complex in ether. After the addition was complete the reaction mixture was allowed to slowly warm to 10 °C (-78 °C, 4 h; -45 °C, 4 h; -20 °C, 4 h; 10 °C, 8 h. This synthesis provided an overall yield of 64% for (-)-lasubine-I.[7 11]

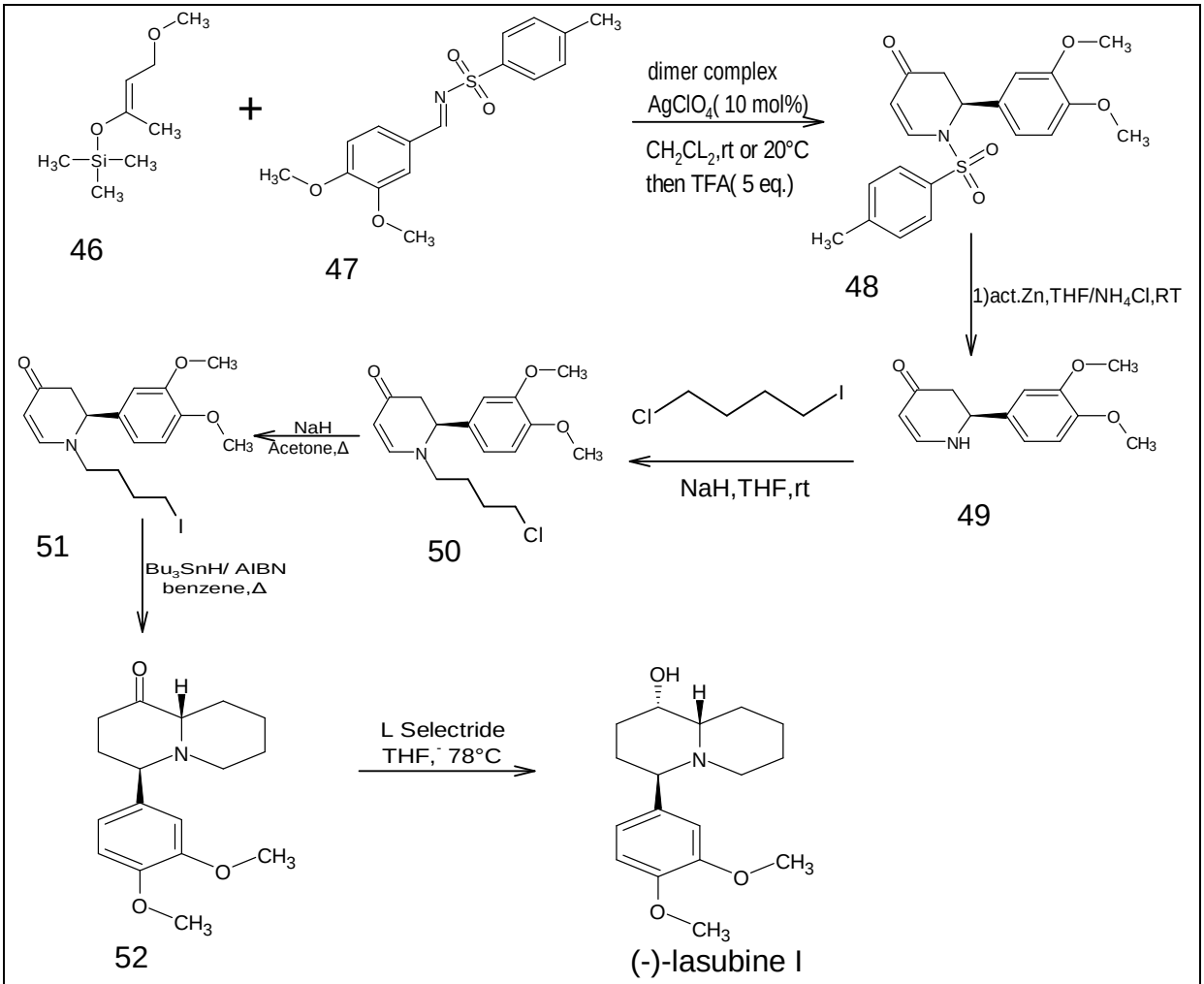


Scheme 9: Asymmetric Synthesis of Functionalized trans-2,6-Disubstituted Piperidines with N-Sulfinyl δ-Amino β -Ketoesters. Synthesis of (−)-Lasubine I .

10. Catalytic Enantioselective Approach to the Stereodivergent Synthesis of (+)-Lasubines I .

Macheno ,et. al. Synthesis of (+)-laubine I by catalytic approach to the stereodivergent is outlined in Scheme 3.[14]The Synthesis was Published in 2007.The synthesis began with enantioselective preparation of *N*-sulfonyl 2,3-dihydropyridones based on the Cu(I)/Fesulphos catalyzed enantioselective formal aza-Diels-Alder reaction between *N*-sulfonylaldimines and Danishefsky's diene. By using this methodology the reaction of the *N*-tosyl imine of 3,4-dimethoxybenzaldehyde (**47**) with Danishefsky's diene, at room temperature in CH2Cl2, in the presence of catalytic amounts of the Cu-Fesulphos bromo dimer complex (5.1 mol %) and AgClO4 (10 mol %), followed by addition of TFA,10 afforded the dihydropyridone in 71%

yield and 86% ee. a higher enantioselectivity (94% ee), preserving a similar chemical yield, was obtained by performing the reaction at -20 °C. Furthur *N*-alkylation of the *N*-H dihydropyridone **49** with 4-chloro-1-iodobutane (NaH, THF) provided the required *N*-functionalized chloro-derivative **50** in 75% yield.Then the reactivity of the radical precursor, the iodo derivative **51** was prepared in almost quantitative yield by reaction of **50** with NaI in acetone. The treatment of the iodo derivative **51** under standard radical cyclization conditions (Bu3SnH, AIBN, benzene, reflux) yielded the quinolizidine ketone **52**,exclusively as the trans isomer (69%).The stereoselective carbonyl reduction of **52** with L-selectride afforded (+)-lasubine I in good yield of 79%.[14]



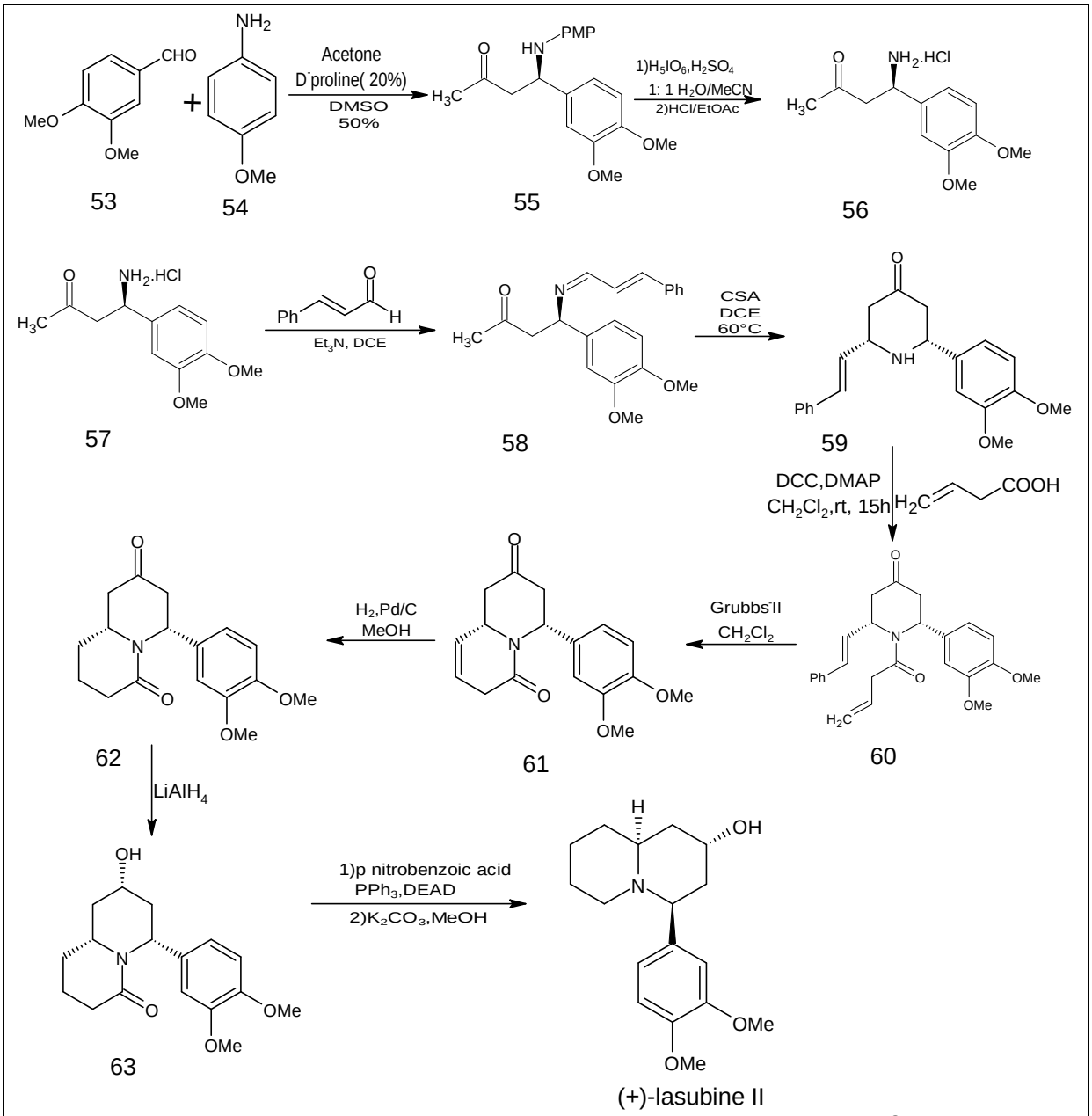
Scheme 10: Catalytic Enantioselective Approach to the Stereodivergent Synthesis of (+)-Lasubines I .

11. An Enantioselective Organocatalytic Approach to Synthesis 0f (+)-Lasubine II.

Jorge Verkade, et. al. Synthesised Enantioselective (+)-Lasubine II Via Organocatalytic Approach in 2009.[16]The Reaction Path way is Summerised in Scheme 11.The Synthesis began with preparation of 1,3 amino ketone.Expensive protected 4-hydroxyproline derivative was used , careful analysis of the D-proline-catalyzed Mannich reaction (20 mol % D-proline, DMSO, rt) and careful monitoring of the reaction progress by HPLC and stopping the reaction at ca. 50% conversion, the compound was able to isolate the (*R*)-aminoketone **55** by precipitation from the reaction mixture as a crystalline solid in 50% yield and >99% ee.

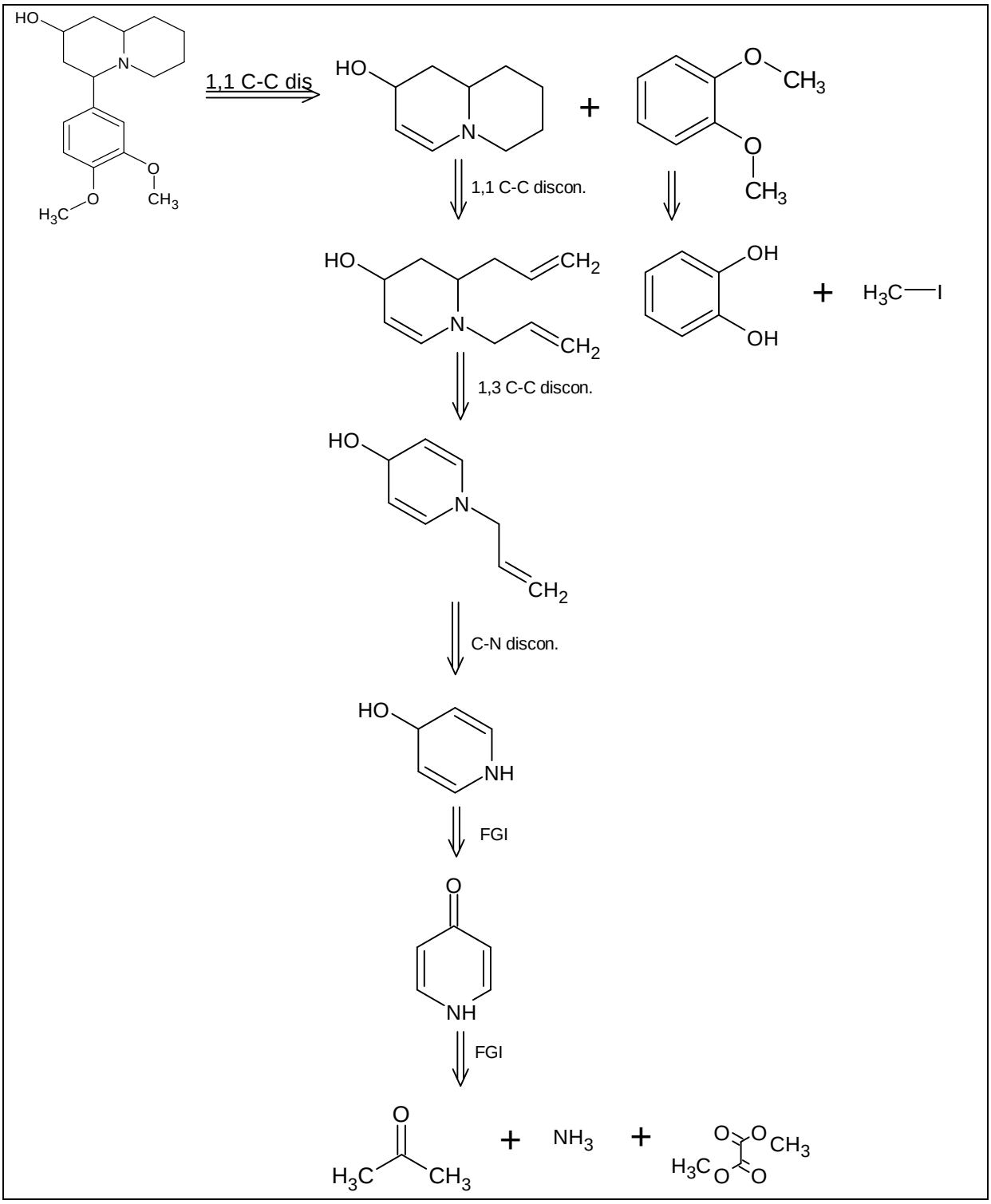
The deprotection of *N*-PMP amine **55**, was carried byn H5IO6 under acidic conditions. Although cleavage of free amine by itself proceeded smoothly,but isolation of the -aminoketone appeared problematic due to self condensation while concentrating the organic layer after workup. This problem was solved by in situ formation of the HCl-salt **56** prior to concentration of the reaction mixture.

The starting material imine **58** was prepared by condensation of **57** with cinnamaldehyde in the presence of triethylamine as a base to liberate the amino group. The condensation was carried out in 1,2-dichloroethane via successive concentration of the reaction mixture under reduced pressure to azeotropically remove water. The Mannich cyclization was then carried by stirring a solution of the crude imine **58** in 1,2- dichloroethane in the presence of an excess of (+)-camphor sulfonic acid (CSA) to yield **59** as a single diastereoisomer. Then amine of the resulting 2,6- disubstituted piperidinone **59** was directly acylated with viny- lacetic acid via standard DCC-coupling, leading to the stable piperidinone **60.** Treatment of This piperidinone **60** with the Grubbs- II catalyst (6 mol %) followed by hydrogenation of the resulting unsaturated lactam **61** led to the bicyclic structure **62** in good overall yield.Then both carbonyls were reduced in a one-pot reaction by LiAlH4 as the reducing agent. The resulting (+)-2-*epi*-lasubine II (**63**) was transformed into (+)-lasubine II by adding p-nitrobenzoicaid ,PPh3 , DEAD and K_2CO_3 ,MeOH via a protocol from zhu,et al. [16]

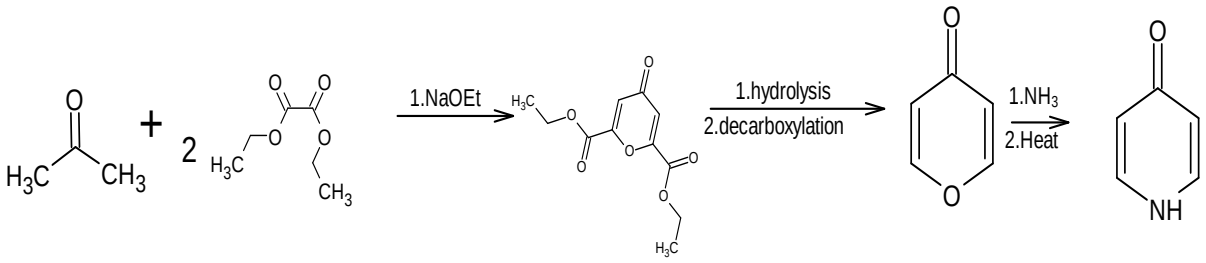


Scheme 11:An Enantioselective Organocatalytic Approach to Synthesis 0f (+)-Lasubine II.

RETEROSYNTHESIS OF LASUBINE

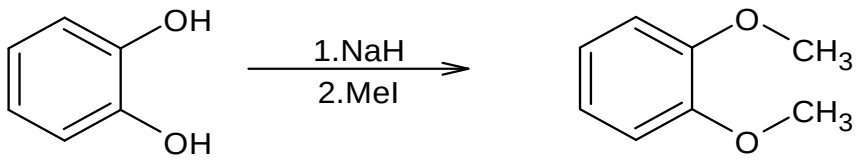


FORWARD SYNTHESIS OF LASUBINE



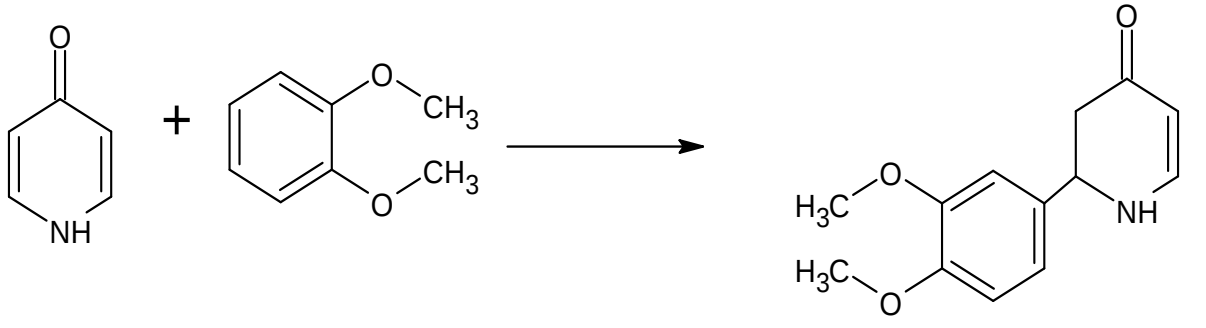
Scheme 12 :- Synthesis of 4-pyridinone

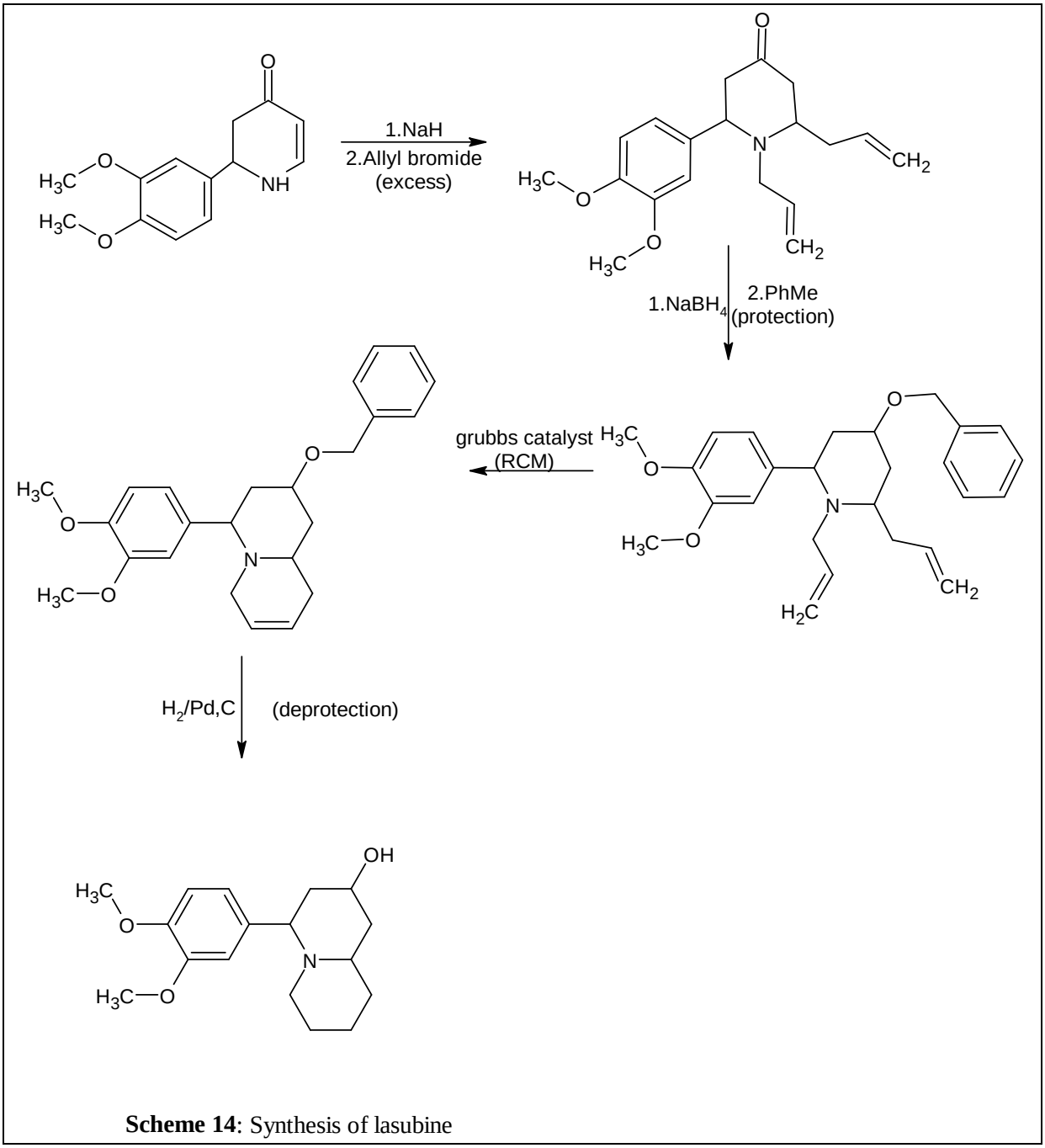
Synthesis of 4-pyridone can be done by Reacting Acetone with Diethyl oxalate in presence of base.Further acid or base catalysed hydrolysis work up for decarboxylation is carried which is heated with ammonia.



Scheme 13:- Synthesis of 1,2-dimethoxybenzene

1,2-dimethoxybenzene can be prepared by reacting Catechol with sodium hydride base and methyl iodide.





Scheme 14: Synthesis of lasubine

Synthesis of Lasubine can be done in 5 steps .First 4-pyridinone is reacted with 1,2-dimethoxybenzene .Then NaH base is added followed by addition of excess of allyl bromide . First allyl bromide is added to nitrogen then at 1,4 position of ketone .Reduction of ketone to alcohol can be carried by $NaBH_4$ and then hydroxy group is protected by benzyl group. Cyclisation of ring can be carried by Grubbs catalyst(RCM).finally hydogentation condition used for deprotection and reduction of double bond simultaneously.

CONCLUSION

The Scope Of Nitrogen based compounds in medicine is growing daily and their diverse analog provide a viable and important path for the discover of drugs with various biological application.

The first Total Synthesis of lasubine by Kibayashi ,et al was done in which overall yield of 4% was obtained with non stereoselectivity of product. The Synthesis by Takano,et al the overall yield was 17% with improvement compared to Kibayashi but also had poor selectivity. Ukaji ,et al synthesis had very poor yield in comparision with other with overall yield of 7% however but had high diasteroselectivity . Comins ,et al Synthesis had good overall yield of 28% and excellent diasteroselectivity. Pilli ,et al synthesis had excellent yield of 48% among all the other synthesis but required an additional step in order to deal with poor stereoselectivity .Remuson, et al Synthesis has very poor stereoselectivity and yield of 2% among all the other synthesis.

The First Enantioselective Synthesis of (-)-Lasubine II by Remuson,et al with overall yield of 14% with good steroselectivity.The Synthesis by Davis, et al synthesisi of (-)-lasubine I. The overall yield was 21% with higher stereoselectivity . J verkade , et al Synthesis 0f (-)-lasubine I had the 48% overall yield and moderate selectivity. Macheno, et al Synthesis of (+)- lasubine II Had the Excellent yield of 79% among all the the other synthesis.

Use of Suitable Catalyst and Other Reaction condition can be carried so that better statergies can be developed to carry Synthesis of lasubine in a better manner to get increased yield and better stereoselctivity.

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