"Construction of 2-Azabicyclo[*m.n.*0]alkane Ring Systems: Towards the Total Synthesis of (-)-Stenine and Related Alkaloids"

THESIS SUBMITTED TO

SAVITRIBAI PHULE PUNE UNIVERSITY

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IN CHEMISTRY

SUBMITTED BY

BINOY MAJUMDER

UNDER THE GUIDANCE OF

Dr. GANESH PANDEY

DIVISION OF ORGANIC CHEMISTRY

CSIR-NATIONAL CHEMICAL LABORATORY

PUNE-411008

MARCH 2019

Dedicated

To

My Parents and All Family Members

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Construction of 2-Azabicyclo[$m.n$.0]alkane Ring Systems: Towards the Total Synthesis of (-)-Stenine and Related Alkaloids**" which is being submitted to the **Savitribai Phule Pune University** for the award of **Doctor of Philosophy** in **Chemistry** by **Mr. Binoy Majumder** was carried out by him under my supervision at the CSIR-National Chemical Laboratory, Pune. A material that has been obtained from other sources has been duly acknowledged in the thesis.

Date: 30|01|2019

Dr. Ganesh Pandey

(Research Guide)

DECLARATION

I declare that the thesis entitled "**Construction of 2-Azabicyclo[*m.n*.0]alkane Ring Systems: Towards the Total Synthesis of (-)-Stenine and Related Alkaloids**" submitted by me for the degree of Doctor of Philosophy is the record of work carried out by me during the period from 10/05/2010 to 30/01/2019 under the guidance of Dr. Ganesh Pandey and has not formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning.

I further declare that the material obtained from other sources has been duly acknowledged in the thesis.

Binoy Majumder

Date: 30/01/2019

Division of organic chemistry,

CSIR-National Chemical Laboratory

Pune-411008

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Binoy Majumder

Contents

"Construction of 2-Azabicyclo[*m.n.*0]alkane Ring Systems: Towards the Total Synthesis of (-)-Stenine and Related Alkaloids"

List of Abbreviations

aq.	Aqueous
Ac	Acyl
Ar	Aryl
bp	Boiling point
Bn	Benzyl
Bu	Butyl
Boc	*t*-Butoxycarbonyl
COSY	Correlated spectroscopy
Cat.	Catalyst
DCM	Dichloromethane
DEPT	Distortionless enhancement by Polarization transfer
DMF	N, N-dimethyl formamide
DMSO	Dimethylsulfoxide
DMAP	4-dimethyl amino pyridine
dba	dibenzylideneacetone
Et	Ethyl
EtOAc	Ethyl Acetate
g	Gram
GC	Gas Chromatography
h	Hour
HMDS	hexamethyl silazide
Hz	Hertz
K*i*	Inhibition constant
M	Molarity (molar)
Mg	Milligram
Min	Minute(s)
mL	Milliliter
mmol	Millimole

mp	Melting Point
MeOH	Methanol
N	Normality
HRMS	High Resolution Mass Spectrometry
MsCl	Methanesulfonyl chloride
Me	Methyl
Nu	Nucleophile
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect/enhancement
NOESY	Nuclear Overhauser Enhancement Spectroscopy
ORTEP	Orthogonal thermal ellipsoid plots
PDC	Pyridinium dichromate
PMB	*para*-Methoxy benzyl
Ph	Phenyl
p-TSA	*p*-Toluenesulfonic acid
py	Pyridine
rt or RT	Room temperature
TBS	*t*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TEA	Triethyl amine
TFA	Trifluoroacetic
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
Tf	Triflate (Trifluoromethanelsulfonate)
TBHP	*tertiary*-butyl hydroperoxide

General Remarks

- All the solvents were purified according to literature procedure.1
  Petroleum ether used in the experiments was of 60-80 o C boiling range.

- Column chromatographic separations were carried out by gradient elution with suitable combination of two solvents and silica gel (60-120 mesh/ 100-200 mesh/ 230-400 mesh).

- Reaction progress was monitored by TLC. TLC was performed on Merck precoated 60 F254 plates and the spots were rendered visible by exposing to UV light, Iodine, phosphomolibdic acid, o-Anisol, KMNO4, ninhydrin solutions.

- IR spectra were recorded on FTIR instrument, for solid either as nujol mull, neat in case of liquid compounds or their solution in chloroform.

- NMR spectra were recorded on Bruker (400 MHz 1H NMR and 100 MHz 13C NMR), Bruker 600 MHz (600 MHz 1H NMR and 150 MHz 13C NMR) and Bruker ultra-shield 800(800 MHz 1H NMR and 200 MHz 13C NMR) 13C peak multiplicity assignments were made based on DEPT data.

- Mass spectra were recorded on PE SCIEX API QSTAR pulser (LC-MS), Agilent LC-MS/HRMS instrument.

- All the melting points recorded are uncorrected and were recorded using electrothermal melting point apparatus(BUCHI, MODEL NO. B540)

- Starting materials were obtained from commercial sources.
- Numbering of compounds, schemes, tables, referencing and figures in abstract and chapters are independent.

Research student	**Binoy Majumder**
Research Guide	Dr. Ganesh Pandey
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<u>Thesis Abstract</u>

"Construction of 2-Azabicyclo[*m.n.*0]alkane Ring Systems: Towards the Total Synthesis of (-)-Stenine and Related Alkaloids"

The present dissertation is divided into four chapters. Chapter one deals with the significance of 2-azabicyclo[*m.n.*0]alkane ring systems in the natural products and literature survey on the preparation of *cis*-octahydroindole, *cis*-decahydroquinoline and *cis*-decahydro-[1*H*]-benzo[*b*] azepine ring systems. Chapter two describes our synthetic planning and a successful general synthetic route for the costruction of the three 2-azabicyclic ring systems using a common intermediate. Chapter three depict the efforts toward the synthesis of *Strychnos* class of alkaloids by utilizing our synthesized hexahydroindole scaffold. Similarly chapter four describes an efficient approach toward the synthesis of stemona class of alkaloids and the synthesis utilizes our synthesized *cis*-decahydro-[1*H*]-benzo[*b*]azepine scaffold.

Chapter 1: 2-azabicyclo[*m.n.*0]alkane ring systems and their importance in the natural product synthesis.

[*m.n.*0]-Bicyclo-2-azaalkane scaffolds are embedded in various biologically important natural products frameworks and their derivatives displaying potent diverse pharmacological and physiological properties. These frameworks are well known and most popular in natural products having 2-azabicyclo[3.4.0]nonane (octahydroindole), 2-azabicyclo[4.4.0]decane (decahydroquinoline) and 2-azabicyclo[5.4.0]undecane (decahydro-1*H*-benzo[*b*]azepine) rings (Fig 1). These three basic scaffolds (i.e. **1**, **2** and **3**) are present in biologically important natural products such as strychnos, stemona, aspidosperma, amaryllidaceae, lycopodium, lepadin and myrioneurinol class of alkaloids.
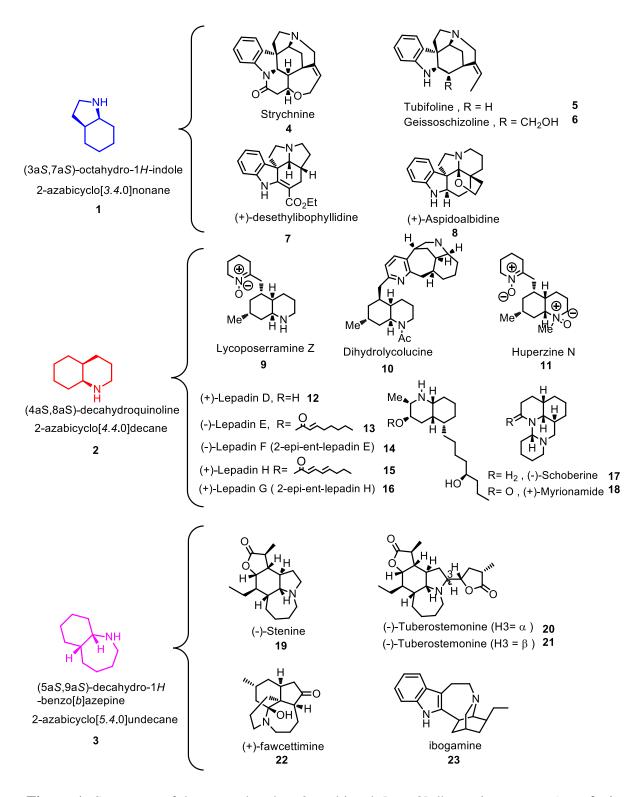
Figure 1: Structures of the most abundant 2-azabicyclo[*m.n*.0]alkane ring system (*m* = 3, 4, 5 and *n* = 4.) including their alternate IUPAC nomenclature related to the both natural products synthesis and drug discovery.

Octahydroindole skeleton is present in strychnos, amaryllidaceae, aspidosperma, erythrina and stemona class of alkaloids. Antimicrobial, antitumor or anticancer, cytotoxic, muscle relaxant and hypotensive activities are known for strychnos alkaloids. Amaryllidaceae alkaloids have DNA binding properties, antitumor, anti-viral, antifungal, and insect antifeedant activity. Aspidosperma species have been commonly used in folk medicine as potential antimalarial agents, antileishmaniasis; anti-inflammatory for uterus and ovary disorder. (+)-Ibophyllidine, (+)-desethylibophyllidine have antitumor activities.

The decahydroquinoline ring system is present in many naturally occurring biologically active alkaloids such as *cis*-phlegmarine, lepadin, myrioneuron and lycopodium. These alkaloids possess very important biological activities for wide range of therapeutic applications including anticancer, neuroprotective (e.g. Alzheimer's disease), analgesic and immunosuppressive.

The alkaloids related to the decahydro-1*H*-benzoazepine architecture comprises of stemona alkaloids such as stenine, tuberostemonine, neostenine, neotuberostemonine. Iboga alkaloids ibogamine and the lycopodium alkaloid fawcettimine also contain decahydro-1*H*-benzoazepine ring. Stemona alkaloids have been used for the treatments of respiratory ailments and also it is associated with insecticidal, antihelmintic, antitussive and various neurochemical effects.

For the synthesis of these alkaloids large scale synthesis of 2-azabicyclic skeleton is required. More important task is the asymmetric construction and proper stereochemical installation of the 2-azabicyclic rings embedded in the polycyclic structures to accomplish the corresponding total syntheses of the alkaloids. The later part of this chapter describes various synthetic strategies developed for the construction of these three 2-azabicyclic scaffolds.

Chapter 2: Development of a General Synthetic Route to Access 2-Azabicyclo[*m.n.*0]alkane Ring Systems.

[6, 5], [6, 6] and [6, 7]-2-Azabicyclic framework offers an excellent platform for systematic scaffolding towards the synthesis of diverse alkaloids. Although, numerous approaches are developed for the construction of these bicyclic rings, there is no general strategy available to construct such kind of azabicyclic scaffolds. In the context of the total synthesis of some alkaloids having these scaffolds, we evaluated to develop a rational strategy to overcome the synthetic challenges arising out due to the complexity of these natural products. To keep this in mind, a common precursor or intermediate was visualised following a well-designed chemical reaction (Fig. 2).

(3a*S*,7a*S*)-octahydro-1*H*-indole
2-Azabicyclo[3.4.0]nonane
1

(4a*S*,8a*S*)-decahydroquinoline
2-Azabicyclo[4.4.0]decane
2

(5a*R*,9a*R*)-decahydro-2H-benzo[b]azepine(*5aS*,*9aS*)-decahydro-
1H-benzo[b]azepine
2-Azabicyclo[5.4.0]undecane
3
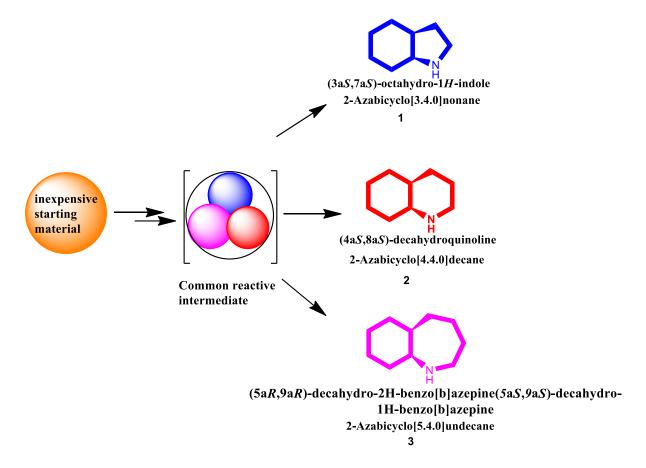
Figure 2: Conceptual overview of using a common intermediate to access 2-azabicyclic skeleton

To demonstrate the synthetic potentiality of our approach, we have chosen to explore the wide range of functionalisation and highly stereoselective ring opening of the facially biased, strained bridge-azabicyclic ring **24** followed by ccyclisation(Scheme 1).

Scheme 1: Bridge-azabicyclic ring opening followed by cyclisation strategy.

Synthesis of hydroindole scaffold:

In order to establish a stereoselective Michael addition step in the synthetic route, vinyl magnesium bromide was used as a Grignard reagent to react with the primary scaffold 7-azabicyclo[2.2.1]hept-2-ene **24**. In the presence of cupric cyanide (CuCN) at -30 °C afforded the Michael addition followed by in situ ring opening product **27**.

Scheme 2: Synthesis of hexahydroindole scaffold.

Reagents and conditions: a) Vinyl magnesium bromide(1.8 eq), CuCN(1 eq), Dry THF + Ether (1:1), -30 °C, 4 h, 41%; b) i) 0.5M 9-BBN(1.5eq), 0 °C to rt, 12 h ii) 3M NaOAc, H₂O₂, 0 °C to rt, 5 h, 62% (91% on brsm); c) mesyl chloride (MsCl), DMAP, Et₃N (5eq), 0 °C to rt, 4 h, 76%.

Hydroboration of terminal olefin and the mesylation of the resulting alcohol **28** provided the cyclised product to obtain the 2-azabicyclo[3.4.0]nonane skeleton (octahydroindole ring) embedded with electron-deficient olefin **29** (scheme 2). Therefore, the olefin would direct for further functionalisation of all the carbon centre of the carbocyclic ring.

The moderate yield (41%) of the Michael addition step using vinyl magnesium bromide and inefficiency for scaling up the hydroboration necessitates to optimise the ring opening step and subsequent cyclisation. Meanwhile, allyl magnesium bromide provided ring opening product **30** with an excellent yield.The oxidative cleavage gave the corresponding aldehyde **31** with one carbon less and subsequent reductive amination with the tethered N-carbamate amine to afford the desire hexahydroindole ring **29** (scheme 3).

Scheme 3: Scalable synthetic route for the synthesis of hexahydroindole ring system.

Reagents and conditions: a) Allyl magnesium bromide(1.8 eq), CuCN(1 eq), Dry THF + Ether (1:1), -30 °C, 4 h, 93%; b) OsO₄ (0.01 eq), NaIO₄ (4eq), 2,6-lutidine(2 eq), dioxane:water(3:1),rt,2 h; c) NaCNBH₃ (2 eq), THF:AcOH(9:1), 20 h, 91%.

Synthesis of *cis*-octahydroquinoline ring system:

With proof of the concept we planned to explore the potential of the synthetic intermediate **24** in the synthesis of other 2-azabicyclic ring system employing the same synthetic sequence The most basic modification of the previously described synthetic route to hexahydroindoles would be to vary the length of the carbon chain in the Grignard reagent to give the corresponding 2-azabicyclic product. After having ring opening, product **32,** we have followed the same reaction pathway involving hydroboration and mesylation followed by cyclization with the tether Boc protected amine to access *cis*-fused bicyclic ring. However, **33** failed to provide any cyclized product **34** under the mesylation condition. We planned to follow deprotection-*N*-cyclization-protection sequence to get the best yield of the cyclized product without any column purification. The mesylate was subjected to *N*-Boc deprotection by in situ generated trimethylsilyliodide (TMSI) followed by *N*-cyclization using ceasium carbonate as a mild base, which gave the crucial cyclized product **34** (scheme 4).

Scheme 4: Synthesis of *cis*-octahydroquinoline ring system

Reagents and conditions: a) Allyl magnesium bromide(1.8 eq), CuCN(1 eq), Dry THF + Ether (1:1), -30 °C, 4 h, 93%; b) i) 0.5M 9-BBN in THF (1.5eq), Dry THF 0 °C to rt, 12 h ii) 3M NaOAc, H₂O₂, 0 °C to rt, 5 h, 71% (90% on brsm); c) i) mesyl chloride(MsCl), Et₃N, DMAP, 0 °C to rt, 2 h; ii) NaI, TMSCl, dry CH₃CN, 0 °C to rt, 4 h; iii) Cs₂CO₃, dry CH₃CN, rt, 48 h; iv) Boc₂O, Et₃N, DMAP, 24 h, overall yield 51%.

Synthesis of *cis*-octahydro-2*H*-benzo[*b*]azepine scaffold:

Using the underlying philosophy and the principles developed for the hexahydroindoles, octahydroquinolines ring systems, we postulate that it should be possible to access azepine ring containing skeleton by lengthening the carbon chain of the corresponding Grignard reagent. The Grignard reagent of **37** was derived from the TBS protected 1,4-bromoalcohol **36** which

we made in multi-gram scale by refluxing tetrahydrofuran in presence of 40% hydrobromic acid (scheme 5).

Scheme 5: Preparation of TBS protected 1,4-bromoalcohol **37**.

Reagents and conditions: a) 40% aq. HBr, reflux, 2 h, 41%; b) TBSCl (1.2 eq), imidazole (2.2 eq), DMAP (0.1 eq) rt, 12 h, 88%.

The TBS protected Grignard reagent was reacted very smoothly with the common intermediate **24** to provide the desired ring opening product **38**, which was subjected to 0.8N hydrochloric acid to deprotect the TBS group. After having the alcohol **39**, applied the same cyclization protocol as in the case of *cis*-octahydroquinoline preparation to access the desire cyclized product *cis*-octahydro-2*H*-benzo[*b*]azepine **41** (scheme 6).

Scheme 6: Synthesis of octahydrobenzo[*b*]azepine ring system.

Reagents and conditions: a) i) 48 (1.8 eq),Mg turnings (2.2 eq),dry ether; ii) CuCN(1 eq), Dry THF + Ether, -60 °C to -30 °C, 4 h, 81%; b) i) 0.8N HCl, 0°C,2 h, ii) NaHCO₃, 0°C, 86%; c)

mesyl chloride (MsCl), Et₃N, DMAP, 0 ᵒC to rt, 2 h; d) i) NaI, TMSCl, dry CH₃CN, 0 ᵒC to rt, 4 h, ii) Cs₂CO₃, dry CH₃CN, rt, 48 h, iii) Boc₂O, Et₃N, DMAP, 24 h, overall yield 48%.

Chapter 3: Synthetic Approach towards the Strychnos Class of Alkaloids.

This chapter represents an overview of *Strychnos* alkaloids including structural features and synthetic challenges. This also describes literature survey on the total synthesis of (-)-tubifoline and (-)-tubifolidine. In the later part of the present chapter, we have shown the utilization of our synthesized hexahydroindole scaffold towards the synthesis of (-)-dehydrotubifoline, (-)-tubifoline and (-)-tubifolidine.

The *Strychnos* alkaloids encompasses an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids. According to their biogenesis, they have been classified into two classes, Strychnan and Aspidospermatan with a topographical relationship. The most of the Strychnan alkaloids possesess curan type of skeleton which contains a pentacyclic 3,5-ethanopyrrolo[2,3-*d*]carbazole framework (Fig. 2) bearing two carbon appendage at C-20 (alkyl, alkylidene or oxygenated) and an oxidized one-carbon substituent C-17) at C-16 (hydroxymethyl, formyl or methoxycarbonyl). More than 125 alkaloids with the curan skeleton have been isolated, among which almost half of are the *Strychnos alkaloids* (figure 3).

42
Curan skeleton and
biogenetic numbering

43 Tubifolidine, R = H
5 Tubifoline, R = H (1,2-didehydro)
6 Geissoschizoline, R= CH_2OH
44 19,20-Dihydroakuammicine,
  R = CO_2Me (2,16-didehydro)

45 Norfluorocurarine, R = CHO
46 Fluorocurarine, R =CHO
  (N_b- methyl)
47 Akuammicine, R = CO_2Me
48 Mossambine. R = CO_2Me
  (14 *S*-OH)

49 Echitamidine, R_1 = (*S*)-CHOHCH$_3$; R_2 = H
50 20-Epilochneridine, R_1 = Et; R_2 = OH
51 N_b-Demethylalstogustine, R_1 = H; R_2 = (*R*)-CHOHCH$_3$
52 Alstogustine (N_b-methyl)
53 19-Epialtogustine (N_b-methyl)

54 Wieland-Gumlich aldehyde

Aspidospermatan alkaloids, R = H, R' = alkyl group

55   Condylcarpine , R = H, R' = CHCH$_3$
56   Iagunamine , R = H, R' = CH(OH)CH$_3$

Figure 3: Representative Members of Curan and Aspidospermatan Alkaloids

Strychnos alkaloids belong to the monoterpenoid indole alkaloid incorporating a spiro[pyrrolidine-3,3'-oxindole] associated with morphan scaffold (figure 4). Morphan scaffold is 2-azabicyclo[3.3.1]nonane framework, prominently featured in many complex and biologically active natural products as well as medicinal compounds of significant interest. Indolomorphans are the most advanced scaffold for the synthesis of strychnos class of alkaloids and it is the overall architecture of the corresponding alkaloids.

Figure 4: Structural features of Curan alkaloids.

Our preliminary focus was to construct the morphan skeleton using our *cis*-hexahydroindole scaffold **29** and then installation of the spiro[3,3ʹ-oxindole]nonane framework at the final step of the synthesis of (-)-tubifoline and (-)-tubifolidine.

After having hexahydroindole scaffold **29** in multi-gram scale in hand, it was envisioned that the vinyl sulphone group will be converted into enone functionality by applying dihydroxylation and subsequent hydroxyl group elimination. Furthermore, the enone would undergo 1, 4-addition to provide the piperidine ring **D** through the formation of C15-C20 bond and the ketone group would be the basis for Fisher indolization to provide diverse structures of indole derivatives. Once *N*-alkylation will be done, the intermediate **60** would be ready for the Heck coupling to form 2-azabicyclo[3.3.1]nonane ring. Fisher indolization on aza-[6,5,6]-tricyclic core **61** would supply the required indolenin structures to furnish the corresponding strychnos alkaloids.

Scheme 7: An Overview of synthetic strategy for the synthesis of strychnos class of alkaloids

To affect the quantitative dihydroxylation of electron deficient olefinic double bond of the **29**, we used citric acid with the osmium tetroxide to accelerate the reaction. The hydroxy group was converted to its mesylate using mesyl chloride and the mesylate was removed under basic condition (Li_2CO_3) to afford the crucial enone **59**, which would carry our synthesis in forward.

Scheme 8: Synthesis of Enone **59**.

Reagents and conditions: a) OsO$_4$ (6 mol%, 0.1M solution in tert-butanol), NMO (6 equiv.), citric acid (3 equiv.), tert-butanol:water (2:1), 3 h at 0 ^{o}C and 30 min at rt, 88%; b) i) MsCl (5 equiv.), dry DCM : dry pyridine (3:1), rt, 24 h, ii) Li$_2$CO$_3$ (5 equiv.), LiCl (10 equiv.), dry DMF, reflux, 2 h, 67%.

After having **59** in hand, the crucial task was the selection of the coupling partner tethered with the amine group for the Heck coupling required to form the piperidine ring **D**. The required iodo compound for *N*-alkylation would be the mesylate product of (*Z*)-2-iodobut-2-1-ol which have been derived from the crotonaldehyde. The iodination of crotonaldehyde was done by using iodine in presence of potassium carbonate (K$_2$CO$_3$) and the reduction of the aldehyde **64** by sodium borohydride (NaBH$_4$) gave required (*Z*)-2-iodobut-2-1-ol **65**. The alcohol **65** yielded the mesylated product **66** in 83% in the presence of mesyl chloride and triethyl amine.

63
crotonaldehyde

64
(Z)-2-iodobut-2-enal

65
(Z)-2-iodobut-2-en-1-ol

66
(Z)-2-iodobut-2-en-1-yl methanesulfonate

Scheme 9: Synthesis of iodo compound **66**.

Reagents and conditions:a)I$_2$, K$_2$CO$_3$, DMAP (cat.), 3 h; b) NaBH$_4$ (3 equiv.), MeOH, 0 ^{o}C, 2 h, 54% for two steps; c) MsCl, triethyl amine, DCM, rt, 2 h, 80%.

The *N*-alkylation process commenced with the deprotection of the N-carbamate using trifluroacetic acid (TFA) and the deprotected amine was subjected to the iodo compound **66** in presence of potassium carbonate which gave desired *N*-alkylated product **60**. The reductive Heck condition using palladium acetate in presence of *tetra*-butyl ammonium chloride (TBAC) and sodium formate was effective reaction condition to perform this cyclization in moderate yield. However, proton NMR studies showed that the product was not the desired one, instead

it formed the aza-[6,5,6]-tricyclic core structure **67** with the isomerisation of the olefin of **61** for gaining stability over another isomer **61**.

Scheme 10: Synthesis of Tricyclic intermediate **67**.

Reagents and conditions: a) i) Trifluoroacetic acid (TFA, 5 eq), dry DCM, 0 °C to rt, 5 h, ii) 66 (1.1 eq), K₂CO₃ (5 eq), dry acetonitrile (ACN), rt, 12 h; b) Pd(OAc)₂ (0.1 eq), TBAC (2.5 eq), HCO₂Na (1.6 eq), dry DMF, 80 °C, 3 h, 48% overall yield.

Owing to our sustained interest towards the synthesis of strychnos alkaloids and on careful observation, we envisioned that though the intermediate **112** have lost the opportunity to unravel our actual synthetic goal, but still there is some possibility to utilize the aza-tricyclic intermediate **112** in the synthesis of tubifoline and tubifolidine. According to synthetic plan, the Fisher indolisation product **113** of the tricyclic intermediate **112** would serve tubifoline **8** on reduction of the olefin and the reduction of imine will provide tubifolidine **7**.

Scheme 11: Synthetic plan for the synthesis of tubifoline and tubifolidine.

Chapter 4: Synthetic Studies towards the Total Synthesis of (-)-Stenine and (-)-Tuberos-temonine:

This chapter begins with a brief introduction to stemona class of alkaloids and literature reports for the toal synthesis of (-)-stenine and (-)-tuberostemonine. This chapter also discusses our approach towards the synthesis of (-)-2-oxostenine, (-)-stenine and (-)-tuberostemonine.

Stenine is a stemona class of alkaloid, isolated from Stemona tuberosa of physiologically active stemonaeceous plants, possess structurally novel and unique azepinoindole skeleton. The challenging molecular architectures of the stenine alkaloids have motivated the development of new strategies for the construction of their skeletons.

Retrosynthetic analysis:

From the perspective of retrosynthetic analysis of **19**, as outlined in the scheme **12**, the 2-oxostenine **70** would be the common precursor for both stenine and tuberostemonine. Stenine could be derived by the adjustment of the oxidation level at ring **A** (amide to amine conversion) of 2-oxostenine and the stereoselective attachment of the furan derived γ-butyrolactone at C-3 of the 2-oxostenine would provide tuberostemonine. After having systematic installation of all the substituent over the cyclohexane ring along with the required azepane ring, the intermediate **71** would be ready for the two sequential cyclisation involving lactonization and amidation to produce 2-oxostenine. The sulfonyl enone **72** could be a significant precursor for the stereoselective installation of the ethyl substituent at C-10 and the hydroxyl group at C-11 position by following 1,4-conjugate addition and subsequent quenching by using oxaziridine of the newly generated enolate. Because of the acidity of the allylic proton of the vinyl sulphone, a directed allylic oxidation could be performed on **41** to obtain allylic oxidised product **73** which will direct the functionalization of alpha carbon center of the ketone by the enolate alkylation of the sulfonyl enone **73**.

Scheme 12: Retrosynthetic analysis for (-)-stenine and (-)-tuberostemonine.

The preparation of *cis*-decahydro-1*H*-benzo-[*b*]-azepine **41** was visualized from our ongoing synthetic exploration of the optically pure 7-azabicyclo[2.2.1]heptene scaffold **24**. The stereoselective Michael addition on facially biased Michael acceptor (olefinic sulphone) **24** and subsequent ring opening due to existing ring strain followed by cyclisation forms the desire compound **41** in multi-gram scale.

After having **41** in hand, we proceeded to functionalize the allylic carbon centre to get the desired allylic oxidised product **73**. Pyridinium dichromate (PDC) in presence of *tertiary*-butyl hydroperoxide (TBHP) resulted moderate yield (35-40% conversion) with the recovery of starting material and it provided 85-90% conversion over two cycles with 65-70% yield. We achieved the stereoselective enolate alkylation product **72** using iodoethyl acetate as an

eletrophile and lithium hexamethylsilazide (LiHMDS) as a base. It was very necessary to desulfonylate the sulfonyl enone **72**, which will generate a enone **74** and that could be utilized for the installation of the ethyl and hydroxyl group through a highly stereoselective 1,4-conjugate addition followed by α-hydroxylation of the insitu generated enolate. Desulfonylation of **74** using aluminium amalgam showed excellent conversion with good yield. The conjugate addition was done using the lower order organocuprate (EtCuLi) reagent and got the desired product **75**. Hydroxy group at C-11 of **71** was installed by generating enolate over intermediate **75,** using lithium diisopropyl amide and subsequent oxidation with the Davis's oxaziridine.

Scheme 13: Synthesis of fully substituted cyclohexane ring **71.**

Reagents and conditions: a) PDC (3 equiv.), t-BuOOH (5M, 8 equiv.), dry DCM, 0 °C to rt, 20h, 66% over 3 cycles; b) 1.8 eq LiHMDS, dry THF, 5 eq iodoethylacetate, -78 °C to -20 °C, 57% (88% on brsm); c) 6 eq Al-Hg, THF:H₂O (9:1), -30 °C to -20 °C, 3h, 86%; d) EtMgBr (2 eq), CuI (1 eq), LiBr (10 eq), TMSCl, dry THF, -78 °C. e) EtMgBr (8 eq), CuI (12 eq), LiBr (15), dry THF, -70 °C to -40 °C, 7.5 h, 81%. : f) 5.2 eq LDA, dry THF, 10 eq Hexamethylphosphoramide (HMPA), 2.2 eq ((1R)-(-)-(10-Camphorsulfonyl)oxaziridine)(Davi's oxaziridine), -78 °C to -10 °C, 82%.

We planned to perform intramolecular aldol reaction followed by subsequent tertiary hydroxy group removal to provide the butenolide ring. This was envisioned by the acetylation of the hydroxyl group (-OH to -AcO) using either highly reactive species acetyl chloride or acetic

anhydride. Accordingly, the hydroxy compound **71** was treated with acetic anhydride (Ac$_2$O) in presence of dry pyridine which gave expected acylated product **76**, confirmed by mass and proton NMR analysis. With the hope to have the aldol product in hand, the *O*-acetylated ketone **76** was treated with Potassium hexamethylsilazide (KHMDS) to give intramolecular aldol reaction followed by the addition of excess acetic anhydride (Ac$_2$O) for the subsequent hydroxyl group removal. As expected, we observed the formation of product **78** in HRMS.

Scheme 14: Formation of the butenolide ring by intramolecular aldol condensation.

Reagents and conditions: a) Ac$_2$O:pyridine(dry) (1:1), 48h, 74%, 97% on brsm; b) 0.5 M KHMDS in toluene (1.2 equiv.), excess Ac$_2$O (30 equiv.), dry THF, -80 ºC to -60 ºC, 8 h.

We are now in the stage to purify the aldol condensation followed by dehydration product **78** to confirm the formation of the butenolide ring.

In summary, an effective synthetic route have been developed for the synthesis of cis-hexahydroindoles, cis-octahydroquinolines and cis-octahydrobenzo[b]azepine embedded with a versatile functionality (vinyl sulphone) for further functionalization towards the synthesis of strychnos and stemona class of alkaloids.

Chapter 1: 2-azabicyclo[*m.n*.0]alkane ring systems and their importance in the natural product synthesis.

1.1. Introduction:

A molecular scaffold present in the natural product provides basic shape, rigidity, or flexibility of a molecule and their three dimensional spatial arrangement of various substituents or appendages promotes molecular interactions with diverse biological targets. Therefore, it has become a valuable basis in the field of medicinal chemistry and drug discovery.[1] [*m.n.*0]-Bicyclo-2-azaalkane scaffolds are embedded in various biologically important natural products frameworks and their derivatives displaying potent diverse pharmacological and physiological properties.

These frameworks are well known and most popular in natural products having 2-azabicyclo [3.4.0]nonane (octahydroindole), 2-azabicyclo[4.4.0]decane (decahydroquinoline) and 2-azabicyclo[5.4.0]undecane (decahydro-1*H*-benzo[b]azepine) rings (Fig 1). These three basic scaffolds (i.e. **1**, **2** and **3**) are present in biologically important natural products such as strychnos,[2] stemona,[3] aspidosperma,[4] amaryllidaceae,[5] lycopodium,[6] lepadin[7] and myrioneurinol[8] class of alkaloids. The stereochemical arrangements of these alkaloids are very important to exhibit its biological activity. Although, both *cis-* and *trans-* stereochemistry of the 2-azabicyclic ring junction is found in these alkaloids, we have focussed our attention to explore alkaloids displaying *cis*-2-azabicyclic scaffolds.

Figure 1: Structures of the most abundant 2-azabicyclo[*m.n*.0]alkane ring system (*m* = 3, 4, 5 and *n* = 4.) including their alternate IUPAC nomenclature related to the both natural products synthesis and drug discovery.

Octahydroindole skeleton is present in strychnos, amaryllidaceae, aspidosperma, and erythrina and stemona class of alkaloids. Antimicrobial, antitumor or anticancer, cytotoxic, muscle relaxant and hypotensive activities are known for strychnos alkaloids.[9] Amaryllidaceae alkaloids have DNA binding properties, antitumor, anti-viral, antifungal, and insect antifeedant activity.[10] Aspidosperma species have been commonly used in folk medicine as potential antimalarial agents, antileishmaniasis; anti-inflammatory for uterus and ovary disorder. It has also been found effective as contraceptive agents, anti-diabetes and for treating stomach disorders, anti-cancer and in fever and rheumatism.[11] Erythrina alkaloids erysotramidine, *β*-erythroidine, and 3-demethoxyerythratidinone and cocculolidine have been widely used in folk medicine. These are known to produce curare-like hypnotic effects and possess general CNS activity. More specific pharmacological effects associated with members of this class of alkaloid family include sedative, hypotensive and neuromuscular blocking activities.[12] (+)-Ibophyllidine, (+)-desethylibophyllidine have antitumor activities.[13]

Similarly hydroindole is a privileged scaffold found in both naturally occuring alkaloids as well as in the marketed drugs. These include aeruginosine 298-A,[14] mesembrine,[15] daphniyunine D,[16] melotenine A,[17] pancracine,[18] stenine,[19] albomaculine,[20] epicoccin G,[21] tubifoline,[22] tabersonine,[23] lycorine[24] and a number of pharmaceutical products such as microcin SF608,[25] U93385,[26] S17092,[27] perindopril.[28] Mavoglurant[29] is under active development by Novartis for the treatment of Fragile X Syndrome (phase II-III), Parkinson's disease (phase II) and Huntington's disease (phase II). Octahydroindoles are also potentially useful as organocatalysts and have been used as proline analogue. [30] Many octahydroindole derivatives have been used as chiral ligands or catalysts.[31]

Figure 2: Octahydroindole motif in diverse nitrogen-containing heterocycles.

The decahydroquinoline ring system is present in many naturally occurring biologically active alkaloids such as *cis*-phlegmarine,[32] lepadin,[33] myrioneuron[34] and lycopodium.[35] These alkaloids possess very important biological activities for wide range of therapeutic applications including anticancer, neuroprotective (e.g. Alzheimer's disease), analgesic and immunosuppressive.[36]

The alkaloids related to the decahydro-1*H*-benzoazepine architecture comprises of stemona alkaloids[3] such as stenine, [37, 19b] tuberostemonine, [38] neostenine, [39] neotuberostemonine.[40] Iboga alkaloids ibogamine[41] and the lycopodium alkaloid fawcettimine[42] also contain decahydro-1*H*-benzoazepine ring. Stemona alkaloids have been used for the treatments of respiratory ailments and also it is associated with insecticidal, antihelmintic, antitussive and various neurochemical effects.[3]

The profound bioactivity, synthetically challenging unique structural features and low natural abundance of these alkaloids have attracted considerable attention of synthetic organic chemist to synthesize these alkaloids in multigram scale. For the synthesis of these alkaloids, large scale synthesis of 2-azabicyclic skeleton is required. More important task is the asymmetric construction and proper stereochemical installation of the 2-azabicyclic rings embedded in the polycyclic structures to accomplish the corresponding total syntheses of the alkaloids which elicited synthetically very useful strategies towards the desired target. The forthcoming section would describe reported synthetic strategies to make 2-azabicyclo[*m.n*.0]alkane scaffolds.

1.1a. Reported synthetic strategies for the construction of 2-azabicyclo[*m.n*.0]alkane ring systems:

1.1a.1. *cis*-hexa and *octa*-hydroindoles:

Wipf et al. have synthesized hexahydroindoles with high enantio- and diastereoselectivity in a single step from L-tyrosine or its derivatives.[43] Formation of hydroindole **45** was effected directly by tyrosine oxidation using hypervalent iodine reagent (iodobenzene diacetate) followed by methanolysis of the in situ formed spirolactone. This group has shown the potentiality of the intermediate **45** in pyrrolidine based alkaloid synthesis with a specific application for the first asymmetric synthesis of (-)-stenine.[44]

Scheme 1: Phenolic oxidation of tyrosine followed by diastereoselective end-group-differentiating cyclisation between amine and enone.

The reaction was very much dependent on the nature of the protective group **R** and also on the scale of the reaction. The high diastereoselective cyclisation was promoted due to destabilizing steric interactions in conformers **43**, especially A [1,3]-strain between the amide oxygen and the methyl ester (E) substituent. The ester group in the conformer **43**, situated just below the dienone π system, prevented the required interaction between the dienone moiety and the amide bond for cyclisation.

Bäckvall has prepared hexahydroindoles by palladium-catalyzed oxidation of conjugated cyclic dienes; two nucleophiles were added in a regio- and stereospecific manner across the diene.[45] Carboxylates, alcohols, and halides were used as nucleophiles. Palladium catalysed reaction of amido diene **47** in the presence of an acid with benzoquinone being used as an electron-transfer catalyst or oxidant afforded *cis*-oxyamidation product **48**. But the reaction of **47** in the absence of lithium chloride gave **49** via a *trans*-1,4-oxyamidation. This dual stereocontrol was achieved by the chloride anion which blocks the coordination of acetate anion in the palladium complex of the catalytic intermediate, thus suppressing the *cis*-migration of the acetate anion. As a result intermediate **50** would react with only external acetate anion to give product **48** whereas intermediate **51** would produce **49** via a *cis*- migration of the acetate anion.

Scheme 2: Palladium –Catalyzed Stereocontrolled Intramolecular 1,4-Additions of amines to Cyclic 1,3-Dienes.

Yeh also achieved a stereoselective synthesis of hexahydroindoles **53** as a single diastereoisomer via a gold(I)-catalyzed intramolecular 1,4-hydroamination of cyclic 1,3-dienes **52**.[46]

n = 1, Ar = phenyl	88%	**53a**
n = 1, Ar = 4-methylphenyl	88%	**53b**
n = 1, Ar = 4-methoxyphenyl	85%	**53c**
n = 1, Ar = 4-fluorophenyl	80%	**53d**
n = 1, Ar = 2,4,6-trimethylphenyl	0%	**53e**

Scheme 3: Intramolecular gold(I)-catalyzed hydroamination of cyclohexa-1,3-dienes.

The reactive catalytic species Ph₃PAuOTf (generated in situ from Ph₃PAuCl and AgOTf) coordinats to the double bond adjacent to the tethered arylsulfonamide and forms an η^2-alkene gold(I) complex **52b.** Reaction of arylsulfonamide moiety from the opposite face of the gold center at the terminal position of the diene, facilitated the generation of η^1-allylgold intermediate **52c** with the newly formed carbon-nitrogen bond. The *cis*-relative stereochemistry at the ring junction was fixed by the tethered arylsulfonamide moiety which
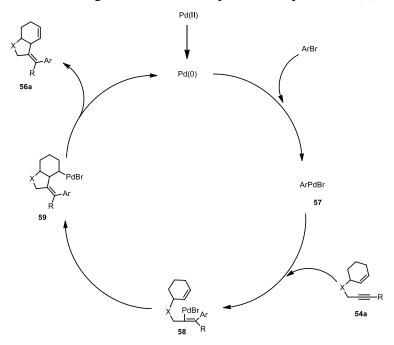
was aligned with the face of the cyclic diene. The triflate assisted allylic isomerisation of **52c** to **52d** and its tautomerisation to **52e** followed by proton transfer from the NH or OH to the carbon atom finally regenerated the active catalytic species from the intermediate **52f** and produced hexahydroindole derivative **53a.**

Scheme 4: A plausible reaction pathway of gold(I)-catalysed intramolecular hydroamination of cyclohexa-1,3-dienes.

Hu, Wang et al. have developed an efficient synthetic protocol for the synthesis of functionalized hexahydroindoles using palladium-catalysed domino coupling/cyclization of 1,6-enynes and aryl halides.[47] 1,6-Enynes reacted very smoothly with the substituted aryl bromides in the presence of 2 mol% palladium acetate as the catalyst, 4 mol% triphenyl phosphine as a ligand and tributylamine as a base, producing corresponding functionalized hexahydroindole derivatives.

Schem 5: Synthesis of hexahydroindoles by palladium –catalysed domino coupling/cyclisation reaction

According to the experimental results obtained by the authors, they proposed a probable reaction mechanism which is described in Scheme 6. The oxidative addition of the aryl bromide to the palladium (0) produced arylpalladium species ArPdBr **57** which inserted in the triple bond of the 1,6-enynes **54a**. The *syn*-carbopalladation of the arylpalladium species **57** with **54a** generated alkenylpalladium intermediate **58** which involved further carbopalladation reaction with the tethered olefin to afford an advanced intermediate **59**. Finally the *syn*-elimination of **59** produced desired product **56a** along with the HPdBr species which would react with the base, used in the reaction, to regenerate the active palladium species Pd (0).

Scheme 6: Proposed reaction mechanism of the reaction.

Oppolzer et al. synthesized hexahydroindole scaffold employing intramolecular Diels-Alder reaction that allows an application of linear precursor **60** to provide a 2-azabicyclic derivative **61** with two stereogenic centers in one cycloaddition step.[48]

Scheme7: Intramolecular Diels-Alder strategy to access hydroindole scaffolds.

Vincent[49a] and Carlos et al.[49b, 49c] have developed a method to synthesize octahydroindole-2-carboxylic acid by the hydrogenation of commercially available (*S*)-indoline-2-carboxylic acid **62** to afford diastereomeric (*S,S,S*)-**63** and (*S,R,R*)-**64** in 90:10 ratio which was purified by after recrystallization. Vincent has used rhodium as a catalyst wheras Carlos used platinum oxide as hydrogenation catalyst at atmospheric pressure. Particularly (*S,S,S*)-**63** isomer has been used as a surrogate of proline and phenylalanine in bradykinin, a linear nonapeptide hormone involved in pain and inflammation.[50] The octahydroindole-2-carboxylic acid motif is present in marine aeruginosins with potent antithrombotic properties.[14, 49d]

Scheme 8: Hydrogenation of octahydroindole-2-carboxylic acid.

Hanessian et al. have synthesized 6-substituted octahydroindole and hexahydroindole-2-carboxylic acid methyl esters by tandem Friedel-Crafts carbocyclization of nonactivated tethered alkenes or alkynes with *N*-Acyloxyiminium ion in an intramolecular fashion.[51] The five membered N-Boc acyliminium ions derived from L-pyroglutamic acid undergoes Lewis acid mediated (BF$_3$.O$_2$Et) tandem Friedel-Crafts carbocyclisation with tethered 4-butenyl and 4-butynyl to give stereodefined desired products **66** and **68** respectively.

Ar	Temperature	Yield
	-20 °C	67%
	-15 °C	58%
	-78 °C	70%
	-35 °C	50%

Scheme 9: Tandem Azonia-Prins/Friedel-Crafts reaction of **65** and **67** with a variety of arenes as a solvent.

Landais et al. devised a strategy to construct 2-azabicyclo[4.3.0]nonane scaffold by Birch reductive alkylation-desymmetrization (BRAD) sequence.[52] Desymmetrization of cyclohexa-2,5-dienes through a diastereoselctive proton-hydroamination cascade produced hexahydroindole derivatives.

Scheme 10: BRAD strategy to access 2-azabicyclo[4.3.0]nonane scaffolds.

According to the reaction mechanism, the reaction did not proceed through a direct hydroamination of one of the diastereotopic olefins but involved a distereoselective protonation of the pentadienyl anion **72** and produced intermediate **75** (more favourable than protonation at C6). This would explain the presence of methoxy group in the chiral auxiliary which was involved to form a tighter chelate with lithium, thus, promoting the stereocontrolled protonation at C2. The resulting lithium amide added selectively onto the 1,3-diene at C6 to afford an allylic anion **66.** The hydroamination intermediate **66** could protonat at C3 predominantly to afford **71a** or **71b.**

Scheme 11: Reaction mechanism of the diastereoselective protonation-hydroamination cascade.

Bonjoch and Bradshaw et al. reported a straightforward asymmetric synthesis of octahydroindoles on the basis of an organocatalyzed Michael addition followed by a tandem Robinson-aza-Michael double cyclization catalysed by PS-BEMP.[53] The strategy promoted the construction of the substituted octahydroindoles with four stereogenic centers, excellent enantioselectivities (up to 95%) and complete diastereoselective control in a single pot operation. At the start of the reaction, the dicarbonyl compound **78** was first reacted with the crotonaldehyde **77** through Michael addition followed by aldol condensation produced cyclohexenone, necessary for the aza-Michael addition. Finally the intramolecular aza-Michael addition to the cyclohexenone moiety gave **80**.

R^1 = Me, heptyl, Ph, 4-OMeC$_6$H$_4$, 4-ClC$_6$H$_4$,
R^2 = H, Bn.

92-95% ee
> 99% dr

Reaction Condition: 1) **79** (10 mol%), LiOAc (0.5 equiv), toluene, 0 °C, 24h; 2) Pd/C, H$_2$, i-PrOH; 3) PS-BEMP, (1 equiv), i-PrOH, rt, 72h

Scheme 12: An organocatalysis-initiated tandem Robinson-aza Michael reaction leading to octahydroindoles.

A C(*sp3*)-H activation protocol has been implemented to construct hexahydroindole framework for the synthesis of aeruginosin marine natural products.[54]

Scheme 13: C(*sp3*)-H activation to access hexahydroindoles.

1.1a.2. *cis*-decahydroquinoline (*cis*-DHQ):

Frogs of the neutropical family Dendrobatidae are the remarkable source of DHQ alkaloids. The most representative decahydroquinoline alkaloids is *cis*-195A (formerly called pumiliotoxin C).[55] There were no conclusive biosynthetic pathways for the origin of this class of alkaloids in frogs. In 1979 Winterfeldt proposed that a polyketide triketone **83** undergoes aldol condensation to produce cyclohexanone **84** and subsequent stepwise double condensation with ammonia followed by reduction forms the DHQ skeleton which propagates in the synthesis of pumilitoxin C **85**.[56] This biosynthetic proposal for the formation of *cis*-DHQ system has been substantiated by the chemical synthesis in 2008 by Amat and Joan Bosch.

Me

Scheme 14: Biosynthetic proposal for the synthesis of *cis*-decahydroquinoline class of alkaloids.

An enatioselective dynamic kinetic resolution and desymmetrization process that involved the cyclocondensation of chiral amino alcohols with racemic, prochiral δ-oxodiesters was developed to prepare enantiopure polysubstituted piperidines.[57] In order to explore the synthetic potential of this method, the *cis*-decahydroquinoline scaffold was accessed by performing cyclocondensation (in toluene at reflux in the presence of isobutyric acid) of (*R*)-phenylglycinol **87** with cyclohexanone-based δ-keto diesters **86** (4:1 mixture of *cis/trans* isomers), which provided oxazolidine intermediate **89** and **90** instead of four (R = H) or eight (R = substituent) diastereomeric mixtures. The process of desymmetrization, produced corresponding tricyclic lactam **91** and **92** from which chiral auxiliary removal provided *cis*-decahydroqinoline. Reduction of the oxazolidine ring generated two diastereoisomers **93** and **94**, separation of the diastereoisomer followed by the removal of the (*R*)-phenylglycinol derived chiral auxiliary afforded corresponding enantiopure *cis*-decahydroquinoline **95** and **96** respectively.

Scheme 15: Enantio-and diastereoconvergent cyclocondensation reactions for the synthesis of enantiopure *cis*-decahydroquinolines.

Over the last three decades diverse array of DHQ skeleton have been isolated which has generated a significant interest to organic synthetic chemist towards the syntheses of this class of alkaloids. Around 80 publications have been dedicated to the syntheses of pumiliotoxin C alone.[58] We will analyse here the synthetic approaches for the lepadin class of alkaloids emphasizing strategic disconnections and the key steps used for the stereoselective assembly of the DHQ ring system. The majority of the syntheses were based on the carbon-carbon bond formation rather than carbon-nitrogen bond formation to construct the 2-azabicyclic ring. It

was noticed that there is a strategic deficiency for the direct stereoselective formation of the DHQ ring via carbon-nitrogen bond formation. A wide range of carbon-carbon bond formation approaches was developed for the syntheses of lepadin class of alkaloids including aldol cyclization, [59] xanthate radical cyclization, [60] alkylation, [61] ene-yne-ene ring closing metathesis[62] and ring opening-ring closing metathesis (ROM, RCM).[63] Aza-cycloaddition was employed for the lepadin synthesis which represented the example for the direct formation of the DHQ ring via carbon-nitrogen bond formation.[64, 65]

Scheme 16: Synthetic approaches for the construction of DHQ ring system in the lepadin alkaloids.

Recently, it was reported two directional synthetic protocol and tandem cyclisation for the construction of *cis*-decahydroquinoline ring system.[66] Two directional syntheses are capable

of elevating the rapidity of the generation of molecular complexity by simultaneously functionalizing each molecule twice per reaction.

Scheme 17: Two directional synthetic approach to construct *cis*-DHQ ring system.

The key features of this strategy were the use of the two-directional synthesis for the preparation of the symmetrical diketoester **110** followed by tandem cyclization using benzyl amine (promoted by titanium chloride) to afford bicyclic intermediate **109**. Hydrogenation of the bicyclic intermediate **109** afforded DHQ ring system **108**. The two-directional cross-metathesis enabled to convert **112** directly into the diketoester **110**. To make more cost effective synthesis of the diketoester **110**, authors have executed a two-step approach involving a two-directional oxidative cleavage of the olefins followed by a two-directional Wittig-olefination of the corresponding aldehyde which produced diketoester **110**. The ketone **112** was prepared in multi-gram scale by reacting 5-bromo-1-pentene **111** with ethyl formate followed by PCC mediated oxidation of the resulting alcohol.
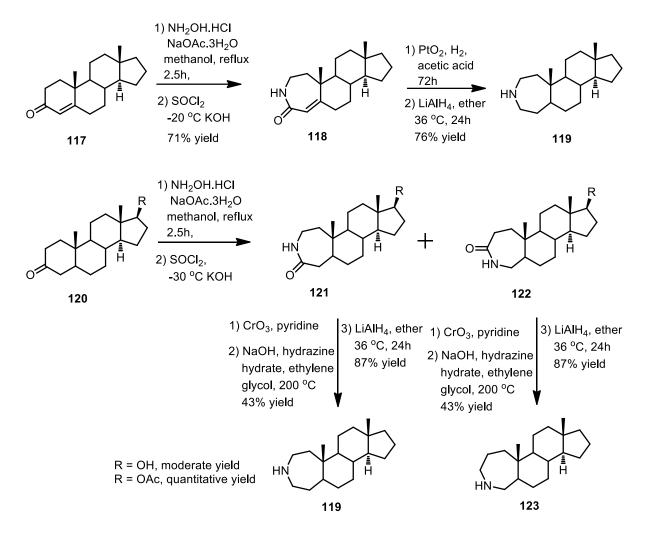
Scheme 18: Two-directional synthesis and tandem cyclization towards functionalized *cis*-DHQ ring system.

Recently Bradshaw and Bonjoch reported a one pot preparation of *cis*-decahydroquinoline ring system by organocatalyzed Michael addition reaction followed by a domino Robinson annulation/intramolecular aza-Michael reaction cascade, promoted by a base (lithium hydroxide) which led to enantiopure *cis*-decahydroquinoline.[67] The dicarbonyl compound **114** was involved in the first Michael addition to the crotonaldehyde **113** which generated the Robinson annulated product **115** via aldol condensation. The aldol condensation provided cyclohexanone intermediate **115** for the neccessary aza-Michael addition giving rise *cis*-decahydroquinoline derivative **116**.

Reaction Condition:

1) **79** (20 mol%), LiOAc (0.5 equiv),toluene, 0 °C, 24h;

2) LiOH.H$_2$O (1 equiv.), i-PrOH, H$_2$O (10 equiv.), 24h

85% ee
> 99%ee after recrystallization

Scheme 19: Organocatalyzed Robinson annulation/ aza-Michael reaction to access *cis*-decahydroquinoline ring system.

1.1a.3. *cis*-decahydro-[1*H*]-benzo[*b*]azepine ring:

The Beckmann rearrangement has often been employed to transform oximes into an amide and the conversion of cyclohexanone oxime into ε-caprolactam.[68] This reaction is used for the construction of *cis*-octahydro-[1*H*]-benzo[*b*]azepine-2(3*H*)-one **119** ring from octahydronaphthalen-1(2*H*)-one **117**.[69] This approach is used to prepare aza-steroids by the Beckmann rearrangement of the **120** to yield *17β*-hydroxy-ε-lactams **121** and **122** followed by reduction.

Scheme 20: Application of Beckmann rearrangement in the synthesis of aza-steroids.

During the synthesis of (-)-ibogamine, construction of the *cis*-decahydro-[1*H*]benzo[*b*]azepine ring was constructed efficiently employing Beckmann rearrangement of the *cis*-octahydronaphthalen-1(2*H*)-one derivative **124** to obtain 7-membered lactam **126** moiety.[70]

Scheme 21: Efficient construction of *cis*-decahydro-[1*H*]-benzo[*b*]azepine skeleton by Beckmann rearrangement.
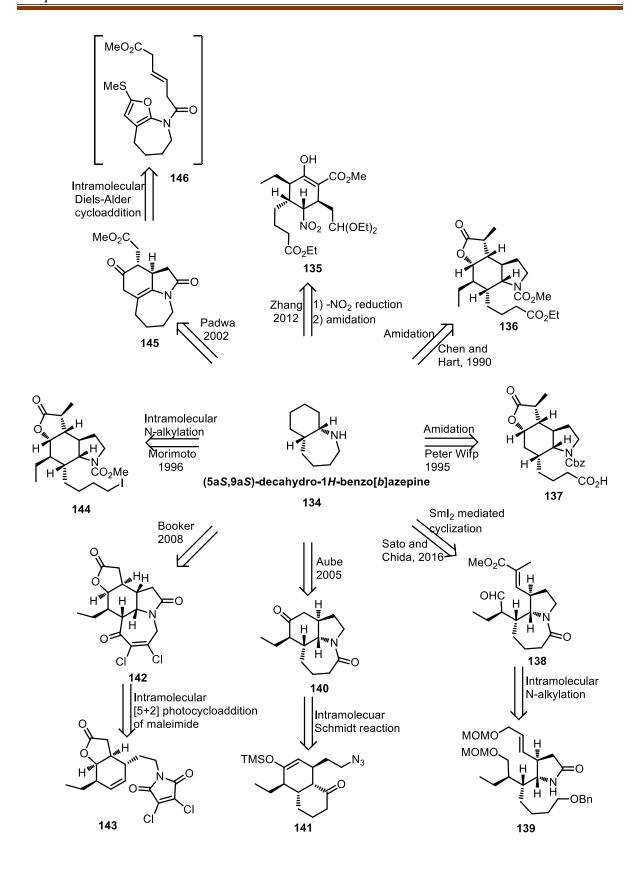
Jung et al. applied Beckmann rearrangement strategy using **129** to construct *cis*-decahydro-[1*H*]-benzo[*b*]azepine skeleton **130** towards the synthesis of stenine.[71]

Scheme 22: Beckmann rearrangement provided 7-membered *cis*-lactam ring towards the synthesis of stenine.

cis-Decahydro-[1*H*]-benzo[*b*]azepine skeleton is also prepared by intramolecular reductive amination for the synthesis of bicyclic alkaloid analogue **132** and **133**.[72]

Scheme 23: Intramolecular reductive amination for the construction of *cis*-decahydro-[1*H*]-benzo[*b*]azepine derivatives.

In the context of the total synthesis of the stemona alkaloids, the organic chemist very often have used different strategies to build 2-azabicyclic azepine ring efficiently with proper stereoselectivity. In many approaches of the synthesis of stenine, the azepine rings have been constructed at late stage using intramolecular *N*-alkylation[39a] and amidation[44, 74, 19b] strategies. However, other excellent strategies in this area include Padwa's intramolecular Diels-Alder cycloaddition[75] and Booker's intramolecular [5+2] photocycloaddition of maleimide.[39b, 40] Jeffry Aube applied intramolecular Schmidt reaction to assemble the *cis*-decahydro-[1*H*]-benzo[*b*]azepine core framework for the synthesis efficient synthesis of (-)-stenine.[19a, 37a]

Scheme 24: Synthetic strategies for the construction of *cis*-decahydro-[1*H*]-benzo[*b*]azepine ring in the synthesis of stenine.

1.1a.4. Summary

The above survey of literature highlights the significance of these three 2-azabicyclic ring systems in the natural products. The synthesis of these core ring systems became the prime tasks to execute the total synthesis of the corresponding alkaloids. A few recent reports on the preparation of hexahydroindole and octahydroindole scaffolds was used to implement the total synthesis of the corresponding natural products.

Several approaches are there to construct *cis*-DHQ ring system for the synthesis of lepadin class of alkaloids. There are very few approaches to synthesize *cis*-DHQ ring for the purpose of the total synthesis of the other corresponding alkaloids and also it lacks a highly stereoselective, enantiopure method for the synthesis of *cis*-DHQ ring system.

The above documented literature reports on the synthesis of *cis*-decahydro-[1*H*]-benzo[*b*]azepine ring demonstrate that there are no any general synthetic strategy or stereoselective method except Beckmann rearrangement to construct the *cis*-decahydro-[1*H*]-benzo[*b*]azepine. Most of the reports contain the formation of *cis*-decahydro-[1*H*]-benzo[*b*]azepine ring at the very late stage of the synthesis involving N-alkylation, amidation strategies and also intramolecular Diels-Alder cycloaddition to make the basic core framework of the stenine, neostenine including *cis*-fused 7-membered azepine ring.

1.2. Objective of the present study:

Considering discussion, it is apparent that there is a need to develop a more general synthetic route towards the synthesis of 2-azabicyclic ring systems which can make this ring system in high diastereo and enantioselectivity in multi-gram scale. Furthermore, it should have structural characteristics to functionalize for making diverse array of polycyclic natural product-based scaffolds. The following chapter would describe our synthetic planning and successful general synthetic route for the costruction of all the three 2-azabicyclic ring systems using a common intermediate.

1.3. References:

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Chapter 2: Development of a General Synthetic Route to Access 2-Azabicyclo[*m.n.*0]alkane Ring Systems.

2.1. Introduction:

Designing a synthetic strategy, which would be step economical and efficient is the most important factor for the success of any synthetic campaign. Towards this end, synthetic approaches of using just one common synthetic intermediate for readily synthesizing an array of diverse natural products is progressively gaining ground and is called 'collective total synthesis'.[1] [6, 5], [6, 6] and [6, 7]-2-Azabicyclic framework offers an excellent platform for systematic scaffolding towards the synthesis of diverse alkaloids. Although, numerous approaches are developed for the construction of these bicyclic rings, there is no general strategy available to construct such kind of azabicyclic scaffolds. In the context of the total synthesis of some alkaloids having these scaffolds, we evaluated to develop a rational strategy to overcome the synthetic challenges arising out due to the complexity of these natural products. To keep this in mind, a common precursor or intermediate was visualised following a well designed chemical reaction (Fig. 1).

(3a*S*,7a*S*)-octahydro-1*H*-indole

2-Azabicyclo[3.4.0]nonane

1a

(4a*S*,8a*S*)-decahydroquinoline

2-Azabicyclo[4.4.0]decane

1b

inexpensive starting material

Common reactive intermediate

(5a*R*,9a*R*)-decahydro-2H-benzo[b]azepine(*5a*S*,*9a*S*)-decahydro-1H-benzo[b]azepine

2-Azabicyclo[5.4.0]undecane

1c

Figure 1: Conceptual overview of using a common intermediate to access 2-azabicyclic skeleton

To demonstrate the synthetic potentiality of our approach, we have choosen to explore the wide range of functionalisaion and highly stereoselective ring opening of the facially biased, strained bridge-azabicyclic ring **2** (Scheme 1)[2] followed by cyclisation.

Scheme 1: Bridge-azabicyclic ring opening followed by cyclisation strategy.

Bridge-azabicyclic intermediate offers a strategic advantage for the systematic variation of structural elements according to the essential motif and the size of the *N*-based heterocycles present in the natural products, and also on the periphery of *N*-based ring heterocycles. Functionalization of the reactive centres of the bridge-bicyclic intermediate uses some elements of reaction control that could be standard in synthetic purpose, but owing to the specific shape and strained nature of the system, strategically bond making, bond breaking with regio- and stereocontrol are also feasible.

The most electrophilic centre of the embedded Michael acceptor in the ring would be used for the proper functionalization according to the desire motif present in the natural products or natural product based scaffolds. The specific shapes of the ring persuade highly stereoselective Michael addition preferring the *exo*-attack over sterically hindered *endo*-attack. The existing ring strain will promote the Michael adduct to release its strain by shifting the olefinic double bond and the ring opening product would be ready for the necessary cyclisation to provide a diverse array of fused bicyclic heterocycles.[3] We planned to use the Grignard reagent as a nucleophilic source in the presence of copper salt to make it a soft nucleophile and the ring size would be decided by the corresponding chain length of the Grignard reagent.

Scheme 2: Divergent synthetic route for the construction of *cis*-2-azabicyclic scaffolds.

2.2. Result and Discussions:

2.2A. Synthesis of common intermediate (1*R*,4*S*)-*tert*-butyl 2-(phenylsulfonyl)-7-azabicyclo[2 .2.1]hept-2-ene-7-carboxylate:

The most important aspect of our approach is the smooth and efficient supply of common intermediate **2** in multi-gram scale. To explore the synthetic versatility of 7-azabicyclo[2.2.1]hept-2-en **2,** it is important to develop first a scalable synthetic route for both racemic as well as in enanatiomeric form, which could execute of our synthetic programme very efficiently for the synthesis of diverse classes of natural products. Synthesis starts from (1*S*,4*R*)-*tert*-butyl 2-oxo-3-(phenylsulfonyl)-7-azabicyclo[2. 2.1]heptane-7-carboxylate **12** which is enabled to prepare in multi-gram-scale.[4] The reduction of the ketone followed by the elimination of the hydroxyl group would provide the primary scaffold **2**. The reduction was carried out by using lithiumborohydride (LiBH$_4$) in THF at -78 °C, produced corresponding alcohol **13** in excellent yield and the mesylation was done quantitatively by the treatment of mesyl chloride in the presence of pyridine as a solvent. The mesylate was eliminated by

refluxing in dichloromethane using pyridine as a base to afford the 7-azabicyclo[2.2.1]hept-2-ene **2**.[2]

Scheme 3: Synthesis of the common intermediate **2**.

The racemic form of **2** was synthesized on multi-gram scale in three steps (First two steps were performed on 200g scale) from the commercially available trimethylsilyl acetylene.[5, 6, 7]

Scheme 4: Synthesis of the common intermediate **2** in racemic form.

As the racemic form of **2** was available on multi-gram scale, we proceeded with the racemic starting material (common intermediate **2**) for our preliminary studies. The key step developed in this approach is the highly stereoselective conjugate addition of Grignard reagent to the bicyclic ring in presence of Cu(II) salt followed by in situ ring opening of the Michael adduct. After a very successful Michael addition using a Grignard reagent, the next step is to evaluate the efficiency of the cyclization through direct N-alkylation or reductive amination/ amidation

strategy to afford desired azabicyclic scaffold. In most of the cases N-alkylation strategy proved to be the straightforward protocol for the cyclization. Once the basic parameters were fixed, the modularity and generality of this process would be evaluated by varying the carbon chain length in the Grignard reagent according to the required ring size.

2.2B. Synthesis of hydroindole scaffold:

In order to establish stereoselective Michael addition step in the synthetic route, vinyl magnesium bromide was used as a Grignard reagent to react with the primary scaffold 7-azabicyclo[2.2.1]hept-2-ene **2**. Reaction in the presence of cupric cyanide (CuCN) at -30 °C using the mixture of dry tetrahydrofuran and dry ether as a solvent (1:1), afforded the Michael addition followed by in situ ring opening to produce **20**.

Scheme 4: Synthesis of hexahydroindole scaffold (**22**).

Reagents and conditions: a) Vinyl magnesium bromide(1.8 eq)solution in dry THF (1.0 M), CuCN(1 eq), Dry THF + Ether (1:1), -30 °C, 4 h, 41%; b) i) 0.5M 9-BBN(1.5eq), 0 °C to rt, 12 h ii) 3M NaOAc, H_2O_2, 0 °C to rt, 5 h, 62% (91% on brsm); c) mesyl chloride (MsCl), DMAP, Et_3N (5eq), 0 °C to rt, 4 h, 76%.

Hydroboration[8] of terminal olefin helped to install alcohol moiet at the terminal end of **20**, which was essential for the crucial cyclisation to obtain fused bicyclic compound **22**. Hydroboration was done by using 0.5M 9-BBN to obtain selective addition of boron hydride on the more reactive terminal olefin rather than on the electron deficient olefin. On quenching with hydrogen peroxide in the presence of mild base, sodium acetate produced the corresponding terminal alcohol in 62% yield. The alcohol **21** was then subjected to the mesylation using mesyl chloride in the presence of triethyl amine and catalytic amount of N, N-dimethyl aminopyridine. It was very pleasing to note that the cyclisation occurred in mesylation condition through the nucleophilic substitution of *O*-mesylate group by the N-

carbamate amine and obtained the 2-azabicyclo[3.4.0]nonane skeleton (octahydroindole ring) embedded with electron-deficient olefin **22**. Therefore, the olefin would direct for further functionalisation of all the carbon centre of the carbocyclic ring.

One of the key problems, we have encountered that although the synthetic route was short but the moderate yield (41%) of the Michael addition step using vinyl magnesium bromide has to be optimised to afford hexahydroindole product **22** in multi-gram quantity and the hydroboration was also not very efficient for scaling up the reaction. Meanwhile we used allyl magnesium bromide for executing the Michael addition to evaluate the generality of this synthetic protocol, and we observed an excellent yield (88%) of the Michael addition on our common intermediate **2** which could give cyclised product by shortening one carbon atom followed by reductive amination sequence. The oxidative cleavage would provide the corresponding aldehyde with one carbon less which would go for reductive amination with the tethered N-carbamate amine to afford the desire hexahydroindole ring **22**. The oxidative cleavage was done by using osmium tetroxide (cat. amount) and sodium periodate in the presence of 2,6-lutidine, which produced the required aldehyde almost in quantitative yield, used for further step without any purification. Reductive amination of aldehyde **24** was carried out with excellent yield (91%) by the treatment of sodiumcyanoborohydride in presence of acetic acid in THF.

Scheme 5: Scalable synthetic route for the synthesis of hexahydroindole ring system (**22**).

Reagents and conditions: a) Allyl magnesium bromide(1.8 eq), CuCN(1 eq), Dry THF + Ether (1:1), -30 ⁰C, 4 h, 93%; b) OsO₄ (0.01 eq), NaIO₄ (4eq), 2,6-lutidine(2 eq), dioxane:water(3:1),rt,2 h; c) NaCNBH₃ (2 eq), THF:AcOH(9:1), 20 h, 91%.

2.2C. Synthesis of *cis*-octahydroquinoline ring system:

With proof of the concept we planned to explore the potential of the synthetic intermediate **2** in the synthesis of other 2-azabicyclic ring system employing the same synthetic sequence. The most basic modification of the previously described synthetic route to hexahydroindoles would

be to vary the length of the carbon chain in the Grignard reagent to give the corresponding 2-azabicyclic product. By lengthening the one carbon atom in the Grignard reagent, it should be possible to obtain the decahydroquinoline ring system embedded with an olefinic sulfone moiety. After having ring opening product **23,** we have followed the same reaction pathway involving hydroboration and mesylation followed by cyclization with the tether Boc protected amine to access *cis*-fused bicyclic ring. However, **25** failed to provide any cyclized product **26** under the mesylation condition. In order to increase the nucleophilicity of the Boc protected amine for the crucial cyclization, the corresponding mesylate of the alcohol **25** was subjected to the strong basic condition (potassium tertiary butoxide) and observed the double bond isomerisation of the vinyl sulphone. It is evident that the strong basic condition is responsible for the double bond isomerization of the vinyl sulphone. Therefore, it is manifested that the cyclization should be done either in mild basic condition or by reductive amination strategy converting the alcohol into aldehyde. However, the reaction did not proceed under mild basic condition (Et$_3$N, K$_2$CO$_3$, and Cs$_2$CO$_3$) and starting material was recovered. It was also very obvious that the nucleophilicity of the nitrogen has reduced due to the presence of the *tert*-butyl carbamate moiety.

We planned to follow deprotection-*N*-cyclization-protection sequence to get the best yield of the cyclized product without any column purification. The mesylate was subjected to *N*-Boc deprotection by in situ generated trimethylsilyliodide (TMSI)[9] followed by *N*-cyclization using ceasium carbonate as a mild base, which gave the crucial cyclized product. The cyclized amine was protected as a *N*-carbamate using Boc$_2$O in presence of triethyl amine to afford the *cis*-decahydroquinoline ring **26** embedded with the olefinic sulphone functionality.

Scheme 6: Synthesis of *cis*-octahydroquinoline ring system (**28**).

Reagents and conditions: a) Allyl magnesium bromide(1.8 eq), CuCN(1 eq), Dry THF + Ether (1:1), -30 ºC, 4 h, 93%; b) i) 0.5M 9-BBN in THF (1.5eq), Dry THF 0 ºC to rt, 12 h ii) 3M NaOAc, H$_2$O$_2$, 0 ºC to rt, 5 h, 71% (90% on brsm); c) i) mesyl chloride(MsCl), Et$_3$N, DMAP,

0 °C to rt, 2 h; ii) NaI, TMSCl, dry CH₃CN, 0 °C to rt, 4 h; iii) Cs₂CO₃, dry CH₃CN, rt, 48 h; iv) Boc₂O, Et₃N, DMAP, 24 h, overall yield 51%.

2.2D. Synthesis of *cis*-octahydro-2*H*-benzo[*b*]azepine scaffold:

Using the underlying philosophy and the principles developed for the hexahydroindoles, octahydroquinolines ring systems, we postulate that it should be possible to access azepine ring containing skeleton by lengthening the carbon chain of the corresponding Grignard reagent. At the outset of the synthesis the adaptation of our synthetic strategy to these heterocycles would be straightforward in concept, but it envisaged to be more challenging due to the difficulties in forming 7-membered rings at the late stage of the synthesis. To effect this, we followed the same synthetic plan involving Michael addition using Grignard reagent in presence of Cu(II) followed by in situ bridge-azabicyclic ring opening and the subsequent cyclisation. The Grignard reagent of **29** was derived from the TBS protected 1,4-bromoalcohol **28** which we made in multi-gram scale by refluxing tetrahydrofuran in presence of 40% hydrobromic acid followed by OTBS protection using TBSCl in presence of imidazole, catalytic amount of DMAP.[10] The TBS protected Grignard reagent was reacted very smoothly with the common intermediate **2** to provide the desired ring opening product **30**, which was subjected to 0.8N hydrochloric acid to deprotect the -OTBS group. After having the alcohol **31**, applied the same cyclization protocol as in the case of *cis*-octahydroquinoline preparation to access the desire cyclized product *cis*-octahydro-2*H*-benzo[*b*]azepine **33**.

Scheme 7: Preparation of the TBS protected 1,4-bromoalcohol **29**

Reagents and conditions: a) 40% aq. HBr, reflux, 2 h, 41%; b) TBSCl (1.2 eq), imidazole (2.2 eq), DMAP (0.1 eq) rt, 12 h, 88%.

Scheme 8: Synthesis of octahydrobenzo[*b*]azepine ring system (**33**).

Reagents and conditions: a) i) 29 (1.8 eq),Mg turnings (2.2 eq),dry ether; ii) CuCN(1 eq), Dry THF + Ether, -60 ℃ to -30 ℃, 4 h, 81%; b) i) 0.8N HCl, 0℃,2 h, ii) NaHCO₃, *0℃, 86%; c) mesyl chloride (MsCl), Et₃N, DMAP, 0 ℃ to rt, 2 h; d) i) NaI, TMSCl, dry CH₃CN, 0 ℃ to rt, 4 h, ii) Cs₂CO₃, dry CH₃CN, rt, 48 h, iii) Boc₂O, Et₃N, DMAP, 24 h, overall yield 48%.*

2.3. Summary:

An effective synthetic route have been developed for the synthesis of *cis*-hexahydroindoles, *cis*-octahydroquinolines and *cis*-octahydrobenzo[*b*]azepine embedded with a versatile functionality (vinyl sulphone) for further functionalization towards the synthesis of corresponding natural products. The successful establishment of this synthetic strategy prompted us to synthesize a diverse array of natural products having these three basic scaffolds. The next chapter will discuss the application of this synthetic strategy and the efforts toward the synthesis of various alkaloids.

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2.5. Experimental Procedures and Spectral Data:

General Remarks:

Solvents used for chromatography were purified and distilled at respective boiling points using known procedures (1). Petroleum ether used in the experiments was of 60-80 °C boiling range. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven dried glassware (110 °C), which were cooled under argon. Solvents for anhydrous reactions were dried according to Perrin *et al.1* Benzene, DCM and triethylamine were distilled over CaH_2 and stored over molecular sieves and KOH, respectively. THF and diethyl ether were distilled over sodium benzophenone ketyl. All commercial reagents were obtained from Sigma-Aldrich and Lancaster Chemical Co. (UK). *n*-BuLi was titrated using diphenylacetic acid as an indicator. Reaction progress was monitored by TLC. TLC was performed on Merck precoated 60 F254 plates and the spots were rendered visible by exposing to UV light, Iodine, phosphomolibdic acid, o-Anisol, KMNO4, ninhydrin solutions. Column chromatography was performed on silica gel 60-120/ 100-200 mesh. Typical syringe and cannula techniques were used to transfer air and moisture-sensitive reagents. IR spectra were recorded on FTIR instrument, for solid either as nujol mull, neat in case of liquid compounds or their solution in chloroform. ^{1}H NMR spectra were recorded on Bruker 400 MHz, and 800 MHz instruments using deuteriated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (br, broadened; s, singlet; d, doublet; t, triplet; dt, doublet of triplet; ddd, doublet of a doublet of a doublet; m, multiplet). 13C NMR spectra were recorded on Bruker 400 and 800 MHz instruments operating at 100 and 200 MHz respectively. 13C NMR chemical shifts are reported in ppm relative to the central line of CDCl3 (δ 77.16). Mass spectra were recorded on Azilant PE SCIEX API QSTAR pulsar (LC-MS). All the melting points were recorded using electrothermal melting point apparatus (BUCHI, MODEL NO. B540). Starting materials were obtained from commercial sources. Numbering of compounds, schemes, tables, referencing and figures in abstract and chapters are independent.

Synthesis of (±) *tert*-butyl ((1*S*,2*S*)-3-(phenylsulfonyl)-2-vinylcyclohex-3-en-1-yl)carbamate (20):

The mixture of **2** (10.0 g, 29.8 mmol) and flame dried CuCN (1.6 g, 17.9 mmol, 0.6 equiv.) in mixture of dry THF and ether (1:1, 150 mL) was charged into a 500 mL two neck jacketed flask equipped with a magnetic stirring bar, argon gas balloon and was cooled to -80 °C followed by vinyl magnesium bromide solution (1.0 M in dry THF, 38.7 mL, 38.7 mmol, 1.3 equiv.) was added dropwise *via* cannula over a period of 30 minutes. The reaction mixture was allowed to stirr at -70 °C for 4 h, then gradually increased the temperature to -30 °C and stirred further for 2 h. The temperature of the reaction mixture was raised to -10 °C and was quenched with saturated aq. NH₄Cl (100 mL). The mixture was stirred for next few hours until it appeared blue colour solution and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over sodium sulfate, concentrated and dried *in vacuo* and purified by column chromatography (hexane : ethyl acetate, 7:3) to obtain **20** as a white gummy solid (4.4 g, 41%)

Yield: 41%

TLC: R_f = 0.37 (SiO₂, Hexane : Ethyl acetate = 3:1)

¹H NMR (400 MHz, CDCl₃) δ: 7.85 − 7.70 (m, 2H), 7.61 − 7.51 (m, 1H), 7.51 − 7.39 (m, 2H), 7.03 (br m, 1H), 5.51 − 5.14 (m, 1H), 5.12 − 4.85 (m, 1H), 4.52 (d, *J* = 8.5 Hz, 1H), 3.60 (br m, 1H), 3.31 (dd, *J* = 7.6, 5.2 Hz, 1H), 2.45 (br m, 2H), 2.14 − 1.78 (m, 1H), 1.78 − 1.56 (m, 1H), 1.36 (br s, *J* = 5.2 Hz, 9H).

¹³C NMR (101 MHz, CDCl₃) δ: 154.77, 141.01, 139.57, 138.11, 133.66, 133.27, 129.01, 128.31, 121.21, 79.55, 48.69, 41.69, 28.36, 25.53, 23.43.

HRMS (ESI): *m/z* calculated for C₁₉H₂₅NO₄SNa ([M + Na]⁺) 386.1402, C₁₉H₂₉N₂O₄S ([M + NH₄]⁺) 381.1848 ; found 386.1406 ([M + Na]⁺) and 381.1855 ([M + NH₄]⁺).

Synthesis of (±) *tert*-butyl ((1*S*,2*S*)-2-(2-hydroxyethyl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl) carbamate (21):

To a solution of the **20** (0.52g, 1.43 mmol) in dry THF (5 mL) was added 0.5 M **9-**BBN in THF (7.4 mL, 3.7 mmol, 2.6 equiv.), at 0 °C. The mixture was stirred at RT for 12 h and the excess 9-BBN was quenched by adding water slowly at 0 °C. The hydroboration mixture was oxidised by adding aq. 3.0 M NaOAc (4.8 mL, 14.3 mmol, 10 equiv.) followed by H_2O_2 (30% in H_2O, 1.5 mL, 14.3 mmol, 10 equiv.). The reaction mixture was stirred at RT for 5 h, brine solution was added and extracted with EtOAc (2 x 25 mL). The combined organic layer was dried over sodium sulphate, concentrated and dried *in vacuo* and purified by column chromatography (hexane:ethyl acetate, 2:3) to provide the product **21** as a colourless oil (0.34 g, 62%, 91% on brsm).

Yield: 62%, 91% on brsm

TLC: R_f = 0.46 (SiO$_2$, Hexane : Ethyl acetate = 2:3)

¹H NMR (400 MHz, CDCl₃) δ: 7.83 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 6.98 (br s, 1H), 5.55 (br s, *J* = 136.6 Hz, 1H), 3.74 (br m, 2H), 3.43 (br m, 1H), 2.67 (br m, 1H), 2.4 – 2.32 (m, *J* = 13.4, 8.7, 3.7 Hz, 2H), 1.96 (br m, 1H), 1.91 – 1.82 (m, 2H), 1.82 – 1.75 (m, 1H), 1.60 – 1.53 (m, 1H), 1.37 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ: 155.74, 143.47, 140.16, 139.85, 133.85, 129.78, 128.22, 79.73, 62.37, 49.81, 35.33, 33.55, 28.79, 25.65, 23.38.

HRMS (ESI): *m/z* calculated for $C_{19}H_{27}NO_5SNa$ ([M+Na]⁺) 404.1508, $C_{19}H_{31}N_2O_5S$ ([M+NH₄]⁺) 399.1959; found 404.1512 ([M+Na]⁺) and 399.1962 ([M+NH₄]⁺).

Synthesis of (±) (3a*S*,7a*S*)-*tert*-butyl 4-(phenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (22):

To a solution of **21** (0.26 g, 0.7 mmol) in dry DCM (5 mL) was added methanesulfonyl chloride (0.07 mL, 0.9 mmol, 1.3 equiv.) followed by triethyl amine (0.5 mL, 3.4 mmol, 5 equiv.) and DMAP (0.1g, 0.8 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 6 h and quenched with water (10.0 mL). The reaction mixture was extracted with EtOAc (2 x 25 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The crude material was dried in *vacuo* and purified by column chromatography (hexane:ethyl acetate, 3:1) to provide the product **22** as a colourless oil (0.19 g, 76%).

Yield: 76%

TLC: R_f = 0.52 (SiO$_2$, Hexane : Ethyl acetate = 3:1)

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.86 – 7.84 (d, *J* = 7.6 Hz, 2H), 7.63 – 7.59 (tt, *J* = 7.4 Hz, 1H), 7.55 – 7.51 (t, *J* = 7.6 Hz, 2H), 7.13 (br s, 1H), 3.84 – 3.64 (m, 1H), 3.38 – 3.34 (dd, *J* = 22.6, 10.5 Hz, 1H), 3.31 – 3.16 (m, 1H), 2.84 – 2.60 (m, 1H), 2.49 – 2.33 (m, 1H), 2.30 – 2.16 (m, 2H), 2.16 – 1.95 (m, 1H), 1.75 – 1.50 (m, 1H), 1.44 – 1.37 (m, 9H), 1.34 – 1.24 (ddd, *J* = 16.8, 12.1, 5.1 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 153.98, 141.00, 140.08, 139.66, 133.38, 129.22, 127.90, 79.45, 55.38, 45.20, 30.40, 28.45, 24.72, 23.30.

HRMS (ESI): *m/z* calculated for C$_{19}$H$_{26}$NO$_4$SNa ([M+Na]$^+$) 386.1402; found 386.1405.

Synthesis of (±) *tert*-butyl ((1*S*,2*S*)-2-allyl-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (23):

2

23

The mixture of **2** (30.0 g, 89.4 mmol) and flame dried CuCN (8.0 g, 89.4 mmol, 1.0 equiv.) in dry THF and ether (1:1, 400 mL) was charged into a 1 L two neck jacketed flask equipped with a magnetic stirring bar, argon gas balloon and was cooled to -60 $^{\circ}$C followed by allyl magnesium bromide solution (1.0 M in diethyl ether, 143.1 mL, 143.1 mmol, 1.6 equiv.) was introduced to the stirring mixture dropwise via cannula over a period of 45 minutes. The reaction mixture was further allowed to stirr for 2 h at -60 $^{\circ}$C, then gradually increased the temperature to -30 $^{\circ}$C over a period of 1 h and stirred further for 2 h at -30 $^{\circ}$C. The temperature of the reaction mixture was allowed to raise to -10 $^{\circ}$C and was quenched with saturated aq. NH$_4$Cl (200 mL). The mixture was stirred for next few hours at room temperature until it appeared blue colour solution and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over sodium sulfate, concentrated and dried *in vacuo* and purified by column chromatography (hexane : ethyl acetate, 7:3) to obtain **23** as a white solid (31.5 g, 93%)

Yield: 93%

TLC: R$_f$ = 0.42 (SiO$_2$, Hexane : Ethyl acetate = 3:1)

m.p.: 103 – 105°C

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.82 (d, *J* = 7.4 Hz, 2H), 7.58 (tt, *J* = 8.5, 6.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.04 (br m, *J* = 19.3 Hz, 1H), 5.76 (td, *J* = 16.7, 7.5 Hz, 1H), 4.99 (dd, *J* = 25.4, 13.6 Hz, 2H), 4.70 (d, *J* = 37.8 Hz, 1H), 3.59 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.80 (s, 1H), 2.61 – 2.48 (m, 1H), 2.48 – 2.33 (m, 2H), 2.33 – 2.19 (m, 1H), 1.74 – 1.61 (m, 2H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 154.78, 141.98, 139.89, 139.73, 137.50, 133.35, 129.25, 127.80, 116.10, 79.28, 49.67, 35.93, 33.88, 28.32, 25.05, 23.28.

HRMS (ESI): *m/z* calculated for C$_{20}$H$_{27}$NO$_4$SNa ([M+Na]$^+$) 377.1661; found .

Synthesis of (±) *tert*-butyl ((1*S*,2*S*)-2-(2-oxoethyl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl)c arbamate (24):

To a stirred solution of **23** (10.0 g, 26.5 mmol) in dioxane-water (3:1, 150 mL) was added 2,6-lutidine (6.1 mL, 52.9 mmol, 2.0 equiv.) followed by OsO4 (0.1 M solution in t-butanol, 2.65 mL,0.26 mmol), and NaIO$_4$ (2.1 gm, 9.75 mmol) at 0 °C. The reaction mixture was stirred at room temperature (25 °C) until TLC revealed no starting material. After the reaction was completed, it was diluted with EtOAc (100 mL) and water (100 mL) was added. The reaction mixture was extracted with EtOAc (100 mL) and the organic layer was separated. The water layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous sodium sulphate. The solvent was filtered and concentrated by rotary evaporation. The crude aldehyde **24** was dried in *vacuo* and proceeded further step for intramolecular reductive amination with the tether *tert*-butyl carbamate.

Synthesis of (±) (3a*S*,7a*S*)-*tert*-butyl 4-(phenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (22):

The crude aldehyde **24** obtained by the oxidative cleavage of the allyl group was dissolved in 150 mL THF: AcOH (9:1) and sodium cyanoborohydride (3.3g g, 52.9 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 20 h. The mixture was neutralized with saturated sodium bicarbonate solution (100 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layer was separated and the water layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulphate, concentrated, dried *in vacuo* and purified by column

chromatography (hexane : ethyl acetate, 3:1) to obtain **22** as a colourless highly viscous oil (8.7 g, 91%).

Yield: 91%

TLC: R_f = 0.52 (SiO$_2$, Hexane : Ethyl acetate = 3:1)

HRMS (ESI): *m/z* calculated for C$_{19}$H$_{26}$NO$_4$SNa ([M+Na]$^+$) 386.1402; found 386.1407.

Synthesis of (±) *tert*-butyl ((1*S*,2*S*)-2-(3-hydroxypropyl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (25):

To a solution of the **23** (1.0 g, 2.6 mmol) in dry THF (10 mL) was added 0.5 M **9-**BBN in THF (7.9 mL, 3.9 mmol, 1.5 equiv.), at 0 °C. The mixture was stirred at room temperature for 12 h and the excess 9-BBN was quenched by adding water slowly at 0 °C. The hydroboration mixture was oxidised by adding aq. 3.0 M NaOAc (5.3 mL, 15.9 mmol, 6 equiv.) followed by H$_2$O$_2$ (30% in H$_2$O, 4.4 mL, 42.4 mmol, 16 equiv.). The reaction mixture was stirred at room temperature for 5 h, brine solution was added and extracted with EtOAc (2 x 25 mL). The combined organic layer was dried over sodium sulphate, concentrated and dried *in vacuo* and purified by column chromatography (hexane:ethyl acetate, 3:7) to provide the product **25** as a colourless oil (0.74 g, 71%, 90% on brsm).

Yield: 71%, 90% on brsm

TLC: R_f = 0.40 (SiO$_2$, Hexane : Ethyl acetate = 2:3)

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.83 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.00 (br m, *J* = 18.4 Hz, 1H), 4.91 (d, *J* = 26.4 Hz, 1H), 3.47 (br m, *J* = 86.3 Hz, 3H), 2.62 (br m, *J* = 41.1 Hz, 1H), 2.32 (br m, 3H), 1.75 − 1.50 (m, 6H), 1.29 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 155.09, 143.09, 139.94, 139.18, 133.47, 129.38, 127.82, 79.61, 61.86, 49.46, 35.55, 32.06, 28.43, 25.15, 23.37, 20.14.

HRMS (ESI): *m/z* calculated for $C_{20}H_{29}NO_5SNa$ ([M+Na]⁺) 418.1664, $C_{20}H_{30}NO_5S$ ([M+H]⁺) 396.1845; found 418.1668 ([M+Na]⁺) and 396.1843 ([M+H]⁺)

Synthesis of (±) (4a*S*,8a*S*)-*tert*-butyl 5-(phenylsulfonyl)-2,3,4,4a,8,8a-hexahydroquinoline -1(7*H*)-carboxylate (26):

To a solution of **25** (1.0 g, 2.5 mmol) in dry DCM (20 mL) in a round-bottom flask equipped with a magnetic stir bar and argon gas balloon was added methanesulfonyl chloride (0.29 mL, 3.8 mmol, 1.5 equiv.) followed by triethyl amine (0.88 mL, 6.3 mmol, 2.5 equiv.) and DMAP (0.37g, 3.0 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 h and quenched with water (15.0 mL). The reaction mixture was extracted with EtOAc (2 x 25 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The crude material was passed through a short column of silica gel (100-200) using hexane:ethyl acetate (1:1), evaporated the solvent by rotary evaporation and dried in *vacuo*.

TLC: R_f = 0.54 (SiO₂, Hexane : Ethyl acetate = 1:1)

¹H NMR (400 MHz, CDCl₃) δ: 7.82 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 6.97 (br m, *J* = 23.5 Hz, 1H), 4.71 (d, *J* = 5.2 Hz, 1H), 4.11 (dd, *J* = 20.0, 6.7 Hz, 2H), 3.43 (br m, 1H), 2.99 (s, 3H), 2.63 (br m, 1H), 2.38 (br m, 2H), 1.85 (br m, *J* = 10.9 Hz, 2H), 1.72 – 1.62 (m, 2H), 1.61 – 1.47 (m, 2H), 1.29 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ: 154.95, 142.90, 139.99, 139.28, 133.53, 129.44, 127.82, 82.21, 79.78, 70.33, 49.30, 37.53, 33.03, 28.38, 25.96, 24.97, 23.32.

HRMS (ESI): *m/z* calculated for $C_{21}H_{31}NO_7S_2Na$ ([M+Na]⁺) 496.1440, $C_{21}H_{32}NO_7S_2$ ([M+H]⁺) 474.1620,; found 496.1454 ([M+Na]⁺) and 474.1630 ([M+H]⁺).

The mesylate compound was pure enough to proceed further for carbamate deprotection by insitu generated trimethylsilyl iodide (TMSI) using NaI and trimethylsilyl chloride (TMSCl).The mixture of freshly distilled trimethylsilyl chloride (0.39 mL, 3.0 mmol, 1.2 equiv.) and flame dried NaI (683.6 g, 4.5 mmol, 1.8 equiv.) in dry acetonitrile (CH₃CN) was charged into a 50 mL two neck round-bottom flask equipped with a magnetic stirring bar, argon gas balloon and was cooled to -0 ºC using ice-water bath. The mixture was stirred for 45 minutes and the solution of the crude mesylate in dry CH₃CN was added. The reaction mixture was stirred for 30 minutes and the ice-bath was removed. The mixture was allowed to stir at room temperature for 4 h and the progress of the reaction was monitored by TLC to confirm the complete removal of the tertiary butyl ester group. The red brown colored reaction mixture was quenched by adding water (5 mL) and was diluted with ethyl acetate (25 mL). The reaction mixture was transferred into a separating funnel and extracted with EtOAc (2 x 25 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The crude material was dried in *vacuo* and proceeded further for cyclisation with the removal of the –OMs (O-mesylate group) by the amine followed by -NBoc protection of the cyclised amine.

To the solution of crude amine in dry CH₃CN (20 mL) was added anhydrous caesium carbonate (1.6 g, 5.0 mmol, 2.0 equiv.) and stirred for 48 h. The reaction mixture was diluted with dichloromethane (DCM) and filtered through a Celite pad. The solution was concentrated by rotary evaporation and the crude material was dissolved in dry DCM (10 mL). To the solution Boc-anhydride (Boc₂O) (5.8 mL, 25.2 mmol, 10.0 equiv.) was added at 0 ºC followed by triethyl amine (1.7 mL, 12.6 mmol, 5.0 equiv.) and DMAP (1.54 g, 12.6 mmol, 5 equiv.) were introduced to the reaction mixture and allowed to stir for 24 h at room temperature. The reaction mixture was concentrated by rotary evaporation, dried *in vacuo* and purified by column chromatography (hexane:ethyl acetate, 7:3) to obtain the product **26** as a colourless liquid (0.48 g, 51%).

Yield: 51%

TLC: R$_f$ = 0.52 (SiO₂, Hexane : Ethyl acetate = 7:3)

^{1}H NMR (400 MHz, CDCl₃) δ: 7.85 (dd, *J* = 20.7, 8.3 Hz, 2H), 7.66 – 7.57 (m, 1H), 7.53 (dd, *J* = 8.9, 4.0 Hz, 2H), 7.09 (br m, 1H), 4.21 – 4.00 (m, 1H), 3.99 – 3.82 (m, 1H), 2.70 (dt, *J* = 25.1, 12.3 Hz, 1H), 2.56 – 2.40 (m, 2H), 2.40 – 2.32 (m, 1H), 2.33 – 2.15 (m, 1H), 2.01 – 1.92 (m, 1H), 1.63 – 1.50 (m, 2H), 1.50 – 1.42 (m, 2H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 154.89, 140.19, 139.54, 133.40, 129.36, 127.92, 79.90, 49.36, 39.57, 34.62, 28.52, 25.87, 25.20, 25.20, 19.30.

HRMS (ESI): *m/z* calculated for C$_{20}$H$_{28}$NO$_4$SNa ([M+Na]$^+$) 400.1558, C$_{20}$H$_{29}$NO$_4$S ([M+H]$^+$) 378.1739; found 400.1558 ([M+Na]$^+$) and 378.1740 ([M+H]$^+$).

Synthesis of 4-bromobutan-1-ol (28):

Aqueous HBr (200.0 g, 1.2 mol, 48% in water) was added drop-wise to refluxing THF (298.2 mL, 1.8 mol, and 1.5 equiv.) over a period of 30 minutes. Refluxing was then continued for 2 hours. Following this the reaction was cooled, neutralised by adding solid NaHCO$_3$ to the reaction mixture and the resulting yellow organic layer was then separated. The organic layer was washed with water (100 mL) followed by brine solution (60 mL). The aqueous layers were then extracted with EtOAc and the organic extracts were combined and concentrated under vacuum to give the crude product **28** (74.4 g, 41%) as a yellow liquid which was used without further purification.

Synthesis of 4-Bromo-1-(t-butyldimethylsilyloxy)butane (29):

TBDMSCl (59.1 g, 392.1 mmol, 1.2 equiv.) was added to the stirred solution of 4-bromo-1-butanol (50.0 g, 326.7 mmol), imidazole (48.9 g, 718.8 mmol, 1.2 equiv.) and 4-dimethylaminopyridine (4.0 g, 32.7 mmol, 0.1 equiv.) in dry CH$_2$Cl$_2$ (800 mL) at 0 °C. The solution was stirred further 2 h at 0 °C, warmed to room temperature (25 °C) and stirring was continued for 12 h. The reaction was quenched with aqueous NH$_4$Cl solution (50 mL), brine solution (100 mL) was added and the organic layer was separated. The water layer was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with aqueous NaCl solution (2 x 50 mL), dried over anhydrous sodium sulphate, filtered and concentrated

by rotary evaporation. The resultant oil was purified by column chromatography using hexane:EtOAc (98:2) to afford 76.8 g (88 %) of the title compound **29** as a colorless oil.

Yield: 88%

TLC: R_f = 0.64 (SiO$_2$, Hexane : Ethyl acetate = 98:2)

^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.64 (t, *J* = 6.1 Hz, 2H), 3.44 (t, *J* = 6.8 Hz, 2H), 1.98 – 1.89 (m, 2H), 1.69 – 1.60 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 62.28, 34.01, 31.42, 29.64, 26.06, 18.43, -5.20.

HRMS (ESI): *m/z* calcd. for C$_{10}$H$_{23}$BrOSiNa$^+$([M+Na]$^+$) 289.0599, 291.0579 , found: 289.0589 ([M+Na]$^+$) and 291.0568 ([M+Na]$^+$)

Synthesis of (±) *tert*-butyl ((1*S*,2*S*)-2-(4-((tert-butyldimethylsilyl)oxy)butyl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (30):

A dry 500 mL three-necked round-bottomed flask was equipped with a magnetic stir bar, 500 mL pressure-equalizing dropping funnel and a reflux condenser under argon balloon pressure. The flask was charged with an excess of thermally activated magnesium turnings (4.8 g, 196.8 mmol, 2.2 equiv.), two small pieces of iodine and stirred the solid mixture for 5 min. 10 mL of dry diethyl ether was added to the reaction mixture. To the stirred mixture was added dropwise a solution of **29** (43.0 g, 160.9 mmol, 1.8 equiv.) in 150 mL of dry diethyl ether. At the end of the addition (2 h) the mixture was stirred further for 1 h to afford the solution of Grignard reagent of **29**.

The mixture of **2** (30.0 g, 89.4 mmol) and flame dried CuCN (8.0 g, 89.4 mmol, 1 equiv.) in dry THF and ether (1:1, 200 mL) was charged into a 500 mL two neck jacketed flask equipped with a magnetic stirring bar, argon gas balloon and was cooled to -60 °C followed by the solution of the Grignard reagent **29** was added dropwise *via* cannula over a period of 30 minutes. The reaction mixture was stirred at that temperature (-60 °C) for 2 h, then gradually increased the temperature to -30 °C and stirred further for 2 h. The temperature of the reaction

mixture was raised to -10 °C and was quenched with saturated aq. NH$_4$Cl (100 mL). The mixture was stirred for next few hours until it appeared blue colour solution and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over sodium sulfate, concentrated and dried *in vacuo* and purified by column chromatography (hexane : ethyl acetate, 3:1) to obtain **30** as a highly viscous liquid (37.9 g, 81%).

Yield: 81%

TLC: R$_f$ = 0.38 (SiO$_2$, Hexane : Ethyl acetate = 4:1)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87 – 7.77 (m, 2H), 7.63 – 7.55 (m, 1H), 7.55 – 7.45 (m, 2H), 7.14 – 6.94 (m, 1H), 4.60 (d, *J* = 7.6 Hz, 1H), 3.67 – 3.58 (m, 1H), 3.54 (m, *J* = 5.3 Hz, 2H), 3.42 (s, 1H), 2.65 (br s, 1H), 2.46 – 2.26 (m, 2H), 1.82 – 1.42 (m, 4H), 1.39 (s, 9H), 1.32 – 1.13 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 155.00, 143.24, 140.40, 138.87, 133.33, 129.31, 127.95, 79.63, 63.25, 49.32, 36.79, 33.09, 29.76, 28.49, 26.14, 25.03, 23.82, 18.51, -5.10.

HRMS (ESI): *m/z* calculated for C$_{27}$H$_{45}$NO$_5$SSiNa ([M+Na]$^+$) 546.2685; found 546.2676 ([M+Na]$^+$).

Synthesis of (±) *tert*-butyl ((1*S*,2*S*)-2-(4-hydroxybutyl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (31):

To a stirred solution of **30** (10.0 g, 19.0 mmol) in THF (150 mL) was added 0.8N HCl (202.8 mL, 162.3 mmol, 8.5 equiv.) at 0 °C. The reaction mixture was stirred further at the same temperature (0 °C) for 2 h until TLC revealed no starting material. After the reaction was completed, diluted with ether (150 mL) and water (100 mL) was added. The reaction mixture was neutralised by adding solid NaHCO$_3$ at 0 °C. The mixture was extracted with EtOAc (100 mL) and the organic layer was separated. The water layer was extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous sodium sulphate. The solvent was filtered and concentrated by rotary evaporation. The crude alcohol **31** was dried in *vacuo* and purified by column chromatography (hexane: ethyl acetate, 1:9) to obtain **31** as a white solid (6.7 g, 86%).

Yield: 86%

TLC: $R_f = 0.34$ (SiO$_2$, Hexane : Ethyl acetate = 3:7)

m.p.: 195-197ºC

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.84 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.55 − 7.48 (m, 2H), 6.98 (br s, 1H), 4.69 (d, J = 7.6 Hz, 1H), 3.67 − 3.56 (m, 3H), 2.62 (br m, J = 25.7 Hz, 1H), 2.39 (br m, 2H), 1.81 (br m, 1H), 1.69 − 1.57 (m, 3H), 1.46 (br m, 2H), 1.40 (s, 9H), 1.26 (br m, J = 9.7 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 155.07, 143.13, 140.15, 138.92, 133.43, 129.37, 127.96, 79.74, 62.18, 49.21, 36.76, 32.46, 29.24, 28.48, 25.49, 25.00, 23.84.

HRMS (ESI): *m/z* calculated for C$_{21}$H$_{31}$NO$_5$SNa ([M+Na]$^+$) 432.1821, C$_{21}$H$_{32}$NO$_5$S ([M+H]$^+$) 410.2001; found 432.1827 ([M+Na]$^+$), 410.2005 ([M+H]$^+$).

Synthesis of (±) (5a*S*,9a*S*)-*tert*-butyl 6-(phenylsulfonyl)-2,3,4,5,5a,8,9,9a-octahydro-1*H*-benzo[*b*]azepine-1-carboxylate (33):

The compound **31** (10.0 g, 24.4 mmol) was converted to the cyclized product **33** (4.6 g, 48% yield) as a white solid applying the same reaction sequence (mesylation, carbamate deprotection, cyclisation and carbamate protection) as described for the synthesis of compound **26** from **25**.

32

(±) 4-((1*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-2-(phenylsulfonyl)cyclohex-2-en-1-yl)butyl methanesulfonate

TLC: R_f = 0.42 (SiO$_2$, Hexane : Ethyl acetate = 2:3)

¹H NMR (400 MHz, CDCl₃) δ: 7.85 (t, *J* = 6.8 Hz, 2H), 7.67 − 7.58 (m, 1H), 7.58 − 7.50 (m, 2H), 7.00 (br m, 1H), 4.83 − 4.62 (m, 1H), 4.28 − 4.13 (m, 2H), 3.50 (br m, *J* = 91.1 Hz, 1H), 3.03 (br m, 3H), 2.65 (br m, *J* = 52.7 Hz, 1H), 2.40 (br m, 2H), 1.76 − 1.60 (m, 4H), 1.58 (br m, *J* = 2.4 Hz, 1H), 1.46 (s, 9H), 1.33 − 1.14 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ: 154.96, 143.06, 140.13, 139.01, 133.45, 129.38, 127.84, 79.70, 69.64, 49.30, 37.48, 36.40, 29.17, 29.13, 28.43, 25.02, 25.01, 23.40.

HRMS (ESI): *m/z* calculated for C$_{22}$H$_{33}$NO$_7$S$_2$ ([M+Na]$^+$) 510.1596, C$_{22}$H$_{37}$N$_2$O$_7$S$_2$ ([M+NH$_4$]$^+$) 505.2042; found 510.1590 ([M+Na]$^+$) and 505.2040 ([M+NH$_4$]$^+$).

33

Yield: 48%

TLC: R_f = 0.48 (SiO$_2$, Hexane : Ethyl acetate = 7:3)
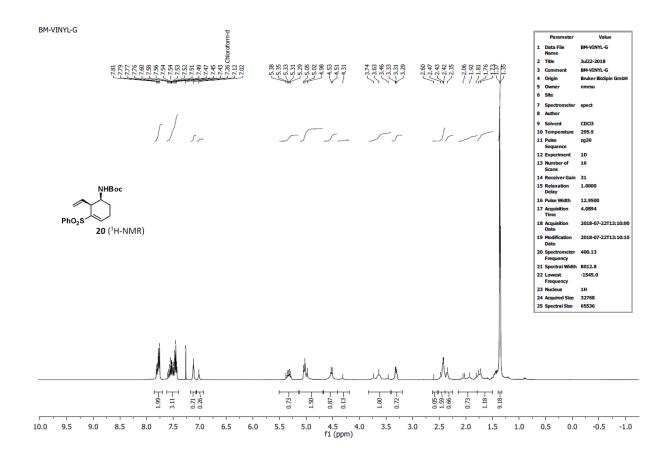
m.p.: 147-149°C
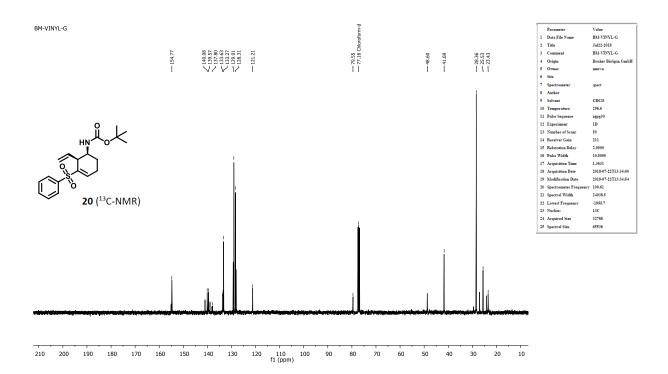
¹H NMR (400 MHz, CDCl₃) δ: 7.84 (d, *J* = 7.4 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.55 − 7.48 (m, 2H), 7.07 − 6.89 (m, 1H), 4.69 (d, *J* = 7.6 Hz, 1H), 3.67 − 3.56 (m, 3H), 2.62 (br m, *J* = 25.7 Hz, 1H), 2.39 (br m, 2H), 1.81 (br m, 1H), 1.69 − 1.57 (m, 3H), 1.48 − 1.45 (m, 2H), 1.40 (s, 9H), 1.28 − 1.23 (m, 3H).
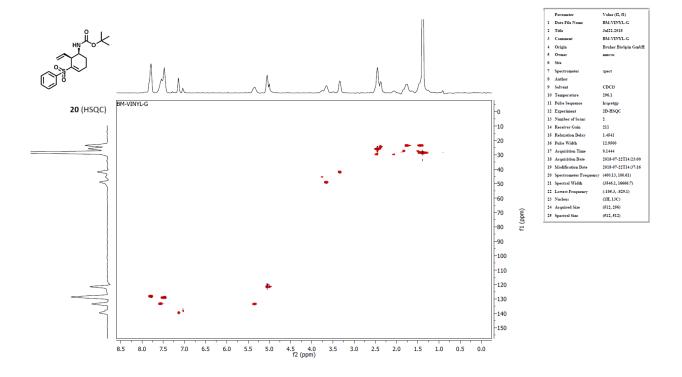
¹³C NMR (101 MHz, CDCl₃) δ: 155.07, 143.13, 140.15, 138.92, 133.43, 129.37, 127.96, 79.74, 62.18, 49.21, 36.76, 32.46, 29.24, 28.48, 25.49, 25.00, 23.84.

HRMS (ESI): *m/z* calculated for C$_{21}$H$_{29}$NO$_4$S ([M+Na]$^+$) 414.1715; found 414.1715 ([M+Na]$^+$).

2.6. Spectras:

BM-VINYL-G

20 (^{1}H-NMR)

	Parameter	Value
1	Data File Name	BM-VINYL-G
2	Title	Jul22-2018
3	Comment	BM-VINYL-G
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	295.9
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	31
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-07-22T13:10:00
19	Modification Date	2018-07-22T13:10:10
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1545.0
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

BM-VINYL-G

154.77

140.08
139.57
137.80
133.63
133.27
129.01
128.31

121.21

79.55
77.16 Chloroform-d

48.60

41.69

28.36
25.53
23.43

20 (^{13}C-NMR)

	Parameter	Value
1	Data File Name	BM-VINYL-G
2	Title	Jul22-2018
3	Comment	BM-VINYL-G
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	296.6
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	60
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	1.3631
18	Acquisition Date	2018-07-22T13:34:00
19	Modification Date	2018-07-22T13:34:54
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1955.7
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

20 (HSQC)

BM-VINYL-G

	Parameter	Value (f2, f1)
1	Data File Name	BM-VINYL-G
2	Title	Jul22-2018
3	Comment	BM-VINYL-G
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	296.1
11	Pulse Sequence	hsqcetgp
12	Experiment	2D-HSQC
13	Number of Scans	2
14	Receiver Gain	211
15	Relaxation Delay	1.4541
16	Pulse Width	12.9500
17	Acquisition Time	0.1444
18	Acquisition Date	2018-07-22T14:23:00
19	Modification Date	2018-07-22T14:37:16
20	Spectrometer Frequency	(400.13, 100.61)
21	Spectral Width	(3546.1, 16666.7)
22	Lowest Frequency	(-105.3, -829.1)
23	Nucleus	(1H, 13C)
24	Acquired Size	(512, 256)
25	Spectral Size	(512, 512)

21 (^{1}H-NMR)

21 (COSY)

BM-V-OH

155.74
143.47
140.16
139.85
133.85
129.78
128.22
79.73
77.?? Chloroform-d
62.37
49.81
35.33
33.55
28.79
25.65
23.38

21 (^{13}C-NMR)

	Parameter	Value
1	Data File Name	BM-V-OH
2	Title	NMR-21.07.2018
3	Comment	BM-V-OH
4	Origin	Bruker BioSpin GmbH
5	Owner	nmr
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	295.9
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	458
14	Receiver Gain	211
15	Relaxation Delay	5.0000
16	Pulse Width	10.0000
17	Acquisition Time	2.9999
18	Acquisition Date	2018-07-30T22:37:39
19	Modification Date	2018-07-30T23:38:49
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1915.9
23	Nucleus	13C
24	Acquired Size	72114
25	Spectral Size	262144

BM-V-OH-DEUTERATED

7.85
7.83
7.62
7.61
7.59
7.55
7.53
7.51
7.51
7.26 Chloroform-d
6.98
4.73
3.73
3.45
3.42
2.68
2.45
2.44
2.41
2.40
2.39
1.93
1.88
1.86
1.80
1.79
1.77
1.75
1.59
1.57
1.55
1.38

D$_2$O

21 in D$_2$O (^{1}H-NMR)

2.00
2.05
1.99
1.00
0.23
2.03
1.00
0.97
2.03
1.13
1.06
0.84
1.13
9.16

	Parameter	Value
1	Data File Name	BM-V-OH-DEUTERATED
2	Title	Jul31-2018-nmrsu
3	Comment	BM-V-OH-DEUTERATED
4	Origin	Bruker BioSpin GmbH
5	Owner	nmr
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	295.5
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	2
14	Receiver Gain	94
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-07-31T13:12:00
19	Modification Date	2018-07-31T13:12:59
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1545.0
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

BM-V-N-CYCLISED

22 (^{1}H-NMR)

WATER

Parameter	Value
1 Data File Name	BM-V-N-CYCLISED
2 Title	Oct03-2017-nmrsu
3 Comment	BM-V-N-CYCLISED
4 Origin	Bruker BioSpin GmbH
5 Owner	nmrsu
6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	295.2
11 Pulse Sequence	zg30
12 Experiment	1D
13 Number of Scans	16
14 Receiver Gain	119
15 Relaxation Delay	1.0000
16 Pulse Width	12.9500
17 Acquisition Time	4.0894
18 Acquisition Date	2017-10-03T11:23:00
19 Modification Date	2017-10-03T11:23:54
20 Spectrometer Frequency	400.13
21 Spectral Width	8012.8
22 Lowest Frequency	-1545.6
23 Nucleus	1H
24 Acquired Size	32768
25 Spectral Size	65536

BM-V-N-CYCLISED

22 (^{13}C-NMR)

Parameter	Value
1 Data File Name	BM-V-N-CYCLISED
2 Title	Oct03-2017
3 Comment	BM-V-N-CYCLISED-13C
4 Origin	Bruker BioSpin GmbH
5 Owner	nmrsu
6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	296.8
11 Pulse Sequence	zgpg30
12 Experiment	1D
13 Number of Scans	2048
14 Receiver Gain	211
15 Relaxation Delay	2.0000
16 Pulse Width	10.0000
17 Acquisition Time	1.3631
18 Acquisition Date	2017-10-03T15:05:00
19 Modification Date	2017-10-03T15:21:10
20 Spectrometer Frequency	100.61
21 Spectral Width	24038.5
22 Lowest Frequency	-1962.2
23 Nucleus	13C
24 Acquired Size	32768
25 Spectral Size	65536

BM-V-N-CYCLISED

22 (DEPT)

	Parameter	Value
1	Data File Name	BM-V-N-CYCLISED
2	Title	Oct03-2017
3	Comment	BM-V-N-CYCLISED-DEPT
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	296.4
11	Pulse Sequence	deptsp135
12	Experiment	1D-DEPT-135
13	Number of Scans	256
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	2.0316
18	Acquisition Date	2017-10-03T15:30:00
19	Modification Date	2017-10-03T15:43:36
20	Spectrometer Frequency	100.61
21	Spectral Width	16129.0
22	Lowest Frequency	-16.0
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

BM-ALLYL-G

23 (^{1}H-NMR)

	Parameter	Value
1	Data File Name	BM-ALLYL-G
2	Title	Jul20-2018
3	Comment	BM-ALLYL-G
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	294.4
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	31
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-07-20T20:15:00
19	Modification Date	2018-07-20T20:15:49
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1645.0
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

BM-ALLYL-G
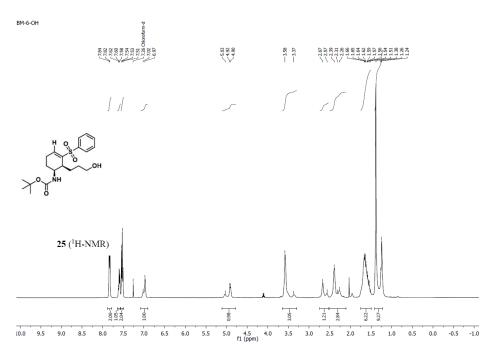
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1	Data File Name	BM-ALLYL-G
2	Title	Jul20-2018
3	Comment	BM-ALLYL-G
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	294.6
11	Pulse Sequence	cosygpppqf
12	Experiment	2D-COSY
13	Number of Scans	4
14	Receiver Gain	20
15	Relaxation Delay	1.9029
16	Pulse Width	12.9500
17	Acquisition Time	0.2888
18	Acquisition Date	2018-07-20T20:20:00
19	Modification Date	2018-07-20T20:39:41
20	Spectrometer Frequency	(400.13, 400.13)
21	Spectral Width	(3546.1, 3546.1)
22	Lowest Frequency	(-102.3, -102.3)
23	Nucleus	(1H, 1H)
24	Acquired Size	(1024, 128)
25	Spectral Size	(1024, 1024)
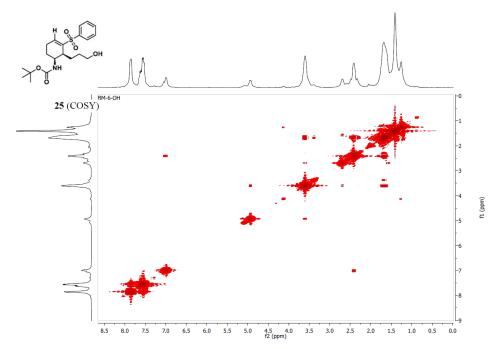
23 (COSY)

23 (^{13}C-NMR)

	Parameter	Value
1	Data File Name	BM-ALLYL-G
2	Title	Jul20-2018
3	Comment	BM-ALLYL-G
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	294.7
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	390
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	1.3631
18	Acquisition Date	2018-07-20T17:55:00
19	Modification Date	2018-07-20T18:05:22
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1960.5
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

23 (HSQC)

25 (¹H-NMR)

25 (COSY)

25 (^{13}C-NMR)

25 (HSQC)

25a (¹H-NMR)

BM-6-OMs

154.95

142.94
140.03
139.25

133.50
129.42
127.81

79.74
77.16 Chloroform-d
70.30

49.31

37.52
36.06

29.08
28.36
25.92
24.96
23.28

25a (^{13}C-NMR)

Parameter	Value
1 Data File Name	BM-6-OMs
2 Title	BM-6-OMs
3 Comment	BM-allyl to mesyl-13C
4 Origin	Bruker BioSpin GmbH
5 Owner	hp
6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	296.3
11 Pulse Sequence	zgpg30
12 Experiment	1D
13 Number of Scans	6144
14 Receiver Gain	14596
15 Relaxation Delay	2.0000
16 Pulse Width	12.6000
17 Acquisition Time	1.3631
18 Acquisition Date	2008-01-10T19:26:12
19 Modification Date	2008-01-10T19:26:22
20 Spectrometer Frequency	100.61
21 Spectral Width	24038.5
22 Lowest Frequency	-1951.7
23 Nucleus	13C
24 Acquired Size	32768
25 Spectral Size	65536

C=O carbon of EtOAc

O-CH₂ carbon of EtOAc

CH₃ carbon of EtOAc

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BM-6-OMs

139.20

133.44
129.35
127.75

70.24

49.24

37.45
35.98

29.01
28.30
25.85
24.90
23.24

25a (DEPT)

Parameter	Value
1 Data File Name	BM-6-OMs
2 Title	BM-6-OMs
3 Comment	BM-allyl to mesyl-13CDEPT
4 Origin	Bruker BioSpin GmbH
5 Owner	hp
6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	296.0
11 Pulse Sequence	dept135
12 Experiment	1D-DEPT-135
13 Number of Scans	1024
14 Receiver Gain	16384
15 Relaxation Delay	2.0000
16 Pulse Width	12.6000
17 Acquisition Time	1.3631
18 Acquisition Date	2008-01-10T21:50:34
19 Modification Date	2008-01-10T21:50:44
20 Spectrometer Frequency	100.61
21 Spectral Width	24038.5
22 Lowest Frequency	-1958.4
23 Nucleus	13C
24 Acquired Size	32768
25 Spectral Size	65536

CH₃ carbon of EtOAc

O-CH₂ carbon of EtOAc

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BM-6-N-CYCLISED

26 (¹H-NMR)

water

	Parameter	Value
1	Data File Name	BM-6-N-CYCLISED
2	Title	Jun19-2018
3	Comment	BM-6-N-CYCLISED
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	294.7
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	104
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-06-19T20:07:00
19	Modification Date	2018-06-19T20:07:30
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1546.2
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

BM-6-N-CYCLISED

26 (¹³C-NMR)

	Parameter	Value
1	Data File Name	BM-6-N-CYCLISED
2	Title	Jun20-2018
3	Comment	BM-6-N-CYCLISED-13C
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	295.5
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	832
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	1.3631
18	Acquisition Date	2018-06-20T11:14:00
19	Modification Date	2018-06-20T11:53:01
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1947.8
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

BM-4-BROMO-OTBS

Br⌒⌒⌒OTBS

29 (^{13}C-NMR)

—7.26 Chloroform-d

3.65
3.64
3.62
3.45
3.44
3.42

1.97
1.95
1.93
1.92
1.90
1.68
1.67
1.66
1.65
1.64
1.63
1.61

0.89

—0.04

	Parameter	Value
1	Data File Name	BM-4-BROMO-OTBS
2	Title	Dec31-2018
3	Comment	BM-4-BROMO-OTBS-PURE
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	rpect
8	Author	
9	Solvent	CDCl3
10	Temperature	298.0
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	4
14	Receiver Gain	31
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-12-31T18:42:00
19	Modification Date	2018-12-31T18:42:24
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1545.4
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

f1 (ppm)

BM-4-BROMO-OTBS

Br⌒⌒⌒OTBS

29 (^{1}H-NMR)

—77.16 Chloroform-d

—62.28

34.01
31.42
29.64
26.06

—18.43

—5.20

	Parameter	Value
1	Data File Name	BM-4-BROMO-OTBS
2	Title	Dec31-2018
3	Comment	BM-4-BROMO-OTBS-PURE-13C
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	rpect
8	Author	
9	Solvent	CDCl3
10	Temperature	298.4
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	113
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	1.3631
18	Acquisition Date	2018-12-31T18:49:00
19	Modification Date	2018-12-31T18:46:02
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1945.3
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	32768

f1 (ppm)

BM-G-OTBS

30 (^{1}H-NMR)

BM-G-OTBS

30 (^{13}C-NMR)

BM-7-OH

7.85
7.84
7.62
7.61
7.59
7.55
7.53
7.51
7.26 Chloroform-d
6.98

4.70
4.68

3.67
3.65
3.64
3.61

2.65
2.58
2.39
1.81
1.67
1.66
1.63
1.61
1.58
1.56
1.46
1.45
1.40
1.27
1.24

31 (¹H-NMR)

2.00
1.11
1.99
1.02
1.01
3.11
1.02
2.11
1.11
3.10
2.14
9.18
3.31

0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

	Parameter	Value
1	Data File Name	BM-7-OH
2	Title	Jun24-2018
3	Comment	BM-7-OH
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	294.3
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	119
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-06-24T13:51:00
19	Modification Date	2018-06-24T13:51:47
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1545.2
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

BM-7-OH

155.07
143.13
140.15
138.92
133.43
129.37
127.96
79.74
62.18
49.21
36.76
32.46
29.24
28.48
25.49
25.00
23.84

31 (¹³C-NMR)

10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

	Parameter	Value
1	Data File Name	BM-7-OH
2	Title	Jun27-2018
3	Comment	BM-7-OH-PURE-13C
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	295.7
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	1536
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	1.3631
18	Acquisition Date	2018-06-27T16:35:00
19	Modification Date	2018-06-27T17:57:34
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1946.6
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

BM-7-OMs

32 (¹H-NMR)

Parameter	Value
1 Data File Name	BM-7-OMs
2 Title	Jun30-2018
3 Comment	BM-7-OMs
4 Origin	Bruker BioSpin GmbH
5 Owner	nmrsu
6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	294.9
11 Pulse Sequence	zg30
12 Experiment	1D
13 Number of Scans	16
14 Receiver Gain	57
15 Relaxation Delay	1.0000
16 Pulse Width	12.9500
17 Acquisition Time	4.0894
18 Acquisition Date	2018-06-30T20:17:00
19 Modification Date	2018-06-30T20:18:31
20 Spectrometer Frequency	400.13
21 Spectral Width	8012.8
22 Lowest Frequency	-1535.4
23 Nucleus	1H
24 Acquired Size	32768
25 Spectral Size	65536

BM-7-OMs

32 (¹³C-NMR)

Parameter	Value
1 Data File Name	BM-7-OMs
2 Title	Jun30-2018
3 Comment	BM-7-OMs-13C
4 Origin	Bruker BioSpin GmbH
5 Owner	nmrsu
6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	295.7
11 Pulse Sequence	zgpg30
12 Experiment	1D
13 Number of Scans	1098
14 Receiver Gain	211
15 Relaxation Delay	2.0000
16 Pulse Width	10.0000
17 Acquisition Time	1.3631
18 Acquisition Date	2018-06-30T20:24:00
19 Modification Date	2018-06-30T21:26:03
20 Spectrometer Frequency	100.61
21 Spectral Width	24038.5
22 Lowest Frequency	-1950.6
23 Nucleus	13C
24 Acquired Size	32768
25 Spectral Size	32768

BM-7-N-CYCLISED

33 (¹H-NMR)

Parameter	Value
1 Data File Name	BM-7-N-CYCLISED
2 Title	Jul17-2018
3 Comment	BM-7-N-CYCLISED
4 Origin	Bruker BioSpin GmbH
5 Owner	nmrsu
6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	295.0
11 Pulse Sequence	zg30
12 Experiment	1D
13 Number of Scans	2
14 Receiver Gain	31
15 Relaxation Delay	1.0000
16 Pulse Width	12.9800
17 Acquisition Time	4.0894
18 Acquisition Date	2018-07-17T11:20:00
19 Modification Date	2018-07-17T11:20:43
20 Spectrometer Frequency	400.13
21 Spectral Width	8012.8
22 Lowest Frequency	-1544.7
23 Nucleus	1H
24 Acquired Size	32768
25 Spectral Size	65536

BM-7-N-CYCLISED

33 (¹³C-NMR)

Parameter	Value
1 Data File Name	BM-7-N-CYCLISED
2 Title	Jul17-2018
3 Comment	BM-7-N-CYCLISED
4 Origin	Bruker BioSpin GmbH
5 Owner	nmrsu
6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	295.9
11 Pulse Sequence	zgpg30
12 Experiment	1D
13 Number of Scans	1536
14 Receiver Gain	211
15 Relaxation Delay	2.0000
16 Pulse Width	10.0000
17 Acquisition Time	1.3631
18 Acquisition Date	2018-07-17T23:47:00
19 Modification Date	2018-07-18T00:33:28
20 Spectrometer Frequency	100.61
21 Spectral Width	24038.5
22 Lowest Frequency	-1956.7
23 Nucleus	13C
24 Acquired Size	32768
25 Spectral Size	65536

33 (HSQC) M-7-N-CYCLISED

Chapter 3: Synthetic Approach towards the Strychnos Class of Alkaloids

3.1. Introduction:

2-Azabicycles possessing octahydroindole skeletons represent an important scaffold because of their prevalence in bioactive natural products and chiral drugs. Among these various alkaloids, we have selected *Strychnos* class of alkaloids. The *Strychnos* alkaloids encompasses an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids.[1] According to their biogenesis, they have been classified into two classes, Strychnan and Aspidospermatan with a topographical relationship.[2] According to the biogenesis of this class of alkaloids proposed by Scott [3] and Heimberger,[4] the alkaloids have been derived from geissoschizine **1**. Initially the extended tetracycle of **1** rearrange into dehydropreakuammicine **2**, which is the biogenetic precursor for the both curan and aspidospermatan alkaloids. The **C**, **D**, **E** tricycle of dehydropreakuammicine opens to give stemmadenine **3**. The condylocarpine skeleton generates with the rotation of the piperidine ring followed by reformation of the bond between **B** and **D** ring. On heating Condyfoline isomerises into tubifoline, but heating tubifoline does not yield condyfoline.

Figure 1: Biogenesis of *Strychnos* alkaloids

The most of the Strychnan alkaloids possesess curan type of skeleton which contains a pentacyclic 3,5-ethanopyrrolo[2,3-*d*]carbazole framework (Fig. 2) bearing two carbon appendage at C-20 (alkyl,alkylidene or oxygenated) and an oxidized one-carbon substituent C-

17) at C-16 (hydroxymethyl, formyl or methoxycarbonyl).[5] More than 125 alkaloids with the curan skeleton have been isolated, among which almost half of are the *Strychnos alkaloids.*

6
Curan skeleton and
biogenetic numbering

7 Tubifolidine, R = H
8 Tubifoline,   R = H (1,2-didehydro)
9 Geissoschizoline, R= CH$_2$OH
10 19,20-Dihydroakuammicine,
     R = CO$_2$Me (2,16-didehydro)

11 Norfluorocurarine, R = CHO
12 Fluorocurarine, R =CHO
     (N$_b$-   methyl)
13 Akuammicine, R = CO$_2$Me
14 Mossambine. R = CO$_2$Me
     (14 *S*-OH)

15 Echitamidine, R$_1$ = (*S*)-CHOHCH$_3$; R$_2$ = H
16 20-Epilochneridine, R$_1$ = Et; R$_2$ = OH
17 N$_b$-Demethylalstogustine, R$_1$ = H; R$_2$ = (*R*)-CHOHCH$_3$
18 Alstogustine (N$_b$-methyl)
19 19-Epialtogustine (N$_b$-methyl)

20 Wieland-Gumlich aldehyde

Aspidospermatan alkaloids, R = H, R′ = alkyl group

21   Condylcarpine , R = H, R' = CHCH$_3$
22   lagunamine , R = H, R' = CH(OH)CH$_3$

Figure 2: Representative Members of Curan and Aspidospermatan Alkaloids

Since the milestone synthesis of strychnine by Woodword, [6] the Strychnan alkaloids have been the subject of intensive synthetic investigation. The complicate structure of the strychnos alkaloids has long been served as an inspiration to develop new synthetic methodology and strategies. Much of this continuing inspiration has been focused on the synthesis of the heptacyclic alkaloid strychnine, [7, 8] while the pentacyclic curan alkaloids have received less attention.

3.1A. Structural features and synthetic challenge:

The curan alkaloids involve the pentacyclic alkaloids of the akuammicine-group as well as the hexacyclic alkaloids of the diaboline and spermostrychnine groups which contain an additional oxygenated ring linking C-17 with the two carbon chain at C-20.[9, 10] Strychnos alkaloids belong to the monoterpenoid indole alkaloid incorporating a spiro[pyrrolidine-3,3'-oxindole] associated with morphan scaffold.[11] Morphan scaffold is 2-azabicyclo[3.3.1]nonane framework, prominently featured in many complex and biologically active natural products as well as medicinal compounds of significant interest. Indolomorphans are the most advanced scaffold for the synthesis of strychnos class of alkaloids and it is the overall architecture of the corresponding alkaloids.

Figure 3: Structural features of Curan alkaloids.

There are several different strategies for the construction of the spiro[pyrrolidine-3,3'-oxindole] **24**,[12] which can be classified into those that form the crucial quaternary center at C-7 in the late stage of the synthesis and those in which the strategic bonds around C-7 are formed at the initial stages of the synthesis.The synthetic strategies to access the morphan skeleton developed so far can be classified into two distinct types: 1) the strategy which start from a carbocyclic ring system and construct the nitrogen ring on top of it; 2) the strategies that start with a piperidine ring and construct the carbocycle.[13a]

3.1A.1. Synthetic approaches from carbocyclic ring:

The majority of the approaches involve C(1) or C(5) atom in the bridge-bicyclic ring forming step, usually with a sp^2 hybridized carbon atom. The most successful approaches involve the formation of the C(4)-C(5) bond which have been applied in the synthesis of the strychnos class of alkaloids**.** The processes contain enolate alkylation, aldol reaction, metal promoted coupling reactions such as the Heck reaction, palladium-catalyzed alkenylation of enolates and radical procedures. The disconnection involving N-C(3) bond is rather unusual since it requires a previous *cis*-stereochemical relationship between the nitrogen and the involved side chain of the cyclcohexane derivative precursor.
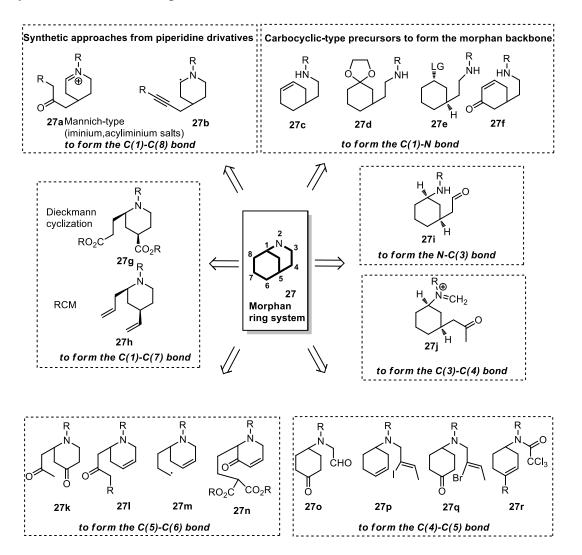
Figure 4: A conceptual overview of strategies to access morphan ring systems.[13b]

3.1A.2. Synthetic approaches from piperidine derivatives:

The construction of the 2-azabicyclo[3.3.1]nonane ring by carbocyclic ring formation from a piperidine ring has been less frequent than the aforementioned approaches, in which heterocyclic ring formation is in the late stage of the process. The most common procedures involve the formation of C(1)-C(8) bond, which usually involves an iminium or acyliminium salt as a counterpart of a nucleophilic species and C(5)-C(6) bond formation involving several strategies such as aldol reaction, Michael addition, radical mediated addition and dienolate coupling reactions. The two protocols Dieckmann cyclization and ring-closing metathesis involved in the formation of C(6)-C(7) bond.[14]

Few synthesis are known in the literature for these two alkaloids and this section would describe the synthetic strategies developed to tackle the synthetic challenge given by indolomorphan scaffolds for the synthesis of (-)-tubifoline and (-)-tubifolidine.

3.2. Literature precedents for the synthesis of (-)-tubifoline and (-)-tubifolidine:

3.2A. Synthesis of Tubifoline and Condyfoline by Harley-Mason:

The first synthesis of tubifoline was reported by Harley and Mason in 1968.[15] The indolizino[8,7-*b*]indole **28** was treated with acetic anhydride, the intermediate acyl ammonium ion underwent a nucleophilic ring opening to **30** and the addition of potassium cyanide to tetraalkylammonium **31** proceeded in the similar manner as to **32**.[16] Presumably the acyl ammonium ion was opened selectively due to the greater partial positive charge at the stabilized α-aryl position.

Scheme 1: Ring expansion of hexahydro-1*H*-indolizino[8,7-*b*]indole to octahydroazonino[5,4-*b*]indole.

To affect the synthesis, indole **28** was opened with a functionalized anhydride and after careful hydrolysis of the ester, all of the necessary carbons for several frameworks had been installed in **33**. Oxidation gave ketone **34**, that cyclized upon exposure to strong base to form the **D** ring of **35**. Exhaustive carbonyl reduction by using Wolf-Kishner condition created the skeleton of stemmadinine **36**. Oxidation of the amine to an iminium species and the subsequent cyclization gave both tubifoline **8** and condyfoline **37**.

Scheme 2: Synthesis of tubifoline and condyfoline by Harley-Mason

3.2B. Synthesis of tubifoline and condyfoline by Ban:

Capitalizing on a novel photocyclization adapted from a Fries type rearrangement that converts the tetrahydro-1*H*-carbazole **38** to **39** with 1,3-shift of acetyl group.[17]

Scheme 3: Fries type rearrangement of indole derivative **38**.

Ban subjected the same condition on tryptamine derived indole derivative **40**, which initially formed the unstable intermediate **41** and **42** with the addition of a tethered nucleophile which finally produced the macrolactam **43** through a subsequent rearrangement. Reduction of the amide gave amine **44**, the amine functionalization and regioselective oxidation intercepted the Harley-Mason's intermediate 3**4**. Following the same synthetic sequence similar to Harley-Mason, Ban continued to make varieties of the corresponding natural products including tubifoline and condyfoline.

Scheme 4: Synthesis of tubifoline and condyfoline by Ban.

Reagents and conditions:a) hv, 300W Hg lamp,ether, 90%; b) LiAlH₄, THF, reflux,4 h,54%; c) EtCHClCOCl, NaHCO₃, DCM, 1 h, 92%; d) I₂O5, 80% (v/v) aq. THF, 18 h, 65%; e) NaOCEtMe₂, THF, reflux, 1 h, 88%, α:β 3:2; f) KOH, N₂H₄.H₂O, ethylene glycol, 2 h, 57%, α:β 1:2; g) B₂H₆, THF, reflux, 1 h, 64%; h) PtO₂, O₂, EtOAc.

3.2C. Formal synthesis of Tubifoline and Condyfoline by Snieckus:

Snieckus approached the synthesis of the stemmadenine ring system differently which did not start with an indole derivative.[18] He used 4-oxo piperidine to install the piperidine ring **D** via Horner-Wadsworth-Emmons (HWE) process which produced **48**. The ethyl group of **49** was appended to the **D** ring by regioselective alkylation of the dienolate.[19] Reduction of the double bond of **49** followed by Madelung cyclization produced indole derivative **50**,[20] which upon demethylation of the amine and exchange of the trichloromethylacetamide for a monochloroacetamide provided macrocyclization precursor **51**. Photocyclization of **51** and reduction of **52** gave stemmadenine skeleton **36** which had previously been used to synthesize tubifoline and condyfoline.

Scheme 5: Synthesis of tubifoline and condyfoline by Snieckus.

Reagents and conditions: a) NaOEt, THF, 88%; b) i) n-BuLi(2eq.), TMEDA, ii) EtBr 80%; c) i) Pd/C, H₂, 85%, ii) t-BuOK, 340 °C, 76%; d) i) Cl₃CCH₂COCl, 44%, ii) Zn, AcOH, 79%, iii) ClCH₂COCl, NaOH, 72%; e) hv, Na₂CO₃, 20% ; f) LiAlH₄, THF, 63%.

3.2D. Asymmetric Synthesis of (-)-Tubifoline and (+)-Condyfoline by Bosch:

Almost two decades later, Bosch performed an asymmetric synthesis of (-)-tubifoline,[21] which was heavily based upon the approach of Snieckus. Enzymatic resolution of a racemic mixture of pyridyl ethanol **53** provided enantiomerically enriched in 96% *ee*. After reduction of the benzylated pyridinium ion to the corresponding tetrahydropyridine **53a**, Johnson-Claisen rearrangement established the significant chiral center in **54**. Indole synthesis and required functional handle substitution gave the cyclization precursor **55**, which is differed from precursor **51** of Snieckus by containing an olefin and optical enrichment. The cyclization produced **56**, reduction of both the amide and the double bond gave intermediate **36** reported by Harley-Mason. Finally oxidative cyclization produced (-)-tubifoline with a trace amount of (+)-condyfoline.

Scheme 6: Asymmetric synthesis of (-)-tubifoline reported by Bosch.

3.2E. Formal Synthesis of Tubifoline and Condyfoline, and Synthesis of Dehydrotubifoline by Takano:

Takano synthesized tubifoline through stemmadenine skeleton, but by a different approach. Alkylation of thioamide **57** with methylbromocrotonate produced sulfonium salt **58** which underwent remarkable cascade reactions upon treatment with a base. Tautomerisation of the sulfonium ion **58** to the thioamino ketene acetal and subsequent Claisen rearrangement followed by isomerisation of the resultant vinyl bond generated **59** with the *E*-ethylidene required for the final product. Bischler-napieralski-type cyclization garnered tetracycle **60** and the reduction of the ester followed by the cyclization formed intermediate **61.** Dissolving metal reduction of **60** generated stemmadenine skleton **62** which was a formal precursor to both tubifoline and condyfoline. Polonovski-Potier cyclization provided dehydrotubifoline **63**.

Scheme 7: Formal synthesis of tubifoline and condyfoline, and synthesis of dehydrotubifoline reported by Takano.[22]

Reagents and conditions: a) CH₂BrCHCHCO₂Me, quantitative; b) NaOMe, 83%; c) i) POCl₃, Δ, ii) NaBH₄, 54% E and 8% Z; d) i) DIBAL, PhH, 0 °C, ii) MsCl; e) Na, NH₃, 81% from the alcohol; f) i) mCPBA, 0°C, ii) TFAA, -78 °C to RT.

3.2F. Synthesis of Tubifoline by Bosch:

All of the approaches discussed so far shared the stemmadenine type skeleton as either the target or the penultimate compound. Bosch et al. have developed a route to tetracyclic uleine (**66**) type alkaloids and these scaffolds as common intermediates containing the A, B, C and D rings of the strychnos alkaloids.

Their synthesis started with **64** which were made in two steps from isonicotinate; an iminium ion was generated *in situ* with acid and indole was added as a nucleophile. The ethyl Grignard was added in the presence of Copper catalyst to install the ethyl substituent and provided a mixture of diastereomers of **65** that were cyclized in a Friedel-Crafts fashion giving the dasycarpidan type structure **66**.[23] Lithium aluminium hydride reduction of the ketone followed by epimer separation and deprotection gave the intermediate **67.** Alkylation of amine **67** provided ethyl acetal which on exchanging generated thiomethyl acetal, a functional handle for the introduction of the next ring. The cyclization was done by using dimethyl(methylthio)

sulfonium fluoroborate (DMTSF) and reduction of the thiomethyl group of **69** with Raney nickel which concomitantly reduced the indolenine and provided tubifolidine. Acylation of the indolenine moiety of **69** proceeded with the tautomerization of the double bond which was followed by desulfurization to give **70.** The deprotection of the compound **70** under basic condition furnished tubifoline.

Scheme 8: Synthesis of tubifoline by Bosch.

Reagents and conditions: a) i) indole, AcOH/H$_2$O, ii) EtMgBr, CuI(cat.), 85%; b) i) Ba(OH)$_2$, ii) PPA, 32%; c) i) LiAlH$_4$, dioxane, Δ, 75%, (separated 1:1 mixture of epimers), ii) Pd(OH)$_2$ (cat), H$_2$, 73% from β epimer; d) i) CH$_2$BrCH(OEt)$_2$, Na$_2$CO$_3$, dioxane,Δ, 58%, ii) BF$_3$OEt$_2$, MeSH, 74%; e) DMTSF [dimethyl(methylthio)sulfonium fluoroborate], 0 °C, 52%; f) i)ClCO$_2$Me, NaH, 67%, ii) Raney Ni, EtOH,Δ, 45%; g) NaOMe, MeOH, Δ, 80%.

3.2G. Synthesis of Tubifolidine by Bonjoch and Bosch:

Synthesis started from the multi-gram availability of the octahydroindole **73**, which was prepared from the 1,3-cyclohexadione **71** through one pot procedure involving the ozonolysis of the allyl group followed by double (inter and intramolecular) reductive amination.[24] The closure of the piperidine D ring was done by forming C15-C20 bond involving intramolecular conjugate addition of the enone derivative **73**. The formation of the indoline ring at the final step of the synthesis was performed by a reductive cyclization of the α-(2-nitrophenyl)ketone moiety which gave tubifolidine.

Scheme 9: Synthesis of tubifolidine by Bosch and Bonjoch.

Reagents and conditions: a) i) O₃ (1 equiv.), DCM, -78 °C. 2 h, ii) CH₃NH₂.HCl (4 equiv.), NaBH₃CN, MeOH, room temp., 4 h, 62% for two steps, iii) ClCO₂CHClCH₃ (1 equiv.) DCE, reflux, 3 h, iv)HMDS (3 equiv.), Me₃SiI (2 equiv.), DCM/pentane (1:1), -20 °C, 6 h, v) PhSeCl (1 equiv.), (PhSe)₂ (1 equiv.), THF, -35 °C, 90 min, vi) O₃ (1 equiv.), DCM, -78 °C, 3 min, then i-PrNH₂ (1 equiv.), 15 min. 52% for 4 steps; b) i)MeOH, reflux, 3 h, ii) Methyl vinyl ketone (1:1), Et₃N, MeOH, room temp., 1.4 h, 74% for two steps; c) i) (R)- α-methylbenzylamine (2 equiv.), 3Aᵒ-molecular sieves, THF, room temp., 4 days, ii) aq. AcOH (20%), room temp., 24 h, 67%; d) (HSCH₂)₂ (8 equiv.), AcOH, BF₃OEt₂ (5 equiv.), room temp., 24 h, 80%; e)Bu₃SnH (15 equiv.), AIBN, benzene, 80 °C, 16 h, 50%.

3.2H. Synthesis of Tubifolidine by Shibasaki:

Synthesis started from the optically pure **76** which was converted into an indole derivative **77** by applying a highly regioselective Fisher method followed by decarboxylation.[25] The protected indole (*tert*-butyl carbamate) underwent aldol condensation followed by dehydration through the mesylate to give **78**. The reduced ester was oxidized into the aldehyde **79**, which was subjected to reductive amination and the resulting amine was cyclized to form the piperidine ring D by employing DDQ as an oxidant. The dithioacetal **68** was finally transformed into tubifolidine.

Scheme 10: Synthesis of tubifolidine by Shibasaki

Reagents and conditions: (a) i) PhNHNH₂.HCl (1.05 equiv), AcOH, 80 °C, ii) LiCl (2.0 equiv), H₂O (1.0 equiv), DMSO, 180 °C, 92% (99% ee) (2 steps); b)i) (Boc)₂O (1.2 equiv), Et₃N (2.0 equiv), DMAP (cat.), CH₂Cl₂, rt, 97%; ii) LDA (1.3 equiv), THF, -78 °C; acetaldehyde (2.0 equiv), iii) MsCl (1.5 equiv), i-Pr₂NEt (3.0 equiv), toluene, rt; DBU (4.3 equiv), 50 °C, 89% (2 steps); c) i) DIBAL (3.0 equiv), toluene, -78 °C, conv. 97%; ii) MnO₂ (excess), pentane, rt, 94%; d) 2,2-dimethoxyethanamine (2.1 equiv), Ti(O-i-Pr)₄ (2.5 equiv), toluene, rt; NaBH₄ (10 equiv), CH₃OH, 0 °C, 96%; e) TFA (excess), anisole (10 equiv), 0 °C, 98%; f) i) DDQ (1.1 equiv), Na₂HPO4 (10 equiv), degassed THF, -20 °C to 0 °C, conv. 67%, ii) H₂ , (Ph₃P)₃RhCl (cat.), benzene:2-PrOH (5 : 1), rt, iii) EtSH (excess), BF₃ .Et₂0 (8 equiv), MS 3A, CH₂Cl₂, 0 °C to rt, 66% (2 steps); f) i) DMTSF (2.1 equiv), CH₂Cl₂, 0 °C, 68%; ii) LiAlH₄ (4.8 equiv), THF, 0 °C, iii) Raney Ni (W2) (excess), EtOH, reflux, 35% (2 steps).

3.2I. Asymmetric synthesis of (-)-Dehydrotubifoline and (-)-Tubifoline by Mori:

A novel approach for the synthesis of indole skeleton was developed by Mori et al. for the purpose of the total synthesis of (-)-tubifoline. Treatment of a cyclohexenol derivative **81** having a silyloxymethyl group at the 2-position with *N*-tosyl-*o*-bromoaniline **82** in the presence of Pd₂dba and (*S*)-BINAPO gave compound **83** with 84% *ee* in 75% yield.[26] The compound **83** was converted into **84** which gave indoline derivative **85** by the treatment of palladium acetate and dimethyl phenyl phosphine in the presence of silver carbonate. The five membered ring C was formed by the allylic oxidation of the necessary protected amine, which was made by the reduction of the cyano group followed by the protection of the amine group using Boc-anhydride. Transposition of the double bond position in the cyclohexene ring gave **88** which

was used to form C15-C20 bond through Heck coupling which resulted dehydrotubifoline. The reduction of olefinic double bond of dehydrotubifoline gave tubifoline in 32% yield.

Scheme 11: Synthesis of (-)-dehydrotubifoline and (-)-tubifoline.

Reagents and conditions: a) Pd₂(dba)₃ .CHCl₃ (2.8 mol %) (S)-BINAPO (5.6 mol %) DMF, rt, 3h, 85%; b) (i) 4 N aqueous HCl, (ii) PBr₃, (iii) NaCN, 86%; c) 2 mol % Pd(OAc)₂, 4 mol % Me₂PPh, Ag₂CO₃ (1 equiv), DMSO, 90 °C, 17 h, 87%;d) (i) LiAlH₄, (ii) Boc₂O, (iii) 10 mol % Pd(OAc)₂, 40 mol % benzoquinone, MnO₂ (2 equiv) AcOH, 50 °C, 20 h, 77%; e) i) 9-BBN,50 °C, then H₂O₂, ii) Swern oxidation, 70%; f) i) PhNTf₂, KHMDS, ii)Pd(OAc)₂, PPh₃, HCO₂H, iPr₂Net, 64%; g) 10 mol % Pd(OAc)₂, Bu₄NCl (1 equiv) K₂CO₃ (5 equiv) DMF, 60 °C, 3 h, 59%; h) H₂, PtO₂, EtOH, rt, 32%.

3.3. Aim of the present study:

Our continuing interest in exploring the application of our synthesized three 2-azabicyclic scaffold led us to envisage to find out an efiicient and scalable synthetic route for the total synthesis of alkaloids with complex architecture. The following section will describe the efforts to establish a synthetic route for the synthesis of strychnos class of alkaloids.

3.4. Designing of a synthetic plan:

The all three scaffolds are equipped with vinyl sulphone functionality which can be elaborated to propagate the synthesis of natural products. Our preliminary focus was to construct the morphan skeleton using our *cis*-hexahydroindole scaffold **1** and then installation of the

spiro[3,3'-oxindole]nonane framework at the final step of the synthesis of (-)-tubifoline and (-)-tubifolidine.

90

cis-hexahydroindole

91

cis-octahydroquinoline

92

cis-octahydrobenzo[*b*]azepine
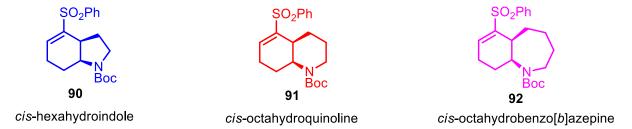
Figure 5: 2-azabicyclo[*m.n*.0]alkane ring system.

The presence of olefinic double bond in the above mentioned three 2-azabicyclic rings allowed the intermediate to undergo various transformation such as conjugate addition,[27] dihydroxylation,[28] epoxidation,[27,29] aziridination,[30] cyclopropylation,[31] Diel-Alder cycloaddition,[32] allylic oxidation for the functionalization of other carbon centers present in cyclohexane ring. We have exploited the all three basic scaffold by using the synthetic potential of embedded olefinic sulphone for the synthesis of natural products.
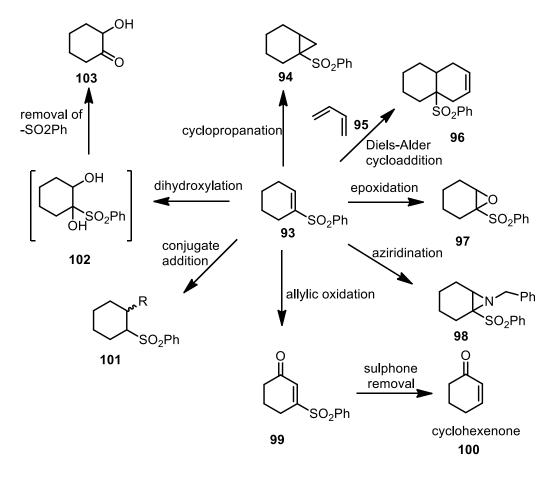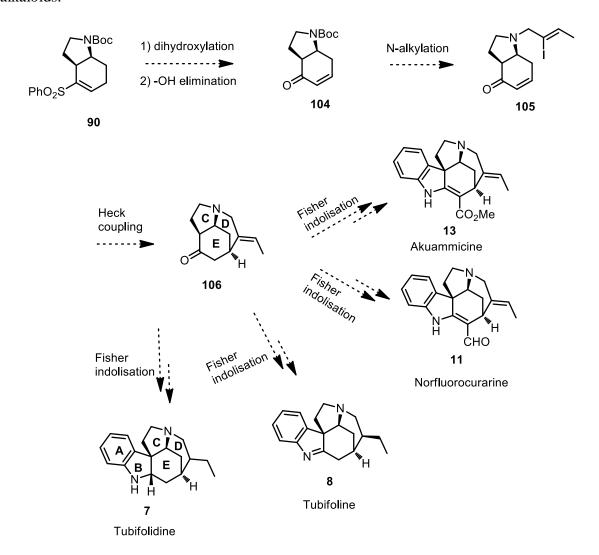
Figure 6: Synthetic versatility of olefinic sulphone embedded in cyclohexane ring.

After having hexahydroindole scaffold **90** in multi-gram scale in hand, it was envisioned that the vinyl sulphone group will be converted into enone functionality by applying dihydroxylation[28g,28h,28i] and subsequent hydroxyl group elimination.[35] Furthermore, the enone functionality which is a combination of two most popular reactive functional group such as a ketone and electron deficient olefinic double bond, would undergo 1, 4-addition to provide the piperidine ring **D** through the formation of C15-C20 bond[33] and the ketone group would be the basis for Fisher indolization to provide diverse structures of indole derivatives.[34] Once *N*-alkylation of **104** will be done,[33] the intermediate **105** would be ready for the Heck coupling to form 2-azabicyclo[3.3.1]nonane ring. Fisher indolization on aza-[6,5,6]-tricyclic core **106** would supply the required indolenin structures to furnish the corresponding strychnos alkaloids.[36]

Scheme 12: An Overview of synthetic strategy for the synthesis of strychnos class of alkaloids.

3.5. Results and discussions:

In order to test the feasibility of our strategy as depicted above, we needed to develop a condition which could provide **104** in good amount and thus we proceeded to prepare alpha keto hydroxy compound in quantitative yield which would provide the desired enone **104** by elimination of the hydroxyl group.

3.5A. Synthesis of 104:

The synthesis of the alpha keto hydroxyl compound **107** commenced with the dihydroxylation of the hexahydroindole scaffold **90**, which was already synthesized in multi-gram quantity from our common scaffold 7-azabicyclo[2.2.1]heptane in a very short and efficient way.

To affect the quantitative dihydroxylation of electron deficient olefinic double bond of the **90**, we used citric acid with the osmium tetroxide to accelerate the reaction.[28] Citric acid makes an adduct with osmium tetroxide, which plays the actual role in dihydroxylation and subsequent removal of sulphone group provided the alpha hydroxyl compound **107** in 88% yield.

Citric acid has been shown to accelerate the reaction rates and improve the yields of *cis*-dihydroxylations of various electron-deficient alkenes. Citric acid strongly binds to osmium tetroxide to form monoglycolate **107a**. Redox addition of monoglycolate **107a** to the vinyl sulphone provided mixed (bis)glycolate **107b** species. Rate-limiting hydrolysis of the mixed (bis)glycolate **107b** afforded the desired acyloin and Os(VI) monoglycolate **107d**.

Scheme 13: Citric acid assisted osmylation of cyclic vinyl sulphone **90**.

Addition of citric acid also increases catalyst turnover by preventing the formation of the catalytically unreactive dioxoosmate dianion species **107c**, which is formed upon deprotonation of hydrated (bis)glycolate **107b.H2O** at higher pH. The co-oxidant NMO convert Os(VI) monoglycolate **107d** into monoglycolate **107a**. The proximal acidic moieties acts as a buffer in hydrated (bis)glycolate **107b.H2O** preventing buildup of dioxoosmate **107c**.

Scheme 14: Synthesis of Enone **104**.
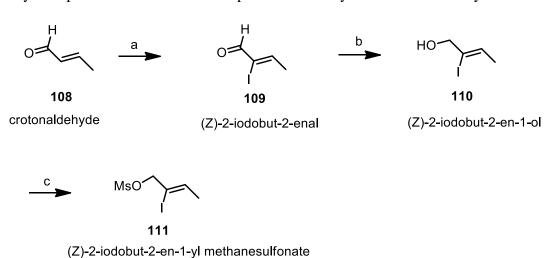
Reagents and conditions: a) OsO₄ (6 mol%, 0.1M solution in tert-butanol), NMO (6 equiv.), citric acid (3 equiv.), tert-butanol:water (2:1), 3 h at 0 °C and 30 min at rt, 88%; b) i) MsCl (5

equiv.), dry DCM : dry pyridine (3:1), rt, 24 h, ii) Li$_2$CO$_3$ (5 equiv.), LiCl (10 equiv.), dry DMF, reflux, 2 h, 67%.

The elimination was effected by converting hydroxyl group to its mesylate and the mesylate was removed under basic condition. Mesylation was done using mesyl chloride in presence of dry pyridine at room temperature and the mesylate was subjected to reflux condition in dry dimethyl formamide (DMF) using lithium carbonate (Li$_2$CO$_3$) as a base to afford the crucial enone **104**,[35] which would carry our synthesis in forward.

3.5B. Synthesis of 111:

After having **104** in hand, the crucial task was the selection of the coupling partner tethered with the amine group for the Heck coupling required to form the piperidine ring **D**. Keeping in mind the geometry of the olefin, we needed the vinyl iodo compound with **Z** configuration. Therefore, the required iodo compound for *N*-alkylation would be the mesylate product of (*Z*)-2-iodobut-2-1-ol which have been derived from the crotonaldehyde. The iodination of crotonaldehyde was done by using iodine in aquous tetrahydrofuran (THF) in presence of potassium carbonate (K$_2$CO$_3$) and the reduction of the aldehyde **109** by sodium borohydride (NaBH$_4$) in methanol which gave required (*Z*)-2-iodobut-2-1-ol **110**. The alcohol **110** yielded the mesylated product **111** in 83% in the presence of mesyl chloride and triethyl amine.[33]

108
crotonaldehyde

109
(Z)-2-iodobut-2-enal

110
(Z)-2-iodobut-2-en-1-ol

111
(Z)-2-iodobut-2-en-1-yl methanesulfonate

Scheme 15: Synthesis of iodo compound **111**.

Reagents and conditions:a)I$_2$, K$_2$CO$_3$, DMAP (cat.), 3 h; b) NaBH$_4$ (3 equiv.), MeOH, 0 ºC, 2 h, 54% for two steps; c) MsCl, triethyl amine, DCM, rt, 2 h, 80%.

3.5C. Synthesis of the aza-[6,5,6]-tricyclic Core 112:

Our next effort was to find a protocol to construct the piperidine ring **D** from the enone **104** in a very efficient way and in enough amount so that we could be able to synthesize various alkaloids. The *N*-alkylation process commenced with the deprotection of the N-carbamate using trifluroacetic acid (TFA) and the deprotected amine was subjected to iodo compound **111** in presence of potassium carbonate which gave desired *N*-alkylated product **105**. [33] At this stage, we started to find an efficient protocol for the construction of the crucial piperidine **D** ring. With the required *N*-alkylated product **105** in hand, we next explored the possibility of performing conjugate addition with the hope to obtain cyclized product using tertiary butyl lithium (*t*-BuLi), but could not produce effective result and failed to provide the desired product. The use of Ni(COD)₂ for the necessary cyclization also could not give the solution.[37] After several attempts, it was noticed that the reductive Heck condition using palladium acetate in presence of tetra butyl ammonium chloride (TBAC) and sodium formate was effective reaction condition to perform this cyclization in moderate yield. [38] However, proton NMR studies showed that the product was not the desired one, instead it formed the aza-[6,5,6]-tricyclic core structure **112** with the isomerisation of the olefin of **106** for gaining stability over another isomer **106**.[38c]

Scheme 16: Synthesis of Tricyclic intermediate **112**.

Reagents and conditions: a) i) Trifluoroacetic acid (TFA, 5 eq), dry DCM, 0 °C to rt, 5 h, ii) 111 (1.1 eq), K₂CO₃ (5 eq), dry acetonitrile (ACN), rt, 12 h; b) Pd(OAc)₂ (0.1 eq), TBAC (2.5 eq), HCO₂Na (1.6 eq), dry DMF, 80 °C, 3 h, 48% overall yield.

This result stipulated that exo-double bond of compound **106** was catalysed again by palladium species generated in the reaction mixture to afford the most stable analogue **112**. According to the mechanism of reductive Heck reaction as well as the nature of the palladium catalyst, it is highly propabable that the isomerisation proceeded due to re-addition-elimination of [HPdX] species (generated in the reaction mixture by the combination of hydrohalic acid and palladium) toward the *exo*- double bond.

After succeeding in carrying out the Heck coupling, we obtained aza-[6,5,6]-tricyclic product **104** in good yield, but it was not that tricyclic intermediate (**106**) as depicted in our proposed synthetic plan.

Owing to our sustained interest towards the synthesis of strychnos alkaloids and on careful observation, we envisioned that though the intermediate **112** have lost the opportunity to unravel our actual synthetic goal, but still there is some possibility to utilize the aza-tricyclic intermediate **112** in the synthesis of tubifoline and tubifolidine. According to synthetic plan, the Fisher indolisation product **113** of the tricyclic intermediate **112** would serve tubifoline **8** on reduction of the olefin and the reduction of imine will provide tubifolidine **7**.

Scheme 17: Synthetic plan for the synthesis of tubifoline and tubifolidine.

3.5D. Re-assessment of the Proposed Synthetic Strategy to Access the Strychnos Alkaloids:

Regrettably, several conditions were tried for the necessary Heck cyclization but in most of the cases starting material decomposed or could not provide the desired tricyclic product **106**. This unfortunate problem of undesired olefin isomerisation outcome in crucial Heck coupling, necessitated a reassessment of the proposed synthetic sequence to access the diverse strychnos alkaloids. Since the hydrohalic acid and the corresponding HPdX species generated in the reaction mixture was responsible for the undesired exo double bond isomerisation, thus we

needed to perform the Heck reaction under basic condition to inhibit the formation of HPdX species, and the product stability should be higher under the applied condition. To address this issue, we first tried to find out the condition for this type of intramolecular Heck cyclisation applied to the similar type of framework. We were very delighted by the literature report that inspired us to develop an alternative synthetic sequence towards the synthesis of various alkaloids. Viresh Rawal reported this type of Heck cyclisation on indole derivatives to make indolo morphan skeleton and the transformation led to the synthesis of dehydrotubifoline. [39]

Scheme 18: Heck coupling to access morphan skeleton reported by Viresh Rawal.

This suggests that we need to have first Fisher indole product of the *N*-alkylated compound **97**, which would provide the desired Heck cyclized product **69**.

Scheme 19: Proposed synthetic sequence for the synthesis of dehydrotubifoline.

Dehydrotubifoline could be used to synthesize akuammicine and other related alkaloids. This cyclization also creates an opportunity to synthesize strychnine by increasing carbon chain length and functional group manipulation of iodo compound.

3.6. Conclusion:

We have been able to construct the morphan skeleton which was the most difficult part of the synthesis. The synthesis of the pivotal CDE ring system of the Strychnos alkaloids has been achieved utilizing the *cis*-hexahydroindole scaffold **90.** The synthetic potential of the embedded olefinic sulphone moiety in the cyclohexane ring has been used to construct the

morphan skeleton. The tricyclic CDE core is a set up for further elaboration toward the total synthesis. Future effort will be aimed at the completion of the target alkaloids as well as the exploration of our synthetic route towards other biologically important alkaloids.

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3.8. Experimental Procedures and Spectral Data:

Synthesis of (±) (3a*S*,7a*S*)-*tert*-butyl 5-hydroxy-4-oxooctahydro-1*H*-indole-1-carboxylate (107):

To a magnetically stirred solution of **90** (2.0 g, 5.5 mmol) in *tert*-butanol/water (v/v 2:1 20mL) was dissolved *N*-methylmorpholine-*N*-oxide (3.8 g, 33.0 mmol, 6 equiv.) and cooled to 0 °C. To above stirred solution, 0.1 M OsO_4 solution in tertiary butanol (1.6 mL, 0.16 mmol, 0.03 equiv.) was added followed by anhydrous citric acid (3.2 g, 16.5 mmol, 3.0 equiv.). The resulting mixture was stirred vigorously at 0 °C for 3 h. The reaction mixture was allowed to warm to room temperature (25 °C) and stirred further for 30 minutes. The stirred mixture was re-cooled to 0 °C, diluted with ethyl acetate (50 mL) and saturated sodium bicarbonate solution (50 mL) was added. The reaction mixture was quenched with saturated sodium thiosulfate ($Na_2S_2O_3$) solution (10 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with brine (1 × 50 mL), dried over anhydrous sodium sulphate (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude product was passed through a short column of silica gel (100-200) using hexane/ethyl acetate (3:2) and concentrated under reduced pressure to provide *α*-hydroxyketone product **107** (1.2 g, 88% yield) as colourless viscous oil.

Yield: 88%

TLC: R*f* = 0.42 (SiO$_2$, Hexane : Ethyl acetate = 1:1)

¹H NMR (400 MHz, CDCl₃) δ: 4.45 (d, *J* = 7.5 Hz, 1H), 4.34 – 4.22 (m, 1H), 4.22 – 4.11 (m, 1H), 4.06 (dt, *J* = 11.3, 6.3 Hz, 1H), 3.95 – 3.83 (m, 1H), 3.66 – 3.46 (m, 2H), 3.43 – 3.27 (m, 1H), 3.17 – 3.01 (m, 1H), 2.97 – 2.87 (m, 1H), 2.65 – 2.46 (m, 1H), 2.46 – 2.34 (m, 1H), 2.31 – 2.16 (m, 2H), 2.04 (dddd, *J* = 15.0, 12.2, 10.4, 7.5 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.72 – 1.49 (m, 2H), 1.47 – 1.40 (m, 9H).

¹³C NMR (101 MHz, CDCl₃) δ: 210.90, 155.01, 79.78, 73.78, 54.91, 46.89, 34.33, 31.23, 28.60, 26.42, 24.09.

HRMS (ESI): *m/z* calculated for $C_{13}H_{21}NO_4Na$ ([M+Na]$^+$) 278.1368; found 278.1368 ([M+Na]$^+$).

Synthesis of (±) (3a*S*,7a*S*)-*tert*-butyl 4-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1-carboxy late (104):

To a solution of **107** (0.7 g, 2.7 mmol) in dry DCM and dry pyridine (3:1, 10 mL) in a round-bottom flask equipped with a magnetic stir bar and argon gas balloon was added methanesulfonyl chloride (1.0 mL, 13.7 mmol, 5 equiv.) at 0 °C. The reaction mixture was allowed to stir at room temperature for 24 h, diluted wih DCM (20 mL) and quenched with water (5.0 mL). The organic layer was separated, washed with water (2 x 10 mL), dried over anhydrous magnesium sulphate ($MgSO_4$), filtered and concentrated by rotary evaporation. The crude mesylate was dissolved in 15 mL of dry DMF together with dry lithium bromide (1.2 g, 13.7 mmol, 5 equiv.) and dry lithium carbonate (3.0 g, 41.1 mmol, and 15 equiv.). The reaction mixture was refluxed for 2 h, then cooled to room temperature and poured into an equal volume of ice- water. Brine solution (10 ml) was added to the reaction mixture and extracted with 2 x 50 mL of ether:hexane (7:3) mixture. The mixture was dried over anhydrous sodium sulphate (Na_2SO_4), evaporated the mixture of solvent by rotary evaporation and was dired in *vacuo*. The crude enone was purified by column chromatography (hexane:ethyl acetate, 3:1) to obtain **104** as a white solid (0.43 g, 67%).

Yield: 67%

TLC: R_f = 0.52 (SiO_2, Hexane : Ethyl acetate = 3:1)

m.p.: 86-87 °C

¹H NMR (400 MHz, CDCl₃) δ 6.86 − 6.81 (ddd, *J* = 10.1, 5.5, 3.0 Hz, 1H), 6.12 − 6.04 (ddd, *J* = 10.2, 2.7, 1.2 Hz, 1H), 4.44 − 4.22 (m, 1H), 3.54 − 3.33 (m, 2H), 2.96 − 2.78 (m, 2H), 2.52 − 2.28 (m, 1H), 2.23 − 2.15 (m, 1H), 2.13 − 1.96 (m, 1H), 1.46 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 198.37, 154.42, 147.70, 129.26, 79.91, 55.41, 48.19, 45.86, 28.65, 25.00.

HRMS (ESI): *m/z* calculated for $C_{13}H_{19}NO_3Na$ ([M+Na]$^+$) 260.1263; found 260.1263 ([M+Na]$^+$).

Synthesis of (Z)-2-iodobut-2-en-1-ol (110):

108

crotonaldehyde

109

(Z)-2-iodobut-2-enal

110

(Z)-2-iodobut-2-en-1-ol

To a stirred solution of crotonaldehyde (**108**) (5.0 g, 71.3 mmol) in THF and water (1:1, 200 mL) was added K_2CO_3 (11.8 g, 85.6 mmol, 1.2 equiv.), I_2 (27.1 g, 107.0 mmol, 1.5 equiv.) and DMAP (1.7 g, 14.3 mmol, 0.2 equiv.) sequentially at room temperature. The reaction mixture was stirred for 3 h, then diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHSO_3$ (100 mL) and 0.1 M HCl (100 mL) successively. The organic layers were dried over anhydrous $NaSO_4$, evaporated the solvents and the crude product (**109**) obtained was used in the next step without any purification. A solution of the crude product in CH_3OH (150 mL) was cooled to 0 °C and $NaBH_4$ (2.7 g, 71.3 mmol) was added in portions. The reaction mixture was stirred for 2 h at 0 °C and the solvent was evaporated. The residue obtained was dissolved in EtOAc (100 mL) and washed with 1 M NaOH solution (30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude alcohol was purified by column chromatography using hexane:ethyl acetate (3:1) to obtain **110** (7.6 g, 54% over 2 steps) as a clear, colorless oil.

Yield: 54%

TLC: R_f = 0.43 (SiO$_2$, Hexane : Ethyl acetate = 4:1)

^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.94 – 5.92 (q, *J* = 6.4 Hz, 1H), 4.20 (d, *J* = 5.3 Hz, 2H), 2.75 (bs, *J* = 6.0 Hz, 1H), 1.77 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 131.21, 109.63, 71.53, 21.48.

HRMS (ESI): *m/z* calcd. for C_4H_7IO ([M+Na]$^+$) 220.9439; found: 220.9442 ([M+Na]$^+$).

(Z)-2-iodobut-2-en-1-yl methanesulfonate (111):

110
(Z)-2-iodobut-2-en-1-ol

111
(Z)-2-iodobut-2-en-1-yl methanesulfonate

To a stirred solution of the alcohol **110** (7.6 g, 38.4 mmol) in dry DCM (150 mL) was added methanesulfonyl chloride (4.4 mL, 57.6 mmol, 1.5 equiv.) dropwise at 0 ºC and the reaction mixture was stirred for 10 minutes at the same temperature. Triethyl amine (8.0 mL, 57.6 mmol, 1.5 equiv.) was added to the reaction mixture and stirred further for 2 h. The excess mesyl chloride was reacted with water (50 mL) and brine solution (30 mL) was added to it. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude mesylate was done by column chromatography using hexane:ethyl acetate (3:1) and obtained the mesylate (8.8 g, 80%) **111** as a pale brown liquid.

Yield: 80%

TLC: R_f = 0.52 (SiO$_2$, Hexane : Ethyl acetate = 3:1)

^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.20 − 6.15 (qt, *J* = 6.4, 1.0 Hz, 1H), 4.87 (dd, 2H), 3.04 (s, 3H), 1.82 − 1.80 (dt, *J* = 6.4, 1.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 138.44, 98.53, 77.44, 38.83, 21.81.

HRMS (ESI): *m/z* calcd. for $C_5H_9IO_3S$ ([M+Na]$^+$) 298.9215; found: 298.9220 ([M+Na]$^+$).

Synthesis of (±) (3a*S*,7a*S*)-1-((Z)-2-iodobut-2-en-1-yl)-3,3a,7,7a-tetrahydro-1*H*-indol-4(2*H*)-one (105):

104

1) TFA
   dry DCM

2) 103
   K$_2$CO$_3$
   dry ACN

105

To a stirred solution of the enone **104** (0.4 g, 1.7 mmol) in dry DCM (5 mL) under argon gas balloon was added trifluoroacetic acid (0.64 mL, 8.4 mmol, 5 equiv.) dropwise at 0 ºC. The

reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was monitored by TLC till the complete removal of the tertiary butyl carbamate group. After complete removal of the Boc group, the reaction mixture was concentrated and the excess TFA was also evaporated by using rotary evaporator.

The crude amine was dissolved in dry acetonitrile (5 mL) equipped with a magnetic stirrer bar and argon gas balloon. The mesylate compound **111** (0.51 g, 1.8 mmol, 1.1 equiv.) and K_2CO_3 (1.1 g, 8.4 mmol, 5 equiv.) were added sequentially to the stirred reaction mixture at room temperature. The reaction mixture was stirred for 12 h and filtered through a short pad of celite. The solvent was evaporated under vaccum and the obtained N-alkylated product was pure enough to proceed further for the crucial Heck cyclisation.

TLC: R_f = 0.52 (SiO$_2$, Hexane : Ethyl acetate = 3:1)

^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.80 – 6.75 (dddd, J = 10.0, 4.6, 3.8, 1.2 Hz, 1H), 6.09 – 6.04 (dt, J = 10.2, 2.0 Hz, 1H), 5.88 – 5.82 (qt, J = 6.4, 5.2, 1.1 Hz, 1H), 3.60 – 3.53 (m, 1H), 3.25 – 3.14 (m, 2H), 3.01 (dt, J = 15.4, 5.6 Hz, 1H), 2.82 – 2.75 (m, 1H), 2.56 – 2.51 (ddd, J = 7.0, 4.4, 2.1 Hz, 2H), 2.37 – 2.22 (m, 2H), 2.07 – 1.97 (m, 1H), 1.76 – 1.74 (ddd, J = 6.4, 1.5, 1.0 Hz, 3H).

Mass: *m/z* calculated for $C_{12}H_{16}NONa$ ([M+Na]$^+$) 340.0174, $C_{12}H_{17}NO$ ([M+H]$^+$) 318.0355; found 340.0167 ([M+Na]$^+$) and 318.0345 ([M+H]$^+$).

Note: As the compound is not stable enough on silica for purification, the data provided was contain the mixture of product and iodo compound.

Synthesis of (±) (3a*S*,6*R*,7a*S*)-8-ethyl-3,3a,5,6,7,7a-hexahydro-1,6-ethenoindol-4(2*H*)-one (112):

A 100 mL two necke round bottom flask was charged with TBAC (dried under vacuum, 1.2 g, 4.2 mmol, 2.5 equiv.). The α, *β*-unsaturated ketone **105**, HCO$_2$Na (0.18 g, 2.7 mmol) and 5 mL dry DMF were added, and the mixture was degassed using Freeze-Pump-Thaw (3 times). To

this suspension Pd(OAc)$_2$ (37.8 mg, 0.17 mmol, 0.1 equiv.) was added at room temperature under argon atmosphere, and degassing was continued for an additional 10 min. The reaction mixture was stirred at 80 °C for 3 h under argon gas balloon and was quenched with H$_2$O (5 mL). The reaction mixture was extracted with EtOAc (2 × 20 mL), organic layer was separated, washed with brine solution (2 × 5 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The obtained residue was subjected to column chromatography on silica gel (100-200 mesh) using hexane:ethyl acetate (3:2) to afford 154.7 mg (48% overall yield for three steps) of the morphan skeleton **112**.
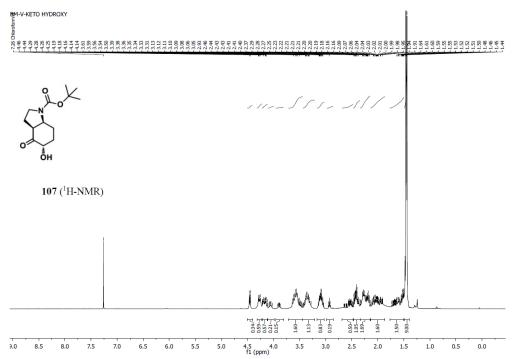
Yield: 48%

TLC: R$_f$ = 0.36 (SiO$_2$, Hexane : Ethyl acetate = 3:1)
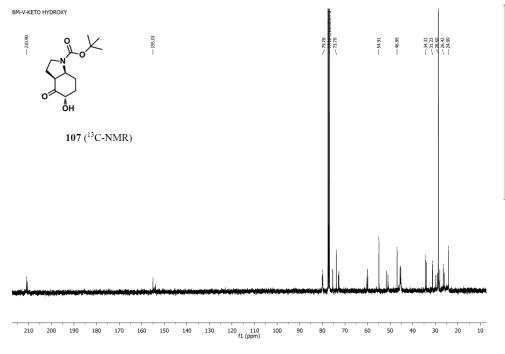
^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.39 (s, 1H), 3.45 (td, *J* = 7.5, 5.0, 2.2 Hz, 1H), 3.01 (dd, *J* = 8.6, 6.6 Hz, 2H), 2.61 – 2.56 (m, 1H), 2.55 – 2.52 (m, 1H), 2.49 – 2.47 (m, 1H), 2.46 – 2.37 (m, 3H), 2.34 – 2.29 (m, 1H), 1.90 – 1.81 (m, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).

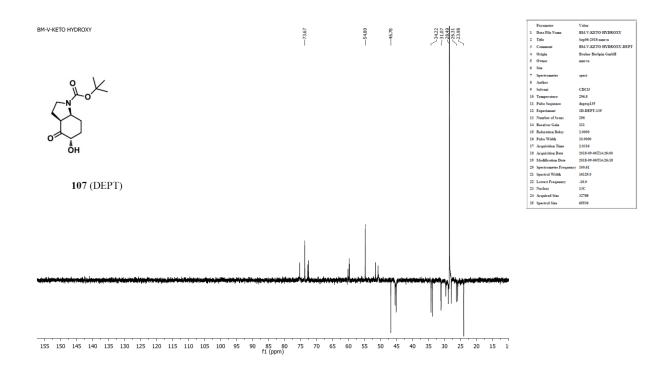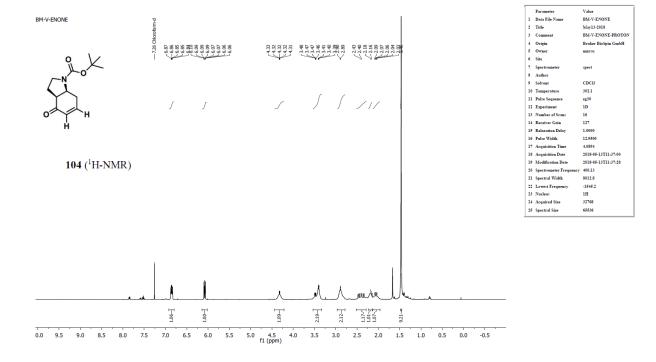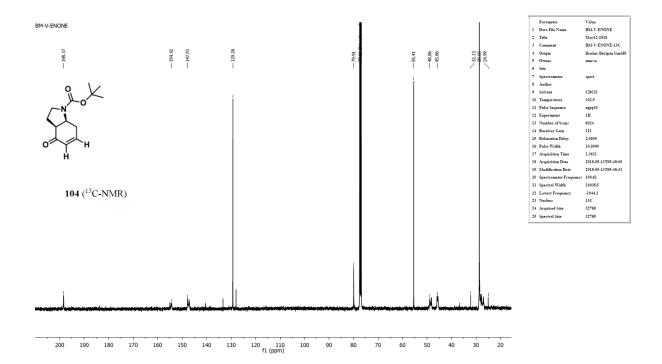**HRMS (ESI)**: *m/z* calculated for C$_{12}$H$_{18}$NO ([M+H]$^+$) 192.1388; found and 192.1365 ([M+H]$^+$).

3.9. Spectras:

107 (¹H-NMR)

107 (¹³C-NMR)

BM-V-KETO HYDROXY

107 (DEPT)

	Parameter	Value
1	Data File Name	BM-V-KETO HYDROXY
2	Title	Sep06-2018-nmrsu
3	Comment	BM-V-KETO HYDROXY-DEPT
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	296.3
11	Pulse Sequence	deptsp135
12	Experiment	1D-DEPT-135
13	Number of Scans	206
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	2.0316
18	Acquisition Date	2018-09-06T14:26:00
19	Modification Date	2018-09-06T14:26:13
20	Spectrometer Frequency	100.61
21	Spectral Width	16129.0
22	Lowest Frequency	-16.0
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

BM-V-ENONE

104 (^{1}H-NMR)

	Parameter	Value
1	Data File Name	BM-V-ENONE
2	Title	May13-2018
3	Comment	BM-V-ENONE-PROTON
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	302.1
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	127
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-05-13T11:37:00
19	Modification Date	2018-05-13T11:37:28
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1545.2
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

104 (^{13}C-NMR)

104 (DEPT)

104 (HSQC)

BM-V-ENONE

	Parameter	Value (f2, f1)
1	Data File Name	BM-V-ENONE
2	Title	May13-2018
3	Comment	BM-V-ENONE-HSQC
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	302.3
11	Pulse Sequence	hsqcetgp
12	Experiment	2D-HSQC
13	Number of Scans	4
14	Receiver Gain	211
15	Relaxation Delay	1.4388
16	Pulse Width	12.9500
17	Acquisition Time	0.1897
18	Acquisition Date	2018-05-13T11:39:00
19	Modification Date	2018-05-13T12:06:40
20	Spectrometer Frequency	(400.13, 100.61)
21	Spectral Width	(3205.1, 16666.7)
22	Lowest Frequency	(64.5, -829.1)
23	Nucleus	(1H, 13C)
24	Acquired Size	(512, 256)
25	Spectral Size	(512, 512)

BM-I-OH

110 (^{1}H-NMR)

	Parameter	Value
1	Data File Name	BM-I-OH
2	Title	May14-2018
3	Comment	BM-I-OH-PROTON
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	303.4
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	31
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-05-14T19:30:00
19	Modification Date	2018-05-14T19:30:44
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1545.0
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

BM-I-OH

110 (¹³C-NMR)

131.21
109.63
77.16 Chloroform-d
71.53
21.48

	Parameter	Value
1	Data File Name	BM-I-OH
2	Title	May-14-2018
3	Comment	BM-I-OH-13C
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	304.1
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	106
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	1.3631
18	Acquisition Date	2018-05-14T19:39:00
19	Modification Date	2018-05-14T19:41:40
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1906.4
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

f1 (ppm)

BM-I-OMs

111 (¹H-NMR)

7.26 Chloroform-d
6.20
6.20
6.19
6.19
6.18
6.18
6.17
6.17
6.16
6.15
6.15
3.04
1.82
1.82
1.82
1.81
1.81
1.80

0.98
2.03
3.07
3.00

	Parameter	Value
1	Data File Name	BM-I-OMs
2	Title	May16-2018
3	Comment	BM-I-OMs-PROTON
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	295.4
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	8
14	Receiver Gain	51
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-05-16T19:32:00
19	Modification Date	2018-05-16T19:32:36
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1545.0
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

f1 (ppm)

BM-I-OMs

138.44

98.53

77.44
77.16 Chloroform-d

38.83

21.81

111 (^{13}C-NMR)

	Parameter	Value
1	Data File Name	BM-I-OMs
2	Title	May16-2018
3	Comment	BM-I-OMs-13C
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	295.8
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	64
14	Receiver Gain	211
15	Relaxation Delay	2.0000
16	Pulse Width	10.0000
17	Acquisition Time	1.3631
18	Acquisition Date	2018-05-16T19:36:00
19	Modification Date	2018-05-16T19:39:28
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1956.9
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

BM-V-ENONE-ALK

7.26 Chloroform-d

105 (^{1}H-NMR)

	Parameter	Value
1	Data File Name	BM-V-ENONE-N-ALK-CRUDE
2	Title	May25-2018
3	Comment	BM-V-ENONE-N-ALK-CRUDE
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	295.3
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	119
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	4.0894
18	Acquisition Date	2018-05-25T11:41:00
19	Modification Date	2018-05-25T11:41:10
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-1845.3
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536

1.05

1.01
0.96

1.15

1.93
0.95
1.00

2.08
2.21
1.21

2.97

BM-V-Morphan

112 (¹H-NMR)

—7.26 Chloroform-d

—5.39

TMS

GREASE

WATER

DCM

	Parameter	Value
1	Data File Name	BM-V-TC
2	Title	BM-V-TC
3	Comment	W 28-02-2018
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	297.9
11	Pulse Sequence	zg
12	Experiment	1D
13	Number of Scans	32
14	Receiver Gain	166
15	Relaxation Delay	1.0000
16	Pulse Width	12.9500
17	Acquisition Time	2.0447
18	Acquisition Date	2018-02-28T19:48:02
19	Modification Date	2018-02-28T19:48:56
20	Spectrometer Frequency	400.13
21	Spectral Width	8012.8
22	Lowest Frequency	-2756.0
23	Nucleus	1H
24	Acquired Size	16384
25	Spectral Size	65536

f1 (ppm)

Chapter 4: Synthetic Studies towards the Total Synthesis of (-)-Stenine and (-)-Tuberostemonine.

4.1. Introduction:

Stenine is a stemona class of alkaloid, isolated from Stemona tuberosa of physiologically active stemonaeceous plants, possess structurally novel and unique azepinoindole skeleton.[1] The Stemona alkaloids represent a class of polycyclic alkaloids with relatively complex structures. Chinese and Japanese traditional medicines have for centuries utilized extracts of stemonaeceous plants as remedies for the treatment of respiratory ailments.[2, 3] Water extract of tuberosa roots used for both insecticidal and medicinal uses.[4]

Medicinal uses are

1) Treatment of respiratory diseases-

      a) Pulmonary tuberculosis

      b) Bronchitis

2) Antihelmintics (anti-parasitic for both human and cattle)

Around one hundred stemona alkaloids are reported, the structure of the thirty of them have been elucidated by X-ray analyses, whereas others were determined from their spectroscopic data and by chemical correlation.[5] One common feature among all the Stemona alkaloids is the presence of 1-azabicyclo [5.3.0]-decane ring system. Stemona alkaloids have been divided into five major groups-

    1. Stenine
    2. Stemoamide
    3. Tuberostemospirone
    4. Stemoamine
    5. Parvistemoline
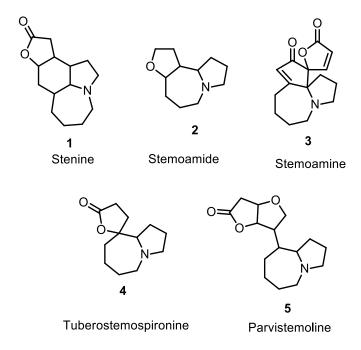
The core structure of the Stemona alkaloids are:

Figure 1: Characteristic structural feature of the *Stemona* alkaloid group

Stenine, tuberostemonine, neostenine and neotuberostemonine belongs to the stenine group.[6]
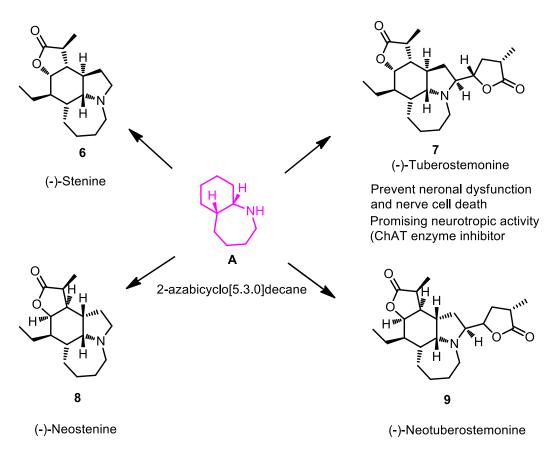

Figure 2: Representative members of Stenine group alkaloids

Recently, interest in these alkaloid is further arose by the demonstration of effective in vivo activity of skeletally related stemona alkaloids, neostenine and neotuberostemonine, against citric acid-induced cough in guinea pig animal models.[6-8] In addition, the Stemona alkaloid tuberostemonine has demonstrated inhibitory activity on excitory transmission at the crayfish neuromuscular junction.[7] The challenging molecular architectures of the stenine alkaloids have motivated the development of new strategies for the construction of their skeletons. However, only a small number of total syntheses have been reported to date [9] and they are still limited to quite a small number of targets, lacks concise synthetic sequence and with good yield. Two asymmetric syntheses have been reported, which involved 25 and 30 synthetic steps, respectively, with poor overall yield.[10a, 10b, 11] Recently, another enantioselective synthesis is published in 14 steps with 5.9% overall yield.[12]

4.2. Literature report on the total synthesis of Stenine:

Before we embark upon our approach, it would be appropriate to examine the synthetic approaches according to their strategies devised for assembling their intricate structures. The major difficulties encountered in developing a synthetic strategy including the proper installation of the multiple stereocenters over the cyclohexane ring are discussed here. Most of the reported synthetic strategies rely on a Diels–Alder reaction as the key step in assembling the core cyclohexane ring.

4.2A. Diels–Alder-Based Strategies:

4.2A.1. First total synthesis of (±)-stenine by Chen and Hart.:

The first total synthesis of racemic stenine was reported by Chen and Hart in 1990 and completed through a 25-step linear sequence, starting from the tetraene **10**.[10a, 10b] The strategy involved stepwise construction of rings C, D, and A, followed by the formation of 7-membered azepine ring B. The synthesis commenced with an *endo*-stereoselective intramolecular Diels–Alder (IMDA) reaction that furnished ring C (**11**). The incorporation of the nitrogen atom by an aminimide variant of the Curtius rearrangement set the stage for ring A formation by a straightforward sequence. An Eschenmoser–Claisen rearrangement (**14-15**) and subsequent iodolactonization (**15-16**) delivered the butanolide **16**.

Scheme 1: Synthesis of (±)-Stenine by Chen and Hart.

Reagents and conditions: a) Et₂AlCl, CHCl₃, 85 °C, 67%; b)NH₂NH₂, MeOH, 87%; c) MeC(OMe)₂NMe₂, xylene,Δ, 93%; d) I₂, THF, H₂O, 75%.

Ring B was subsequently formed by lactam formation after two-carbon homologation of the side chain at C-9. Finally, Keck radical allylation at C-10, conversion of the allylic moiety into the requisite ethyl substituent, methylation at C-13 on the convex side of the tetracyclic system, and adjustment of the oxidation level at ring B by converting amide to amine, led to the target compound Stenine. This pioneering synthesis paved the way for the utilization of other IMDA-based strategies and established the iodolactonization/Keck allylation sequence for the stereoselective installation of the ethyl group at C-10.

4.2A.2. Asymmetric total synthesis of (-)-Stenine by Morimoto et al.:

Morimoto et al. accomplished a highly stereocontrolled, 25-step synthesis of (−)-stenine,[11a, 11b] which involved key IMDA which led to the simultaneous construction of a decalin skeleton and four of the six stereogenic centers of the ring C. The Me₂AlCl-catalyzed IMDA reaction of the (*E, E, E*)-triene **17**, bearing an oxazolidinone chiral auxiliary, proceeded smoothly to produce the corresponding cycloadduct **18** with good facial and complete *endo* selectivity. Sequential manipulation of the cycloadduct and introduction of the nitrogen functionality by employing a modified Curtius rearrangement (as in Hart's approach) furnished bicyclic

intermediate **19**. Rings A and D were formed by regioselective enolization of **19** under thermodynamically controlled conditions followed by oxidative cleavage and stereoselective iodolactonization, to afford the tricyclic intermediate **20**. Allylation at C-10 and methylation at C-13 were also accomplished by following the similar reaction condition used by Hart and subsequent operations provided the intermediate **20** containing butanolide ring. Finally, after removal of the methoxycarbonyl group, ring B was constructed by means of a 7-*exo-tet* cyclization.

Scheme 2: Asymmetric synthesis of (-)-stenine by Morimoto et al.

4.2A.3. Synthesis of Stenine by Jeffrey Aube (2002):

Aubé's group executed a formal synthesis of racemic stenine in a 21 step sequence starting from pentane-1,5-diol.[12a] The key feature of the synthesis is the domino Diels−Alder/Schmidt reaction which provided the formation of the rings A, B, C and the four stereocenters of the cyclohexane moiety in a single chemical step, from the acyclic azidodiene precursor **22.**

Treatment of **22** with $MeAlCl_2$ afforded the azepinoindole **24** via cycloadduct **23** in 43% yield. The overall transformation involved an *endo* IMDA cycloaddition, followed by a ring forming (ring A) and ring (ring B) expansion process. Following the previous synthetic sequence,

subsequent iodolactonization (**24-25**), stereoselective Keck allylation, and α- methylation lactone provided intermediate **26**, which could be transformed into stenine by applying the same synthetic protocol developed by Hart.

Scheme 3: Synthesis of Stenine reported by Aube.

Reagents and conditions:a)MeAlCl₂, DCM, reflux, 43%; b) i) Na, NH₃, ii) CrO₃, H₂SO₄, iii) I₂, NaHCO₃, 80% for 3 steps; c) i) allyltributyltin, AIBN,benzene, ii) LiHMDS, MeI, 67% for two steps.

4.2A.4. Synthesis of Stenine by Aube (2nd generation approach):

Having completed the synthetic effort towards the synthesis of stenine, their attention turned to further development of the tandem Diels−Alder/intramolecular Schmidt reaction. In particular, we noticed that the sequence could nicely accommodate intermolecular Diels−Alder reaction. In a second-generation approach, Aubé and co-workers improved the efficiency of the synthesis by combining an attractive intermolecular Diels−Alder reaction with a Schmidt rearrangement which minimized fewer steps in starting material preparation than in the case of intramolecular Diels-Alder/Schmidt sequence.[12b] Treatment of the azidosilyloxydiene **28** with cyclohexenone **27** in presence of stannic chloride (*SnCl₄*) afforded azepinoindole **30** that originated from an *exo* selective Diels−Alder process which provided major product in 45% yield. The most attractive feature of this new approach was that it allowed the early incorporation of C-10 ethyl side chain with the correct relative configuration. An axially directed alkylation at C-12 of the intermediate **30** was performed by using methyl bromo

acetate as an alkylating reagent in the presence of a base *LiHMDS*. Subsequent reduction of the ketone set the butyrolactone moiety by lactonization and the synthesis was completed by well established procedures involving methylation of the lactone ring followed by amide to amine conversion by using Lawesson's reagent/Raney nickel. The total synthesis was accomplished in nine steps from commercially available reagents and in 14% overall yield which is very impressive.

Scheme 4: Synthesis of Stenine reported by Aube (2nd generation approach).

Reagents and conditions: a) SnCl4, -78 °C to rt, 70%; b) i) LiHMDS, BrCH2CO2Me, 73%, ii) NaBH4, 64%.

4.2A.5. Padwa's strategy for the synthesis of stenine:

In 2002, Padwa and Ginn reported a synthesis of racemic stenine starting from *N*-trimethylsilyl ε-caprolactam (**32**) in a 17-step sequence involving an exceptional Diels–Alder/ring opening/1,2-methylthio shift cascade to attach rings A and C onto a precursor azepinone (ring B) in a single operation.[13] Methylsulfenylation of one of the sulfur atoms of **33** with dimethyl (methylthio) sulfonium tetrafluoroborate (DMTSF) induced a thionium-promoted cyclization and the resulting dihydrofuran readily furnished furan **34** with the loss of acetic acid. Intramolecular Diels-Alder (IMDA) cycloaddition followed by nitrogen-assisted ring opening generated a zwitterionic intermediate (**39**), which after a 1,2-methylthio shift, provided the tricyclic lactam **35**. Subsequent reduction fixed the desired A/C *trans* and B/C *cis* ring fusions. The butyrolactone ring formation was done through iodolactonization of **36,** which proceeded

by a stereoselective Keck allylation by Hart's protocol for the installation of the ethyl group at C10 position and the synthesis was completed by following the established procedure known in the literature.

Scheme 5: Synthesis of Stenine by Padwa.

Reagents and conditions: a) i) LDA, ii) (MeS)₂CHCHO, iii) Ac₂O 80% for 3 steps, iv) MeO₂CCH₂CH=CHCH₂COCl, 85%, b) DMTSF, NEt₃, 80%; c) i) Raney-Ni, EtOH, 92%; ii) NaBH₄, CeCl₃, MeOH, 77%; iii) Crabtree's catalyst, H₂, CH₂Cl₂, iv) MsCl, NEt₃, DBU, 64% for two steps. d) i) LiOH, H₂O, ii) I₂, MeCN, 64%.

Scheme 6: Diels-Alder/ring opening/1,2-methylthio shift cascade.

4.2B. Wipf's Strategy for the First Asymmetric Synthesis of (-)-Stenine:

The first enantioselective total synthesis of (−)-stenine was reported by Wipf and his co-workers in 1995, [14a] which involved a 26-step linear sequence starting from L-tyrosine. L-tyrosine was converted into the key intermediate indolone **41** (enantio- and diastereomerically pure) in a single step by the phenolic oxidation of **40** using hypervalent iodine reagent. The *cis*-fused indolone is converted into the *trans*-fused stenine core upon reduction of a π-

allylpalladium complex (**41-42**). An Eschenmoser–Claisen rearrangement was used for the butyrolactone ring formation by iodolactonization of **44**. Subsequent Keck allylation was employed to install ethyl group at C10 position, acid amine coupling was used for B ring formation and functional group manipulations provided the target alkaloid **6**.

Scheme 7: First asymmetric synthesis of (-)-Stenine by Peter Wifp.

Reagents and conditions:a)PhI(OAc)₂, NaHCO₃, MeOH, 21-40 ºC, 40-60%; b)i) Bz₂O, Et₃N, ii) NaBH₄, CeCl₃.7H₂O, 89%, iii) Pd₂(dba)₃.CHCl₃, Bu₃P, HCO₂H/Et₃N, 88%; c)i) TPAP, NMO, ii) KHMDS, -80 ºC, HC=CH(CH₂)OTf, 46%; d)i) NaBH₄, CeCl₃.7H₂O, ii) H₃CC(OMe)₂NMe₂, 130 ºC, 77%.

4.2C. Wifp's strategy for the First and Only Asymmetric Synthesis of (-)-Tuberostemonine:

In their subsequent work, they have used the same *trans*-hexahydroindole **46** as a key intermediate in the enantioselective synthesis of (–)-tuberostemonine through a 24-step linear sequence.[14b] The most significant features of the synthesis is the azepine formation by RCM of **47** followed by regioselective hydrogenation, and the stereoselective attachment of the "east"-side γ-butyrolactone at C-3 by the treatment of a Weinreb amide derivative of **48** with the lithiated asymmetric orthoester **49**. An Eschenmoser–Claisen rearrangement (**50-51**), selenolactonization, Keck allylation, and finally selective α-methylation of the fused lactone afforded (-)-tuberostemonine.

Scheme 8: Asymmetric synthesis of (-)-tuberostemonine by Peter Wifp.

4.2D. Enantioselective Total Synthesis of (-)-Stenine by Zhang et al.:

In 2012, Zhang et al. reported an enantioselective sequential double Michael addition to assemble a densely substituted cyclohexane core **57** and that the key azepinoindole intermediate **58** was obtained by reductive amination followed by amidation.[15a, 15b] The enantioselective Michael addition of nitroolefin **52** to β-ketoester **53** provided intermediate **54** which was processed for the required carbocyclization through the second intramolecular Michael addition. The C-alkylation of the tricyclic ketone **58** using ethyl bromoacetate and *LiHMDS* as a base followed by reduction of the carbonyl group set the formation of lactone ring. The methylation of lactone ring and conversion of amide to amine employing established protocol, produced the target alkaloid (-)-stenine.

Scheme 9: Enantioselective total synthesis of (-)-stenine by Zhang et al.

Reagents and conditions: a) 56, 5 ºC, the KOH/SiO₂, THF, sonicated in a water bath at 35 ºC, 80% yield; b) i) acetic acid, H₂O, 90 ºC, then Zn powder. The crude product was then heated to 90 ºC in toluene, 81% yield; ii) LiCl, H₂O, DMSO, 155 ºC, 89% yield; c) [(CH₃)₃Si]₂NLi, THF, -78 ºC, ethyl bromoacetate, 78% yield; d) i) NaBH₄, MeOH, 0 ºC, 51% yield after recrystallization; ii) [(CH₃)₃Si]₂NLi, THF, -78 ºC, MeI, 65% yield; iii) Lawesson's reagent, CH₂Cl₂, iv) Raney Ni, EtOH, 25 ºC, 90% yield over two steps.

4.2E. Asymmetric Total Synthesis of (-)-Stenine by Fujioka et al.:

In 2012, Fujioka et al. developed a new asymmetric desymmetrization strategy that employed intramolecular haloetherification reaction of cyclohexadiene acetal **60** to generate substituted cyclohexane **62**.[16] This reaction enabled the installation of the multiple chiral stereocenters over the cyclohexane ring, which proceeded via a rigid cationic intermediate **61** and utilized the chiral cationic auxiliary as a template that remained in the product. Hydroboration and subsequent oxidation of the cyclohexane derivative **62** provided the enone **63**, which was 63

was utilized to install another three stereocenters by enolate alkylation and 1,4-conjugate addition resulted **64**. Hydrolysis of the acetal group in **64** followed by reductive amination of the resulting aldehyde and intramolecular Mitsunobu cyclization produced the intermediate **65**. The enolate alkylation, intramolecular amidation and reduction of ketone for the necessary lactone ring formation provided lactam **67** which was transformed to (-)-stenine by the known protocol established in the literature.

Scheme 10: Asymmetric total synthesis of (-)-stenine by Fujioka et al.

Reagents and conditions:a) NBS, MeOH, CH₃CN, -40 ᵒC to 0 ᵒC, 63%; b) i) thexylborane, ii) PDC, 53%; c) i)) LiHMDS (1.2 equiv), allyl iodide (3.0 equiv), HMPA (10 equiv), THF, -78 ᵒC, 3 h, 92 %, ii) 4-pentenyl magnesium bromide (2.0 equiv), CuI (0.5 equiv), THF, -78 ᵒC, 3 h, 90 %; d) i)LiHMDS (1.5 equiv), ethyl iodide (10 equiv), HMPA (10 equiv), THF, -78 ᵒC to RT, 24 h, 57 % (80 % brsm), ii) O₃, CH₂Cl₂, -78 ᵒC, 15 min, then PPh₃ (8.0 equiv), RT, 1 h, 81 %, iii) PDC (10 equiv), DMF, RT, 24 h; iv) TMSCHN₂ (2.5 equiv), benzene/MeOH 4:1, RT, 30 min, 70 % (2 steps); e) i) Cs₂CO₃ (3.0 equiv), PhSH (1.5 equiv), CH₃CN, RT, 12 h, ii) toluene, reflux, 24 h, 95 % (2 steps), iii) NaBH₄ (3.0 equiv), MeOH, 0 ᵒC, 1.5 h, 64 %. PDC =pyridinium dichromate.

4.3. Summary of the literature reports:

From the above survey of literature reports, it is evident that only two asymmetric syntheses have been reported, which involved 25 and 30 synthetic steps with poor overall yield.[11a, 11b, 14a, 14b] Recently, another enantioselective synthesis have been published in 14 steps with 5.9% overall yield.[12] Biologically more potent alkaloid (-)-tuberostemonine has only one total synthesis reported involiving 24 steps with 1.4% overall yield.

4.4. Objective of the present study:

Biological studies of the alkaloids belonging to the stenine group revealed that there is a high demand of supply of sufficient number of compounds for their preclinical studies. Therefore, with the aim of developing an efficient and scalable synthetic strategy we took up this challenge to develop a conceptually new synthetic route to maximize the supply of the required amount for total biological screening and preclinical studies.

4.5. Retrosynthetic analysis:

From the perspective of retrosynthetic analysis of **6,** as outlined in the scheme **11**, the 2-oxostenine **68** would be the common precursor for both stenine and tuberostemonine. Stenine could be derived by the adjustment of the oxidation level at ring **A** (amide to amine conversion) of 2-oxostenine and the stereoselective attachment of the furan derived γ-butyrolactone at C-3 of the 2-oxostenine would provide tuberostemonine. After having systematic installation of all the substituent over the cyclohexane ring along with the required azepane ring, the intermediate **69** would be ready for the two sequential cyclisation involving lactonization and amidation to produce 2-oxostenine. The most important task of setting up the key cyclohexane ring **C** containing six contiguous stereocenters with proper stereochemical arrangement and associated **A**, **B** and **D** ring junction stereochemistry. All the substituent could be installed sequentially and stereochemistry would be guided by newly generated functionality and stereocentre embedded in the cyclohexane ring. The sulfonyl enone **70** could be a significant precursor for the stereoselective installation of the ethyl substituent at C-10 and the hydroxyl group at C-11 position by following 1,4-conjugate addition and subsequent quenching by using oxaziridine of the newly generated enolate. The stereochemistry of the conjugate addition of the sulphonyl enone would be amenable by other functionalities installed at the outset of our synthetic programme.

Scheme 11: Retrosynthetic analysis for (-)-stenine and (-)-tuberostemonine.

The electron withdrawing property of the vinyl sulphone functionality embedded in the cyclohexane ring of the intermediate **72** would guide to functionalize the next carbon centre of the cyclohexane ring and that will direct the functionalization of another carbon centre. Because of the acidity of the allylic proton of the vinyl sulphone, a directed allylic oxidation could be performed on **72** to obtain allylic oxidised product **71** which will direct the functionalization of alpha carbon center of the ketone by the enolate alkylation of the sulfonyl enone.

The preparation of *cis*-decahydro-1*H*-benzo-[*b*]-azepine (**72**) was visualized from our ongoing synthetic exploration of the optically pure 7-azabicyclo[2.2.1]heptene scaffold **74**, which could be alluded by a stereoselective Michael addition on facially biased Michael acceptor (olefinic sulphone) followed by subsequent ring opening due to existing ring strain in **74.**

4.6. Results and discussions:

Retrosynthetic analysis was alluded to consider the multi-gram availability of the *cis*-octahydro-2*H*-benzo[*b*]azepine intermediate **72** to achieve target alkaloids. We succeeded in making the ring opened product **73** in multi-gram scale by conjugate addition and in situ opening of the azabicyclic ring and also achieved the cyclised product **72** in good yield. The preparation of the intermediate **72** have already discussed in detail in the chapter **3**.

4.6.1. Synthesis of the allylic oxidised compound 71:

After having **72** in hand, we proceeded to functionalize the allylic carbon centre by employing known allylic oxidation protocol in the literature. Corey's allylic oxidation condition was employed on the intermediate **72**, but could not provide the allylic oxidised product in good yield (10-15%). [17]

Scheme 12: allylic oxidation using Corey's protocol.

Reagents and conditions: a) Pd(OH)₂/C, t-BuOOH, K₂CO₃, DCM, 0 °C to RT, 24h.

Therefore, we turned our attention to chromium based oxidant to get the desired allylic oxidised product **71**.[17] Pyridinium dichromate (PDC) in presence of tertiary butyl hydroperoxide (TBHP) resulted moderate yield (35-40% conversion) with the recovery of starting material and it provided 85-90% conversion over two cycles with 65-70% yield.

Scheme 13: Allylic oxidation of **72**.

Reagents and conditions: a) PDC (3 equiv.), t-BuOOH (5M, 8 equiv.), dry DCM, 0 °C to RT, 20h, 66% over 3 cycles.

4.6.2. Synthesis of the fully functionalized cyclohexane derivative 69:

The synthesis of the key cyclohexane ring C would set our synthetic plan towards the target alkaloids. As we have planned the newly installed carbonyl functionality to direct the fuctionalization of adjacent carbon center. Accordingly, we achieved the stereoselective

enolate alkylation using iodoethyl acetate as an eletrophile and lithium hexamethylsilazide (LiHMDS) as a base.[12b, 15a, 15b] The alkylation provided the desired product **70** in 57% yield (88% on brsm) and the stereoselctivity was guided by the azepane ring formed at the outset of our synthesis. It was very necessary to desulfonylate the sulfonyl enone **70**, which will generate a enone **75** and that could be utilized for the installation of the ethyl and hydroxyl group through a highly stereoselective 1,4-conjugate addition followed by α-hydroxylation of the insitu generated enolate. The desulfonylation was attempted using the very popular reaction condition sodium-amalgam (6% Na-Hg) in tetrahydrofuran and methanol,[19] but this gave very poor result with the formation of complex reaction mixture. We planned to employ a mild condition for the effective desulfonylation and fortunately we got an excellent conversion with good yield (88%) using aluminium amalgam in presence of tetrahydrofuran and water at -30 °C.[20]

Scheme 14: Enolate alkylation and desulfonylation of **71**.

Reagents and conditions: a) 1.8 eq LiHMDS, dry THF, 5 eq iodoethylacetate, -78 °C to -20 °C, 57% (88% on brsm); b) 6 eq Al-Hg, THF:H₂O (9:1), -30 °C to -20 °C, 3h, 86%.

The efficient desulfonylation of **70** built a strong platform for the stereoselective installation of ethyl group and subsequent hydroxyl group incorporation. To accomplish conjugate addition, the desulfonylated product **75** was subjected to the Gilman reagent diethyl cuprate lithium (Et₂CuLi) in presence of trimethylsilyl chloride (TMSCl),[21] but it was unreactive to the enone **75**, probably due to the steric hindrance for the 1, 4-conjugate addition.[22]

Scheme 15: Failed attempt of 1, 4-conjugate addition of **75** using higher order organocuprate reagent.

Reagents and conditions: a) EtMgBr (2 eq), CuI (1 eq), LiBr (10 eq), TMSCl, dry THF, -78 °C.

While boron trifluoride etherate was used to activate the carbonyl group of the enone, the mass analysis confirmed the ethyl incorporation, but carbamate protection of amine could not survived. Keeping in mind steric factor of the enone, we went through literature reports and found that lower order organocuprates ($RCuBF_3$) in presence of borontrifluoride etherate ($BF_3.OEt_2$) are able to add to sterically congested enones in moderate yield.[23] Inspired by the literature report, we also employed the lower order organocuprate (EtCuLi) reagent and smoothly formed the desired product **76** with 81% yield.[24]

Scheme 16: 1, 4-conjugate addition of **75** using lower order organocuprate reagent (EtCuLi).

Reagents and conditions: a) EtMgBr (8 eq), CuI (12 eq), LiBr (15), dry THF, -70 ᵒC to -40 ᵒC, 7.5 h, 81%.

After succeeding in carrying out the 1,4-conjugate addition, we visualised that hydroxy group at C-11 would be necessary to form the butenolide ring, which we enabled to install by generating enolate over intermediate **76,** using lithium diisopropyl amide and subsequent oxidation with the Davis's oxaziridine.[25a, 25b] The stereoselctivity was guided by the adjacent β-stereochemistry of the ethyl group resulting α-stereochemistry of the hydroxyl group.

Scheme 17: α-hydroxylation of the ketone **76**.

Reagents and conditions: a) 5.2 eq LDA, dry THF, 10 eq Hexamethylphosphoramide (HMPA), 2.2 eq ((1R)-(-)-(10-Camphorsulfonyl)oxaziridine)(Davi's oxaziridine), -78 ᵒC to -10 ᵒC, 82%.

The fully substituted cyclohexane derivative **69** was very crucial advanced intermediate for the accomplishment of the synthesis. According to retrosynthesis, we were just two important

cyclization step away from our target alkaloids. The lactonisation and lactamisation through amidation would conclude the synthesis. We then moved forward with our all efforts to make the butenolide ring.

4.6.3. Synthesis of the butenolide ring D:

With the required fully substituted cyclohexane derivative **69** in hand, we planned to make first a butenolide ring with the methyl substitution at C-14, which upon selective hydrogenation would provide both *15α* and *15β*-stenine. To obtain the desired butenolide ring, we thought to employ a Wittig-Horner olefination on the ketone followed by intramolecular lactonization.[26] But it was very unfortunate that after using five equivalent of Wittig-Horner reagent also the ketone could not reacted and the subsequent betain ring formation was also failed. As a result we observed only recovery of starting material, probably steric congestion could be the factor for this failure.

Scheme 18: Failed attempt of Wittig-Horner reaction on the ketone **69**.

Alternatively, we thought to perform intramolecular Wittig-Horner olefination to get the desired butenolide ring. [27] Accordingly, we proceeded to prepare the corresponding phosphonate ester of the hydroxy ketone **69** for the intramolecular Wittig-Horner reaction. The hydroxy ketone **69** was subjected to the required phosphono acetyl chloride in presence of triethyl amine, whch could produce the required acylation product of the hydroxyl ketone **69** for the Wittig-Horner olefination.

Scheme 19: Failed attempt for the acylation of the hydroxyl group of **69** using phosphonoacetyl chloride **79**.

*Reagents and conditions: a) **79**, Et₃N, 0 °C to RT; b) **79**, NaH, 0 °C to RT.*

However, it failed to give any conversion; instead starting material **69** was recovered back. The steric congestion and the nucleophilicity of the hydroxyl group could be the major reason for this inertness towards the acid chloride. Furthermore, we decided to use a strong base for this acylation reaction which would provide the required butenolide ring through in situ Wittig-Horner olefination of the corresponding tether phosphonate ester. Attempt to get the butenolide product from the hydroxyl ketone intermediate **69** by using phophono acetyl chloride and sodium hydride as a base also failed to provide the desired lactone **81**. With this failure in mind, further we thought to proceed stepwise formation of the butenolide ring through the corresponding phosphonate ester intermediate **80**. Accordingly, we attempted the *N,N-Dicyclohexylcarbodimide (DCC)* mediated coupling of hydroxyl group and the corresponding phosphono acetic acid **82**.[27]

Scheme 20: Failed attempt for the DCC mediated coupling between the hydroxyl group of **69** and phosphonoacetic acid **82**.

Reagents and conditions: a) 82, DCC, dry DCM, 0 ºC to RT.

However, this attempt again gave very disappointing result and recovered the starting material. These unfortunate outcome regarding the reactivity of the hydroxyl group of the intermediate **69** stipulating a detail investigation on the nucleophilicity of the hydroxyl group and reassessment of the strategy to form the butenolide ring. After having detailed study on the ^{1}H nmr, ^{13}C nmr and HSQC data of the intermediate **69**, we found four discrete peaks for the corresponding hydroxy proton (-OH proton) in the ^{1}H nmr spectra of **69,** which confirmed that the protons of the hydroxy groups are engaged in hydrogen bonding probably with the adjacent ketone group. This hydrogen bonding results in lowering of the nuclephiliciy of the oxygen atom of the hydroxyl group.

Therefore, to obtain desired lactone ring, there were only left with options of either hydroxyl group or ketone functionality manipulation, however, both were not responsive towards the electrophillic or nucleophillic addition, respectively. Therefore, we needed to employ highly reactive species for the functional group manipulation in case of both hydroxyl as well as with

ketone. After having this conclusive decision, we were in a big dilemma for the selection of the proper candidate among the hydroxyl group and the ketone group to generate a proper functionality which would solve this issue. Instead of intramolecular Wittig-Horner, we planned to perform intramolecular aldol reaction followed by subsequent tertiary hydroxy group removal to provide the butenolide ring. This was envisioned by the acetylation of the hydroxyl group (-OH to -AcO) using either highly reactive species acetyl chloride or acetic anhydride. Accordingly, the hydroxy compound **69** was treated with acetic anhydride (Ac$_2$O) in presence of dry pyridine which gave expected acylated product **83**,[28] in good yield (74%, 97% on brsm), confirmed by mass and proton NMR analysis. With the hope to have the aldol product in hand, the *O*-acetylated ketone **83** was treated with Potassium hexamethyl silazide (KHMDS) to give intramolecular aldol reaction followed by the addition of excess acetic anhydride (Ac$_2$O) for the subsequent hydroxyl group removal.[29]

Scheme 21: Formation of the butenolide ring by intramolecular aldol condensation. *Reagents and conditions: a) Ac$_2$O:pyridine(dry) (1:1), 48h, 74%, 97% on brsm; b) 0.5 M KHMDS in toluene (1.2 equiv.), excess Ac$_2$O (30 equiv.), dry THF, -80 °C to -60 °C, 8 h.*

As expected, we observed the formation of product in HRMS. We are now in the stage to purify the aldol condensation followed by dehydration product to confirm the formation of the butenolide ring.

4.7. Conclusion:

We have developed a highly stereoselective and flexible synthetic route toward the synthesis of stemona alkaloids. The bridg-azabicyclic ring opening provided the crucial cyclohexane ring with two stereocenters and embedded vinyl sulphone functionality which propagated to the

formation of associated azepane and butenolide ring. The fully functionalized cyclohexane ring C was achieved with high stereoselectivity. The intramolecular amidation will complete the synthesis of 2-oxostenine which will be involved further in the total synthesis of stenine and tuberostemonine.

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4.9. Experimental Procedures and Spectral Data:

Synthesis of (±) (5a*S*,9a*S*)-*tert*-butyl 8-oxo-6-(phenylsulfonyl)-2,3,4,5,5a,8,9,9a-octahydro -1*H* -benzo[*b*] azepine-1-carboxylate (71):

To a solution of the cyclised product **72** (4.0 g, 10.2 mmol) in 50 mL dry DCM in an ace pressure tube equipped with a magnetic stir bar was added pyridinium dichromate (5.7 g, 15.3 mmol, 1.5 equiv.) at room temperature and stirred until PDC dissolved completely. The red coloured solution was cooled to 0 °C under argon gas balloon and to it was added 5.0 M tertiary butyl hydroperoxide solution in decane (8.2 mL, 40.8 mmol, 4 equiv.). The pressure tube was sealed and stirred the reaction mixture 3 h at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred further 7 h at RT. The reaction mixture was recooled to 0 °C, equal amount of PDC and TBHP was added sequentially. The reaction mixture was stirred further 3 h at 0 °C and then 7 h at RT. The reaction was monitored by TLC. When TLC showed incomplete consumption of the starting material, the reaction mixture was diluted with ether (100 mL) and filtered through a short pad of celite. The solvent was evaporated by rotary evaporator, dried under vacuum and the crude allylic oxidised product was subjected to the same reaction oxidation for the complete consumption of the starting material **72**. Purification of the crude allylic oxidised product was done by column chromatography using hexane:ethyl acetate (3:1) and obtained product (2.7 g, 66%) as a white solid.

Yield: 66%

TLC: R_f = 0.48 (SiO$_2$, Hexane : Ethyl acetate = 3:1)

m.p.: 114-116 °C

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.91 (d, *J* = 7.5 Hz, 2H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 6.55 (s, 1H), 4.81 – 4.39 (m, 1H), 4.02 – 3.66 (m, 1H), 2.96 (br m, 1H), 2.85 (br m, 1H), 2.78 (br m, 1H), 2.57 – 2.38 (m, 1H), 2.33 (br m, *J* = 23.7, 14.8 Hz, 1H), 2.08 (br m, *J* = 13.6, 13.0, 5.5 Hz, 1H), 1.89 (br m, *J* = 20.7, 11.9 Hz, 1H), 1.70 (br m, 1H), 1.36 (s, 9H), 1.25 (br m, 2H).

13C NMR (101 MHz, CDCl₃) δ: 196.41, 162.06, 154.70, 137.76, 134.71, 130.64, 129.82, 128.81, 80.47, 53.75, 41.11, 38.55, 38.11, 28.32, 27.21, 27.01, 24.40.

HRMS (ESI): *m/z* calculated for $C_{21}H_{27}NO_5SNa$ ([M+Na]⁺) 428.1508, $C_{21}H_{28}NO_5S$ ([M+H]⁺) 406.1688; found 428.1510 ([M+Na]⁺) and 406.1681 ([M+H]⁺).

Synthesis of (±) (5a*S*,9*S*,9a*S*)-*tert*-butyl 9-(2-ethoxy-2-oxoethyl)-8-oxo-6-(phenylsulfonyl)-2, 3,4,5,5a,8,9,9a-octahydro-1*H*-benzo[*b*]azepine-1-carboxylate (70):

The solution of allylic oxidised compund **71** (2.0 g, 4.9 mmol) in dry THF (15 mL) was charged into a 50 mL two neck jacketed flask equipped with a magnetic stirring bar, argon gas balloon and was cooled to -80 °C. To the stirring solution 1.0 M LiHMDS solution in dry THF (8.8 mL, 8.8 mmol, 1.8 equiv.) was added dropwise. The reaction mixture was allowed to warm to -60 °C and stirred at that temperature (-60 °C) for 2 h, then gradually increased to +10 °C to -20 °C within 1 h and stirred further at -20 °C for 1 h. The reaction mixture was recooled to -70 °C and iodo ethyl acetate (2.9 mL, 24.6 mmol, 5 equiv.) was added to the reaction mixture. After stirring the reaction mixture 2 h at -70 °C, gradually increased the temperature by +10 °C to -20 °C over 3 h and stirred further for 1 h. The reaction was quenched with saturated aq. NH₄Cl (50 mL) and was extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, dried *in vacuo* and purified by column chromatography (hexane:ethyl acetate, 3:1) to obtain **70** as a colourless liquid (1.4 g, 57%). The starting material **71** recovered 0.73 g.

Yield: 57%, 88% on brsm

TLC: R$_f$ = 0.52 (SiO₂, Hexane : Ethyl acetate = 3:1)

1H NMR (400 MHz, CDCl₃) δ: 7.92 (dd, *J* = 9.8, 8.0 Hz, 2H), 7.76 − 7.67 (m, 1H), 7.61 (dd, *J* = 13.6, 7.5 Hz, 2H), 6.58 (s, 1H), 4.69 − 4.47 (m, 1H), 4.22 − 4.04 (m, 2H), 3.85 − 3.58 (m, 1H), 3.30 − 3.12 (m, 1H), 3.03 − 2.86 (m, 1H), 2.84 − 2.69 (m, 1H), 2.64 − 2.50 (m, 1H), 2.47 − 2.40 (m, 1H), 2.39 − 2.26 (m, 2H), 2.13 − 1.95 (m, 2H), 1.44 (s, 9H), 1.26 (br m, 5H).

¹³C NMR (101 MHz, CDCl₃) δ: 197.09, 171.93, 161.20, 154.73, 137.73, 134.68, 130.26, 129.77, 128.76, 80.47, 60.97, 54.82, 42.40, 41.94, 38.70, 30.39, 28.33, 27.13, 25.98, 24.65, 14.16.

HRMS (ESI): *m/z* calculated for $C_{25}H_{33}NO_7SNa$ ([M+Na]⁺) 514.1875; found 514.1870 ([M+Na]⁺).

Synthesis of (±) (5a*R*,9*S*,9a*R*)-*tert*-butyl 9-(2-ethoxy-2-oxoethyl)-8-oxo-2,3,4,5,5a,8,9,9a-octahydro-1*H*-benzo[*b*]azepine-1-carboxylate (75):

Commercially available thin aluminum foil (0.33 g, 12.2 mmol, 6 equiv.) in strips about 0.8 cm long and 0.5 cm wide, were placed in a 50 mL beaker and was added 2% solution of mercury(II) chloride (0.33 g, 1.2 mmol, 1 equiv.) to cover the aluminum completely. The solution was allowed to act upon aluminum for about 4 minutes. The excess solution of mercury (II) chloride (HgCl₂) was then poured off and the obtained aluminum amalgam (Al-Hg) was washed with water, ethanol, and finally with moist ether. The aluminum amalgam was covered with 5 mL of moist ether and was transferred to the stirred solution of **70** (1.0 g, 2.0 mmol) in 20 mL THF:H₂O (9:1) at -30 °C. The reaction mixture was stirred further for 2 h at the same temperature and was allowed to warm to -20 °C. After stirring for 30 minutes, the reaction was monitored by TLC and stirring was continued until the TLC showed the starting material disappeared. The reaction mixture was diluted with ether (100 mL) and filtered through a short pad of celite. The solution was dried over anhydrous sodium sulfate, concentrated, dried *in vacuo* and purified by column chromatography (hexane:ethyl acetate, 3:1) to obtain **75** (0.61 g, 86%) as a colourless liquid.

Yield: 86%

TLC: R*f* = 0.42 (SiO₂, Hexane : Ethyl acetate = 4:1)

¹H NMR (400 MHz, CDCl₃) δ: 6.82 – 6.72 (m, 1H), 5.96 (dd, *J* = 10.2 Hz, 1H), 4.70 (dd, *J* = 38.3, 13.6, 5.8 Hz, 1H), 4.24 – 4.09 (m, 2H), 3.75 (dd, *J* = 14.8, 5.9 Hz) and 3.01 – 2.88(1H), 3.57 (dd, *J* = 15.1, 6.6 Hz, 1H), 3.23 (ddd, *J* = 10.8, 7.9, 4.0 Hz, 1H), 3.01 – 2.88 (m, 2H), 2.67

– 2.53 (m, 2H), 2.38 (dd, *J* = 16.7, 4.0 Hz) and 2.67 – 2.53(1H), 2.26 (dd, *J* = 16.6, 3.5 Hz, 1H), 2.06 – 1.99 (m, 1H), 1.97 – 1.91 (m, 1H), 1.79 – 1.72 (m, 1H), 1.57 – 1.53 (m, 1H), 1.45 (s, 9H), 1.29 – 1.24 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ: 198.68, 172.93, 156.03, 151.66, 127.25, 80.10, 60.82, 54.36, 43.42, 42.94, 39.18, 30.67, 28.50, 26.23, 26.01, 24.77, 14.31.

HRMS (ESI): *m/z* calculated for $C_{19}H_{29}NO_5Na$ ([M+Na]⁺) 374.1943, $C_{19}H_{30}NO_5$ ([M+H]⁺) 352.2124; found 374.1942 ([M+Na]⁺) and 352.2122 ([M+H]⁺).

Synthesis of (±) (5a*R*,6*S*,9*S*,9a*R*)-*tert*-butyl 9-(2-ethoxy-2-oxoethyl)-6-ethyl-8-oxo decahy dro-1*H*-benzo[*b*]azepine-1-carboxylate (76):

75 **76**

The mixture of anhydrous LiBr (1.8 g, 21.3 mmol, 15 equiv.) and flame dried CuI (3.2 g, 17.1 mmol, 12 equiv.) in dry ether (15 mL) was charged into a 100 mL two neck jacketed flask equipped with a magnetic stirring bar, argon gas balloon and was cooled to -20 °C followed by addition of 3.0 M ethyl magnesium bromide solution (3.8 mL, 11.4 mmol, 8 equiv.) dropwise. The reaction mixture was stirred at the same temperature for 30 minutes, then cooled to -70 °C and the solution of **75** (0.5 g, 1.4 mmol) in dry ether (5 mL) was added to the stirring reaction mixture. After stirring 2 h at -70 °C, gradually temperature of the reaction mixture was raised by +10 °C to -40 °C within 1 h and stirred further for 4 h till the completion of the reaction. The progress of the reaction was monitored by TLC, diluted with dry ether (30 mL) and was quenched with saturated aqueous solution of NH₄Cl (5 mL) at -40 °C. After stirring 30 minutes, the temperature was gradually increased to 0 °C, added more saturated aqueous solution of NH₄Cl (15 mL) and the temperature raised to RT (25 °C). The organic layer was separated and the water layer was extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, dried *in vacuo* and purified by column chromatography (hexane:ethyl acetate, 5:1) to obtain **76** as a highly viscous liquid (0.4 g, 81%).

Yield: 81%

TLC: R_f = 0.56 (SiO$_2$, Hexane : Ethyl acetate = 5:1)

^{1}H NMR (400 MHz, CDCl$_3$) δ: 4.19 – 4.05 (m, 2H), 3.68 (br m, 1H), 3.59 (br m, 1H), 3.18 (br m, 1H), 3.01 – 2.76 (m, 1H), 2.71 – 2.54 (m, 2H), 2.36 – 2.07 (m, 2H), 2.05 – 1.94 (m, 1H), 1.90 (br m, 2H), 1.78 (br m, 2H), 1.54 (br m, J = 23.3, 13.3, 6.1 Hz, 4H), 1.43 (s, 9H), 1.25 (td, J = 7.1, 1.2 Hz, 5H), 0.94 – 0.86 (m, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 208.87, 173.08, 155.85, 79.84, 60.71, 56.01, 46.23, 45.01, 42.11, 41.94, 38.92, 30.69, 29.11, 28.52, 26.79, 25.98, 24.94, 14.30, 11.94.

HRMS (ESI): *m/z* calculated for C$_{21}$H$_{35}$NO$_5$Na ([M+Na]$^+$) 404.2413, C$_{21}$H$_{36}$NO$_5$ ([M+H]$^+$) 382.2593; found 404.2420 ([M+Na]$^+$) and 382.2602 ([M+H]$^+$).

Synthesis of (±) (5aR,6R,7S,9S,9aR)-*tert*-butyl 9-(2-ethoxy-2-oxoethyl)-6-ethyl-7-hydroxy -8-oxodecahydro-1H-benzo[b]azepine-1-carboxylate (69):

Dry i-Pr$_2$NH (0.51 mL, 3.62 mmol, 9.2 equiv.) in dry THF (2 mL) was taken into a 25 mL two neck jacketed flask equipped with a magnetic stirring bar, argon gas balloon and was cooled to -0 °C followed by addition of 2.2 M n-BuLi solution (0.93 mL, 2.0 mmol, 5.2 eq) in hexane dropwise. Stirring at 0 °C was continued for 30 min and cooled the solution to -70 °C. The solution of **76** (0.15 g, 0.39 mmol) in dry THF (2 mL) was added to the stirring solution of LDA in dry THF and stirring it further for 1 h. The temperature of the reaction mixture was gradually raised by +10 °C to -15 °C within 1 h for the purpose of complete carbanion generation and recooled it to -70 °C. Hexamethylphosphoramide (HMPA, 0.61 mL, 3.9 mmol, 10 equiv.) in dry THF (1 mL) and (1R)-(-)-(10-Camphorsulfonyl)oxaziridine (0.2 g, 0.86 mmol, 2.2 equiv.) in dry THF (1 mL) was added to the reaction mixture sequentially and stirred at -78 °C for 1 h. The temperature of the reaction mixture was further gradually raise by +10 °C to -10 °C and stirred at -10 °C for 2 h. The reaction was quenched with saturated aq. NH$_4$Cl (5 mL) and was extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over

anhydrous sodium sulfate, concentrated, dried *in vacuo* and purified by column chromatography (hexane:ethyl acetate, 6:1) to obtain **69** as a colourless liquid (0.12 g, 82%).

Yield: 82%

TLC: R_f = 0.56 (SiO$_2$, Hexane : Ethyl acetate = 6:1)

^{1}H NMR (800 MHz, CDCl$_3$) δ: 5.52 – 5.25 (m, 1H), 4.68 (d, J = 7.4 Hz), 4.51 (d, J = 7.5 Hz), 3.73 (t, J = 11.9 Hz), 3.47 (d, J = 5.7 Hz) [1H], 4.30 – 4.22 (m), 3.96 (dd, J = 14.1, 5.1 Hz), [1H], 4.22 – 4.08 (m, 2H), 3.60 (d, J = 15.1 Hz),), 3.73 (t, J = 11.9 Hz), 2.56 (dd, J = 13.4, 3.5 Hz) [1H], 3.19 – 3.09 (m), 2.35 – 2.29 (m) [2H], 2.89 – 2.79 (m, 1H), 2.77 – 2.66 (m, 1H), 2.56 (dd, J = 13.4, 3.5 Hz), 2.38 (dd, J = 15.2, 4.5 Hz), [1H],), 2.54 – 2.49 (m, 1H), 2.54 – 2.49 (m), 2.27 – 2.18 (m) [2H], 2.14 – 2.00 (m, 1H), 1.94 – 1.80 (m, 1H), 1.67 (br m, J = 12.4 Hz, 1H), 1.57 – 1.49 (m, 2H), 1.45 – 1.40 (m, 10H), 1.30 (dd, J = 7.1 Hz, 2H), 1.27 (dd, J = 12.1, 4.9 Hz, 1H), 1.22 – 1.13 (m, 1H), 0.99 (dt, J = 15.5, 8.7 Hz, 1H), 0.91 (t, J = 7.4 Hz, 1H), 0.84 (t, J = 7.4 Hz, 2H).

^{13}C NMR (201 MHz, CDCl$_3$) δ: 205.56, 175.15, 155.57, 79.91, 70.56, 61.07, 52.63, 42.00, 40.08, 39.72, 36.29, 36.14, 31.20, 28.44, 26.08, 23.70, 20.53, 14.21, 9.69.

HRMS (ESI): *m/z* calculated for C$_{21}$H$_{35}$NO$_6$Na ([M+Na]$^+$) 420.2362, C$_{21}$H$_{36}$NO$_6$ ([M+H]$^+$) 398.2543; found 420.2369 ([M+Na]$^+$) and 398.2543 ([M+H]$^+$).

Synthesis of (±) (5a*R*,6*R*,7*S*,9*S*,9a*R*)-*tert*-butyl 7-acetoxy-9-(2-ethoxy-2-oxoethyl)-6-ethyl-8-oxodecahydro-1*H*-benzo[*b*]azepine-1-carboxylate (83):

To a stirred solution of the **69** (100 mg, 0.25 mmol) in dry pyridine (1 mL) under argon gas balloon was added acetic anhydride (Ac$_2$O, 1 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The progress of the reaction was monitored by TLC till the significant conversion of hydroxyl functionality into –OAc group. The reaction mixture was concentrated and the excess Ac$_2$O was also evaporated by using

rotary evaporator. Purification of the crude acetylated product was done by column chromatography using hexane : ethyl acetate (6:1) and obtained the **83** (81.7 mg, 74%) as a colourless liquid and starting material **69 was** recovered 24.2 mg.

Yield: 74%, 97% on brsm

TLC: R_f = 0.50 (SiO$_2$, Hexane : Ethyl acetate = 6:1)

^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.01 (d, J = 7.3 Hz, 1H), 4.16 – 4.07 (m, 2H), 4.04 – 3.97 (m, 1H), 3.89 (dd, J = 14.4, 3.9 Hz, 1H), 3.69 – 3.58 (m, 1H), 3.24 – 3.13 (m, 1H), 2.82 (dd, J = 16.9, 5.5 Hz, 1H), 2.73 – 2.63 (m, 1H), 2.62 – 2.51 (m, 1H), 2.50 – 2.45 (m, 1H), 2.44 – 2.33 (m, 1H), 2.29 – 2.19 (m, 2H), 2.17 (s, 1H), 2.08 (s, 2H), 1.42 (s, 9H), 1.25 (t, 3H), 1.20 (dd, J = 14.0, 6.8 Hz, 2H), 1.13 (dd, J = 14.1, 7.2 Hz, 1H), 0.92 (t, 2H), 0.83 (t, J = 7.4 Hz, 3H).
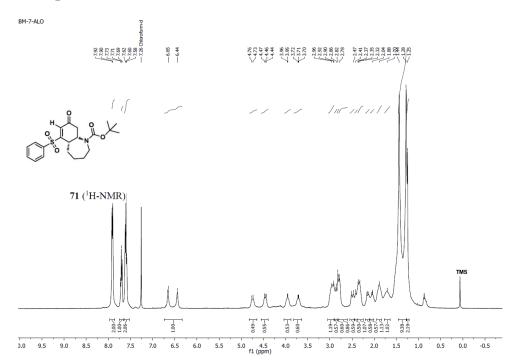
HRMS (ESI): *m/z* calculated for C$_{23}$H$_{37}$NO$_7$Na ([M+Na]$^+$) 462.2468, C$_{23}$H$_{38}$NO$_7$ ([M+H]$^+$) 440.2648; found 462.2472 ([M+Na]$^+$) and 440.2645 ([M+H]$^+$).

Synthesis of (±) (4*R*,4a*R*,9a*R*,10*R*,10a*S*)-*tert*-butyl 4-(2-ethoxy-2-oxoethyl)-10-ethyl-2-oxo-4,4a,7,8,9,9a,10,10a-octahydro-2*H*-benzofuro[5,6-*b*]azepine-5(6*H*)-carboxylate (85):
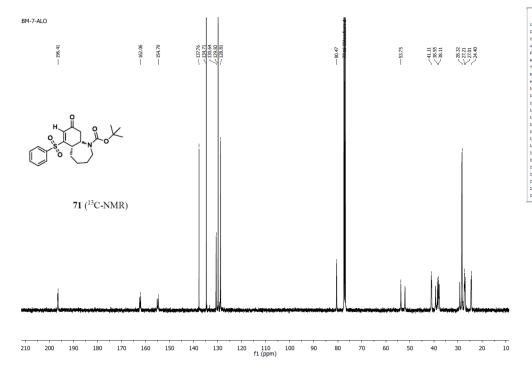
The solution of O-acetylated compund **83** (10.0 mg, 0.022 mmol) in dry THF (0.5 mL) was charged into a 10 mL two neck jacketed flask equipped with a magnetic stirring bar, argon gas balloon and was cooled to -80 °C. To this stirring solution of 0.5 M KHMDS in dry toluene (0.054 mL, 0.027 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred at -80 °C for 1 h. Excess acetic anhydride (Ac$_2$O, 0.058 mL, 614.3 mmol, 30.0 equiv.) was added to the reaction mixture and the reaction mixture was allowed to warm to -60 °C. After stirring at -60 °C for 8 h, the reaction was quenched with saturated aq. NH$_4$Cl (2 mL) and was extracted with EtOAc (2 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, dried *in vacuo*.

HRMS (ESI): *m/z* calculated for $C_{23}H_{35}NO_6Na$ ($[M+Na]^+$) 444.2362; found 444.2351 ($[M+Na]^+$).

4.10. Spectras:

BM-7-ALO

71 (^{1}H-NMR)

TMS

BM-7-ALO

71 (^{13}C-NMR)

BM-7-C-ALK

70 (^{1}H-NMR)

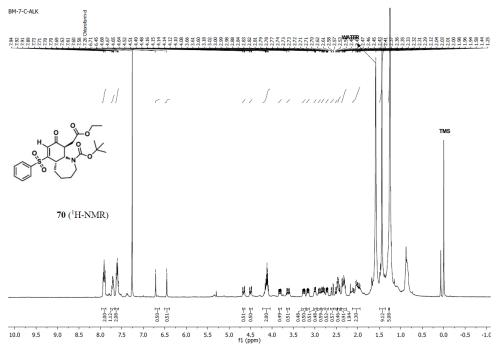|	Parameter	Value
1	Data File Name	BM-7-G-ALK
2	Title	BM-7-G-ALK- PROTON
3	Comment	
4	Origin	UXNMR, Bruker Analytische Messtechnik GmbH
5	Owner	root
6	Site	
7	Spectrometer	av400
8	Author	
9	Solvent	CDCl3
10	Temperature	300.0
11	Pulse Sequence	zg30
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	181
15	Relaxation Delay	1.0000
16	Pulse Width	10.2500
17	Acquisition Time	3.9715
18	Acquisition Date	1971-02-14T09:21:00
19	Modification Date	2015-02-14T04:51:00
20	Spectrometer Frequency	400.23
21	Spectral Width	8250.8
22	Lowest Frequency	-1664.0
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	32768

BM-7-C-ALK

70 (^{13}C-NMR)

	Parameter	Value
1	Data File Name	BM-7-C-ALK
2	Title	BM-7-C-ALK-PROTON
3	Comment	
4	Origin	UXNMR, Bruker Analytische Messtechnik GmbH
5	Owner	root
6	Site	
7	Spectrometer	av400
8	Author	
9	Solvent	CDCl3
10	Temperature	300.0
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	6144
14	Receiver Gain	11585
15	Relaxation Delay	2.0000
16	Pulse Width	14.5000
17	Acquisition Time	1.3631
18	Acquisition Date	1971-05-23T01:13:12
19	Modification Date	2015-05-22T21:43:00
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1992.4
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

75 (¹H-NMR)

75 (COSY)

BM-7-DSO

198.68

172.93

156.03
151.66

127.25

80.10

60.82
54.36

43.42
42.94
39.18

30.67
28.50
26.23
26.01
24.77

14.31

75 (^{13}C-NMR)

	Parameter	Value
1	Data File Name	BM-7-DSO
2	Title	BM-7-DESULFO-13C
3	Comment	
4	Origin	UXNMR, Bruker Analytische Messtechnik GmbH
5	Owner	root
6	Site	
7	Spectrometer	av400
8	Author	
9	Solvent	CDCl3
10	Temperature	300.0
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	4096
14	Receiver Gain	5161
15	Relaxation Delay	2.0000
16	Pulse Width	14.5000
17	Acquisition Time	1.3631
18	Acquisition Date	1970-01-25T16:00:45
19	Modification Date	2018-01-25T11:30:00
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1996.4
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

BM-7-DSO

151.95

127.52

61.10

54.63

43.70
43.21
39.45

30.95
28.78
26.50
26.28
25.06

14.59

75 (DEPT)

	Parameter	Value
1	Data File Name	BM-7-DSO
2	Title	BM-7-DESULFO-DEPT
3	Comment	
4	Origin	UXNMR, Bruker Analytische Messtechnik GmbH
5	Owner	root
6	Site	
7	Spectrometer	av400
8	Author	
9	Solvent	CDCl3
10	Temperature	300.0
11	Pulse Sequence	deptl35
12	Experiment	1D-DEPT-135
13	Number of Scans	1024
14	Receiver Gain	16384
15	Relaxation Delay	2.0000
16	Pulse Width	14.5000
17	Acquisition Time	1.3631
18	Acquisition Date	1970-01-25T16:58:49
19	Modification Date	2018-01-25T12:28:00
20	Spectrometer Frequency	100.61
21	Spectral Width	24038.5
22	Lowest Frequency	-1958.4
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

75 (HSQC) BM-7-DSO

75 (NOESY) BM-7-DSO

BM-7-CON

76 (¹H-NMR)

BM-7-CON

76 (¹³C-NMR)

76 (DEPT)

69 (¹H-NMR)

BM-7-CON-OH

205.56

175.15

155.57

79.91
Chloroform
70.56
61.07
52.63
42.00
40.08
39.72
36.29
36.14
31.20
28.44
26.08
23.70
20.53
14.21
9.69

69 (^{13}C-NMR)

	Parameter	Value
1	Data File Name	BM-7-CON-OH
2	Title	BM-7-CON-OH-13C
3	Comment	BM-7-CON-OH-13C
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrrn
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	300.0
11	Pulse Sequence	zgpg30
12	Experiment	1D
13	Number of Scans	2024
14	Receiver Gain	3
15	Relaxation Delay	2.0000
16	Pulse Width	11.8000
17	Acquisition Time	0.6826
18	Acquisition Date	2016-04-05T04:35:03
19	Modification Date	2016-04-05T11:37:26
20	Spectrometer Frequency	201.21
21	Spectral Width	48076.9
22	Lowest Frequency	-3893.5
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	131072

BM-7-CON-OH

70.44
67.41
60.95
52.51
41.88
39.96
39.59
36.16
36.02
30.60
28.31
25.96
23.58
20.40
14.09
9.57

69 (DEPT)

	Parameter	Value
1	Data File Name	BM-7-CON-OH
2	Title	BM-7-CON-OH-DEPT
3	Comment	BM-7-CON-OH-DEPT
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrrn
6	Site	
7	Spectrometer	spect
8	Author	
9	Solvent	CDCl3
10	Temperature	300.0
11	Pulse Sequence	dept135
12	Experiment	1D-DEPT-135
13	Number of Scans	512
14	Receiver Gain	203
15	Relaxation Delay	2.0000
16	Pulse Width	11.8000
17	Acquisition Time	0.6826
18	Acquisition Date	2016-04-05T06:31:00
19	Modification Date	2016-04-05T12:01:02
20	Spectrometer Frequency	201.21
21	Spectral Width	48076.9
22	Lowest Frequency	-3917.6
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	32768

69 (HSQC)
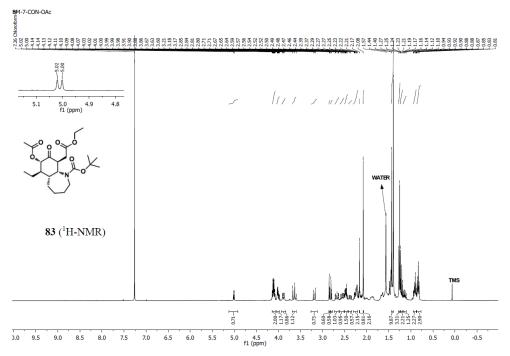

83 (^{1}H-NMR)

List of Publications

1. Total synthesis of (+)-*trans*- dihydronarciclasine from(+)-7-azabicyclo[2.2.1]heptanone.

   Tetrahedron 74 (2018) 5752-5757.
   Ganesh Pandey*, Rushil Fernandes, Debasis Dey, **Binoy Majumder**.

2. Development of a general synthetic route to access 2-azabicyclo [*m.n.*0]alkane ring systems and synthetic approach towards the *Strychnos* class of alkaloids.

   Ganesh Pandey*, **Binoy Majumder**. (Manuscript under preparation)

3. Synthetic Studies towards the total synthesis of (-)-Stenine and (-)-Tuberostemonine.

   Ganesh Pandey*, **Binoy Majumder**. (Manuscript under preparation)

Erratum