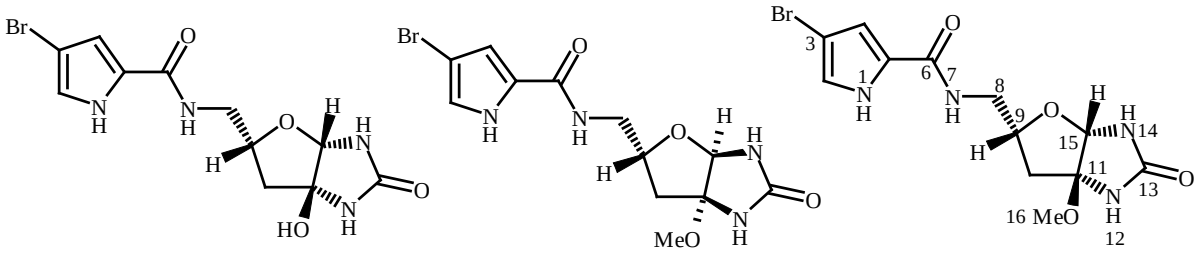
ABSTRACT

The thesis entitled "**Synthetic studies toward Slagenins B and C, Some rigid bicyclo heterocyclic scaffolds and Histrionicotoxin 235A**" consists of three chapters. Chapter I describes the synthesis of Slagenins B and C. Synthesis of rigid bicyclo heterocycle scaffolds is outlined in the Chapter II. Chapter III involves synthetic studies toward Histrionicotoxin 235A.

Chapter-I: Enantioselective total synthesis of slagenin B and C

Bromopyrrole alkaloids reveal pharmacological activity, including C-erB-2 kinase and cyclin depend kinase-(cdk4) inhibitors, α-adrenoceptor blockers, antagonists of serotonergic receptor, actomyosin ATPase activators etc. Kobayashi *et al.* have isolated bromopyrrole alkaloids from the Okinawan marine sponge *Agelas nakamurai* named Slagenins A-C, which are available in nature only in minute amounts, because of this it is quite interesting to develop a novel, simple, and economical method for the enantiomerically pure total syntheses of these bromopyrrole alkaloids.



Slagenin A (**1**) Slagenin B (**2**) Slagenin C (**3**)

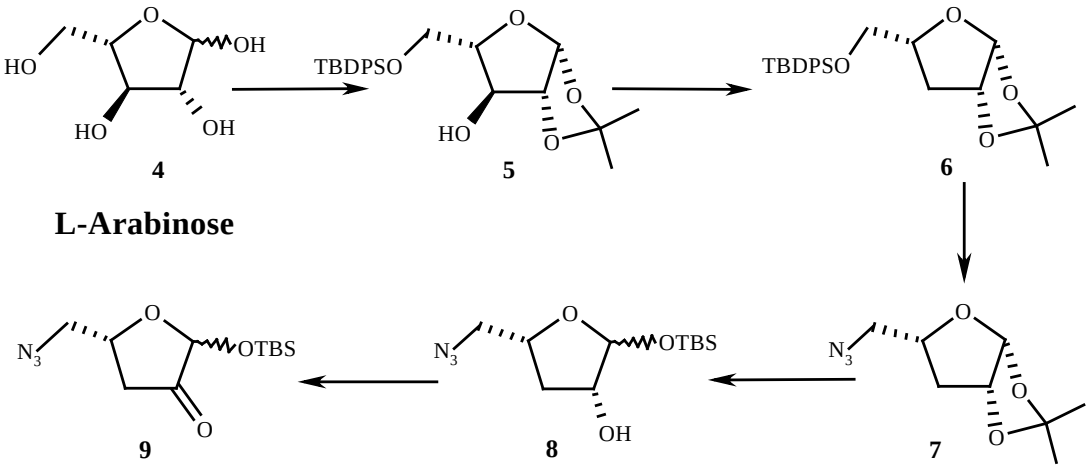
Figure 1. *Structures of Novel Bromopyrrole Alkaloids Slagenins A–C*

The 1st chapter of this thesis describes the enantioselective total synthesis of naturally occurring slagenins B and C starting from L-arabinose as a chiral precursor.

Synthetic approach

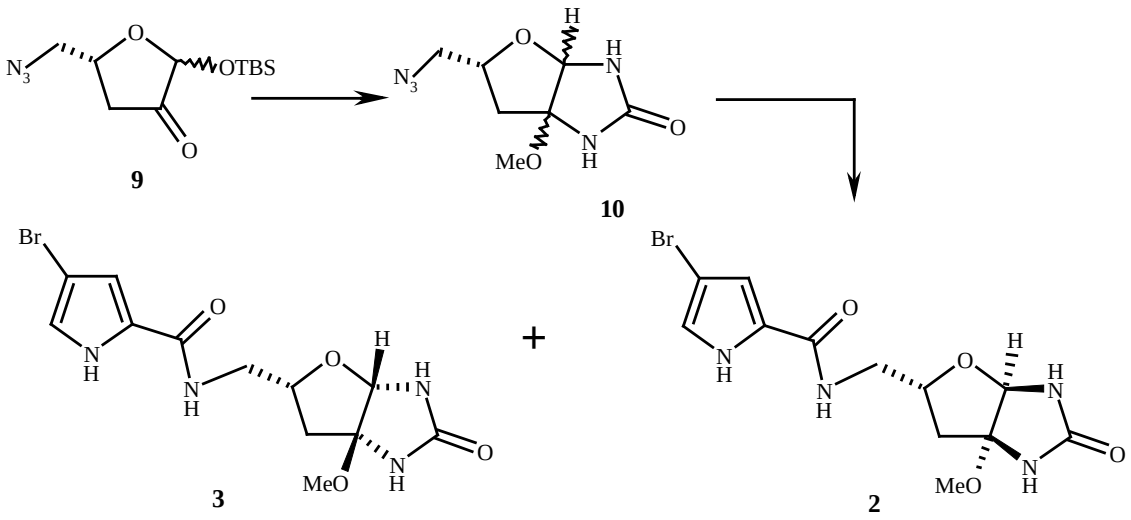
We began our research on the enantioselective synthesis of slagenins with the preparation of the key intermediate 2-ulose derivative (**9**) from the known 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-L-arabinofuranose (**5**) in five steps. Compound **5** was subjected to Barton's radical deoxygenation reaction to furnish the 3-deoxy derivative (**6**). Transformation of **6** into the azido derivative (**7**) involved removal of the silyl group, *O*-tosylation and nucleophilic displacement with NaN_3 in DMF. Our next target was to introduce imidazolidine ring system across C_1-C_2 segment of **7**. For this endeavor, the isopropylidene group was cleaved under acidic condition and the resulting diol was selectively silylated as TBS ether (**8**). Swern oxidation of **8** provided the 2-ulose derivative (**9**) whose ^1H NMR spectrum showed downfield shift of protons located at C-1 and C-3 (Scheme 1).

Scheme 1



With the key intermediate **9** in hand, the one pot reaction of **9** with urea in presence of 40% aqueous HF in methanol afforded **10**, which could not be separated from each other by silica gel chromatography. Undergoing the hydrogenation of this mixture over 10% Pd/C in methanol and the follow-up acylation with 4-bromo-2-(trichloroacetyl)pyrrole in DMF at rt furnished a mixture of **2** and **3** (Scheme 2).

Scheme 2



The two diastereomers **2** and **3** were isolated by silica gel chromatography providing slagenin B (**2**) and C (**3**) as pure products. The NMR (^{1}H, ^{13}C, and NOESY), IR, and mass spectral data for compound **2** and **3** were in satisfactory agreement with those reported for naturally isolated slagenin **B** (**2**) and **C** (**3**). The observed optical rotation of synthetic slagenin B (**2**) was $[\alpha]_D$ +36 ^{o} (*c* 0.2 in MeOH) [lit. $[\alpha]_D$ +33 ^{o} (*c* 0.2 in MeOH)] and of slagenin C (**3**) was $[\alpha]_D$ –39 ^{o} (*c* 0.2 in MeOH) [lit. $[\alpha]_D$ –35 ^{o} (*c* 0.2 in MeOH)].

Chapter-II: Synthesis of some rigid bicyclo heterocyclic scaffolds

The synthesis of novel and rigid scaffolds for diversification using combinatorial chemistry techniques has been an important goal in the discovery of new biologically active molecules. Recently, significant attention has also been focused on the synthesis of small molecule libraries based on natural product or natural product-like structures. We have initiated studies in this area employing the bicyclo[3,1,2]octane moiety as a rigid core template for elaboration using parallel synthesis techniques. We have focused our initial efforts on the preparation of highly functionalized bicyclo heterocyclic compound with general structure **A** using a scaffold that is reminiscent of bicyclo heterocyclic subunits found in the antibacterial agents such as norfloxacin, enoxacin, ciprofloxacin and difloxacin (Fig. 2).

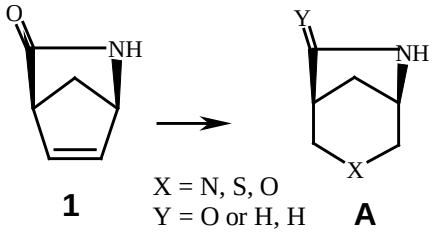
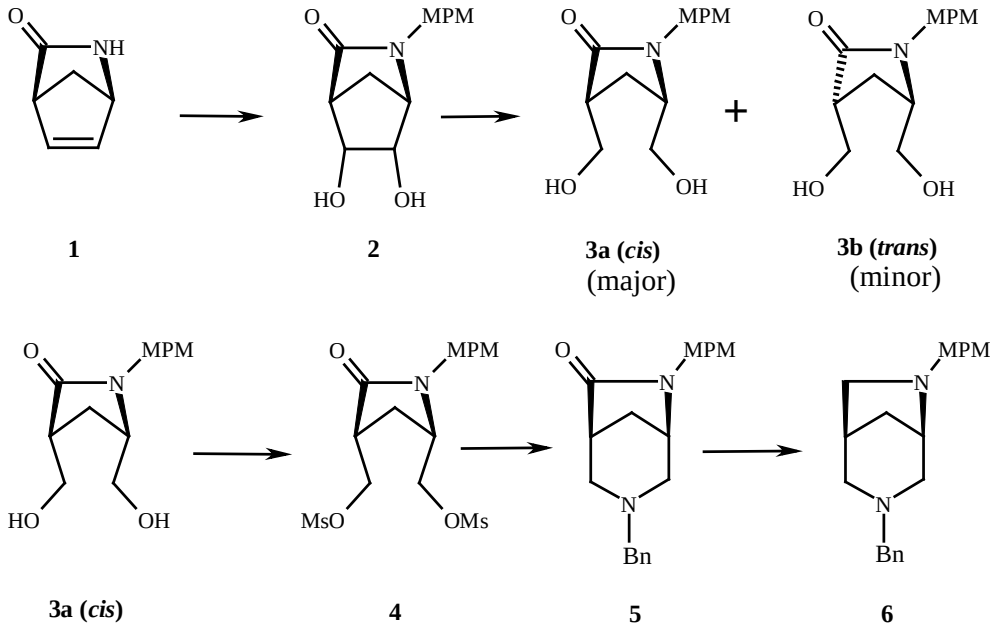


Figure 2. *Structures of the aza-bicyclo[3,1,2]octane*

Vince's lactam was used as an ideal precursor to design some novel and unique bicyclo-heterocyclic molecules, which can serve as scaffolds in combinatorial chemistry. In addition, we developed a new enzymatic route to resolve racemic Vince's lactam that could produce both (+)- or (–)-isomers with more than 99 % ee.

N-(*p*-methoxybenzyl) derivative of Vince's lactam (**1**), underwent dihydroxylation with OsO_4 in presence of *N*-methyl-morpholine *N*-oxide to provide the diol derivative (**2**), which in two steps produced a diastereomeric mixture of 3,5-dihydroxymethyl pyrrolidin-2-one (**3**) which turned out to be a 4:1 mixture of *cis* and *trans* diol derivatives (**3a** and **3b**) (Scheme 3).

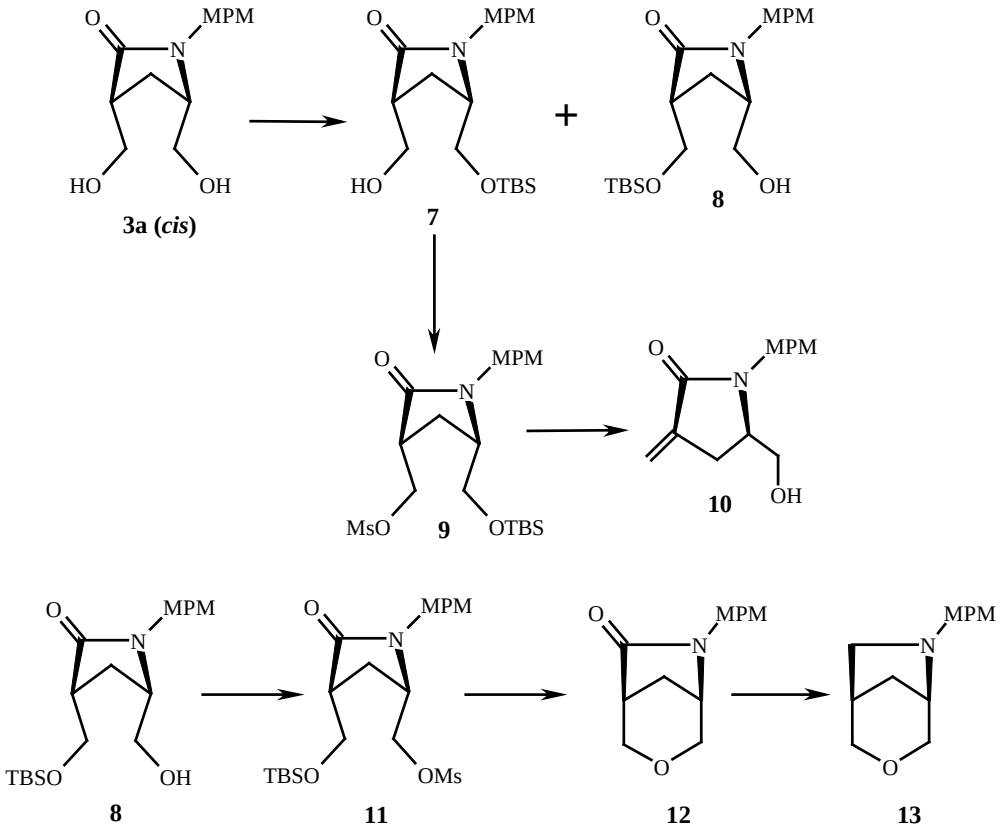
Scheme 3



The major isomer (**3**a) on treatment with $MeSO_2Cl$ and Et_3N gave the dimesylate derivative (**4**), which on exposure to benzyl amine containing excess of $NaHCO_3$ produced the diazabicyclo-lactam derivative (**5**). Reduction of **5** with 2 M solution of $Me_2S{:}BH_3$ in THF furnished the diazabicyclic derivative (**6**).

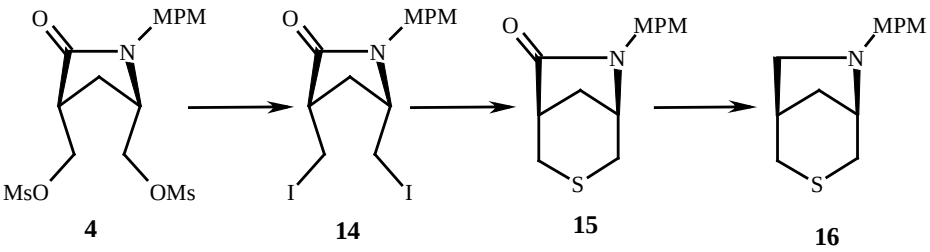
Our next concern was to synthesize the oxa-aza-bicyclic derivative (**12/13**). For this **3a** was protected as TBS ether where it formed a regiomeric mixture of **7** and **8**. Compound **7** was mesylated and then treated with Bu_4NF solution to get the oxa-aza derivative (**12**) but it produced some eliminated product (**10**). However **8** on mesylation and exposure to Bu_4NF solution in THF formed the oxa-aza-bicyclic derivative (**12**), which was confirmed from the ^1H, ^{13}C NMR and mass spectroscopic data. The reduction of **12** with $Me_2S{:}BH_3$ gave **13** whose structure was fully concurrent with the assigned structure (Scheme 4).

Scheme 4



Our final target was to make the thia-aza-bicyclic derivatives. Thus treatment of the dimesylate (**4**) with sodium sulfide, DMSO-CH_3CN produced the aza-thia-bicyclic derivative (**15**) in low yield but **4** after conversion into the corresponding di-iodo (**14**) followed by treatment with Na_2S in DMSO-CH_3CN furnished **15** in good yield. The carbonyl group was reduced with $Me_2S{:}BH_3$ complex to give the bicyclo heterocyclic-thia-aza derivative (**16**) (Scheme 5).

Scheme 5



4 **14** **15** **16**

The above mentioned scaffolds could be obtained in optically pure forms, from chiral Vince's lactam, the respective enantiomers of which were prepared with more than 99% ee by enzymatic resolution using two new strains; *k. citrophila* provided (–)-Vince's lactam while *A. viscous* produced (+)-Vince's lactam.

Chapter – III: The total synthesis of (–)-Histrionicotoxin 235A.

The family of histrionicotoxin alkaloids share a common 1-azaspiro[5,5]undecane ring system. The nature of the side chain present on this bicyclic spiro skeleton distinguishes the members of histrionicotoxin family. These were isolated from poison-dart frog *Dendrobates histrionicus*, which were mainly found in South American countries. (–)-Histrionicotoxin and its analogues have attracted considerable pharmacological interest as noncompetitive inhibitors of the nicotinic acetylcholine receptor and as probes to study neuromuscular signal transmission. Great strides have been made to accomplish the model as well as the total synthesis of histrionicotoxin alkaloids utilizing many brilliant strategies. A carbohydrate based synthetic approach was preluded, although we believe that a chiron approach from a carbohydrate residue offers distinct advantages while constructing the

azaspiro-undecane ring system. In this chapter we report the synthesis of commonly observed 1-azaspiro[5,5]undecane ring system of (–)-histrionicotoxin 235A and histrionicotoxin family starting from D (+)-glucose. The functional group distributions in **16** and **20** are exploitable for the total synthesis of these alkaloids.

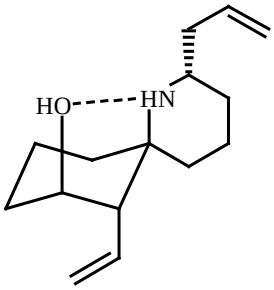


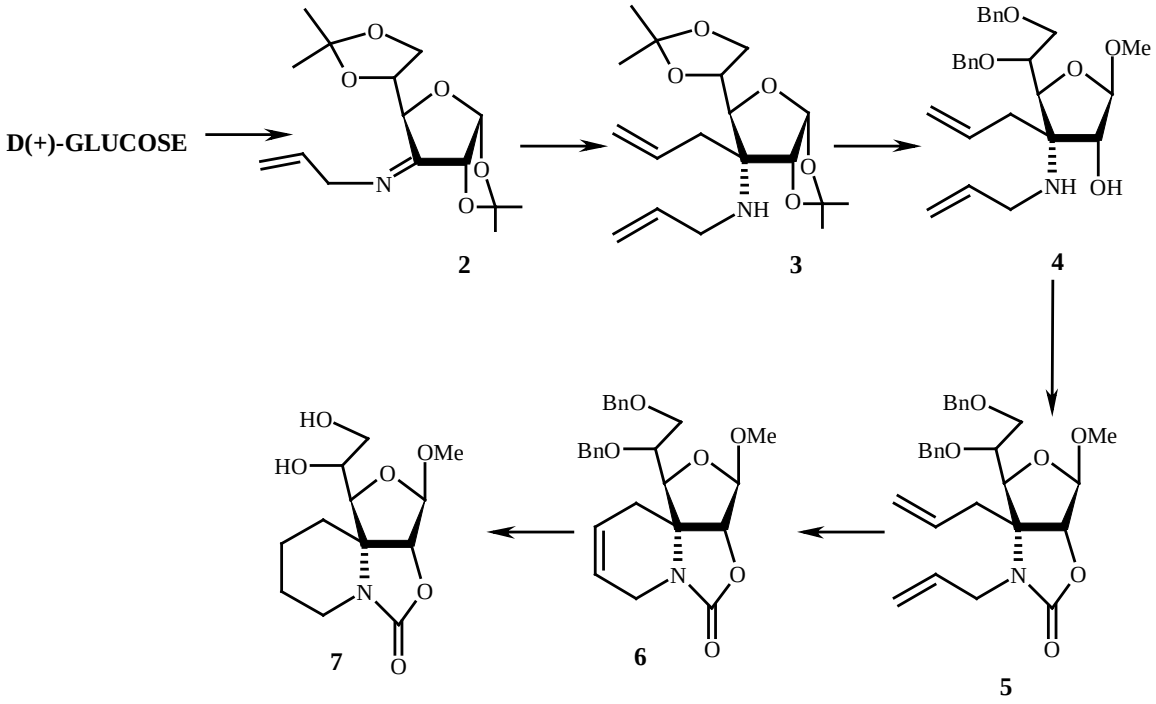
Figure 3. *Structure of Histrionicotoxin 235A (**1**)*

A three-pronged strategy was crafted for synthetic trails: a) addition of allyllithium to an allyl imine followed by RCM; b) a zinc-mediated domino elimination–alkylations of methyl 5-iodopentofuranosides followed by RCM. c) Nucleophilic substitution and electrophilic addition for the generation of two other stereocenters.

Our initial approach started with a diastereospecific addition of allyl lithium to the allyl imine (**2**)**,** derived from D (+)-glucose in three steps. The high diastereoselectivity in this allylation can be explained by inherent steric hindrance from the 1,2-isopropylidine moiety.

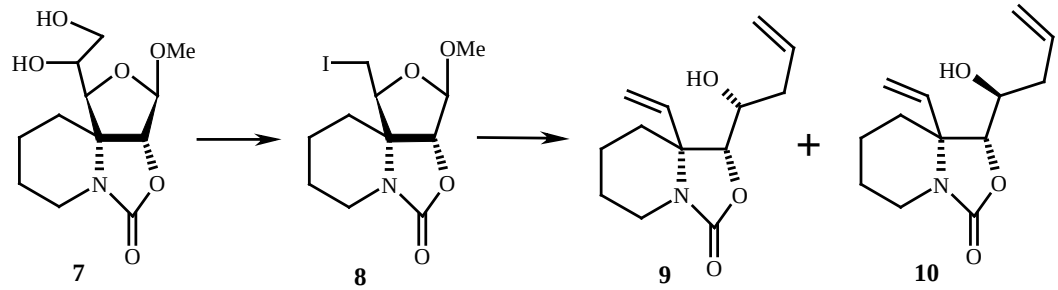
With the advent of efficient catalysts, the ring-closing metathesis (RCM) reaction has emerged as a powerful process for cyclization of dienes. In the synthetic direction, compound **3** on selective deprotection of the 5,6-acetonide group, dibenzylation and acidic hydrolysis of the 1,2-acetonide with 10% H_2SO_4 in methanol gave the *β*-methyl glycoside derivative (**4**). **4** was converted to the carbamate derivative (**5**) which was subjected to RCM using 1st generation Grubbs' catalyst followed by hydrogenation with 10% Pd/C to give the piperidine derivative (**7**) (Scheme 6).

Scheme 6



The next issue that needed attention was constructing the carbo-cyclic ring for which we sought to explore the domino reaction. For example, oxidative cleavage of **7** with sodium meta-periodate followed by reduction and subsequent treatment of the resulting alcohol with triphenylphosphine/iodine/imidazole gave the key iodo derivative (**8**). Reductive elimination and *in situ* Barbier allylation was accomplished by treating the iodo derivative (**8**) with Zn in THF/water/allyl bromide under sonication at 45 ^{o}C and this afforded the homo allylic alcohols (**9**) and (**10**) in 1:9 diastereomeric ratio (Scheme 7).

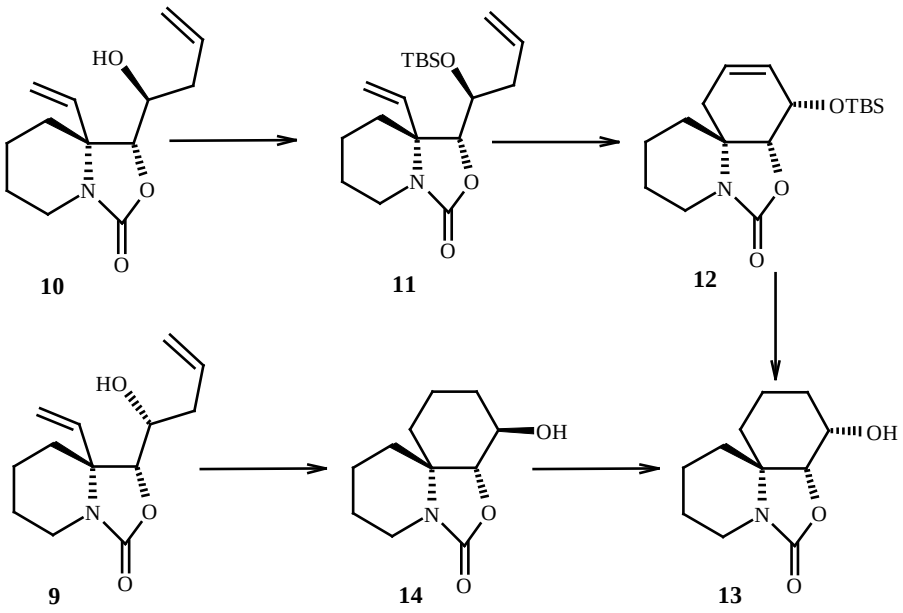
Scheme 7



The two diastereomers were separated by column chromatography and each of these two diastereomers were used for next reaction. The major isomer (**10**) was at first protected

as TBS-ether with TBDMSTf and then underwent RCM reaction using 1st generation Grubbs' catalyst followed by hydrogenation producing the spiro cyclic ring derivative (**13**). The stereochemistry of **13** was confirmed by single crystal X-Ray crystallography (Scheme 8)

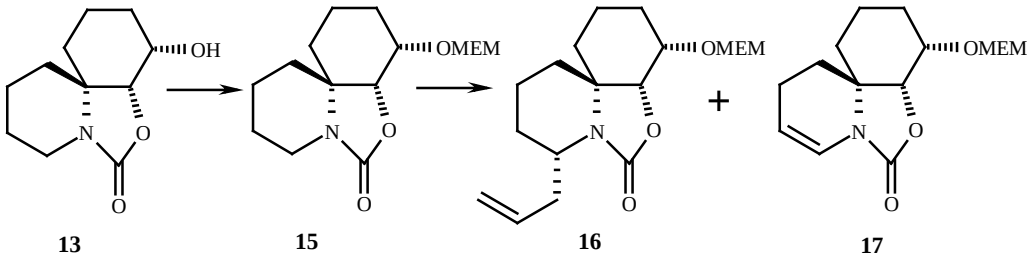
Scheme 8



The minor isomer **9** underwent same set of reactions to provide the azaspiro derivative (**14**), having opposite configuration at C-8 compared to **13**. In order to invert the C-8 center, it was first oxidized with Dess-Martin periodinane (DMP) and then reduced by sodium borohydride to give **13** (scheme 8).

In order to functionalize the C-2 center adjacent to nitrogen with an allylic group, compound **13** was protected as MEM- ether to **15**, which was treated with allyl bromide in the presence of *s*-BuLi and TMEDA at 0 ^{o}C to give **16** as a single isomer along with the eliminated product (**17**). The exclusive formation of **16** was assigned on the basis of complex-induced proximity effects according to which, in a carbamate directed lithiation reaction, the carbonyl group of the carbamate first complexes with *s*-BuLi to influence the lithiation from the same face of the ring system (**15**) (Scheme 9).

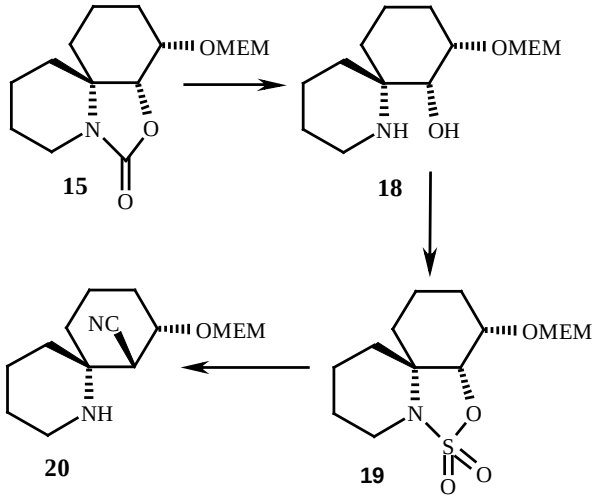
Scheme 9



Our next objective was the introduction of cyano group at C-7 of **18** for which we envisaged the nucleophilic displacement reaction.

As a model study, we attempted the displacement reaction with carbamate **15** whose alkali hydrolysis furnished the amino alcohol (**18**), which on treatment with SO_2Cl_2 formed the cyclic sulfamidate (**19**). Compound **19** underwent nucleophilic displacement reaction with NaCN to give the cyano derivative (**20**). The ^{1}H NMR, ^{13}C NMR, IR spectrum confirmed all the structures (Scheme 10).

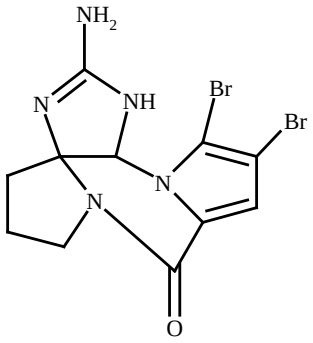
Scheme 10



In conclusion, we have achieved the carbohydrate-based synthesis of key aza-spiro ring system present in histrionicotoxin group of alkaloids family from easily accessible D (+)-glucose.

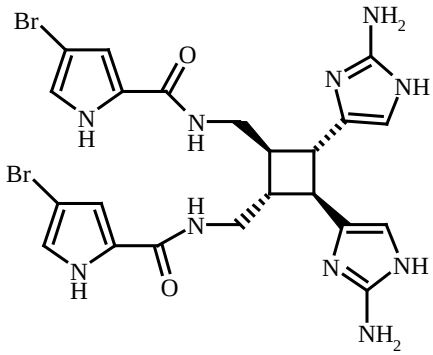
Nature has been producing a range of diverse and often highly complex secondary metabolites, which exhibit one or more variety of pharmacological activity. In this regard marine sponge has distinctive admiration as secondary metabolites, which are sources of unpreluded structural diversity.[1] Bromo pyrrole alkaloids are one type of secondary metabolites which exhibit C-erB-2 kinase and cyclin depend kinase–(cdk4) inhibitors, α-adrenoceptor blockers,[2] antagonists of serotonergic receptor,[3] actomyosin ATPase activators[4] etc. During the studies on bioactive substances from marine organisms, Kobayashi *et al.*[5] examined the extracts of numerous marine sponges and isolated several bromopyrrole alkaloids. Among these species *Agelasiidae*, *Axinellidae* and *Hymeniacidonidae* families constitute the bromopyrrole alkaloids (Fig. 1).

Figure 1. (i) *Axinellidae* family

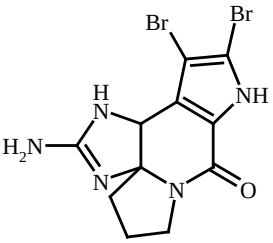


Bromophakellin

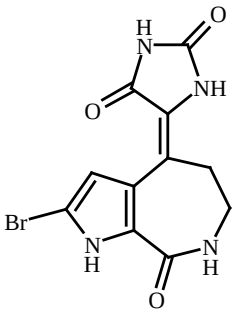
ii) Agelasiidae family



Sceptrin

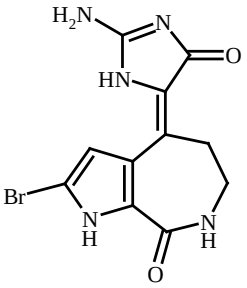


Dibromo cantharelline

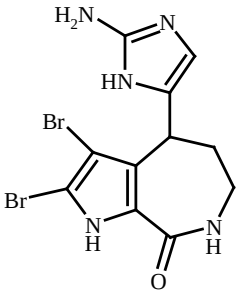


Axinohydantoin

(iii) *Hymeniacidonidae* family



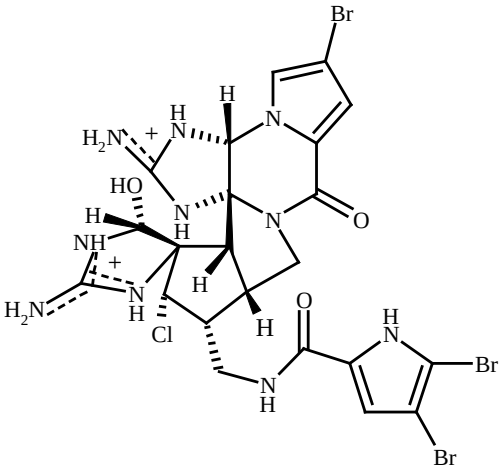
Hymenialdisine



Hymenine

During the exploration of Okinawan marine sponges, Kobyashi *et al.* isolated a fused-hexacyclic alkaloid possessing two bromopyrrole carbonyl groups and two guanidine units, named konbu'acidin A,[6] with cdk4 inhibitory activity from an Okinawan marine sponge *Hymeniacidon* sp. (Fig. 2).

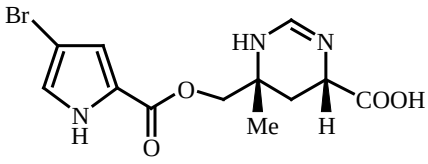
Figure 2. *Hymeniacidon* sp.



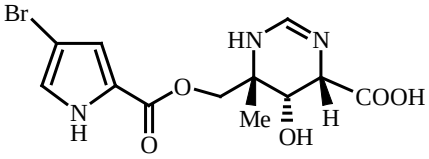
Konbu’acidin A

From Okinawan sponge *Hymeniacidon* sp. three novel compounds, named manzacidins[7] A-D (**1-4**), belonging to an unprecedented class of bromopyrrole alkaloids with an unusual 3,4,5,6-tetrahydropyrimidine ring were isolated (Fig. 3).

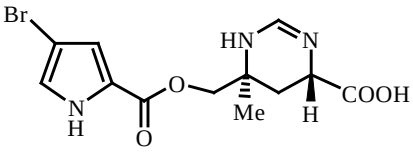
Figure 3. *Hymeniacidon* sp.



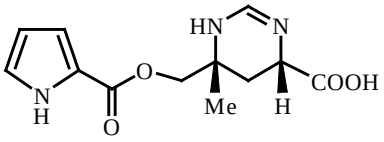
Manzacidin A (**1**)



Manzacidin B (**2**)



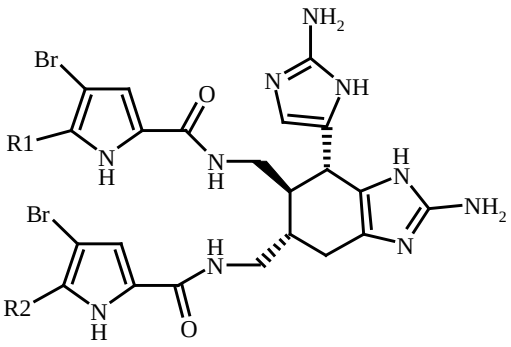
Manzacidin C (3)



Manzacidin D (4)

Three bromopyrrole alkaloids, ageliferin (**1**), bromoageliferin (**2**), and dibromoageliferin (**3**), have been isolated as potent actomyosin ATPase activators from the Okinawan marine *sponge Agelas* sp.[4] (Fig. 4).

Figure 4. *Agelas* sp.

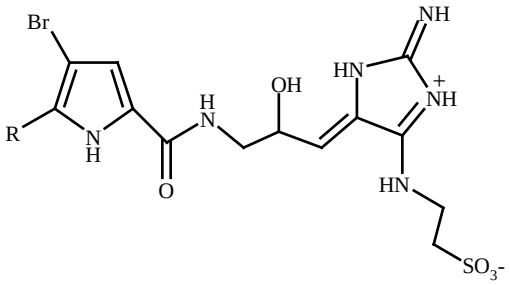


1 R1 = H, R2 = H
2 R1 = H, R2 = Br
3 R1 = R2 = Br

Ageliferin (**1**), bromoageliferin (**2**), and dibromoageliferin (**3**)

Some other bromopyrrole alkaloids isolated from Okinawan marine sponge *hymeniacidon* sp., are Taurocidins[8] A (**1**) and B (**2**) possessing tyrosin kinase activity (Fig. 5).

Figure 5. *Hymeniacidon* sp.



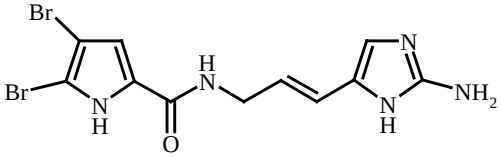
A (1) R= Br
B (2) R = H

Taurocidins A (**1**) and B (**2**)

In the last 25 years, sponges of the genus *Agelas* (order Agelasida, family Agelasidae) have been extensively investigated yielding a prodigious harvest of new natural compounds, going from α-glycosphingolipids to derivatize terpenoids and bromopyrrole alkaloids. These compounds, characterized by a mono or dibromopyrrole-2-carboxylic acid moiety linked to an imidazoline ring through an aliphatic chain, show bioactivities apparently related to particular structural features. Alkaloids like keramadine, oroidin (**1**),[9] (Fig. 6) and clathrodine,[10] in which the two heterocyclic nuclei are linked by a linear chain, show serotonergic and/or cholinergic antagonist activities.

Oroidin (**1**) is a major metabolite of several species of marine sponges of the genus *Agelas* and is the basis of the oroidin group of alkaloids. It was first isolated in 1971 from *Agelas oroides* but its structure was established in 1973 and proven by total synthesis in 1986.[11]

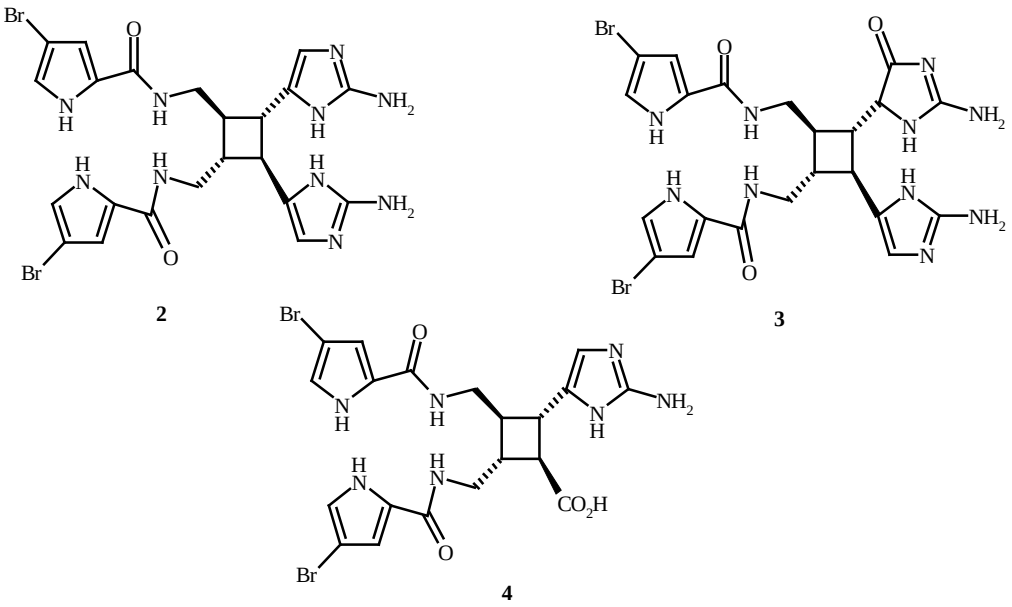
Figure 6. *Agelas* sp.



Oroidin (**1**)

Subsequently, many other species of *Agelas*, *Axinella*, *Acanthella*, *Hymeniacidon*, *Phakellia* and *Pseudaxinyssa* have been reported to contain high levels of oroidin or cyclic analogues. It is thus clear that oroidin alkaloids are useful chemotaxonomic markers for axinellid sponges that were once allied with the Agelasida. In 1981, Faulkner and co-workers isolated sceptrin[12] (**2**) from *Agelas sceptrum*. Formally, sceptrin is related to debromooroidin by a head-to-head [2 + 2]-cycloaddition that must be photochemically allowed. As oroidin is achiral, if this were a photochemical reaction, sceptrin ought to have been isolated as a racemic mixture. In contrast, sceptrin is chiral ($[\alpha]_D$ –7.4 ^{o}) suggesting that it is formed by an enzyme catalysed reaction. If this is the case, it will be the first example of a biological [2 + 2] cycloaddition or, indeed, any pericyclic reaction. Slight variations on the structure of sceptrin (**2**) [eg dibromosceptrin, debromosceptrin, oxysceptrin (**3**) and nakamuric acid (**4**)] have been isolated in subsequent work from *Agelas* cf *nemoechinata*, *A. conifer* and *A. nakamurai*.[13] These compounds are also of pharmaceutical interest as many have shown α-adrenoceptor blocking activity that does not interfere with the action of potassium chloride or seratonin.[14] Specifically, sceptrin (**2**) and its analogues have potent antibacterial/antifungal activities,[15] anti-muscarinic activity,[16] anti-histaminic activity[17] and oxysceptrin is also a potent actomyosin ATPase activator (Fig. 7).

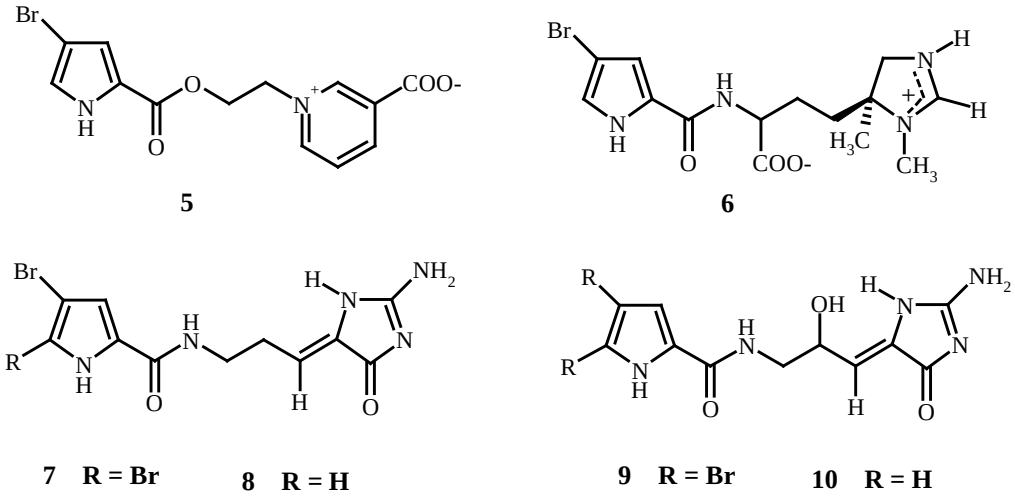
Figure 7. *Agelas* sp.



Sceptrin (**2**), dibromosceptrin, debromosceptrin, oxysceptrin (**3**) and nakamuric acid (**4**)

During continuing efforts to identify new biologically active substances from marine sources, Kobyashi *et al.* have recently focused on *Agelas* sponges, studying the secondary metabolism, and, in particular, the alkaloid composition of four Caribbean species, namely *A. clathrodes, A. comfera, A. dispar, and A.longissima.* From these organisms they isolated a series of structurally related alkaloids, characterized by a short linear chain connecting two heteroaromatic rings: agelongine[18] (**5**, a pyridinium alkaloid that they recently reported as selective antiserotonergic agent), clathramides[19] (**6**), and dispacamides A[20] (**7**), B (**8**), C (**9**) and D (**10**) (Fig.8).

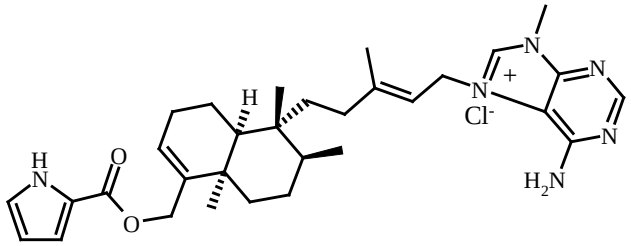
Figure 8. *Agelas* sp.



Agelongine (**5**), clathramides (**6**), and dispacamides A (**7**), B (**8**), C (**9**) and D (**10**)

Ageline B (**11**) is an example of a pyrrole-2-carboxylic acid derivative attached to the terpenoid through an ester bond.[21] Natural products containing a tetrahydropyrimidine ring are rare, and these apparently are the first examples from marine sources (Fig.9).[22]

Figure 9. *Agelas*.sp

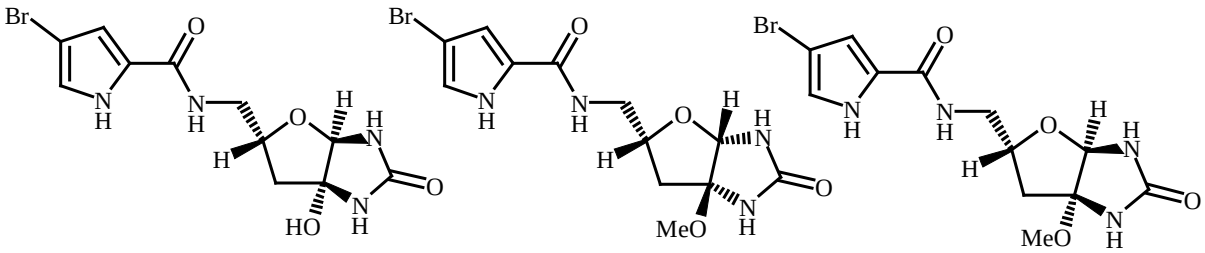


Ageline B (**11**)

Studies Directed Toward the Stereoselective Synthesis of Slagenins B and C:

Recently, an exciting new class of bromopyrrole alkaloids slagenins A-C (**1-3**) was discovered by Kobayashi *et al.*[23] from the Okinawan marine sponge *Agelas nakamurai* (Fig.10). Slagenins A-C revealed cytotoxicity against routine leukemia L1210 cells *in vitro* with IC_{50} values of 7.5 and 7.0 g/mL.

Figure 10. *Agelas*.sp



Slagenin A (**1**) Slagenin B (**2**) Slagenin C (**3**)

Due to their interesting physical properties the synthesis of slagenins have attracted considerable attention from synthetic chemists.

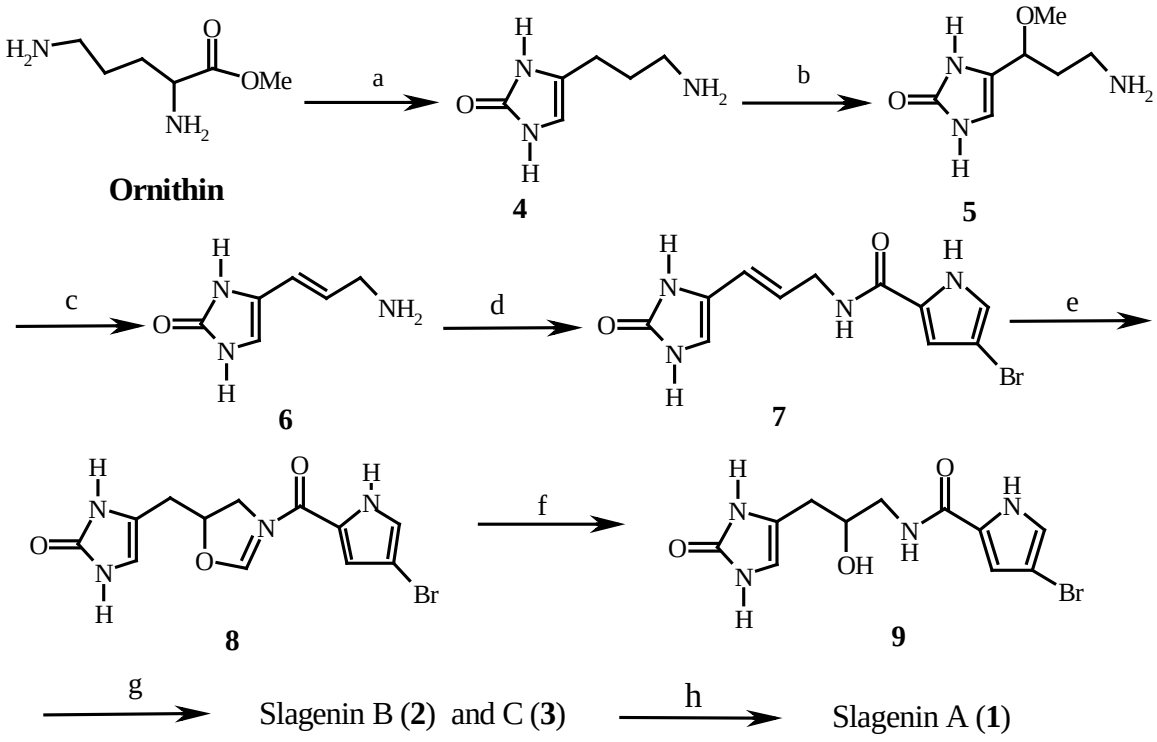
Past Work

Horne Approach[24]

The first synthesis described by Horne and co-workers involved racemic preparations of slagenins. But their absolute stereochemistry remains unexplored.

This synthetic approach centers on the introduction of the *β*-hydroxy substituent in imidazolone (**9**) and its subsequent oxidative cyclization to the requisite slagenin core. Ornithin, which was converted into the imidazolidine derivative (**4**) by Fischer esterification, Akabari reduction and condensation by potassium cyanate (Scheme 1). Treatment of **4** with *N*-chlorosuccinimide in methanol afforded the *β*-methoxy derivative (**5**). Trifluoroacetic acid caused elimination of MeOH, which produced the olefin derivative (**6**). Acylation of **6** with 4-bromo-2-(trichloroacetyl)pyrrole gave **7** as a solid. Compound **7** was converted to the oxazoline derivative (**8**) in near quantitative yield with methanesulfonic acid. Aqueous acid caused cleavage of the oxazoline in **8**, producing the alcohol derivative (**9**) upon neutralization with base. When a methanol solution of **9** was treated with NCS (23 ^{o}C, 30 min), a 1:1 diastereomeric mixture of slagenins B (**2**) and C (**3**) were produced. Upon heating in the presence of acid, both **2** and **3** were converted to slagenin A (**1**).

Scheme 1

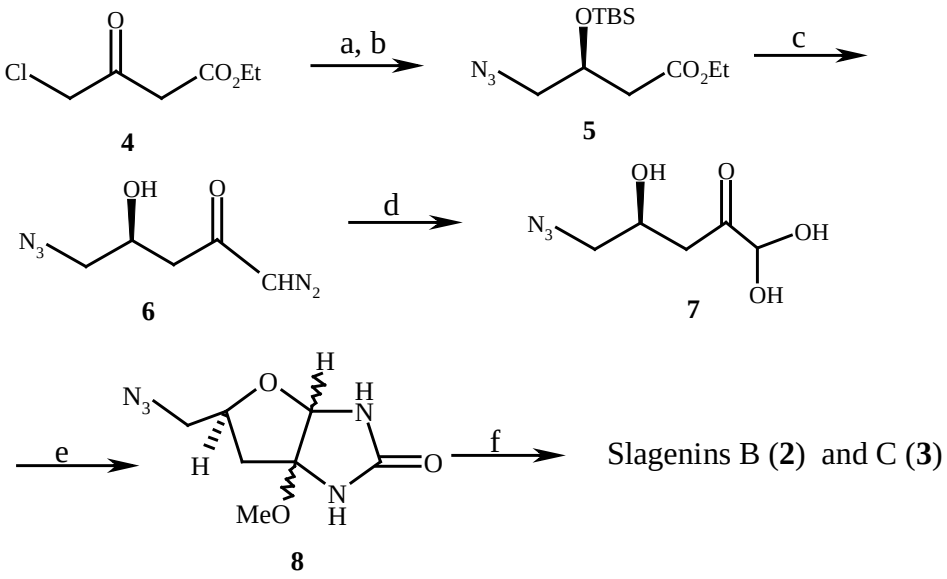


Reagents and conditions: a) Na (Hg), KOCN; b) NCS, MeOH, 23 ^{o}C, 1 h; c) TFA, 23 ^{o}C, 5 h; d) 4-Bromo-2-(trichloroacetyl)pyrrole, DMF, rt, 1 h; e) $MeSO_3H$, 23 ^{o}C, 3 h; f) 5% HCl, reflux, 2 h; g) NCS, MeOH; h) H^+, 80 ^{o}C.

Jiang Approach[25]

Jiang *et al.* revealed synthesis of the antipodes of slagenins B and C. Here they started from ethyl 4-chloroacetoacetate. Hydrogenation of ethyl 4-chloroacetoacetate (**4**) over $Ru(OAc)_2$(*R*-BINAP) and then protection as TBS ether, followed by displacement of 4-chloro with azide, gave compound **5**. Ester (**5**) was saponified to give acid, which was converted into the *β*-diazoketone derivative (**6**)**.** Oxidation of diazoketone (**6**) afforded the glyoxal hydrate (**7**). Finally, one-pot treatment of the glyoxal mixture containing **7** with aqueous HF and urea in methanol gave compound **8** in a 9:5 mixture of two diastereoisomers, which after reduction and acylation with 4-bromo-2-(trichloroacetyl)pyrrole to get compounds **2** and **3** i.e slagenin B and slagenin C (Scheme 2).

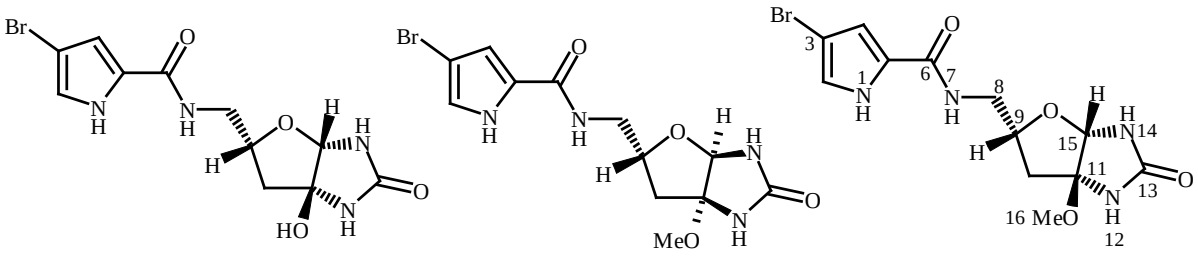
Scheme 2



4 **5** **6** **7** **8**

Reagents and conditions: (a) H_2, 0.1 mol % $Ru(OAc)_2$(RBINAP), EtOH, 40 atm, 100 °C; (b) (1) TBSCl, imidazole, DMF, 45 °C, (2) NaN_3, DMF, 90 °C; c) (1) 2 equiv LiOH, acetone-water, rt, (2) H+; (3) isobutyl chlorocarbonate, NEt_3, dry THF, –20 °C to –10 °C; (4) 2 equiv. diazomethane; (d) DMD-acetone; e) 40% aqueous HF, urea, methanol, rt; f) H_2, Pd/C, methanol; 4-bromo-2-(trichloroacetyl)pyrrole, DMF.

Kobayashi *et al.*[5] have examined the extracts of various marine sponges and isolated several bromopyrrole alkaloids. They have investigated bioactive constitutents of *Agelas sp*, and three novel compounds, named slagenins A-C [23] (Figure 10). These natural products constitute a group of cytotoxic secondary metabolites and isolated from the Okinawan marine sponge *Agelas nakamurai*. These are structurally interesting natural products and possess a highly functionalized tetrahydrofuro[2,3-d]imidazolidin-2-one moiety whose relative stereochemistry was elucidated by 2 D NMR spectroscopy. In Nature, these are available in only minuscule. Because of significant structural interest and more detailed pharmacological investigations it became the goal of the current project to develop efficient syntheses for these bromopyrrole alkaloids.



Slagenin A (**1**) Slagenin B (**2**) Slagenin C (**3**)

Figure 10. *Structures of Novel Bromopyrrole Alkaloids Slagenins A – C*

Slagenins B (**2**) and C (**3**) exhibited cytotoxicity against routine leukemia L1210 cells *in vitro* with IC_{50} values of 7.5 and 7.0 g/mL, respectively, whereas slagenin A (**1**) did not show such activity. They are characterized by the presence of tetrahydrofuro[2,3-d]imidazolidin-2-one moiety. Two groups have reported synthesis of these metabolites.

We report in this letter the first enantioselective total synthesis of naturally occurring slagenins B and C starting from L–arabinose (**4**), as a chiral precursor.

Retrosynthetic Analysis

Slagenins possess a *cis* fused tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety with three stereogenic centers, of which C11 has a quaternary carbon. The key to the synthetic scheme was the generation of the three stereogenic centers in the moiety. The slagenin bicycle core can be retrosynthesized, in the most direct way, to the condensation of urea with the corresponding dihydrofuran-3-one (**I**) (Fig. 11).

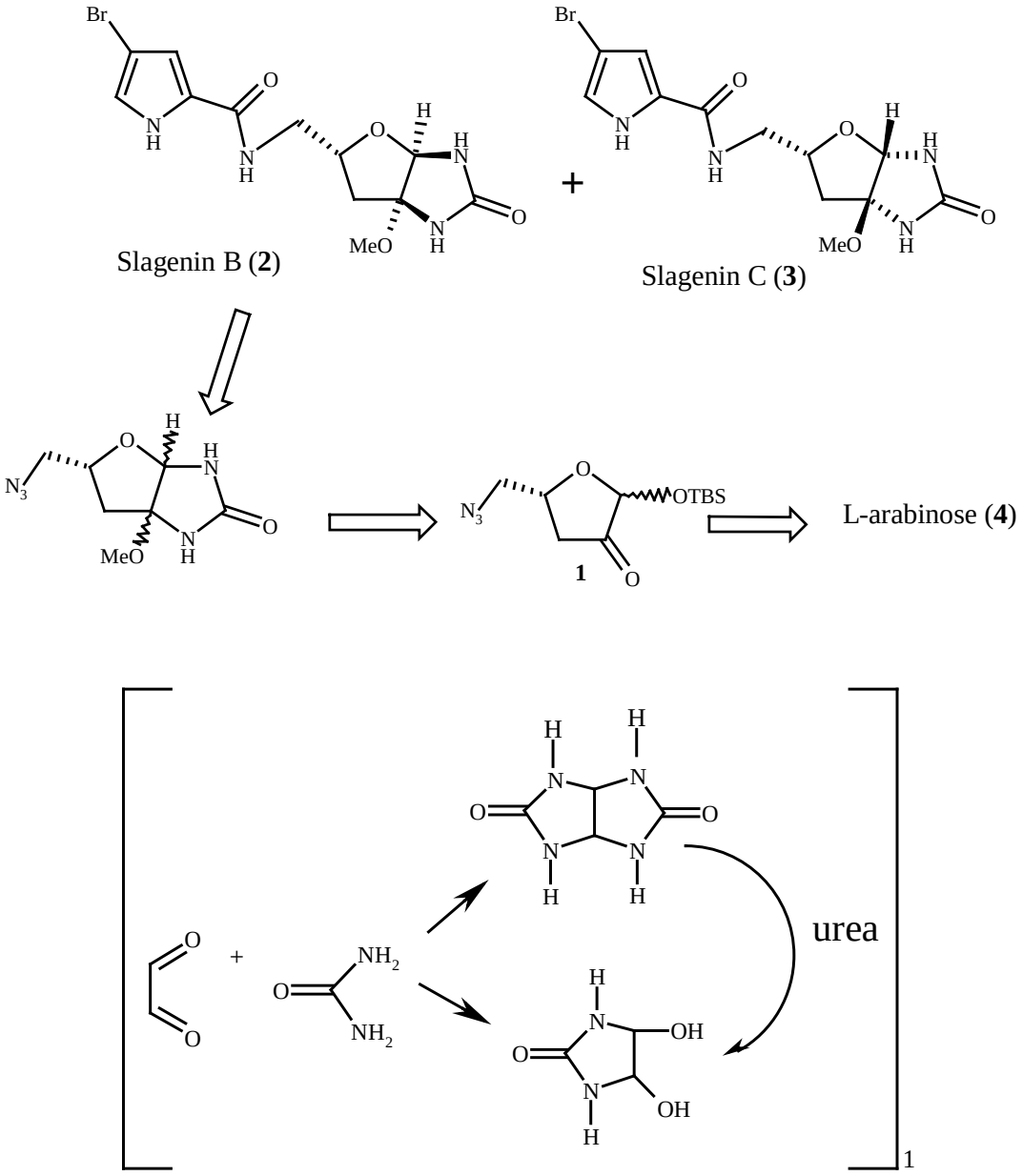


Figure 11. *Retrosynthetic strategy for the synthesis of slagenin B and slagenin C*

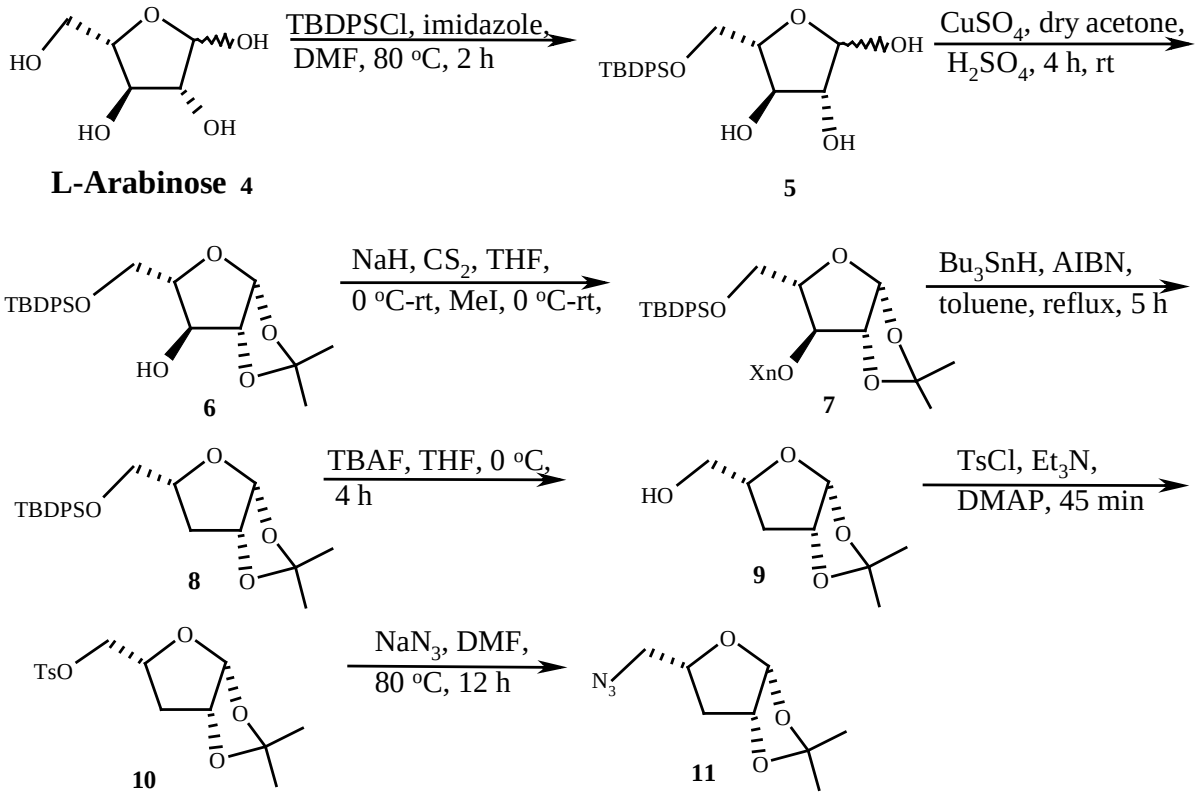
It might be expected that, due to the obvious strain of a *trans*-[3.3.0]bicycle, condensation would result in the bicyclo derivative with *cis*-fusion. The other two stereogenic centers would be generated in an enatioselective fashion from commercially available L-arabinose (**4**).

The execution of this general strategy is discussed below.

Synthetic approach

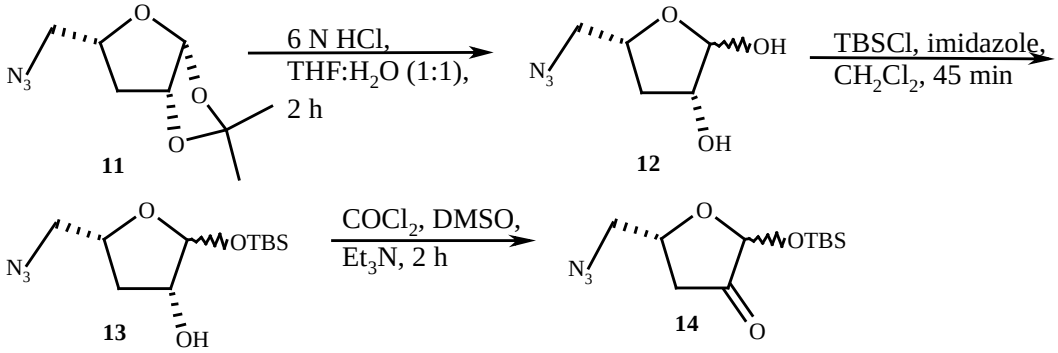
Starting from L-arabinose (**4**), the 3-deoxy-L-arabinose derivative (**8**) was prepared by adapting the reported procedure.[26] Selective protection of 5-OH with TBDPSCl in DMF at 140 °C in the presence of imidazole gave compound **5**. Treatment of of **5** with acetone in the presence of anhydrous $CuSO_4$ and a catalytic amount H_2SO_4 afforded the 1,2-*O*-isopropylidene-β-L-arabinose derivative (**6**). The spectroscopic data of **6** was in good agreement with the assigned structure. Our next concern was to deoxygenate the hydroxy group at C-3 by using Barton's radical deoxygenation protocol.[27] Thus, **6** was converted into its xanthate derivative **7** by treating with NaH, CS_2 and MeI in THF. The structure of **7** was confirmed by its ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. In the ^{1}H NMR spectra the methyl group showed a singlet at 2.54 ppm Compound **7** was treated with Bu_3SnH in presence of AIBN in refluxing toluene for 5 h to give the 3-deoxy derivative (**8**). The structure of **8** was confirmed by its ^{1}H NMR, ^{13}C NMR and elemental analysis. For instance, the ^{1}H NMR spectrum of **8** showed characteristic resonances due to H-3, 3′ at 1.97 and 2.11 ppm. The H-2 proton appeared at 5.70 ppm as a doublet (J = 3.6 Hz). Other protons resonated at their respective values confirming the structure of **8**. The cleavage of silyl ether[28] group was accomplished by exposing **8** with Bu_4NF in THF at 0 ^{o}C. The resulting product **9** was ready for azidation. The ^{1}H, ^{13}C NMR, spectra and elemental analysis of **9** were in agreement with assigned structure. Treatment of **9** with TsCl and pyridine in CH_2Cl_2 gave the corresponding 5-*O*-tosylate (**10**), which was transformed into the azide derivative (**11**)[29] by reacting with sodium azide in DMF (Scheme 3). The structure of **11** was confirmed by the ^{1}H, ^{13}C NMR, IR and mass spectroscopy. In the ^{1}H NMR spectrum H-5 proton resonated at 3.15 ppm (dd, J = 6.1, 12.6 Hz) while H-5′ appeared at 3.68 (dd, J = 8.1, 12.6 Hz).

Scheme 3



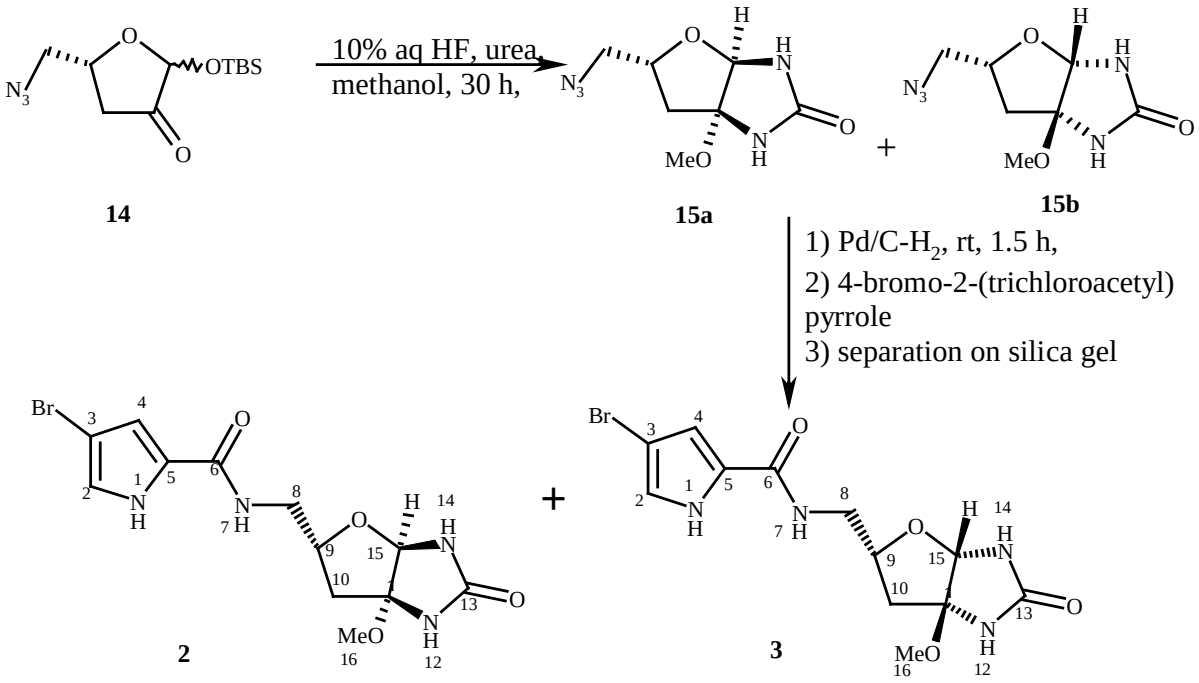
In order to install the imidazolidine ring system across C_1-C_2 segment of **11**, hydrolysis of isopropylidine group present in **11** was effected with 6 N HCl in H_2O:THF (1:1) at rt for 2 h to give the diol derivative (**12**). The anomeric OH was selectively silylated with TBSCl-imidazole[30] to give **12** whose Swern oxidation[31] by using $(COCl)_2$, DMSO and Et_3N in CH_2Cl_2 at –78 °C provided the 2-ulose derivative (**14**). It's ^1H NMR spectrum showed downfield shift of protons located at C-1 and C-3 due to carbonyl group at C-2. In the ^{13}C NMR spectrum the carbonyl group appeared at 206.7 ppm (Scheme 4).

Scheme 4



One-pot treatment[32] of the 2-ulose derivative (**14**) with urea in presence of 40% aqueous HF in methanol gave a mixture of two diastereoisomers. On the basis of ^{1}H NMR spectrum the ratio of 9:1 for the two diastereoisomers (**15a** and **15b**) was established. **15a** and **15b** could not be separated by silica gel chromatography. The mixture **15a** and **15b** as such was reduced in the presence of 10% Pd/C in methanol to give the amino derivative which was acylated[33] with 4-bromo-2-(trichloroacetyl)pyrrole[34] to afford a mixture of **2** and **3** (Scheme 5). Compounds **2** and **3** were separated by silica gel chromatography and analysed spectroscopically.

Scheme 5



The NOESY spectrum of **2** showed correlations for H-9 to both H-12 and H-14, while H-15 to H_3-16; H-10α to H-7, and H-10α to H-15, indicated that the bicyclic system of **2** was fused in a *cis*-geometry. It also revealed that H-9, H-15, and methoxy group at C-11 were in ß, α, and α-orientation.

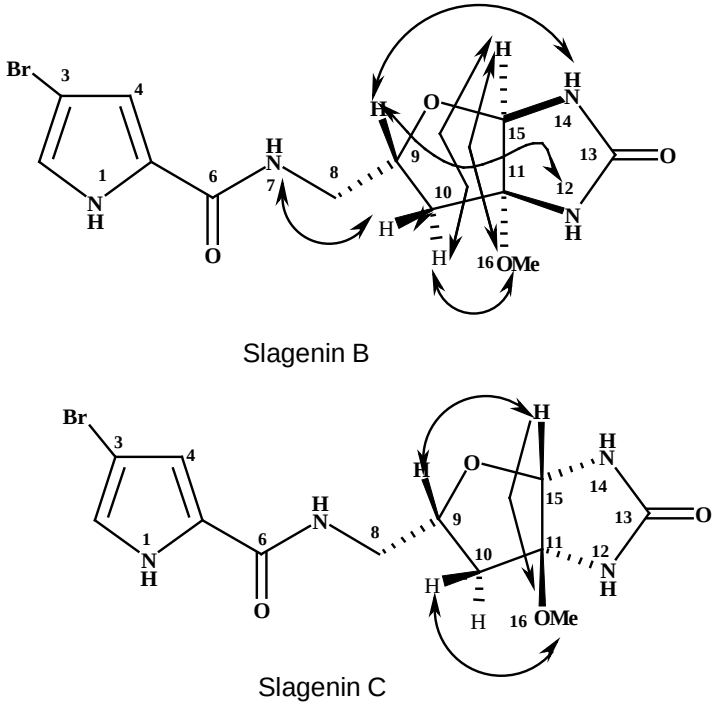


Figure 12: *NOE of slagenin B and slagenin C*

For compound **3**, the NOESY correlations for H-9 to H-15 and for H-15 to H_3 -16 implied that H-9, H-15, and the methoxy group at C-11 were all in ß-orientation. Therefore, the absolute structures of **2** and **3** were respectively assigned as (9*R*, 11*R*, 15*R*)-**2** and (9*R*,11*S*,15*S*)-**3** (Figure 3). Comparison of the specific rotation of synthetic **2**; $[\alpha]_D$ +36 ^{o} (*c* 0.5, MeOH) with naturally isolated slagenin **B** (**2**) $[\alpha]_D$ +33 ^{o} (*c* 0.2, MeOH)] and synthetic **3** $[\alpha]_D$ –39 ° (*c* 0.2, MeOH) with naturally isolated slagenin **C** (**3**) $[\alpha]_D$ –35 ^{o} (*c* 0.2, MeOH) further confirmed the absolute configuration of our synthetic products.

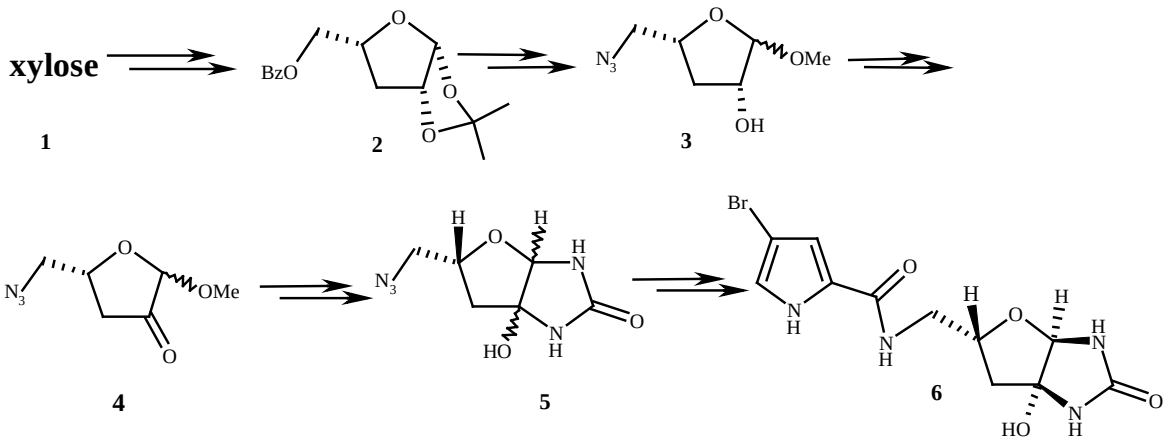
A short total synthesis for the (–)-slagenin B and the (+)-slagenin C has been accomplished starting from L-arabinose. An enantioselective synthetic approach for preparing the *cis*-fused tetrahydrofuro[2,3-d]imidazolidin-2-one skeleton from glyoxal hydrate derivative and

urea has been developed. Furthermore, the absolute structures of naturally isolated slagenins B and C were established as (9*R*, 11*R*, 15*R*)-B (**2**) and (9*R*, 11*S*, 15*S*)-C (**3**), respectively.

Post work

In 2003, Jiang, *et al*. reported[37] the synthesis of the antipodes of slagenin A-C and single isomer of slagenin A. There they used L-xylose (**1**), as starting material. The 3-deoxy-L-ribose derivative (**2**) was prepared by adapting the reported procedures.[38] Removal of the benzoyl protecting group, tosylation, azidation followed by methanolysis with refluxing 1% I_2-MeOH gave compound **3.** Oxidation of compound **3** gave the 2-ulose derivative (**4**), which on treatment with 0.1 mol/L of aqueous HCl in THF and condensation with urea *in situ* afforded **5**, which is inseparable mixture of two isomer. Undergoing the hydrogenation of this mixture over 10% Pd/C in methanol and the followup acylation with 4-bromo-2-(trichloroacetyl)pyrrole in DMF, only a single compound slagenin A (**6**) was obtained (Scheme 6).

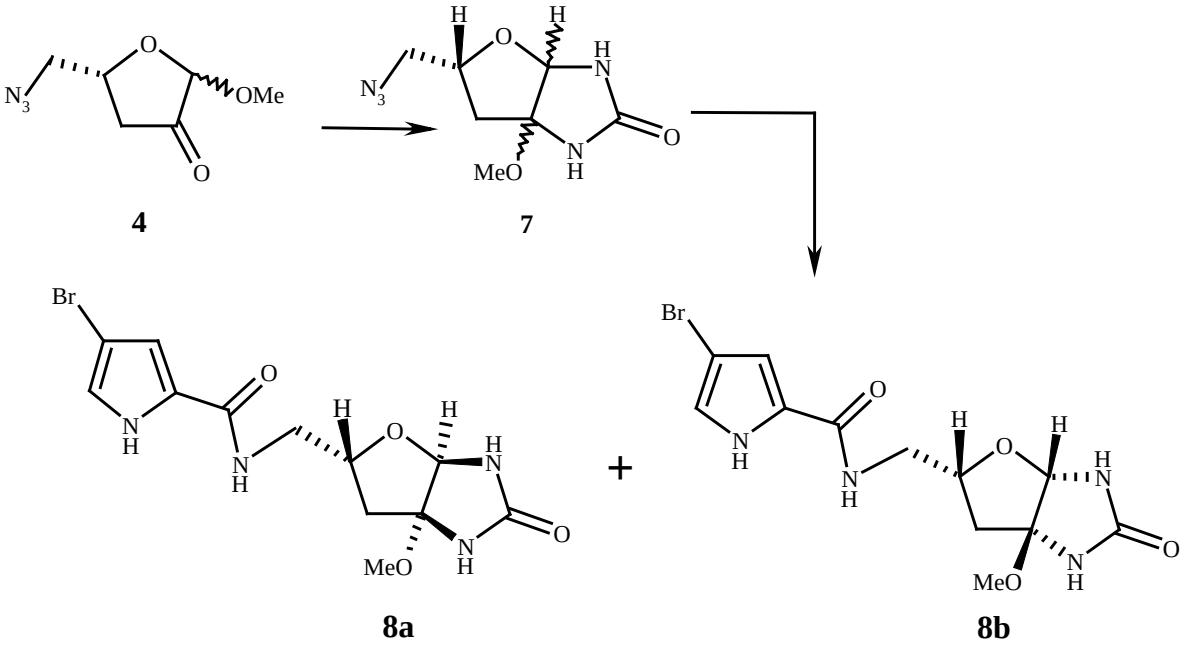
Scheme 6



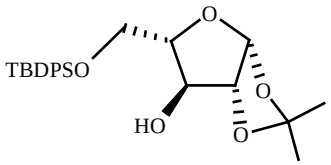
Finally, compound **4** was heated at reflux with urea in 5% HCl-methanol solution to afford inseparable diastereoisomers **7** in a ratio of 3.8:1, which on acylation with 4-bromo-2-(trichloroacetyl)pyrrole gave slagenins B (**8a**) and C (**8b**) with a ratio of 3.8:1. Thus, the enantioselective synthesis of slagenins A-C, which was characterized by the efficient condensation of 2-methoxydihydrofuran-3-one and urea to prepare the *cis*-fused

tetrahydrofuro[2,3-*d*]imidazolidin-2-one skeleton, further established the absolute stereochemistry of slagenins (Scheme 7).

Scheme 7



5-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidine-β-L-arabinofuranose (6)[26]



L-arabinose (**4**) (15.0 g, 100 mmol), TBDPSCl (25.6 mL, 100 mmol) and imidazole (13.6 g, 200 mmol) were heated at 60 ^{o}C for 2 h. DMF was removed, the residue poured into 1 N HCl (250 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with $NaHCO_3$, dried and concentrated. The residue was then purified on silica gel by using EtOAc-hexane to get compound **5** (19.0 g, 49%) as a liquid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.06 (s, 9 H), 3.59-3.84 (m, 2 H), 3.94 (s, 1 H), 4.22 (d, 1 H, *J* = 7.7 Hz), 4.36-4.76 (m, 2 H), 5.38 (s, 1 H), 7.38 (m, 6 H), 7.70 (m, 4 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.9, 26.6, 64.0, 77.4, 79.7, 85.8, 102.9, 127.7, 129.8, 132.6, 135.4.

Compound **5** (19.4 g, 50.0 mmol), anhydrous cupper sulfate (22.0 g, 138.0 mmol) and conc. H_2SO_4 (1 mL) in dry acetone (150 mL) were stirred for 4 h, neutralized with calcium hydroxide, filtered and concentrated The residue was purified on silica gel by using EtOAc-hexane to get **6** (19.1 g, 89%).

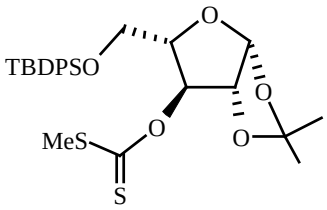
$[\alpha]_D$ = –5 ^{o} (*c* 1, in $CHCl_3$), Lit.[26] $[\alpha]_D$ = –5 ^{o}(*c* 1, in $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.06 (s, 9 H), 1.30 (s, 3 H), 1.35 (s, 3 H), 2.25 (brs, 1 H), 3.81 (s, 1 H), 3.84 (d, 1 H, *J* = 1.0 Hz), 4.05 (ddd, 1 H, *J* = 2.9, 6.5, 9.3 Hz), 4.40 (d, 1 H, *J* = 2.6 Hz), 4.53 (d, 1 H, *J* = 4.1 Hz), 5.87 (d, 1 H, *J* = 4.1 Hz), 7.40 (m, 6 H), 7.70 (m, 4 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.1, 25.9, 26.8, 63.6, 75.7, 86.9, 87.5, 105.5, 112.2, 127.6, 129.6, 133.0, 133.1, 135.4.

Ms: m/z 413 (M^+-15).

5-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidine-3-*O*-[(methylthio)-thiocarbonyl]-β-L-arabinofuranose (7)



To a suspension of NaH (60% dispersion in oil, 2.6 g, 66.6 mmol) in dry THF (120 mL) at 0 ^oC, compound **6** (15.0 g, 35.0 mmol) in THF (50 mL) was added. After 30 min carbon disulfide (4.2 mL, 70.0 mmol) and after 45 min methyl iodide (10.0 mL, 70.0 mmol) was introduced. After 1 h, water was added, concentrated and extracted with ethyl acetate, which was washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by eluting with EtOAc-hexane (1:49), to give **7** (17.9 g, 99%) as a yellow liquid.

$[\alpha]_D$ = +20 ^{o} (*c* 1, in $CHCl_3$).

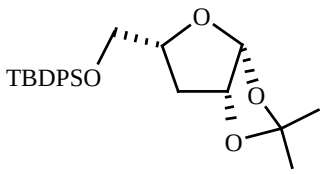
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.00 (s, 9 H), 1.20 (s, 3 H), 1.22 (s, 3 H), 2.54 (s, 3 H), 3.77 (m, 2 H), 4.21 (t, 1 H, *J* = 6.8 Hz), 4.62 (d, 1 H, *J* = 3.8 Hz), 5.88 (d, 1 H, *J* = 3.8 Hz), 6.08 (d, 1 H, *J* = 1.5 Hz), 7.31 (m, 6 H), 7.58 (m, 4 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.3, 19.4, 25.9, 26.6, 26.9, 63.7, 84.4, 85.3, 85.5, 106.0, 112.7, 127.8, 129.8, 133.3, 135.7, 214.4.

Ms: m/z 517 (M^+–1).

Anal. Calcd. $C_{26}H_{34}O_5SiS$: C, 60.20; H, 6.55; S, 12.35. Found: C, 60.31; H, 6.67; S, 12.14.

5-*O*-*tert*-Butyldiphenylsilyl-3-deoxy-1,2-*O*-isopropylidine-β-L-arabinofuranose (8)



A stirred solution of **7** (6.0 g, 11.6 mmol), Bu_3SnH (5.0 g, 17.4 mmol), AIBN (8 mg) in toluene (80 mL) under argon was heated under reflux for 5 h. Solvent was removed and the residue was purified on silica gel by using EtOAc-hexane (1:19) to give **8** (4.0 g, 84%) as syrup.

$[\alpha]_D$ = –6 ^{o} (*c* 1, in $CHCl_3$).

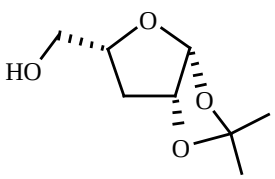
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.98 (s, 9 H), 1.25 (s, 3 H), 1.28 (s, 3 H), 1.97 (m, 1 H), 2.11 (m, 1 H), 3.74 (m, 1 H), 4.31 (m, 2 H), 4.84 (m, 1 H), 5.70 (d, 1 H, *J* = 3.6 Hz), 7.30 (m, 6 H), 7.60 (m, 4 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.1, 25.9, 26.8, 33.6, 66.1, 80.5, 80.9, 85.0, 80.9, 106.5, 111.8, 127.5, 129.4, 133.6, 135.4.

MS: m/z 397 (M^+–15)

Anal. Calcd. $C_{24}H_{32}O_4Si$: C, 69.80; H, 7.66; Found: C, 69.86; H, 7.47.

3-Deoxy-1,2-*O*-isopropylidine-β-L-arabinofuranose (9)



To a solution of compound **8** (5.0 g, 12.1 mmol) in THF (24.2 mL, 24.2 mmol), 1 M solution of Bu_4NF was added and stirred for 4 h. It was quenched with saturated NH_4Cl and concentrated. The residue was partition between CH_2Cl_2 and water. The organic layer was

separated and washed with brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by eluting with EtOAc-hexane (1:1) to give **9** (1.7 g, 81%) a colorless solid.

M.P = 79 ^{o}C.

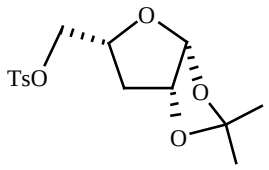
[α]$_D$ = –27 ^{o} (*c* 1, in $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.24 (s, 3 H), 1.48 (s, 3 H), 1.90 (dd, 1 H, *J* = 2.9, 3.2 Hz), 2.08 (dd, 1 H, *J* = 6.5, 6.5 Hz), 2.86 (s, 1 H), 3.50 (dd, 1 H, *J* = 4.5 Hz), 3.73 (dd, 1 H, *J* = 7.6, 8.1 Hz), 4.22 (m, 1 H), 4.67 (m, 1 H), 5.73 (dd, 1 H, *J* = 4.8 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.4, 26.5, 32.8, 64.3, 80.2, 81.0, 105.8, 111.6.

Anal. Calcd. $C_8H_{14}O_4$: C, 55.14 H, 8.04. Found: C, 55.34; H, 7.99.

3-Deoxy-1,2-*O*-isopropylidine-5-*O*-*p*-toluenesulfonyl-β-L-arabinofuranose (10)



To a solution of **9** (4.5 g, 25.8 mmol), Et_3N (8.9 mL, 64.5 mmol) and DMAP (10.0 mg) in CH_2Cl_2 (30 mL) was added *p*-toluenesulfonyl chloride (7.0 g, 38.5 mmol) at 0 ^{o}C. The reaction mixture was stirred for 45 min at rt, diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:9) to give **10** (7.9 g, 93%), as a solid.

M.P = 78 ^{o}C.

[α]$_D$ = –40 ^{o} (*c* 1, in $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.16 (s, 3 H), 1.25 (s, 3 H), 1.09 (dd, 2 H, *J* = 2.3, 2.6 Hz), 2.73 (s, 3 H), 4.08 (dd, 1 H, *J* = 6.8, 9.5 Hz), 4.15 (dd, 1 H, *J* = 6.9, 9.5 Hz), 4.34 (dd, 1 H, *J*

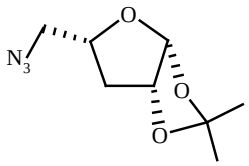
= 2.4 Hz), 4.82 (m, 1 H), 5.70 (d, 1 H, *J* = 3.9 Hz), 7.22 (d, 2 H, *J* = 8.3 Hz), 7.73 (d, 2 H, *J* = 8.2 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.1, 25.2, 26.2, 33.0, 70.9, 77.2, 79.4, 106.3, 111.6, 127.6, 129.5, 132.6, 144.4.

MS: m/z 313 (M^+–15).

Anal. Calcd. $C_{15}H_{20}O_6S$: C, 54.87; H, 6.09; S, 9.75; Found: C, 54.98; H, 6.17; S, 10.06.

5-Azido-3,5-dideoxy-1,2-*O*-isopropylidine-β-L-arabinofuranose (11)



Sodium azide (2.1 g, 32 mmol), and **10** (3.0 g, 9.1 mmol) in dry DMF (30 mL) was heated at 85 ^oC for 12 h under nitrogen. The reaction mixture was poured in water, extracted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue purified on silica gel by eluting with EtOAc-hexane (1:9) to give **11** (1.5 g, 82%) as a yellow liquid.

$[\alpha]_D$ = –90 ^{o} (*c* 1, in $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26 (s, 3 H), 1.50 (s, 3 H), 2.11 (ddd, 2 H, *J* = 5.7, 7.5, 15.1 Hz), 3.15 (dd, 1 H, *J* = 6.1, 12.6 Hz), 3.68 (dd, 1 H, *J* = 8.1, 12.6 Hz), 4.23 (m, 1 H), 4.67 (m, 1 H), 5.61 (d, 1 H, *J* = 4.2 Hz).

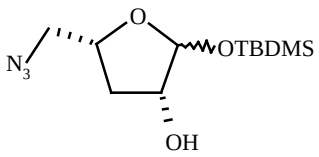
^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.8, 27.0, 34.4, 54.7, 79.6, 80.5, 106.7, 112.3.

IR: 2100 cm^{-1}.

Ms: m/z 184 (M^+–15).

Anal. Calcd. $C_8H_{13}N_3O_3$: C, 48.2; H, 6.53; N, 21.10. Found: C, 47.9; H, 6.39; N, 21.46.

5-Azido-1-*O*-*tert*-butyldimethylsilyl-3,5-dideoxy-αβ-L-arabinofuranose (13)



Compound **11** (2.0 g, 10.1 mmol) and 6 N HCl:THF (1:1, 12 mL) were stirred at rt for 2 h, neutralized with Na_2CO_3 and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by using EtOAc-hexane (4:1) to give **12** (1.4 g, 87%).

A mixture of **12** (1.0 g, 6.3 mmol), imidazole (1.3 g, 18.8 mmol), TBDMSCl (0.95 g, 6.3 mmol) in CH_2Cl_2 (10 mL) was stirred for 45 min and diluted with CH_2Cl_2. The organic layer was washed with water, brine, dried (over Na_2SO_4), concentrated, and the residue was purified on silica gel by eluting with EtOAc-hexane (3:17) to give **13** (1.25 g, 73%), as a syrup.

For major isomer **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.09 (d, 6 H, *J* = 1.4 Hz), 0.87 (s, 9 H), 1.63 (brq, 1 H), 2.32 - 2.52 (m, 2 H), 3.47 (d, 1 H, *J* = 4.3 Hz), 3.58 (d, 1 H, *J* = 3.2 Hz), 4.00 (d, 1 H, *J* = 5.3 Hz), 4.36 (t, 1 H, *J* = 9.6 Hz), 5.24 (s, 1 H).

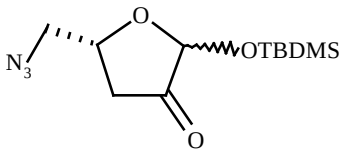
^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.3, –4.6, 17.7, 25.6, 34.5, 54.8, 56.2, 72.3, 75.9, 76.4, 96.0, 103.6.

For minor isomer **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.11 (d, 6 H, *J* = 2.9 Hz), 0.94 (s, 9 H), 1.57 (d, 1 H, *J* = 3.4 Hz), 2.32 (m, 2 H), 3.40 (d, 1 H, *J* = 3.7 Hz), 3.65 (d, 1 H, *J* = 2.9 Hz), 4.03–4.20 (m, 1 H), 4.36 (t, 1 H, *J* = 3.2 Hz), 5.21 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.0, –4.2, 17.8, 25.5, 34.8, 35.2, 55.3, 55.5, 72.2, 76.1, 76.6, 96.5.

Anal. Calcd. $C_{11}H_{23}N_3O_3Si$: C, 48.33; H, 8.42; N, 15.38. Found: C, 48.38; H, 8.46; N, 15.39.

5-Azido-1-*O*-*tert*-butyldimethylsilyl-3,5-dideoxy-αβ-L-arabinofuran-2-ulose (14)



To a solution of oxalyl chloride (0.08 mL, 0.87 mmol) in dry DMSO (0.12 mL, 1.7 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added **13** (80.0 mg, 0.29 mmol). Stirring was continued for additional 1 h, and then Et_3N (0.32 mL, 2.3 mmol) was added, stirred for another 1 h at –78 °C. The reaction was decomposed by adding brine solution and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2. The combined organic layer was washed with water, dried (over Na_2SO_4), concentrated and the residue was purified on silica gel by eluting with EtOAc-hexane (1:25) to give **14** (60.0 mg, 75%) as a yellow liquid.

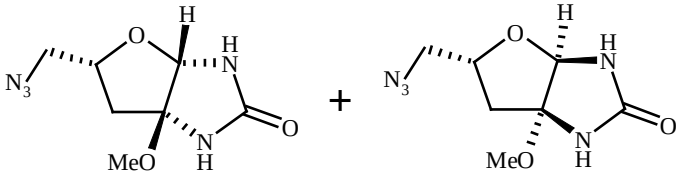
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.15 (s, 6 H), 0.89 (s, 9 H), 2.33 (dt, 1 H, *J* = 0.84, 7.5, 8.4 Hz), 2.52 (dd, 1 H, *J* = 6.4 Hz), 3.41 (dd, 1 H, *J* = 3.7, 12.8 Hz), 3.56 (dd, 1 H, *J* = 5.2, 12.8 Hz), 4.69 (m, 1 H), 5.02 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.4, –4.9, 17.8, 25.2, 35.6, 53.3, 73.8, 93.1, 206.7.

MS: m/z 243 (M^+ – 28).

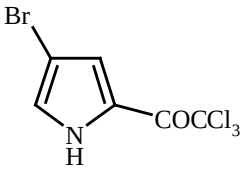
Anal.Cald value $C_{11}H_{21}N_3O_3Si$: C, 48.15; H, 8.08; N, 15.40; Found: C, 48.05; H, 8.28; N, 15.76.

5-Azidomethyl-6a-methoxy-hexahydro-furo[2,3-d]imidazol-2-one (15)



To a solution of glyoxal **14** (20.0 mg, 0.074 mmol) and urea (11.0 mg, 0.2 mmol) in MeOH (3 mL), was added 40% aqueous HF (0.15 mL) and stirred at ambient temperature for 30 h. It was diluted with ethyl acetate (20 mL), washed with saturated sodium hydrogen carbonate and brine. The organic layer was dried (over anhydrous Na_2SO_4), and concentrated. Flash chromatography on silica gel by using 0-2.5% methanol-EtOAc afforded (**15a +15b**) 13.0 mg, 83% as yellow oil, which was used for next reaction.

4-Bromo-2-(trichloroacetyl)pyrrole



To a solution of trichloroacetyl chloride (9.5 mL, 0.085 mmol) in ether (30 mL) pyrrole (5.0 g, 0.075 mmol) was added over a period of 2 h. The new violet ether solution began to reflux slightly during addition. Refluxing was continuing for another 1 h. and then quenched with water, washed with $NaHCO_3$ (6.5 g, in 20 mL water). The red ether solution was extracted with water, washed with brine, dried and concentrated. The residue was chromatographed on silica gel by using EtOAc-hexane (3:47) to get trichloroacetyl pyrrole (14.2 g, 89%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.14 (m, 1 H), 5.94 (m, 1 H), 6.15 (m, 1 H), 8.54 (brs, 1 H).

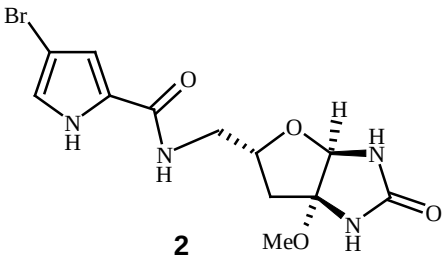
To a solution of 2-(trichloroacetyl)pyrrole (4.0 g, 18.8 mmol) in THF (30 mL) at –10 ^{o}C *N*-bromosuccinimide (3.4 g, 18.8 mmol) was added and stirred for 1 h. Quenched with

water, remove THF, extracted with ethylacetate, washed with brine, dried and concentrated. The residue was chromatographed on silica gel by eluting with EtOAc-hexane (3:47) to give **13** (4.5 g, 82%) as a white crystalline solid**.**

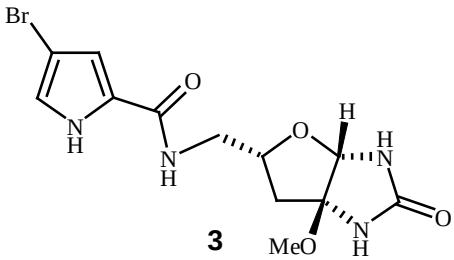
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.11 (m, 1 H), 7.29 (m, 1 H), 9.77 (brs, 1 H).

MS: m/z 291 (M^+)

Synthesis of Slagenin B and Slagenin C (2 and 3)



2



3

The solution of compound **15** (13.0 mg, 0.061 mmol) and 10% Pd/C in methanol (5 mL) was hydrogenated at normal temperature and pressure for 1.5 h and then filtered through celite. Filtrate was concentrated and the resulting crude amine was added to 4-bromo-2-(trichloroacetyl)pyrrole (36.0 mg, 0.13 mmol) in DMF (5 mL). The solution was stirred for 12 h, and concentrated to remove DMF. The residue was dissolved in ethyl acetate and the washed with saturated aqueous NaCl. The organic layer was dried (over anhydrous Na_2SO_4), concentrated and the residue was chromatographed on silica gel by eluting with EtOAc. The first to be eluted was **2** (14.0 mg, 56%).

For major isomer **2: $[\alpha]_D$** = +36 ^{o} (*c* 0.2, in MeOH).

^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.76 (t, 1 H, *J* = 11.9 Hz), 2.17 (dd, 1 H, *J* = 11.9, 3.9 Hz), 3.15 (s, 3 H), 3.48 (m, 2 H), 4.04 (m, 1 H), 5.19 (s, 1 H), 6.86 (d, 1 H, *J* = 6.9 Hz), 6.96 (d, 1 H, *J* = 6.9 Hz), 7.50 (s, 1 H), 8.42 (t, 1 H, *J* = 5.7 Hz), 11.88 (s, 1 H).

^{13}C NMR (DMSO-d_6, 125 MHz): δ 41.4, 41.6, 50.3, 76.1, 88.5, 94.8, 97.9, 112.0, 121.3, 126.8, 155.5, 159.0.

Further elution with 1% MeOH-EtOAc afforded **3** (6.0 mg, 24%), as a liquid**.**

For minor isomer **3:** $[\alpha]_D$ = –39 ^{o} (*c* 0.2, in MeOH).

^{1}H NMR (DMSO-d_6, 125 MHz): δ 1.90 (dd, 1 H, *J* = 6.4, 12.8 Hz), 2.29 (dd, 1 H, *J* = 6.7, 12.8 Hz), 3.17 (s, 3 H), 3.40 (m, 2 H), 4.19 (m, 2 H), 5.12 (s, 1 H), 6.87 (s, 1 H), 7.65 (s, 1 H), 7.69 (s, 1 H), 8.24 (t, 1 H, *J* = 5.1 Hz), 11.86 (s, 1 H).

^{13}C NMR (DMSO-d_6, 50 MHz): δ 40.8, 42.9, 49.8, 76.2, 89.5, 95.0, 97.3, 111.8, 121.2, 126.8, 159.4, 159.7.

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INTRODUCTION

Synthetic organic chemistry has always been a frontier area of research in order to develop efficient methodologies, novel reactions, and processes that will lead to the synthesis of desired target molecules and their derivatives[1] for understanding biological functions or the behavior of materials which can lead to novel drug/drugs like materials with interesting properties.

There is a tremendous awareness among chemists to develop novel synthetic methodologies that leads to the natural product like molecules, and simpler analogues of natural products. Combinatorial chemistry dealing with libraries of organic molecules emerged during the last decade.[2] In a classical manner, lead compounds are derived from natural products. Synthesis of analogues is then undertaken to obtain specific compound(s) in large quantities or to obtain simpler analogues that may exhibit similar biological response. Overall, traditional medicinal chemistry approaches have been time consuming and expensive. However, applying combinatorial chemistry, large sets of organic/bioorganic compounds were attained in short periods of time, either by applying parallel high-throughput synthesis or by a mix and split technology. In the coming years, it is expected that combinatorial chemistry will play a crucial role in understanding the biological functions of new targets or in the identification of novel targets in the area of genomics and proteomics research. Over the past few years, we have observed the impact of combinatorial chemistry in the development of high-throughput synthesis of focused libraries. It is anticipated that the next era will involve diversity-based synthesis of natural product like compounds. Recently, Schreiber has given an elegant description of the differences between target oriented synthesis and diversity-based synthesis.[3] As Schreiber explains, in a drug discovery process, target-oriented synthesis of small molecules is undertaken on the basis of retrosynthetic analysis. In general, this approach requires preselection of the protein target(s), which are then utilized for developing small molecules as selective binding agents, either by traditional methods or by solid-phase combinatorial chemistry, based on organic synthesis which will further be applied in a parallel manner or by using a mix and split technology for developing high-throughput organic synthesis.

In contrast, and as described by Schreiber, diversity-based organic synthesis is not focused towards a given target. Rather, it is used for identifying new targets or for understanding biological functions of new targets. Moreover, it does not rely upon retrosynthetic analysis and is aimed at developing novel methodologies for obtaining small molecules with structural complexity and diversity.[4]

Modern drug discovery involves screening of small molecules for their ability to bind to a preselected protein target. Target oriented synthesis of these molecules; efficiently a collection of small molecules capable of perturbing any disease related biological pathway, leading eventually to the identification of therapeutic protein targets capable of being modulated by small molecules. In this respect we are interested in bicyloheterocyclic scaffolds because most of the bicylo heterocyclic compounds show biological activity,[5] as for example, ciprofloxacin, norfloxacin, enoxacin, difloxacin etc. The introduction of nalidixic acid,[6] a large number of 6-fluoroquinolones (substituted differently in position 1) have been synthesized and among these several analogues containing a piperazinyl group substituent at 7th position were found to be useful for antibacterial agents.[7] It is known that aminopyrrolidine derivatives have better activity than the corresponding piperazine analogues, which are generally less toxic, more soluble and more hydrophilic, seemed to be very attractive (Fig. 1).

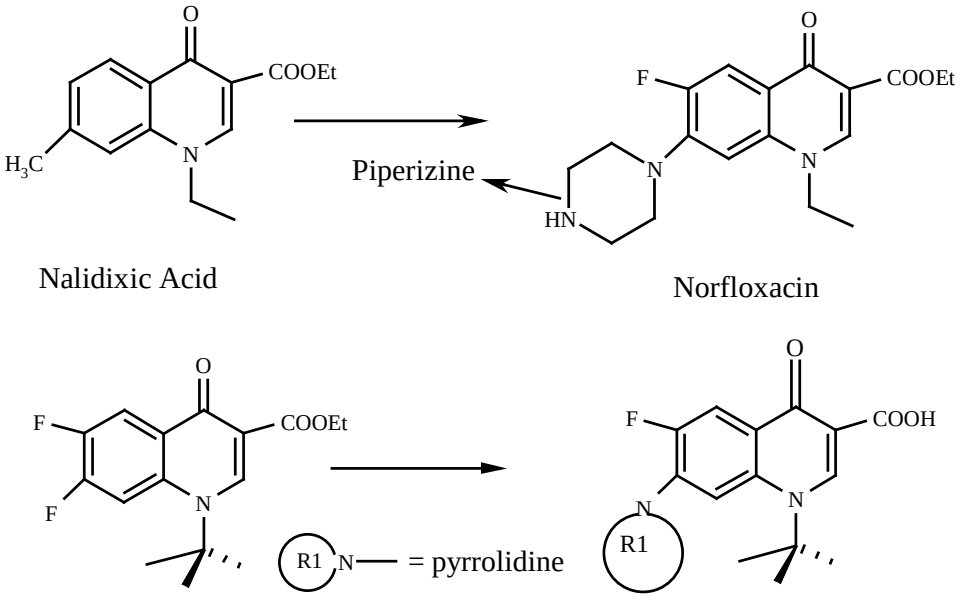


Figure 1: *Pyrrolidine group substituted at 7th position of 6-fluoroquinolones*

By introduction of several diazabicyclo unit (Fig.2) in 1,4-dihydro-6,7 difluoro-4-oxo-quinolone system it showed the best activity *in vivo* with low toxicity and good pharmacokinetics profile than *in vitro*.

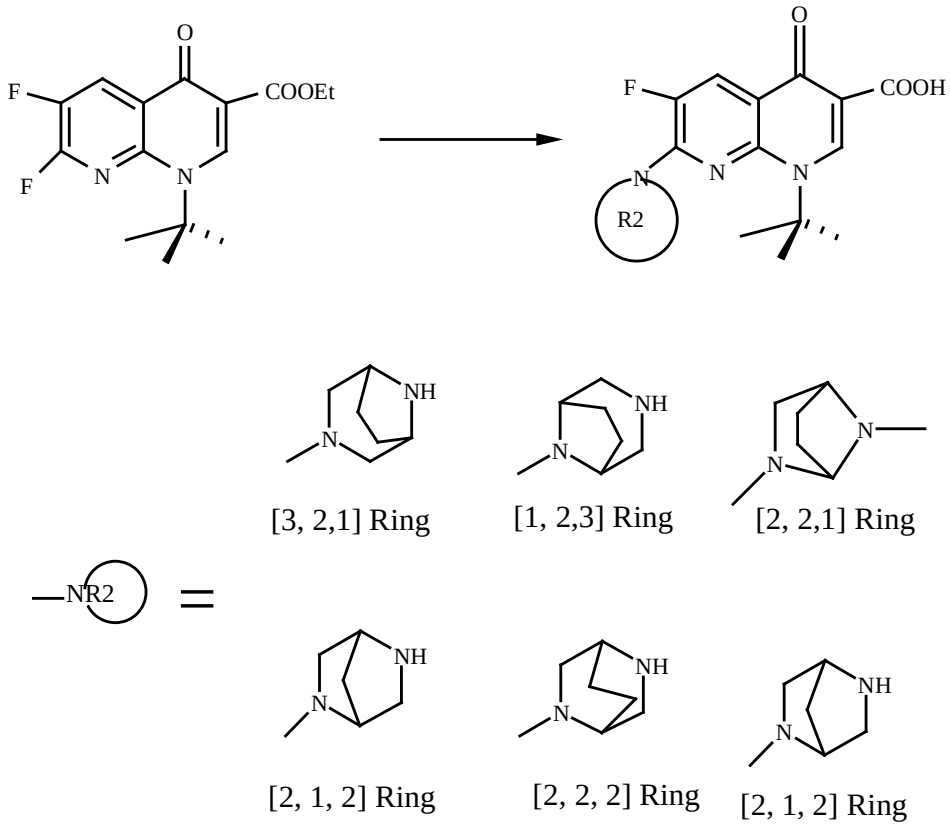
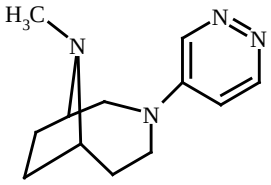


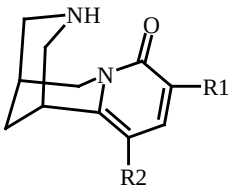
Figure 2: *Different bicyclic bases attached to 7th position of 6-fluoroquinolones*

Over recent years, there has been steadily increasing interest in nAChR (acetylcholine receptor) agonists as potential analgesics and therapeutics for the treatment of various neurological and mental disorders related to a decrease in cholinergic function.[8] Thus, for the advancement of nAChR-based therapeutics, many efforts have been directed toward the identification and characterization of novel, potent nAChR ligands. This was stimulated by considerable evidence suggesting that selective neuronal nAChR agonists may provide therapeutic utility in the treatment of Alzheimer's and Parkinson's diseases, attention deficit/hyperactivity disorder, schizophrenia, and depression. Additionally, the discovery of the alkaloidal toxin epibatidine as a potent analgesic acting *via* neuronal nAChR has evoked renewed interest in targeting nAChRs also for analgesia. However, the potential therapeutic

actions of the prototypical nAChR agonists such as the natural alkaloids (-)-epibatidine, (-)-nicotine, (-)-cytisine, (+)-anatoxin-a, diazabicyclo[4.2.1]nonane- and quinuclidin-2-ene are accompanied by a variety of untoward effects. Nevertheless, the emerging diversity of nAChR subtypes opens up the possibility of developing receptor subtype selective therapeutic agents with or without substantially attenuated side effects (Fig.3).



Diazabicyclo[4.2.1] nonane derivative



(-) cytisine

R_1 = I
R2 = I

Figure 3: *Different diaza bicyclo heterocyclic bases*

Portoghese *et al.*[9] found that *N*-Methyl-*N*-Benzyl quaternary derivatives of (1*S*, 2*S*)-2-oxa-5-azabicyclo[2.2.1]heptane has the effect of an asymmetric quaternary 'N' on anticolinergic activity (There are also cases of plants containing hallucinogenic substances ingested deliberately. Toxic manifestations of plants mainly involve the gastrointestinal, cardiovascular, and central nervous activity). They observed for the guinea pig ileum that compound **7** and **8** were 1/750 and l/500 as active as atropine sulfate (pA2 = 8.1) in their effect upon antagonizing the stimulant action of methacholine as suggested by parallel shifts of dose-response curves to higher concentration. The analysis of co-variance showed that the difference in the slopes of dose-response curves for **7** (6.94) and **8** (6.86) were not statistically significant. These data are indicative of competitive postganglionic blockade and show that in the bicyclic system the effects of enantiomeric quaternary 'N' on anticholinergic activity were comparable. The agonist activities of **9** and **14** were approximately l/2500 that of methacholine (Fig. 4).

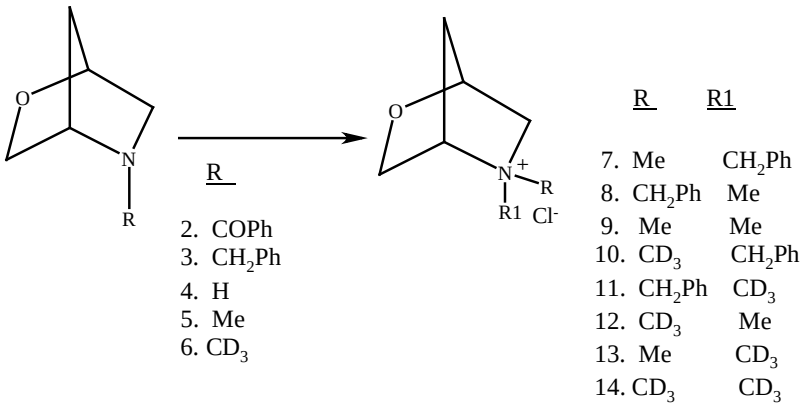


Figure 4: *Oxa-azabicyclo[2.2.1] heptane system*

Like chiral norbornanes containing endocyclic heteroatoms (O, N) at the 2- and/or 4-position, the bicyclic system of *N*-tosyl-2-thia-5-azabicyclo[2.2.1]heptane is also reported (Fig.5).

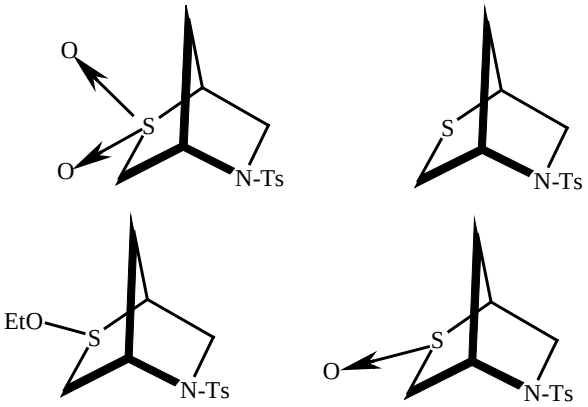


Figure 5: *Different thia-azabicyclo[2.2.1]heptane system*

The emphasis of our research is the exploration of new technologies and strategies for the efficient generation of small-molecule combinatorial libraries. In this project our goal is the efficient synthesis of bicyclic scaffolds using powerful organic reactions.

PRESENT WORK

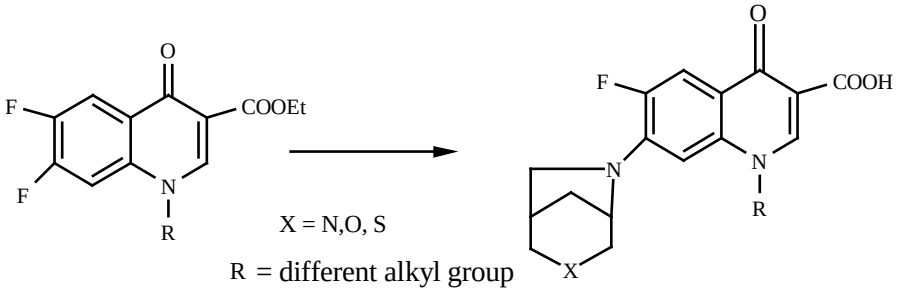
Combinatorial chemistry has emerged as one of the most promising approaches to drug discovery and is now a widely used technology both in academic and industrial contexts.

In order to increase the diversity of new structures for biological assay, we have undertaken studies to prepare a series of nonstructure based molecules amenable to assembly *via* combinatorial methods. For the preparation of libraries with a large number of diversity it is necessary not only to efficiently control reactivity but also to develop new scaffolds.

The emphasis of our research is the exploration of new technologies and strategies for the efficient generation of small-molecule combinatorial libraries.[10] We decided to synthesize new bicyclo heterocyclic scaffolds,[11a,b] the choice of which was based upon two factors: first, the molecules belonging to this family are known to exhibit potent biological activity, secondly, they display a tridimensional rigid skeleton which would of great interest for discovery groups. Among other plans our target was to attach bicyclo heterocyclic ring compound to quinolone system and to see the biological activity (Fig. 6) of the newly derived quinlone derivatives.[12]

From the literature,[12] we observed that several diazabicyclo unit attached to 1,4-dihydro-6,7 difluoro-4-oxo-quinolone system showed perhaps the best activity *in vivo* with low toxicity and good pharmacokinetics profile. Portoghese *et al.*[9] reported that oxa-azabicyclo[2.2.1]heptane has the effect of an asymmetric quaternary N on anticolinergic activity and toxic manifestations of plants involve the gastrointestinal, cardiovascular, and central nervous activity. Therefore, design and synthesis of new scaffolds inheriting rigidity and diversity, have attracted unprecedented significance particularly in new pharmaceutical and agrochemical discovery.

Figure 6



As part of our research programme we have realized that cheap and commercially available Vince's lactam (**1**) could be an ideal precursor to rationally design some novel and unique N, O, S containing bicyclo heterocyclic scaffolds for combinatorial chemistry research. It is a versatile raw material manufactured on a commercial scale by Lonza through a Diels Alder cycloaddition between cyclopentadiene and methanesulphonylcyanide (Fig.7).[13]

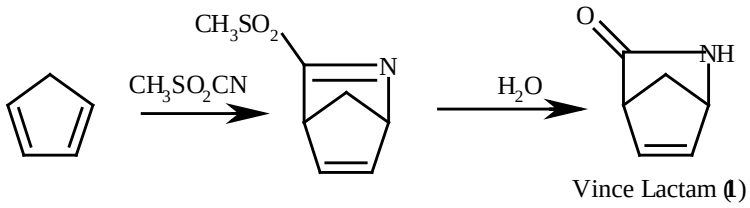
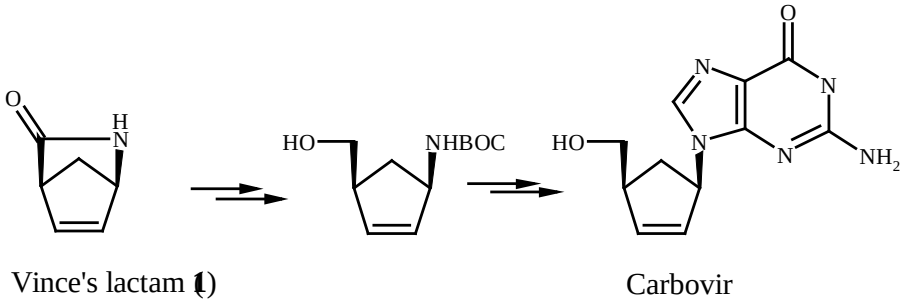


Figure 7: *Lonza's cyclic process for the synthesis of Vince's lactam*

Although it's utility in the preparation of anti-AIDS drug (–)-carbovir[14] had been explored (Fig 8), other chemical transformations remained unexplored. Vince's lactam contains a five membered lactam ring fused to a cyclopentene ring system. Although most of the chemical modifications have been done by opening the lactam ring keeping five membered cyclopentene ring intact, we felt that novel scaffolds could be prepared by first cleaving the cyclopentene ring (keeping five membered lactam ring intact) followed by subsequent chemical tranformation. This strategy has enabled us to synthesize some bicyclo[3.2.1]heterocyclic ring system which formed the basic objective of this chapter.

Figure 8

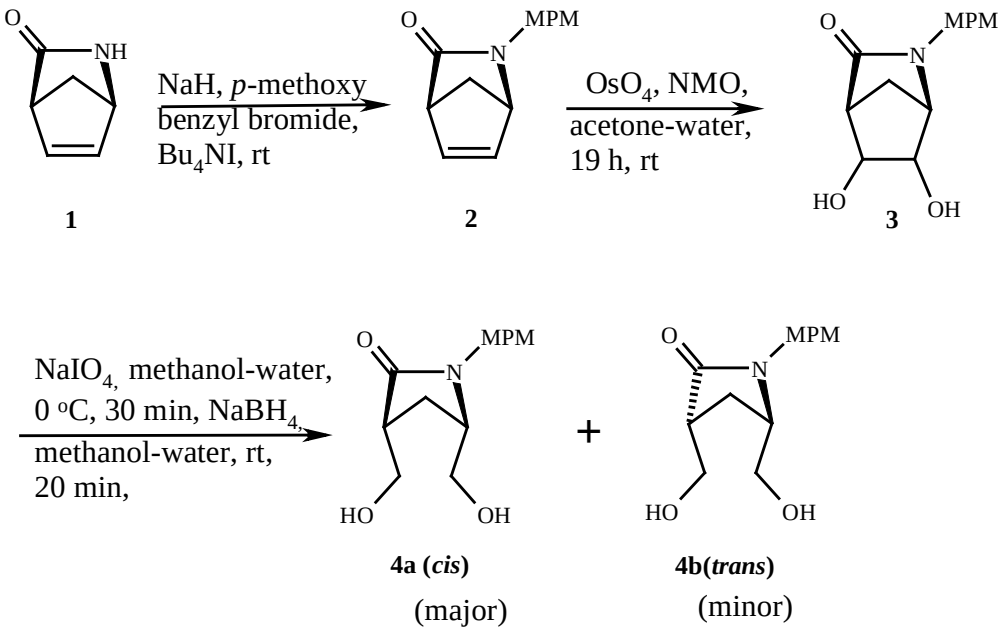


Vince's lactam (**1**) Carbovir

Figure 8: *Synthesis of (–)-carbovir from Vince's lactam*

Accordingly, the journey began with Vince's lactam (**1**), which was converted into the *N*-(*p*-methoxybenzyl)ether (**2**) by using *p*-methoxybenzyl bromide and NaH. In the ^{1}H NMR spectrum of **2**, two doublets at 6.82 ppm (J = 8.0 Hz) and 7.09 ppm (J = 8.0 Hz) due to four aromatic protons was observed. Subsequent oxidative cleavage of C=C was effected in two steps. For this task, compound **2** was treated with catalytic OsO_4 in presence of 4-methyl-morpholine *N*-oxide to provide the diol (**3**).[15] The product was readily confirmed by the ^{1}H, ^{13}C NMR and mass spectroscopic data. In the ^{1}H NMR spectrum, the two methine protons attached to hydroxy groups were located at 4.02 ppm (J = 16.0 Hz) and 4.29 ppm (J = 15.2 Hz) as doublets. The characteristic doublet at 1.68 ppm (J = 9.5 Hz) and 1.89 ppm (J = 9. 5 Hz), was attributed to the methylene group. The ^{13}C NMR and elemental analysis further supported the assigned structure. Compound **3** with sodium periodate in aqueous methanol gave rather an unstable dialdehyde which was immediately reduced with $NaBH_4$ in methanol at 0 ^{o}C to produce a diastereomeric mixture of 3,5-dihydroxymethyl-pyrrolidin-2-one (**4**). The ^{1}H NMR spectrum and HPLC of **4** revealed the presence of 4:1 mixture of *cis* and *trans* diol derivatives (**4a** and **4b**). The mixture was subjected to liquid chromatography to give the pure *cis*-product (**4a**) whose stereo-structure was established at a later stage (scheme 1).

Scheme 1



1 **2** **3**

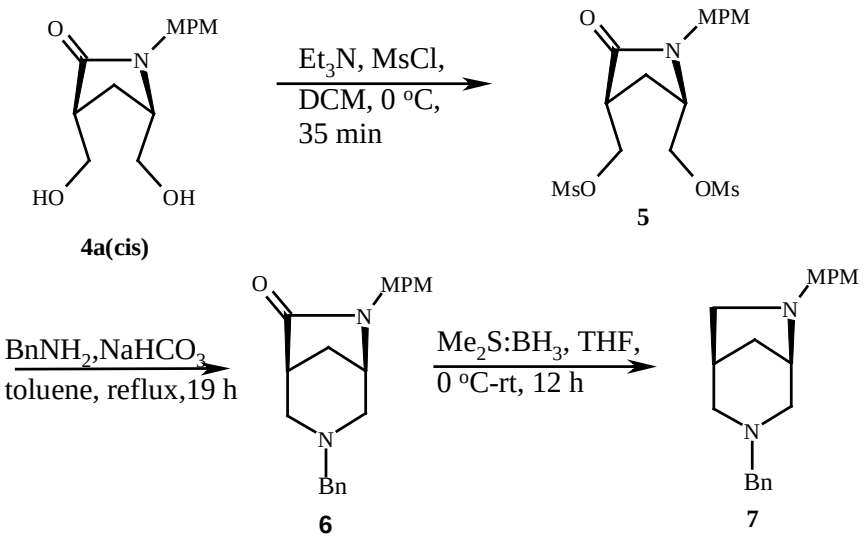
4a (*cis*) (major) **4b(*trans*)** (minor)

The dimesylate (**5**) was derived from **4a** by exposing to $MeSO_2Cl$ and Et_3N in CH_2Cl_2 at rt and identified by the ^1H NMR spectrum. The two characteristic singlets due to methyl groups of mesylate were located at 2.89 ppm and 2.95 ppm while rest of the spectrum was consistent with the assigned structure. The mass spectroscopy showed a peak at *m/z* 421 (M^+).

Having got the compound **5** in hand we envisaged cyclization protocols in order to get the diaza compound. For this we used the nucleophilic displacement reaction. On treatment with benzyl amine containing excess of $NaHCO_3$ in refluxing toluene for 19 h, the dimesylate (**5**) was converted into the diazabicyclo-lactam derivative (**6**). The structural feature of **6** was unambiguously corroborated from the combined ^1H, ^{13}C NMR and mass spectroscopic data. For instance, the ^1H NMR spectrum of **6** clearly revealed the signals due to benzylic protons, at 3.49 ppm (J = 13.9 Hz), as an AB quartet and five aromatic protons located at 7.20 ppm. The mass spectrum showed a peak at *m/z* 336 (M^+). The reduction of the amide bond[16] was effected with 2 M solution of $Me_2S{:}BH_3$ in THF to furnish the diazabicyclic derivative (**7**) whose structure was supported by the ^1H, ^{13}C NMR and mass spectroscopic data. The DEPT spectrum revealed the presence of five methylene groups

resonating at 36.5, 53.8, 54.2, 56.6, 58.7 and 62.1 ppm also supported the structure of **7** (scheme 2).

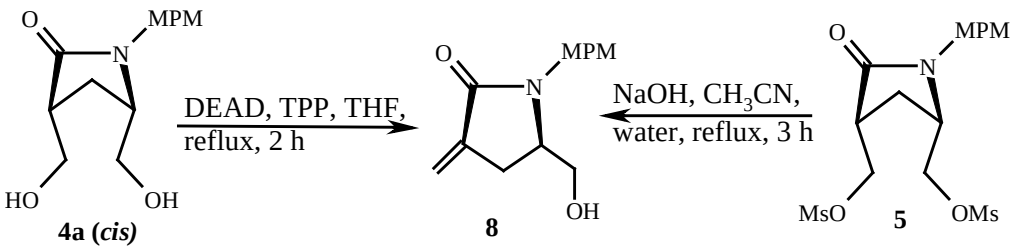
Scheme 2



It is pertinent to mention that the cyclization of **5** to **6** clearly substantiate the assignment of *cis* structure to the parent compound **4a**. The *trans* product would have resisted the cyclization step.

Our next concern was to make the oxa-aza-bicyclic derivative (**13/14**). Though there are several methods[17,18] for the formation of cyclic ether, the most common are the base catalysed intramolecular cyclization of ditosylate or dimesylate or Mitsunobu[17] reaction of the diol. Accordingly, the diol (**4a**) was treated with TPP, DEAD in refluxing THF. However, the reaction met with failure. The isolated compound did not correspond to the expected product **13**. Based on the ^{1}H NMR and ^{13}C NMR spectroscopic data, the structure of dehydration product (**8**) was proposed. For instance, the ^{1}H NMR spectrum of **8** clearly revealed signals due to *exo*-methylene protons, at 5.32 ppm (J = 2.1 Hz), and 5.97 ppm (J = 2.7 Hz) as triplets whereas peaks due to C=C were observed at 114.6 and 138.7 ppm. The signals due to ring methylene were showed at 2.72 ppm as a multiplet. The reaction of the dimesylate (**5**) with aq. NaOH in refluxing CH_3CN also gave the same eliminated product (**8**) (Scheme 3). This eliminated product was formed exclusively because of the adjacent carbonyl group.

Scheme 3

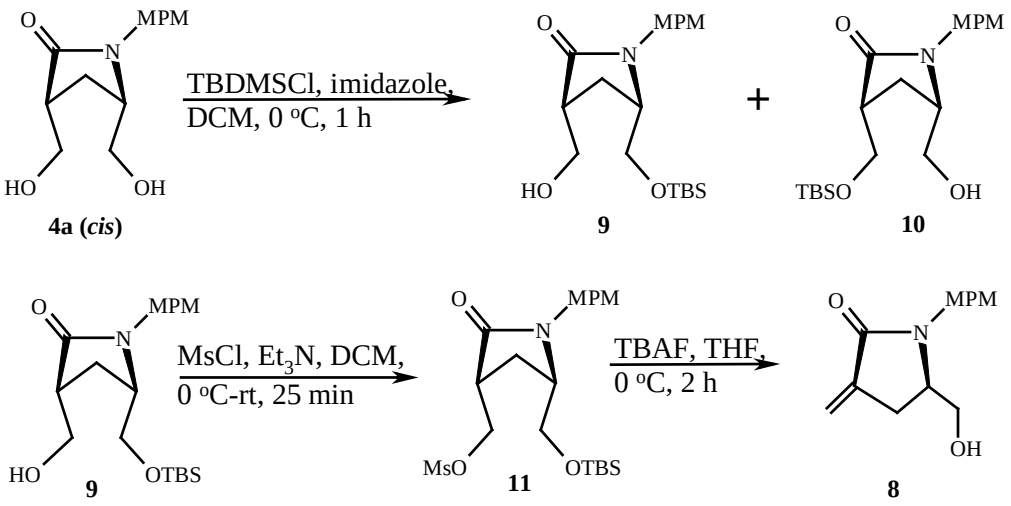


Intramolecular cyclization by nucleophilic displacement of hydroxytosylate or hydroxymesylate to yield a tetrahydropyran, has been employed in various approaches to polyether antibiotics.[19a,b,c,d]

Kishi *et al.*[19a] used intramolecular cyclization of 1,5-hydroxytosylate for the synthesis of compound related to antibiotic X-14547A. Still *et al.*[19b] synthesized monensin by intramolecular cyclization of monomesylated 1,4-diol in presence of sodium acetate. Kishi *et al.*[19c] also used same methodology for the synthesis of narasin.

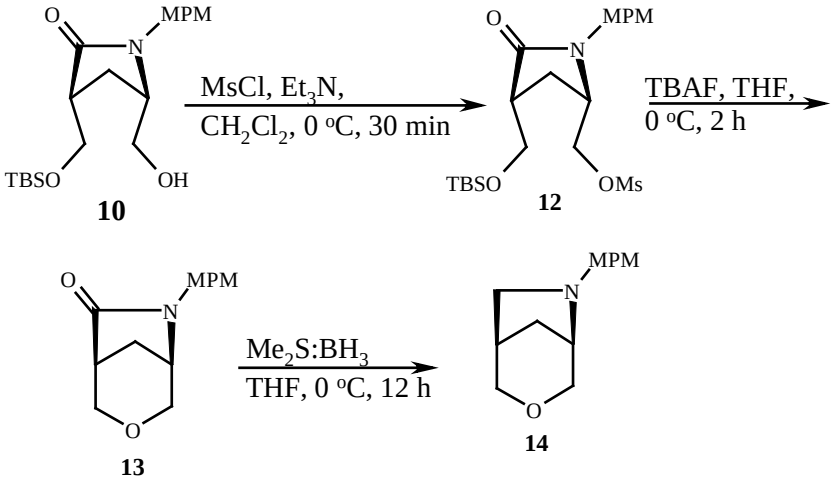
In order to circumvent the problem as revealed above it was apparent that a mono-mesyl derivative of **4a** could be an appropriate choice. The reaction of **4a** with TBDMSCl in presence of imidazole in CH_2Cl_2 at 0 ^oC afforded the monosilylated derivative (**9**) (50%) and the regiomeric product (**10**) (35%). Compound **9** was mesylated with $MeSO_2Cl$ and Et_3N in CH_2Cl_2 at rt to obtain **11**, from where we expected to get oxa-aza-bicyclic derivative on exposure to Bu_4NF solution but we failed and obtained the same eliminated product (**8)** identical with the product described above (scheme 4).

Scheme 4



Hence, we next investigated this reaction with the intermediate **12**, which was easily obtained from **10** on mesylation with $MeSO_2Cl$. The product **12** on exposure to Bu_4NF solution in THF gave the oxa-aza-bicyclic derivative (**13**).[20] The structure was unambiguously corroborated from the relevant chemical shifts in the ^1H NMR spectrum. For example, peaks due to TBS and mesyl groups were disappeared while two methylene groups resonated at 3.45 ppm (2 H, J = 11.4 Hz) and 3.58 ppm (2 H, J = 11.4 Hz) as doublets. Reductive chemistry was next undertaken with $Me_2S{:}BH_3$ to provide **14**. The product was readily confirmed by the ^1H NMR, ^{13}C NMR and mass spectral studies. The conspicuous absence of peak due to carbonyl in the ^{13}C spectrum and appearance of peaks at 29.6, 35.2, 60.5, 62.3, 73.1 ppm in the DEPT spectrum, characteristic of CH_2 group indicated the product **14** (Scheme 5).

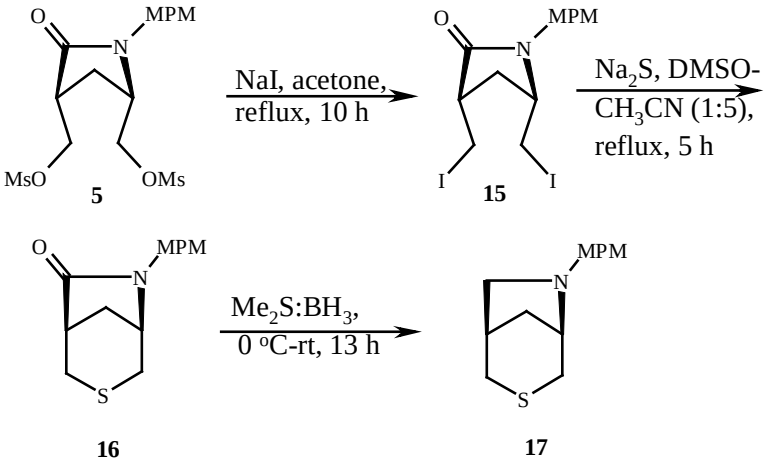
Scheme 5



The final endeavor was elected to incorporate sulfur into the bicyclic ring. For preparing thia-aza-bicyclic[21] derivatives, the succeeding step was the conversion of dimesylate (**5**) to cyclic thia-aza compound. Since the one-pot transformation with sodium sulfide and DMSO-CH_3CN[22] was observed as a low-yielding (10%) process in the synthesis of aza-thia-bicyclic derivative (**16**), a two-step procedure was followed. Accordingly, the dimesylate derivative (**4a**) was converted into the corresponding diiodo (**15**)[23] with sodium iodide in refluxing acetone, the structure of which was adequately substantiated by spectral studies. For instance, the ^{1}H NMR spectrum of **15** clearly revealed the signals due to methylene attached to iodine between 3.14-3.40 ppm as a multiplet. The conversion of suitably posed di-iodo (**15**) into the cyclic thio-ether (**16**)[24] *via* elctrophilic substitution with Na_2S in DMSO and CH_3CN at 80 ^{o}C for 5 h in good yield. The introduction of S was confirmed from elemental analysis. With the thia-aza-pyrrolidinone derivative (**16**) in hand, we completed the synthesis of bicyclic ring compound study by reduction of **16** with $Me_2S{:}BH_3$ complex to give the thia-aza derivative (**17**) (Scheme 6). The structural feature of **17** was explicitly supported from the combined spectral data of the ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. For instance, the ^{1}H NMR spectrum of **17** clearly exposed the signals due to methylene attached to sulfur at 2.99 ppm as a multiplet and 3.29 ppm as a triplet (J = 4.6 Hz). The five methylene carbons in the DEPT spectrum, resonating at 31.1,

34.6, 37.0, 53.8, 56.2 ppm and mass spectrum at *m/z* 249 (M^+) also assigned the structure **17**.

Scheme 6

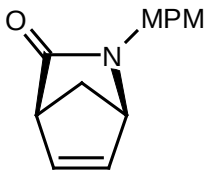


In order to make the above-described scaffolds in optically pure forms, we need the synthesis of chiral Vince's lactam. Both the enantiomers of Vince's lactam were prepared with more than 99% ee by enzymatic resolution using two new stains. For instance, *k. citrophila* provided (–)-Vince's lactam while *A. viscous* produced (+)-Vince's lactam that was discussed later on.

Conclusion:

In conclusion, we have developed some novel and unique scaffold molecules starting from easily accessible Vince's lactam. These rigid structures are useful for combi-chem library synthesis of small molecules, which is under investigation in our laboratory.

(3*S, 6*R**)-*N*-(4-Methoxybenzyl)-1-azabicyclo[2.2.1]hept-4-en-2-one (2)**



Vince's lactam (**1**) (6.6 g, 60.5 mmol) in dry DMF (40 mL) was cooled to 0 ^{o}C and NaH (60% dispersion in oil, 3.3 g, 83.0 mmol) was added portion-wise at 0 ^{o}C. After 30 min at rt *p*-methoxybenzyl bromide (13.3 g, 66.5 mmol) and Bu_4NI (0.3 g) were added and stirred for 1 h. After usual work up the residue was purified on silica gel by eluting with EtOAc-hexane (4:1) to give (**2**) (12.9 g, 93%) as oil.

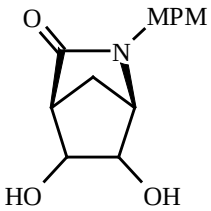
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.03 (m, 1 H), 2.27 (m, 1 H), 3.35 (br s, 1 H), 3.80 (s, 3 H), 3.98 (d, 1 H, *J* = 14.0 Hz), 4.00 (br s, 1 H), 4.31 (d, 1 H, *J* = 14.0 Hz), 6.50 (s, 2 H), 6.82 (d, 2 H, *J* = 8.0 Hz), 7.09 (d, 2 H, *J* = 8.0 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 46.5, 53.0, 54.4, 57.5, 61.8, 112.9, 113.3, 127.7, 129.0, 136.1, 139.1, 158.5, 178.8.

MS: m/z 229 (M^+).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.10; H, 6.45; N, 6.11.

(3*S,6*R**)-*N*-(4-Methoxybenzyl)-4,5-dihydroxy-1-azabicyclo[2.2.1]heptan-2-one (3)**



A mixture of **2** (15.0 g, 65.5 mmol), 50% aq NMO solution (5.4 mL, 196.5 mmol), OsO_4 (80.0 mg, 0.281 mmol) in toluene (2 mL), acetone (40 mL) and water (60 mL) was

stirred at rt for 18 h. Saturated $NaHSO_3$ solution was introduced to quench the reaction. After 1 h, solid was filtered, washed with water and CCl_4 and recrystallized from methanol to obtain (**3**) (13.0 g, 75%).

Mp = 205 ^oC

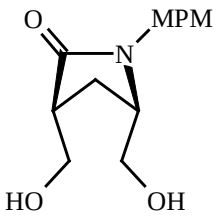
^{1}H NMR (DMSO-d$_6$, 200 MHz): δ 1.68 (br d, 1 H, *J* = 9.5 Hz), 1.89 (br d, 1 H, *J* = 9.5 Hz), 2.44 (s, 1 H), 3.60 (m, 1 H), 3.73 (s, 3 H), 4.02 (d, 1 H, *J* = 16.0 Hz), 4.29 (d, 1 H, *J* = 15.2 Hz), 4.90 (d, 1 H, *J* = 5.1 Hz), 5.06 (d, 1 H, *J* = 5.1 Hz), 6.90 (d, 2 H, *J* = 8.0 Hz), 7.17 (d, 2 H, *J* = 8.0 Hz).

^{13}C NMR (DMSO-d$_6$, 50 MHz): δ 33.9, 43.7, 52.2, 55.3, 62.3, 68.3, 69.4, 114.2, 129.3, 129.7, 158.8, 174.4.

MS: m/z 263 (M^+).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32; Found: C, 63.69; H, 6.40; N, 5.03.

(3*S, 6*R**)-*N*-(4-Methoxybenzyl)-3,5-*bis*-hydroxymethylpyrrolidin-2-one (4a)**



A mixture of **3** (4.2 g, 16.0 mmol), $NaIO_4$ (6.7 g, 31.1 mmol), water (50 mL), and methanol (200 mL) was stirred at rt for 30 min and filtered. To the filtrate $NaBH_4$ (0.9 g, 23.8 mmol) was added. After stirring for 20 min, the reaction mixture was concentrated, diluted with water, extracted with CH_2Cl_2 and washed with brine, dried (over Na_2SO_4) and concentrated. The residue was chromatographed on silica gel by eluting with EtOAc-MeOH (1:1) to furnish **4a** (3.5 g, 83%) as oil**.**

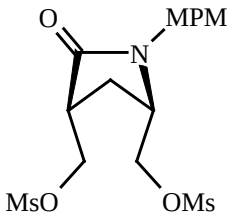
^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.10 (m, 2 H), 2.70 (m, 1 H), 3.47 (m, 4 H), 3.69 (m, 1 H), 3.74 (s, 3 H), 4.04 (d, 1 H, *J* = 8.9 Hz), 4.87 (d, 1 H, *J* = 14.7 Hz), 6.77 (d, 2 H, *J* = 8.0 Hz), 7.09 (d, 2 H, *J* = 8.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.9, 43.7, 55.1, 57.1, 61.8, 62.5, 114.0, 128.2, 129.0, 158.9, 176.8.

MS: m/z 265 (M^+).

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.42; H, 7.28; N, 5.12.

(3*S,6*R**)-*N*-(4-Methoxybenzyl)-3,5-*bis*-(methansulfonyloxymethyl)pyrrolidin-2-one (5)**



A mixture of **4a** (1.8 g, 6.8 mmol), Et_3N (3.6 mL), DMAP (50.0 mg, 0.41 mmol), $MeSO_2Cl$ (1.3 mL, 17.0 mmol) was stirred at rt for 35 min, diluted with CH_2Cl_2 and washed with water (50 mL), and brine, dried (over Na_2SO_4) and concentrated. The residue was triturated with EtOAc-hexane (2:3) to afford dimesylate (**5**) (2.5 g, 87%) as a solid (Recrystalized from EtOAc-Hexane).

Mp = 115 °C

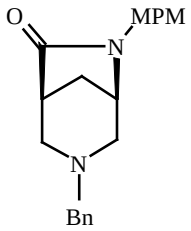
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.15 (m, 1 H), 2.89, 2.95 (2s, 6 H), 3.07 (m, 2 H), 3.64 (m, 1 H), 3.71 (s, 3 H), 4.09 (m, 2 H), 4.21 (dd, 1 H, *J* = 3.1, 12.1 Hz), 4.32 (dd, 1 H, *J* = 3.1, 10.7 Hz), 4.56 (dd, 1 H, *J* = 4.5, 10.7 Hz), 4.92 (d, 1 H *J* = 15.1 Hz), 6.83 (d, 2 H, *J* = 8.0 Hz), 7.10 (d, 2 H, *J* = 8.0 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.5, 36.9, 37.3, 40.7, 44.4, 54.1, 55.2, 68.5, 69.1, 114.2, 127.7, 129.1, 159.3, 172.6.

MS: m/z 421 (M^+).

Anal. Calcd for $C_{16}H_{23}NO_8S_2$: C, 45.59; H, 5.50; N, 3.32; S, 15.21. Found: C, 45.56; H, 5.36; N, 3.28; S, 15.22.

(3*S, 6*R**)-1-*N*-(4-Methoxybenzyl)-5-benzyl-1,5-diazabicyclo[3.2.1]octan-2-one (6)**



A solution of **5** (5.8 g, 13.8 mmol), benzylamine (1.47 g, 13.8 mmol), and $NaHCO_3$ (2.76 g, 27.6 mmol) in toluene (50 mL) was heated under reflux for 19 h and concentrated. The residue was partitioned between EtOAc-water. The organic layer was dried (over Na_2SO_4), concentrated and chromatographed on silica gel by using EtOAc-hexane (2:3) to furnish **6** (3.8 g, 82%) as syrup.

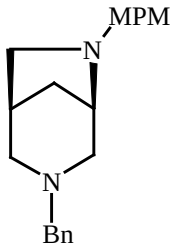
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45 (d, 1 H, *J* = 11.1 Hz), 1.95 (d, 1 H, *J* = 11.1 Hz), 2.05 (m, 1 H), 2.18 (d, 1 H, *J* = 9.7 Hz), 2.46 (t, 1 H, *J* = 4.1 Hz), 2.70 (m, 1 H), 3.09 (m, 1 H), 3.32 (t, 1 H, *J* = 4.1 Hz), 3.49 (AB q, 2 H, *J* = 13.9 Hz), 3.67 (s, 3 H), 3.69 (d, 1 H, *J* = 13.9 Hz), 4.79 (d, 1 H, *J* = 13.9 Hz), 6.69 (d, 2 H, *J* = 7.2 Hz), 7.01 (d, 2 H, *J* = 7.2 Hz), 7.20 (s, 5 H).

^{13}CNMR ($CDCl_3$, 50 MHz): δ 35.7, 40.7, 43.9, 50.0, 53.3, 53.8, 54.8, 60.9, 113.7, 128.0, 129.1, 137.4, 158.7, 176.3.

MS: m/z 336 (M^+).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found**:** C, 74.63; H, 7.38; N, 8.32.

(3*S, 6*R**)-1-*N*-[4-Methoxybenzyl]-5-benzyl-1, 5-diazabicyclo[3.2.1]octane (7)**



To a stirred solution of **6** (0.4 g, 1.2 mmol) in dry THF (10 mL) was added a 2 M solution of $Me_2S.BH_3$ in THF (1.8 mL, 3.6 mmol) under nitrogen at 0 ^oC. The reaction was stirred for 12 h, quenched with methanol and concentrated. The residue was chromatographed on silica gel by using EtOAc-hexane (3:7) to provide **7** (0.34 g, 89%), as syrup.

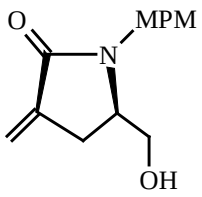
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.43 (d, 1 H, *J* = 12.3 Hz), 2.01 (d, 2 H, *J* = 12.3 Hz), 2.20 (d, 1 H, *J* = 9.2 Hz), 2.29 (m, 1 H), 2.75 (d, 2 H, *J* = 12.3 Hz), 2.93 (d, 1 H, *J* = 12.3 Hz), 3.15 (m, 2 H), 3.52 (AB q, 2 H, *J* = 12.3 Hz), 3.76 (s, 3 H), 3.89 (AB q, 2 H, *J* = 12.3 Hz), 6.83 (d, 2 H, *J* = 8.0 Hz), 7.2-7.5 (m, 7 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 34.7, 36.5, 53.8, 54.2, 54.9, 55.9, 56.6, 58.7, 62.1, 113.5, 126.9, 127.9, 128.9, 129.7, 130.8, 138.5, 158.4.

MS: m/z 322 (M^+).

Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69; Found: C, 77.91; H, 8.34; N, 8.89.

(5*S)-*N*-(4-Methoxybenzyl)-3-methylene-5-hydroxymethylpyrolidin-2-one (8)**



To a solution of **5** (2.0 g, 4.4 mmol) in CH_3CN (15 mL) was added 2 N NaOH (10 mL) and then reflux for 3 h. After completion of reaction, neutralized with acetic acid, concentrated to remove CH_3CN and diluted with ethylacetate. The organic layer was separated, concentrated and chromatographed on silica gel to obtain the same eliminated product (**8**).

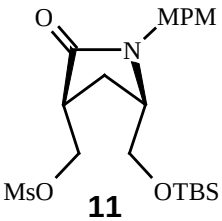
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.72 (m, 2 H), 3.52 (m, 2 H), 3.77 (s, 3 H), 3.82 (m, 2 H), 4.12 (d, 1 H, *J* = 14.9 Hz), 4.93 (d, 1 H, *J* = 14.7 Hz), 5.32 (t, 1 H, *J* = 2.1 Hz), 5.97 (t, 1 H, *J* = 2.7 Hz), 6.81 (d, 2 H, *J* = 8.8 Hz), 7.16 (d, 2 H, *J* = 8.8 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.7, 43.5, 54.3, 54.6, 61.1, 113.2, 114.6, 127.6, 128.6, 138.7, 158.2, 167.9.

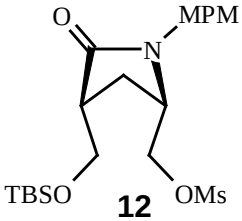
MS: m/z 247 (M^+).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.01; H, 6.93; N, 5.66. Found**:** C, 67.77; H, 6.88; N, 5.49.

(3*S*,6*R)-*N*-(4-Methoxybenzyl)-5-(methansulphonyloxymethyl)-3-(*tert*-butyl dimethylsilyloxymethyl)pyrrolidin-2-one (11) and (3*S**,6*R**)-*N*-(4-Methoxybenzyl) -3-methansulphonyloxymethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-2-one (12)**



11



12

Compound (**4a**) (6.2 g, 23.5 mmol), imidazole (2.4 g, 35.5 mmol), and TBDMSCl (3.5 g, 23.5 mmol) in CH_2Cl_2 (50 mL) was stirred for 1 h at 0 ^oC and concentrated. The residue was chromatographed on silica gel by using EtOAc-hexane (1:3). The first compound to be eluted was (**10**) (3.1 g, 35%) which was treated with Et_3N (1.5 mL, 11.1 mmol), DMAP (45 mg, 0.37 mmol), $MeSO_2Cl$ (0.42 mL, 5.5 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC for 30 min. The reaction mixture was diluted with water and organic layer was separated. The organic layer was washed with water, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by eluting with EtOAc-hexane (1:3) to give **12** (2.4 g, 95%), as syrup.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 6 H), 0.86 (s, 9 H), 1.81 (m, 1 H), 2.29 (m, 1 H), 2.58 (m, 1 H), 2.79 (s, 3 H), 3.48 (m, 1 H), 3.68 (m, 1 H), 3.73 (s, 3 H), 4.09 (m, 3 H), 4.23 (d, 1 H, *J* = 14.8 Hz), 4.68 (d, 1 H, *J* = 14.8 Hz), 6.78 (d, 2 H, *J* = 8.1 Hz), 7.13 (d, 2 H, *J* = 8.1 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.9, 25.8, 36.9, 43.7, 44.6, 54.5, 54.9, 62.1, 69.7, 113.9, 128.6, 129.0, 158.9, 174.6.

MS: m/z 457 (M^+).

Anal. Calcd for $C_{21}H_{35}NO_6SSi$: C, 55.11; H, 7.71; N, 3.06; S, 7.01. Found: C, 54.80; H, 7.58; N, 3.15; S, 6.92.

Further elution gave **9** (4.5 g, 50%), which was mesylated with $MeSO_2Cl$ (1.5 mL, 19.6 mmol) and Et_3N (5 mL) as described above, to give **11** (3.2 g, 83%), as an oil.

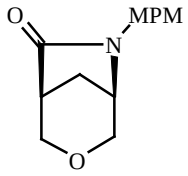
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.03 (s, 6 H), 0.84 (s, 9 H), 1.93 (m, 1 H), 2.24 (m, 1 H), 2.67 (m, 1 H), 2.89 (s, 3 H), 3.65-3.74 (m, 3 H), 3.74 (s, 3 H), 3.93 (m, 2 H), 4.08 (d, 1 H, *J* = 14.5 Hz), 4.92 (d, 1 H, *J* = 14.5 Hz), 6.80 (d, 2 H, *J* = 8.6 Hz), 7.14 (d, 2 H, *J* = 8.6 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.7, 25.7, 37.5, 42.6, 44.3, 54.5, 55.2, 62.4, 68.2,114.3, 127.9, 129.2, 159.3, 176.2.

MS: m/z 457 (M^+).

Anal. Calcd for $C_{21}H_{35}NO_6SSi$: C, 55.14; H, 7.65; S, 7.00. Found: C, 55.10; H, 7.53; S, 6.92.

(3*S, 6*R**)-1-*N*-(4-Methoxybenzyl)-5-oxa-1-azabicyclo[3.2.1]octan-2-one (13)**



To a solution of **11** (2.0 g, 4.4 mmol) in THF (20 mL) was added 1 M solution of Bu_4NF in THF (6.6 mL, 6.6 mmol). The mixture was stirred at rt for 2 h. After addition of saturated NH_4Cl, the organic layer was separated, concentrated and chromatographed on silica gel by eluting with EtOAc-hexane (3:2) to give **8** (0.97 g, 90%).

Compound **12** (2.1 g, 4.6 mmol) and 1 M solution of Bu_4NF in THF (6.8 mL, 6.8 mmol) was stirred at rt for 2 h and concentrated. The residue was partitioned between extracted with ethylacetate and water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel by eluting with EtOAc-hexane (3:2) to give oxa-aza pyrrolidinone compound **13** (0.97 g, 85%), as syrup.

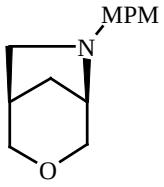
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.83 (d, 1 H, *J* = 10.7 Hz), 2.29 (m, 1 H), 2.70 (m, 1 H), 3.45 (d, 2 H, *J* = 11.4 Hz), 3.58 (d, 2 H, *J* = 11.4 Hz), 3.79 (s, 3 H), 3.98 (m, 1 H), 4.04 (d, 1 H, *J* = 14.9 Hz), 4.82 (d, 1 H, *J* = 14.9 Hz), 6.84 (d, 2 H, *J* = 9.3 Hz), 7.19 (d, 2 H, *J* = 9.3 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 34.2, 40.9, 42.8, 53.6, 53.8, 62.9, 65.8, 112.8, 127.5, 127.9, 157.9, 173.9.

MS: m/z 247 (M^+).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.91; H, 6.65; N, 5.41.

(3*S, 6*R**)-1-*N*-(4-Methoxybenzyl)-5-oxa-1-azabicyclo[3.2.1]octane (14)**



Compound **13** (0.18 g, 0.73 mmol) in THF (3 mL) and $Me_2S{:}BH_3$ (2 M in THF 0.73 mL, 1.45 mmol) were stirred at rt for 12 h and then worked up as described above to give oxa-aza-bicyclic derivative (**14**) (0.14 g, 82%), as a syrup.

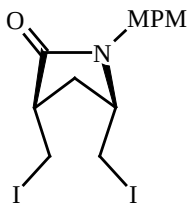
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.72 (d, 1 H, *J* = 10.8 Hz), 2.05 (m, 1 H), 2.24 (m, 1 H), 2.83 (m, 1 H), 2.99 (d, 1 H, *J* = 9.4 Hz), 3.01 (m, 1 H), 3.11 (m, 1 H), 3.43 (d, 1 H, *J* = 11.5 Hz), 3.79 (s, 3 H), 3.89 (m, 4 H), 6.83 (d, 2 H, *J* = 8.9 Hz), 7.34 (d, 2 H, *J* = 8.9 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.6, 35.2, 36.4, 55.1, 60.5, 62.3, 66.7, 73.1, 113.0, 113.7, 126.2, 129.8, 133.9, 159.6.

MS: m/z 233 (M^+).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.31; H, 8.47; N, 6.00.

(3*S, 6*R**)-*N*-(4-Methoxybenzyl)-3,5-*bis*-iodomethyl-*N*-pyrrolidin-2-one (15)**



A solution of **5** (4.0 g, 9.5 mmol) and anhydrous sodium iodide (3.6 g, 23.7 mmol) in dry acetone (30 mL) was heated under reflux for 10 h. The residue was partitioned between

EtOAc and water. The organic layer was washed with sodium sulfite solution, brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel by eluting with EtOAc-hexane (1:9) to get **15** (4.1 g, 89%) as syrup.

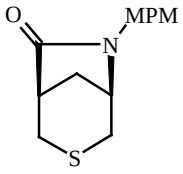
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.53 (m, 1 H), 2.45 (m, 1 H), 2.70-3.08 (m, 1 H), 3.14-3.40 (m, 4 H), 3.53-3.63 (m, 1 H), 3.79 (s, 3 H), 3.84 (dd, 1 H, *J* = 15.1, 29.8 Hz), 4.97 (dd, 1 H, *J* = 15.4, 25.8 Hz), 6.86 (m, 2 H), 7.11 (q, 2 H, *J* = 8.6 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.7, 33.2, 41.6, 43.3, 43.7, 53.5, 54.8, 113.8, 126.8, 127.3, 128.8, 129.2, 1 58.8, 172.7.

MS: m/z 485 (M^+)

Anal. Calcd for $C_{14}H_{17}NI_2O_2$: C, 34.66; H, 3.53; N, 2.89. Found**:** C, 34.41; H, 3.46; N, 2.67.

(3*S, 6*R**)-1- *N*-(4-Methoxybenzyl)-5-thia-1-azabicyclo[3.2.1]octan-2-one (16)**



Compound (**15**) (1.0 g, 2.1 mmol) and $Na_2S{\cdot}9H_2O$ (0.5 g, 2.1 mmol) in DMSO (2 mL) and MeCN (10 mL) were heated under reflux for 5 h. The reaction mixture was concentrated to remove MeCN, diluted with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel by using EtOAc-hexane (1:1) to furnish cyclic product (**16**) (0.43 g, 79%) as syrup.

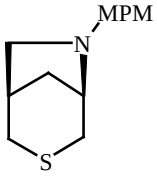
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.52 (d, 1 H, *J* = 11.0 Hz), 2.10 (m, 1 H), 2.35 (dd, 1 H, *J* = 3.3, 13.7 Hz), 2.5-2.9 (m, 4 H), 3.61 (m, 1 H), 3.71 (s, 3 H), 3.87 (d, 1 H, *J* = 13.7 Hz), 4.87 (d, 1 H, *J* = 13.7 Hz), 6.78 (d, 2 H, *J* = 7.5 Hz), 7.14 (d, 2 H, *J* = 7.5 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.6, 29.3, 34.5, 40.0, 43.5, 52.9, 54.9, 113.7, 113.9, 128.1, 129.2, 158.8, 175.0.

MS: m/z 263 (M^+).

Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.87; H, 6.51; N, 5.32; S, 12.16. Found: C, 63.64; H, 6.32; N, 5.32; S, 12.00.

(3*S, 6*R**)-1-*N*-[4-Methoxybenzyl]-5-thia-1-azabicyclo[3.2.1]octane (17)**



To compound **16** (100.0 mg, 0.38 mmol) in dry THF (3 mL) was added $Me_2S.BH_3$ (2 M solution in THF, 0.57 mL, 1.14 mmol) and the mixture were stirred at rt under nitrogen for 13 h. The residue was quenched with methanol and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:6) to provide **17** (74.0 mg, 78%) as syrup.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44 (d, 1 H, *J* = 11.9 Hz), 1.97 (m, 1 H), 2.23 (m, 1 H), 2.53 (m, 2 H), 2.66 (d, 1 H, *J* = 13.3 Hz), 2.99 (m, 2 H), 3.10 (m, 1 H), 3.29 (t, 1 H, *J* = 4.6 Hz), 3.72 (s, 3 H), 3.94 (d, 2 H, *J* = 3.0 Hz), 6.75 (d, 2 H, *J* = 8.2 Hz), 7.25 (d, 2 H, *J* = 8.2 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.1, 31.1, 34.6, 37.0, 53.8, 55.1, 56.2, 56.7, 113.6, 129.7, 159.7.

Ms: m/z 249 (M^+).

Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62; S, 12.85. Found: C, 67.19; H, 7.49; N, 5.57; S, 12.64.

The concept of chirality has been in existence since the discovery by Louis Pasteur in 1847.[25] This chiral chemistry hold great promise for business and industry, because studies have indicated a growth in demand of more than 9% annually through 2005 for chiral raw materials, intermediates and active ingredients. In fact, two-thirds of the prescription drugs now on the market are chiral, making the single enantiomer forms (the majority of new chiral drugs) a significant driver for continued investment in chiral chemistry. Additional applications for this emerging technology include agrochemicals as well as flavours and fragrances**.**

Chiral, derived from the Greek word *'cheir'* (hand), refers to the way two otherwise identical molecules, like hands, can be non-superimposable mirror images of each other. These species are referred to as enantiomers' and are physically and chemically identical however, they react selectively[26] when interacting with other chiral molecules (including enzymes and other chiral biomolecules). This diastereomeric interaction with biological systems has been at the forefront of chiral drug chemistry for the past 30 years. The importance of chirality in the context of the biological function has been fully appreciated and therefore efforts to develop technology with commercial viability of many researchers. The outlook of asymmetric synthesis dates back to 1890, with Emil Fischer's remarkable piece of chemical research on the cyanohydrins in sugar unit.[27] Many recall the use of thalidomide in the 1960s where one isomer treated for the symptoms of morning sickness in pregnant women, yet the other isomer caused severe birth defects. Back then, chemists and scientists didn't understand the potential problems inherent in using racemic[28] forms of chiral drugs. They have ever since taken it as challenge to induce chiralities in a molecule. Enatioselective catalysis is bringing about a revolution in asymmetric synthesis. Seldom has there been an area of chemistry where the scientific goals are so challenging; the economic benefits so obvious, and the ethical reasons for doing research are so compelling.

Over the years, scientists have developed several methods for obtaining single enantiomeric forms of chiral drugs or their intermediates, including racemate resolution (through classical diastereomer separation), chiral pool synthesis, chiral adjunct synthesis (stoichiometric),

enzymatic catalysis, microbial synthesis and chemical asymmetric catalysis. The effectiveness of each method is highly application-dependent, making a 'one-size-fits-all' approach challenging at best. The scientific community is divided as to whether or not a universal approach will ever be discovered given the scope and complexity of the functionalities, targets and transformations. Most agree that, at this stage, a comprehensive 'toolbox' of technologies is needed to approach a wide variety of targets.

The case for enantiomeric purity can be made anywhere that chemicals and biological materials interact. This is most prevalent in the pharmaceutical industry where health and safety are critical and heavily regulated. Significantly reducing or even eliminating side effects while enhancing drug performance represents a strong impetus for developing better paths to enantiomerically pure compounds. Increasingly stringent government regulations within the pharmaceutical industry have resulted in further research to develop enantiomerically pure drugs. Lengthy approval processes can progress more expediently when the enantiomerically pure form is supplied. In addition, many pharmaceutical companies are racing to develop the single enantiomer form of a previously patented racemic compound to help extend patent life.

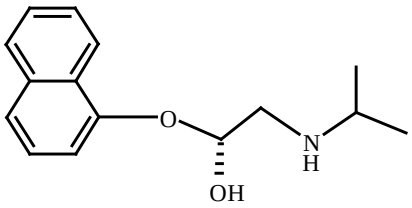
Single-enantiomer drugs are increasingly assuming importance to the pharmaceutical industry, mainly fuelled by regulatory authorities' insistence on chiral drugs. Drugs work by reacting with receptors in the body that have a specific physical shape. In most cases, one isomer of the drug binds better with the receptors compared to the other. This enantiomer is primarily responsible for producing the therapeutic activity the drug is intended to deliver. The other isomer has minimum effect on the drug's activity. However, there are drugs where both isomers fit the receptor site, but, in such cases, the binding will be less tight and therefore the drug will be less active.

Besides side effects, there are other advantages of using a more active isomer of a drug. The dosage given to a patient will be reduced significantly. For instance, for arthritic pain, 600 mg of ibuprofen is indicated. Now, if only the active isomer is given, the dose will come down to 6 mg. Similarly, in case of salbutamol, the dose is reduced to 1 mg from 4 mg. Also, there is less likelihood of side effects from the unwanted isomeric form.

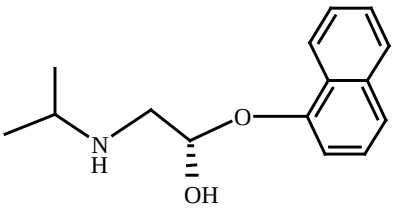
For manufacturers, single isomers provide a means to double drug production, which ultimately results in less wastage. But, the most strategic advantage to drug companies is

that chiral drugs provides the opportunities for racemic switching, whereby a drug that has previously been marketed as racemate can be re-developed and introduced as its optically active form. This is useful for companies wishing to extend the patent protection of a key product.

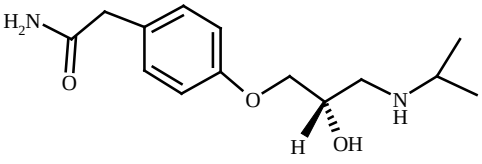
Activities of enantiomers of some drugs is depicted in table 1. Probably the most well known and tragic example of a drug where the isomer causes serious side effects is in the case of ethambutolit[29] the *SS* isomer that is in active tuberculosis with a endismic ratio of about 200, the *RR* isomer causes optical neutries that can result in blindness. There are other examples such as penicillamine used for anti-arthritic activity where the (*S*)-enantiomer is active while the (*R*)-form is extremely toxic. Similarly, the D-form of anti-Parkinson's drug levodopa causes granulocytopenia. Similarly, racemic atenolol is presently being marketed for the treatment of hypertension, angima and has shown promise in the treatment of post myocardial infarctism, the *S* isomer has recently been found to avoid the occasional side effects of lower heart rate sometimes encountered with the racemate.



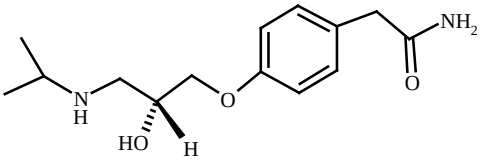
(*S*)-Propranolol
Beta-blocker



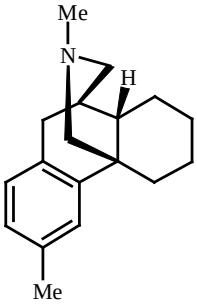
(*R*)-Propranolol
Vaginal contraceptive



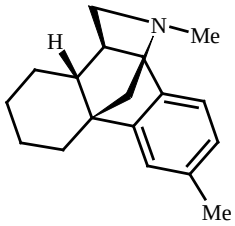
(*S*)- Atenolol
Hypertension, Angima



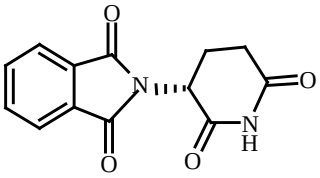
(*R*)- Atenolol
Lowered heart rate



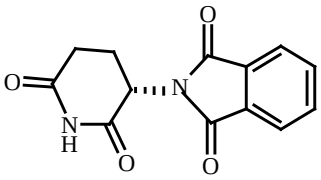
Levomethorphan
potent narotic



Dextromethorphan
common cough
suppresent



(*S*) -Thalidomide
Sedative



(*R*) -Thalidomide
Tetratogen

Table 1: *Activities of enantiomers of some drugs*

The *R, S* forms of most drugs are metabolized by different biochemical path and at different rates. Therefore it is virtually impossible to follow the biochemical fate and actions of the individual isomers when the dose is a racemic mixture. There are also differences in how individuals react to the *R* and *S* forms of a drug.[30]

The United States Food and Drug Administration (FDA) guidelines state that the development and marketing of chiral drugs as racemates should not be prohibited, the final approval must be based on complete information with regard to the pharmacodynamics and pharmacokinetics[31] of all the individual isomers and the racemic mixture. For e.g, regularity requirements include a stipulation that the bioavalibility of a drug be demonstrated. Since the two isomers of a chiral drug generally inhibit widely differing pharmacokinetics, it seems obvious that establishing the bioavalibility of the drug from a racemate is a complete task, which necessitates separation of the enantiomers and investigation of the pharmacokinetics as molecular entities.

The final consent must be based on proper assessment of clinical investigations that compare the safety and efficacy of a racemate and its individual enantiomers. It was concluded, “Whenever a drug can be obtained in a variety of chemically equivalent forms (such as enantiomers), it is both good for sciences and sense to explore the potential for differences between these two forms *in vivo*”. The different methods to obtain enantiomerically pure compound include classical optical resolution, *via* diastereomers, chromatographic separation of enantiomers, recrystallization, enzymatic resolution, chemical kinetic resolution and asymmetric synthesis.

The implications of the revolution in stereochemistry may be more thoughtful than biotechnology. Chiral, cis/trans, regiospecific, syn/anti and other forms of stereochemical isomers will have enormous economic impact. Chiral technology is at the forefront of a new revolution, which combines the disciplines of organic chemistry and biotechnology. Rational drug design, receptor-based drugs, enzyme inhibitors, advanced compound screening and small molecule research all involve, for the most part, chiral molecules. Chiral molecules also include biochemicals, new types of pesticides, aromas/flavors, polymers, advanced liquid crystals, and nonlinear optical materials. As a result of their unique properties, chiral compounds will experience rapidly accelerating demand in the coming years.

It was common practice for a pharmaceutical company to market a chiral drug as the racemate. In many cases the desired activity resides solely in one enantiomer, the mirror image enantiomer either totally inactive or carries some undesired properties that have been tolerated as an unavoidable necessity. This approach in effects meant that dose of drug was contaminated with an equal weight of an isomer, which usually had no therapeutic value, but had the potential to cause unsuspected deleterious side effects.

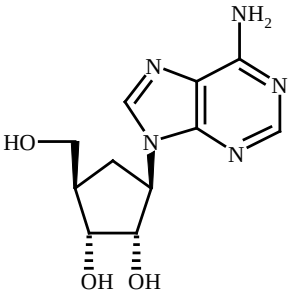
All chiral forms of a drug now have to be tested rigorously for possible side effects and for stability in *vivo* before approval. The US FDA insists on switching to the pure enantiomer for older drugs and only approves single isomer of new chiral drugs. To get approvals for chiral drugs in India, companies need to demonstrate toxicity profile, human studies and bioequivalence.

In this area, we choose Vince's lactam because carbocyclic nucleosides, where the ribose oxygen of nucleosides has been replaced by a methylene group have grown in prominence as chemotherapeutic agents[32] for the treatment of viral infections (e.g, HIV, herps) and as cardiac vasodilators. A benefit is that the absence of ribosyl oxygen prevents cleavage by nucleases to ribose plus base leading to greater bioavalibility.[33a,b] For the purpose of pharmaceuticals agents, it is necessary that the carbocyclic nucleosides are in a

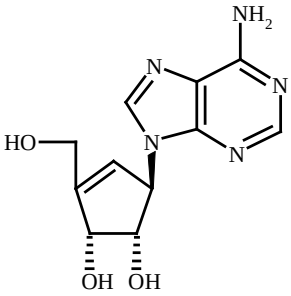
single enantiomer form and generally corresponds to natural configuration. While the carbocyclic analog of adenosine was first described by Shealy and Clayton[34] in 1966, it was the discovery that the natural carbocyclic nucleosides, aristeromycin (**1**)[35] and neplanocin A (**2**),[36] display antibiotic and antitumor activity that sparked the search for other CANS (Carbocyclic analogs of nucleosides) with biological activity (Figure 1). Among the antiviral CANS discovered in the search for agents active against human immunodeficiency virus (HIV), the most promising are carbovir (**3**),[37] the structurally related abacavir (**4**)[38] as well as BCA (**5**).[39]

The byclic lactam, 2-azabicyclo[2.2.1]hept-5-ene-3-one[40] in its racemic form, is a versatile synthon for the preparation of carbocyclic nucleosides. There are several synthetic pathways to the carbocyclic nucleosides where resolution into the enantiomer could be effected but the most economical was to have access through the single enantiomer of the lactam. The use of the (–) enantiomer of the lactam as the precursor of the anti HIV agent (–) carbovir has been described.

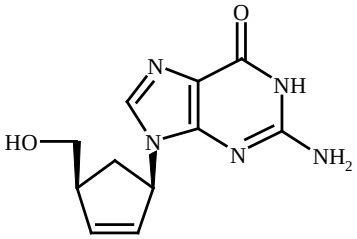
Figure 1



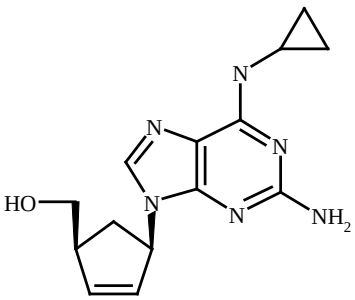
1 (aristeromycin)



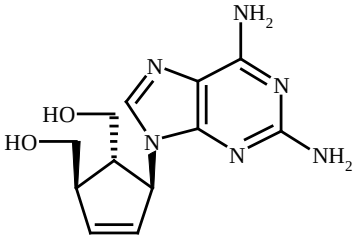
2 (neplanocin A)



3 (carbovir)



4 (abacavir)



5 (-) BCA

In view of the utility of carbocyclic nucleosides we described the resolution of the (–) enantiomer of the Vince's lactam as the precursor of the anti-HIV agent (–) carbovir, abacavir as well as BCA.

It is pertinent to mention that the different methods to obtain enantiomerically pure compound include classical optical resolution, *via* diastereomers, chromatographic separation of enantiomers, recrystallization, enzymatic resolution, chemical kinetic resolution and asymmetric synthesis.

Here we describe results obtained with two new enantiocomplementary whole cell biocatalysts, and the lactamase.

Two methods for enzymatic hydrolysis are reported. First one was reported by Taylor *et al.*[14] where they used two microbial stains a) *Rhodococcus sp* (ENZAI) for [1(*R*), 4(*S*)]-(–)- and b) *Pseudomonas solanacearum* (ENZA20) for [1(*S*), 4(*R*)]-(+). These microbial stains could be used effectively for the rapid resolution of **1** in an aqueous solution to give solutions containing one enantiomer of the bicyclic lactam and the other as the ring opened amino acid. The resulting process could be used at the multi-kilogram scale (up to 100g / L). Taylor, *et al*, has used the second method, where they used *Pseudomonas fluorescence strains* (ENZA22) and another was *Aureobacterium* (ENZA25). Stability and degree of selectivity was high.

Herewith we wished to report the resolution of Vince's lactam by using two different microbial stains. For instance, *k. citrophila* provided (–)-Vince's lactam while *A. viscous* produced (+)-Vince's lactam.

Resolution of Vince's lactam by the above-described microbial stains is shown Figure 2.

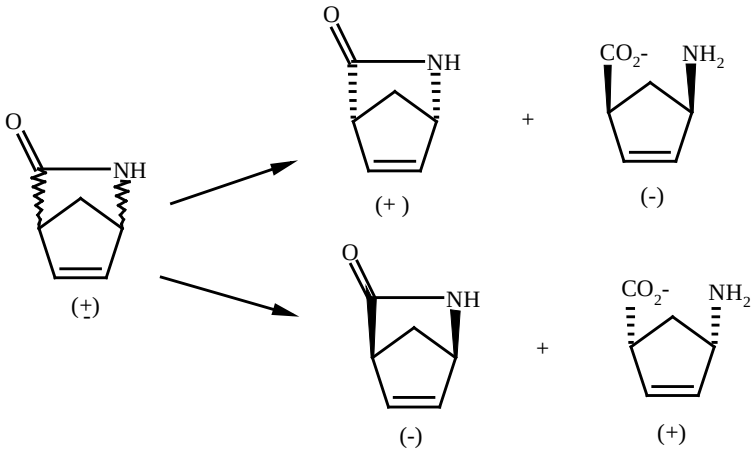


Figure 2: *Resolution of Vince's lactam*

In conclusion, we developed the enzymatic resolution of racemic Vince's lactam using biocatalyst *k. citrophila* for (–)-Vince's lactam while *A. viscous* for (+)-Vince's lactam.and also we have some novel and unique bicyclic heterocyclic scaffold molecules starting from easily accessible Vince's lactam that we discussed earlier.

Procedure for preparation of cells and enzymatic resolution

i) K. citrophilla (ATCC No.21285) was grown in 10 mL medium containing yeast extract (0.5 g, 5%), peptone (0.1 g, 1%), sodium chloride (0.2 g, 2%), sodium glutamate (0.5 g, 5%) and phenyl acetic acid (0.2 g, 2%) at pH 7.2-7.3 for 24 h with shaking at 150 rpm. It was transferred to a 1L flask containing 300 mL medium (yeast extract 15.0 g, peptone 3.0 g, sodium chloride 6.0 g, sodium glutamate 15.0 g, phenyl acetic acid 2.0 g) and incubated at 28-30 ^{o}C for 24 h on rotary shakers (150 rpm). The whole culture was then harvested by centrifugation and biomass was used for the reaction.

ii) A.Viscous (NCIM No. 2451) was grown in 10 mL medium containing beef extract (0.3 g, 3%), peptone (0.1 g, 1%) and sodium chloride (0.8 g, 8 %) at pH 7.2-7.3 for 24 h with shaking at 150 rpm. It was transferred to 1L flask containing 300 mL medium (beef extract 9.0 g, peptone 3.0 g, sodium chloride 24.0 g) and incubated at 28-30 ^{o}C for 24 h on rotary shakers (150 rpm). The whole culture was then harvested by centrifugation and used for the reaction.

[1*R*, 4*S*]-(–)-2-Azabicyclo[2.2.1]hept-5-en-3-one (1)

(±)- **1** (1.0 g, 9.2 mmol) was suspended in phosphate buffer (50 mL, pH 7.5) and then 5 g of wet cell mass of culture *k. citrophilla* (ATCC No.21285) was added. After stirring for 24 h, the cell mass was removed by filtration over a bed of celite. The filtrate was extracted with CH_2Cl_2. Concentration of solvent gave (–)-**1** (0.318 g, 32%).

M.P = 94-95 ^{o}C, Lit m.p = 93-95 ^{o}C.

$[\alpha]_D$ = –552 ^{o} (*c* 1, CH_2Cl_2), Lit $[\alpha]_D$ = –557 ^{o} (*c* 1, CH_2Cl_2), e.e = 99.1%.

[1*S*, 4*R*]-(+)-2-Azabicyclo[2.2.1]hept-5-en-3-one (1)

(±)-**1** (1.0 g, 9.2 mmol) was suspended in phosphate buffer (50 mL, pH 7.5) and then 5 g of wet cell mass of culture *A.Viscous* (NCIM No.2451) was added. After stirring for 21 h,

the cell mass was removed by filtration over a bed of celite. The filtrate was extracted with CH_2Cl_2. Concentration of solvent gave (+)-**1** (0.312 g, 31%).

M.P = 93-95 ^{o}C, Lit m.p 94-95 ^{o}C;

$[\alpha]_D$ = +554 ^{o} (*c* 1, CH_2Cl_2), Lit $[\alpha]_D$ = +557 ^{o} (*c* 1, CH_2Cl_2), e.e = 99.4%.

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Baeyer first introduced the name "Spirocyclane" in 1900.[1] Spirocyclic structures are found in wide range of natural compounds isolated from various sources.[2-8] The complexity of these ring structures is represented by the quaternary carbon center and two fused rings. The different types of spirocyclic compounds are discussed below.

Gelsemine

Gelsemine (Fig. 1) was found to be the major component of the alkaloids in *Gelsemium sempervirens*, have unique hexacyclic cage and spiro-oxindole structure.

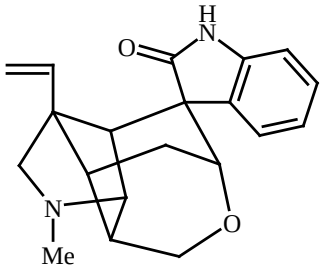
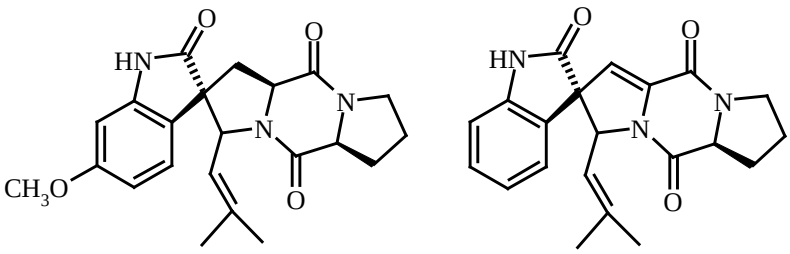


Figure 1. *Gelsemine*

Spirotryprostatins

The diketopiperazine type alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*[3,4] are Spirotryprostatin A and B (Fig. 2).



spirotryprostatin A spirotryprostatin B

Figure 2: *Spirotryprostatin A and B*

Ginkgolide B

Ginkgo biloba, termed the "living fossil" by Darwin, has ancestors dating back to 230 million years.[9,10] Extracts of *Ginkgo biloba* have been used as herbal medicines for 5000 years in China and Japan to treat a variety of conditions, such as coughs, asthma, and circulatory disorders, and is currently undergoing clinical evaluation for treatment of dementia[11, 12] (Fig. 3).

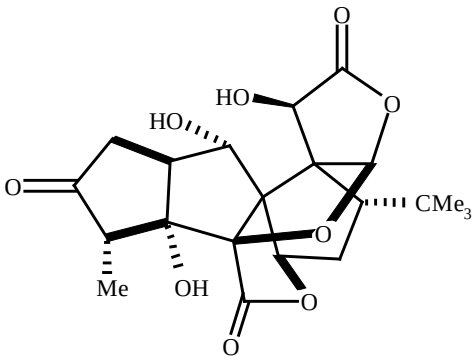
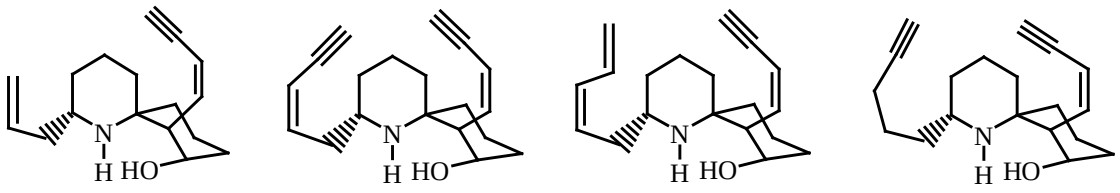


Figure 3. *Ginkgolide B*

(–)-Histrionicotoxin

The first members of unusual spiropiperidine-containing alkaloids, isolated from the brightly colored poison-dart frog *Dendrobates histrionicus* found in South American countries[13] is (–)-Histrionicotoxin (HTX). (–)-Histrionicotoxin and its analogues, aza spirocyclic alkaloids have paying attention to pharmacological interest as noncompetitive inhibitors of the nicotinic acetylcholine receptor and as probes to study neuromuscular signal transmission (Fig. 4) [14,15]

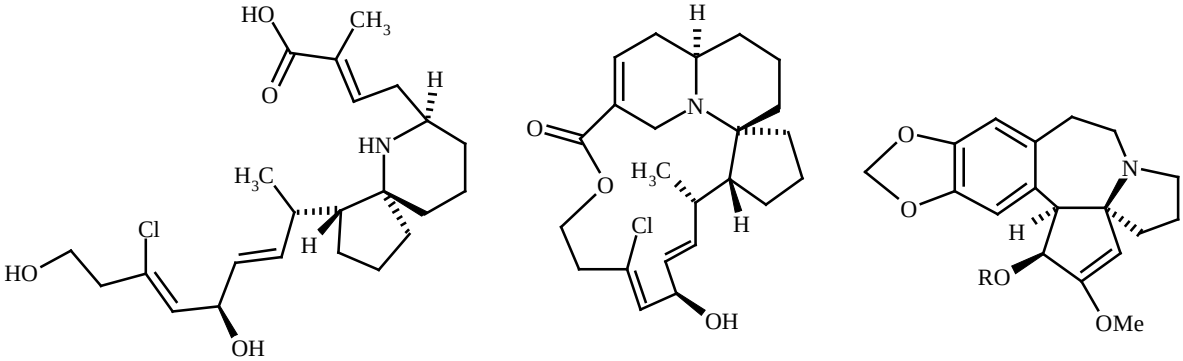


HTX 259A **5** | HTX | HTX 285E **6** | HTX 285C **7**

Figure 4: *Alkaloids containing azaspirocyclic ring system*

Pinnaic acid, Halichlorine and Cephalotaxine

Pinnaic acid, isolated from the Okinawan bivalic *Pinna muricata*, exhibits inhibitory activity against phospholipase A2.[16] Halichlorine, produced by the marine sponge *Halichondria okadai*, was found to inhibit the vascular cell adhesion molecule-1 (VCAM-1).[17] Cephalotaxine, the major alkaloid of *Cephalotaxus harringtonia* var. *drupacea*, and its esters (harringtonines) show high antileukaemic activity (Fig. 5).

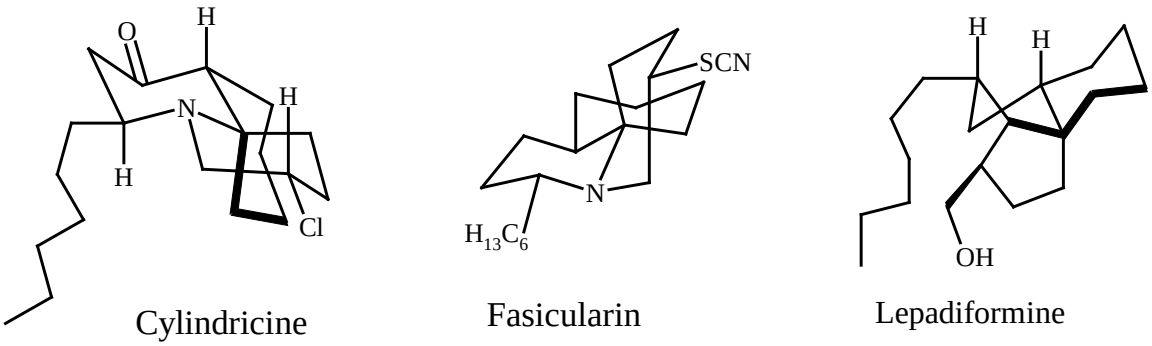


Pinnaic acid Halichlorine R= H, (-) Cephalotaxine

Figure 5: *Alkaloids containing azaspirocyclic ring system*

Fasicularin

Fasicularin was recently isolated from a marine invertebrate, the ascidian *Nephteis fasicularis* and is quite similar to that of cylindricine B and lepadiformine which have been isolated from the ascidians *Clavelina cylindrica* and *C. lepadiformis*, respectively. The compound was discovered using a yeast strain in which the RAD 52 gene had been deleted, thus rendering the organism incapable of recombination and repair of DNA double strand breaks (Fig 6).[18]



Cylindricine Fasicularin Lepadiformine

Figure 6: *Alkaloids containing azaspirocyclic ring system*

Our endeavor was to synthesize the aza-spirobicyclic compound (–)-Histrionicotoxin 235A as a part of our research programme.

Historical background of Histrionicotoxin

In 1823, a western traveler by the name of Captain Charles Stuart Cochrane reported on his expeditions around the lowland tropical rain forests of Colombia. He encountered tribes of native Indians who used poisoned arrows and blowgun darts for hunting. Eventually, he discovered that the poison had been extracted from small brightly colored frogs. One of these poisons is called histrionicotoxin, named after the subspecies from which it is extracted, *Dendrobates*[19] *histrionicus*. Histrionicotoxin, is a spirocyclic piperidine, and is one of a family of eleven compounds, which differ in their side-chains. Some exhibit acetylenic functionality (as in histrionicotoxin-HTX- itself), and others have allenic side-chains or saturated side-chains (perhydrohistrionicotoxin). The spirocyclic core of the HTX family is unique in the world of natural products and has therefore the subject of much study in the chemical community. The *cis*-enyne moiety is also a very unusual feature in the natural product kingdom. The closest that nature comes to producing this type of unsaturation is in the bacterium-derived compounds known as ene diynes, including such antibiotics as calicheamicin, and also the neocarzinostatins, esperamicins. The toxins that have been isolated originate from small glands on the backs of the frogs, which were originally thought to produce, and then store the poison. Interestingly, when the frogs are kept in captivity, the levels of the toxins that they produce are severely diminished, and in most species it is not produced at all. This has led to the assertion nowadays that the toxins are somehow introduced into the frog *via* diet or by some other outside influence.

Biological Aspects

A. High-affinity and selectivity of neosurugatoxin for the inhibition of ^{22}Na influx *via* nicotinic receptor-ion channel in cultured bovine adrenal medullary cells: Comparative study with histrionicotoxin:[20]

In cultured bovine adrenal medullary cells, neosurugatoxin and histrionicotoxin inhibited carbachol-induced influx of ^{22}Na, ^{45}Ca and secretion of catecholamines with IC_{50} of 27 nM and 3 μM, respectively. The inhibitory effects of neosurugatoxin were reversed by the increased concentrations of carbachol, whereas those of histrionicotoxin were not. Histrionicotoxin at concentrations higher than 10 μM also reduced veratridine-induced influx of ^{22}Na, ^{45}Ca and secretion of catecholamines, while neosurugatoxin had no effects. High K-induced ^{45}Ca influx and catecholamine secretion were not altered by either neosurugatoxin or histrionicotoxin.

The present findings suggest (1)[21] neosurugatoxin competitively inhibits nicotinic receptor-ion channel complex at nanomolar concentrations, but has no effects on voltage-dependent Na channel and voltage-dependent Ca channel; (2) histrionicotoxin at micromolar concentrations non-competitively suppresses nicotinic receptor-ion channel complex. Higher concentrations of histrionicotoxin also interferes with voltage-dependent Na channel, but has no effect on voltage-dependent Ca channel; (3) neosurugatoxin, due to its high-affinity and selectivity, may be a useful probe for studying nicotinic receptors in nervous tissues.

B. Effects of histrionicotoxin derivatives on ion channels and acetylcholine receptor-channel complexes in bullfrog sympathetic ganglia.[22]

1. Four synthetic histrionicotoxin derivatives (H_8^-, H_{12}^-, $C_4H_{10}^-$ and $C_5H_{10}^-$HTX) were applied to bullfrog *(Rana catesbeiana)* sympathetic ganglia and their effects were compared electrophysiologically.

2. The derivatives (60–100μM) blocked both acetylcholine receptor-channel complex (ACh RC complex) and Na^+ channel to cause a transmission failure. They also blocked K^+ and Ca^{2+} channels.

3. Although all 4 derivatives exhibited similar effects, their potencies on respective ionic channels differed from one another.

4. Two types of (presumably subsynaptic and extrasynaptic) ACh RC complexes in ganglion cells were distinguished based on their differential sensitivities to HTX derivatives.

C. HTX has very similar spatial arrangements to the neurotransmitter acetylcholine. The distance between the nitrogen and the hydroxyl groups in both acetylcholine and HTX is approximately 2.7 angstroms. It is due to this similarity that the toxin can affect the nervous system binding sites for exogenous and endogenous non-competitive inhibitors of the nicotinic acetylcholine receptor.[23]

The histrionicotoxins have been shown to be potent nicotinic non-competitive antagonists. This means that HTX acts as a ligand that antagonises the response to acetylcholine without actually blocking the binding sites of acetylcholine. The toxin has the ability to block the channel associated with the protein-bound acetylcholine receptor known as the IMRC (ionic conductance modulator receptor complex). Nicotinic acetylcholine receptors (AChRs) are a family of transmembrane glycoproteins including both the muscle-type and the neuronal-type AChR. Both AChR subtypes share several structural and functional properties with other ligand-gated ionchannel receptors, namely the Q-aminobutyric acid (GABAA and GABAC type), the glycine, and the 5-hydroxytryptamine (5-HT3 type) receptor. The neurotransmitter-gated ion channel superfamily has physiological importance since all their members play pivotal roles in fast synaptic transmission throughout both the central and the peripheral nervous system.

D. Unlike the highly toxic batrachotoxins (also derived frogs), HTX shows a fairly low toxicity level in mammals. An administered dose of 5-10 mg/Kg in mice only induces slight locomotive difficulties and prostration. Although the molecule has a low toxicity level, it does draw particular biological interest due to its excellent selectivity for the nicotinic acetylcholine receptor.

E. Role of local anesthetics on both cholinergic and serotonergic ionotropic receptors:[24]

The effects of three local anesthetics and histrionicotoxin on the equilibrium and kinetic properties of carbamoylcholine binding to IAS-labeled membrane fragments are different. Incubation of the membrane-bound receptor with high concentrations of local anesthetic led to an apparent simplification of the agonist binding kinetics, and the results can be

interpreted in terms of a common model. H12-HTX, however, at saturating concentrations, did not significantly perturb the carb binding kinetics and therefore acts in this system in a much different way from any of the local anesthetics examined.

F. Histrionicotoxin, decreased the amplitude and time-course of the endplate current, and altered the voltage dependence of the half-decay time. In addition, the toxin produced a characteristic nonlinearity in the current-voltage relationship of the endplate current when 3-s voltage conditioning steps were used.[25]

Synthetic Methodologies

Stereoselective methodologies in constructing the spirocenter[26] have allowed for the total syntheses of many spirocenter containing natural compounds over the years.

The construction of the spirocycles can be roughly categorized into alkylation, rearrangement, cycloaddition and cleavage of bridged systems. The intramolecular alkylation on the quaternary carbon is one of the most common methods in constructing spirocenters. The alkylation can either take place as a direct substitution or as a 1,4-addition (Fig. 7).

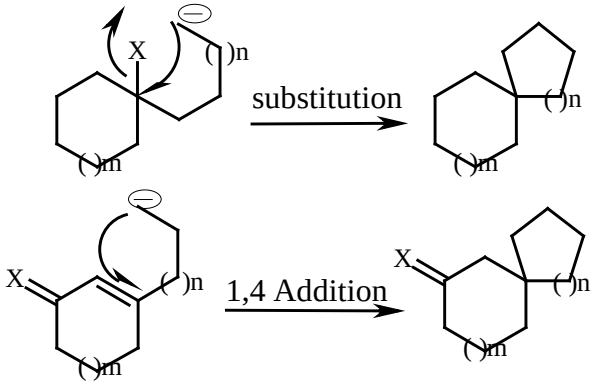


Figure 7. *Alkylation method*

Vinylcyclopropanol/ vinylcyclobutanol rearrangement

Iwata[27] have reported the stereoselective synthesis of spiro[5.5]undecane systems using Lewis acid promoted spiroannulation of *bis*-acetals. Ficini[28] have synthesized the acoradiene by tandem reaction involving yamine. Spiroannulation *via* intermolecular 1,4 addition has also been shown for the synthesis of the core structure of alkaloid Manzamine

A.[29] Rearrangement reactions have found wide application in the synthesis of spirocenters, due to their ability to form multiple stereocenters in one step. For example, a vinylcyclopropanol/ vinylcyclobutanol rearrangement (Fig. 8) [30,31] have been reported for the synthesis of spirocycles by Trost.

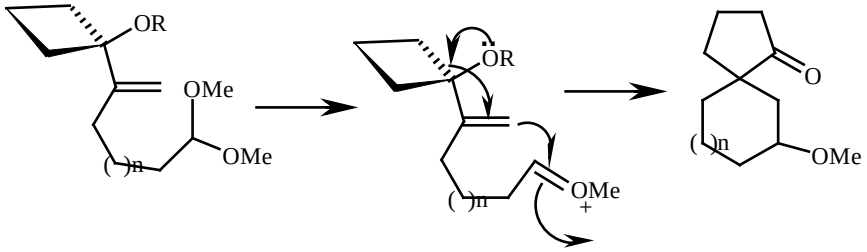


Figure 8. *Vinylcyclopropane/ vinylcyclobutane Rearrangement*

Prins - Pinacol rearrangement

Spiro systems containing medium to large-size rings with controlled stereochemistry have been successfully synthesized using Prins-Pinacol rearrangement where the diastereoselectivity is explained by an extended transition state,[32] analogous to the enolates. The combination of Prins cyclization followed by Pinacol rearrangement, which has been used in the synthesis of five-membered rings,[33] has also been applied to the synthesis of spiro[4.5]decan-5-ones by Overman and co-workers[34] (Fig. 9).

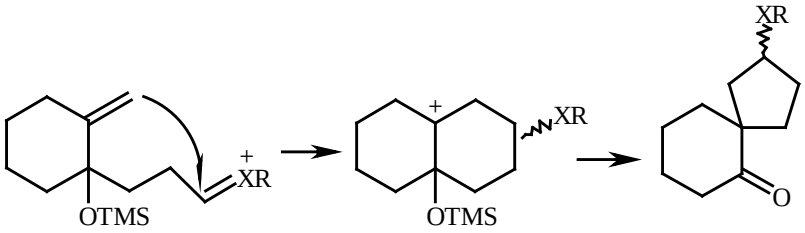


Figure 9. *Prins-Pinacol Spiroannulation*

Cope-like divinylpropanerearrangement

A radical cyclization[35] was used to construct the spiro-oxindole center of the gelsemine by Overman. In the same year, Speckamp's lab[36] published another total synthesis of gelsemine with improved stereoselectivity during the formation of key spiro-oxindole compound through an intramolecular Heck reaction.[37] The only synthesis with complete

control over the formation of spiro-oxindole center was achieved by Fukuyama's lab (Fig. 8).[38] The Spirocenter was constructed in the early stage of the synthesis through a Cope-like divinylpropanerearrangement (Fig. 10).[39]

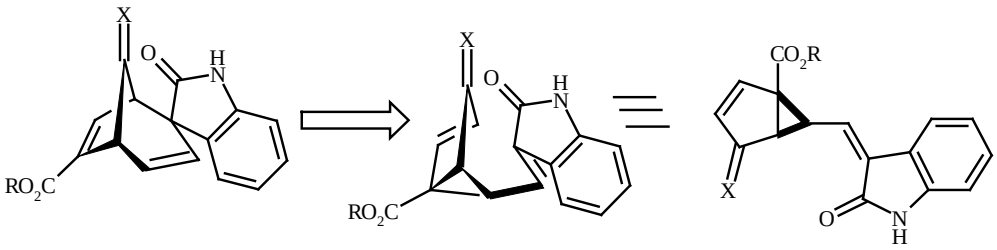


Figure 10. *Fukuyama's Retrosynthesis of Gelsemine*

Asymmetric [1,3]-dipolar cycloaddition

Danishefsky *et al.* have synthesized the key spiro-oxindole center of Spirotryprostatin A *via* a Pinacole-type rearrangement.[40,41] Williams was successful in synthesizing both the antipodes of spirotryprostatin B by forming the core pyrrolidine ring through an asymmetric [1,3]-dipolar cycloaddition. In another recent synthesis of spirotryprostatin B, Overman[42] successfully utilized an asymmetric Heck insertion followed by trapping of allylpalladium intermediate by nitrogen nucleophiles (Fig. 11).

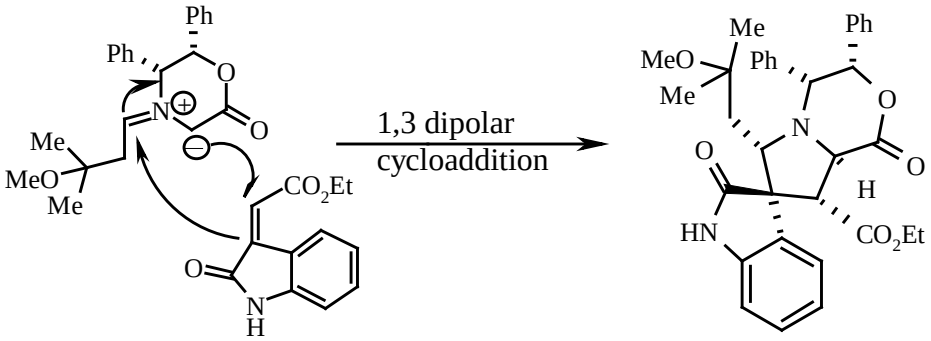


Figure 11. *Spiroannulation*

Ginkgolide B

This complex structure of Ginkgolide B, possessing six rings, eleven stereogenic centers, ten oxygenated carbons, and four contiguous fully substituted carbons, including a spirocenter have fascinated toward the total synthesis[43,44] of.this molecule. Corey synthesized the Ginkgolide B, using intramolecular alkylation of acetal. Crimmins and co-

workers approach to the formation of spirocenter is an intramolecular [2+2] photocyclization.[45] Some other novel ways have also emerged through the years, such as ring closing metathesis,[46,47] intramolecular condensation,[48] ene reaction and metal catalyzed reactions.[49-51]

Pinnaic acid and halichlorine

The azaspiro core of pinnaic acid, subunit of the marine natural product halichlorine was prepared starting from the known 'Meyers-lactam'. The synthesis involved a B-alkyl-Suzuki coupling followed by a highly stereoselective intramolecular Michael addition and an intramolecular Mannich ring closure[52,53] (Fig.12).

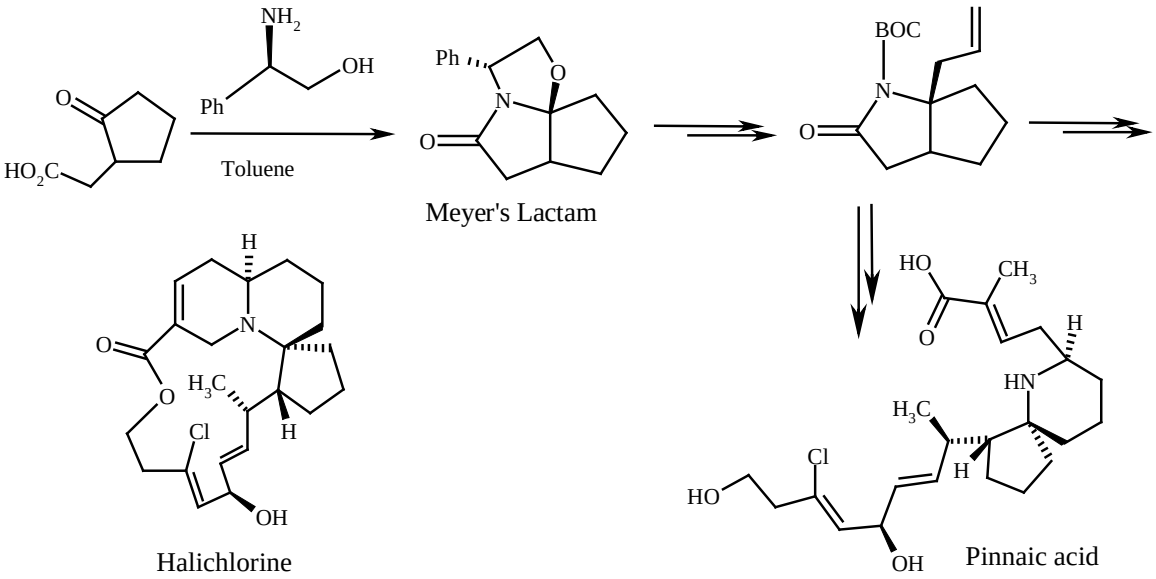


Figure 12: *Suzuki reaction and a stereoselective 1,6 Michael-type cyclization.*

Fasicularin

Dake *et al.*[54] have synthesized complex nitrogen-containing spirocyclic Fasicularin by semi-Pinacol type rearrangement of cyclopentanol containing substrates through epoxide ring expansion by the action of a Bronsted or Lewis acid (Fig. 13).

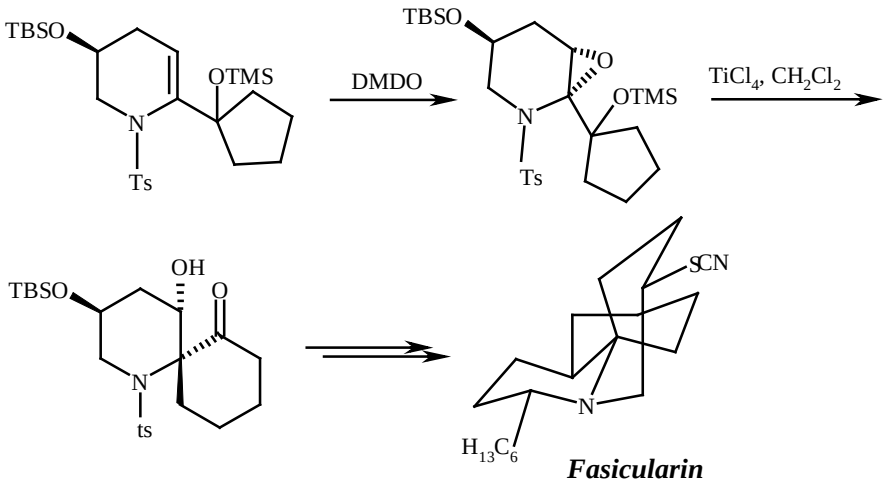


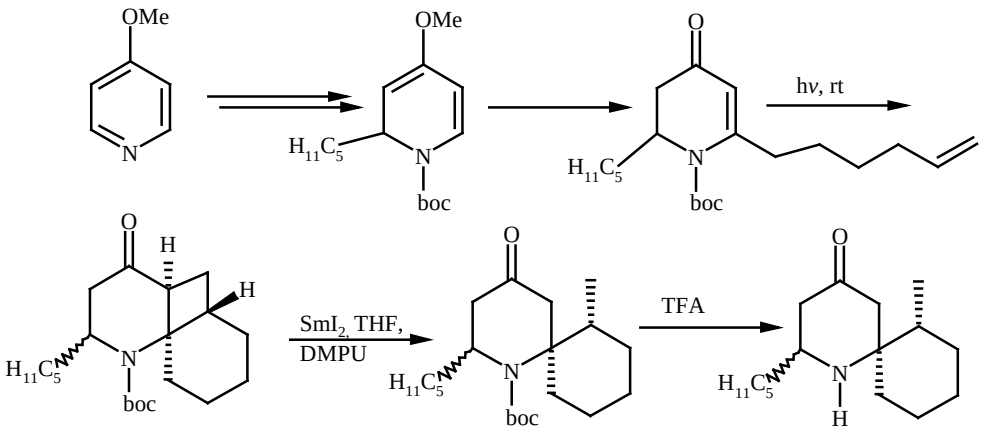
Figure 13: *Semi Pinacol type rearrangement.*

Many synthetic effort toward the synthesis of simpler perhydrohistrionicotoxin have been reported,[55,56,57,58] not only due to its novel spiropiperidine structure but also due to its ever-diminishing supply from the natural sources. Three total[59,60] and one formal[61] syntheses of (–) histrionicotoxin have been reported and two of them targeting the naturally occurring enantiomer. There are also three protocols for synthesis of the [5,5]aza-spirobicyclic system.[62] Some of the previous synthesis of saturated and unsaturated histrionicotoxins are discussed below.

Comins Approach[55]

Comins *et al*. have synthesized aza spiro ring system of perhydrohistrionicotoxin by using intramolecular photocycloaddition of 2,3-dihydro-4-pyridone and a SmI_2 mediated cyclobutane ring opening as key step (Scheme 1)

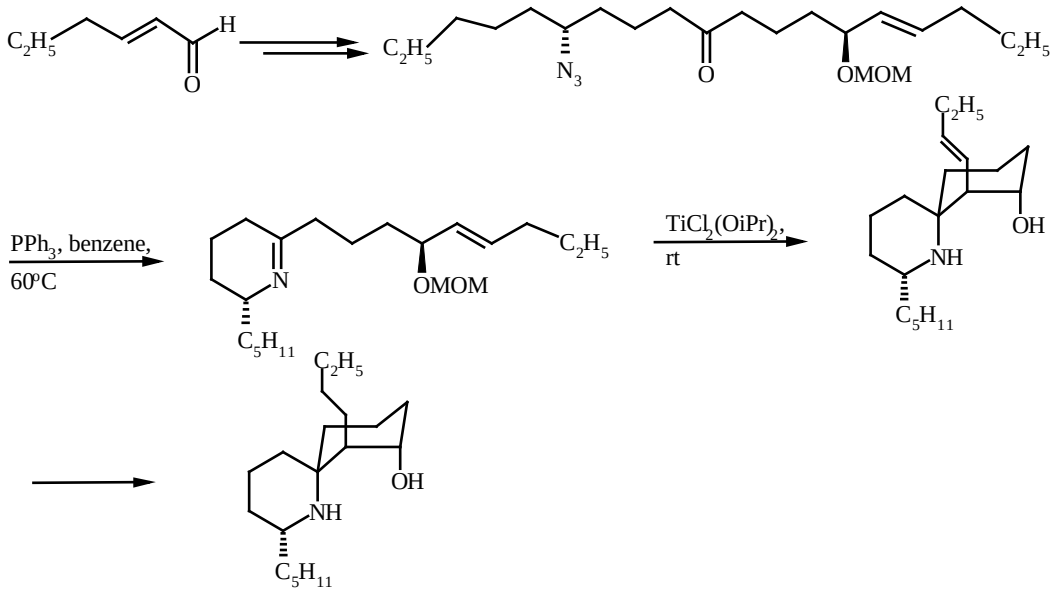
Scheme 1



Tanner Approach [57]

Tanner *et al.* in 1998 have reported the perhydrohistrionicotoxin synthesis. There they used Lewis acid mediated intramolecular imine-ene-type reaction for the key spirocyclic ring (scheme 2).

Scheme 2

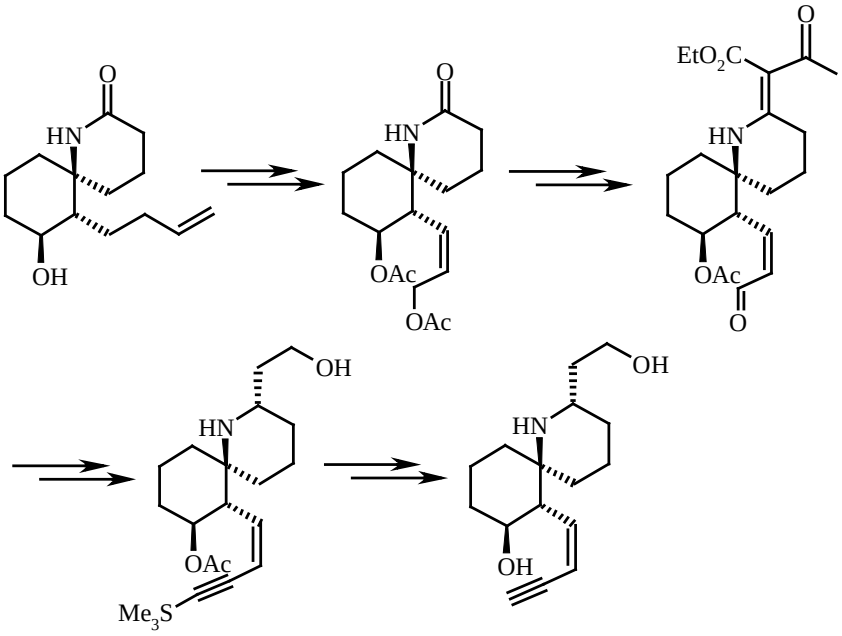


Kishi's Approach[58]

Kishi's route started with an advanced intermediate, which he utilized for his previous synthesis of octahydro-HTX. Unfortunately, it was found that simultaneous introduction of

the two side-chains was not possible, and therefore a stepwise approach was undertaken for installing these chains individually (Scheme 3).

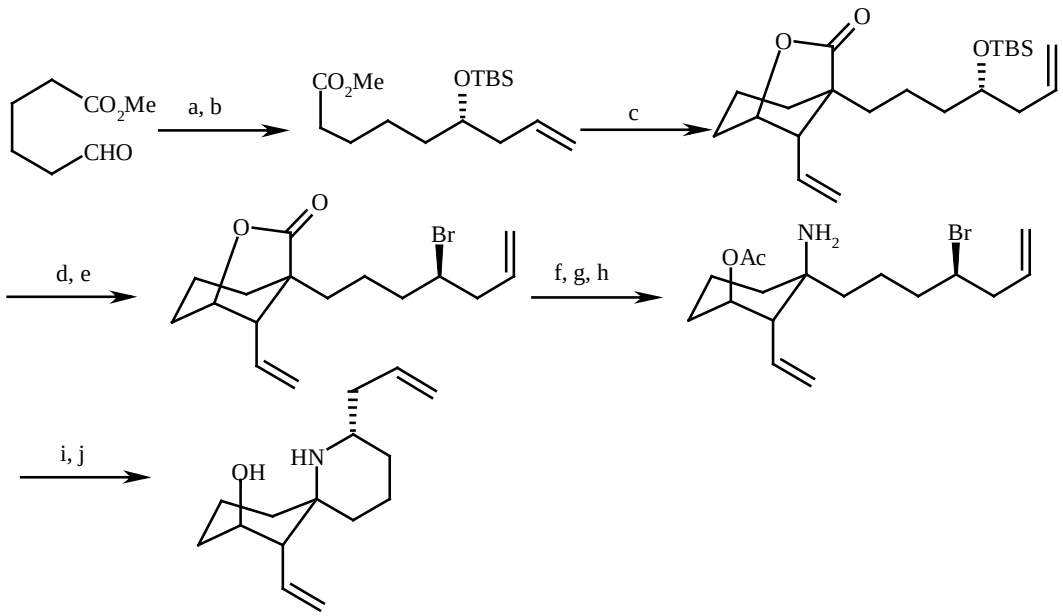
Scheme 3



Stork Approach[59]

Five years after Kishi's total synthesis, the Stork group published their work on the first asymmetric synthesis of (–)-HTX. In this elegant synthesis, new methodology was developed specifically with a view to installing the *cis*-enyne side-chains. Stork also previously used in his group for the creation of the quaternary center in a stereoselective fashion (Scheme 4).

Scheme 4

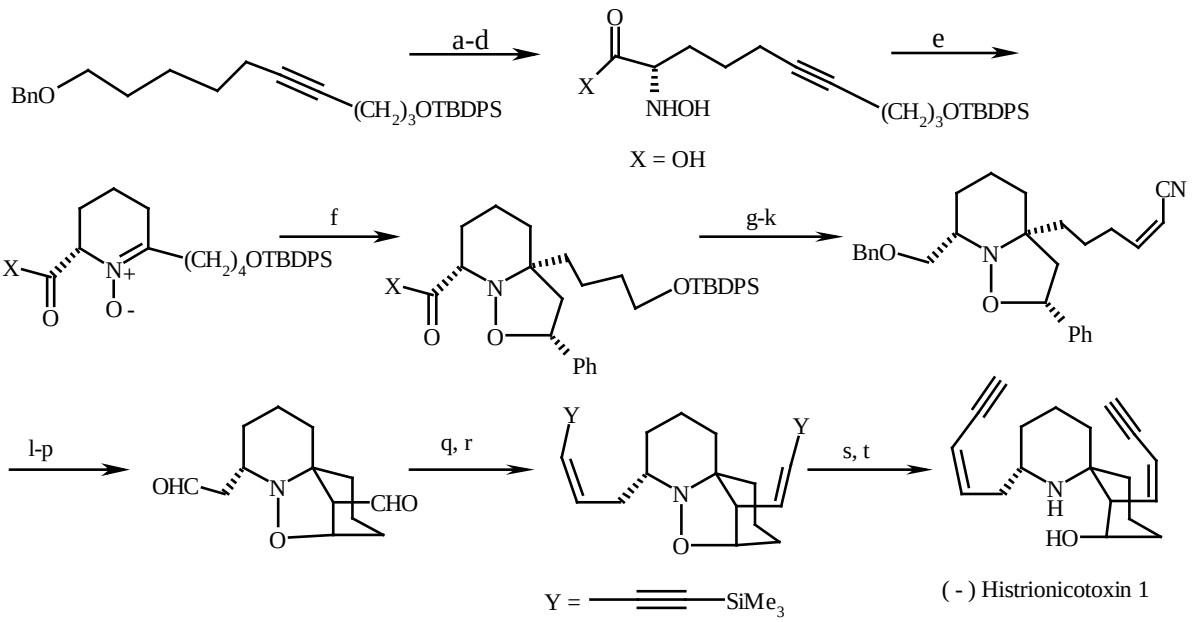


Reagents and conditions: a) –78 °C to rt, B-allyldiisopinocampheylborane, 2 h; (b) *t*-$BuMe_2SiC1$, imidazole, CH_2C1_2, cat. DMAP, 2 days; (c) LDA, HMPA/THF (6:11 v/v), trans-(2*S*,3*S*)-3-(3-bromopropyl)-2-ethenyloxirane, –78 °C to rt, 40 min, then LDA, –78 °C to rt, 2 h; (d) 5% HCI, THF, 12 h; (e) Ph_3P, CBr_4, ether, 2 h; (f) NH_4CI, AlMe,, PhH, 50 °C, 40 h; (g) Ac_2O, Py, DMAP; (h) $(CF_3CO_2)_2$1Ph, CH_3CN, H_2O, 3 days; (i) Et_3N, CICH,CH,CI, 65-70 °C, 2 h; j) MeOH, aqueous Na_2CO_3, 24 h.

Holmes Approach[60]

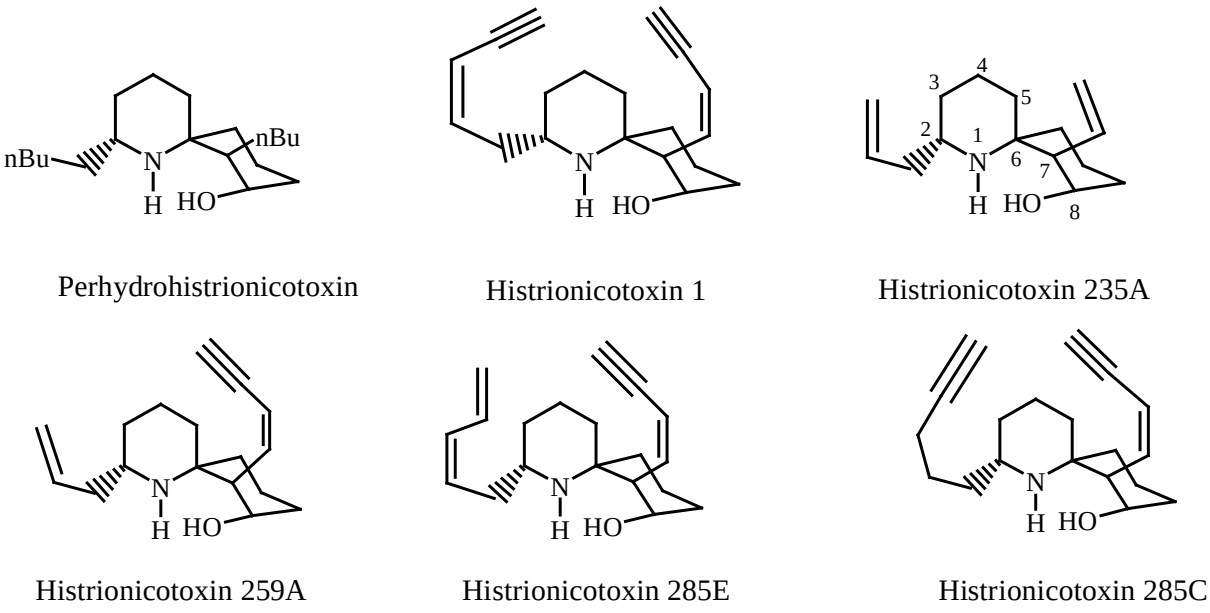
A recently published total synthesis of (–)-histrionicotoxin by Holmes and co-workers formed the spiropiperidine core from a [3+2] cycloaddition, followed by an amine-alkyne cyclisation and cleavage of the strained N-O bond (scheme 5).

Scheme 5



Reagents and conditions: (a) BCl_3.DMS, CH_2Cl_2; (b) Jones reagent, acetone; (c) NEt_3, pivaloyl chloride, 0 °C, (1*R*)-(+)-10,2-camphorsultam, *n*-BuLi, THF, –78 °C; (d) $NaN(TMS)_2$, 1-chloro-1-nitrosocyclohexane, THF, HCl (aq); (e) toluene, 80 °C, 6 h; (f) styrene, 75 °C; (g) $LiAlH_4$, THF, 0 °C; (h) NaH, BnBr, THF; (i) HF, CH_3CN; (j) TPAP, NMO, 4 Å sieves; (k) Me_3SiCH_2CN, *n*-BuLi, THF, –78 °C, $B(O^iPr)$; (l) toluene, sealed tube, 190 °C, 3.5 h; (m) BCl_3.DMS, CH_2Cl_2; (n) MsCl, NEt_3, DMAP, CH_2Cl_2; (o) NaCN, DMSO, 4 Å sieves, 55 °C; (p) DIBAL-H, toluene, –78 °C; (q) $KN(TMS)_2$, $[Ph_3PCH_2I]^+I^-$, THF, –78 °C; (r) $Pd(PPh_3)_4$, CuI, Et_2NH, Me_3Si-C≡CH; (s) Zn, AcOH, 30 min; (t) K_2CO_3, MeOH.

Histrionicotoxins, the archetype of a group of spiropiperidine-containing alkaloids from the brightly coloured poison arrow frog *Dendrobates histronicus* native to the Amazon rain forests of Southern Columbia was first isolated by Daly, Witkop and co-workers in 1971.[6] They all share a common 1-azaspiro[5.5]undecan-8-ol ring system with unsaturated C4 or C5 side chains at both the 2 and 7 positions with three group at three chiral center are in axial position but they are stable due to NH-OH hydrogen bond. The nature and length of the side chains distinguish the different members of the histrionicotoxin family (Fig. 14).



Perhydrohistrionicotoxin | Histrionicotoxin 1 | Histrionicotoxin 235A

Histrionicotoxin 259A | Histrionicotoxin 285E | Histrionicotoxin 285C

Figure 14: *The novel spiropiperidine-containing alkaloids*

They have been shown to be potent non-competitive blockers of neuromuscular, ganglionic and central neuronal nicotinic channels, but as yet, the specific effect of the side chain functionalities on their activity has been the subject of only limited study. Protection of *Dendrobates* sp. has restricted the supply of natural material making synthetic routes greater in demand.

Retrosynthetic analysis of Histrionicotoxin 235A

Our intended strategy for histrionicotoxin 235A is based upon a Chiron[63] approach from D (+)-glucose, a strategy that so far has never been employed in the synthesis of this type compound of enduring interest. The crux of our strategy will be the construction of the key 1-azaspiro[5,5]undecane ring system and introduction of C-1 to C-4 moiety in one go and thus creating considerable flexibility in making analogues for future endeavors. The retrosynthetic analysis is shown in Figure15.

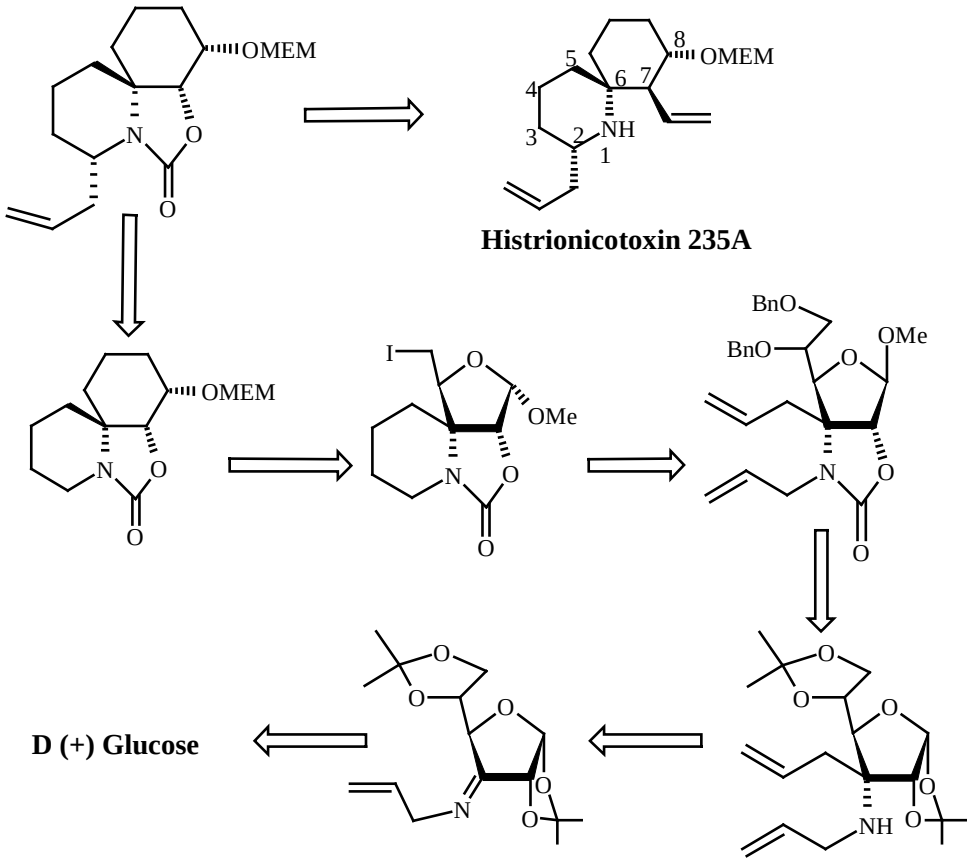


Figure 15. *Retrosynthetic strategy for the synthesis of histrionicotoxin 235A*

Our approach consists two ring closing methathesis reactions to construct the two key rings i.e. piperidine and cyclohexane. The stereo-controlled construction of the piperidine ring systems will be addressed *via* addition of allyl lithium to imine derived from the 1,2-*O*-isopropylidine-3-ulose derivative and allyl amine followed by RCM. After selective functional group transformations, a zinc-mediated domino elimination–allylation of the

derived methyl 5-iodopentofuranoside to yield diallyl system, which will be then subjected for RCM to furnish carbocyclic ring system. Two other functional groups with required special disposition will be appended by a nucleophilic substitution with allyl lithium and an electrophilic addition of cyanide and subsequent transformations.

Formation of quaternary center

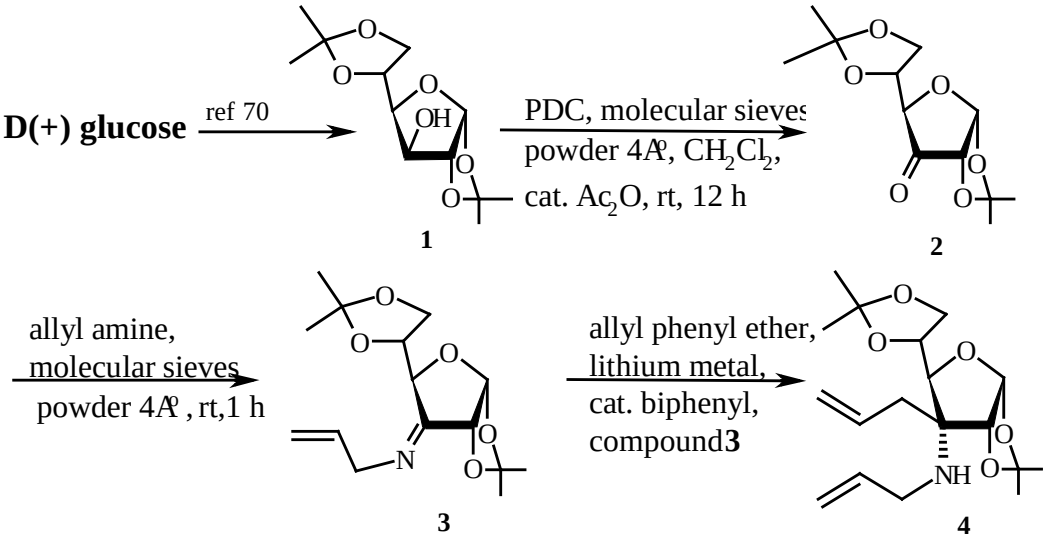
The first issue to be resolved in our strategy will be the formation of quaternary center containing nitrogen involving allylation on an imine derived from 1,2:5,6-di-*O*-isopropylidine-*ribo*-hexofuranos-3-ulose (**2**). Addition of organometallics to imines is a potentially valuable method for the preparation of secondary amines. However, these reactions have typically been plagued by competitive enolization, reduction, and bimolecular coupling reactions caused by the relatively poor electrophilicity of the imine carbon and the competing loss of a α-proton. Due to the attractiveness of organometallic compounds several different methods have been employed in an attempt to circumvent these problems.

A large portion of these efforts has focused on allylation using a variety of allyl-metal reagents.[64] Addition of allylic organometallic species to the imine function and its derivatives constitute a potentially valuable method for the preparation of homoallyl amines. Significant advances in the Barbier-type imine allylation have been developed in recent years.[65] The metals being used include In, $CrCl_2/BF_3.OEt_2$, Ta, Bi/Bu_4NBr, $Al/TiCl_4$ (cat.), Al, $Zn/PbCl_2$, and $Al/PbBr_2$ (cat.)/$BF_3.OEt_2$, and the imines are mainly limited to aryl aldimines,[66] other imines are fraught with low reactivity. On the other hand, the most reactive and readily made allylic organometallic of lithium, magnesium, and zinc add to imines, which are derived from nonenolizable or alpha-alkyl substituted aliphatic aldehydes. Reformatsky reagents,[67] Grignard reagents, higher order cuprates,[68] zinc-copper reagents and dialkyl zinc[69] have been also utilized with limited success.

Our synthesis started with D(+)-glucose which was converted to the glucose-diacetonide derivative (**1**) with acetone in presence of $CuSO_4$ and catalytic H_2SO_4.[70] The 3-hydroxy group was oxidized[71] with PDC in CH_2Cl_2 in the presence of powder molecular sieves and catalytic acetic anhydride to give the 3-ulose derivative (**2**). The allyl imine derivative (**3**)[72] of **2** was formed by treating with allyl amine in presence of anhydrous

sodium sulfate at rt for 1 h. The ^{1}H NMR and ^{13}C NMR spectra of **3** were in agreement with the assigned structure. In the ^{1}H NMR spectrum of **3**, *N*-allylic protons appeared at 3.96 ppm (J = 7.1, 7.9 Hz) and 4.03 ppm (J = 7.1, 8.3 Hz) as a doublet of doublet, olefinic protons at 5.12 ppm (ddd, 1 H, J = 1.9, 3.4, 17.4 Hz), 5.25 ppm (ddd, 1 H, J = 1.9, 2.9, 10.1 Hz) and 5.88 ppm (m, 1 H) while the anomeric proton was located at 6.03 ppm (d, J = 4.8 Hz). In the ^{13}C NMR spectrum the peaks due to imine group appeared at 170.6 ppm and olefinic carbons at 115.4 and 134.9 ppm. The proposed allylation of imine **3** was carried out using allyl lithium[73] at 0 ^{o}C which gave exclusively one diastereomer **4** (Scheme 5). The stereochemical outcome of this reaction can be explained by the preferential attack of allyl anion from the β-face due to the steric hindrance imparted by the 1,2-acetonide group.[63] The structure was confirmed by the ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data. The ^{1}H NMR spectrum of compound **4** showed a characteristic signal from internal olefin protons between 5.82-6.09 ppm as multiplets while terminal olefinic protons appeared between 5.01-5.22 ppm. In addition, a doublet due to H-1 was observed at 5.51 ppm (J = 3.0 Hz). The signals due to *N*-allyl group appeared as a doublet of a doublet of a triplet at 3.26 ppm (J = 2.3, 5.4, 14.7 Hz), 3.49 ppm (J = 2.3, 6.2, 12.0 Hz), the *C*-allyl group indicated as doublets of a doublet at 2.18 ppm (J = 6.8, 1.2 Hz) and at 2.46 ppm (J = 6.8, 0.9 Hz). The resonances for the other protons were in accord with the proposed structure **4**. After having addressed the construction of the key quaternary center with an amine functional group, now the objective was set to examine the RCM reaction in order to build the piperidine ring system.

Scheme 5



A brief overview on the olefin metathesis (RCM)

RCM is a very successful method for making of cyclic compound.[74] The fundamental discovery by Karl Ziegler[75] is that catalysts formed in situ from certain transition metal salts and main group alkylating agents promote the polymerization of olefins under unprecedentedly mild conditions has had a tremendous impact on chemical research as well as on industrial production. Early on it was discovered that some Ziegler-type catalysts do not only lead to the addition polymerization of olefins, but can also effect a mechanistically entirely different process, that is, the mutual alkylidene exchange reaction of alkenes. So what is metathesis? The dictionary definition is "the interchange of atoms or groups of atoms between two molecules. This process has become synthetically useful since the discovery, over the last 10 years, of various well-defined transition metal carbene complexes, which catalyze alkene metathesis. One of the most widely used of these is Grubbs' catalyst. The classic alkene metathesis reaction in synthesis is ring closing

metathesis, illustrated below together with the accepted mechanism for the catalysed reaction.

However, alkene metathesis has rather wider applications than just in ring closure. It has been applied industrially for many years to ring opening metathesis polymerisation (ROMP). For small molecules, alkene-alkyne metathesis, crossed metathesis, and tandem processes such as ring opening followed by crossed metathesis, have found a variety of applications. Some ways in which these can be used are illustrated below.

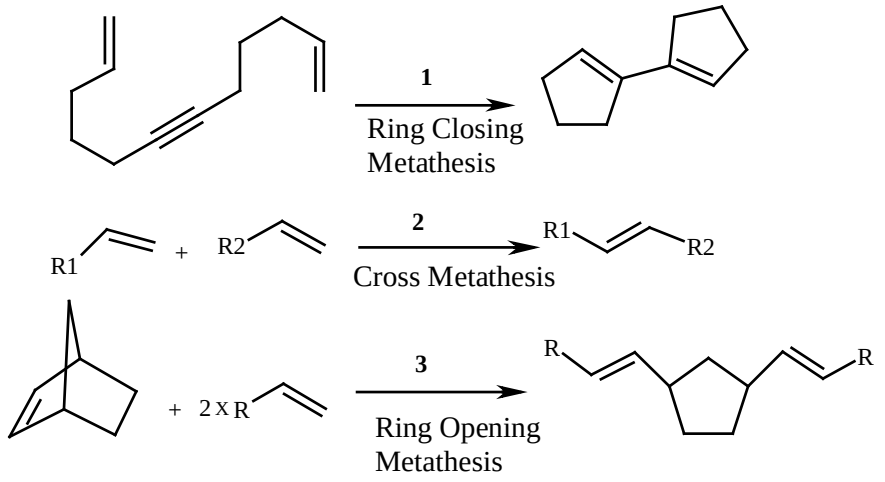


Figure 16. *Three classic alkene metathesis*

The discovery of metal alkylidene complexes, followed by the insight that some species of this type constitute well-behaved single-component catalysts for olefin metathesis, gave the essential clue for settling the long lasting debate on the actual mechanism of this transformation (Chauvin mechanism) and has triggered the development of a new generation of high performance, reasonably stable, and most importantly exceedingly tolerant catalysts or catalyst precursors (Fig. 17).

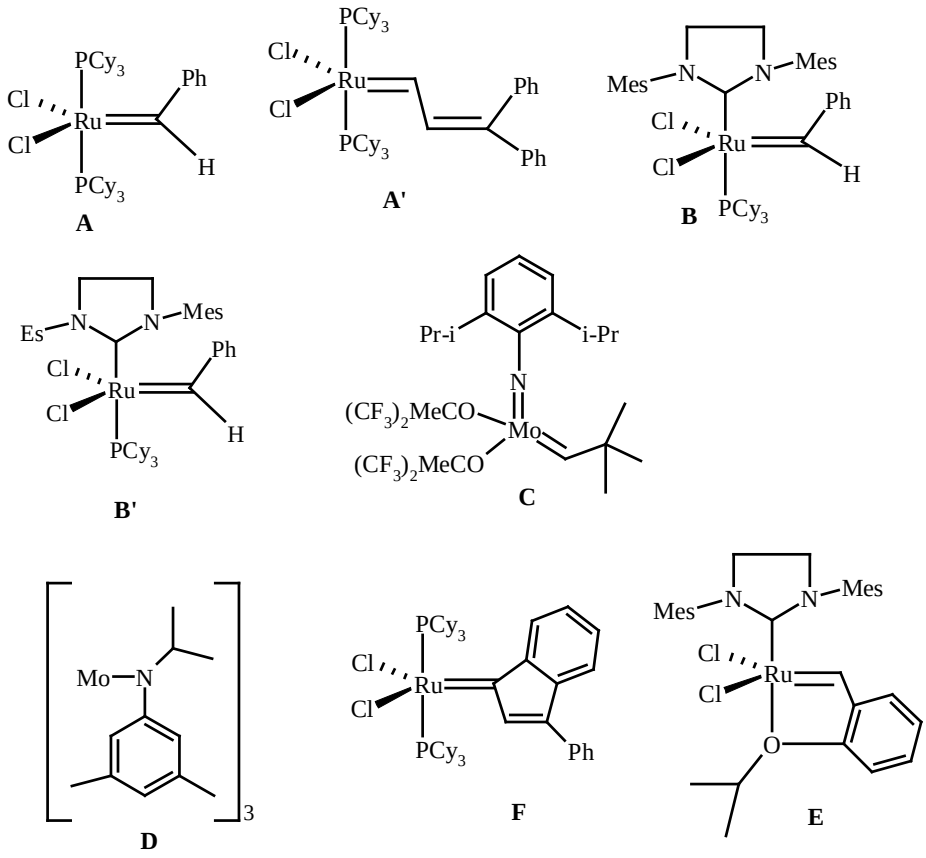


Figure 17: *Catalysts for olefin metathesis*

Figure 17 depicts some of these catalysts (or precatalysts that convert into metal alkylidenes in situ), among which the tungsten or molybdenum alkylidene complexes ***C*** *developed by Schrock and co-workers and the ruthenium carbene complexes* ***A*** *introduced by Grubbs and co-workers are undoubtedly the most popular and versatile ones. Both reagents are now commercially available. The generally accepted mechanism of metathesis reactions (Chauvin mechanism) consists of a sequence of formal [2+2] cycloadditions/cycloreversions involving alkenes, metal carbenes, and metallacyclobutane intermediates (for possible exceptions, since all individual steps of the catalytic cycle are reversible, an equilibrium mixture of olefins is obtained). Therefore, it is necessary to shift this equilibrium in one direction in order to make metathesis productive in preparative terms. The mechanism of one such application, the ring-closing metathesis (RCM) of a diene, is shown in Fig. 18. In this particular case, the forward process is entropically driven*

because RCM cuts one substrate molecule into two products. If one of them is volatile (ethene, propene, etc.) the desired cycloalkene will accumulate in the reaction mixture.

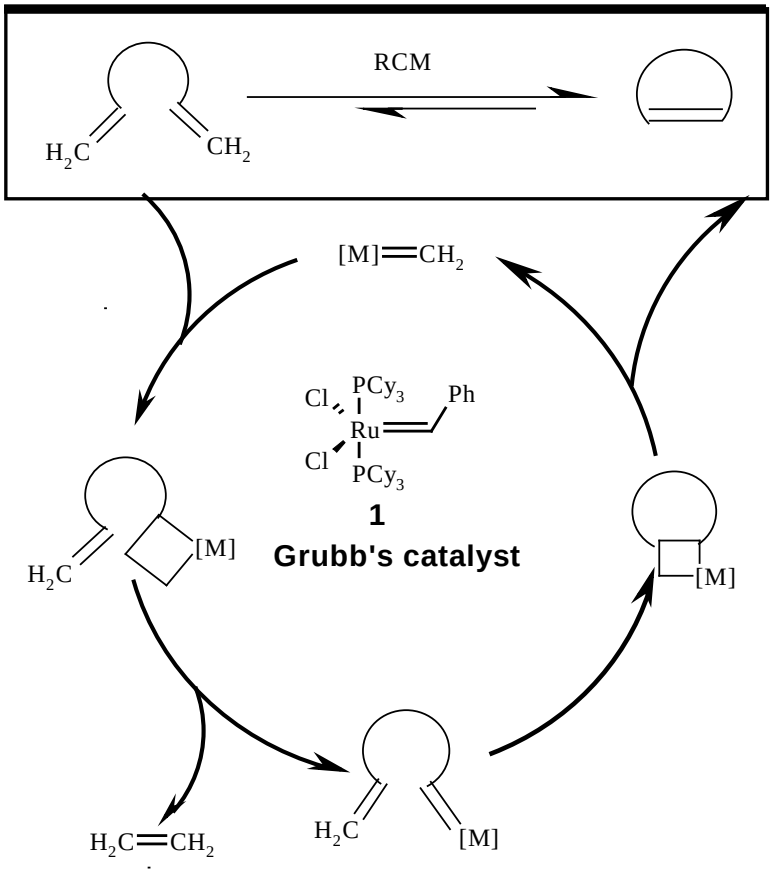


Figure 18: *Mechanism of ring closing metathesis*

Our initial attempts consisting the RCM reaction of the diene derivative (**4**) with Grubbs' catalyst was very low yielding (**5**, <5%) and most of the starting material was recovered. Anticipating an inactivation of the catalyst because of the amine, we planned to protect the secondary amine with either Boc or Cbz groups. Surprisingly, under several conditions attempted, protection of **4** with either Boc_2O or CbzCl was found to be sluggish and resulted only with the recovery of starting material. The difficulties encounter during the protection of amine **4** were attributed to the steric crowding.

Having met with difficulties either to conduct RCM or to protect the amine (**4**), we had modify our strategy. In our new protocol, the construction of piperidine ring has been postponed to an advanced oxalzolidinone intermediate **10**, in which C(2)-O and the C(3)-N

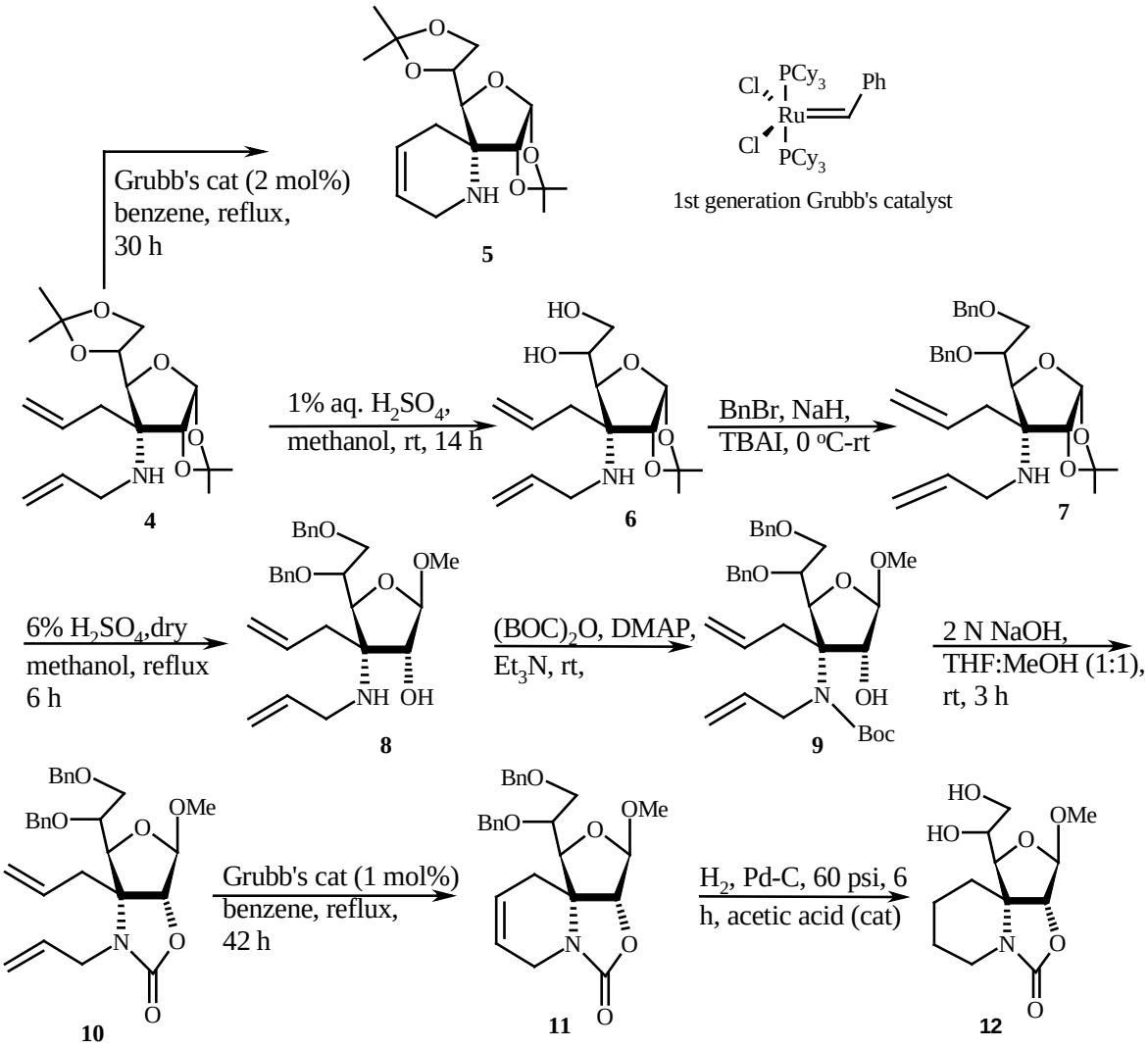
formed the key oxazolidinone ring. This was supposed to resolve both the protection of secondary amine and also the steric crowding around the C(3)-carbon.

In this context, selective deprotection of the 5,6-acetonide group of **4** was carried out with 1% aq. H_2SO_4 in methanol at rt for 14 h. The resulting diol (**6**) was protected by using NaH, benzyl bromide in THF in presence of cat TBAI to give the dibenzyl ether derivative (**7**). The spectral and analytical data of **7** were in complete agreement with the assigned structure. It is interesting to note that NH group of **6** remained unaffected during benzylation reaction reaction, again due to steric reasons. Deprotection of the 1,2-acetonide group and concomitant methyl glycosidation of **7** was carried out in refluxing 6% methanolic H_2SO_4 for 6 h to give **8**. The structure of β-methyl glycoside derivative (**8**) was established by the ^1H and ^{13}C NMR spectral analysis. The peak due to isopropylidine departed while a singlet at 3.35 ppm due to methoxy group appeared. The anomeric proton of **8** resonated at 4.77 ppm, as a singlet indicating a 1,2-*trans* relationship. While rest of the spectrum was in complete agreement with the assigned structure. In addition, the ^{13}C NMR spectrum and elemental analysis confirmed the structure of **8**. Compound **8** on treatment with $(BOC)_2O$ in CH_2Cl_2 in presence of DMAP at 0 ^oC furnished[76] **9** whose ^1H, ^{13}C NMR spectral data established the structure of **9**. For example, a singlet at 1.47 ppm due to BOC group was observed in it's ^1H NMR spectrum. Compound **9** was converted to the corresponding cyclic carbamate derivative (**10**) by using NaOH in methanol:THF (1:1).[77] The ^1H and ^{13}C NMR, IR spectroscopic studies of **10** revealed the assigned structure.

The cyclic carbamate derivative (**10**) was subjected to RCM reaction using 1st generation Grubbs' catalyst in benzene at 80 ^oC to obtain **11**, which was confirmed by the NMR spectroscopy where characteristic signals of the two terminal olefin proton disappeared, the internal olefin protons resonated at 5.43 ppm as a multiplet.

The next step called for the hydrogenation of double bond present in **11** and successfully accomplished with 10% Pd/C in methanol with cat. acetic acid at 60 psi for 6 h to provide the piperidine ring system (**12**) (Scheme 6). The structure of **12** was supported by its ^1H NMR, ^{13}C NMR and mass spectroscopic data. In the ^1H NMR spectrum of **12**, signals due to H-1 and H-2 appeared at 4.37 and 4.92 ppm as singlets respectively and methylene protons were appeared as a multiplet between 1.49-1.87 ppm. The mass spectrum showed a peak at *m/z* 273 (M^+ +1).

Scheme 6



Carbocyclic ring formation

Our next target was to form carbocyclic ring for this, we envisaged the zinc-mediated domino elimination–alkylation of methyl 5-iodopentofuranoside. Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of molecular complexity.[78] Domino reactions are becoming a very attractive tool in this regard.[79,80] In these processes several bond forming transformations take place under the same reaction conditions, without adding additional reagent, and in which the subsequent reactions are due to the functionality formed in the previous step. The need for synthetic efficiency is particularly acute in the area of carbohydrate chemistry.[81]

Carbohydrates are densely functionalized molecules, and as a result their synthetic application often requires many reaction steps, usually for manipulation of different protecting groups. In particular the conversion of carbohydrates into carbocycles is a major task and has been the subject of many studies because most biologically important molecules and natural products contain a polyhydroxylated five-or six-membered carbocycle (Fig.19). [82, 83]

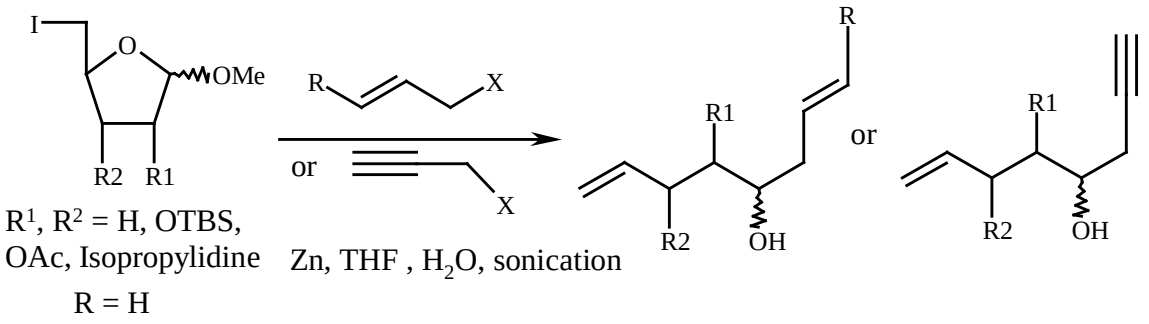


Figure 19: *Domino reaction under sonication*

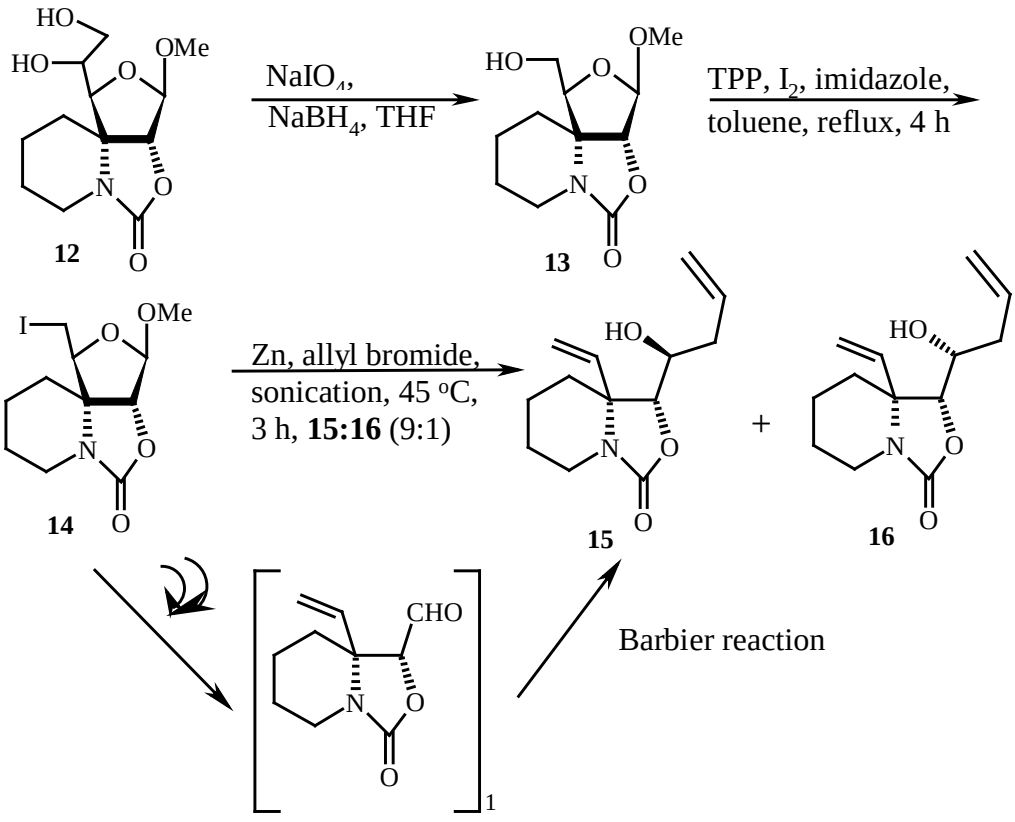
Madsen *et al.* reported the domino reaction that allowed stereocontrolled synthesis of carbohydrate-derived dienes from iodo glycosides in the presence of activated zinc dust [84] and Barbier type[85] reaction with allyl bromide in tetrahydrofuran (THF) under sonication conditions at 40 ^{o}C with high yield. Zinc would then serve a dual function by promoting both the reductive elimination and alkylation i.e a C–C double bond, a C–C single bond fornation in the same pot. There they report no Wurtz coupling of the starting iodofurano-sides,[86] and the conditions were sufficiently mild to prevent the intermediate aldehyde from undergoing side reactions before the allylation. Simple reflux instead of sonication proved less reliable and sometimes caused the reaction to stall, presumably due to precipitation of zinc (II) salts, epimerization and decomposition of the intermediate aldehyde. The solvent was also an important parameter in the domino reaction. The reductive elimination of the iodo glycosides proceeded slowly in THF alone with zinc dust but the THF:H_2O ratio influenced the rate in the sense that more H_2O generally enhanced the rate of the overall transformation. So we have applied this method with carbamate ribofuranoside.

Compound **12** on sodium periodate cleavage followed by reduction gave the monohydroxy derivative (**13)**. The structure of **13** was supported by its ^{1}H NMR, ^{13}C NMR

and mass spectroscopic data. Compound **13** was converted into the iodo derivative (**14**) with TPP, imidazole and iodine in refluxing toluene. The structure of **14** was supported by NMR value and mass spectroscopic data. The mass spectroscopy showed a peak at *m/z* 354 (M^++1).

Our next step involved zinc-mediated domino elimination-alkylation protocol. Thus compound **14** was treated with activated Zn and allyl bromide in THF:H_2O in a sonicator bath at 45 ^oC under argon to give two product (**15** and **16**) with 9:1 diastereomeric ratio (Scheme 7). The diastereo-selectivity could be rationalized on the basis of the Felkin-Anh model[87] (Fig 20), which helped us to characterize the stereochemical assignments. The unambiguous stereochemical assignments were confirmed at a later stage of the synthetic scheme.

Scheme 7

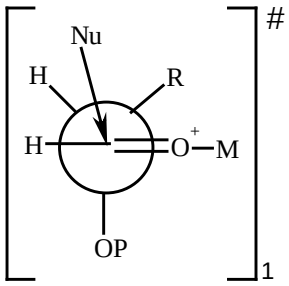


Are Felkin-selective reactions of α-heteroatom aldehydes going through the Felkin-Anh transition state?

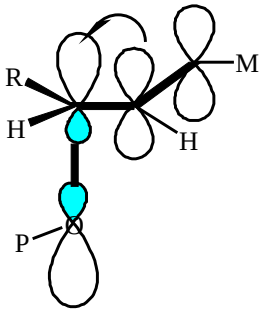
• leads directly to staggered conformation, Felkin-Anh product

• best acceptor σ* orbital aligned parallel to π and π* orbitals of carbonyl: hyperconjugative stabilization (πC=O ⟷ σ*C-OP)

Felkin Anh Model



• assumes a covalent transition state in which FMO stabilization dominates



(πC=O ⟷ σ*C-OP)

Accordingly, the *Felkin-Anh* transition state in our system can be represented as:

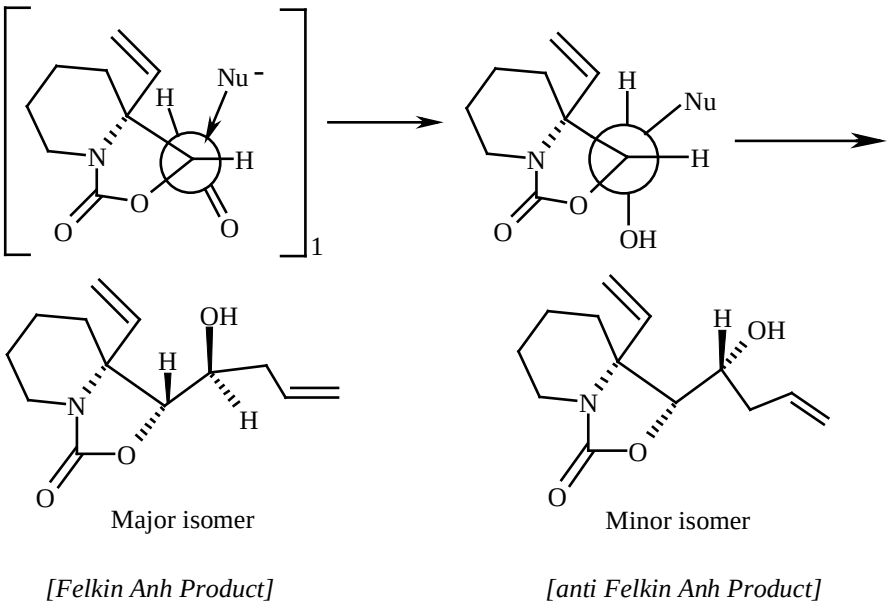


Figure 20: *The transition state of Domino reaction*

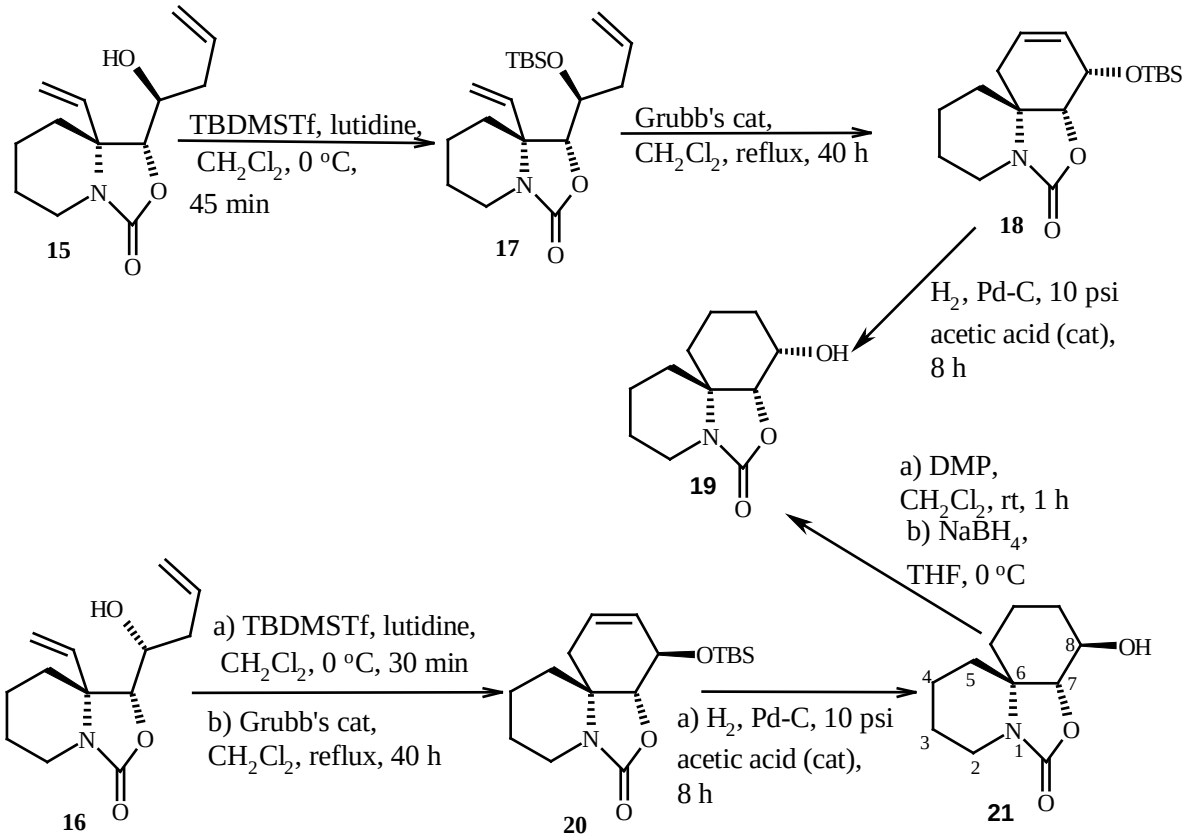
The mixture was recourse to silica gel chromatography whereupon pure products **15** and **16** were isolated and thoroughly investigated by the ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

The major isomer (**15**) was first protected as a TBS ether with TBS-OTf[88] to give **17** whose ^{1}H NMR spectrum displayed for three singlets in the upfield region at 0.09 ppm (3 H), 0.13 ppm (3 H) and 0.91 ppm (9 H) indicating TBS group was present. Compound **17** underwent RCM reaction using 1st generation Grubbs' catalyst in benzene at 80 ^{o}C to get **18**, which was fully analysed by the ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. For example, in its ^{1}H NMR spectrum the two olefin protons of the carbocyclic moiety appeared at 5.75 ppm (2.5, 5.7, 10.2 Hz) as a doublet of a doublet of a doublet and 5.94 ppm as a multiplet while rest of the spectrum was in complete agreement with the assigned structure. The mass spectrum showed a peak at *m/z* 324 (M^{+}+1).

The reduction of double bond as well as deprotection of TBS ether occurred when **17** was explored to H_2 and 10% Pd-C in methanol with cat. acetic acid to give the spirocyclic ring derivative (**19**). Its ^{1}H NMR, ^{13}C NMR supported the structure of **19**. For instance, in the ^{1}H NMR spectrum, the absence of olefinic proton as well as TBS were conspicuous. The methylene protons appeared in the region of 1.25-1.92 ppm as a multiplet clearly indicated

the structure of **19**. The DEPT spectrum of **19** revealed the presence of seven methylene carbon resonated at 17.6, 18.7, 23.7, 26.4, 26.9, 31.0 and 37.4 ppm. The stereochemistry of compound **19** was confirmed by single crystal X-Ray diffraction[89] which assisted in identifying the two diastereomers (Scheme 8). The ORTEP diagram of **19** (Figure 21) revealed the newly generated OH group in the domino reaction at C-8 and the cyclic carbamate i.e the C_7-OH were on the same side. The details of crystal data and structure refinement (Table 1), bond length, bond angles (Table 2) and torsional angle (Table 3) are given at the end of this section (Page No. 131-135). This also revealed that the assigned structure of **15** and **16** were correct.

Scheme 8



The minor isomer (**16**) was subjected to the same set of reactions as described in scheme 8 to provide the azaspiro derivative (**21**), in which the hydroxy group at C-8 was having opposite configuration to that of **19**. In order to invert the center, it was first oxidized

with Dess-Mertin periodinane (DMP) and then reduced with sodium borohydride. The resulting product was in complete agreement with the sample obtained earlier.

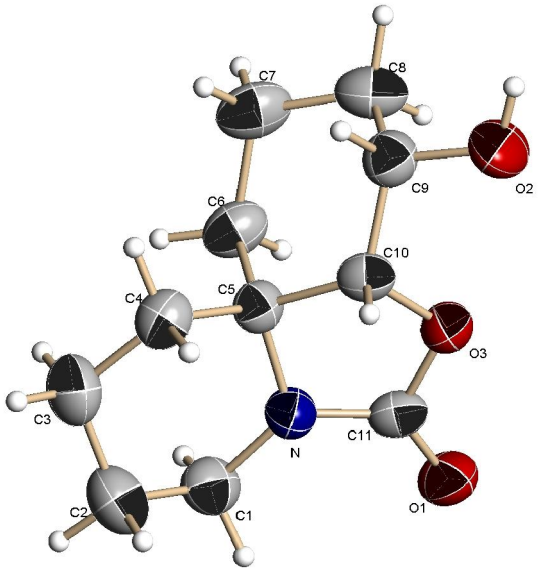
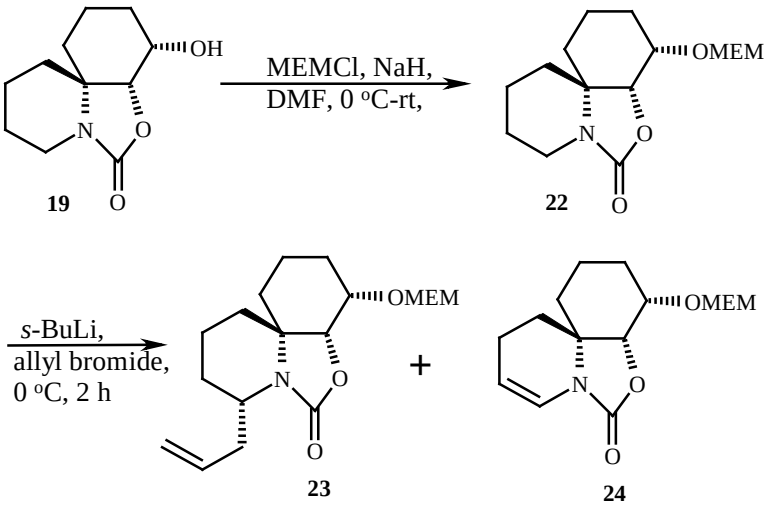


Figure 21: ***ORTEP diagram of compound 19*** (Ellipsoids are drawn at 40% probability)

Next target was to install allyl group at C-2 stereochemically. For this task, **19** was protected as MEM-ether to give **22** whose ^{1}H NMR spectrum displayed two singlets at 3.45 ppm (OCH_3) and 4.87 ppm (O-CH_2-O). The four methylene protons (O-CH_2CH_2-O-) reonated at 3.55 ppm (2 H, *J* = 4.5 Hz), 3.68 ppm (1 H, *J* = 4.5 Hz) and 3.70 ppm (1 H, *J* = 4.6 Hz). Allylation of **22** in presence of *s*-BuLi gave **23.**[90] Allylation occurred on the dipolestabilized carbanion, which was generated from amide and underwent electrophilic substitution. The anion generated at the carbon adjacent to nitrogen, was stabilized by carbonyl group of carbamate through a five membered chelation. The anion was generated at 0 ^{o}C with *s*-BuLi in presence of TMEDA and then electrophilic attack by allyl bromide at this temperature provided only one stereoselective product (**23**) with some eliminated product (**24**). The structural feature of **23** was suggested by the ^{1}H NMR, ^{13}C NMR spectral data. For instance, the ^{1}H NMR spectrum of **23** clearly revealed the signals due to olefinic protons at 5.07 and 5.77 ppm as multiplets and the methylene protons appeared at 1.84 ppm

(m), 1.98 ppm (dt, *J* = 4.3, 11.8 Hz). The structure of compound **24** was corroborated from the NMR spectroscopic data. In it's ^{1}H NMR spectrum the signals due to olefin appeared at 4.97 ppm as a multiplet and 6.57 ppm (*J* = 2.1, 8.3 Hz) as a triplet and the olefinic carbons at 120.8 ppm and 121.0 ppm. The determination of correct stereochemistry of newly formed centre was very intricate. We have taken all spectroscopic data along with COSY, NOESY, however, the protons at C-2 and C-7, which we envisaged to have some spatial interaction between them didn't show any interaction probably due to longer spacing. Based on literature[91a,b] procedent and complex-induced proximity effects, we believed that the allylic group occupied α-position. It is obvious that the carbonyl group of the carbamate first complexes with *s*-BuLi to influence the lithiation from the same face of the ring system (**23**) [91a,b] (Scheme 9).

Scheme 9



The mechanism for the carbamate directed lithiation followed by nuclephilic attack by allyl bromide for the formation of **23** is shown below.

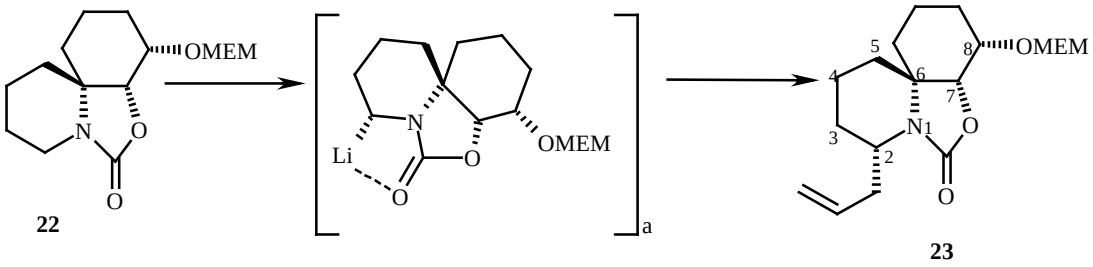


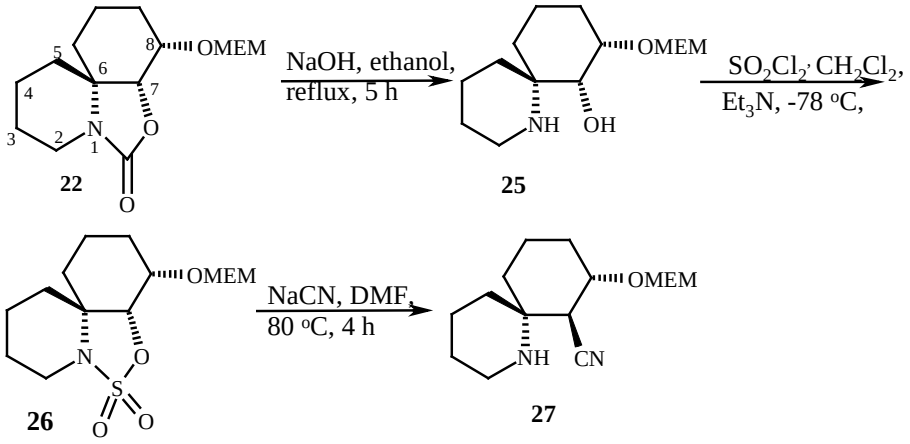
Figure 22: *Mechanism of allylation of compound **22** for the formation of **23***

Compound **23** was an enantioselective protocol to the key aza-spiro system present in histrionicotoxin group of alkaloids family.

Our next concern was the introduction of cyano group at C-7 of **23** by nucleophilic displacement reaction. In order to activate the hydroxyl group, the use of cyclic sulfamidate methodology was envisaged.

Before subjecting **23** to the above envisaged reaction, we decided to study on a model compound (**22**). In **22**, as compared to the real substrate **23**, the allylic group at C-2 was missing. The carbamate (**22**) on alkali hydrolysis[92] furnished the amino alcohol derivative (**25**). Treatment of **25** with SO_2Cl_2 at –78 ^oC gave the cyclic sulfamidate[93] (**26**) whose ^1H NMR and ^{13}C NMR spectral data were in agreement with the assigned structure. In it's ^1H NMR spectrum, a downfield shift of H-7 proton was noted. (4.62 ppm compared to 4.02 ppm for **25**). The cyclic sulfate (**26**) underwent nucleophilic substitution with NaCN (1.5 equiv.)[94] in DMF at 80 °C for 4 h followed by acid hydrolysis to give the cyano derivative (**27**). The IR spectrum revealed a peak at 2240 cm^{-1} corresponding to C≡N. The ^{13}C NMR spectrum showed C≡N signal at 120 ppm.

Scheme 10

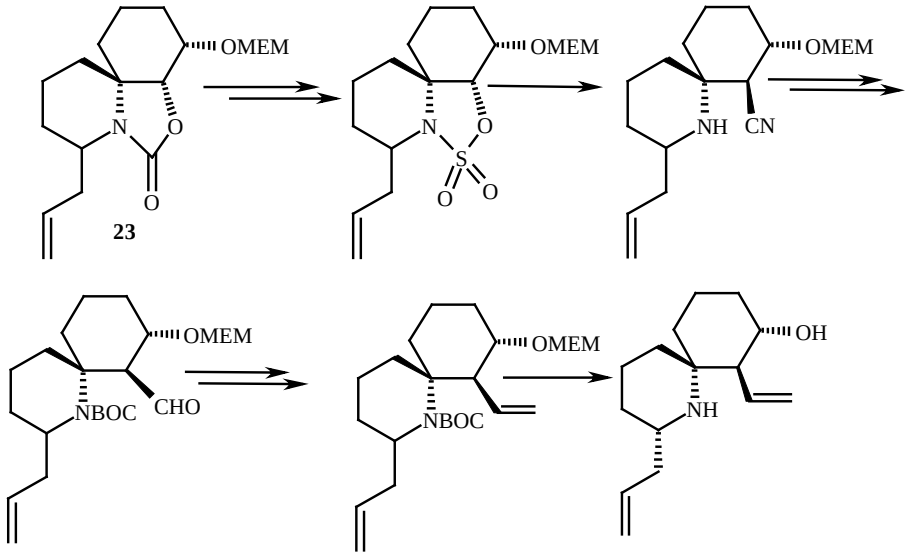


The overall objective of our synthetic endeavor has been fulfilled to some extent. The introduction of the allylic group at C-2 was successfully accomplished, the CN group was installed by SN_2 protocol. What remained to be done to repeat the SN_2 nucleophilic substitution reaction of allylic substituted precursor **23**. This intermediate would then be obtained elaborated to histrionicotoxin 235A. I am pleased to inform that my Ph.D

colleague is working on this problem to complete the synthesis of naturally occurring histrionicotoxin 235A.

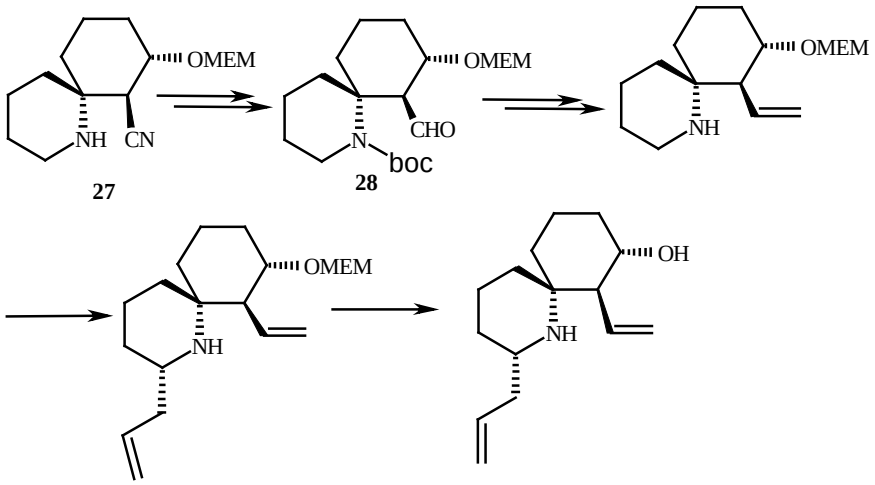
The proposed scheme for the synthesis of histrionicotoxin 235A from allylated precursor **23** through cyanide substitution reaction and Wittig olefination is shown below (scheme11).

Scheme 11

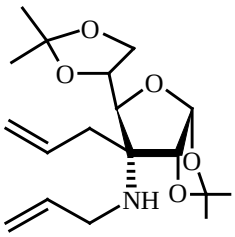


The total synthesis of histrionicotoxin 235A will be obtained from the cyano derivative (**27**) through the intermediate vinyl derivative (**28**) followed by the imine alkylation[95] has also been proposed (scheme 12).

Scheme 12



3-*C*-Allyl-3'-*N*-allyl-3-deoxy-1,2:5,6-di-*O*-isopropylidine-α-D-allofuranose (4)



Compound **2** (10.0 g, 38.7 mmol), allyl amine (3.2 g, 42.6 mmol) and molecular sieves powder (2.0 g) were stirred for 1 h at rt, filtered through celite, washed with benzene and concentrated to give **3** (10.9 g, 95%), as a brown liquid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32 (s, 3 H), 1.33 (s, 3 H), 1.42 (s, 3 H), 1.43 (s, 3 H), 3.96 (dd, 1 H, *J* = 7.1, 7.9 Hz), 4.03 (dd, 1 H, *J* = 7.1, 8.3 Hz) 4.09-4.26 (m, 1 H), 4.28-4.37 (m, 1 H), 4.40 (dt, 1 H, *J* = 2.3, 6.8 Hz), 4.65 (m, 1 H), 4.87 (d, 1 H, *J* = 4.7 Hz), 5.12 (ddd, 1 H, *J* = 1.9, 3.4, 17.4 Hz), 5.25 (ddd, 1 H, *J* = 1.9, 2.9, 10.1 Hz), 5.88 (m, 1 H), 6.03 (d, 1 H, *J* = 4.8 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.1, 25.8, 27.0, 27.2, 56.3, 63.7, 74.5, 77.5, 79.3, 104.5, 109.1, 112.9, 115.4, 134.9, 170.6.

To a suspension of of freshly cut lithium pieces (2.54 g, 0.37 g.- atom) and biphenyl (5.0 mg) in THF (50 mL), was cooled to –15 ^{o}C and then allyl phenyl ether (25.2 mL, 183 mmol) in anhydrous THF (26 mL) was added drop wise. After 45 min. the cooling bath was removed and the reaction mixture was stirred for an additional 15 min. The dark red solution solution of allyl lithium was cannulated to a new flask. Compound **3** (10.9 g, 36.7 mmol) in THF (50 mL) was introduced. After stirring at rt for 2 h the reaction was quenched with saturated NH_4Cl, filtered through celite and washed with ethyl acetate-hexane. The combined filtrate was washed with 1 N NaOH (2 x 30 mL), brine, dried (over Na_2SO_4), and

concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:9) to give **4** (8.2 g, 66%), as a yellow liquid.

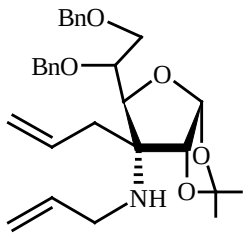
$[\alpha]_D$ = +53 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31 (s, 3 H), 1.34 (s, 3 H), 1.42 (s, 3 H), 1.54 (s, 3 H), 2.18 (dd, 1 H, *J* = 6.8, 1.2 Hz), 2.46 (dd, 1 H, *J* = 6.8, 0.9 Hz), 3.26 (ddt, 1 H, *J* = 2.3, 5.4, 14.7 Hz), 3.49 (ddt, 1 H, *J* = 2.3, 6.2, 12.0 Hz), 3.85 (m, 2 H), 4.10 (m, 2 H), 4.33 (d, 1 H, *J* = 3.0 Hz), 5.01-5.22 (m, 4 H), 5.51 (d, 1 H, *J* = 3.0 Hz), 5.82-6.09 (m, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.7, 25.6, 25.8, 26.2, 34.1, 45.5, 65.6, 67.5, 72.3, 73.8, 83.3, 102.5, 108.6, 111.0, 114.5, 117.4, 127.5, 132.7, 136.8**.**

Ms: 340 (M+ 1).

3-*C*-Allyl-3'-*N*-allyl-3-deoxy-5,6-di-*O*-benzyl-1,2-*O*-isopropylidine-α-D-allofuranose (7)



1% aqueous H_2SO_4 (30 mL) and compound **4** (8.9 g, 26.3 mmol) in methanol (30 mL) were stirred at rt for 14 h, neutralized with K_2CO_3, filtered and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (over Na_2SO_4), and concentrated. The crude residue was purified on silica gel by eluting with EtOAc-hexane (1:1) to give **6** (7.0 g, 89%), as a liquid.

$[\alpha]_D$ = +75 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR (acetone-d6, 200 MHz): δ 1.32 (s, 3 H), 1.50 (s, 3 H), 2.42 (m, 2 H), 3.22-3.52 (m, 5 H), 3.72 (m, 2 H), 3.89 (m, 1 H), 4.50 (d, 1 H, *J* = 3.9 Hz), 5.0-5.29 (m, 4 H), 5.67 (d, 1 H, *J* = 3.9 Hz), 5.84-6.17 (m, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.3, 26.7, 34.7, 48.1, 63.7, 66.5, 69.4, 78.3, 81.0, 104.1, 111.5, 115.9, 118.3, 132.5, 135.8.

MS: m/z 300 (M^++1).

Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68; Found: C, 59.84; H, 8.31; N, 4.73.

Compound **6** (16.0 g, 53.5 mmol), in dry THF (100 mL) was cooled to 0 ^{o}C and NaH (60% dispersion in oil, 3.2 g, 80.2 mmol) was added portion-wise at 0 ^{o}C. After 30 min at rt benzyl bromide (14.0 mL, 117.7 mmol) and Bu_4NI (98.0 mg, 0.25 mmol) were added and stirred for 3 h. After usual work up the residue was purified on silica gel by eluting with EtOAc-hexane (1:19) to afford a yellow liquid **7** (23.0 g, 90%).

$[\alpha]_D$ = +28 ^{o} (*c* 1, $CHCl_3$).

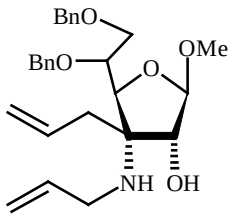
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31 (s, 3 H), 1.52 (s, 3 H), 1.98 (brs, 1 H), 2.21 (dd, 1 H, *J* = 6.8, 14.6 Hz), 2.34 (dd, 1 H, *J* = 7.8, 14.6 Hz), 3.18 - 3.39 (m, 2 H), 3.66 (dd, 1 H, *J* = 6.1, 9.7 Hz), 3.81 - 4.02 (m, 3 H), 4.30 (d, 1 H, *J* = 3.6 Hz), 4.56 (brt, 3 H), 4.83 - 5.11 (m, 5 H), 5.57 (d, 1 H, *J* = 3.6 Hz), 5.74-6.02 (m, 2 H), 7.32 (m, 10 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.4, 26.8, 35.8, 46.4, 66.5, 71.7, 72.0, 73.2, 76.7, 80.4, 83.7, 103.0, 111.5, 114.8, 117.4, 127.4, 127.7, 128.0, 128.1, 133.8, 137.3, 138.3.

MS: m/z 480 (M^++1).

Anal. Calcd for $C_{29}H_{37}NO_5$: C, 72.62; H, 7.78; N, 2.92; Found: C, 72.94; H, 8.01; N, 2.85.

Methyl 3-*C*-allyl-3'-*N*-allyl-3-deoxy-5,6-di-*O*-benzyl-β-D-allofuranoside (8)



A solution of compound **7** (6.3 g, 13.2 mol) and conc. H_2SO_4 (3 mL) in dry methanol (80 mL), was refluxed for 6 h, neutralized with K_2CO_3, filtered and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (over Na_2SO_4) and concentrated to give a residue, which was purified on silica gel by eluting with EtOAc-hexane (1:9) to give **8** (5.1 g, 86%), as a yellow liquid.

$[\alpha]_D$ = –69 ^{o} (*c* 1, $CHCl_3$).

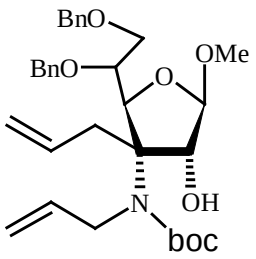
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.41 (ddt, 1 H, *J* = 1.6, 3.4, 5.4 Hz), 2.61 (q, 1 H, *J* = 7.6 Hz), 2.90 (ddt, 1 H, *J* = 1.5, 3.4, 4.8 Hz), 3.16-3.30 (m, 1 H), 3.35 (s, 3 H), 3.61 (dd, 1 H, *J* = 3.4, 10.4 Hz), 3.69 (s, 1 H), 3.78-3.93 (m, 3 H), 4.42 (d, 1 H, *J* = 11.2 Hz), 4.58 (s, 2 H), 4.77 (s, 1 H), 4.83 (d, 1 H, *J* = 11.2 Hz), 4.97-5.16 (m, 4 H), 5.66-5.96 (m, 2 H), 7.32 (m, 10 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 34.9, 45.5, 55.0, 64.1, 70.7, 70.9, 72.8, 77.2, 77.4, 81.2, 109.1, 114.9, 117.1, 127.1, 127.7, 134.1, 135.7, 137.8.

MS: m/z 454 (M^++1).

Anal. Calcd for $C_{27}H_{35}NO_5$: C, 71.52; H, 7.78; N, 3.09; Found: C, 71.56, H, 7.54; N, 2.96.

Methyl 3-*C*-allyl-3'-(*N*-allyl-*N*'-*tert*-butoxycarbonyl)-3-deoxy-5,6-di-*O*-benzyl-β-D-allofuranoside (9)



8 (8.0 g 17.6 mmol), triethylamine (7.3 mL, 53.0 mmol), $(BOC)_2O$ (4.8 g, 21.2 mmol), DMAP (10.0 mg, 0.09 mmol) in CH_2Cl_2 (30 mL) were stirred at rt for 30 min and concentrated. The crude residue was purified on silica gel by eluting with EtOAc-hexane (1:9) to afford a yellow liquid **9** (8.9 g, 94%).

$[\alpha]_D = -18^{o}$ (*c* 1, $CHCl_3$).

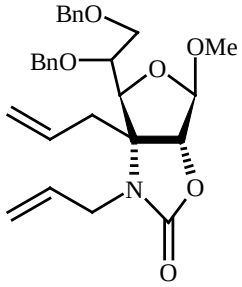
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.47 (s, 9 H), 2.45 (dd, 1 H, *J* = 6.3, 10.5 Hz), 2.66 (dd, 1 H, *J* = 6.8, 11.5 Hz), 3.10 (dd, 1 H, *J* = 5.8, 13.3 Hz), 3.27 (dd, 1 H, *J* = 5.8, 14.1 Hz), 3.36 (s, 3 H), 3.62 - 3.67 (m, 2 H), 3.88 (d, 1 H, *J* = 8.9 Hz), 4.08 (d, 1 H, *J* = 8.9 Hz), 4.48 (d, 1 H, *J* = 11.2 Hz), 4.59 (brd, 2 H), 4.80 (brd, 1 H), 4.86 (brd, 2 H) 4.92-5.17 (m, 4 H), 5.69 - 5.99 (m, 2 H), 7.32 (m, 10 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.6, 34.9, 45.8, 55.4, 64.7, 71.2, 71.6, 73.3, 77.8, 82.1, 82.1, 83.5, 106.9, 114.6, 117.8, 127.3, 127.4, 127.7, 128.1, 133.8, 137.3, 138.3, 152.4.

MS: m/z 555 (M^++2).

Anal. Calcd for $C_{32}H_{43}NO_7$: C, 69.42; H, 7.83; N, 2.53; Found: C, 69.22; H, 7.90; N, 2.71.

3,3a-Dially-4-[1,2-*bis*-(benzyloxy)ethyl]-6-methoxytetrahydrofuro[3,4-d][1,3]oxazol-2 (3H)-one (10)



9 (3.0 g, 5.4 mmol) and NaOH (12.0 mg, 0.32 mmol) in THF:MeOH (1:1, 15 mL), were stirred at rt for 3 h, quenched with acetic acid and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (over Na_2SO_4), and concentrated**.** The residue was purified on silica gel by eluting with EtOAc-hexane (1:9) to furnish **10** (2.2 g, 84%), as a white solid.

M.P = 79 ^{o}C

[α]$_D$ = –49 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.24 (dd, 1 H, *J* = 7.9, 14.9 Hz), 2.95 (dd, 1 H, *J* = 5.5, 13.6 Hz), 3.18-3.41 (m, 1 H), 3.31 (s, 3 H), 3.59-3.73 (m, 2 H), 3.75 (d, 1 H, *J* = 5.9 Hz), 3.90 (d, 1 H, *J* = 9.2 Hz), 4.20 (d, 1 H, *J* = 9.2 Hz), 4.40 (d, 1 H, *J* = 11.5 Hz), 4.50-4.65 (m, 3 H), 4.88 (d, 2 H, *J* = 14.1 Hz), 4.95-5.22 (m, 4 H), 5.54-5.95 (m, 2 H), 7.34 (m, 10 H).

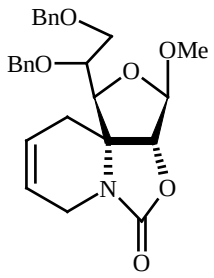
^{13}C NMR ($CDCl_3$, 50 MHz): δ 34.0, 43.7, 55.9, 69.5, 71.3, 72.4, 73.1, 77.7, 83.7, 84.6, 108.0, 117.5, 120.0, 126.5, 126.9, 127.4, 127.5, 127.6, 128.1, 131.6, 132.7, 137.7, 137.5, 137.8, 156.2.

MS: m/z 480 (M^++1).

IR: 1752 cm^{-1}.

Anal. Calcd for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94; N, 2.92; Found: C, 69.96; H, 7.13; N, 2.92.

1-[1,2-*bis*-(Benzyloxy)ethyl]-3-methoxy-3,3a,7,10-tetrahydrofuro[3´,4´:4,5] [1,3]oxazolo[3,4-a]pyridin-5-one (11)



Compound **10** (5.0 g, 10.4 mmol) and Grubbs' cat. (85.0 mg, 1 mol%) in benzene (80 mL) was degassed under argon atmosphere and then refluxed for 30 h. After that additional Grubbs' cat. (60.0 mg, 0.7 mol%) was added and refluxing continued for another 12 h. The solvent was evaporated and the residue was purified on silica gel by using EtOAc-hexane (1:9) as eluent to give **11** (4.1 g, 87%), as a yellow liquid.

$[\alpha]_D$ = –37 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.42 (m, 2 H), 3.30 (s, 3 H), 3.61 (dd, 1 H, *J* = 2.1, 9.9 Hz), 3.72 (m, 1 H), 3.85 (dd, 1 H, *J* = 2.0, 9.9 Hz), 4.13 (m, 1 H), 4.20 (d, 1 H, *J* = 9.9 Hz), 4.36 (s, 1 H), 4.40 (d, 2 H, *J* = 9.9 Hz), 4.53 (t, 2 H, *J* = 9.6 Hz), 4.77 (d, 1 H, *J* = 10.9 Hz), 4.92 (t, 1 H, *J* = 9.6 Hz), 5.43 (m, 2 H), 7.31 (m, 10 H).

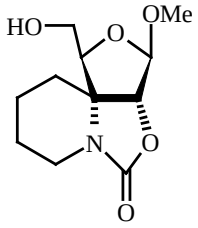
^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.9, 39.2, 56.0, 69.5, 71.5, 73.3, 78.3, 81.9, 88.1, 109.0, 121.5, 124.2, 127.5, 127.6, 128.1, 128.2, 137.9, 137.9, 154.9.

Ms: 452 (M+ 1).

Anal. Calcd. For $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10; Found: C, 68.86; H, 6.33; N, 3.02.

1-Hydroxymethyl-3-methoxyhexahydro-2,4-dioxa-5a-aza-cyclopenta[*c*]inden-5-one

(13)



A suspension of **11** (2.0 g, 4.4 mmol), cat.acetic acid, 10% Pd/C (0.2 g) in methanol (30 mL) was hydrogenated at rt and at 60 psi. The reaction was completed in 6 h, filtered through celite, concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:9) to afford a white solid **12** (1.0 g, 83%).

M.P = 161 ^{o}C

$[\alpha]_D$ = –105 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.49-1.87 (m, 6 H), 2.27 (d, 1 H, *J* = 11.5 Hz), 2.59 (brs, 2 H), 2.96 (dt, 1 H, *J* = 2.9, 12.8 Hz), 3.42 (s, 3 H), 3.81 (m, 3 H), 4.18 (d, 1 H, *J* = 8.6 Hz), 4.37 (s, 1 H), 4.92 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.8, 23.7, 28.4, 39.6, 55.7, 63.5, 69.7, 70.4, 83.2, 87.5, 108.2, 155.1.

MS: m/z 273 (M^{+}+1).

Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; Found: C, 52.88; H, 6.91.

Compound **12** (5.0 g, 18.3 mmol), sodium metaperiodate (5.9 g, 27.4 mmol) in water (3 mL) and CH_2Cl_2 (20 mL) were stirred at rt for 30 min and filtered. Organic layer was washed with $Na_2S_2O_3$, brine, dried and concentrated to get the aldehyde (4.0 g, 91%). It was dissolved in THF (20 mL) and then $NaBH_4$ (0.18 g, 4.6 mmol) was added portion wise and stirred at rt for 2 h. Sat. NH_4Cl was added, filtered and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:1) to get a white solid **13** (3.1 g, 77%).

M.P = 116 ^{o}C

[α]$_D$ = –115 ^{o} (*c* 1, $CHCl_3$).

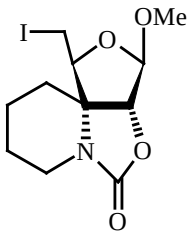
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44-1.77 (m, 5 H), 1.96 (m, 1 H), 2.25 (m, 1 H), 2.88-3.03 (m, 1 H), 3.49 (s, 3 H), 3.38-4.02 (m, 2 H), 3.66 (brs, 1 H), 3.77-3.96 (m, 2 H), 4.42 (s, 1 H), 4.46 (t, 1 H, *J* = 3.1 Hz), 5.0 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.2, 24.3, 28.0, 39.4, 55.4, 62.4, 69.0, 84.1, 86.9, 108.6, 154.8.

MS: m/z 244 (M^++1).

Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.32; H, 7.04; N, 5.76; Found: C, 54.48; H, 7.06; N, 5.71.

1-Iodomethyl-3-methoxyhexahydro-2,4-dioxa-5a-aza-cyclopenta[*c*]inden-5-one (14)



13 (3.0 g, 12.3 mmol), TPP (6.5 g, 24.7 mmol), I_2 (6.3 g, 24.7 mmol) and imidazole (1.7 g, 24.7 mmol) in toluene (15 mL) were refluxed for 4 h. Toluene was removed, the residue partitioned between water and ethyl acetate. The organic phase was washed with $NaHCO_3$, $Na_2S_2O_3$, brine, dried, and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:4) to get a solid compound **14** (4.0 g, 91%)**.**

M.P = 170 ^{o}C

[α]$_D$ = –3 ^{o} (*c* 1, $CHCl_3$).

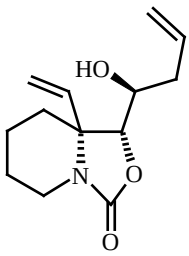
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32-2.03 (m, 6 H), 2.89 (m, 1 H), 3.29 (dd, 1 H, *J* = 2.9, 10.3 Hz), 3.45 (dd, 1 H, *J* = 10.3, 11.8 Hz), 3.47 (s, 3 H), 3.89 (brd, 1 H), 4.44 (s, 1 H), 4.45 (dd, 1 H, *J* = 2.9, 11.8 Hz), 4.96 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 6.3, 21.1, 24.1, 28.8, 39.4, 56.7, 68.5, 84.3, 87.3, 108.4, 154.4.

Ms: m/z 354 (M^+ + 1).

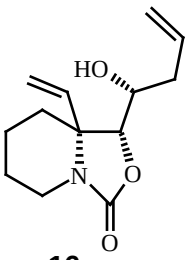
Anal. Calcd. for $C_{11}H_{16}NO_4I$: C, 37.40; H, 4.57; N, 3.96; Found: C, 37.15; H 4.50**;** N, 3.90.

(1*R*,8a*R*)-1-[(1*S*)-1-hydroxybut-3-en-1-yl]-8a-vinylhexahydro-[1,3]oxazolo[3,4-a] pyridin-3-one (15) and (1*R*, 8a*R*)-1-[(1*R*)-1-hydroxybut-3-en-1-yl]-8a-vinylhexahydro-[1,3]oxazolo[3,4-a]pyridin-3-one (16)



15

+



16

Zn powder (6.3 g, 96.0 mmol), allyl bromide (2.4 g, 28.8 mmol) and iodofuranoside (**14**) (3.4 g, 9.6 mmol) in THF:H_2O (3:1, 30 mL) under argon atmosphere were sonicated at 40 ^oC until TLC revealed full consumption of the starting material. It took 3 h. The reaction mixture was filtered through celite and washed with ether. Removal of solvent gave the residue, which was purified on silica gel by using EtOAc-hexane (1:4) to get one isomer **15** (1.4 g, 61%).

15: **$[\alpha]_D$** = +5 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30-1.74 (m, 6 H), 2.02-2.25 (m, 2 H), 2.48 (m, 1 H), 2.87 (m, 1 H), 3.69 (m, 2 H), 3.76 (dd, 1 H, *J* = 9.3, 1.3 Hz), 5.11 (m, 3 H), 5.57 (d, 1 H, *J* = 9.3 Hz), 5.62-5.80 (m, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.3, 24.0, 35.9, 38.3, 38.5, 63.5, 68.1, 86.6, 118.1, 118.4, 133.2, 134.8, 155.9.

Ms: 238 ($M^+ + 1$).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 54.32; H, 7.04; N, 5.76; Found: C, 54.48; H, 7.18; N, 5.71

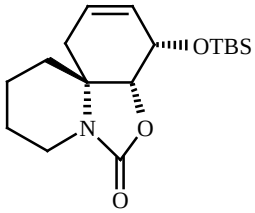
Further elution gave another isomer **16** (0.02 g, 8%).

16: **$[\alpha]_D$** = –3 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ1.38-1.81 (m, 6 H), 2.04 (m, 1 H), 2.28 (m, 2 H), 2.58 (brs, 1 H), 2.88 (m, 1 H), 3.75 (m, 1 H), 3.95 (d, 1 H, *J* = 5.4 Hz), 5.05-5.18 (m, 2 H), 5.25 (d, 1 H, *J* = 17.4 Hz), 5.52 (d, 1 H, *J* = 10.9 Hz), 5.67-5.92 (m, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.7, 24.3, 34.6, 37.2, 38.9, 62.9, 69.1, 86.4, 118.2, 120.1, 133.4, 134.5, 156.4.

(4*S*,4a*R*,11a*R*)-4-{[*tert*-Butyldimethylsilyl]oxy}-4,4a,8,9,10,11-hexahydro-1H -pyrido[1,2-c] [1,3]benzoxazol-6-one (18)



15 (1.4 g, 5.9 mmol), lutidine (1.4 mL, 11.8 mmol) and TBDMSTf (2.0 mL, 8.9 mmol) in CH_2Cl_2 (10 mL) were stirred for 45 min. The reaction mixture was diluted with CH_2Cl_2, washed with 2 N HCl (30 mL), and the combined organic layer was dried (over Na_2SO_4), concentrated and the residue was purified on silica gel by eluting with EtOAc-hexane (1:9) to get **17** (1.93 g, 93%).

[α]$_D$ = +15 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.09 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 1.30-1.79 (m, 6 H), 2.10 (m, 1 H), 2.45 (m, 1 H), 2.89 (dd, 1 H, *J* = 3.5, 12.8 Hz), 3.77 (m, 1 H), 4.02 (m, 2 H), 5.10-5.23 (m, 3 H), 5.45 (dd, 1 H, *J* = 1.2, 10.7 Hz), 5.55 (dd, 1 H, *J* = 10.5, 16.1 Hz), 5.79 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ –4.8, –3.7, 17.7, 19.4, 24.1, 25.7, 35.9, 37.2, 38.1, 62.8, 69.8, 85.2, 118.2, 118.7, 132.0, 134.9, 155.4.

Ms: m/z 352 (M^++ 1).

Anal. Calcd. for $C_{19}H_{33}NSiO_3$: C, 64.91; N, 3.98; Found: C, 64.82; N, 3.98.

17 (0.2 g, 0.56 mmol) and Grubbs' cat. (4.6 mg, 0.1 mol%) in CH_2Cl_2 (40 mL) was refluxed for 24 h under argon atmosphere. After that additional Grubbs cat. (3.0 mg, 0.06 mol%) was added and refluxing for another 16 h. The solvent was evaporated and the residue was purified on silica gel by using EtOAc-hexane (1:9) to give a white crystalline solid **18** (0.17 g, 92%).

M.P = 136 ^{o}C

[α]$_D$ = –72 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.09 (s, 6 H), 0.80 (s, 9 H), 1.44-1.85 (m, 6 H), 2.09-2.23 (m, 1 H), 2.41 (ddt, 1 H, *J* = 2.4, 6.8, 9.2 Hz), 2.90 (dd, 1 H, *J* = 3.0, 12.6, 22.6 Hz), 3.70 (m, 1 H), 3.96 (ddd, 1 H, *J* = 2.5, 5.7, 9.7 Hz), 4.18 (br d, 1 H), 5.75 (ddd, 1 H, *J* = 2.5, 5.7, 10.2 Hz), 5.94 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.1, –4.9, 17.7, 19.0, 24.0, 25.4, 29.4, 34.5, 37.7, 58.9, 66.7, 83.9, 123.1, 126.3, 155.5.

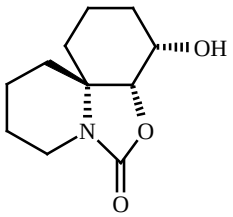
Ms: m/z 324 (M^+ + 1).

Anal. Calcd. for $C_{17}H_{29}NO_3Si$: C, 63.15; N, 4.33. Found: C, 63.29; N, 4.22.

20: **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.47-1.90 (m, 12 H), 2.18 (m, 1 H), 2.46 (ddt, 1 H, *J* = 2.8, 5.2, 9.8 Hz), 2.81-2.97 (m, 1 H), 3.62-3.76 (m, 1 H), 3.90-4.00 (ddd, 1 H, *J* = 2.5, 5.7, 9.4 Hz), 4.20 (brt, 1 H), 5.78 (ddd, 1 H, *J* = 2.5, 5.7, 10.2 Hz), 5.90-5.99 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ –4.6, –4.4, 18.2, 19.5, 24.4, 25.8, 29.9, 34.9, 36.1, 59.3, 67.1, 84.4, 123.3, 126.8, 156.0.

(4*S*,4a*R*,11a*R*)-4-Hydroxy octahydro-1H-pyrido[1,2-c] [1,3]benzoxazol-6-one (19)



Compound **18** (0.12 g, 0.37 mmol), acetic acid (cat.) and 10% Pd/C (0.02 g) in methanol (10 mL) were hydrogenated at rt and at 10 psi. The reaction was completed in 8 h, filtered through celite and concentrated. The residue was purified on silica gel by using EtOAc- hexane (1:9) to afford **19** (70.0 mg, 90%), as a white solid.

M.P = 112 ^{o}C

$[\alpha]_D$ = –40 ^{o} (*c* 1, $CHCl_3$).

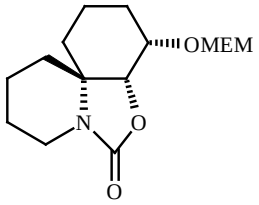
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25-1.92 (m, 12 H), 2.81 (t, 1 H, *J* = 12.8 Hz), 3.25 (brs, 1H), 3.56-3.90 (m, 2 H), 4.17 (d, 1 H, *J* = 3.6 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.6, 18.7, 23.7, 26.4, 26.9, 31.0, 37.4, 58.9, 66.6, 83.7, 155.9.

MS: m/z 212 (M^{+}+1).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.55; N, 6.63; Found: C, 62.26; N, 6.52.

(4*S*,4a*R*,11a*R*)-4-[(2-Methoxyethoxy) methoxy]octahydro-1H-pyrido[1,2-c] [1,3] benzoxazol-6-one (22)



19 (0.38 g, 1.8 mmol) in a solvent mixture of dry THF:DMF (9:1, 12 mL) was cooled to 0 ^{o}C, and NaH (60% dispersion in oil, 0.14 g, 3.6 mmol) was added portion-wise. After 30 min MEMCl (0.32 mL, 2.7 mmol) was added and stirred for 12 h. After usual work up the residue was purified on silica gel by using EtOAc-hexane (1:4) to get **22** (0.45 g, 83%).

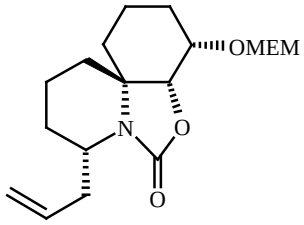
[α]$_D$ = –30 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 (m, 1 H), 1.35-1.56 (m, 4 H), 1.67-1.90 (m, 7 H), 2.80 (dt, 1 H, *J* = 3.1, 13.3 Hz), 3.45 (s, 3 H), 3.55 (t, 2 H, *J* = 4.5 Hz), 3.68 (t, 1 H, *J* = 4.5 Hz), 3.70 (t, 1 H, *J* = 4.6 Hz), 3.75 (m, 1 H), 3.80 (m, 1 H), 4.25 (d, 1 H, *J* = 13.7 Hz), 4.87 (s, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.7, 18.9, 23.9, 24.8, 26.8, 31.8, 37.6, 58.5, 58.6, 66.6, 71.3, 72.3, 82.1, 93.8, 155.5.

Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68; Found: C, 60.34; H, 8.32; N, 4.58.

(4*S*,4a*R*,8*S*,11a*R*)-8-Allyl-4-[(2-methoxyethoxy)methoxy]octahydro-1H-pyrido[1,2-c] [1,3]benzoxazol-6-one (23)



To a solution of **22** (0.1 g, 0.33 mmol) and TMEDA (0.05 mL, 0.33 mmol) in THF (5 mL) at 0 ^{o}C, *s*-BuLi (0.4 mL, 0.5 mmol) in hexane was added. After 40 min allyl bromide (0.06 mL, 0.05 mmol) in THF (3 mL) was introduced and stirred for 2 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:9) to get **23** (0.05 g, 42%)**.**

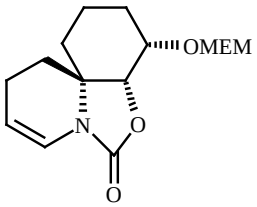
[α]$_D$ = –39 ^{o} (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.27 (m, 2 H), 1.42 (m, 2 H), 1.72 (m, 6 H), 1.84 (m, 1 H), 1.98 (dt, 1 H, *J* = 4.3, 11.8 Hz), 2.70 (qu, 1 H), 3.06 (m, 1 H), 3.20 (m, 1 H), 3.38 (s, 3 H), 3.56 (t, 2 H, *J* = 8.6 Hz), 3.70 (m, 1 H), 3.78 (m, 1 H), 3.83 (m, 1 H), 4.13 (d, 1 H, *J* = 5.4 Hz), 4.80 (s, 2 H), 5.07 (m, 2 H), 5.77 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.7, 19.5, 25.9, 27.7, 30.6, 36.2, 51.4, 58.9, 61.8, 67.1, 71.9, 72.7, 80.9, 94.3, 117.5, 134.9, 156.2.

Anal. Calcd. for $C_{18}H_{29}NO_5$: C, 63.69; H 8.61; N, 4.13; Found: C, 63.72, H, 8.51, N, 4.25.

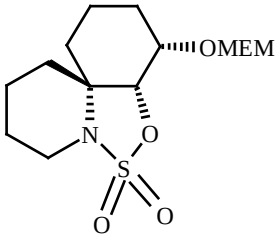
Further elution gave another side product **24** (0.02 g, 18%).



^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.29-2.01 (m, 8 H), 2.23 (m, 2 H), 3.39 (s, 3 H), 3.49 (m, 2 H), 3.66 (t, 1 H, *J* = 4.4 Hz), 3.75 (m, 2 H), 4.35 (d, 1 H, *J* = 3.2 Hz), 4.82 (s, 2 H), 4.97 (m, 1 H), 6.57 (dt, 1 H, *J* = 2.1, 8.3 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.2, 18.7, 25.4, 27.9, 29.2, 58.9, 67.2, 71.8, 72.8, 82.9, 94.3, 105.3, 120.8, 121.0, 150.9.

(4*S*,4a*R*,11a*R*)-4-[(2-Methoxyethoxy) methoxy]octahydro-1H-pyrido[1,2-c] [1,2,3] benzoxathiazole 6,6-dioxide (26)



22 (0.12 g, 0.40 mmol) and NaOH (0.02 g, 0.60 mmol) in dry ethanol (10 mL) were refluxed for 5 h and quenched with dilute acetic acid. After removal of solvent the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried (over Na_2SO_4), and concentrated to get the residue, which was purified on silica gel by using MeOH-CH_2Cl_2 (1:9) to get **25** (70.0 mg, 76%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.17-1.31 (m, 2 H), 1.47-2.15 (m, 12 H), 2.94-3.04 (m, 1 H), 3.35-3.39 (m, 1 H), 3.39 (s, 3 H), 3.55-3.58 (m, 2 H), 3.67 (m, 1 H), 3.72 (dd, 2 H, *J* = 4.4, 8.3 Hz), 4.02 (m, 1 H), 4.77 (dd, 2 H, *J* = 6.5, 11.2 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.5, 17.9, 21.6, 25.0, 26.3, 27.8, 38.9, 44.5, 58.4, 59.7, 66.6, 69.4, 71.4, 73.6, 93.5.

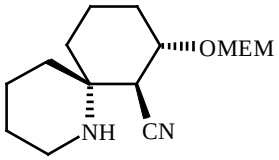
Compound **25** (0.05 g, 0.18 mmol) and triethylamine (0.1 mL, 0.7 mmol) in dry CH_2Cl_2 (20 mL) was cooled to –78 ^oC, and after 45 min SO_2Cl_2 (0.4 mL, 0.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise, stirred at this temperature for additional 1 h. After stirring for another 6 h at rt, solvent was removed to get the residue, which was purified on silica gel by using EtOAc-hexane (1:3) to get **26** (45.0 mg, 73%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.10-1.21 (m, 2 H), 1.36-1.54 (m, 4 H), 1.59-1.83 (m, 6 H), 1.94 (m, 1 H), 2.83 (dt, 1 H, *J* = 4.7, 12.8 Hz), 3.32 (s, 3 H), 3.46-3.51 (m, 2 H), 3.59-3.68 (m, 2 H), 3.79 (m, 1 H), 4.62 (d, 1 H, *J* = 2.6 Hz), 4.80 (d, 2 H, *J* = 1.6 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.6, 19.0, 23.2, 23.4, 25.4, 29.0, 37.7, 58.4, 61.9, 66.6, 71.2, 72.4, 88.8, 93.8.

Anal. Calcd for $C_{14}H_{25}NO_6S$: C, 50.14; H, 7.51; N, 4.18; S, 9.56; Found: C, 50.10; H, 7.32; N, 4.32; S, 10.00.

(6*R*,7*S*,8*S*)-8-[(2-Methoxyethoxy) methoxy]-1-azaspiro[5,5]undecane-7-carbonitrile (27)



26 (25.0 mg, 0.07 mmol) and sodium cyanide (2.0 mg, 0.35 mmol) in dry DMF (5 mL) were heated at 80 ^{o}C. After 4 h, solvent was removed, hydrolyzed with biphasic sulfuric acid-ether mixture and neutralized with $NaHCO_3$. The organic layer was washed with brine, concentrated to get the residue, which was purified on silica gel by using EtOAc-hexane (1:3) to furnish **27** (13.0 mg, 62%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.21-1.32 (m, 1 H), 1.40-1.52 (m, 4 H), 1.73 (m, 2 H), 1.98-2.05 (m, 6 H), 2.94 (m, 3 H), 3.36 (s, 3 H), 3.52-3.61 (m, 2 H), 3.68-3.72 (m, 2 H), 3.79-3.84 (m, 1 H), 4.82 (d, 1 H, *J* = 8.1 Hz), 5.0 (d, 1 H, *J* = 8.1 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.3, 24.7, 28.1, 29.2, 34.1, 37.0, 43.7, 58.8, 67.5, 70.2, 71.5, 77.2, 92.0, 120.9.

IR: 2240 cm^{-1} (small intense).

X-Ray Crystal data for compound 19 ($C_{11}H_{17}NO_3$)

Table 1

Crystal data and structure refinement for Compound 19 ($C_{11}H_{17}NO_3$)

Empirical formula	$C_{11}H_{17}NO_3$
Formula weight	211.26
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 9.163(3) Å alpha = 90° b = 9.252(3) Å beta = 90° c = 12.973(5)Å gamma = 90°
Volume	1099.8(6) $Å^3$ Z, Calculated density 4, 1.276 mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	456
crystal size	0.27 x 0.09 x 0.03 mm
Theta range for data collection	2.70 to 23.27 deg.
Limiting indices	-8<=h<=10, -9<=k<=10, -10<=l<=14
Reflections collected / unique	4771 / 1583 [R(int) = 0.0711]
Completeness to theta = 23.27	100.0 %
Max. and min. transmission	0.9970 and 0.9752
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	1583 / 0 / 140
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0586, wR2 = 0.0739
R indices (all data)	R1 = 0.1075, wR2 = 0.0841
Absolute structure parameter	2(2)
Largest diff. peak and hole	0.138 and -0.149 e.A$^{o\ -3}$

Table 2

Bond lengths [Å] and angles [deg] for compound 19($C_{11}H_{17}NO_3$)

O(1)-C(11)	1.207(4)	O(2)-C(9)	1.415(4)
O(2)-H(2)	0.83(4)	O(3)-C(11)	1.357(4)
O(3)-C(10)	1.455(3)	N-C(11)	1.346(4)
N-C(1)	1.445(4)	N-C(5)	1.456(4)
C(1)-C(2)	1.513(4)	C(1)-H(1A)	0.9700
C(1)-H(1B)	0.9700	C(2)-C(3)	1.519(5)
C(2)-H(2A)	0.9700	C(2)-H(2B)	0.9700
C(3)-C(4)	1.528(5)	C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700	C(4)-C(5)	1.513(4)
C(4)-H(4A)	0.9700	C(4)-H(4B)	0.9700
C(5)-C(10)	1.521(5)	C(5)-C(6)	1.536(5)
C(6)-C(7)	1.507(5)	C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700	C(7)-C(8)	1.526(5)
C(7)-H(7A)	0.9700	C(7)-H(7B)	0.9700

C(8)-C(9)	1.516(6)	C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700	C(9)-C(10)	1.497(5)
C(9)-H(9)	0.9800	C(10)-H(10)	0.9800
C(9)-O(2)-H(2)	114(3)	C(11)-O(3)-C(10)	107.4(3)
C(11)-N-C(1)	124.4(3)	C(11)-N-C(5)	110.6(3)
C(1)-N-C(5)	120.6(3)	N-C(1)-C(2)	108.9(3)
N-C(1)-H(1A)	109.9	C(2)-C(1)-H(1A)	109.9
N-C(1)-H(1B)	109.9	C(2)-C(1)-H(1B)	109.9
H(1A)-C(1)-H(1B)	108.3	C(1)-C(2)-C(3)	110.9(3)
C(1)-C(2)-H(2A)	109.5	C(3)-C(2)-H(2A)	109.5
C(1)-C(2)-H(2B)	109.5	C(3)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	108.0	C(2)-C(3)-C(4)	111.9(4)
C(2)-C(3)-H(3A)	109.2	C(4)-C(3)-H(3A)	109.2
C(2)-C(3)-H(3B)	109.2	C(4)-C(3)-H(3B)	109.2
H(3A)-C(3)-H(3B)	107.9	C(5)-C(4)-C(3)	110.8(3)
C(5)-C(4)-H(4A)	109.5	C(3)-C(4)-H(4A)	109.5
C(5)-C(4)-H(4B)	109.5	C(3)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	108.1	N-C(5)-C(4)	109.9(3)
N-C(5)-C(10)	97.4(3)	C(4)-C(5)-C(10)	114.3(3)
N-C(5)-C(6)	109.4(3)	C(4)-C(5)-C(6)	114.0(3)
C(10)-C(5)-C(6)	110.6(3)	C(7)-C(6)-C(5)	113.9(3)
C(7)-C(6)-H(6A)	108.8	C(5)-C(6)-H(6A)	108.8
C(7)-C(6)-H(6B)	108.8	C(5)-C(6)-H(6B)	108.8
H(6A)-C(6)-H(6B)	107.7	C(6)-C(7)-C(8)	110.6(3)
C(6)-C(7)-H(7A)	109.5	C(8)-C(7)-H(7A)	109.5

C(6)-C(7)-H(7B)	109.5	C(8)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	108.1	C(9)-C(8)-C(7)	108.8(3)
C(9)-C(8)-H(8A)	109.9	C(7)-C(8)-H(8A)	109.9
C(9)-C(8)-H(8B)	109.9	C(7)-C(8)-H(8B)	109.9
H(8A)-C(8)-H(8B)	108.3	O(2)-C(9)-C(10)	108.0(3)
O(2)-C(9)-C(8)	112.0(4)	C(10)-C(9)-C(8)	112.2(4)
O(2)-C(9)-H(9)	108.1	C(10)-C(9)-H(9)	108.1
C(8)-C(9)-H(9)	108.1	O(3)-C(10)-C(9)	111.2(3)
O(3)-C(10)-C(5)	103.0(3)	C(9)-C(10)-C(5)	117.2(3)
O(3)-C(10)-H(10)	108.4	C(9)-C(10)-H(10)	108.4
C(5)-C(10)-H(10)	108.4	O(1)-C(11)-N	128.9(4)
O(1)-C(11)-O(3)	122.3(4)	N-C(11)-O(3)	108.8(3)

Table 3

Torsion angles [deg] for compound 19($C_{11}H_{17}NO_3$)

C(11)-N-C(1)-C(2)	153.2(4)	C(5)-N-C(1)-C(2)	52.6(4)
N-C(1)-C(2)-C(3)	51.9(4)	C(1)-C(2)-C(3)-C(4)	-56.3(4)
C(2)-C(3)-C(4)-C(5)	54.7(4)	C(11)-N-C(5)-C(4)	-150.9(3)
C(1)-N-C(5)-C(4)	51.6(4)	C(11)-N-C(5)-C(10)	-31.7(4)
C(1)-N-C(5)-C(10)	170.8(3)	C(11)-N-C(5)-C(6)	83.2(4)
C(1)-N-C(5)-C(6)	-74.2(5)	C(3)-C(4)-C(5)-N	-49.1(4)
C(3)-C(4)-C(5)-C(10)	-157.4(3)	C(3)-C(4)-C(5)-C(6)	74.0(4)
N-C(5)-C(6)-C(7)	-152.1(3)	C(4)-C(5)-C(6)-C(7)	84.5(4)

C(10)-C(5)-C(6)-C(7)	-46.0(4)	C(5)-C(6)-C(7)-C(8)	57.2(4)
C(6)-C(7)-C(8)-C(9)	-60.7(4)	C(7)-C(8)-C(9)-O(2)	177.8(3)
C(7)-C(8)-C(9)-C(10)	56.1(4)	C(11)-O(3)-C(10)-C(9)	-153.3(3)
C(11)-O(3)-C(10)-C(5)	-27.0(3)	O(2)-C(9)-C(10)-O(3)	-54.8(4)
C(8)-C(9)-C(10)-O(3)	69.2(4)	O(2)-C(9)-C(10)-C(5)	-172.8(3)
C(8)-C(9)-C(10)-C(5)	-48.9(4)	N-C(5)-C(10)-O(3)	33.8(3)
C(4)-C(5)-C(10)-O(3)	149.5(3)	C(6)-C(5)-C(10)-O(3)	-80.2(3)
N-C(5)-C(10)-C(9)	156.1(4)	C(4)-C(5)-C(10)-C(9)	-88.1(4)
C(6)-C(5)-C(10)-C(9)	42.1(4)	C(1)-N-C(11)-O(1)	-7.4(7)
C(5)-N-C(11)-O(1)	-163.8(4)	C(1)-N-C(11)-O(3)	173.3(3)
C(5)-N-C(11)-O(3)	16.9(5)	C(10)-O(3)-C(11)-O(1)	-171.9(4)
C(10)-O(3)-C(11)-N	7.4(4)		

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89. Crystallographic data for the structure **19** in this paper have been deposited with the Cambridge Crystallographic data Centre as supplementary publication number CCDC-246855. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK.

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PUBLICATIONS

1. Carbohydrate-Based Synthesis of Naturally Occurring Marine Metabolites Slagenins B and C. Mukund K. Gurjar*, **Smritilekha Bera. *Org. Lett.* 2002, *4,* 3569-3570.**

2. Synthesis of Rigid Bicycloheterocyclic Scaffolds from Vince's Lactam (Enzymatic Resolution of Vince's Lactam)**.** Mukund K. Gurjar,* **Smritilekha Bera,** Rohini R. Joshi, and Ramesh A. Joshi. ***Heterocycles,* 2003, *60,* 2293-2303.**

3**.** An enantioselective synthesis of 1-azaspiro[5.5]undecane Ring system of histrionicotoxin from D-glucose. Mukund K. Gurjar*, **Smritilekha Bera.** (***Communicated***).