SUMMARY

Our research work concerns the synthesis and stereochemistry of nitrogen heterocycles, which form structural motifs on azasteroids and alkaloids. The thesis has an appendix, where we describe our studies on the application of Blaise reaction for the synthesis of β-keto esters.

Thus thesis entitled "*Studies on the synthesis and stereochemistry of selected saturated heterocycles*" is divided into three chapters and an appendix.

Chapter 1: Synthesis and stereo-chemical studies on 8-azasteroid fragments.

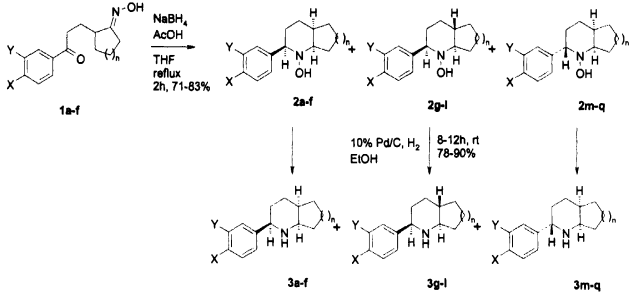
Chapter 2: Stereochemistry of quinolizidines by dynamic NMR spectral studies.

Chapter 3: Synthesis and stereochemistry of manzamine fragments *via* olefin metathesis reaction and

Appendix: Applications of Blaise reaction for synthesis of β-keto esters a precursor for Nazarov reagent.

1 Synthesis and stereochemical studies on 8-azasteroid fragments

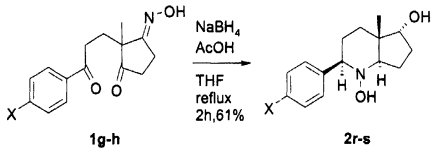
The perhydro-1-quinolinol and perhydrocyclopenta[*b*]pyridin-1-ol framework fits well into 8-azasteroids. We have achieved the synthesis of 2-arylperhydro-1-quinolinols (**2a-c**, **2g-i**, **2m-n**) and 2-arylperhydrocyclopenta[*b*]pyridin-1-ols (**2d-f, 2h-l, 2o-q**) and discerned their stereochemistry by analysis of their spectra. Condensation of readily available Mannich bases and cyclic ketones provided 1,5-diketones, which served as precursors for the synthesis of saturated nitrogen heterocycles. The mono-oximes **1a-f**, generated from corresponding 1,5-diketones were subjected to reduction with sodium borohydride and acetic acid to furnish three isomers of cyclic *N*-hydroxylamines **2a-q.** The isomers were separated and characterized on the basis of spectroscopic studies (IR, ^{1}H NMR, ^{13}C NMR, 2D NMR – NOE, HMBC, HSQC, and COSY – MS, HRMS) and in some cases by X-ray crystal structure determination. The hydroxylamines **2a-q** was further reduced with H_2, Pd/C to get corresponding secondary amines **3a-q** (Scheme 1).



1a, **2a**, **2g**, **2m**, **3a**, **3g**, **3m**: X = Y = H, n = 1; **1b**, **2b**, **2n**, **3b**, **3h**: X = OMe, Y = H, n = 1
1c, **2c**, **2i**, **2n**, **3c**, **3l**, **3n**: X = Y = OMe, n = 1; **1d**, **2d**, **2j**, **2o**, **3d**, **3j**, **3o**: X = Y = H, n = 2
1e, **2e**, **2k**, **2p**, **3e**, **3k**, **3p**: X = OMe, Y = H, n = 2; **1f**, **2f**, **2l**, **2q**, **3f**, **3l**, **3q**: X = Y = OMe, n = 2

Scheme 1

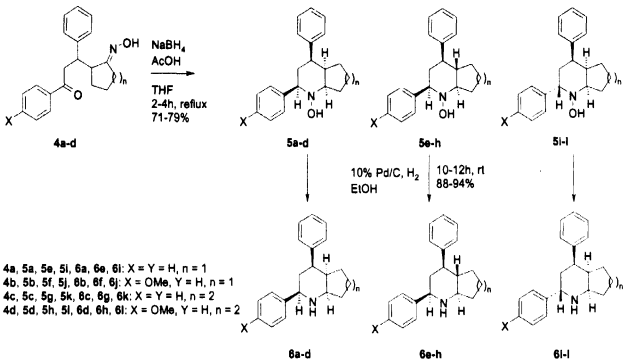
Presently developed reductive intramolecular cyclization (RIC) protocol on keto-oximes was extended to the synthesis of 8-azaestradiol fragments **2r-s**. In both cases mono-oximes **1g-h** on RIC reaction provided single diastereomers **2r-s** (Scheme 2). The hydroxylamine **2s** fits well on the framework of the hormone 17-α-estradiol.



1g, **2r**: X = H, **1h**, **2s**: X = OMe

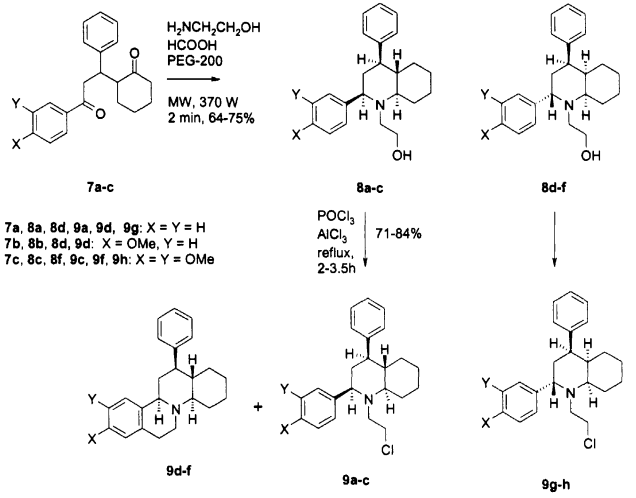
Scheme 2

These RIC reactions were repeated on the mono-oximes **4a-d** incorporating C12 (steroidal numbering) phenyl ring to provide cyclic hydroxylamines **5a-l**. The hydroxylamines **5a-l** were independently reduced to get cyclic secondary amines **6a-l** (Scheme 3).



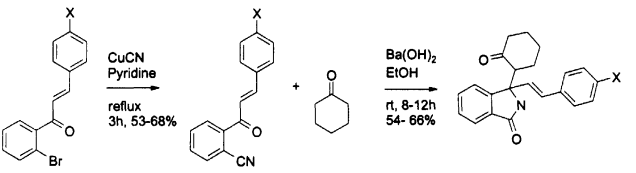
Scheme 3

The microwave mediated reductive amination of the 1,5-diketones **7a-f** with ethanolammonim formate provided two isomers of bicyclic ethanolamines **8a-k** (Scheme 3). Chromatographically separated isomers were subjected to reaction with $AlCl_3$in $POCl_3$ with an intention to form 8-azasteroid skeleton. However, only in the case of **8a** we have obtained 12-phenyl-8-azasteroid **9d.** Remaining all ethanolamine derivatives provided only corresponding alkyl chlorides **9a-h** (Scheme 4).



Scheme 4

In a quest to prepare *B*-nor-8-azasteroids, the chalcones **10a-c** generated from 2-bromoacetophenone and aryl aldehydes were subjected to reaction with CuCN to get 2-cyano chalcones **11a-c**. Reaction of the cyano chalcones **11a-c** and cyclic ketones provided interesting isoindoles **12a-f** instead of anticipated conjugate addition products (Scheme 5).

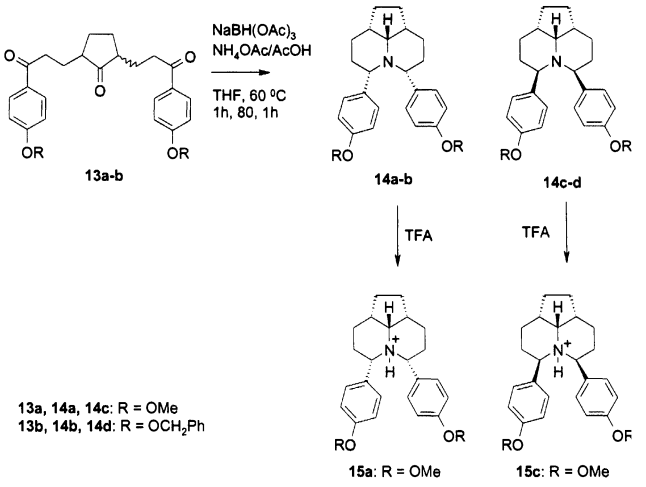


10a, **11a**, **12a**: X = H; **10b**, **11b**, **12b**: X = OMe

Scheme 5

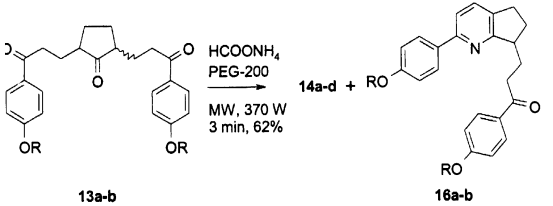
2. Stereochemistry of quinolizines by dynamic NMR spectral studies

The 1,5,9-triketones **13a-b** were reduced with $NaBH(OAc)_3$ to furnish two isomers of quinolizines **14a,c**, which were separated by chromatography. Dynamic NMR studies were conducted on **14a** and **14c** in temperature range of -140 °C and +50 °C. The quinolizines displayed dynamic behavior for aryl rotation, inversion at nitrogen centre and conformational changes in six-membered ring. The DNMR studies showed that aryl rotation gets arrested at about -40 °C, where as the conformational flexibility became slow at -140 °C. The nitrogen inversion has similar dynamic behavior as that of C-C bond rotation around sp^2-sp^3 carbons. Corresponding salts of quinolizines **15a,c** were prepared to arrest the nitrogen inversion and to study their stereochemical behavior. The structure and conformation of the two corresponding ammonium salts **14a** and **14c** were also obtained in solution by the same techniques in addition, their solid-state structures were confirmed by single crystal XRD data and theoretical studies (Scheme 6).



Scheme 6

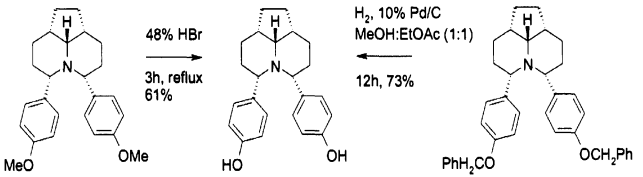
When an attempt was made to prepare quinolizines under the influence of microwaves using $HCOONH_4$ in PEG-200, the reaction provided cyclopenta[*b*]pyridines **16a-b** in addition to reductive amination cyclization products **14a-d** (Scheme 7).



13a, 14a, 14c, 16a: R = OMe; **13b, 14b, 14d, 16b**: R = OCH_2Ph

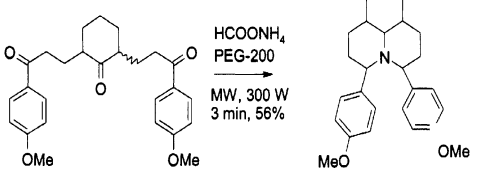
Scheme 7

Towards the synthesis of quinolizine based crown ethers, we deprotected the hydroxyl group of **14a** to obtain bis-phenol **17**. Similarly hydrogenation of **14b** provided bis-phenol **17** (Scheme 8).



Scheme 8

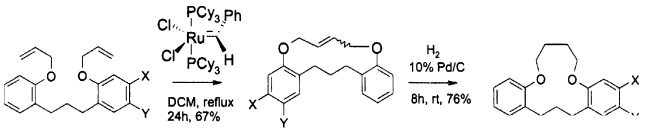
We extended the reductive amination method for the synthesis of isomeric 3,5-di(4-methoxyphenyl)perhydropyrido[3,2,1-*ij*]quinolines **19a,b** from corresponding triketone **18**. We have also prepared corresponding quaternary salts from **19a,b** to study their conformational behavior (Scheme 9).



Scheme 9

3 Synthesis and stereochemistry of manzamine fragments *via* olefin metathesis reaction

Manzamine alkaloids incorporate 13-membered nitrogen heterocyclic structure and this unit is crucial for their biological activity. We synthesized the 13-membered ring structures with at least two oxygen atoms in the ring to understand their stereochemical and ionophoric properties. Grubb's olefin metathesis was used as a key reaction in the synthesis. Initially, dibenzo-13-crown-2 **22a-c**, were prepared starting from diaryl propanes **20a-c**. The ring-closing olefin metathesis (RCM) reaction on **20a-c** provided *E*-olefins **21a-c** exclusively (Scheme 10).

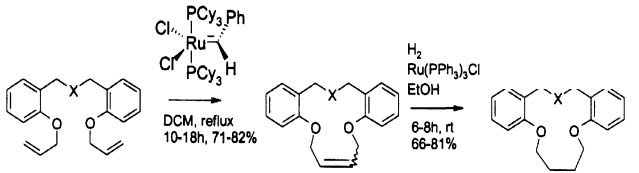


20a-c **21a-c: E/Z = 100:0** **22a-c**

20a, 21a, 22a: X = Y = H; **20b, 21b, 22b:** X = H, Y = Cl; **20c, 21c,** 22c: X = Me, Y = Cl

Scheme 10

Exclusive arrival of *E*-isomer **21a-c** in RCM reaction prompted us to study the influence of hetero-atom on the stereochemistry of the alkene. Accordingly, the bis-allyl ethers **23a-c** were prepared and subjected to RCM reaction (Scheme 11). Indeed, in each case the *E*/*Z* ratios in the products **24a-c** were different, indicating the influence of the hetero-atom on the intermediate ruthenium complexes. Reduction of the double bond present in **24a** and **24c** furnished corresponding crown ethers **25a-b** (Scheme 11).



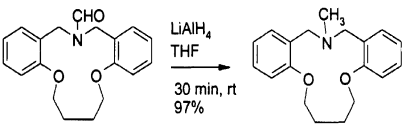
23a-c **24a-c** **25a-b**

24a: *E*/*Z* : 29:71; **24b**: *E*/*Z* : 100:0; **24c**: *E*/*Z* : 57:43

23a, 24a, 25a: X = N-CHO; **23b, 24b**: X = O; **23c, 24c, 25b**: X = S

Scheme 11

Reduction of the formyl group in **25a** furnished *N*-methyl aza-oxa-crown **26** (Scheme 12)

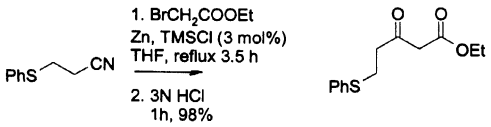


25a **26**

Scheme 12

Appendix: **Applications of Blaise reaction for synthesis of β-keto esters. A facile synthesis of the precursor for Nazarov reagent**

We employed Blaise reaction for the synthesis of the precursor for Nazarov's reagent **28**. When Blaise condensation was conducted on 2-(phenylsulfanyl)ethyl cyanide **27,** with ethyl bromoacetate and *insitu* zinc activated with 3 mol% of TMSCl β-ketoester **28** was obtained in quantitative yield. The β-ketoester **28** serves as a precursor for Nazarov reagent (Scheme 13).



27 **28**

Scheme 13