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AN ENANTIOSELECTIVE APPROACH TO SYNTHESIS OF ADVANCED CHIRAL TEMPLATES FOR THE CONSTRUCTION OF INDOLIC AND INDOLIZIDINIC ALKALOIDS

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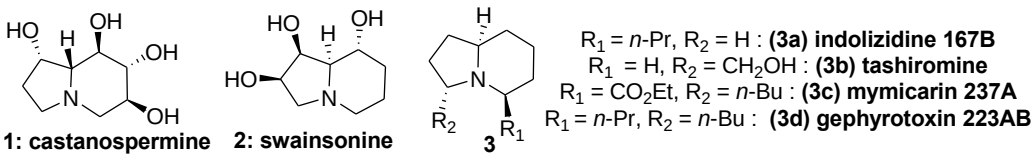
Abstract – A new approach for the syntheses of chiral indolic and indolizidinic templates is presented. They were obtained in three steps starting from a chiral primary amino-vinylsilane. The key step was the *N*-acyliminium π-cyclization, leading diastereoselectively to the formation of the six membered ring templates.

Indolizidines or their unsaturated analogues are among of the most important structural motifs found abundantly in nature. Their sources are extremely divers varying from marine and terrestrial materials to organisms, such as plants, bacteria, fungi, vertebrates and invertebrates.[1] For example, alkaloids **1,2** (Scheme 1) are well-known for their ability to function as excellent inhibitors of biologically important pathways. These include the binding and processing of glycoproteins, potent glycosidase inhibitory activities,[2] activity against AIDS virus HIV and some carcinogenic cells as well as against other important pathologies.[3] In addition, gephyrotoxins such as **3a-d** show significant biological activities as exemplified by the ability of many of them to act as non-competitive blockers of neuromuscular transmission by interacting with nAChRS (nicotinic acetylcholine receptors) of the CNS.[4]

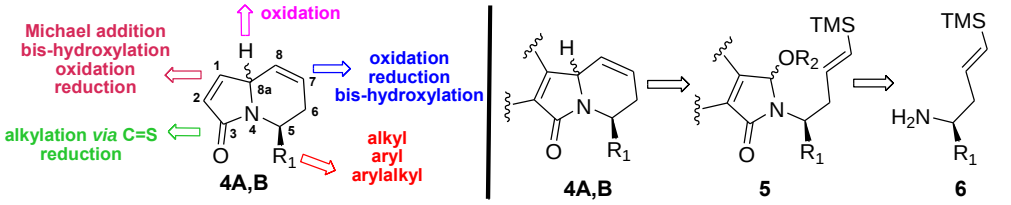
Scheme 1. Representative Natural products containing indolizidine unit.



Although a vast amount of work towards these bicyclic alkaloids in both chiral and racemic syntheses has been appeared in the literature, the challenges of a plethora of the innovative strategies developed and used for this purpose rest the introduction of chirality and several functional groups to the indolizidine scaffold. The latter fact is often problematic and consequently leads to the use of multistep sequences.

In light of the limitations encountered during these investigations and taking into account the interesting biological profiles and potential of these structures as valuable candidates for new therapeutic agents, the demand for direct and straightforward methods has become increasingly clear. In this context, the design of simple aza-bicyclic templates capable of driving by simple additional manipulations to structural diversity and complexity including subgroups of these alkaloids is of high interest in organic synthesis.[5]

Scheme 2. Retrosynthetic pathway leading to the advanced chiral indolizidine templates **4A,B**.



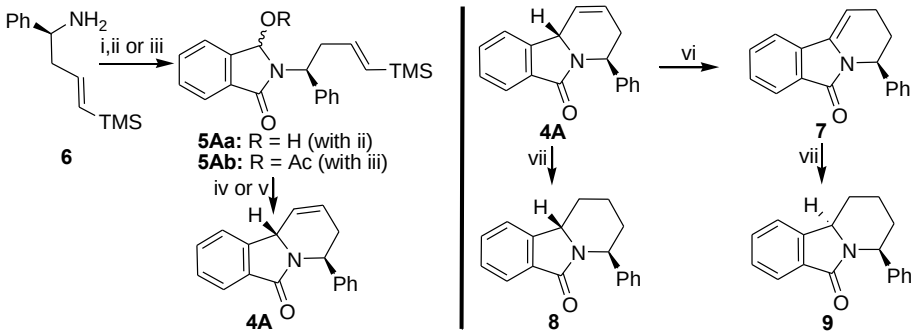
Our objective herein was directed towards the enantioselective synthesis of the aza-bicyclic systems **4A,B** (Scheme 2). The latter, equipped with appropriates functionalities, could tolerate numerous and known synthetic manipulations[6] to provide a large number of polyhydroxylated indoizidine alkaloids, gephyrotoxins and corresponding benzoindolizidines with different degrees of unsaturations.

Accordingly, the *N*-acyliminium ions chemistry using enantiopure amino-vinylsilane[7] and imide as starting materials would appear to provide an ideal solution of this dilemma. Retrosynthetically, we envisioned that we could establish the *R/S* stereochemistry at C_{8a}-position selectively through π-cationic cyclization of precursor **5**, which can be prepared easily in a two step-sequence from amine **6** (Scheme 2).

We focused in the first place our study on the synthesis of the phtalimide derivative **4A** (Schemes 2, 3). Indeed, we anticipated that our approach would be less problematic using an aromatic ring in place of the double bond on the five membered ring system (phtalimide compared to maleimide). The primary amine **6** was converted in two steps, condensation with phtalic anhydride followed by the reduction of the resulting imide with $LiEt_3BH$, to the hydroxylactam **5Aa** in 74% overall yield. This one was isolated in a one to one ratio of the two diastereoisomers, implying no stereocontrol from the stereocenter presents on the side chain. The cyclization was first performed in the presence of two equivalents of $BF_3.OEt_2$ as Lewis acid and led to the tricyclic system **4A** in 70% yield. Recently, an efficient method using bismuth (III) triflate as a Lewis acid catalyst was reported by some of us to generate the formation of *N*-acyliminium species.[8] In order to use easier and cleaner conditions, we applied this new experimental procedure to the acetoxylactam **5Ab** obtained from the corresponding imide by a simple one-pot

reduction/acetylation methodology in 67% yield.[9] As a matter of fact, when we performed this catalytic acid-mediated π-cationic cyclization with $Bi(OTf)_3$ (1 mol%), we were pleased to isolate compound **4A** in similar yield than with $BF_3.OEt_2$ (69% instead of 70%).[10] This result shows that the use of 1 mol% of $Bi(OTf)_3$ is as efficient as the use of a stoechiometric amount of $BF_3.OEt_2$ (200 mol%). In addition the catalytic sequence can be applied with success to cyclizations involving vinylsilane moiety providing 6-membered ring possessing an unsaturation. In both cases, only one diastereoisomer was formed during the cyclization process thanks to the phenyl substituent presents on the side chain.[11] A *syn* relationship between the angular H of the newly formed stereogenic center and the phenyl substituent was firstly deduced from previously published works.[12,13]

Scheme 3. Synthesis of the benzoindolizidine template **4A** and its reduction and epimerization reactions.



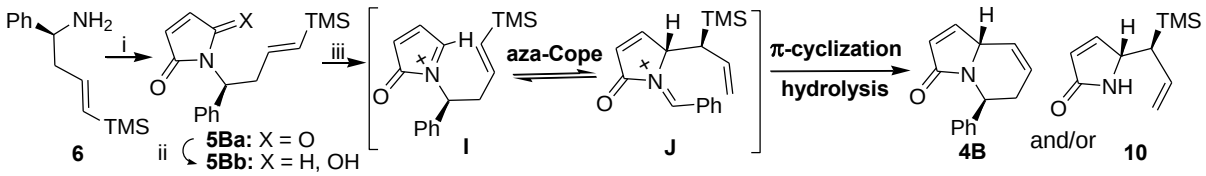
Key: (i) phtalic anhydride (1 equiv), Et_3N (cat.), toluene, Dean-Stark apparatus, 24 h, 92%; (ii) $LiEt_3BH$ (1.4 equiv), CH_2Cl_2, - 78 °C, 10 min, 80%; (iii) $LiEt_3BH$ (1.4 equiv), CH_2Cl_2, - 78 °C, 10 min, then Ac_2O (1.4 equiv), - 78 °C, 2 h, 67%; (iv) $BF_3.OEt_2$ (2 equiv), CH_2Cl_2, rt, 8 h, 70%; (v) $Bi(OTf)_3$ (0.01 equiv), CH_3CN, rt, 8 h, 69%; (vi) MeONa (1.2 equiv), MeOH, 30 min, 84%; (vii) Pd on carbon (0.1 equiv), H_2 (1 atm), EtOH, rt, 24 h, 63% for **8** and 69% for **9**.

With the aim to confirm the stereochemistry of the newly created stereocenter and to study the possibility of epimerization of this one in order to reach the *trans* relationship presents in gephyrotoxins (Scheme 1, **3a,c,d**) we investigated the migration of the double bond and its reduction. Treated in basic conditions (MeONa in MeOH), compound **4A** gave the conjugate more stable isomer **7** in 84% yield. The hydrogenation process was applied on both **4A** and **7** and provided the reduced products **8** and **9** in 63% and 69%, respectively, as two diastereoisomers, epimers at the carbon of the ring junction (Scheme 3). The total diastereoselectivity observed during the reduction of **7** can be explained by the steric hindrance of the phenyl substituent, involving the approach by the hydrogen on the more reachable face and implying the formation of the *trans* diastereomer. Thus, we obtained the same relative stereochemistry than the one in gephyrotoxins and that result confirmed, by comparison, the *cis* relationship in product **8**.

Encouraged by these results, we turned our attention to the maleimide derivative in view to synthesis our main target, the bicyclic system **4B** (Scheme 4). So, condensation of amine **6** onto maleic anhydride led to the imide **5Ba** in 88% yield. The selective 1,2 reduction of the C=O bond *versus* the 1,4 was found to be troublesome, only the treatment by the couple $NaBH_4/CeCl_3$ in methanol produced the desired

hydroxylactam **5Bb** in 86% yield. When reacted with two equivalents of $BF_3.OEt_2$, **5Bb** led to the formation of the expected bicyclic compound **4B** but with a low yield of 25% partially explained by the presence of the allylsilane derivative **10** in 8% yield and other non-characterized side products. The diene **4B** was obtained as a single diastereoisomer[11] and despite the low yield this result legitimates our strategy. For its part, the compound **10** was a result and an evidence of the aza-Cope transposition between the *N*-acyliminium ions **I** and **J**, this last one giving after hydrolysis the debenzylated molecule **10**.

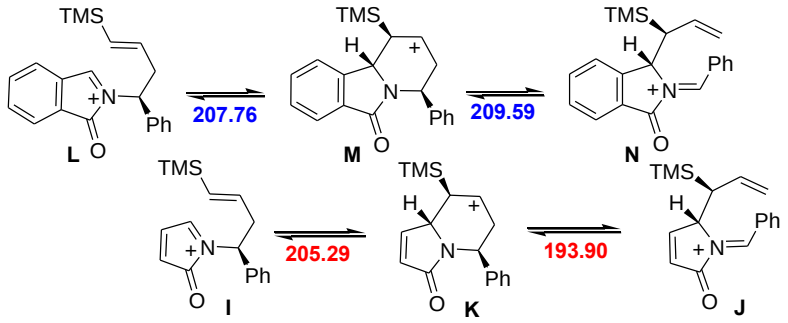
Scheme 4. Synthesis of the indolizidine template **4B**.



Key: (i) maleic anhydride (1 equiv), Et_3N (cat.), toluene, Dean-Stark apparatus, 48 h, 88%; (ii) $NaBH_4$ (1 equiv), $CeCl_3$ (1 equiv), MeOH, rt, 8 h, 86%; (iii) $BF_3.OEt_2$ (2 equiv), CH_2Cl_2, rt, 3 h, 25% for **4B** and 8% for **10**.

A dramatic change in the course of the π-cyclizations between **5Aa,b** and **5Bb** was observed, the first giving good yields and the second providing poor yields and side reactions. This significant difference is the direct consequence of the presence or not of an aromatic ring on the pyrrolidine one. In order to get an idea about these results, we calculated[14] the transition state energies between the six possible cationic species **I-N** in accordance with the results published earlier on iminium series (Scheme 5).[17] The cation products **N** or **J** would be obtained from **L** or **I** by the way of **M** or **K** common intermediates for both the aza-Cope process but also the formation of the cyclic systems **4A,B**. The passage from **M** to **N** is higher in energy than the one from **M** to **L** (1.83 Kcal.mol^{-1}) while the energies between **K** and **J** is lower than the one between **K** and **I** (-11.39 Kcal.mol^{-1}). This huge difference in energy could explain the dramatic change in reactivity. As a consequence, the phtalimidic derivative leading cleanly to the desired tricyclic product **4A** and the maleimidic derivative giving way to the competitive aza-Cope reaction.

Scheme 5. Transition state energies between cationic species **I,J,K** and **L,M,N** in Kcal.mol^{-1}.



In conclusion, we have demonstrated that chiral amino-vinylsilane is suitable for the synthesis of aza-bicyclic templates. The efficiency of the *N*-acyliminium ions chemistry for the α-amidocyclization

was shown to be substrate dependant, giving or not an aza-Cope rearrangement. The templates **4A,B** obtained in three steps from the primary amines should be convenient intermediates for the access to both polyhydroxylated indolizidines and gephyrotoxins. Works are currently underway in our group in order to avoid the aza-Cope competitive reaction and to apply this methodology to the synthesis of alkaloids.

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10. **Procedures for the π-cyclization. Protocol (a):** $BF_3.OEt_2$ (130 μL, 1.0 mmol) was added at room temperature to a solution of hydroxy lactam **5Aa** or **5Ba** (0.5 mmol) in CH_2Cl_2 (5 mL). After one night of stirring, the reaction was cooled to 0 °C and carefully quenched by addition of a saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL), the organic layers were combined, dried over $MgSO_4$ and evaporated. The residue was then purified by chromatography on SiO_2 column using AcOEt/cyclohexane as eluenting mixture and provided cycles **4A** and **4B** in 70% and 25% yields, respectively, for two steps. **Protocol (b):** $Bi(OTf)_3$ (0.01 equiv) was added in one portion to a stirred solution of acetoxy lactam **5Ab** (197 mg, 0.5 mmol) in MeCN (2.5 mL). When the reaction was over (monitored by TLC) a saturated aqueous solution with $NaHCO_3$ was added. The aqueous layer was then extracted with CH_2Cl_2 (3×5 mL), the organic layers were combined, dried over $MgSO_4$ and evaporated under *vacuo*. The residue was than purified by chromatography on SiO_2 column using same eluent as outlined above to provide in 69% yield compound **4A.** This product was isolated as a colorless gummy. (AcOEt/cyclohexane, 30:70). $[\alpha]^{20}_D$ -88 (*c* 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 7.86 (d, *J*=7.8Hz, 1H), 7.52-7.24 (m, 8H), 5.98 (s, 2H), 5.87 (t, *J*=3.9Hz, 1H), 4.70-4.63 (m, 1H), 2.72 (bs, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 167.2, 144.0, 140.0, 132.0, 131.7, 128.7, 128.3, 127.5, 127.3, 125.6, 125.2, 124.0, 122.1, 54.7, 48.6, 27.6. **Data for 4B.** This product was isolated as a colorless gummy from hydroxy lactam **5Ba** by using **Protocol (a)**. (AcOEt/cyclohexane, 30:70). ^{1}H NMR (200 MHz, $CDCl_3$): 7.40-7.26 (m, 5H), 7.04 (dd, *J*=5.4 and 2.3Hz, 1H), 6.17 (dd, *J*=5.4 and 2.3Hz, 1H), 5.99 (dq, *J*=10.1 and 2.3Hz, 1H), 5.94 (dd, *J*=10.2 and 2.3Hz, 1H), 5.68 (t, *J*=4.8Hz, 1H), 4.42-4.42 (m, 1H), 2.70-2.61 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 167.3, 147.3, 140.8, 139.4, 133.9, 134.2, 129.1, 127.9, 122.7, 58.20, 48.79, 28.03.
11. Determined by ^{1}H-NMR analysis on the crude mixture.
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