AN INTRAMOLECULAR RING CONTRACTION APPROACH TO THE SYNTHESIS OF INDOLIZIDINE ALKALOIDS

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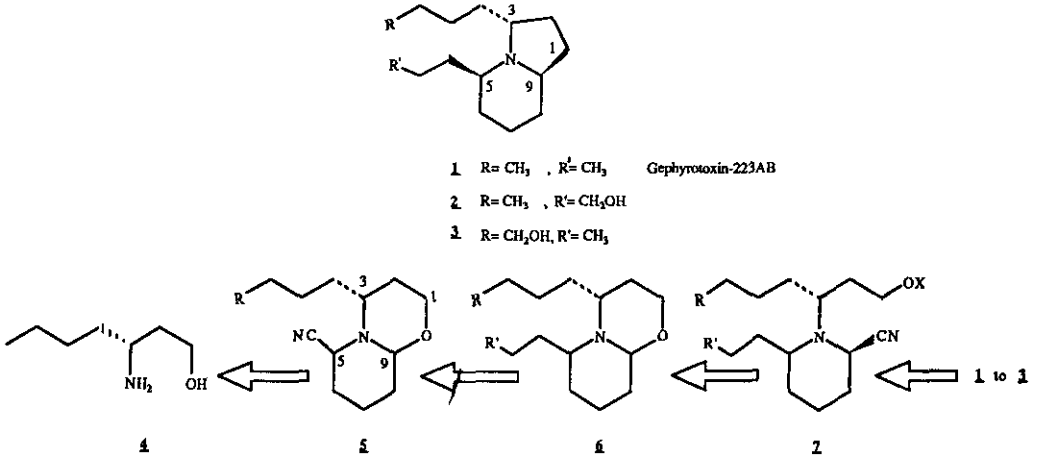
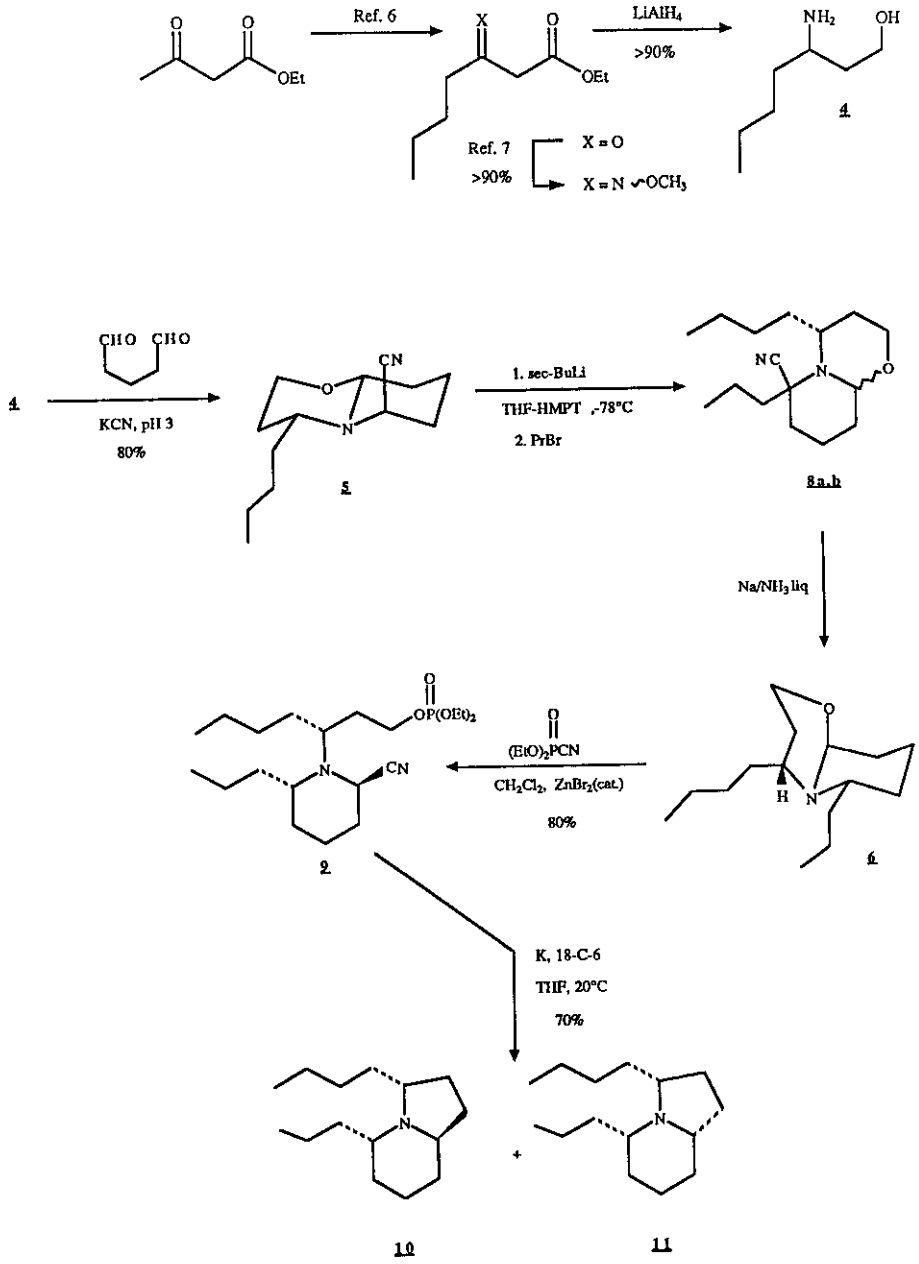
Abstract — Reaction of the anion of synthon 5 with PrBr followed by reductive decyanation gave the key intermediate 8. Ring opening of 8, on treatment with diethyl cyanophosphonate, produced 9. Compound 9 reacted with K plus 18-crown-6 in THF to give a 9:1 mixture of indolizidines 10 and 11.

The often important biological activities displayed by the indolizidine alkaloids has stimulated the development of synthetic strategies for the construction of the bicyclic ring system of this class of compounds[1]. Our interest in the synthesis of the indolizidine alkaloids from dendrobatid frogs also stems form a consideration of their biological activities and has led us to investigate the approach illustrated in scheme 1 as a route to the known alkaloids 1 - 3 [1] as well as structural analogs. In essence this approach can be divided into three stages : preparation of the 1,4-dihydropyridine equivalent 5 from the appropriate aminoalcohol 4, introduction of the side chain at C-5[3], and finally, contraction of the tetrahydro-1,3-oxazine system of intermediate 6 producing the pyrrolidine ring of the product molecule. As described in this communication for the synthesis of the gephyrotoxin-223AB isomers 10 and 11 this latter transformation can be achieved in two steps involving i) opening of the tetrahydro-1,3-oxazine ring of 6 (R=Pr) to give 7, and ii) ring closure by direct generation of an anion α- to nitrogen in 7 followed by intramolecular displacement of the group OX.




Ref. 6
LiAlH4
>90%
NH2
OH
OEt
X = O
X = N OCH3
Ref. 7
>90%
CHO CHO
KCN, pH 3
80%
CN
1. sec-BuLi
THF-HMPT -78°C
2. PrBr
NC
Na/NH3 liq
OP(OEt)2
(EtO)2PCN
CH2Cl2, ZnBr2(cat.)
80%
K, 18-C-6
THF, 20°C
70%
+

Scheme 2

At the present time all our experiments have been carried out on the racemic form of synthon 5,[4] as the α-amino alcohol precursor to this molecule is readily prepared in ~ 60% overall yield, on a multigram scale (scheme 2).[5-7] Synthon 5, obtained by reaction of 4 with glutaraldehyde and KCN following established procedure,[2] was isolated as a colourless oil in 80% yield after column chromatography on silica-gel (hexane:ether ; 1.5:1). Reaction of 5 with sec-BuLi in THF-HMPT at -78°C followed by addition of PrBr gave compound 8 as a mixture of epimers at C-9.[8] In order to avoid unnecessary loss of these sensitive compounds on contact with column adsorbants the mixture was immediately reacted with Na/NH_3 liq.[10] producing a single product 6 (R=Pr), isolated as a colourless oil (57% overall yield from 5).[5] Analysis of the 2D-nmr spectra for this compound revealed that it possessed a cis ring junction with the butyl side chain in the axial orientation. In this conformation important steric (peri) interactions with the C-5 propyl substituent are diminished.

For the crucial ring opening step diethyl cyanophosphonate proved to be the reagent of choice as its reaction with 6 in the presence of $ZnBr_2$ (cat.) resulted in simultaneous creation of a new α-aminonitrile center at C-9 and conversion of the ring-B oxygen atom to a phosphate leaving group. Compound 9 was thus obtained in 80% yield after column purification (alumina ; ether). As all subsequent attempts to form an anion at C-9 failed using alkyllithium or amide bases we decided to explore the possibility of using the anion that is generated α- to nitrogen on reaction of α-aminonitriles under dissolving metal conditions as a nucleophile in the ring closure step. To our knowledge this approach has not as yet been exploited in synthesis. As might be expected, the reaction of 9 with Na/NH_3 liq. resulted in exchange of the cyano group for a hydrogen before cyclization had time to occur. The phosphate ester group remained intact under these conditions however, which encouraged us to conduct further experiments in THF as a non protic solvent using potassium metal in combination with 18-crown-6.[11] Under these conditions decyanation and ring closure was observed leading to formation of a 9:1 mixture of indolizidines 10 and 11 in 70% combined yield. The structures of these products, isomeric to gephyrotoxin 223, were determined from their 2D-NMR spectra, and from a comparison of their ^{13}C chemical shift values with these reported in the literature.[12] That the 5,9-trans indolizidine 10 with the correct C-3,9 relative stereochemistry is the major product indicates that the intermediate anion in the ring closure reaction is pyramidal and trans-diaxial to the non bonding pair of electrons on nitrogen[16]. The stereospecific formation of 6 from 8 is also consistent with this model.[10]

Work is currently in progress in our laboratory to adapt this ring contraction approach to the synthesis of the natural compounds 1 to 3, and to explore the scope of our new method for generating and alkylating anions α- to non stabilized 3-amines.[13] This interesting reaction provides an "Umpolung" of the reactivity of electron-deficient iminium ions.

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3 The atoms in synthon 5 and its derivatives are numbered such that there is a direct correspondance with the numerotation of alkaloids 1 and 3.

4 Relative stereochemical relationships only are implied in structures 5-11. The preparation of optically pure 4 by a modification of the sequence in scheme 1 is under study.

5 Satisfactory ir, ms, ^{1}H and ^{13}C nmr, and microanalyses were obtained for all compounds described.

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8 The alkylation reaction leading to 8ab appears to be stereospecific. The assignment of the propyl group to the equatorial position is based on analogy with the results obtained for cyano substituted cyclohexanes[9a] and on the results of theoretical calculations[9b].

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Received, 7th March, 1988