Syntheses of indole alkaloids and analogs containing the aspidosperma skeleton

PhD theses

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1. Introduction, our aims

Nowadays the Medicinal Chemistry Research attaches significance to searching and biological testing of natural products, although other research technics also gained in high importance. The research of natural products (e.g.: alkaloids) will play an important role in the future, as the living organisms provide chiral molecules with complex structures for pharmacological testing.

Most of the indole alkaloids isolated from plants can be classified to alkaloids of the aspidosperma group. At the beginning of my PhD studies we planned to develop a new, simple total synthesis of the aspidosperma skeleton, as well as the synthesis of some alkaloids and analogs. Our aim was the examination of the isomerization process during the build up of the D ring of the aspidosperma skeleton. Later on our targets were broadened and we tried to develop the syntheses of alkaloids containing an epoxy ring starting from natural tabersonine.
2. Synthesis of alkaloids and alkaloid-like molecules containing the aspidosperma skeleton

The build-up of the aspidosperma skeleton was carried out by a new convergent synthetic strategy following the biosynthetic-route through stable secodin-type intermediates (7a, 7b). The 6 triptamine analog which contains a hidden anilinoacrylate structural unit was chosen as a key-intermediate of our strategy. The synthesis of this compound (6) was started from a hydroxy-methyl group containing triptamine derivative (1) which was synthetized formerly in our research group (1→2→3→4→5→6)(Scheme 1).

![Scheme 1](image)

At the key step the secodin derivatives (7a, 7b) — the precursors of the pentacyclic skeleton — were obtained from the reaction of the 6 primer-amine and aldehydes or aldehyde-equivalents. Then the water elimination from the molecules resulted in dien structures (8) which were instantly reacted with the dienofil part of the D ring leading to the formation of 3-oxovincadifformine (9a), the alkaloid 3-oxominovincine (9b) respectively. From 9a and 9b the alkaloid vinkadifformine (9c) and the minovincne (9d) can be obtained in one step according to the former results of our research group (Scheme 2).

* The compounds described in this chapter are racemates, but only one of the antipodes is shown.
3. Stereoselective oxidation reactions of compounds with the aspidospermane and quebrachamine ring system. First synthesis of some alkaloids containing the epoxy ring

Continuing our studies we worked out the syntheses of alkaloids containing an epoxy ring in position 14,15 of the aspidosperma or quebrachamine skeleton starting from natural tabersonoine ((-)-10).

At first we tried to epoxidize the C14-C15 double-bond of tabersonine ((-)-10) with dimethyldioxirane. In this reaction ring transformation of aspidospermane → eburnane was only experienced (11a+b) (Scheme 3).
Then we tried to carry out the epoxidation by modifying the ring system first and then with changing the oxidizing agent. We found that the oxidation of the quebrachamine ring system ((+)-12a and (+)-12b) with tert-butyl-hydroperoxide in the presence of trifluoroacetic acid resulted in molecules containing the epoxy ring with 14S,15R configurations ((+)-13a and (+)-13b). The stereoselectivity of the oxidation reactions is due to the geometry of the ring system as was substantiated by molecular-mechanical computations. On the basis of the results, we worked out the first synthesis of the epoxy ring containing alkaloid (-)-lochnericine ((-)-14) (Scheme 4).

![Scheme 4](image)

In our further research we intended to form the epoxy ring in a simpler pentacyclic system, a compound ((-)-15) readily obtained from (-)-tabersonine ((-)-10). When the oxidation was tried with m-chloroperbenzoic acid the isolable product ((-)-16) was containing the epoxy ring with 14R and 15S configurations exclusively (Scheme 5). The stereoselectivity of the reaction could be successfully explained also in this case by molecular-mechanical computations.
Getting wise to the above facts the first syntheses of \((-\)-mehranine (\((-\)-17), \((+\)-voaphylline (\((+\)-18) and \((+\)-hecubine (\((+\)-19) were achieved (Figure 1).

4. Structural observations around compounds with aspidospermane and D-secoaspidopermane skeleton* 

Over the last three decades the synthesis of most plant alkaloids having an aspidospermane skeleton had been achieved. In earlier studies related to the convergent synthesis of aspidospermane, pseudoaspidospermane alkaloids and some alkaloid-like compounds, we observed partial or complete inversion of C7 and C21 in several cases (e.g.: 20 $\rightarrow$ 9a, or 21 $\rightarrow$ 9c)(Scheme 6).

* The compounds described in this chapter are racemates, but only one of the antipodes is shown.
The literature offers only in a few cases some hints about the possible mechanism of the conversions; therefore we decided to conduct further research in order to find a plausible rationalization.

The selected compounds were vincadifformine (9c), and the isomers of 20-desetilvincadifformine (22, 23), as well as their synthetic intermediates (24, 25, 26, 27) (Figure 2).

Figure 2
First we studied the behaviour of molecules under reductive conditions in acidic medium. The structures of the final products unequivocally show that the treatment with sodium borodeuteride of the imminum-cation intermediates, formed in hot acetic acid, resulted in their conversion into derivatives containing deuterium at C-21 (29), whereas the reactions effected with sodium borohydride in deuteroacetic acid gave products deuterated at C-16 (30) (Scheme 7).

![Scheme 7](image)

The aforementioned experimental results proved the existence of the imminum-cation intermediate (32), but did not gave any information about the possibility of an imine-enamine (32-33) tautomerism.

It seemed promising to carry out reactions in deutero cation containing medium, hoping that we would find deuterium show-up at C20. The chosen compounds were heated in deuteroacetic acid at reflux whereupon – proving our conception - deuteration took place at C20 in some cases (34) (Scheme 8).
Our results confirm the following mechanism (Scheme 9): in acidic medium the protonation and the splitting of C7-C21 bond resulted in an imminum kation (32), then the loss of proton enables 32 to undergo a two-directional cyclization involving the reactive atoms C7 and C21 (→28a →28b). On the other hand our studies — which were carried out in boiling deuteroacetic acid — proved that in several cases there must be an equilibration of the imminium salt (32) with the corresponding enamine (33).
5. Summary

A new biomimetic synthetic pathway has been developed to build up molecules with the aspidospermane skeleton. A simple synthesis of 3-oxovincadifformine and the alkaloid 3-oxominovincine has been realized. Using stereoselective oxidation reactions the first syntheses of the alkaloids (-)-mehranine, (+)-voaphylline, (+)-hecubine, and of (-)-lochnericine, all of them containing the epoxy ring, were achieved. During the build up of the D ring of the aspidosperma skeleton we observed the cis/trans isomerisation of the D/E rings. We succeeded in to stabilize the imminium intermediate of the mechanism with deuterium containing reactants, and to prove the existence of the equilibrium of the imminium salt and the corresponding enamine.
Publications:


