

## Biomimetic syntheses of alkaloids based on tetrahydropyridine

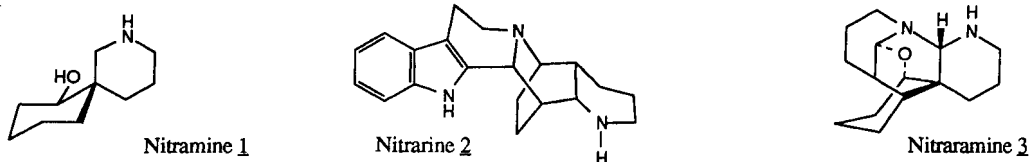
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**Abstract.** Many of the alkaloids found in *Nitraria* and *Lupine* species can be envisaged to arise from two simple building blocks, namely tryptamine and tetrahydropyridine. In particular in the *Nitraria* species, the alkaloids occur as racemates, in some cases, despite multi stereocenters. We assume that these alkaloids might be formed without interference of enzymes via spontaneous reactions of highly reactive intermediates. By carrying out a biomimetic approach many of these alkaloids were obtained via chemical synthesis, based on reactive precursors. The paper reviews the preparation of racemic Nitramine, Lupinine, Nazlinin, Nitrarine/Nitramidine, Spartein and Nitramine from tryptamine and the trimer of tetrahydropyridine, based on imine-enamine chemistry.

A variety of alkaloids, like Nitramine **1**, Nitrarine **2** and Nitramine **3**, have been isolated from different species of the *Nitraria* family (ref. 1). An interesting feature of these alkaloids is the fact that they are isolated as racemates, even in cases where the molecule contains four or five stereocenters (ref. 2). This has been observed before for alkaloids like akuammicine (ref. 3), yuehchukene (ref. 4) and lucidine (ref. 5).

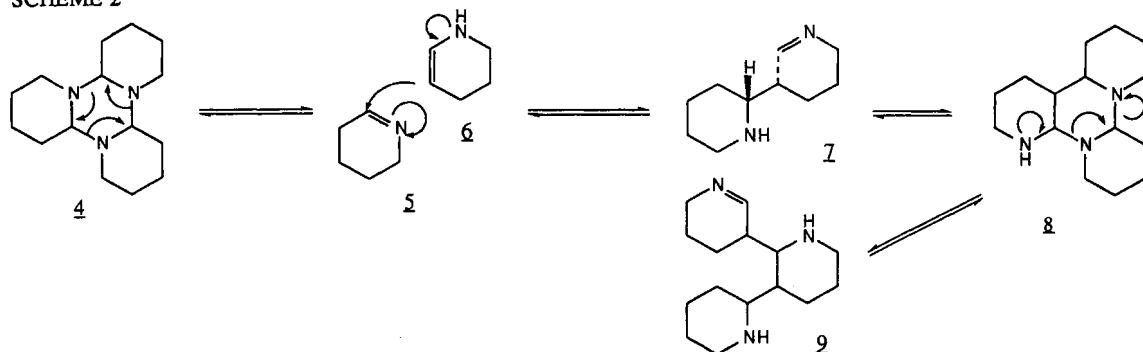
SCHEME 1



Although it is widely accepted, that plant enzymes play a role in the biosynthetic steps in the plants (ref. 6), it has been suggested before that in some cases a nonenzymic pathway cannot be excluded (ref. 3, 5). Also, in plants, nature has been carrying out one experiment after another to evolve an efficient defense mechanism. Many of the poisonous alkaloids found in plants today have helped these species to survive during thousands of centuries in a hostile environment by protecting them against animal consumption. This would imply that at a certain point in the evolution of the plant, more or less by coincidence, very reactive molecules are formed, which give rise to the spontaneous uncatalyzed formation of complex alkaloid skeletons as racemates. In later stages the plant might selectively convert one of the antipodes into chiral products or enzymatically destroy an antipode. Viewed in this way, the presence of racemic alkaloids in plants would be an indication, that these plants are in relatively early stages of their development. In terms of evolution this implies that the end-products of today might be the intermediates for future alkaloids.

The purpose of our research is to show that once the correct reactive biosynthetic precursors are prepared, the spontaneous formation of the racemic alkaloids can also be achieved in the laboratory under more or less biological conditions.

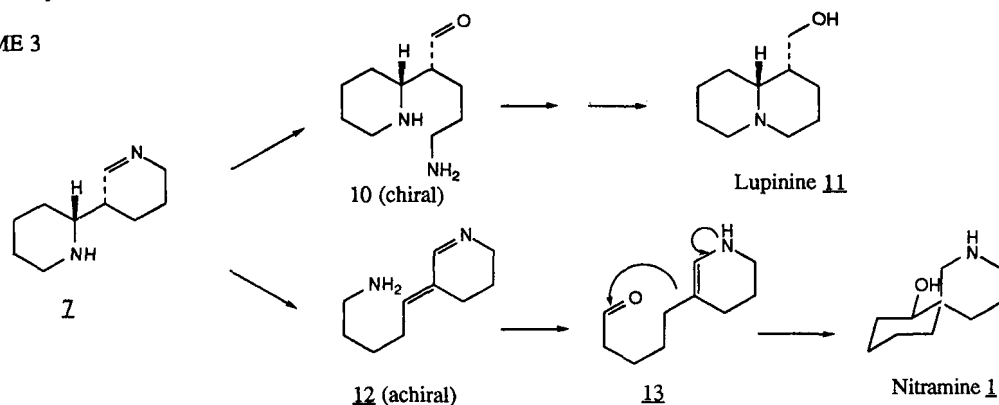
SCHEME 2



Nature is capable of producing an immense variety of rather different products based on a very small number of building blocks, like for instance acetyl-CoA. In the case of Nitraria alkaloids like Nitramine **1**, one can envisage a biosynthesis, based on lysine, via two units of tetrahydropyridine. Tetrahydropyridine exists as an equilibrium mixture of an imine **5** and the corresponding enamine **6**. Since these molecules are electrophilic and nucleophilic species respectively, reactions can be expected and indeed occur leading to a dimer and different trimers, depending on pH. Molecules like **5**, **6** or **7**, once formed in nature from lysine, possess the reactivity which might lead to spontaneous formation of a variety of products.

In the laboratory synthesis the starting material is  $\alpha$ -tripiperidein **4** which can be decomposed in water at pH 7. As indicated in scheme 2, formation of other trimers is possible. For the biosynthesis of Nitraria and Lupine alkaloids tetrahydroanabasine **7** is an important starting material. Opening one ring via **10** (scheme 3) leads to the lupine alkaloids (ref. 7), whereas retro-Michael reaction via **12** followed by oxidation and hydrolysis to **13** constitute a simple route to the racemic spirocyclic Nitraria alkaloids (ref. 8).

SCHEME 3

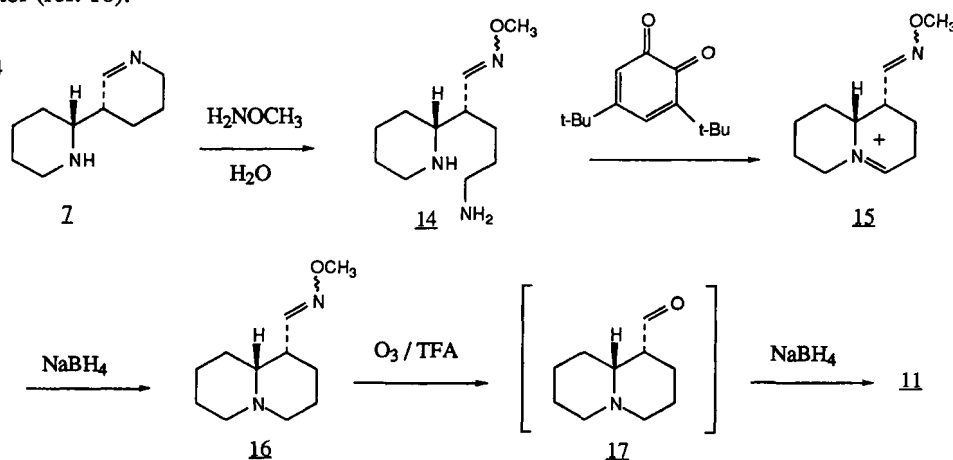


The instability of the tetrahydropyridines is a drawback in many cases for the laboratory synthesis of the reactive precursor, since we can not afford steps with low yields which might be acceptable for the plants in evolution. So, in the first instance, we carried out the synthesis of nitraria alkaloids using the far more stable glutarimide synthons. Thus Nitramine **1** was synthesized from the Wittig condensation product of N-benzyl triphenylphosphorylidene-glutarimide and glutaric aldehyde. After spirocyclization, reductive steps had to be carried out to obtain racemic **1** (ref. 8).

The synthesis of racemic lupinine and epi-lupinine could be carried out with synthons in the correct oxidation state starting from tetrahydroanabasine. The ring opening as depicted in Scheme 4 was realized with methoxyamine, leading in 98% yield to **14**, in which the stereochemistry was preserved. Oxidation was carried out with the commercially available di-*t*-butyl orthoquinone to **15** (45%) (ref. 9).

This reaction is strongly related to the copper containing amine oxidases, which use TPQ as the cofactor (ref. 10).

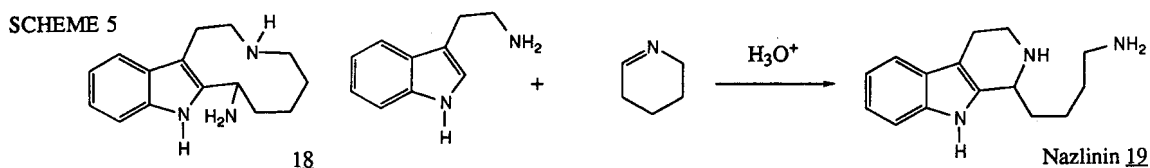
SCHEME 4



Under basic conditions **15** is converted into the corresponding enamine, which could be reduced to **16** (89%). The hydrolysis of the oxime requires very mild conditions to avoid epimerization of the intermediate aldehyde **17** to the more stable epilupinine skeleton. Pure racemic lupinine **11** was obtained via ozonolysis of **16** at  $-50^\circ$  followed by addition of  $\text{NaBH}_4$ . Under a variety of more vigorous conditions a mixture of lupinine and epilupinine was obtained. (ref. 11)

Recently, the alkaloid Nazlinin was also isolated from *Nitraria Schoberi* as a racemate. On the basis of spectral data the authors assigned structure **18** to the molecule (ref. 12). This structure surprised us, since it is not obvious how **18** could be generated from tryptamine and tetrahydropyridine, bearing in mind that an optically inactive product suggests a non enzymatic route to its formation. Since based on our biosynthetic hypotheses structure **19** seemed much more likely for Nazlinin, we decided to prepare this molecule.

A reaction of tryptamine with tetrahydropyridine, obtained by us *in situ* under acid conditions from trimer **4**, yielded in one step **19** (72 %) with the same molecular formula and identical spectral characteristics as those reported for Nazlinin. Unequivocal structural proof was obtained from the  $^1\text{H-NMR}$  spectra of the diacetyl- derivative, which showed the presence of the  $\text{CH}_2\text{-NHAc}$  moiety in Nazlinin. (ref. 13). Also the reported fragmentation pattern (8) in the mass spectrometer could be explained on the basis of structure **19**. Later, total synthesis of **12** showed this to be a different compound indeed (ref. 14), thus supporting our hypothesis concerning the biosynthetic formation of Nazlinin.

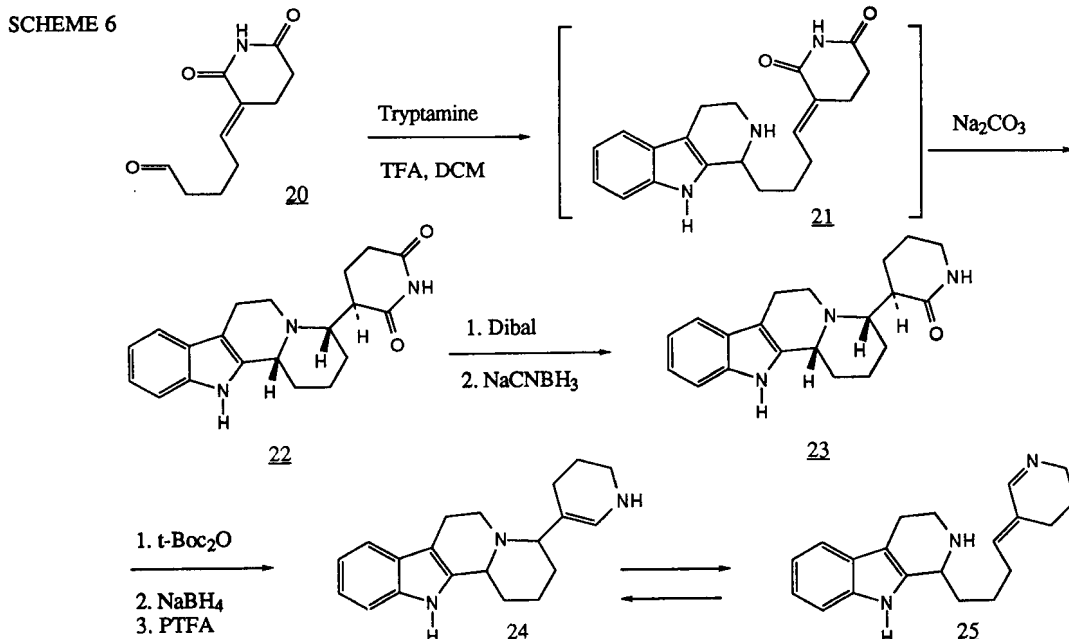


To obtain further support for our suggestion that spontaneous cyclization of reactive molecules can lead to rather complex racemic alkaloids, we turned our attention towards Nitrarine **2**, isolated as a racemate from *Nitraria Schoberi* and *Nitraria komarovii* (ref. 2b). The ultimate reactive precursor **26** for the alkaloid, containing an imine and an enamine function was obtained again via glutarimide chemistry, as described above for Nitrarine. (ref. 15, scheme 6).

Thus, starting from the Wittig reaction product **20** of triphenylphosphoralidene glutarimide and glutaraldehyde, via condensation with tryptamine, followed by basic work up of the reaction products, **22** was obtained as a mixture of C3' epimers (72:28) via spontaneous cyclization (72%).

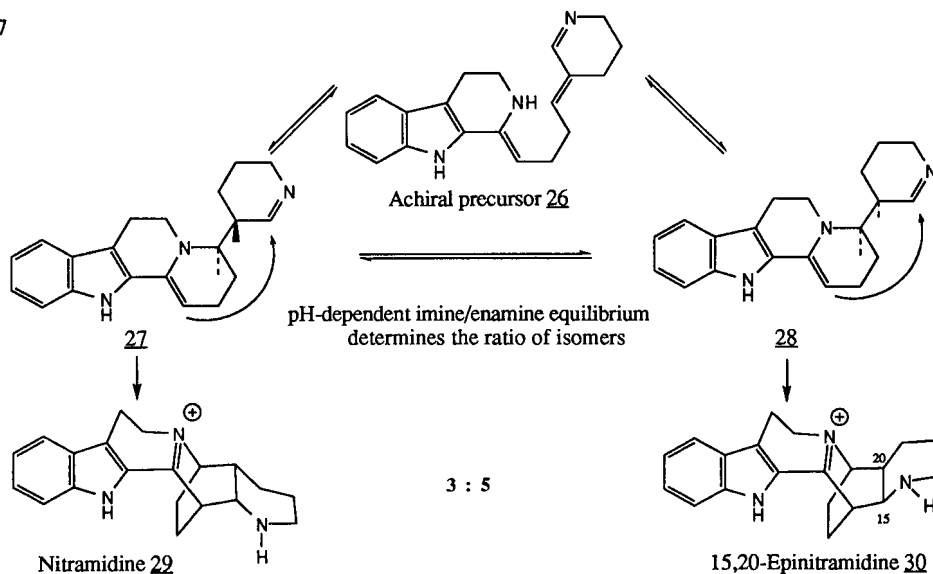
The structure of the main isomer was confirmed by X-ray crystallography of a crystalline 1:1 complex with dichloromethane. Compound **22** could be reduced to the corresponding piperidine derivative with  $\text{LiAlH}_4$ , in which however, the desired carbon carbon double bond could not be introduced, due to instability of the products under the reaction conditions.

Stepwise reduction of **22** with Dibal occurred regioselectively at the least hindered carbonyl group. The mixture of hydroxy lactams was immediately converted into **23** with  $\text{NaCNBH}_3$  under acid conditions. Reduction of the lactam to the corresponding imine was problematic, so a three step procedure was carried out via the N-Boc protected system. The lactam thus activated was reduced with  $\text{NaBH}_4$  followed by elimination of water and thermal removal of the indole N-Boc groups with conc HCl. This resulted in the formation of an equilibrium mixture of **24** and **25**.



An extra oxidation step is required to obtain the reactive precursor **26**, which is in equilibrium with **27** and **28**. This reaction was carried out with mercuric acetate / EDTA at the Boc protected level. Addition of HCl to the product removed the Boc group after which spontaneous cyclization occurred, giving two isomers Nitramidine **29** and 15,20 epinitramidine **30** (scheme 7). The presence of Nitramidine besides Nitrarine in the plants has also been established. (ref. 2)

SCHEME 7

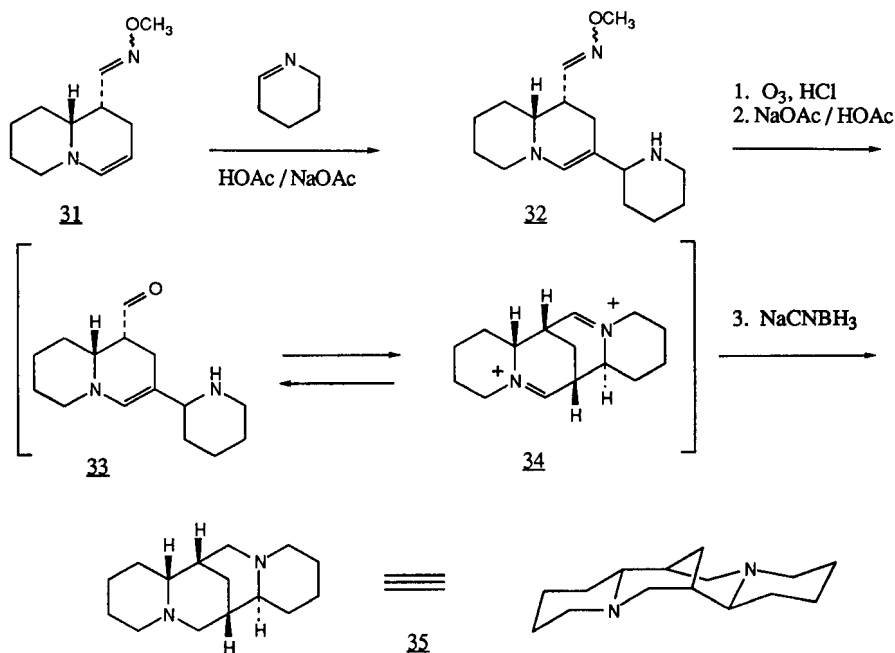


When after cyclization the reaction mixture is reduced *in situ* with NaBH<sub>4</sub> Nitrarine **2** and 15,20-Epinitrarine are obtained.

Another alkaloid, present in Lupine species is the tripiperidine Spartein **35**. It is not difficult to envisage that the biosynthesis of spartein requires addition of an extra piperidine unit to the lupinine (or tetrahydroanabasine) skeleton. Thus we carried out the reaction between enamine **31** and tetrahydropyridine. (Scheme 8).

When in this case the oxime was split under very mild conditions with ozone (ref. 16), imine / enamine equilibria are established in the aldehyde **33** under buffered acidic reaction conditions (NaOAc/HOAc). The diastereomer in which both substituents occupy axial positions can cyclize to **34**. Without isolation, the cyclization product was converted with NaCNBH<sub>3</sub> into racemic Spartein (21%). When the oxime **32** was split under reductive conditions with TiCl<sub>3</sub> / HCl at elevated temperatures, reduction with NaCNBH<sub>3</sub> resulted in the formation of a 1:1 mixture of Spartein and β-isospartein.

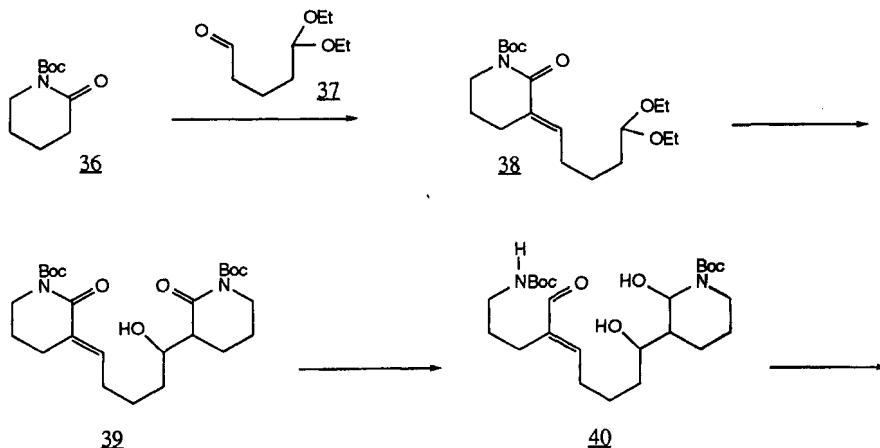
SCHEME 8



The formation of the more complex alkaloid Nitramine **3**, despite its six stereocenters present in *Nitraria Schoberi* as a racemate, can be envisaged from the highly symmetrical intermediate **41** ( $C_{2v}$  symmetry), containing two conjugated imine functions with several possibilities of forming imine/enamine equilibria (scheme 10).

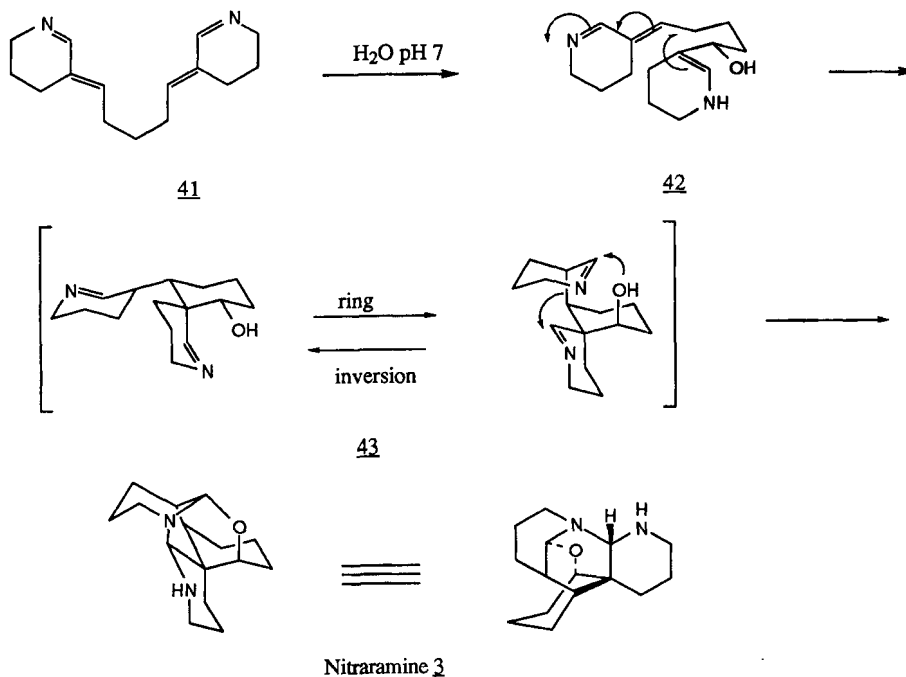
In this case we utilized *N*-Boc piperidone as an intermediate (ref. 17), since in the case of Nitramine, this had proven to be a very useful synthon. Reactions of glutaraldehyde and tetrahydropyridine gave rise to very complicated mixtures which were not of practical value for a laboratory synthesis. So the lithium enolate of **36** was condensed with protected glutaraldehyde derivative **37** (ref. 18).

SCHEME 9



Without isolation, the condensation product was converted into **38** via mesylation and elimination. After hydrolysis of the acetal function a second condensation with the lithium enolate of **36** was carried out. In **39** the carbon framework for the spontaneous cyclization has been constructed; it only requires adjustment of the oxidation state. Lithium triethylborohydride proved to be effective for this reduction, leading to the unstable precursors **40** (ref. 19). Acid treatment (trifluoroacetic acid in dichloromethane) resulted in removal of the Boc groups and elimination of water to yield **41**. Although this interesting compound was not very stable a  $^1\text{H}$  NMR spectrum could be obtained from its TFA salt to establish its presence in the reaction mixture.

SCHEME 10



When **17** was heated with aqueous phosphate buffer at pH 7, the expected three successive cyclizations took place giving rise to the formation of Nitraramine in approximately 20% yield. As indicated in scheme 10, in the alcohol **43** cyclization can be easily envisaged if one of the dihydropyridine rings and the OH group both occupy axial positions. Especially in this case, where Nitraramine was synthesized for the first time, the strength of the biomimetic approach based on hypothetical biosynthetic schemes has clearly proven its usefulness.

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