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Evolution-Based Synthesis of Racemic Alkaloids

M. J. Wanner and G. J. Koomen

Amsterdam Institute of Molecular Studies, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands.

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 the presence of many stereocenters. We assume that racemic 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 by us via chemical synthesis, based on this concept of reactive precursors. The paper discusses the preparation of racemic Lupinine, Spartein and Nitraramine from tryptamine and the trimer of tetrahydropyridine, based on imine-enamine chemistry. Preliminary biomimetic studis on the synthesis of Manzamines and Ingenamines from 3-alkylpyridinium dimers are reported.

INTRODUCTION

A variety of alkaloids, like Nitramin 1, Nitrarine 2, Nazlinin 3 and Nitraramine 4, have been isolated from different species of the Nitraria family[1]. An interesting feature of these alkaloids is the fact that they are isolated as racemates, even in cases where the molecule contains five or six stereocenters[2]. This has been observed before for alkaloids like Akuammicine[3], Yuehchukene [4] and Lucidene [5].

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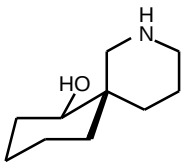
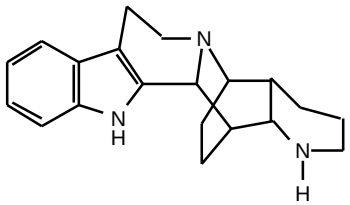
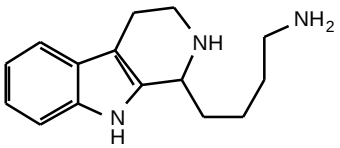


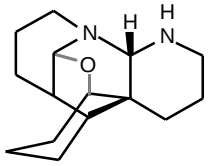
Nitramine 1



Nitrarine 2



Nazlinin 3



Nitraramine 4

SCHEME 1

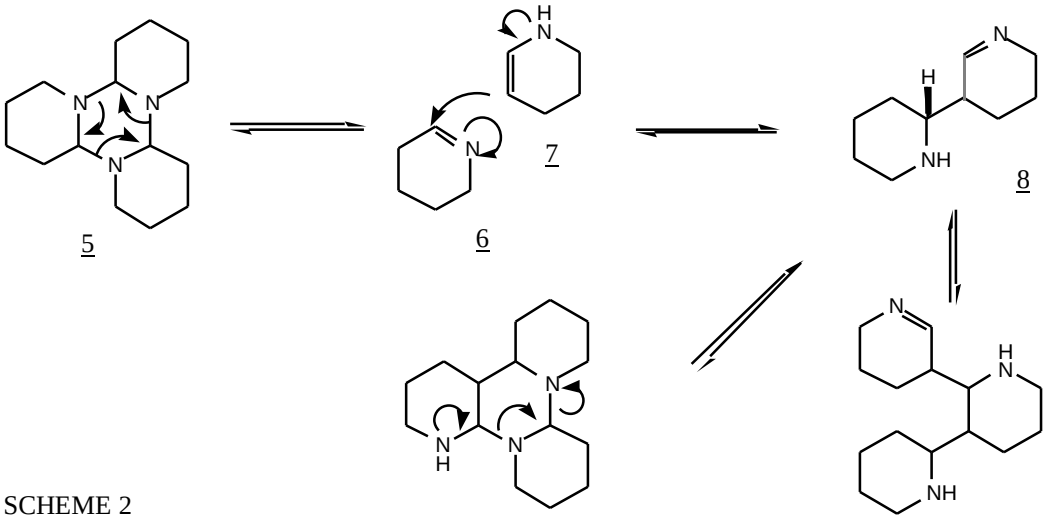
Although it is widely accepted, that plant enzymes play a role in the biosynthetic steps in the plants[6], it has been suggested before that in some cases a nonenzymic pathway cannot be excluded[3,5]. Also, in the evolution of plants, nature has been carrying out one experiment after another to evolve 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 ultimately might be used as 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. The success of this approach in the biomimnetic synthesis of Nitramine 1[7] and the indole alkaloids Nitrarine 2[8] and Nazlinin 3 [9-11] has been described elsewhere.

SYNTHESIS OF LUPININE BASED ON TETRAHYDROPYRIDINE

Nature is capable of producing an immense variety of rather different products from a very small number of building blocks, like for instance acetyl-CoA. In the case of Nitraria alkaloids like

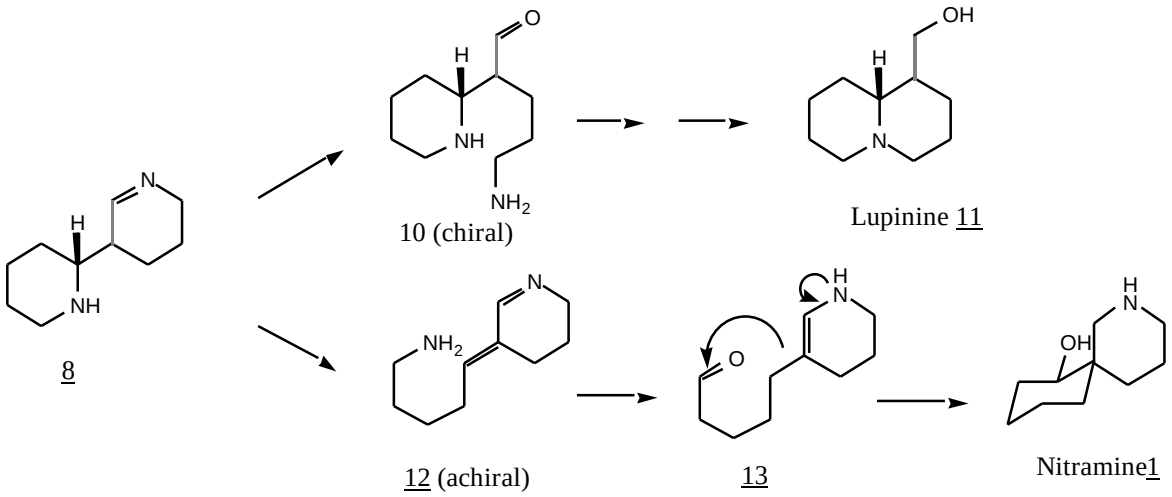
Nitramine 1, one can envisage a biosynthesis via two units of tetrahydropyridine, which can be formed readily from lysine via decarboxylation and oxidative deamination,. Tetrahydropyridine exists as an equilibrium mixture of an imine 6 and the corresponding enamine 7. Since these molecules are electrophilic and nucleophilic species respectively, several reactions can be expected and indeed occur leading to a dimer and different trimers, depending on pH. Molecules like 6, 7 or 8 once formed in nature from lysine, possess the reactivity which might lead to spontaneous formation of a variety of products.



SCHEME 2

In the laboratory synthesis the starting material is α-tripiperidein 5 which can be decomposed in water at pH 7. As indicated in scheme 2, formation of other trimers is possible.

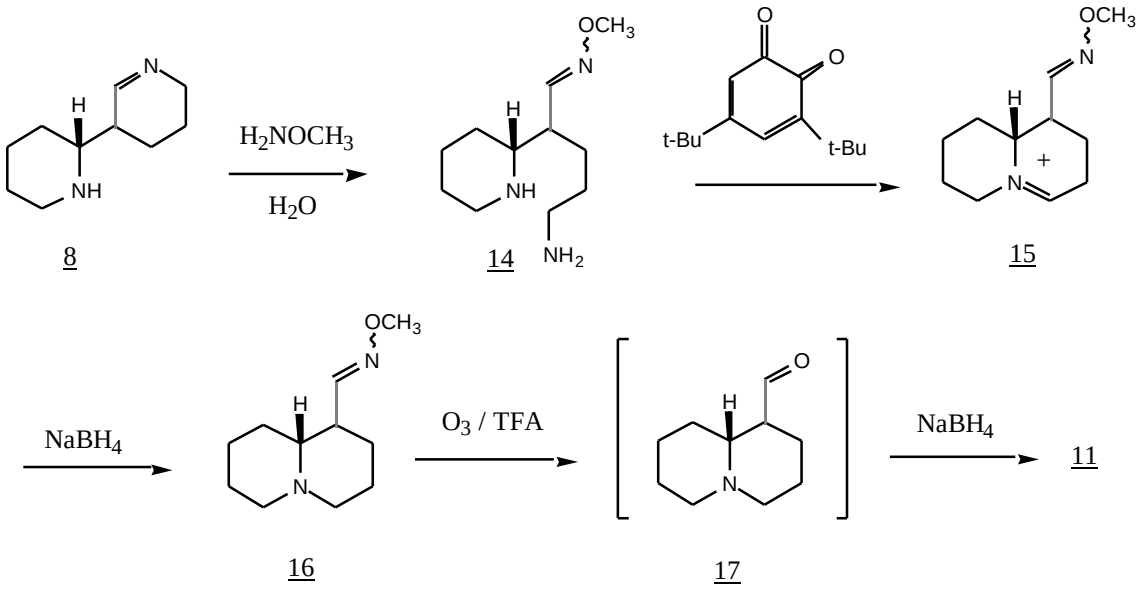
For the biosynthesis of Nitraria and Lupine alkaloids tetrahydroanabasine 8 is an important starting material, showing the close relation between the two alkaloid skeletons. Opening one ring via 10 (scheme 3) leads to the optically active lupine alkaloids[12], whereas retro-Michael reaction via 12 followed by oxidation and hydrolysis to 13 constitutes a simple route to the racemic spirocyclic Nitraria alkaloids [7].



SCHEME 3

Also in the lab the synthesis of racemic lupinine and epi-lupinine could be carried out from tetrahydroanabasine 8. 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%) [13]

This reaction is strongly related to those catalyzed by the copper containing amine oxidases, which use TPQ as the cofactor [14].



SCHEME 4

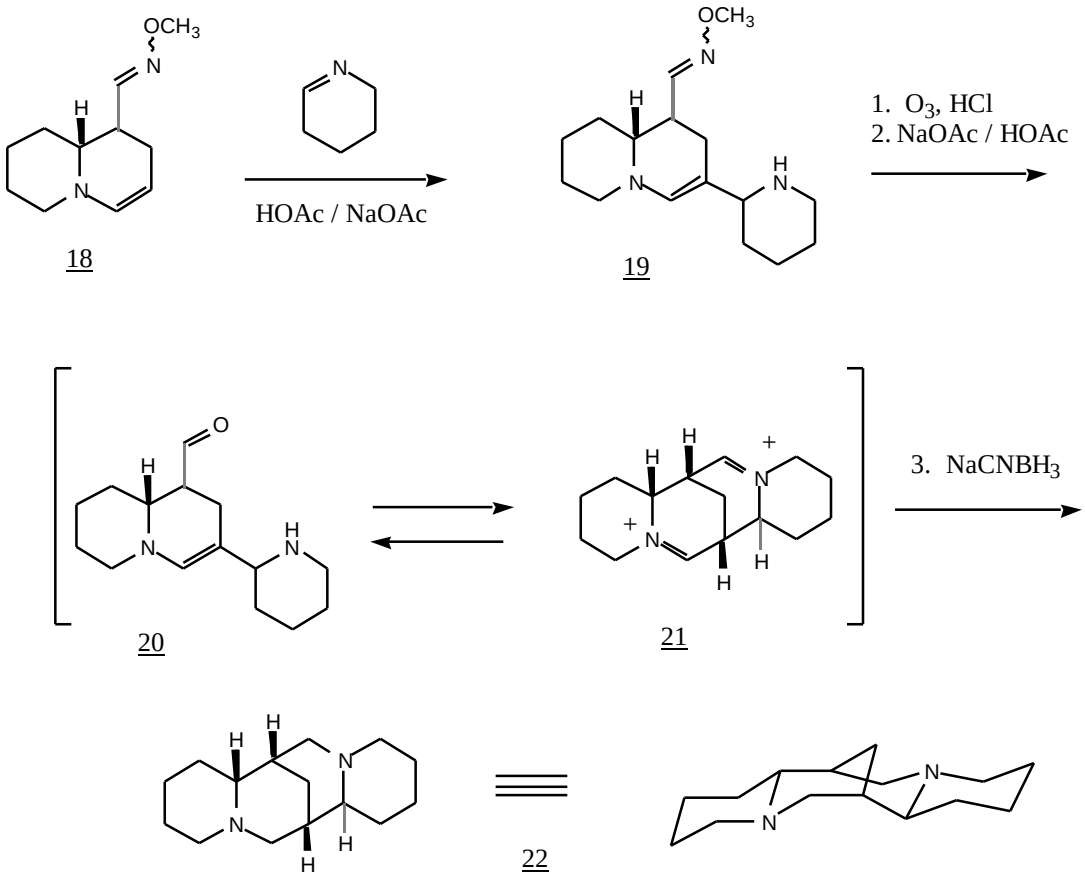
Under basic conditions 15 is converted into the corresponding enamine, which could be reduced to 16 (89%). The hydrolysis of the oxime requires very mild conditions to avoid epimerization of the intermediate aldehyde 17 to the more stable epilupinine skeleton. Pure racemic lupinine 11

was obtained via ozonolysis of 16 at -50° followed by addition of $NaBH_4$. Under a variety of more vigorous conditions a mixture of lupinine and epilupinine was obtained.[15]

SYNTHESIS OF SPARTEIN FROM THR LUPININE SKELETON

Another alkaloid, present in Lupine species is the tripiperidine Spartein 22. Although, at first glance, the relation between spartein and lupinine is not obvious, is is attractive to envisage that the biosynthesis of spartein only requires addition of one extra tetrahydropyridine moiety to the lupinine (or tetrahydroanabasine) skeleton. The question is, whether this process can be mimicked non-enzymic in the laboratory. Thus we carried out the reaction between enamine 8 and tetrahydropyridine. (Scheme 5).

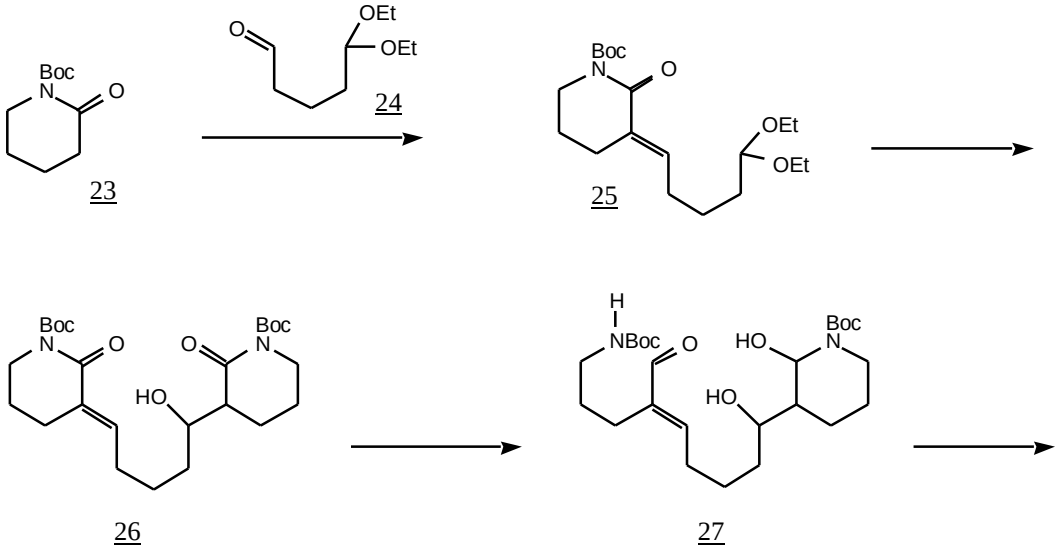
When in this case the oxime was split under very mild conditions with ozone [16], imine / enamine equilibria are established in the aldehyde 20 under buffered acidic reaction conditions (NaOAc/HOAc). The diastereomer in which both substituents occupy axial positions can cyclize to 21. Without isolation, the cyclization product was converted with $NaCNBH_3$ into racemic Spartein (21%). When the oxime 19 was split under reductive conditions with $TiCl_3$ / HCl at elevated temperatures, reduction with $NaCNBH_3$ resulted in the formation of a 1:1 mixture of Spartein and β-isospartein.



SCHEME 5

SYNTHESIS OF NITRARAMINE VIA PIPERIDONE UNITS.

The formation of the more complex alkaloid Nitraramine 4, despite its six stereocenters present in Nitraria Schoberi as a racemate, can be envisaged from the highly symmetrical intermediate 28 (C_{2v} symmetry), containing two conjugated imine functions with several possibilities of forming imine / enamime equilibria (Scheme 7).

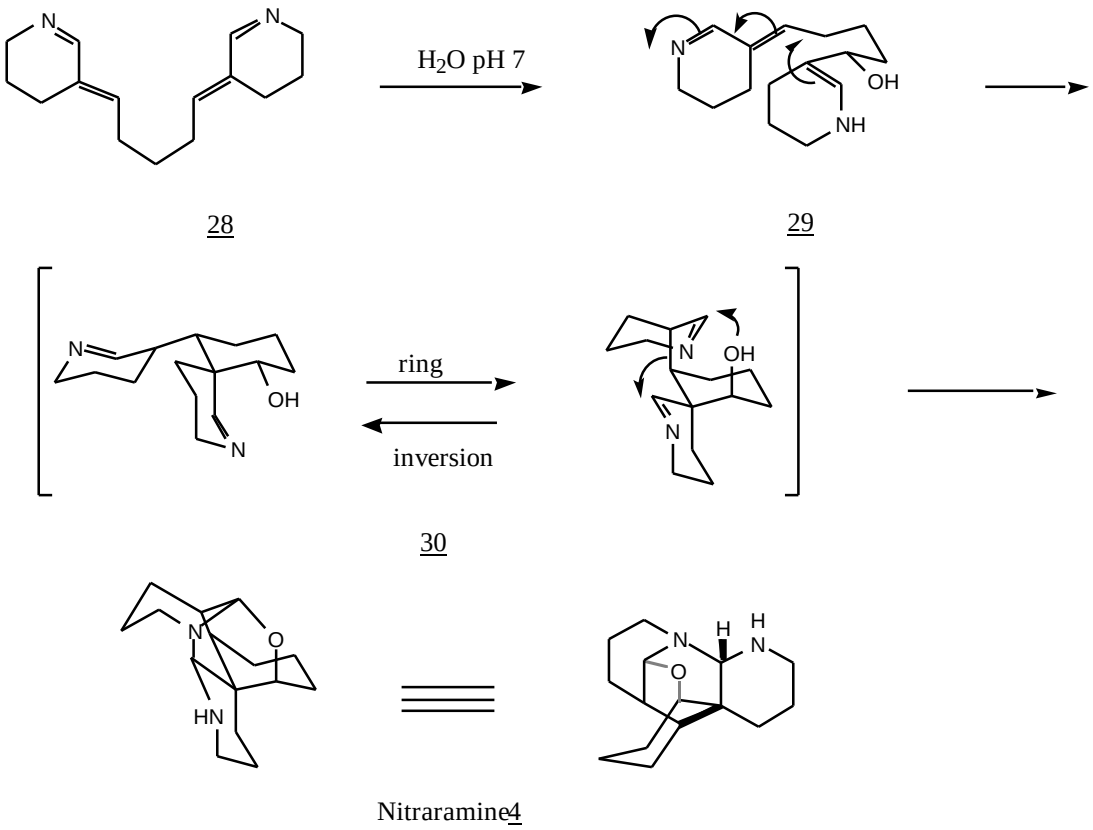


SCHEME 6

Although in principle, synthesis of 28 could be realized va imine/enamine chemistry, we preferred to utilize more stable synthons in order to obtain the reactive bioprecursor 28 in a more efficient way. We assume however, that in the plant, where more time is available and lower yields are acceptable, the imine/enamine route is followed.

In this case we utilized N-Boc piperidone as an intermediate[17], since in the case of Nitrarine, 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, protected glutaraldehyde derivative 24 was condensed with the lithium enolate of 23 (Scheme 6) [18].

Without isolation, the condensation product was converted into 25 via mesylation and elimination. After hydrolysis of the acetal function, a second condensation with the lithium enolate of 23 was carried out. In 26 the complete 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 a mixture of the unstable precursors 27 [19]. Although, due to the conjugation with the double bond one of the piperidine rings opened, the resulting aldehyde is in equilibrium withe hydroxypiperideine sytem. Acid treatment (trifluoroacetic acid in dichloromethane) resulted in removal of the Boc groups and elimination of water to yield 28 in one step. Although this interesting compound was not very stable, a ^{1}H NMR spectrum could be obtained from its TFA salt to establish its presence in the reaction mixture.



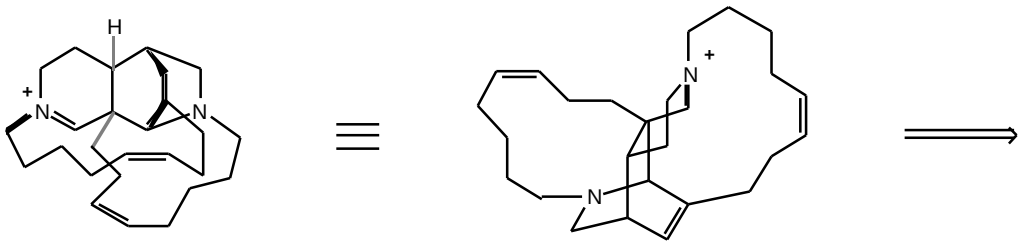
SCHEME 7

When 28 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 7, in the alcohol 30 cyclization can be easily envisaged if one of the dihydropyridine rings and the OH group both occupy axial positions.

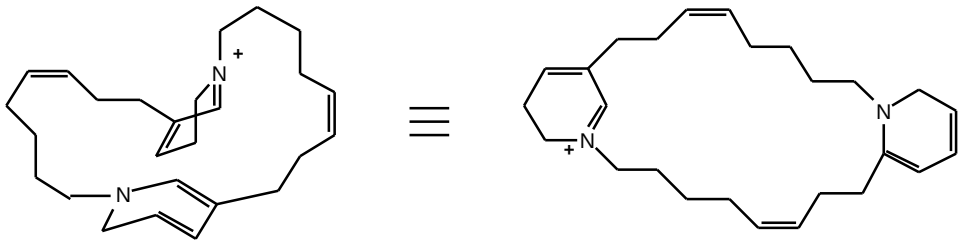
Especially in this case, where Nitraramine was synthesized for the first time, the biomimetic approach based on hypothetical biosynthetic schemes has clearly proven its usefulness.

Recently we tried to apply this the biomimetic approach in the synthesis of Manzamines, Ingenamines, Saraines and other complex alkaloids, isolated from marine organisms.

The synthesis is based on the retrosynthetic scheme (Scheme 8), ultimately leading to macrocyclic 3-alkylpyridinium dimers 34. Also these macrocyclic bispyridinium alkaloids occur in the same sponges, for instance as cyclostelletamines.[20)]



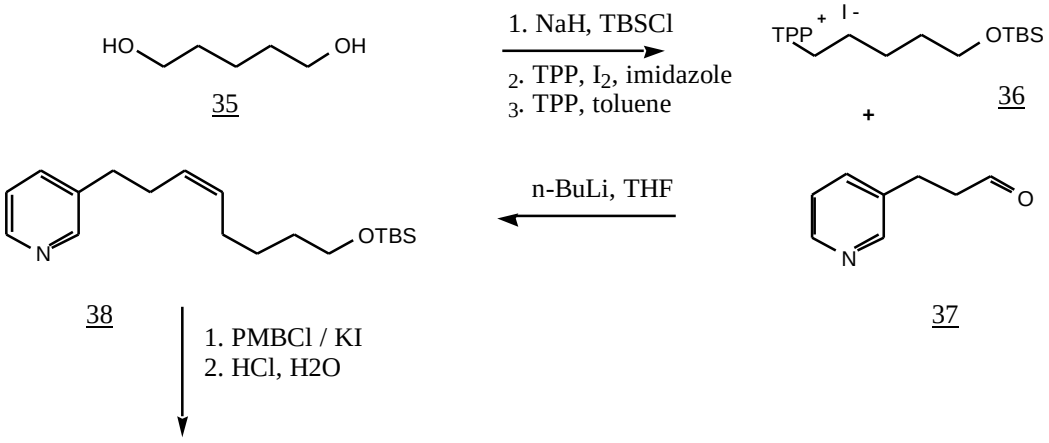
Manzamine skeleton31 32

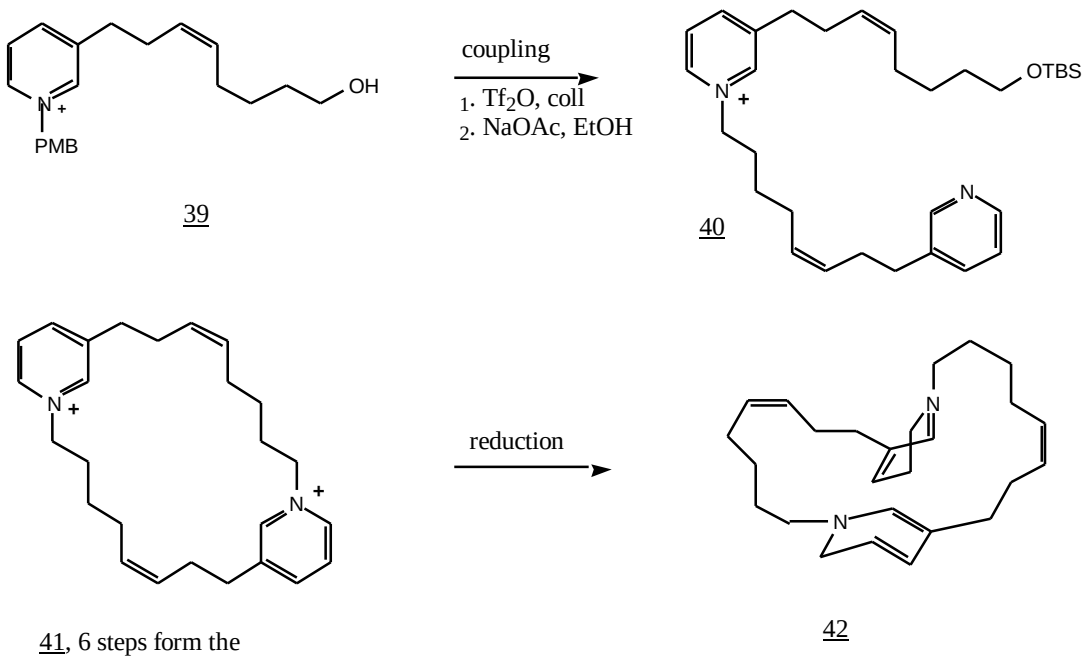


33 34

SCHEME 8

Synthesis of macrocyclic 3-alkylpyridinium dimers has been realized according to Scheme 9. In this approach, with one of the pyridine nitrogens protected, the synthesis of asymmetric macrocycles bispyridines is also possible and in fact synthesis of all cyclostelletamines A-F was realized recently, using p-methoxybenzyl protection[21]





SCHEME 9

Via the same approach, the "Baldwin precursor" 41 was obtained in excellent yields. Reduction experiments combined with an in situ Diels-Alder cyclization were not successful yet.

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