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Biomimetic investigations from reactive lysine-derived C_5 units: one step synthesis of complex polycyclic alkaloids from the *Nitraria* genus

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Abstract—A single biomimetic cascade sequence featuring intermolecular followed by intramolecular cyclizations allowed the biomimetic synthesis of nitraramine and the formation of an interesting original cage-like structure from simple C_5 lysine-derived metabolites. In the course of the study, the structure and spectral data of 1-epinitraramine were also revisited.

1. Introduction

1.1. The *Nitraria* genus

Plants from the *Nitraria* genus (Zygophyllaceae) are bushes that can grow up to 2 m high. They have fleshy leaves, little white flowers (with five petals and 15 stamens), and their fruits have three pyramidal chambers. Well adapted to arid climate, species of *Nitraria* are found in desert regions of south-east Europe (*Nitraria komarovii*, *Nitraria sibirica*) and middle-east (*Nitraria schoberi*) but also in Australia (*Nitraria billardieri*) and Africa, in northern and occidental parts of the Sahara desert, and in Mauritania (*Nitraria tridendata* or *Nitraria retusa*).

1.2. *Nitraria* alkaloids

Isolated from aerial parts of the plants, alkaloids of the *Nitraria* genus are classically classified into three major groups (Fig. 1):[1] tripiperidine alkaloids (e.g., schoberine), indole alkaloids (e.g., nitrarine), and the group of spiro alkaloids. The latter can be divided in two sub-groups: simple spiro alkaloids (e.g., sibirine) and complex spiro alkaloids (e.g., nitraramine **1**, 1-epinitraramine **2**).

These piperidine alkaloids from *Nitraria* species constitute a singular class of natural compounds both in terms of chemical diversity (e.g., many 3-spiropiperidines) and biosynthetic origin. In fact, a particularly primitive lysine-based metabolism can account for the biogenesis of these alkaloids. Moreover, the fact that numerous *Nitraria* alkaloids are present as chiral but as racemic forms in nature strongly suggests a minimum enzymatic intervention, at least for the key diversity-generating cyclizations.[2]

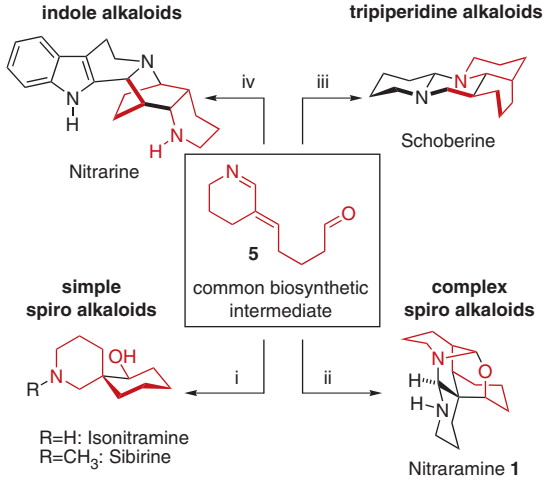

Figure 1. Central biosynthetic role of intermediate **5**.

1.3. Biosynthesis

The biosynthesis of many of these compounds can be explained by the assembly of simple C_5 units derived from L-lysine, such as 2-piperideine **3** and glutaraldehyde **6** (Scheme 1). The formation of an endocyclic enamine **3** from lysine is a known step in the biosynthesis of many alkaloids such as

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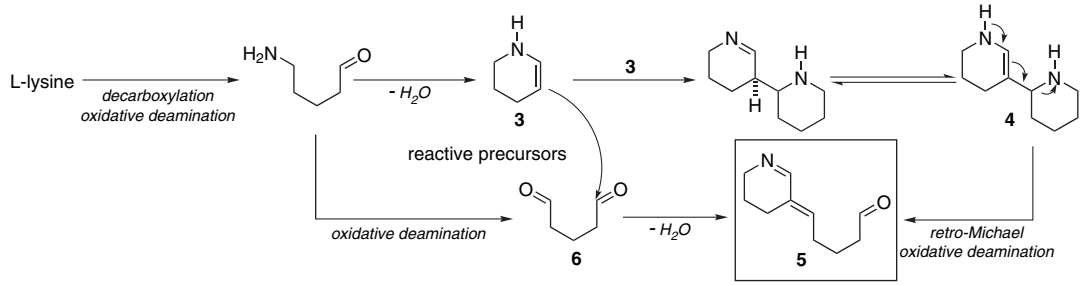
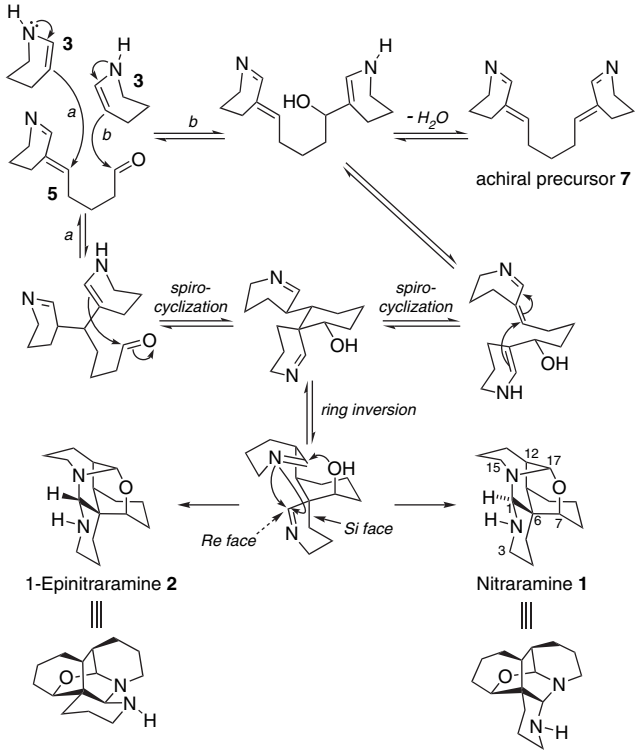


Scheme 1. Different possibilities for the biosynthesis of intermediate **5**.

those of the *Lupinus* genus. Dimerization of 2-piperideine **3** into tetrahydroanabasine **4** followed by opening and oxidation could lead to an intermediate **5**,[1,3] but the attack of a 2-piperideine unit on a molecule of glutaraldehyde followed by a dehydration step could also be a potential path for the formation of this pivotal key precursor (Scheme 1) that spiro, indole, and tripiperidine alkaloids share. Compound **5** can then be reduced and undergo a spirocyclization process, leading to the formation of simple spiro alkaloids (Fig. 1, i). It can also react with an additional molecule of 2-piperideine, either through C-alkylation, in which case it will afford the required intermediates for the formation of complex spiro alkaloids (Fig. 1, ii), or through N-alkylation and in that case eventually leads to the formation of tripiperidine alkaloids (Fig. 1, iii). Finally, intermediate **5** can react with a molecule of tryptamine via a Pictet–Spengler reaction to afford indole alkaloids such as nitrarine (Fig. 1, iv).

One of the products derived from **5** is nitraramine **1**,[4] a small but complex intricate structure, isolated from *Nitraria schoberi*.[5] From **5**, the formation of **1** can be explained through a series of virtually equilibrated reactions essentially consisting of imine/enamine tautomerism, Michael/retro-Michael, Mannich/retro-Mannich reactions, and hydrations/dehydrations. In the last step, following a ring inversion, a nucleophilic attack of the hydroxyl group, and a last aza-Mannich reaction onto the remaining iminium system afforded **1**. In this context, the formation of 1-epinitraramine, which was assigned the structure **2**,[6] in conjunction with **1**, has been explained by a likely attack on the *Si*-face or the *Re*-face of the iminium, during the aminal formation to produce **1** and **2**, respectively (Scheme 2).



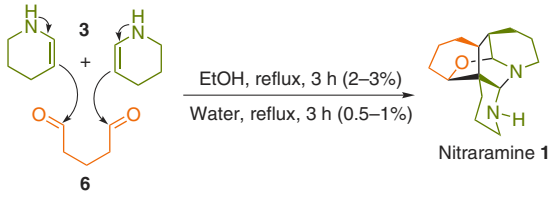
Scheme 2. Proposed biogenetic pathway to nitraramine **1**.

In this paper we discuss a full account of the assembly of **1** from simple precursors[7] as well as the absence of formation of **2**, which states the high stereoselectivity of the reaction cascade. Other molecules formed during the 'dynamic combinatorial process' have also been characterized and are presented herein.

2. Chemistry

2.1. Biomimetic total synthesis of nitraramine 1

In connection with their biosynthetic hypothesis, Koomen and Wanner targeted the plausible achiral intermediate **7** by a stepwise approach in their pioneering beautiful synthesis of **1** (7 steps, ~0.5% yield).[5] On the basis of the proposed biosynthetic pathway and considering the different possibilities for the formation of intermediate **5** discussed above, we reasoned that it should be possible to access directly the nitraramine **1** from much simpler precursors than the ones chosen by Koomen and Wanner (Scheme 3). A reaction between 2 equiv of 2-piperideine **3** and 1 equiv of glutaraldehyde **6** should logically lead to the assembly of **1**, as no oxidation or reduction step is required for starting the reaction from these precursors.



Scheme 3. Biomimetic synthesis of **1**.

From this observation, we decided to develop a one-step synthesis of this particular original molecule, by reacting commercial glutaraldehyde with 2 equiv of 2-piperideine formed

in situ from its crystalline trimeric form, which was simply obtained from piperidine[8] treated with *N*-chloro-succinimide and sodium methanoate.

To carry out the reaction in a polar solvent that could be easily removed under reduced pressure, we figured that ethanol was the most convenient solvent. The mixture was stirred under reflux to allow a better dissociation of the trimer into 2-piperideine **3** but also to provide the energy required for the ring inversion step of the biomimetic cascade sequence. After 3 h of reaction, the crude reaction mixture showed a complex TLC profile.

By mixing the reactive precursors without any control on the reaction outcome to select specific associations, we knew that we would obtain many different products amongst which we would have to identify and isolate the desired alkaloid. To guide our search for nitraramine within the mixture, we had limited but relatively precise information at our disposal consisting mainly in ^{13}C and ^{1}H NMR data. Despite certain differences, all ^{1}H NMR spectra displayed a singlet at 3.5 ppm, attributed to the aminal H-1, which permitted the identification of the product and enabled the exact location of **1** to be determined on TLC (CH_2Cl_2/MeOH 9:1, R_f=0.35).

Relying on what had been previously published in literature,[5] we at first opted for purification on silica gel column eluted with methylene chloride/methanol 95:5. Even though silica gel made it possible to refine the crude mixture by providing, after several columns, fractions enriched with nitraramine **1**, it appeared virtually impossible to obtain the latter totally free of impurities. We therefore decided to change the solid phase to basic alumina and to use an elution gradient. After different tries, optimal conditions were defined and it turned out that pure nitraramine **1** could be obtained by two consecutive basic alumina columns eluted with a gradient of methylene chloride/methanol from 99:1 to 96:4. This method provided pure **1** as colorless crystals in 2–3% yield.

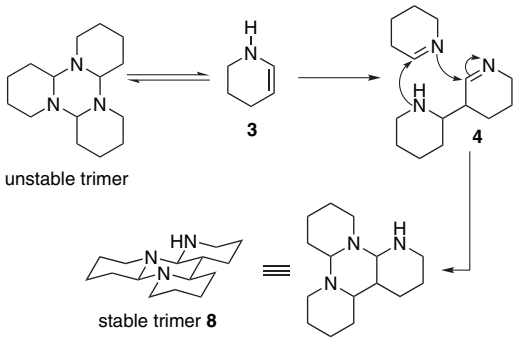
At first sight this yield may seem rather deceiving but one needs to consider that it is the global yield of a total synthesis in the course of which five new bonds (including three carbon–carbon bonds) and six chiral centers (including one spiro-carbon) were formed in a single vessel. Starting material is inexpensive and experimental procedure is very simple, permitting the whole synthesis to be carried out in less than a day.

In ideal biomimetic conditions the reaction should be conductible in water; the same condensation protocol was therefore tried in boiling water (citrate buffer 4%) and the resulting TLC profile of the crude reaction mixture was similar to the one obtained in ethanol. After purification, pure nitraramine **1** was obtained but in lower yield (0.5–1%), probably due to an important loss of material in water during workup.

2.2. Other molecules formed during the process

Given the yield of just a few percents, one can rightfully wonder how all the residual material has reacted. Even though it was not our priority to do so, we decided to investigate the reaction products other than the expected alkaloid **1**. Thus, we were able to characterize two molecules formed in significant proportions during the reaction process: stable trimer **8** (15–20%) and the much more complex and original molecule **9** (8–10%).

Trimer **8** is a known product that we expected in the reaction mixture and it was easily identified by comparison of the obtained spectral data with that of prior literature data (^{1}H NMR and ^{13}C NMR spectra).[8] The formation of this compound can be easily explained by the reaction of one 2-piperideine **3** unit on a molecule of tetrahydroanabasine **4** (which is itself obtained from two 2-piperideine units), as shown in Scheme 4.



Scheme 4. Proposed formation path for trimer **8**.

Moreover, it was observed that when a solution of trimeric **3** in ether was left at room temperature, the rearrangement took place, resulting in the formation of **8**, and that within 48 h all the material was converted.

For the structural determination of compound **9** the process was more complicated, especially because of numerous ^{1}H NMR signals, which were overlapping one another in the CH_2 region (1–2 ppm), making exploitation of the information impossible.

The product was slightly less polar than compound **8** and its IR spectrum showed the absence of N–H bonds. Mass spectroscopy (ESI-MS) gave a quasi-molecular ion peak $[M+H]^+$ at *m*/*z* 248 and a unique fragment ion peak at *m*/*z* 165.

The ^{13}C NMR spectrum showed the presence of five CH and 10 CH_2 that constituted a mass of 205 to which three nitrogen atoms had to be added to get the right molecular weight and give the molecular formula $C_{15}H_{25}N_3$, requiring five degrees of unsaturation. Given the absence of ethylenic signals, it was obvious that these came from the presence of cycles.

The analysis of the COSY spectrum turned out not to be as informative as it should have been. Most signals were overlapping one another between 1 and 2 ppm and it was impossible to determine any sequence between CH_2. Nevertheless, it was possible to identify the most substituents of tertiary carbons, thanks to the correlation signals on the HSQC spectrum, and three segments were determined. Considering the number of nitrogen atoms and the different couplings observed on the ^{1}H NMR spectra, we were able to assemble these fragments in a bicyclic system, as shown in Figure 2.

Relative configuration of carbons 2′ and 3″ was given by the coupling constant that existed between the ^{1}H NMR signals

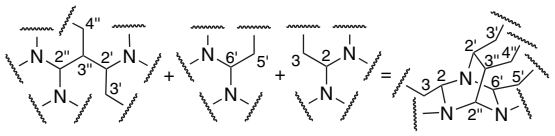


Figure 2. Construction of the central bicyclic system of molecule **9**.

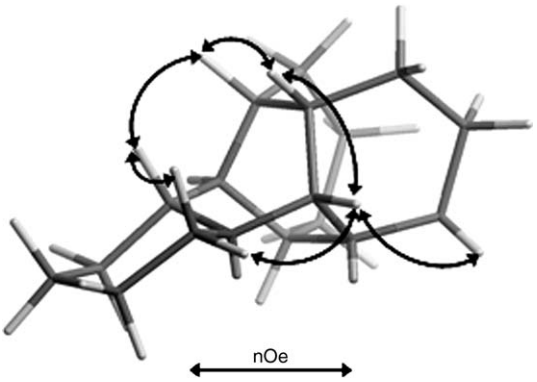


Figure 3. Selected NOESY correlations for molecule **9**.

(J=11.5 Hz) and the difference between carbons 2 and 6′ was made by an analysis of the NOESY spectrum (see Fig. 3). The central bicyclic structure was confirmed by the HMBC correlations (the most significant ones are shown on Fig. 4).

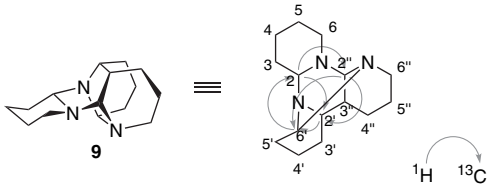
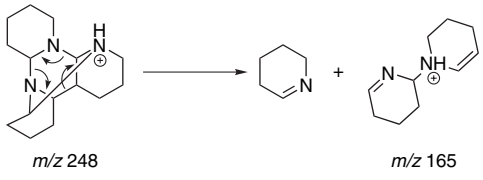


Figure 4. Selected HMBC correlations for molecule **9**.

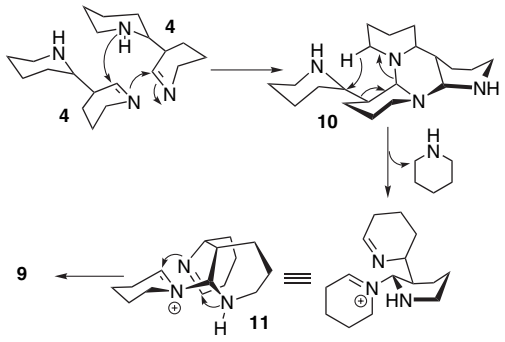
At that point, there were still six residual CH_2 to assign in order to complete the last three cycles of the structure. Keeping in mind the reagents and preferring six-membered rings, we realized that only one structure could be considered. Configurations of the peripheral cycles were determined on the basis of the observation of the ^1H NMR signals (i.e., multiplicities and coupling constants).

Moreover, the obtained structure could explain the observed fragment ion peak at m/z 165 on the ESI-MS mass spectrum, through a mechanism shown in Scheme 5.



Scheme 5. Proposed fragmentation mechanism.

A plausible hypothesis for the formation of compound **9** from piperideine-derived units is shown in Scheme 6. Two tetrahydroanabasine units react to give rise to compound **10** which is rearranged by a hydride transfer to yield molecule **11**.[9] The attack of the imine by the free secondary amine followed by the reduction of the iminium completes the synthesis of compound **9**.



Scheme 6. Possible formation mechanism proposed for molecule **9**.

Our structural hypothesis is strengthened by the fact that the molecule could result from the association of two units of tetrahydroanabasine **4**, which also contributes to the formation of compound **8** found in large quantity in the mixture. This observation led us to think that the low yield for the formation of **1** was probably widely due to the formation of a large amount of **4**.

2.3. Revision of the previously reported 1-epinitraramine 2

It appeared clearly, when comparing compiled NMR data,[10] that relatively important variations existed in chemical shifts observed for the same product. We simply could not find two totally superimposable spectra. Various hypotheses were considered to explain the phenomena until the NMR analysis of a diluted solution of nitraramine **1** gave us a spectrum equivalent to the one attributed by Quirion and colleagues to 1-epinitraramine **2**, in their 1995 article.[6]

After a closer study of the spectra obtained during our experiments, we realized that a relation existed between the concentration of **1** and the corresponding NMR signals (regarding chemical shifts as well as signal shape/multiplicity). We therefore decided to carry out an NMR study on samples of different nitraramine concentrations. The results clearly demonstrated that the compound previously described as 1-epinitraramine **2** was in fact diluted nitraramine **1** in $CDCl_3$ (Fig. 5 shows the most significantly variable area of the spectrum, under different concentration conditions). As a matter of fact, the observed spectrum for a solution of about 6 mg mL^{-1} is equivalent to the one attributed to 1-epinitraramine,[6] and the spectrum observed for about 24 mg mL^{-1} equivalent to the one attributed to nitraramine by Quirion and colleagues.[6]

The phenomena still needed an explanation and we came to think that it could come from the influence of acid traces, found in $CDCl_3$, on the protonation state of the molecule (the most variable signals were the ones attributed to protons that are close to nitrogen atoms). To confirm the hypothesis we decided to collect the contents of all NMR tubes that gave ‘epinitraramine-like’ spectra and made a single batch that

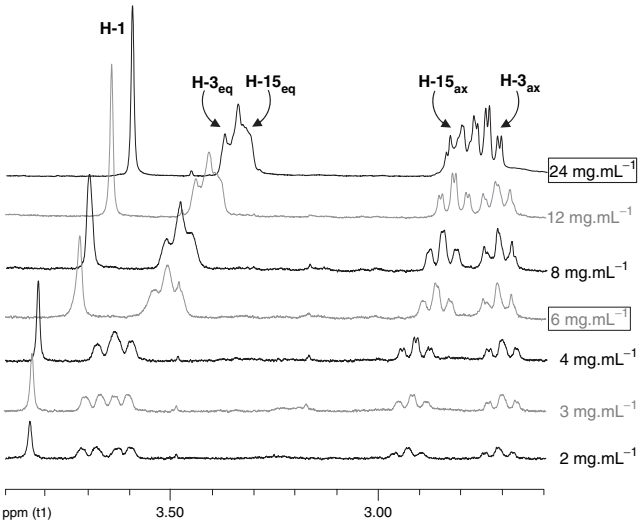


Figure 5. Concentration influence on chemical shifts of **1** (400 MHz, 25 °C).

we treated with K_2CO_3. The dried product was then dissolved in $CDCl_3$ (that had previously been filtered on basic alumina to remove traces of acid), and an NMR analysis was performed. The obtained spectrum was the one corresponding to what had been reported by Koomen and Wanner as **1**. The product was then sequentially diluted with $CDCl_3$ (previously filtered on basic alumina) until no product could be detected by NMR analysis and all observable spectra were identical to the one obtained with concentrated nitraramine.

Each spectrum on Figure 5 probably reflects a different degree of protonation, showing different average of the two chemical forms. In fact, according to the ^{1}H NMR chemical shift time scale, protonated/deprotonated states are considered in fast exchange giving rise to a weighted averaged spectrum of extreme values (i.e., δ (protonated) and δ (free base)).

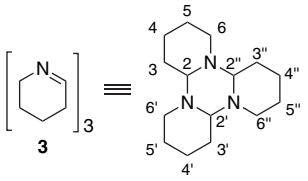
For these reasons, 1-epinitraramine **2**, which was only characterized upon NMR analysis by Quirion and colleagues, is likely to be an experimental artefact. The existence of 1-epinitraramine cannot be totally excluded but if it does exist, it's rather surprising that it has never been encountered in plants containing nitraramine. In terms of chemical assembly, the cascade involved in the formation of **1** appears therefore to be highly stereoselective.

3. Conclusion

The low yield of **1** reflects the multiple biomimetic coupling possibilities of lysine-derived precursors **3** and **6** but states for the incontestable spontaneous formation of **1** from fundamental C_5 units presumably derived from lysine. Bearing in mind that the poor yield of our synthesis is a significant drawback, one can add that the easiness and reliability of the reaction conditions from costless reagents permit the preparation of pure **1** in a few hour time scale. Therefore, the described total synthesis of **1** competes largely with scarce extraction from natural sources (which are present only in restricted areas) and with the previous total synthesis. Enough material has been prepared for needed biological screening of this intriguing complex small molecule. Furthermore, total synthesis unexpectedly led to a structural reassignment of 1-epinitraramine **2**.[11] Finally, the chemistry of simple C_5 lysine-type molecules[12] presented in this paper offers further opportunities toward biomimetic synthesis[13] and molecular self-assembly of complex natural product-like skeletons,[14] as illustrated by the formation of compound **9**.

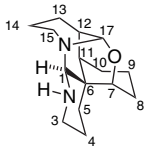
4. Experimental

4.1. Synthesis of 3 from piperidine



In a round bottom flask (1 L), *N*-chloro-succinimide (65 g, 0.5 mol) was stirred in ether (450 mL) and the suspension was cooled to 4 °C in an ice bath. Piperidine (40 mL, 0.47 mol) was then slowly added. After 2 h under agitation at room temperature, the mixture was filtered and the filtrate was washed with water (2×250 mL), and then dried. After filtration, three-third of the solvent was removed under reduced pressure and sodium methanoate (267 mL of a 2 N solution in methanol) was added carefully. The mixture was stirred under reflux for 45 min after which water was added until total dissolution of the formed salt (NaCl). An extraction with ether was performed and the organic phase was dried. After solvent evaporation, a thick yellow oil (crystallizing at 4 °C) was obtained (27 g, 70%). Compound **3**: yellow crystals; ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.1 (C-2), 46.5 (C-6), 29.5 (C-3), 26.3 (C-5), 22.8 ppm (C-4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (3H, m, H-2), 2.55 (3H, m), 1.65–1.95 (6H, m), 1.25–1.62 (12H, m), 1.18 ppm (3H, m); Mass (ESI-MS) $[M+H]^+$ 250.

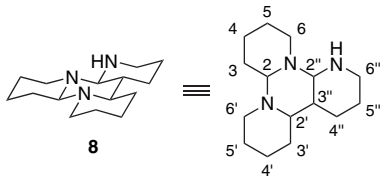
4.2. Synthesis of 1 from 3



2-Piperideine **3** (in its trimeric form, 5 g, 0.06 mol) was dissolved in ethanol (500 mL). Immediately after dissolution, glutaraldehyde (0.5 equiv, 0.03 mol, 12 mL of 25% aqueous solution) was added. The mixture was stirred under reflux for 3 h and then concentrated under reduced pressure. Purification of the crude mixture was performed on two consecutive alumina columns (CH_2Cl_2/MeOH 99:1, 98:2, 97:3, and finally 96:4) and monitored by TLC on silica gel (CH_2Cl_2/MeOH 9:1) to furnish pure nitraramine **1** (165–225 mg, 2–3%). Compound **1**: colorless crystals; R_f=0.35 (silica gel, CH_2Cl_2/MeOH 9:1); IR (film, $CHCl_3$): ν_{max}=2928, 1635, 1066 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$ filtered through

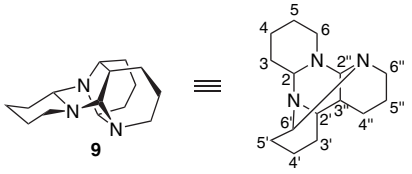
activated alumina) δ 82.2 (C-17), 75.9 (C-1), 66.5 (C-7), 50.5 (C-15), 45.1 (C-3), 38.8 (C-11), 38.0 (C-12), 32.4 (C-6), 30.4 (C-5), 28.4 (C-8), 25.2 (C-13), 24.1 (C-10), 21.6 (C-4), 15.3 (C-9), 14.6 ppm (C-14); ^{1}H NMR (400 MHz, $CDCl_3$ filtered through activated alumina) δ 4.43 (1H, m, H-7), 4.06 (1H, d, J=2 Hz, H-17), 3.36 (1H, s, H-1), 3.10 (2H, m, H-3_{eq}, H-15_{eq}), 2.68 (2H, m, H-15_{ax}, H-3_{ax}), 2.17–2.13 (1H, m, J_{gem}=13.7 Hz, H-5_{eq}), 2.00 (1H, m, H-12), 1.87–1.38 (10H, m), 1.26–1.22 (1H, m, H-10_{ax}), 1.16 (1H, m, H-11), 1.09–1.00 ppm (2H, m, H-14_{ax}, H-5_{ax}); HRMS (ES) calculated for $C_{15}H_{24}N_2OH^+$ $[M+H]^+$: 249.1967, found: 249.1969.

4.3. Trimer 8



Compound ***8***: $C_{15}H_{27}N_3$; waxy yellow solid; R_f=0.70 (silica gel, CH_2Cl_2/MeOH 90:10); IR (film, $CHCl_3$) ν_{max}=3300, 2935, 1651, 1442 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.7 (C-2), 81.7 (C-2″), 63.9 (C-2′), 48.2 (C-6), 47.7 (C-6′), 45.4 (C-6″), 43.3 (C-3″), 29.4 (C-3′), 28.3 (C-3), 27.3 (C-5), 26.1 (C-5′), 25.8 (C-5″), 25.0 (C-4′), 23.1 (C-4″), 22.9 ppm (C-4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.56 (1H, m, H-6_{eq}), 2.95 (2H, m, H-$6'_{eq}$, H-$6''_{eq}$), 2.42 (3H, m, H-2, H-2′, H-$6''_{ax}$), 1.05–1.72 (19H, m), 0.78 ppm (1H, qd, J_{ax-ax}=12.5 Hz, J_{ax-eq}=5 Hz, H-$5''_{ax}$); Mass (ESI-MS) $[M+H]^+$ 250.

4.4. Compound 9



Compound ***9***: $C_{15}H_{25}N_3$; yellow wax; R_f=0.75 (silica gel, CH_2Cl_2/MeOH 90:10); IR (film, $CHCl_3$) ν_{max}=3020, 1215 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.8 (C-2″), 83.5 (C-6′), 61.5 (C-2), 57.4 (C-2′), 56.2 (C-6), 50.2 (C-3), 46.7 (C-6″), 35.4 (C-3″), 33.0, 31.0, 27.4, 26.4, 25.3, 24.7, 20.8 ppm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (1H, t/dd, J=10 Hz, H-2), 3.69 (1H, sd, J=2 Hz, H-2″), 3.54 (1H, t, J=8 Hz, H-6_{eq}), 3.53 (1H, s large, H-6′), 3.34 (1H, dd, J=14, 6 Hz, H-$6''_{eq}$), 3.10 (1H, td, J=14, 6 Hz, H-$6''_{ax}$), 2.71 (1H, m, H-6_{ax}), 2.63 (1H, ddd, J=11, 5 Hz, H-2′), 2.51 (1H, ddd, J=11 Hz, H-3_{eq}), 2.44 (1H, m), 2.05 (1H, td, J=11, 2 Hz, H-3_{ax}), 1.68–1.98 (5H, m), 1.60 (1+1H, ddd, J=11, 5 Hz, H-3″), 1.09–1.55 ppm (7H, m); HRMS (ES) calculated for $C_{15}H_{25}N_3H^+$ $[M+H]^+$ 248.2082, found $[M+H]^+$ 248.2085.

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