# Biomimetic Synthesis of Nitraramine

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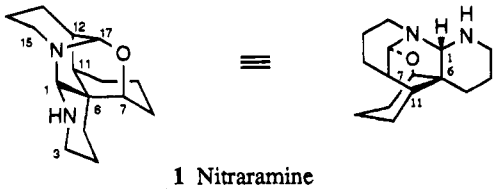
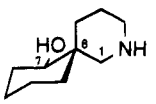
The synthesis of a possible biosynthetic precursor (**9**) of nitraramine (**1**) is described, utilizing *N*-Boc-piperidone as an equivalent of didehydropiperidine **4**. Heating this reactive, achiral intermediate **9** in aqueous solution results in the stereoselective formation of natural nitraramine via three successive cyclization reactions. Since nitraramine and several other *Nitraria* alkaloids are obtained from *Nitraria* species in racemic form, this synthesis provides additional support for our hypothesis of non-enzyme-catalyzed formation of these alkaloids.

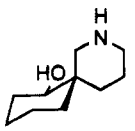
Alkaloids containing a 3-spiropiperidine structural unit are exclusively obtained from plants of the *Nitraria* genus. The *Nitraria* spiroalkaloids that contain 10 carbon atoms such as nitramine (**2**) and isonitramine (**3**) are most likely biogenetically derived from two piperidine synthons.[1,2] Nitraramine (**1**) was isolated in 1975 from *Nitraria schoberi*,[3] and the unusual structure of this considerably more complicated alkaloid was established by X-ray analysis in 1985.[4] Nitraramine is a 15 carbon-atom-containing spiroalkaloid and is probably derived from three piperidine equivalents. Three boat-formed rings in the center of the molecule form an oxazabicyclooctane ring system, which is surrounded by three chair-formed six-membered rings, thus creating a completely rigid structure.



**1** Nitraramine



**2** Nitramine



**3** Isonitramine

Remarkable is the racemic form in which nitraramine and several other *Nitraria* alkaloids occur in nature. In a recent publication[5] Heathcock and co-workers synthesized petrosin, a racemic bisquinolizidone sponge alkaloid containing eight stereocenters. They nicely demonstrated that postbiosynthetic equilibrations are responsible for the racemic form in which petrosin is isolated from its natural source. Nitraramine (**1**), however, is a configurationally stable molecule[6] and racemization via retroreactions is unlikely. Racemization experiments with enantiomerically pure material should give additional information in this respect; however, separation of nitraramine into enantiomers was unsuccesful until now.[7] After some earlier synthetic approaches[2] we describe here a synthesis that is based on the retrobiogenetic analysis we recently proposed[1] and we will show that three successive cyclization reactions smoothly take place, once the reactive precursor anticipated is obtained. The ease with which this process occurs chemically (water, reflux) combined with the racemic form of natural nitraramine give an indication that no enzymes are involved in the stereochemically important spirocyclization reaction (Scheme 4). Another example of imine/enamine based cyclization reactions of achiral precursors in aqueous solution was recently provided by our biomimetic synthesis[8] of the indole alkaloids nitrarine and nitramidine, also obtained as racemates form from *Nitraria* plants.

**Biogenetic Hypothesis.** Distinction should be made between the biosynthetic origin of these *Nitraria* alkaloids and for instance histrionicotoxine, which contains a 2-spiropiperidine ring system. A clear relationship exists between the Lupine alkaloids and those of the *Nitraria* family[1] (Scheme 1). Labeling studies[9] in Lupine species have established dipiperidine **5** (tetrahydroanabasine) as the biogenetic precursor for piperidine alkaloids such as lupinine and sparteine. Although lysine, via cadaverine, is shown to be the precursor of **5**, the existence of the instable didehydropiperidine **4**[10] as an intermediate has not been confirmed. An alternative ring opening of the saturated piperidinering in **5** leads to **6**, providing aldehyde **7** after oxidative deamination. An indication for this ring opening reaction is found in aqueous solutions of synthetic **5**[11] (dihydrobromide), showing the presence of about 30% of the open form **6** according to $^1$H-NMR spectroscopy. Condensation of **7** with the enamine form of didehydropiperidine **4** gives precursor **8**, which is probably in equilibrium with the

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1995.

(1) For a review on *Nitraria* alkaloids see: Wanner, M. J.; Koomen, G. J. Stereoselectivity in Synthesis and Biosynthesis of Lupine an Nitraria Alkaloids. In *Studies in Natural Products Chemistry 14*; Atta-ur-Rahman, Ed., Elsevier: Amsterdam, 1994, p 731–768.

(2) Wanner, M. J.; Koomen, G. J. *Tetrahedron* **1992**, *48*, 3935.

(3) Novgorodova, N. Yu.; Maekh, S. Kh.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1975**, 435. *Chem. Nat. Compd. (Engl. Transl.)* **1975**, 455.

(4) Tashkodzhaev, B.; Ibragimov, A. A.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1985**, 692; *Chem. Nat. Compd. (Engl. Transl.)* **1985**, 649.

(5) Scott, R. W.; Epperson, J. R.; Heathcock, C. H. *J. Am. Chem. Soc.* **1994**, *116*, 8853.

(6) Nitraramine is for instance stable in 40% $H_2SO_4$ up to 80 °C during 10 h: Ibragimov, A. A.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1986**, 730. *Chem. Nat. Compd. (Engl. Transl.)* **1986**, 680.

(7) We attempted resolution of nitraramine by crystallization with 1 and 2 equivs of the following reagents: (*S*)-(+)-mandelic acid; (1*R*)-(−)-10-camphorsulfonic acid; (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate.

(8) Wanner, M. J.; Koomen, G. J. *J. Org. Chem.* **1994**, *59*, 7479.

(9) Golebiewski, W. M.; Spenser, I. D. *Can. J. Chem.* **1985**, *63*, 2707.

(10) Didehydropiperidine **4** can be prepared in situ from its crystalline, symmetrical trimer α-tripiperidine: Schöpf, C.; Komzak, A.; Braun, F.; Jacobi, E.; *Chem. Ber.* **1951**, *84*, 698.

(11) For an efficient synthesis of crystalline **5** see Schöpf, C.; Braun, F.; Koop, H.; Werner, G. *Liebigs Annalen* **1962**, *658*, 157.

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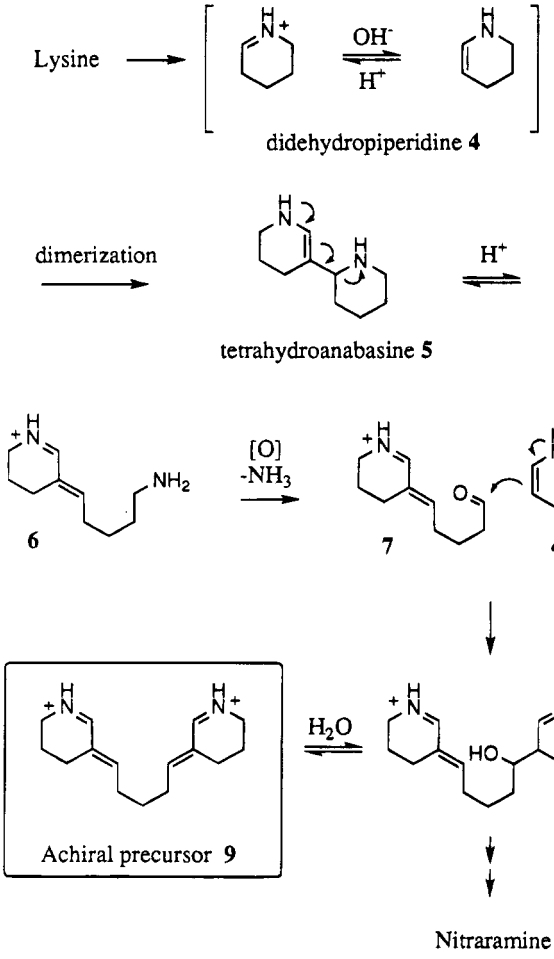
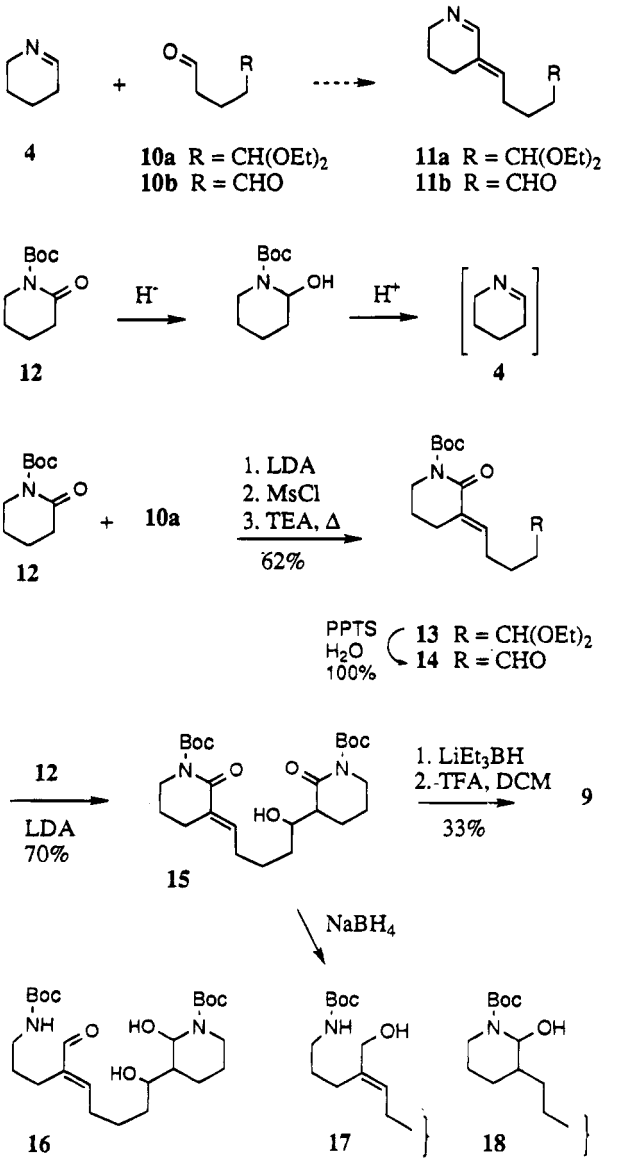
**Scheme 1. Biogenetic Hypothesis**



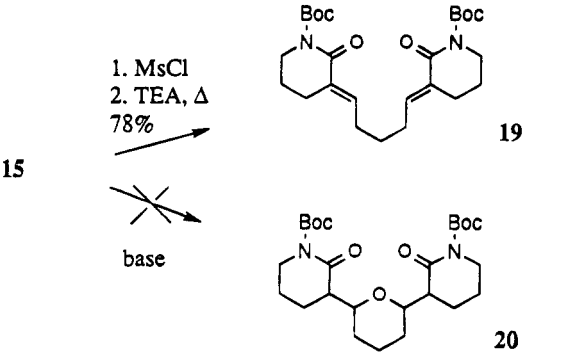

corresponding α,β-unsaturated imine **9**. Conversion of this achiral precursor **9** into nitraramine will be discussed in the chemistry part.

**Chemistry.** Initially our biomimetic synthesis was performed by condensation reactions of glutaric aldehyde **10b** with in situ-generated didehydropiperidine **4** in aqueous solution. Although these reactants have the correct oxidation state to obtain nitraramine, the capricious reactivity of glutaric aldehyde caused several undesired side reactions. Protection of one of the aldehyde functionalities in glutaric aldehyde gave acetal **10a**, which was submitted to condensation reactions with didehydropiperidine **4** according to a literature procedure, describing the synthesis of 3-alkylidene substituted piperidines from aromatic and aliphatic aldehydes.[12] None of the anticipated ene-imine product **11a** could be obtained, however, due to limited stability of the imine functionality. Next we switched to *N*-Boc-piperidinone **12**,[13] a stable piperidine equivalent that can be converted efficiently into **4** via a reduction/deprotection sequence.[8] The lithium enolate of *N*-Boc-piperidinone[14] was alkylated with aldehyde **10b** and without isolation, the resulting mixture of diastereomeric alcohols was converted into α,β-unsaturated lactam **13** (*E*:*Z* = 15:1) via mesylation and triethylamine-catalyzed elimination. This elimination effectively "protects" the OH during the next alkylation step. The acetal functionality of **13** was

**Scheme 2**



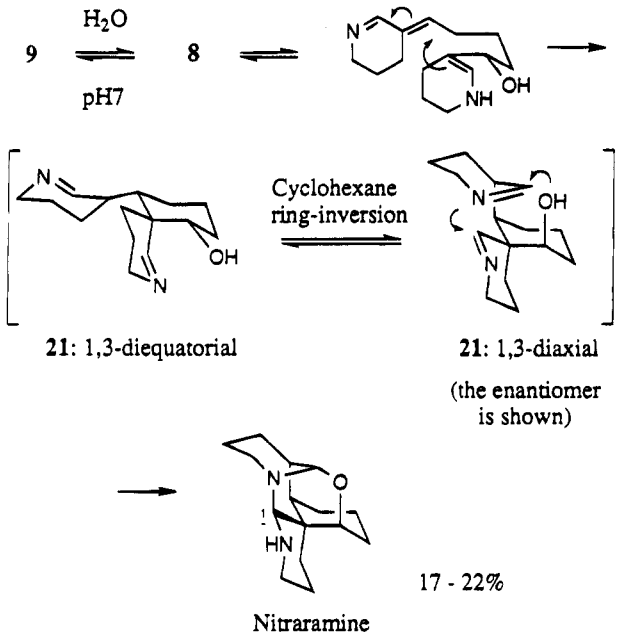

**Scheme 3**




hydrolyzed with PPTS as catalyst, and the aldehyde **14** was alkylated with a second equivalent of the lithium enolate of **12** to give **15**, representing the carbon framework that is required for the cyclization reactions. Water elimination as described for **13** produced the symmetrical dimer **19** (Scheme 3), the lactam analogue of **9**. Adjusting the oxidation state of both piperidone carbonyls in **15** turned out to be problematic. Our initial goal, protection of both hydroxyls and the double bond in the form of pyran **20** (Scheme 3) was not possible since base-catalyzed conjugate addition of the alcohol function in

(12) Nomura, Y.; Bando, T.; Takeuchi, Y.; Tomoda, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3199.
(13) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.
(14) Campi, E. M.; Chong, J. M.; Jackson, W. R.; Van Der Schoot, M. *Tetrahedron* **1994**, *50*, 2533.

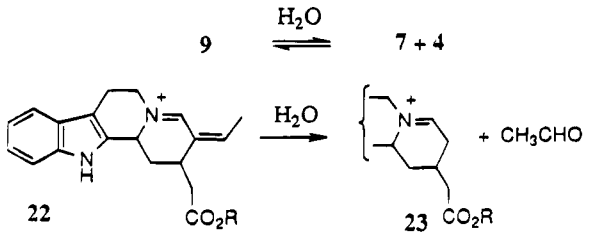
**Scheme 4**




**15** could not be accomplished. $NaBH_4$ in methanol, which is suitable for most *N*-Boc-piperidone reductions[8] worked well for the saturated lactam part of **15**, but resulted in complete overreduction of the α,β-unsaturated lactam to form the corresponding ring opened allylic alcohol **17**. Among the more selective reducing agents lithium triethylborohydride is superior for reductions of *N*-acyl lactams.[15] In our situation both lactam carbonyls of **15** were reduced, leading to the unstable precursor **16** in moderate yield. It should be noted that after aqueous workup the unsaturated hydroxypiperidine ring preferred the conjugated aldehyde form. 1,4-Reduction of the unsaturated lactam moiety followed by 1,2-reduction to form **18** lowered the yield. Acid-catalyzed removal of the Boc-substituents in **16** was performed with TFA in dichloromethane, leading to symmetrical dimer **9**[16] probably via elimination of water from **8** as is shown in Scheme 1.

Cyclization reactions with **9** (Scheme 4) were performed at reflux temperature in buffered aqueous solutions at pH 7, leading directly to nitraramine as the only isomer. Spirocyclization of **8** completes the carbon-framework, and via cyclohexane ring-inversion of **21** the required 1,3-diaxial conformation for the two final acetal-forming steps is obtained. Although stereoisomerism is possible, especially at C1, none of these compounds was observed in $^1H$ NMR spectra of crude reaction mixtures. It should be noted that 1-epi-nitraramine was recently isolated from *Nitraria billardieri* by Quirion[17] et al. The moderate yield of the last step may be caused by a cleavage reaction, which actually represents a reversion of the proposed biosynthesis. A literature example of such a hydrolytic ene-imine cleavage reaction can be found in the biomimetic deethylation of geissoschizine derivative **22** to **23** as described by Lounasmaa et al.[18] (Scheme 5).

**Scheme 5**




Identification of nitraramine was possible by comparison of $^1H$ and $^{13}C$ NMR spectra with data from the literature.[17,19] Extensive 2D NMR-spectroscopy was performed on both nitraramine and its mono-hydrochloride, resulting in a partial revision of the literature chemical shift assignments.

In summary, it was demonstrated that water at neutral pH is an effective catalyst for biomimetic cyclization reactions with the imines and enamines that might be present in *Nitraria* species. Synthesis of the appropriate precursors, which *in vivo* would require several redox-enzymes, was accomplished with *N*-Boc-piperidone as a didehydropiperidine equivalent.

## Experimental Section

**General Information.** NMR spectra were obtained from a 400 MHz Bruker spectrometer. Thin layer chromatography (TLC) was performed on silica gel-coated plastic sheets. Chromatography refers to flash chromatography on silica gel (0.030–0.075 mm). When ammonia-containing eluents were used, the silica gel was pretreated with this eluent.

**3-(2-Piperidinyl)-2,3-didehydropiperidine Dihydrobromide (5) and 1-Amino-5-(1,2-didehydropiperidin-3-ylidene)pentane (6).** Crystalline **5**·2HBr (tetrahydroanabasine, hydrate) was prepared from didehydropiperidine **4**[10] as described by Schöpf et al.[11] $^1H$ NMR (DMSO-$d_6$ + 2 drops of $D_2O$) **5**: δ 4.8 (m), 3.46 (m, 4H), 3.1 (m, 2H), 2.15–1.4 (m, 10H). **6**: δ 8.58 (s, 1H), 7.0 (m, $J$ = 7.4 Hz, 1H), 3.62 (t, $J$ = 5.3 Hz, 2H), 2.49 (t, $J$ = 6.2 Hz, 2H), 2.39 (dt, J = 7.1 Hz, 2H), 1.9–1.3 (m, 4H).

**5,5-Diethoxypentanal (10a).** A solution of glutaric aldehyde (25% in water, 150 mL, 0.385 mol) in EtOH (1.5 L, 99%) was stirred with Dowex 50WX8 ($H^+$-form, 2.0 g) at 20 °C during 4 days. The catalyst was removed by filtration, and the resulting solution was stirred with solid $NaHCO_3$ during 30 min, filtered, and evaporated in vacuo. The residue was coevaporated with ethyl acetate (2 × 100 mL) and with PE 60/80 (100 mL), dissolved in PE 60/80 (200 mL), and separated by chromatography on silica (Φ 10 cm, PE 60/80/EtOAc 3/1; TLC-spots were made visible with anisaldehyde/sulfuric acid). A mixture of diacetals (open and cyclic) was eluted first, followed by monoacetal **10a**, which was obtained in pure form by distillation (8.9 g, 51.1 mmol, 13%): Bp 42–45 °C/0.6 mbar; $^1H$ NMR ($CDCl_3$)[20] δ 9.76 (t, $J$ = 1.4 Hz, 1H), 4.48 (t, $J$ = 5.2 Hz, 1H), 3.7–3.4 (m, 4H), 2.47 (dt, $J$ = 1.4 Hz, $J$ = 7.0 Hz, 2H), 1.74–1.61 (m, 4H), 1.19 (t, $J$ = 7.0 Hz, 6H); $^{13}C$ NMR ($CDCl_3$)[20] δ 202.28, 102.51, 61.15, 43.52, 32.91, 17.34, 15.26; IR ($CHCl_3$) 1720 $cm^{-1}$.

**1,1-Diethoxy-5-[*N*-(*tert*-butyloxycarbonyl)-2-oxopiperidin-3-ylidene]pentane (13).** *N*-(*tert*-Butoxycarbonyl)-2-piperidinone (**12**)[13] (7.96 g, 40 mmol, crystallized from hexanes at −20 °C) was added to a solution of LDA (44 mmol) in THF (120 mL) at −78 °C. The reaction mixture was allowed to warm to −20 °C, stirred at this temperature during 1 h, and cooled to −78 °C. Aldehyde **10a** (6.96 g, 40 mmol) was added dropwise, and the mixture was stirred at this temperature for

(15) (a) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447. (b) Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053.

(16) Ene-imine **9** was only stable in solution and could be observed by NMR in the form of its TFA-salt; see Experimental Section.

(17) We wish to thank Dr. J.-C. Quirion for sending us spectra of nitraramine and 1-*epi*-nitraramine. Shen, M. Y.; Zuanazzi, J. A.; Kan, C.; Quirion, J.-C.; Husson, H.-P.; Bick, I. R. C. Alkaloids from *Nitraria billardieri*: *Nat. Prod. Lett.* **1995**, *6*, 119.

(18) Lounasmaa, M; Jokela, R.; Halonen, M, Miettinen, J. *Heterocycles* **1993**, *36*, 2523.

(19) Ibragimov, A. A.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1988**, 82. *Chem. Nat. Compd. (Engl. Transl.)* **1988**, 71.

(20) Traces of acid in the $CDCl_3$ are removed by filtration over basic $Al_2O_3$.

1 h and quenched with saturated $NH_4Cl$ solution. Extractive workup (ether) yielded the crude alcohol, which was dissolved in a mixture of dry toluene (50 mL) and triethylamine (8.3 mL, 60 mmol). Methanesulfonyl chloride (3.5 mL, 45 mmol) was added dropwise at 0 °C, and the mixture was allowed to warm to room temperature. Additional triethylamine (13.8 mL, 100 mmol) was added and the mixture was refluxed during 6 h. Aqueous workup and chromatographic separation (PE 60/80/EtOAc 3/1) gave first impure **13** *Z*-isomer (0.6 g, 4%) and next **13** *E*-isomer (8.75 g, 62%) both as a syrup. *Z*-isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 5.82 (t, $J$ = 7.1 Hz); *E*-isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 6.89 (m, $J$ = 7.5 Hz), 4.41 (t, $J$ = 5.4 Hz, 1H), 3.64–3.39 (m, 6H), 2.40 (m, 2H), 2.10 (q, $J$ = 6.4 Hz, 2H), 1.80 (m, $J$ = 5.4 Hz, 2H), 1.56 (m, 2H), 1.48 (s, 9H), 1.14 (t, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 167.1, 153.2, 142.2, 130.1, 102.6, 82.65, 61.02, 45.77, 33.21, 28.06, 27.99, 24.30, 23.60, 22.22, 15.27; IR ($CHCl_3$) 1755, 1705, 1620 $cm^{-1}$; HRMS (FAB) obs mass 378.2180 ($MNa^+$), calcd for $C_{19}H_{33}NO_5Na$ 378.2383; obs mass 356.2400 ($MH^+$), calcd for $C_{19}H_{34}NO_5$ 356.2503.

**5-[*N*-(*tert*-Butyloxycarbonyl)-2-oxopiperidin-3-ylidene]-pentanal (14).** Acetal **13** (3.55 g, 10 mmol) was stirred with PPTS (0.12 g) in a mixture of water (5 mL) and acetone (150 mL) at 20 °C during 4 days. The reaction mixture was partitioned between PE 60/80 (200 mL) and dilute NaCl solution (100 mL) to remove the catalyst. Extraction and drying yielded **14** (2.8 g, 100%), which was pure enough for further transformations. $^1H$ NMR ($CDCl_3$) $\delta$ 9.72 (t, $J$ = 1.5 Hz, 1H), 6.86 (m, $J$ = 5.5 Hz, 1H), 3.64 (m, 2H), 2.43 (m, 4H), 2.13 (q, $J$ = 7.5 Hz, 2H), 1.88–1.71 (m, 4H), 1.49 (s, 9H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 201.8, 165.1, 153.1, 140.8, 130.9, 82.79, 45.80, 43.07, 27.99, 27.39, 24.33, 22.17, 20.77; IR ($CHCl_3$) 1755, 1720, 1700, 1620 $cm^{-1}$, HRMS obs mass 281.1649, calcd for $C_{15}H_{23}O_4N$ 281.1570.

**1-[*N*-(*tert*-Butyloxycarbonyl)-2-oxopiperidin-3-yl]-5-hydroxy-5-[*N*-(*tert*-butyloxycarbonyl)-2-oxopiperidin-3-ylidene]pentane (15).** A solution of the lithium enolate of *N*-(*tert*-butoxycarbonyl)-2-piperidinone (**12**) (2.2 mmol) in THF was prepared as described for **11a**. A solution of aldehyde **14** (0.56 g, 2 mmol) in THF was added at −78 °C, and the reaction mixture was stirred at this temperature during 2 h. Extractive workup ($NH_4Cl$, ether) and chromatography (EtOAc/PE 60/80 2/1) gave **15** (0.67 g, 70%) as a mixture of isomers: $^1H$ NMR ($CDCl_3$) $\delta$ 6.90 (m, 1H), 4.1 (b, 1H), 3.76 (m, 1H), 3.7–3.46 (m, 3H), 2.5–1.5 (m), 1.48 (s, 9H), 1.47 (s, 9H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.9, 173.8, 165.2, 153.2, 151.9, 142.1, 141.9, 130.2, 83.18, 82.58, 71.48, 70.22, 48.79, 45.76, 45.45, 45.08, 33.19, 32.57, 2836, 28.10, 27.93, 25.11, 24.33, 23.94, 22.78, 22.29, 21.97, 21.69, 19.87; IR ($CHCl_3$) 3500 (br), 1757, 1680–1720, 1620 $cm^{-1}$; HRMS (FAB) obs mass 503.2649 ($MNa^+$), calcd for $C_{25}H_{40}N_2O_7Na$ 503.2816; obs mass 481.2825 ($MH^+$), calcd for $C_{25}H_{41}N_2O_7$ 481.3010.

**1,5-Bis[*N*-(*tert*-butyloxycarbonyl)-2-oxopiperidin-3-ylidene]pentane (19).** Alcohol **15** (48 mg, 0.1 mmol) was eliminated with triethylamine and methanesulfonyl chloride as described for compound **13** yielding **19** *Z,E*-isomer (2 mg, 4%) and **19** *E,E*-isomer (36 mg, 78%). **19** *Z,E*-isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 6.93 (m, 1H), 5.84 (m, 1H), 3.66 (m, 4H), 2.59 (m, 2H), 2.15 (m, 2H), 2.45(m, 4H), 1.85 (m, 4H), 1.6 (m, 2H), 1.533 (s, 9H, 1.531 (s, 9H); **19** *E,E*-isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 6.91 (s, 2H), 3.66 (m, 4H), 2.42 (m, 4H), 2.14 (m, 4H), 1.84 (m, 4H), 1.61 (m, 2H), 1.52 (m, 18H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 165.1, 153.2, 141.3, 130.6, 82.71, 45.77, 28.04, 27.46, 27.08, 24.41, 22.28; IR ($CHCl_3$) 1755, 1705, 1620 $cm^{-1}$; HRMS no $M^+$ observed.

**Reduction of 15 with $NaBH_4$.** Excess sodium borohydride was added in portions to a solution of **15** (0.12 g, 0.25 mmol) in MeOH (5 mL) at 40–50 °C over a period of 4 h. Aqueous workup and chromatography ($CH_2Cl_2$/EtOH 93/7) gave **17** (0.072 g, 60%) as a mixture of isomers: $^1H$ NMR ($CDCl_3$) $\delta$ 5.42 (t, $J$ = 7.1 Hz, 1H), 4.8 (b, 2H), 3.99 (bs, 2H), 3.9–3.4 (b, 7H), 1.41 (s, 18H); IR ($CHCl_3$) 3550–3200 (br), 3450, 1700, 1690 $cm^{-1}$; HRMS (FAB) no $M^+$ observed.

**Reduction of 15 to 16 with Lithium Triethylborohydride.** Lithium triethylborohydride (3.8 mL of a 1 M solution in THF, 3.8 mmol) was added dropwise to a solution of **15** (0.74 g, 1.55 mmol) in THF (15 mL) at −78 °C. After a total reaction time of 2.5 h the reaction was quenched with acetic acid (0.2 mL). Aqueous $NaHCO_3$ workup, extraction with ethyl acetate, and chromatography using $CH_2Cl_2$/EtOH 93/7 as eluent yielded **16** (0.25 g, 33%) as a syrup. $^1H$ NMR ($CDCl_3$) $\delta$ 9.34 (s, 1H), 6.51 (t, $J$ = 7.3 Hz, 1H), 5.67 (bs, 1H), 4.81 (b, 1H), 3.8–3.0 (m, 7H), 2.39 (m, 2H), 2.56 (m, 2H), 2.0–1.2 (m, 8H), 1.46–1.42 (4 x s, 18H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 195.0, 155.8, 154.9, 142.8, 79.9, 73.32, 72.82; IR ($CHCl_3$) 3600–3200 (br) 1685, 1670 $cm^{-1}$; HRMS (FAB) no $M^+$ observed.

**Acidic Hydrolysis of 16 and Cyclization to Nitraramine.** Trifluoroacetic acid (0.5 mL) was added in one portion to an ice-cold solution of **16** (0.11 g, 0.22 mmol) in $CH_2Cl_2$ (1 mL). After 15 min at 0 °C the mixture was stirred at room temperature for 30 min and evaporated in vacuo (bath $T$ < 25 °C). The oily residue (**9** TFA salt) was dissolved in $CDCl_3$ by the addition of $CD_3OD$ (2 drops): $^1H$ NMR ($CDCl_3$) $\delta$ 8.43 (bs, 2H), 6.87 (bt, 2H), 3.65 (m, 4H), 2.50 (m, 4H), 2.42 (m, 4H), 1.98 (m, 4H), 1.74 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 169.2, 129.8, 43.86, 29.10, 25.53, 20.68, 18.78. This bis-iminium salt was not stable enough for further analysis and was evaporated directly after the acid-treatment and dissolved in a pH 7 phosphate buffer (20 mL). The resulting solution was refluxed under nitrogen during 20 h, made alkaline with excess solid sodium carbonate, and extracted three times with ethyl acetate. The organic layer was dried ($Na_2SO_4$), and removal of the solvents gave a crude alkaloid mixture, (15–30 mg) containing ca. 50% nitraramine. Chromatography ($CH_2Cl_2$/methanol/$NH_4OH$ 90/10/1) gave nitraramine **1** (17–22%) as a glass. An analytical pure sample was prepared from the easily crystallizing monohydrochloride. A solution of nitraramine in ethanol was treated with concd HCl. The solvents and the excess of HCl were removed by coevaporation with methanol, and the dihydrochloride was dissolved in ethanol and treated with a small excess of triethylamine. Evaporation and crystallization from $CH_2Cl_2$/ethyl acetate produced triethylamine hydrochloride, which was removed by filtration. The filtrate was evaporated to dryness and nitraramine hydrochloride crystallized from a small amount of ethanol by precipitation with ethyl acetate. The free base was obtained in pure form by treatment of nitraramine hydrochloride with aqueous $K_2CO_3$ followed by ether extraction. **Nitraramine (1):** $^1H$ NMR ($CDCl_3$) $\delta$ 4.43 (m, 1H, H-7), 4.07 (d, $J$ = 2.5 Hz, 1H, H-17), 3.34 (s, 1H, H-1), 3.11–3.07 (m, H-3eq), 3.07–3.04 (m, 1H, H-15eq), 2.79–2.71 (m, H-15ax), 2.69–2.61 (m, H-3ax), 2.19–2.14 (m, $J_{gem}$ = 13.8 Hz, H-5eq), 2.01 (m, H-12), 1.9–1.45 (m, 7H), 1.44–1.32 (m, 3H, 2H-4, H-9ax), 1.26–1.23 (m, H-10), 1.17 (m, H-11), 1.11–1.01 (m, 2H, H-14ax, H-5ax); $^{13}C$ NMR ($CDCl_3$) $\delta$ 82.30 (C-17), 75.95 (C-1), 66.54 (C-7), 50.50 (C-15), 45.35 (C-3), 38.84 (C-11), 37.99 (C-12), 32.37 (C-6), 30.55 (C-5), 28.50 (C-8), 25.22 (C-13), 24.12 (C-10), 21.94 (C-4), 15.40 (C-9) 14.61 (C-14); MS $m/z$ (%) 248 (100), 219 (18), 204 (30), 190 (13), 176 (15), 162 (18), 150 (35); HRMS obs mass 248.1899, calcd for $C_{15}H_{24}N_2O$ 248.1857. **Nitraramine monohydrochloride:** mp: 223–225 °C; $^1H$ NMR ($D_2O$) $\delta$ 4.34 (m, 1H, H-7), 4.23 (d, 1H, $J$ = 2.5 Hz, H-17), 4.18 (s, 1H, H-1), 3.38–3.33 (m, 1H, $J_{gem}$ = 12.9 Hz, H-3eq), 3.12–3.07 (m, 1H, H-15eq), 3.11–3.04 (m, 1H, H-3ax), 2.83–2.77 (m, 1H, H-15ax), 2.36–2.31 (m, $J_{gem}$= 14.5 Hz, H-5eq), 2.19–2.16 (m, 1H, H-12), 1.85–1.6 (m, 9H), 1.51–1.48 (m, 2H, H-11), 1.44–1.36 (m, 1H, H-5ax), 1.4–1.35 (m, 1H, H-10), 1.3–1.2 (m, 1H, H-14ax); $^{13}C$ NMR ($D_2O$) $\delta$ 84.20, 77.74, 69.45, 52.90, 46.02, 39.85, 39.47, 35.22, 30.07, 29.80, 26.98, 25.63, 20.17, 16.73, 16.54; MS $m/z$ (%) 248 (100), 231 (5), 220 (8), 204 (28), 162 (20), 150 (31); HRMS obs mass 248.1909, calcd for $C_{15}H_{24}N_2O$ 248.1857. **Nitraramine dihydrochloride:** $^1H$ NMR ($D_2O$) $\delta$ 4.79 (d, $J$ = 2.5 Hz, H-17), 4.63 (s, 1H, H-1), 4.45 (m, 1H, H-17), 3.59–3.41 (m, 2H, H-3eq, H-15eq), 3.21–3.13 (m, 2H, H-3ax, H-15ax), 2.38 (m, 1H, H-12), 2.39–2.33 (m, 1H), 1.85–1.35 (m, 14H); $^{13}C$ NMR ($D_2O$) $\delta$ 85.55, 75.05, 70.42, 54.14, 47.80, 38.39, 37.96, 35.27, 29.26, 28.28, 26.70, 25.43, 19.78, 16.39, 16.01.

**Supporting Information Available:** Copies of the 1D and 2D NMR spectra of nitraramine **1** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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