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Novel Alkaloids from *Myrioneuron nutans*

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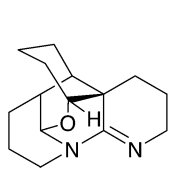
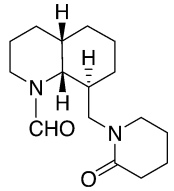
Two new alkaloids, dehydronitraramine (**1**) and *N*-formylmyrionine (**2**) were isolated from the leaves of *Myrioneuron nutans*, and their structures were determined from spectroscopic analysis, including mass spectrometry and 2D-NMR spectroscopy. The absolute configuration 8*S*, 9*R*, 10*S* of *N*-formylmyrionine (**2**) was established by *N*-formylation of the known (8*S*,9*R*,10*S*)-myrionine and then comparison of the optical rotation of the natural *N*-formylmyrionine (**2**) with that of the semi-synthetic (8*S*,9*R*,10*S*)-*N*-formylmyrionine. Dehydronitraramine (**1**) displayed a moderate antiplasmodial activity against *Plasmodium falciparum* with an IC_{50} value of 16 μM, whereas both **1** and **2** showed a weak cytotoxicity against KB cells.

Introduction

Myrioneuron nutans (Rubiaceae),[1] a small tree native in North Vietnam, was selected in the course of a screening program of Vietnamese plants for their cytotoxicity against tumor cells (the alkaloid extract of the leaves of *M. nutans* showed cytotoxic activity against KB cells with an IC_{50} value of 50 μg/mL) and for the high content of alkaloids present in this species. We previously reported the isolation from this plant and the syntheses of two 1,3-oxazines (myrioxazines A and B) and of the *cis*-decahydroquinoline (DHQ) derivatives, myrionine, myrionidine and schoberine.[2–6] In continuation of our research on alkaloids from *M. nutans*, further purification of the crude alkaloid fraction led to the isolation of two novel alkaloids, dehydronitraramine (**1**) and *N*-formylmyrionine (**2**). Compound **2** was determined as (8*S*,9*R*,10*S*)-*N*-formylmyrionine by *N*-formylation of the previously described (8*S*,9*R*,10*S*)-myrionine.[3,6] Comparison of the optical rotation of **2** ($[\alpha]_D^{20}$ = +35.9, *c* = 1, MeOH) with that of the semi-synthetic (8*S*,9*R*,10*S*)-*N*-formylmyrionine $[\alpha]_D^{20}$ = +36.8 (*c* = 1, MeOH) allowed assignment of the absolute configuration (8*S*,9*R*,10*S*) for the natural *N*-formylmyrionine (**2**).



dehydronitraramine (**1**)



N-formylmyrionine (**2**)

Results and Discussion

The dried and ground leaves (5.0 kg) of *M. nutans* were extracted with CH_2Cl_2 at basic pH, and the crude alkaloid obtained by acid-base purification was separated by column chromatography over silica gel (CH_2Cl_2/MeOH) to yield dehydronitraramine (**1**, 6 mg) and *N*-formylmyrionine (**2**, 37 mg).

Dehydronitraramine (**1**) was isolated as an optically active colourless solid, m.p. 115–116 °C, $[\alpha]_D^{20}$ = +9.3 (*c* = 0.5, MeOH). The molecular formula $C_{15}H_{22}N_2O$ was assigned for **1** on the basis of the protonated molecular ion $[M + H]^+$ at *m*/*z* 247.1817 (calcd. 247.1810 for $C_{15}H_{23}N_2O$) observed in the HR-ESI mass spectrum. Its ^1H and ^{13}C NMR spectra had signals for 15 carbons and 22 protons, including nine methylenes, four methines and two quaternary carbons (one sp^3 at δ_C = 40.3 and one sp^2 at δ_C = 172.1, Table 1). IR absorption at 1651 cm^{-1} was assigned to an imine functionality. Thus, the six degrees of unsaturation deduced from the molecular formula of **1** were distributed into one double bond and five rings. From the ^1H-^1H COSY 90 spectrum, the two structural fragments **A** and **B** were clearly depicted as drawn with bold bonds in Figure 1. The **A**-fragment was defined as follows: starting from the CH-7 proton (δ_H = 3.88) to the CH_2-15 methylene (δ_H = 4.54 and 3.15), a set of correlations was observed, involving

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successively CH_2-8, CH_2-9, CH_2-10, CH-11, CH-12, CH_2-13 and CH_2-14, together with a correlation of CH-12 (δ_H = 2.52) with the deshielded CH-17 (δ_H = 4.74). The chemical shifts of CH-7 (δ_H = 3.88 and δ_C = 70.9) and CH_2-15 (δ_H = 4.54 and 3.15, δ_C = 52.8) suggested their linkages to oxygen and nitrogen atoms respectively, and those of CH-17 (δ_H = 4.74 and δ_C = 84.5), indicated its connections to both oxygen and nitrogen atoms. Similarly, the chemical shift of CH_2-3 (δ_H = 3.75 and 3.51, and δ_C = 42.4) suggested its bonding to a nitrogen atom and it was correlated to CH_2-4 (δ_H = 1.88 and 1.82), which in turn showed cross-peaks with CH_2-5 (δ_H = 2.07 and 1.66), determining a $-(CH_2)_3-$ system (**B**-substructure). Connections of the two **A**- and **B**-fragments with the quaternary carbons C-6 and C-1 resulted from the analysis of the HMBC spectrum of **1**. The methylenes CH_2-5 (δ_H = 1.66 and 2.07), CH_2-8 (δ_H = 1.51 and 1.79), CH_2-10 (δ_H = 1.54 and 1.80) and the methine CH-7 (δ_H = 3.88) were ^2J or ^3J correlated to the quaternary carbon C-6 (δ_C = 40.3).

Table 1. NMR spectroscopic data (^{1}H: 400.13 MHz, ^{13}C: 75.47 MHz, $CDCl_3$) for dehydronitraramine (**1**).

No.	δ_C	δ_H m (*J* in Hz)	No.	δ_C	δ_H m (*J* in Hz)
1	172.6		10	23.3	1.80 m
3	42.4	3.75 ddd (14.2, 4.3, 4.3)			1.54 m
		3.51 ddd (14.2, 9.4, 4.3)	11	35.8	1.60 m
4	18.4	1.88 m	12	43.1	2.52 br. s
		1.82 m	13	27.9	1.87 m
5	24.3	2.07 m			1.58 m
		1.66 m	14	19.5	1.60 m
6	40.3				1.45 m
7	70.9	3.88 br. s	15	52.8	4.54 ddd (14.4, 2.1, 2.1)
8	13.3	1.79 m			3.15 ddd (14.4, 12.6, 3.5)
		1.51 m	17	84.5	4.74 d (2.5)
9	23.7	1.75 m			
		1.55 m			

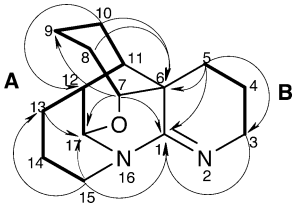


Figure 1. COSY (—) and selected HBMC correlations (^{1}H→^{13}C) for **1**.

The above analysis indicated that C-6 was linked to both C-11 and C-7 of the **A**-fragment, as well as to C-5 of the **B**-fragment. Furthermore, the sp^2 quaternary imine carbon C-1 (δ_C = 172.6) was correlated to CH_2-3 (δ_H = 3.51 and 3.75), CH_2-5 (δ_H = 1.66 and 2.07), CH-7 (δ_H = 3.88) and CH_2-15 (δ_H = 3.15 and 4.54), indicating its linkage to C-6, N-2 and N-16. Thus, the methylenes CH_2-3 and CH_2-15 were bonded to N-2 and N-16, respectively. In addition, C-17 (δ_C = 84.5) was correlated to CH_2-15 (δ_H = 3.15 and 4.54) and hence, linked to N-16. Due to the correlation of the oxymethine carbon C-7 (δ_C = 70.9) with H-17, the bonding of O-18 oxygen atom with both C-7 and C-17 carbons was established. The planar structure of **1** was thus assigned as drawn in Figure 1.

The relative configuration of **1** was assigned from $^3J_{H-H}$ coupling constants analysis and NOE data. The signal for H-17 was a doublet with a small coupling constant (J = 2.5 Hz) in the ^{1}H NMR spectrum, indicating its *cis*-relationship with H-12, which was a broad singlet, and was thus equatorial on the **a**-ring. Furthermore, H-7 and H-11 appeared as broad singlets in the ^{1}H NMR spectrum, indicating their equatorial disposition on the **d**-ring. As shown in the NOESY spectrum, H-17 had strong spatial interactions with H-13_{ax} and H-15_{ax}. They were axial on the **a**-ring which was in a chair form. Similarly, the **d**-ring was determined as a chair conformation from spatial cross-peaks of H-8_{ax} with both H-10_{ax} and CH_2-5. In addition, a strong correlation between H-11 and H-14_{ax} was also observed. Finally, complete analysis of the NOESY spectrum determined the relative configuration of **1** in which the **b**- and **c**-rings were in boat conformations (Figure 2). This new alkaloid was named dehydronitraramine, as it appeared to be an imine derivative of nitraramine, which has been previously isolated from several *Nitraria* species.[7–13]

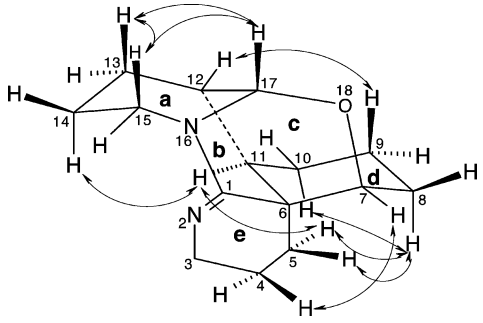


Figure 2. Key NOESY interactions of **1**.

N-formylmyrionine (**2**) was isolated as an optically active crystalline solid [m.p. 119–123 °C (Et_2O/EtOH), $[\alpha]_D^{20}$ = +35.9, c = 1, MeOH]. Its HR-ESI mass spectrum displayed the protonated molecular ion $[M + H]^+$ at m/z 279.2082 (calcd. 279.2073 for $C_{16}H_{27}N_2O_2$). Its IR spectrum showed the presence of carbonyl groups ($\tilde{\nu}_{max}$: 1666, 1645, 1636 and 1625 cm^{-1}). The ^{1}H NMR spectrum of **2** enclosed two nearly similar sets of signals with a ratio of 6:4 suggesting it was a mixture of two isomers. HPLC analysis (RP-8 column, detection at λ_{max} 220 nm) of this mixture showed two peaks, which were then separated by preparative HPLC. However, when analyzed by ^{1}H NMR, the two purified compounds had the same ^{1}H NMR spectrum, which was identical with that of the initial mixture **2**. This observation indicated that these two isomers were able to readily interconvert into a conformational equilibrium. Due to their different proportions, the chemical shifts of these two isomers were separately assigned from 2D-NMR spectroscopy. The major component showed, in the ^{1}H-^{1}H COSY 90 spectrum, a set of successive correlations from CH_2-2 (δ_H = 3.38 and 3.33) to H-9 (δ_H = 4.10). The last protons (H-

9) and H-8 (δ_H = 2.42) were further correlated with H-10 (δ_H = 1.75) and CH_2-11 (δ_H = 3.67 and 2.43), respectively forming the **A**-substructure (Figure 3). Furthermore, connections from CH_2-14 (δ_H = 2.31) to CH_2-17 (δ_H = 3.24) via CH_2-15 (δ_H = 1.71) and CH_2-16 (δ_H = 1.72) suggested a $-(CH_2)_4-$ system (**B**-substructure). The chemical shifts of CH_2-2, CH-9, CH_2-11 and CH_2-17 were explained by their linkages to nitrogen atoms (Table 2).

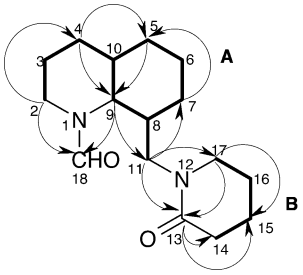


Figure 3. COSY (—) and key HMBC ($^1H \rightarrow ^{13}C$) correlations for **2a** and **2b**.

HMBC analysis allowed linking the two **A**- and **B**-substructures as follows: C-2 (δ_C = 42.1) was correlated with H-9 (δ_H = 4.10) indicating that CH_2-2 and CH-9 were bonded to N-1 and formed a decahydroquinoline system. The carbonyl C-13 (δ_C = 169.9) displayed cross-peaks with CH_2-11 (δ_H = 3.67 and 2.43), CH_2-14 (δ_H = 2.31) and CH_2-17 (δ_H = 3.24), determining the 2-piperidinone moiety, which was linked to the decahydroquinoline moiety by the N-12–C-11 bond. Finally, strong correlations of the formyl carbon C-18 with both CH_2-2 and H-9 were observed, indicating that the formyl group was linked to N-1. Complete analysis of the HMBC correlations established the planar structure of the major isomer **2a** (Figure 3). In the same way, 1D and 2D-NMR analyses permitted determining the same planar structure for the minor isomer **2b**, the chemical shifts of which are reported in Table 2.

The relative configuration of the major isomer **2a** was determined from $^3J_{H-H}$ coupling constants and NOESY data analysis. The signal of H-9 appeared as a doublet of doublets with two coupling constants (an *anti*, J = 11.3 Hz, and a *gauche*, J = 4.4 Hz). In addition, H-8 presented four large coupling constants (J = 9.2, 10.4, 11.3 and 11.7 Hz) and a small one (J = 2.2 Hz), which implied that H-8 and H-9 were in a *trans*-diaxial relationship and that H-9 and H-10 were in a *gauche* disposition, indicating a *cis*-fused junction for the **a**/**b**-rings (Figure 4). The major isomer **2a** was thus an 8β-alkyl-*cis*-DHQ derivative, which adopted the N-out conformation (the nitrogen group is equatorial on the cyclohexane ring). It is important to note that, as **2** is an 8β-alkyl-*cis*-DHQ derivative, the H-9 proton in the N-in form of **2**, where the nitrogen group is axial on the cyclohexane ring, should provide two *gauche* coupling constants with H-8 and H-10 (Figure 5).

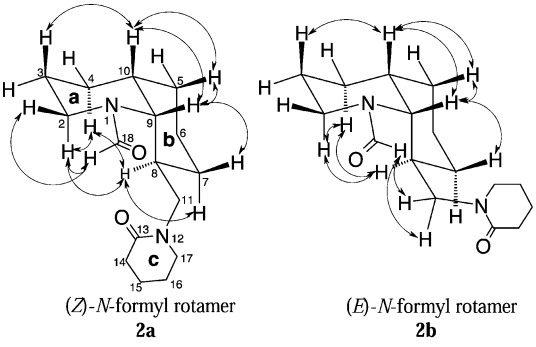


Figure 4. Selected NOE interactions for (*Z*)- and (*E*)-*N*-formylmyrionine (**2a** and **2b**).

Table 2. NMR spectroscopic data (^1H: 400.13 MHz, ^{13}C: 75.47 MHz, $CDCl_3$) for (*Z*)- and (*E*)-*N*-formylmyrionines (**2a** and **2b**).

No.	**2a**		**2b**	
	δ_C	δ_H m (J in Hz)	δ_C	δ_H m (J in Hz)
2	42.1	3.38 ddd (13.7, 13.7, 3.1)	35.7	4.27 ddd (13.2, 4.5, 2.4)
		3.33 ddd (13.7, 5.1, 1.7)		2.62 ddd (13.2, 13.2, 3.4)
3	26.6	1.74 m	25.1	1.69 m
		1.40 m		1.43 m
4	24.8	1.82 m	25.1	1.69 m
		1.40 m		1.43 m
5	30.8	1.54 m	30.9	1.54 m
6	20.1	1.47 m	20.0	1.47 m
		1.34 m		1.34 m
7	29.9	1.82 m	29.4	1.75 m
		1.03 dddd (11.7, 11.7, 11.7, 3.9)		0.99 dddd (13.2, 13.2, 13.2, 3.8)
8	31.7	2.42 ddddd (11.7, 11.3, 10.4, 9.2, 2.2)	30.7	2.37 ddddd (13.2, 12.0, 10.3, 4.5, 2.0)
9	52.6	4.10 dd (11.3, 4.4)	60.4	3.17 dd (12.0, 3.8)
10	35.1	1.75 m	36.9	1.82 m
11	51.8	3.67 dd (18.9, 10.4)	50.4	3.16 dd (13.3, 10.3)
		2.43 dd (18.9, 9.2)		3.06 dd (13.3, 4.5)
13	169.9		170.0	
14	32.2	2.31 m	32.2	2.31 m
15	21.1	1.71 m	21.1	1.71 m
16	23.3	1.72 m	23.1	1.72 m
17	51.0	3.24 m	49.1	3.17 m
18	161.4	8.03 s	160.8	7.97 s

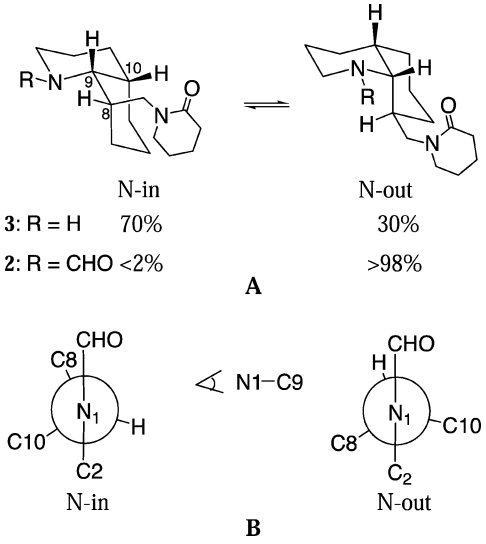


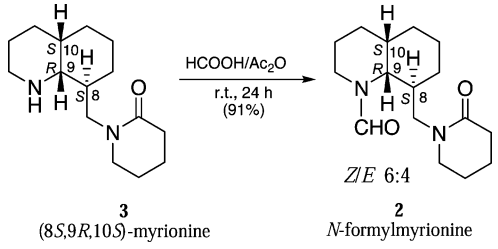
Figure 5. **A**: N-in/N-out ratio for *N*-formylmyrionine (**2**) and myrionine (**3**) in $CDCl_3$; **B**: Newman projections (viewing N-1–C9) in N-in and N-out conformations of **2**.

For the minor compound **2b**, H-9 showed an *anti* coupling constant (J = 12.0 Hz) and a *gauche* one (J = 3.8 Hz), while H-8 presented 3 large (J = 10.3, 12.0 and 13.2 Hz) and 2 small (J = 4.5 and 2.0 Hz) coupling constants. The coupling constant between H-8 and H-9 (J = 11.3 Hz) was characteristic of a *trans*-diaxial relationship (Table 2). A *cis*-fused junction was thus determined for the **a/b**-rings as indicated by the *gauche* coupling constant between H-9 and H-10 (J = 3.8 Hz). These data indicated that the minor isomer **2b** had the same relative configuration as the major one **2a** and also adopted the N-out conformation. The N-out conformers in both **2a** and **2b** were also signified by the upfield proton chemical shifts of CH_2-7 (Table 2).

Analysis of the NOE data for the two isomers **2a** and **2b** revealed the interactions of H-9 with H-5_{ax}, H-7_{ax} and H-10, as well as those of H-8 with H-2_{ax} and H-4_{ax}. The differences between **2a** and **2b** in the NOESY spectra were due to the interactions of the formyl proton H-18 which was correlated to H-2_{eq} for the major isomer **2a**, but with CH_2-11 for the minor one **2b**. This observation determined (*Z*)-*N*-formylmyrionine **2a** as major rotamer and (*E*)-*N*-formylmyrionine **2b** as minor one. Hence, the isomerisation of **2** was due to the *N*-CHO bond rotation. The relative configuration of **2** was thus established as 8*S**,9*R**,10*S** (Figure 4).

We have previously described that (8*S*,9*R*,10*S*)-myrionine (**3**) isolated from *M. nutans*, showed a conformational equilibrium between the N-in and N-out conformers (ratio of 7:3 in favour of the N-in conformer in $CDCl_3$ at 233 K).[3] At 328 K, an average conformation between N-in and N-out with sharp signals was observed in the 1D-NMR spectra of **3**. In the case of *N*-formylmyrionine (**2**), only the N-out form was observed in the 1D-NMR spectra in $CDCl_3$ at 298 K, which depicted sharp signals (Figure 5**A**). The preference of the N-out over the N-in conformers of **2** could be explained by the fact that the presence of the formyl group at N-1 forced the bonds of this nitrogen to be coplanar. Due to a (1,3)-type constraint[16–18] between the CHO group and the 1-methyl-2-piperidinone group fixed at C-8, the N-in conformer of **2** was disfavoured. This was clear with the Newman representation by viewing along the N1–C9 bond. In the N-in conformer of **2**, the C-9–C-8 and N-1–CHO bonds were nearly eclipsed, while in the N-out conformer, the C-9–H and N-1–CHO bonds were quite staggered. Thus, steric hindrance between the CHO group and C-8 was stronger than that between the CHO and H-9 (Figure 5**B**).

The absolute configuration of **2** was correlated to that of (8*S*,9*R*,10*S*)-myrionine (**3**) which has been previously established by X-ray crystallography and by its total asymmetric synthesis.[3] Hence, (8*S*,9*R*,10*S*)-myrionine was formylated by using a $HCOOH/Ac_2O$ mixture at room temperature to afford (8*S*,9*R*,10*S*)-*N*-formylmyrionine in 91% yield.[14,15] ^1H NMR analysis in the same conditions of the semi-synthetic (8*S*,9*R*,10*S*)-*N*-formylmyrionine showed that it had the same *Z*/*E* ratio (6:4) as the natural compound. Comparing the NMR spectroscopic data and optical rotation of the natural *N*-formylmyrionine (**2**) ($[\alpha]_D^{20}$ = +35.9, c = 1, MeOH) with those of the semi-synthetic one ($[\alpha]_D^{20}$ = +36.8, c = 1, MeOH) depicted that they were identical and the absolute configuration of **2** was thus established as 8*S*,9*R*,10*S* (Scheme 1).



Scheme 1. Formylation of (8*S*,9*R*,10*S*)-myrionine (**3**).

Compounds **1** and **2** were evaluated for their cytotoxicity. Both dehydronitraramine (**1**) and *N*-formylmyrionine (**2**) induced very weak or no inhibition of KB cell proliferation, with an IC_{50} of 101 and >360 μM, respectively. However, **1** showed a stronger antiplasmodial activity against *Plasmodium falciparum* (FcB1 strain) (IC_{50} of 16 μM). This observation suggested that their moderate antiplasmodial activity should not be due to their cytotoxicity.

Experimental Section

General Information: Infrared spectra were recorded as thin films on NaCl plates on a Fourier transform spectrometer (FTIR) Nicolet Impact 400. Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter, using a sodium (589, D line) lamp. Mass spectra were performed by using Electrospray-MS with an API Q-STAR PULSARi spectrometer of Applied Biosystems. ^{13}C NMR spectra were recorded with an AC 300 Bruker spectrometer operating at 75.47 MHz. ^1H and 2D-NMR spectra were recorded with an Avance 400 Bruker spectrometer operating at 400.13 MHz. ^1H chemical shifts were referenced relative

to $CHCl_3$ at δ = 7.24 ppm and ^{13}C chemical shifts to the central peak of $CDCl_3$ at δ = 77.0 ppm. For HMBC experiments the delay (1/2*J*) was 70 ms, and for the NOESY experiments the mixing time was 150 ms.

Extraction and Isolation: *M. nutans* Drake was collected in North Vietnam in June 2000 and a specimen (VN 700) was deposited at the Institute of Ecology and Natural Resources, Vietnam Academy of Science and Technology, Vietnam. The dried and ground leaves (5 kg) were alkalinized with aqueous NH_4OH (10%) and extracted with CH_2Cl_2. After evaporation to dryness, the residue was suspended in an aqueous 5% HCl solution, and then extracted with CH_2Cl_2. The alkaloid residue obtained after solvent removal under reduced pressure, was separated by chromatography over a silica gel column, eluting with a gradient of CH_2Cl_2/MeOH (from 0 to 100% of MeOH) to provide dehydronitraramine (**1**, 6 mg, 0.00012%) and *N*-formylmyrionine (**2**, 37 mg, 0.00074%).

Dehydronitraramine (1): Colorless solid (Et_2O/EtOH); M.p. 115–116 °C, $[\alpha]_D^{20}$ = +9.3 (*c* = 0.5, MeOH). IR (thin film, NaCl): $\tilde{\nu}_{max}$ = 2932, 2865, 1651, 1379, 1364, 1336, 1315, 1120, 1081, 1067, 1026, 955, 909, 862, 835, 728 cm^{-1}. HR-ESI-MS (TOF): calcd. for $C_{15}H_{23}N_2O$ 247.1810 $[M + H]^+$; found 247.1817. ESI-MS-MS (TOF) on $[M + H]^+$ ion: *m*/*z* = 247 $[M + H]^+$, 236, 219, 206, 191, 176, 160, 151, 147, 122, 96, 79, 67, 55. For NMR spectroscopic data, see Table 1.

***N*-Formyl myrionine (2):** Crystalline solid (Et_2O/EtOH); M.p. 119–123 °C, $[\alpha]_D^{20}$ = +35.9 (*c* = 1, MeOH). IR (thin film, NaCl): $\tilde{\nu}_{max}$ = 2936, 2866, 1666, 1645, 1636, 1625, 1500, 1468, 1438, 1356, 1315, 1269, 1245, 1184, 1163, 1131, 1096, 988, 853, 730, 672, 438 cm^{-1}. HR-ESI-MS (TOF): calcd. for $C_{16}H_{27}N_2O_2$ 279.2073 $[M + H]^+$; found 279.2082. ESI-MS-MS (TOF) on $[M + H]^+$ ion: *m*/*z* = 279 $[M + H]^+$, 251, 234, 152, 135, 112, 107, 100, 93, 84, 79, 67. When analysed by semi-preparative HPLC on an RP-18 column, using MeOH/H_2O = 3:2 as the eluent (detection UV 220 nm, 1 mL/min), two peaks were observed at 18 and 19 min. The two components were isolated and analysed by ^1H NMR, both giving the same spectra as the starting *E*/*Z* mixture in the same proportions. For NMR spectroscopic data, see Table 2.

Formylation of (8*S*,9*R*,10*S*)-Myrionine: To a solution of pyridine (0.5 mL) containing (8*S*,9*R*,10*S*)-myrionine (10 mg, 0.04 mmol) was added a mixture of HCOOH/Ac_2O (4:1, 1 mL). The resulting mixture was stirred at room temp. for 24 h. Water was added, and the reaction mixture was extracted with CH_2Cl_2 (4 × 5 mL). The solvent was removed under diminished pressure, and the residue was purified by preparative TLC to afford (8*S*,9*R*,10*S*)-*N*-formylmyrionine (9.5 mg, 91% yield). $[\alpha]_D^{20}$ = +36.8 (*c* = 1, MeOH). The ^1H NMR spectrum was identical with that of the natural compound (**2**).

Cytotoxicity and Antiplasmodial Assay: Assays were performed using the previously described protocols.[5,6]

Supporting Information (see also the footnote on the first page of this article): NMR and MS spectra of dehydronitraramine (**1**) and *N*-formylmyrionine (**2**).

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